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Stereotactic radiosurgery for the treatment of vestibular schwannoma requiring intervention[1]

Extract

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Key statement

Research question

The objective of this investigation is to assess the benefit of treatment with single-session stereotactic radiosurgery (SRS) using linear accelerators or cobalt-60 gamma sources in comparison with microsurgical resection in patients with vestibular schwannoma requiring intervention (primary, recurrence, or residual tissue) with regard to patient-relevant outcomes.

Conclusion

Results on patient-relevant outcomes which were usable for the report were found in a total of 3 non-randomized prospective comparative studies with a follow-up duration of about 2 years. For each of the outcomes of facial paresis and hearing ability, there is a hint of greater benefit of SRS in comparison with microsurgical resection.

No data were available for the outcome of serious adverse events. With regard to the remaining outcomes, there is no hint of any greater benefit or harm of SRS in comparison with microsurgical resection. These outcomes include mortality, dizziness, headache, tinnitus, balance impairment, unfitness to work, adverse events as in complications of therapy and reinterventions as well as health-related quality of life.

Based on the benefit-harm assessment across outcomes, this results in a hint of greater benefit of SRS in comparison with microsurgical resection in patients with vestibular schwannoma requiring intervention.

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List of abbreviations

Abbreviation	Meaning
AAO-HNS	American Academy of Otolaryngology – Head and Neck Surgery
AE	adverse event
CI	confidence interval
CN	cranial nerve
GBI	Glasgow Benefit Inventory
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MD	mean difference
MRI	magnetic resonance imaging
OR	odds ratio
PANQOL	Penn Acoustic Neuroma Quality of Life
PCS	Physical Component Summary
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short-Form Health Survey
SRS	stereotactic radiosurgery

1 Background

Vestibular schwannoma (formerly known as acoustic neuroma) is a benign, usually slow-growing tumour which typically develops from the vestibular nerve (balance nerve) [1]. About 8% of all intracranial tumours are vestibular schwannomas, more than 90% of which are unilateral [1,2]. The condition is usually diagnosed at the age of about 50 years [1,2]. Its incidence is 1 to 2 cases per 100 000 population per year [1]. Symptoms include, in particular, hearing deficits, tinnitus, dizziness, and facial paraesthesia [1,2].

The exact aetiology of vestibular schwannoma is unknown. Potential risk factors include low-dose radiation for benign diseases of the head and neck during childhood, the use of mobile phones, and noise exposure [2]. In this context, neurofibromatosis type 2 represents a special case because 90% to 95% of patients with this genetic condition develop bilateral vestibular schwannoma [3]. These bilateral tumours are usually diagnosed at an age of about 30 years [3].

Vestibular schwannoma can be stratified according to the Hannover, House, Koos, or Sterkers classification system, which are each based on the size and extension of the tumour [1]. The primary diagnostic tool is typically magnetic resonance imaging (MRI) [1].

The choice of treatment method is largely based on tumour characteristics (size, location, and growth), patient history, and patient preference [1,4-7]. Options include watchful waiting, microsurgical resection, radiotherapy, and a combination thereof [1,2,7]. Watchful waiting requires periodic MRI scans about every 12 months and is an option particularly suitable for small, non-growing, asymptomatic tumours. Radiotherapy is an alternative for older patients and those with high surgical risk [1,2]. Microsurgery is typically used to treat symptomatic and/or larger space-occupying lesions; depending on tumour location, it involves a transtemporal, translabyrinthine, suboccipital, or retrosigmoidal approach [1,2]. For radiotherapy of vestibular schwannoma, single-session stereotactic radiosurgery (SRS) with linear accelerators or cobalt-60 gamma sources is available, among others. It involves immobilizing the head and exposing the target tissue in the head to precisely-targeted, high-dose radiation in a single session [2,8].

2 Research question

The objective of this investigation is to assess the benefit of treatment with single-session stereotactic radiosurgery using linear accelerators or cobalt-60 gamma sources in comparison with microsurgical resection in patients with vestibular schwannoma requiring intervention (primary, recurrence, or residual tissue) with regard to patient-relevant outcomes.

3 Methods

The target population of the benefit assessment is patients with vestibular schwannoma requiring intervention (primary, recurrence, or residual tissue after partial resection). The experimental intervention is single-session stereotactic radiosurgery (SRS) using linear accelerators or cobalt-60 gamma sources. The comparator intervention is microsurgical resection.

