Radiosurgery is best practice for medium-sized vestibular schwannoma.
A systematic survey of the evidence from controlled intervention studies.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001345
Article Type:	Research
Date Submitted by the Author:	05-Jul-2012
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical management
Keywords:	Vestibular Schwannoma, Excision, Radiosurgery, RADIOTHERAPY, NEUROSURGERY, Neurotology < OTOLARYNGOLOGY

ABSTRACT

Objectives. Largely, watchful waiting is the starting policy for patients with small or medium-sized vestibular schwannoma, because of slow growth and relatively minor complaints, that will not improve by tumor treatment. If intervention (microsurgery, radiosurgery or fractionated radiotherapy) becomes necessary, the preference appears to be subjective, while it might be based on research-based evidence. This study addresses the existing evidence based on controlled studies of these interventions.

Design. A systematic Boolean search was performed focused on controlled intervention studies. The retrieved studies were classified according to the Oxford Centre of Evidence-based Medicine levels and quality of the individual studies was assessed and graded according to the Sign-50 criteria on cohort studies.

Data sources. Pubmed/Medline, Embase, Cochrane Central Register of Controlled Trials and reference lists.

Study selection. Seven prospective and retrospective observational, controlled studies with clinical and economic outcomes and quality of life data published before november 2011.

Data extraction and synthesis. Two independent reviewers assessed the methodological quality of the studies and abstracted the outcome data.

Results. The yield was seven studies, all comparing radiosurgery and microsurgery. All but one were confined to solitary tumors less than 30 mm diameter and had no earlier intervention. No randomised studies, nor controlled studies on fractionated radiotherapy were retrieved. Four studies qualified for trustworthy conclusions. In all four radiosurgery showed best outcome: there was no direct mortality, no surgical or anaesthesiological complications, better facial nerve outcome, better preservation of useful hearing, better quality of life, better and quicker return to previous work and less health-related costs.

Conclusion. Growth control by radiosurgery emerges as best practice for solitary vestibular schwannomas up to 30 mm cisternal diameter.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours. [1] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, mostly slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo

or imbalance, the diagnosis is accepted without histological verification. A solid registration is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The majority may not grow for years; the average growth is 1 to 2 millimetres per year.[4-5] But if the tumour grows, the rate in the first year seems on average 5-10 mm.[6] There are no proven parameters predicting a tumour to grow and to what extent.[7-8]

The mild natural course with relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours a starting policy of watchful waiting using regular MRI follow-up. However, in case of a sizeable tumour, that obliterates the cistern of the cerebellopontine angle (CPA) or after substantial growth during follow-up, an indication for intervention evolves. The choice is between microsurgical resection for any tumour size and radiosurgery for small and medium-sized tumours or stereotactic radiotherapy for tumour over 25-30 mm diameter. This study addresses the existing evidence based on controlled studies of these interventions.

Methods

PubMed / Medline and Embase were searched in November 2011 for controlled clinical trials. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatosis) and (management OR treatment OR therapy OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). The retrieved 728 and 632 articles, respectively, were screened by title and by abstract if necessary. We found seven intervention studies with a control arm. Their reference-lists were also screened, but yielded no other studies. We also searched the Cochrane Central Register of Controlled Trials without finding further studies.

Two independent reviewers classified the study designs according to the Oxford Centre of Evidence-based Medicine (CEBM) and abstracted the outcome data. (http://www.cebm.net/index.aspx?o=1025) They assessed the quality of individual studies using the Sign-50 quality criteria for cohort studies. (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9]

Results

No randomized clinical trials were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria; one of these had blinded outcome measurement. [10-11] Both studies are of level 2b according to the Oxford CEBM. (Table 1) The search retrieved another five retrospective cohort studies with a matched control group, all comparing microsurgery and radiosurgery and of level 3b.[12-16] We identified no controlled studies involving fractionated stereotactical radiotherapy.

Table 1.

Retrieved intervention studies for vestibular schwannoma; Oxford CEBM grades of evidence for quality of study design

Evidence level	Description studies	Number	Outcome
1	randomized clinical trials	None	
2b	non-randomized controlled clinical trials (prospective)	2	radiosurgery better than microsurgery in both studies
3b	observational studies with matched controls (retrospective)	5	radiosurgery better than microsurgery in all 5 studies
4	observational studies without controls (case series of various surgical approaches, radiosurgery and fractionated stereotactic radiotherapy)	many	typical outcome: preference for treatment studied

The quality of the individual studies was assessed by judging factors that might increase or decrease the confidence on the strength of association between the intervention and the outcome. Four main items were assessed: selection of subjects, outcome measure, known confounders, statistical analysis. (Appendix 1) At the inception, in six out of seven studies all patients were at the same stage of disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The indication for an intervention was clearly defined only in one study. In the other studies just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patients' characteristics were quite similar in the study groups. Only the average age was higher in almost all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but one study causing possible advantage for the surgery arm. There was minimal or no losses to follow-up in all but one study. Intervention-associated morbidity was the primary outcome in all but one; the one study focused on intervention costs. After summation of the number of items that downgrade the confidence in outcome (bold NO in appendix 1), four studies remained that showed trustworthy association between intervention and outcome.

Table 2. Outcome of all seven controlled studies comparing microsurgery (MS) and radiosurgery (RS): Advantage for radiosurgery in all studies (tumours <30mm)

author publ yr	EBM Level	therapy + no.	follow-up (range)	2nd inter-vention	facial intact[a]	useful hearing[b]	Complic[c]	hosp. days	work resume	costs[d] US $	quality of life[e]
Pollock 2006	2b	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 4%	83 **98***	5 **63***	33 **11***	? ?	? ?	? ?	↓ =*
Myrseth 2009	2b	MS 28 RS 60	≥ 2 yr	incompl 18% 2%	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 % 93	? ?	SF36= **GBI ↑***
Pollock	3b	MS 40	3 yr median	0	78	14	38	9,5	?	↓ 53%*	↓ 45 %

1995		RS 47	(2.1-4 yr)	0	**91***	**75***	**13***	**1.4***	?		↓ 26
Myrseth 2005	3b	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	6% 5%	80 **95***	5 **32***	47 **4***	? ?	? ?	? ?	↓ =*
Regis 2002	3b	MS 110 RS 97	≥ 3 yr	recur 9% 3%	67 **100***	36 **50***	41 **8***	23 **3***	66 % **99***	? ?	↓ 39 % ↓ **9***
Karpinos 2002	3b	MS 18 RS 49	4yr median (0.3-7 yr)	0 4%	69 **96***	40 44	48 **5***	2-16 **1-2***	88 % 94	? ?	? ?
vRoijen 1996	3b	MS 49 RS 80	?	? ?	90 **98***	? ?	23 0	13 **1***	83 % **98***	24k **9.3k***	↓ 30 % ↓ **19***

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d. costs of treatment (direct) and delay in restart work (indirect costs); k=1000, price level 1995;

e. quality of life from questionnaires as ShortForm36, Glasgow Benefit Inventory, Pellet Questionnaire, Health and Labour Questionnaire;

* and bold: significantly better

The outcomes considered most important to patients are specified in Table 2. There was 1% mortality in the only microsurgery arm involving more than 100 patients (not in table).[15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation, better quality of life with a faster return to previous work and lower financial costs.

Discussion

A recent survey in Germany amongst 739 vestibular schwannoma patients showed that about 70% was informed only on microsurgery and not on the radiosurgery option.[17] In our Rotterdam practice for many years, if an intervention is indicated, we offer radiosurgery as the first choice for vestibular schwannomas up to 25 mm cisternal diameter. The discrepancy is obvious and probably not limited to two countries or a few institutions. Both interventions are equally highly effective as demonstrated by numerous case series. [4] Appreciating a patients' individual preference, ideally counselling is based on the outcome of high-quality clinical trials. We searched for evidence and found that radiosurgery is best practice in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold-standard of evidence-based practise. Regarding vestibular schwannomas, however, we most probably will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept blinded fate to decide for them to undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[18-19] The validity of high-quality observational studies is demonstrated by remarkable similar results in randomized and observational studies when comparing treatments. [20-22] Such studies may provide

trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for these patients. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. According to Sign-50, this is the basic thought behind the assessment of quality of individual studies in appendix 1.