The investigation examined the following patient-relevant outcomes:

- Mortality
- Morbidity (particularly dizziness, hearing ability, facial paresis, and other neurological symptoms)
- Health-related quality of life
- Adverse events
- Length of hospital stay

Randomized controlled trials (RCTs) were to be primarily included in the benefit assessment. Where no RCTs were available, non-randomized, prospective, comparative studies were to be included, e.g. quasi-randomized controlled studies, non-randomized controlled studies with active allocation of the intervention following a preplanned rule, or prospective comparative cohort studies with passive allocation of the intervention. There were no restrictions regarding the study duration.

The systematic search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: trial registries, manufacturer queries, documents sent by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), viewing of reference lists, documents made available from hearing procedures, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, study-level criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were organized according to outcomes and described.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter is the case if no data are available or the available data do not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

4 Results

4.1 Results of the information retrieval

For the research question, information retrieval resulted in 5 relevant non-randomized prospective comparative studies. No planned or ongoing studies were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 6 November 2020.

Table 1: Study pool of the benefit assessment

Study		Available documents		
	Full publication (in professional journals)	Registry entry / results report from the study registries	Clinical study report from manufacturer documents (not publicly accessible)	Other documents
Carlson 2021	Yes [9,10]	No	No	No
Di Maio 2009[a]	Yes [11]	No	No	No
Myrseth 2009	Yes [12]	No	No	No
Pollock 2006	Yes [13]	No	No	No
Wagner 2011[b]	Yes [14]	No	No	No

a: The study was included only formally because it provides combined analyses for patients with stereotactic radiosurgery and radiotherapy. Subgroup analyses for patients with stereotactic radiosurgery are not included in the publication and cannot be provided by the authors.
b: The study was included only formally because the treatment decision was taken based on tumour size and no stratified analysis by tumour size or other adjusted analyses were available. Generally, it lacks a presentation of patient characteristics which would allow assessing the comparability of groups.

4.2 Characteristics of the studies included in the assessment

The **Di Maio 2009** [11] and **Wagner 2011** [14] studies are not presented below. While these studies met the inclusion criteria, their results were unusable[2].

The 3-arm monocentric study **Carlson 2021** [9,10] conducted in the USA included adult patients with unilateral vestibular schwannoma for whom 1 data survey at baseline and at least 1 further survey from follow-up were available.

In principle, the determinative factor for allocation was patient preferences with regard to their allocation to the 3 treatment groups. Of the 313 who had presented, a total of 244 (78%) met the inclusion criteria. Among these 244 patients, 48 (20%) were treated with SRS and 118 (48%) with microsurgery, while 78 (32%) underwent watchful waiting. The average duration

[2] The analyses of the Di Maio 2009 study combined patients with SRS and those with radiotherapy. Subgroup analyses for patients with SRS are not included in the publication and cannot be provided by the authors.
In Wagner 2011, the treatment decision was made based on tumour size. No stratified analysis by tumour size or other adjusted analyses are available. Generally, it lacks a presentation of patient characteristics which would allow assessing the comparability of groups.

of follow-up observation was 2.1 years. Below, only the 2 treatment groups relevant for the present assessment are discussed. The average age of patients in the microsurgery group was lower than for those in the SRS group (52 years versus 61 years, $p < 0.001$; IQWiG calculation). In addition, patients in the microsurgery group had larger tumours than those in the SRS group ($p = 0.002$; IQWiG calculation). At baseline, the groups were comparable in the remaining patient characteristics, such as sex, hearing ability, and facial paresis.

SRS was performed with cobalt-60 gamma sources. The median tumour margin dose was 12.5 Gray. For the microsurgical procedure, the retrosigmoidal approach was most commonly used (n = 71; 60%), followed by the translabyrinthine (n = 45; 38%), transtemporal (n = 1; 1%), and transotic approaches (n = 1; 1%). In 18 of the 118 cases (15%), subtotal resection was performed.

The Norwegian study **Myrseth 2009** [12] included adult patients who had a unilateral, new vestibular schwannoma ≤ 2.5 cm in diameter which was deemed to require intervention due to evidence of tumour growth or a size > 2.0 cm in the cerebellopontine angle. Patients with neurofibromatosis type 2 were excluded.

Allocation to treatment groups was based on patient preference, except where the surgical option was contraindicated. In some patients, referring neurosurgery centres had specified the type of therapy. Originally, the study had been planned as a randomized trial, but due to patients rejecting randomization, they were allocated as described above. The study analysed 88 of 91 included patients. Among these, 60 patients were treated by SRS and 28 by microsurgery. The duration of follow-up observation was 2 years. Patients in the SRS group had a higher average age than those in the microsurgery group (57.5 years versus 52.5 years: $p = 0.06$). At baseline, all included patients had normal facial nerve function (House-Brackmann scale), 43% had serviceable hearing, 83% suffered from tinnitus, 48% from dizziness, and 39% from balance impairment. No noticeable differences between treatment groups were found in this regard.