All retrieved controlled studies compared the same two interventions and rightly focused on adverse events, including costs, of the intervention. Only Van Roijen et al. did not report on intervention-associated morbidity, but concentrated on quality of live and costs, rendering no specific clinical outcome. All seven comparative studies consistently pointed to radiosurgery as being best intervention for their research question. Some studies, however, provide more confidence, that their outcome is associated with the two interventions studied, as elucidated in appendix 1. A major scientific hazard in all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In six studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Subjects of study had a solitary vestibular schwannoma sized less than 30mm, no invalidating symptoms at baseline and no earlier intervention. Only in the study by Karpinos et al. the source population differed and included NF2 patients with bilateral tumours and patients having had earlier surgery. This prevented a favourable overall good quality judgment. In addition, this study had an inacceptable high loss to follow-up of over 20%. The two prospective studies had no losses at all. Imbalance existed for age, but the disadvantage was at the side of the best outcome. The same applied to frail patients, who were also inclined to end up in the radiosurgery arm.

All but one study reported on the same clinical outcome measures, that is function preservation of the involved cranial nerves, treatment complications and quality of life. Only van Roijen et al. did not report on clinical outcome, but concentrated on quality of live and costs. In two studies there were co-driven interventions, evoking a relevant weakness to the confidence of the outcome. Although only one study clearly defined the starting point of an intervention, confounding by indication appears unlikely, since major adverse events, like invalidating neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of the intervention. The risk that such outcome occurs due to chance is not realistic. Therefore, the overall assessment of study quality gave confidence in four studies. Consistently, all four showed advantage for radiosurgery of significant magnitude, when directly compared in a controlled manner with microsurgical excision.

One might argue that a weakness of some of the four studies is the relative small size and short follow-up. However, patients' outcome in the assessed comparative studies are in accord with the long-term outcome in sizeable contemporary series as summarised in a recent meta-analysis.[4] On the one hand, after microsurgery about 2% requires additional treatment. Especially the rates of facial nerve palsy and

other surgical morbidities are not trivial at 10-30% and 20-40%, respectively (also table 2).[4] Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively. [23] On the other hand, radiosurgery for vestibular schwannoma is a day care with 2-4% of patients requiring additional treatment and fewer than 2% experienced some facial or trigeminal neuropathy. It has no direct mortality and the risk of incapacitating complications is negligible.[4] Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. This is a disadvantage, at least psychologically. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[24] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.[25] Contrastingly, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S. hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[23] If the low-threshold radiosurgery is not employed too enthusiastically, but on proper indication, the risk of death by a radiation-induced tumour is not relevant. Undeniably, the mortality rate is much smaller and occurs many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[26-28] Also, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table 2) Based on this systematic review of controlled studies, we conclude that - if an intervention wisely should not to be postponed - radiosurgery is best practice for patients with vestibular schwannoma up to 30 mm cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw en prof.dr. Cees J.J. Avezaat for them initiating and stimulating evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data analysis. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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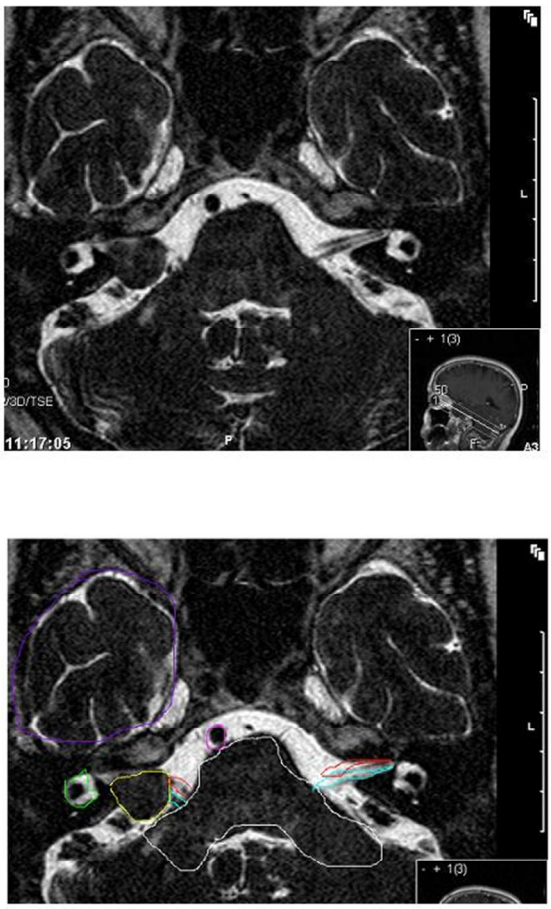

Figure 1. Axial T2 weighted MRI with a still discernible CSF-interface between tumour and brain. The largest diameter of the tumour in the CPA cistern is 14 mm.
Yellow: vestibular schwannoma, Green: labyrinth, Red: ipsi- and contralateral facial nerve
Blue: ipsi- and contralateral vestibulo-cochlear nerve, White: brainstem and cerebellar peduncle
Purple: caudal temporal lobe, Pink: basilar artery

135x210mm (120 x 120 DPI)

Appendix 1. SIGN 50 checklist on cohort studies comparing microsurgery (MS) and radiosurgery (RS)

authors and publication year	Pollock 2006	Myrseth 2009	Pollock 1995	Myrseth 2005	Regis 2002	Karpinos 2002	van Roijen 1996
design	prospective consecutive predefined inclusion crit.	prospective consecutive predefined inclusion crit.	retrospective consecutive matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls
allocation to treatment arm	preference patient	preference patient	preference patient and surgeon	preference patient	2 hospitals preference surgeon/patient	miscellaneous criteria by surgeon	2 hospitals preference surgeon/patient
same primary endpoint: intervention-associated morbidity	Yes	Yes	Yes	Yes	Yes	Yes	**No**
SELECTION OF SUBJECTS							
source population: adult, solitary VS<30mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	No	Yes
eligibility criteria: proven growth or predefined cisternal size	No	Yes	No	No	No	No	No
exclusion criteria NOT more strict for MS because of age and co-morbidity	Yes	No	No	No	No	No	No
participation rate NOT lower for MS because of specific RS referral	Yes	No	No	No	No	No	No
same baseline cranial nerve deficits	Yes	Yes	Yes	Yes	**No**	Yes	**No**
consecutive series and loss to follow up < 10%	Yes	Yes	Yes	Yes	**No**	**No**	**No**
adequate analysis drop outs	Yes	Yes	No	Yes	**No**	**No**	**No**
OUTCOME ASSESSMENT							
pre-specified endpoint	Yes	Yes	Yes	Yes	Yes	Yes	Yes
mortality addressed	Yes	Yes	No	Yes	Yes	Yes	No.
blinded outcome measurement	Yes	**No**	**No**	**No**	**No**	**No**	**No**
same measure new cranial nerve deficit	Yes	Yes	Yes	Yes	Yes	Yes	**No**
same measure quality of live scores	Yes	Yes	Yes	Yes	Yes	**No**	Yes
repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	**No**	**No**
CONFOUNDING VARIABLES							
NOT substantial larger tumour size in MS arm	Yes	Yes	Yes	Yes	Yes	No	Yes
NOT substantial higher age in RS arm	No	Yes	No	No	No	No	Yes
NOT less fit patients in RS arm	Yes	No	No	No	No	No	No
one single intervention in each arm	Yes	Yes	Yes	**No**	Yes	**No**	Yes
STATISTICAL ANALYSIS							
statistical measure of precision	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OVERALL ASSESSMENT							
number of relevant 'no'	0	1	1	2	4	6	7
overall judgment	++	++	+	+	-	-	-
NO commercial funding	Yes	Yes	Yes	Yes	Yes	Yes	No
confidence effect is due to intervention	Yes	Yes	Yes	Yes	No	No	No
outcome applicable to source population	Yes	Yes	Yes	Yes	No	No	No

Yes: well covered or adequately addressed, increasing confidence that outcome is cause by the interventions

No: poorly or not addressed or not reported; cause for bias. Bold: possible relevant bias, decreasing confidence

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

What intervention is best practice for vestibular schwannomas?
A systematic review of controlled studies.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001345.R1
Article Type:	Research
Date Submitted by the Author:	21-Nov-2012
Complete List of Authors:	Wolbers, John; Erasmus University Medical Centre, Neurosurgery Dallenga, Alof; Neurosurgery van Linge, Anne; Otorhinolaryngology Mendez Romero, Alejandra; Radiation Oncology
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical management, Ear, nose and throat/otolaryngology, Qualitative research
Keywords:	Vestibular Schwannoma, Excision, Radiosurgery, RADIOTHERAPY, NEUROSURGERY, Neurotology < OTOLARYNGOLOGY