SRS was conducted under local anaesthesia with cobalt-60 sources and a special planning software with automatic positioning system. The tumour margin dose was 12 Gray. Microsurgical resection was carried out by means of suboccipital craniotomy with free bone flap, which was then replaced in the original site. In 1 patient with severe dizziness, the resection was carried out using a translabyrinthine approach. In all patients, cranial nerve (CN) VII, but not CN VIII, was monitored. The surgical team possessed expertise in both neurosurgery and ENT surgery. In 5 cases of the microsurgery group, the tumour could not be removed in its entirety.

The monocentric US study **Pollock 2006** [13] included adult patients with unilateral, untreated vestibular schwannoma < 3 cm in diameter. However, it excluded patients with neurofibromatosis type 2, those with recurrence as well as patients ineligible for resection.

From June 2000 through July 2002, a total of 162 patients with vestibular schwannoma presented; from among these patients, 21 (13%) were recommended watchful waiting, and 9 (6%) were treated at different centres. Among the remaining 132 patients, 89 were eligible for study participation, and

82 of these patients consented to take part in the study. Allocation to the two treatment groups was based on patient preference, following discussion of the options: 46 patients (56%) were treated with SRS and 36 (44%) with microsurgery. The mean follow-up duration for both treatment arms was 42 months, with a minimum duration of 12 months and a maximum duration of 62 months. On average, patients in the microsurgery group were older than those in the SRS group (48.2 years versus 53.9 years; p = 0.03). At baseline, the groups were comparable in terms of the remaining patient characteristics, such as sex, hearing ability, tinnitus, dizziness, and tumour size.

SRS was performed with cobalt-60 gamma sources following dose planning with the aid of MRI. The mean tumour margin dose was 12.2 Gray. The microsurgical procedure was selected taking into account patient preference, hearing ability, and tumour size. Most commonly used was the retrosigmoidal approach (n = 25; 69%), followed by the translabyrinthine (n = 9; 25%), and transtemporal approaches (n = 2; 6%). In 3 of the 36 cases, the tumour could not be removed in its entirety.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 3 studies. Table 2 presents an overview of the data on patient-relevant outcomes from the included studies. None of the studies contained explicit information on the outcome of serious adverse events (SAEs).

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes											
	Mortality	Facial paresis	Hearing ability	Dizziness	Headache	Tinnitus	Balance impairment	Unfitness to work	SAE	AE: complications of therapy and reinterventions	Length of hospital stay	Health-related quality of life
Carlson 2021	–	○[a]	●	○[b]	●	●	○[b]	–	–	○[a]	–	●
Myrseth 2009	●	●	●	●	–	●	●	●	–	●	●	●
Pollock 2006	–	●	●	●	●	–	–	–	–	●	●	●

●: Data were reported and were usable.
○: Data were reported but unusable for the benefit assessment.
–: Either no data were reported (no further information) or the outcome was not surveyed.
a: The treatment groups differ statistically significantly in age and tumour size at baseline. / For this outcome, no adjusted analysis is available.
b: No analyses of the individual components are available for the combined outcome of dizziness or balance impairment, consisting of the individual components of dizziness and balance impairment.
AE: adverse event; SAE: serious adverse event

4.4 Assessment of the risk of bias of results

Due to the study design of the included nonrandomized prospective comparative studies (particularly lack of randomization), the risk of bias at study level is generally deemed high for all 3 studies. Given the high risk of bias at study level, all reported results on patient-relevant outcomes must be considered potentially highly biased as well. The risk of bias at outcome level was not assessed separately. The qualitative certainty of results of the 3 studies was rated as very low. Therefore, conclusions on benefit can be drawn only in case of effects so large that they cannot be explained by bias alone (dramatic effect).

4.5 Results on patient-relevant outcomes

If multiple analysis time points were available for a patient-relevant outcome, the most recent survey time point generally determined the conclusion on the available evidence (provided that it did not contradict earlier survey time points); this is because the long-term treatment goal for vestibular schwannoma requiring intervention is reducing morbidity and improving the quality of life. If data were available from multiple studies, they were combined in a metaanalysis using a model with fixed effect.

4.5.1 Results on mortality

For the outcome of mortality, data from Myrseth 2009 were available. No deaths occurred in the 2-year study period.

For the outcome of mortality, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.2 Results on facial paresis

For the outcome of facial paresis, measured with the House-Brackman score, data were available from the Myrseth 2009 and Pollock 2006 studies. Since only grade I corresponds to normal facial function, the remaining grades, II through VI, were operationalized as facial paresis. The metaanalytical summary of the most recent survey time point (24 months or 42 months [mean]) showed a statistically significant effect in favour of SRS in comparison with microsurgical resection (odds ratio [OR]: 0.06; 95% confidence interval [CI]: [0.02; 0.21]; $p < 0.001$). The chance of suffering facial paresis was about 17 times lower with SRS than with microsurgical resection. An effect of this size cannot be explained by bias alone (dramatic effect).

For the outcome of facial paresis, there is consequently a hint of greater benefit of SRS in comparison with microsurgical resection.

4.5.3 Results on hearing ability

For the outcome of hearing ability, data were available from 3 studies. Hearing ability was deemed serviceable at Grade 1 or 2 of the Gardner-Robertson or AAO-HNS (American Academy of Otolaryngology – Head and Neck Surgery) hearing classification scales.

Due to inadequate presentation of results and different operationalizations of the outcome, it was impossible to calculate an overall estimator. Myrseth 2009 (Gardner-Robertson scale) showed, at 24 months, a statistically significant difference in favour of SRS in comparison with microsurgical resection (OR: 22.93; 95% CI: [1.33; 396.64]; p = 0.002). The chance of preserving serviceable hearing was about 23 times higher with SRS than with microsurgical resection. Pollock 2006 (AAO-HNS classification) showed, after 42 months (mean), a statistically significant difference in favour of SRS in comparison with microsurgical resection (p < 0.001; no further information). In Carlson 2021, hearing ability was surveyed using a Likert scale ranging from 1 (normal hearing) to 10 (completely deaf). At the time point 2.1 years (mean), a statistically significant difference in favour of SRS was found in comparison with microsurgical resection (mean difference [MD]: -1.60; 95% CI: [-2.63; -0.57]; p = 0.002). However, the preservation of serviceable hearing cannot be assessed with this survey instrument; therefore, this analysis must be deemed to supplement the relevant analyses from Myrseth 2009 and Pollock 2006. Overall, effects so large that they cannot be explained by bias alone (dramatic effects) were found, particularly in the Myrseth 2009 study.

For the outcome of hearing ability, there is consequently a hint of greater benefit of SRS in comparison with microsurgical resection.

4.5.4 Results on dizziness

For the outcome of dizziness, data were available from 2 studies. In Myrseth 2009, data were collected using a visual analogue scale, and in Pollock 2006, with the Dizziness Handicap Inventory (scores ranging from 0 to 100, with higher scores corresponding to greater perceived burden). The 2 instruments were deemed sufficiently similar for conducting a metaanalysis. For the last survey time point (24 months and 42 months, respectively [mean]), a numerical advantage of SRS over microsurgical resection was found, but no statistically significant difference between groups (MD: -5.97; 95% CI: [-11.98; 0.04]; p = 0.052).

For the outcome of dizziness, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.5 Results on headache

For the outcome of headache, data were available from 2 studies. Due to the different operationalizations of the outcome, it was impossible to calculate an overall estimator. In Carlson 2021, the outcome was surveyed using a Likert scale with scores ranging from 1 to 10 (higher scores corresponding to greater perceived burden). In Pollock 2006, data were collected using the Headache Survey, which asks questions on frequency, duration, intensity, treatment, and unfitness to work due to headache. According to the answer options, the score ranges from 1 to 20 (higher scores corresponding to greater perceived burden). Neither Carlson 2021 after 2.1 years (mean) nor Pollock 2006 after 42 months (mean) showed a statistically significant difference between groups (p = 0.871 and p = 0.29, respectively).

For the outcome of headache, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.6 Results on tinnitus

For the outcome of tinnitus, data were available from 2 studies. In Carlson 2021, the outcome was surveyed using a Likert scale with scores ranging from 1 to 10 (higher scores corresponding to greater perceived burden). In Myrseth 2009, the outcome was surveyed using a visual analogue scale from 0 to 100 (higher scores corresponding to greater perceived burden). Since except for the score range, both scales are comparable, the score range of the Carlson 2021 study was adjusted by multiplying by 10. The metaanalysis of the most recent survey time point (2.1 years [mean] or 24 months) showed a statistically significant effect to the disadvantage of SRS in comparison with microsurgical resection (MD: 9.27; 95% CI: [0.84; 17.71]; p = 0.031). A mean value difference of about 9 on a scale of 1 to 100 is of a magnitude which could be explained by bias alone. Hence, there is no dramatic effect.

For the outcome of tinnitus, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.7 Results on balance impairment

For the outcome of balance impairment, data were available from Myrseth 2009. After 24 months, 45.0% of patients in the SRS group and 50.0% of those in the microsurgery group reported suffering from balance impairment. The difference was statistically insignificant (no further information available).

For the outcome of balance impairment, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.8 Results on unfitness to work

For the outcome of unfitness to work, data were available from 1 study. Myrseth 2009 surveyed whether patients were working, on sick leave, disabled, or retired at baseline and after 24 months. This Norwegian study lacks specific operationalizations of the individual status options which would allow distinguishing them from one another. Being on sick leave is viewed as a status particularly relevant to patients; it has been analysed together with the other status options. With regard to the 4 status options, after 24 months, no statistically significant differences were found between groups (p = 0.924; for details, see Section A3.3.9 of the full report).

For the outcome of unfitness to work, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.5.9 Results on SAEs

The 3 studies provided no data on the outcome of SAEs.

For the outcome of SAEs, there is consequently no hint of greater or lesser harm of SRS in comparison with microsurgical resection.

4.5.10 Results on AEs – complications of therapy and reinterventions

For the outcome of "adverse events (AEs) – complications of therapy and reinterventions", data from 2 studies were available. In Myrseth 2009, no AEs were reported for any of the 60 patients treated with SRS. After microsurgical resection, 9 AEs occurred in 28 patients (32.1%). This included plastic surgery for correcting postoperative facial paresis (n = 5), cerebrospinal fluid leaks (n = 2), asymptomatic small haematoma in the resection cavity identified by computed tomography (n = 1) and hoarseness, which disappeared after several weeks (n = 1). In Pollock 2006, after SRS, 46 patients had a total of 3 AEs. They were deteriorating ataxia (n = 2) and trigeminal neuralgia (n = 1). Following microsurgical resection, a total of 13 AEs occurred in a population of 36 persons. They included cerebrospinal fluid leak (n = 5), tarsorrhaphy (n = 5), use of gold eyelid weights (n = 1), leg vein thrombosis (n = 1), and wound infection (n = 1).

The total rate of AEs is deemed not to be interpretable, and an effect estimator was not calculated. Firstly, the available data do not allow assessing the severity of individual AEs, and secondly, multiple inclusion of the same patient cannot be ruled out. Further, the reported AEs are not based on a recognizable, systematic survey method. Consequently, a benefit assessment was not carried out.

In both studies, reinterventions occurred exclusively after SRS. In Myrseth 2009, 1 in 60 patients (1.7%) had microsurgical tumour resection secondary to tumour growth within 24 months, while in Pollock 2006, this was the case for 2 of 46 patients (4%) within 42 months. The metaanalytical summary showed no statistically significant difference between groups (OR: 2.62; 95% CI: [0.29; 23.57]; p = 0.390).

For the outcome "AEs – complications of therapy and reinterventions", there is consequently no hint of greater or lesser harm of SRS in comparison with microsurgical resection.

4.5.11 Results on length of hospital stay

For the outcome of length of hospital stay, data were available from 2 studies. Due to inadequate presentation of results, it was not possible to calculate an overall estimator. Myrseth 2009 showed a statistically significant effect in favour of SRS in comparison with microsurgical resection (mean [min; max]: 2.5 [2;5] days in comparison with 12.5 [10;30] days; $p < 0.001$). In Pollock 2006, SRS was conducted on an outpatient basis. The mean length of hospital stay after microsurgical resection was 5.1 days (no further information available). Overall, effects so large that they cannot be explained by bias alone (dramatic effects) were found.

For the outcome of length of hospital stay, there is consequently a hint of greater benefit of SRS in comparison with microsurgical resection.

4.5.12 Results on health-related quality of life

For the outcome of health-related quality of life, data were available from 3 studies. In Carlson 2021, the outcome was surveyed using the Penn Acoustic Neuroma Quality of Life (PANQOL) scale. The total score and the 7 domains each have a score range of 0 to 100, with higher scores corresponding to lower perceived burden. After 2.1 years (mean), the total score revealed a numerical advantage of SRS in comparison with microsurgical resection, but there was no statistically significant difference between groups (MD: 5.00; 95% CI: [-3.41; 13.41]; p = 0.242). Since the total score is pivotal for the benefit assessment, a presentation of the 7 domains is deliberately omitted in this section (for further results, see Section A3.3.13 of the full report).

For the PANQOL scale, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

In Myrseth 2009, the outcome was surveyed using the Glasgow Benefit Inventory (GBI). The total score and the 3 domains each have a score range of -100 to 100, with higher scores corresponding to lower perceived burden. After 24 months, the total score showed a statistically significant effect in favour of SRS in comparison with microsurgical resection (MD: 13.90; 95% CI: [3.02; 24.78]; p = 0.013). A mean value difference of about 14 on a scale of -100 to 100 is of a magnitude that can be explained by bias alone. Hence, there is no dramatic effect. Since the total score is decisive for the conclusion on benefit, a presentation of the 3 domains was deliberately omitted (for further results, see Section A3.3.13 of the full report).

For the GBI, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

In Pollock 2006, the outcome was surveyed with the Tinnitus Survey and the 36-item Short-Form Health Survey (SF-36). The Tinnitus Survey assesses the extent to which tinnitus impacts health-related quality of life. The instrument has a score range of 0 to 100, with higher scores corresponding to greater perceived burden. After 42 months (mean), no statistically significant difference between groups was found (p = 0.29).

The two summary scores of the SF-36, the Mental Component Summary (MCS) and the Physical Component Summary (PCS), each have a score range of 0 to 100. Higher scores correspond to lower perceived burden. After 42 months (mean), the MCS showed a numeric advantage of SRS (MD: 3.30; 95% CI: [-0.41; 7.01]; p = 0.080), while the PCS revealed a numeric disadvantage of SRS (MD: -0.70; 95% CI: [-5.35; 3.95]; p = 0,765); however, neither MCS nor PCS showed a statistically significant difference between groups.

For the Tinnitus Survey and the SF-36, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

Overall, for the outcome of health-related quality of life, there is consequently no hint of greater or lesser benefit of SRS in comparison with microsurgical resection.

4.6 Overall evaluation of results

Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

Outcomes											
Mortality	**Facial paresis**	**Hearing ability**	**Dizziness**	**Headache**	**Tinnitus**	**Balance impairment**	**Unfitness to work**	**SAE**	**AE: complications of therapy and reinterventions**	**Length of hospital stay**	**Health-related quality of life**
(⇔)	⇗	⇗	⇔	⇔	⇔	⇔	⇔	–	(⇔)	⇗	⇔

⇗: Hint of greater benefit of stereotactic radiosurgery in comparison with microsurgical resection
⇔: no hint, indication, or proof; homogeneous result
(⇔): no hint, indication or proof, homogeneous result; the 95% confidence interval for relative effect is so imprecise that neither halving nor doubling of the effect can be ruled out
-: no data reported

AE: adverse event; SAE: serious adverse event

Assessment of the volume of unpublished data

For assessing the volume of unpublished data, the results of the information retrieval are used below. The search in study registries did not identify any completed studies. This means that there are no known completed studies whose results have not yet been published. However, it also means that no study registry entries were found for the 5 included studies. It is therefore conceivable for unregistered studies to have been completed, without their results having been published to date. However, no specific evidence suggests this to be the case.

As part of information retrieval, queries about unpublished study results were sent to 11 manufacturers of devices used for the experimental intervention. The responses received from 6 manufacturers did not suggest the presence of unpublished results. The remaining 5 manufacturers did not respond to the query or to the subsequent reminder.

Although the existence of unpublished data cannot be fully ruled out, the overall picture does not suggest that there are any unpublished study results. Therefore, no consequences arise for the conclusion of the report.

Weighing of benefits versus harm

For the outcomes of facial paresis, hearing ability, and length of hospital stay, there is a hint of greater benefit of SRS in comparison with microsurgical resection in patients with vestibular schwannoma requiring intervention.

The studies do not report any data on the outcome of SAEs. However, analyses on the outcomes of mortality, facial paresis, and AEs as in complications of therapy and reinterventions are available. These analyses are deemed sufficient for assessing harm with regard to the research question. There is no hint of greater harm of SRS in comparison with microsurgical resection.

Hence, the greater benefit of SRS is not offset by greater harm with regard to the previously described outcomes in comparison with microsurgical resection.

5 Classification of the assessment result

The conclusions are based on 3 studies with usable results in which patients with unilateral vestibular schwannoma were treated with either SRS or microsurgical resection. The target population for the present report was patients with vestibular schwannoma requiring intervention. Consequently, the treatment strategy of watchful waiting was disregarded. Further treatment approaches, such as fractionated radiotherapy or the a priori intended combination therapy of microsurgical resection and SRS were not subject of the report as commissioned.

Bilateral vestibular schwannoma is typically seen in neurofibromatosis type 2. However, patients with this genetic disorder were explicitly excluded from 2 studies, and the 3rd study did not provide any information on this topic. In this context, the authors of guidelines note the lack of data from prospective studies on the treatment of vestibular schwannoma in patients with neurofibromatosis type 2 [7]. In principle, treatment options are SRS and microsurgical resection [5-7].

The 3 nonrandomized prospective comparative studies exhibit methodological deficits which affect the qualitative certainty of results. In all studies, rather than being actively allocated to treatment arms following a preplanned rule, patients were allocated largely according to their own preferences. Consequently, there were differences in group sizes as well as between treatment groups with regard to prognostic factors such as age or tumour size. Only the Carlson 2021 study took into account prognostically relevant factors in its analysis. However, the study fails to clearly report the percentage of patients for whom the survey was at least partially retrospectively. Due to methodological deficits, the qualitative certainty of results in the 3 studies is rated as very low; therefore, a hint of greater benefit or harm can be derived only in case of effects so large that they cannot be explained by bias alone (dramatic effects).

For each of the outcomes of facial paresis and hearing ability, there is a hint of greater benefit of SRS in comparison with microsurgical resection. For each of the outcomes of reintervention due to tumour growth and health-related quality of life, there is no hint of greater or lesser benefit of SRS in comparison with microsurgical resection. These conclusions are drawn on the basis of the last survey time point, which the studies had at about 2 years. Since the long-term goal of treatment of vestibular schwannoma requiring intervention is reducing morbidity and improving the quality of life, data from prospective comparative studies beyond a period of 2 years would be desirable, particularly for hearing ability, reintervention, and health-related quality of life. In a retrospective comparative study with a follow-up duration of 5 years, for instance, hearing ability continuously decreased after SRS, while only minor deterioration was observed after microsurgical resection [15]. Therefore, it remains unclear whether, for the outcome of hearing ability, the hint of greater benefit of SRS over microsurgical resection persists beyond a period of 2 years. Based on the search in study registries, there are no known ongoing prospective comparative studies which might be suitable for complementing the evidence on long-term results. However, the result of the search in trial registries is of limited informative value since no registry entries were found for any of the 5 included studies. In this

context, please note that for any research on humans, the Declaration of Helsinki [16] calls not only for publication of results, but also, since 2008, for prior study registration in publicly accessible databases.

In summary, the conclusion is based on studies with patients with unilateral vestibular schwannoma who were generally eligible for both SRS and microsurgical resection. According to the guideline, this prerequisite is most likely met by patients with a symptomatic, medium-sized tumour (Koos grades III to IV; 3 cm). As already discussed in the Background section, tumour characteristics (size, location, and growth) play an important role in the treatment decision, but factors such as patient history and patient preference must be taken into account as well [1,4-7].

6 Conclusion

Results on patient-relevant outcomes which were usable for the report were found in a total of 3 non-randomized prospective comparative studies with a follow-up duration of about 2 years. For each of the outcomes of facial paresis and hearing ability, there is a hint of greater benefit of SRS in comparison with microsurgical resection.

No data were available for the outcome of SAEs. With regard to the remaining outcomes, there is no hint of any greater benefit or harm of SRS in comparison with microsurgical resection. These outcomes include mortality, dizziness, headache, tinnitus, balance impairment, unfitness to work, adverse events as in complications of therapy and reinterventions as well as health-related quality of life.

Based on the benefit-harm assessment across outcomes, this results in a hint of greater benefit of SRS in comparison with microsurgical resection in patients with vestibular schwannoma requiring intervention.

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Please see full final report for full reference list.

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https://www.iqwig.de/en/projects/n20-03.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to November 05, 2020

The following filters were adopted:

- RCT: Lefebvre [17] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)
- Non-randomized studies: Waffenschmidt [18] – Search filter with best sensitivity for controlled NRS (Ovid MEDLINE, adapted from PubMed)

#	**Searches**
1	Neuroma, Acoustic/
2	Cerebellopontine Angle/
3	(vestibular* adj1 schwannoma*).ti,ab.
4	(acoustic adj1 (neuroma* or tumor*)).ti,ab.
5	((cerebellopontine* adj1 angle*) and (tumor* or tumour*)).ti,ab.
6	or/1-5
7	Radiosurgery/
8	(gamma* adj1 knife*).ti,ab.
9	(linac* or (linear* adj1 accelerator*)).ab,ti.
10	(cyber knife* or cyberknife*).ab,ti.
11	(stereotactic* adj1 radiosurg*).ti,ab.
12	or/7-11
13	and/6,12
14	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
15	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
16	or/14-15
17	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
18	hi.fs. or case report.mp.
19	or/17-18
20	16 not 19
21	Randomized Controlled Trial.pt.
22	Controlled Clinical Trial.pt.
23	(randomized or placebo or randomly or trial or groups).ab.
24	drug therapy.fs.

#	**Searches**
25	or/21-24
26	exp animals/ not humans/
27	25 not 26
28	cochrane database of systematic reviews.jn.
29	(search or MEDLINE or systematic review).tw.
30	meta analysis.pt.
31	or/28-30
32	(27 or 31) not (comment or editorial).pt.
33	13 and (20 or 32)
34	33 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations November 05, 2020

#	**Searches**
1	(vestibular* adj1 schwannoma*).ti,ab.
2	(acoustic adj1 (neuroma* or tumor*)).ti,ab.
3	((cerebellopontine* adj1 angle*) and (tumor* or tumour*)).ti,ab.
4	or/1-3
5	(gamma* adj1 knife*).ti,ab.
6	(linac* or (linear* adj1 accelerator*)).ab,ti.
7	(cyber knife* or cyberknife*).ab,ti.
8	radiosurg*.ti,ab.
9	or/5-8
10	and/4,9
11	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
12	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
13	or/11-12
14	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
15	hi.fs. or case report.mp.
16	or/14-15
17	13 not 16
18	(clinical trial* or random* or placebo).ti,ab.
19	trial.ti.
20	(search or meta analysis or medline or systematic review).ti,ab.
21	or/18-20
22	21 not (comment or editorial).pt.

#	Searches
23	10 and (17 or 22)
24	23 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 November 05

The following filters were adopted:

- RCT: Wong [19] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	acoustic neuroma/
2	"acoustic neurinoma"/
3	(vestibular* adj1 schwannoma*).ti,ab.
4	(acoustic adj1 (neuroma* or tumor*)).ti,ab.
5	((cerebellopontine* adj1 angle*) and (tumor* or tumour*)).ti,ab.
6	or/1-5
7	exp radiosurgery/
8	gamma knife/
9	(gamma* adj1 knife*).ti,ab.
10	(linac* or (linear* adj1 accelerator*)).mp.
11	(cyber knife* or cyberknife*).mp.
12	(stereotactic* adj1 radiosurg*).ti,ab.
13	or/7-12
14	and/6,13
15	(random* or double-blind*).tw.
16	placebo*.mp.
17	or/15-16
18	(meta analysis or systematic review or MEDLINE).tw.
19	14 and (17 or 18)
20	19 not medline.cr.
21	20 not (exp animal/ not exp humans/)
22	21 not (Conference Abstract or Conference Review or Editorial).pt.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2020
- Cochrane Database of Systematic Reviews Issue 11 of 12, November 2020

ID	Search
#1	MeSH descriptor: [Neuroma, Acoustic] this term only
#2	MeSH descriptor: [Cerebellopontine Angle] this term only
#3	(vestibular* near/1 schwannoma*):ti,ab
#4	(acoustic* near/1 (neuroma* or tumor*)):ti,ab
#5	((cerebellopontine* near/1 angle*) and (tumor* or tumour*)):ti,ab
#6	#1 or #2 OR #3 or #4 or #5
#7	MeSH descriptor: [Radiosurgery] this term only
#8	(gamma* near/1 knife*):ti,ab
#9	(linac* or (linear* near/1 accelerator*)):ti,ab
#10	(cyber knife* or cyberknife*):ti,ab
#11	(stereotactic* near/1 radiosurg*):ti,ab
#12	#7 or #8 or #9 or #10 or #11
#13	#6 and #12
#14	#13 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#15	#14 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#16	#13 in Cochrane Reviews, Cochrane Protocols
#17	#15 in Trials

4. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	((schwannoma* OR acoustic OR cerebellopontine*) AND (gamma OR knife OR linac* OR accelerator* OR cyberknife* or radiosurg*))

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(gamma knife OR cyber knife OR linear accelerator OR stereotactic radiosurgery) AND (brain metastasis OR cerebral metastasis OR cavity resection OR acoustic neuroma)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
gamma knife OR cyber knife OR cyberknife OR linear accelerator OR linac OR stereotactic (without Synonyms)