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Appendix 2.FlowchartSelectionStudies.vsd

Article summary

Article focus

- Quest for best practice if an intervention for solitary vestibular schwannoma is considered necessary
- Systematic search for evidence from controlled intervention studies

Key messages

- Only observational cohort studies comparing microsurgery and radiosurgery were found.
- Four studies were more likely to give unbiased results.
- Consistently, radiosurgery emerges as best practice for tumours smaller than 30 mm cisternal diameter.

Strengths and limitations of this study

- All eligible studies compared the same interventions: microsurgical excision and radiosurgery
- All four trustworthy controlled studies unanimously pointed to the same intervention as best practise.
- Patients' outcomes in the assessed comparative studies are in accord with long-term outcomes in sizeable contemporary case-series.
- The conclusion is restricted to solitary vestibular schwannomas smaller than 30 mm.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours.[1] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, mostly slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological verification. A solid registration is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The majority may hardly or not grow for years; the average growth is 1 to 2 millimetres per year.[4 5] But if the tumour grows, the rate in the first year seems on average 5-10 mm.[6] There are no parameters known that predict which tumour will grow and to what extent.[7 8]

The mild natural course with relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours a starting policy of watchful waiting using regular MRI follow-up. However, in case of a sizeable tumour, that obliterates the cistern of the cerebellopontine angle (CPA) or after substantial growth during follow-up, principally an indication for intervention evolves. In most centres, the choice is between microsurgical resection for any tumour size and

radiosurgery for small and medium-sized tumours or stereotactic radiotherapy for tumour over 25-30 mm diameter. In several reviews numerous case series have been summarised.[4]
Understandably, because inherent to the limitations of case series, these reviewers did not arrive at clear statements. In this study, we focus and limit our search for best practice to comparative, controlled trials on interventions for vestibular schwannoma.

Methods

PubMed / Medline and Embase were searched in November 2011 for controlled intervention studies on vestibular schwannomas. We imposed no restrictions on the kind of intervention or patient characteristics. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatoses) and (management OR therapy OR treatment OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). (Appendix 1) No language, publication rate or other search restriction were imposed. The retrieved articles were screened by title and by abstract if necessary. The reference lists of studies meeting the eligibility criteria were screened. We also searched the Cochrane Central Register of Controlled Trials without finding further studies. The six eligibility criteria include controlled, intervention study, on newly-diagnosed, solitary, vestibular schwannoma reporting on clinical outcome. (Appendix 2)
The two neurosurgeons of our team classified the study designs according to the Oxford Centre of Evidence-based Medicine (CEBM; http://www.cebm.net/index.aspx?o=1025), and assessed the quality (that is risk of bias) of individual studies based on the Sign-50 quality criteria for cohort studies. The quality was assessed by judging factors that were considered relevant for the disease under study. These factors are delineated in Appendix 3. (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9] We abstracted the primary clinical outcome data: mortality, treatment failure (that is second intervention necessary), function of cranial nerves 7 and 8, other intervention-associated complications and the data on quality of life. These outcome measures are the most important to the patient. Secondary outcome measures, being duration of hospital stay and work resume were also addressed. Appendix 3 on risk of bias and table 2 on outcome measures served as a format for data-extraction. Disagreements between the two reviewers were resolved by consensus.

Table 1. Patients' pre-intervention characteristics; only sporadic vestibular schwannomas

Author publ yr	EBM Level[a]	Intervention[b] included no	Male:Fem	age yr	n.trigem. deficit %	n. facial deficit %[c]	useful hearing %[d]	tumour size[e] mean mm	previous treatment %
Pollock 2006	2b	MS: 36 RS: 46	19:17 27:19	48 54	0 0	0 0	61 65	14 12	no no
Myrseth 2009	2b	MS: 28 RS: 60	12:16 36:24*	53 58	? ?	0 0	44 42	18 16	no no
Pollock 1995	3b	MS: 40 RS: 47	18:22 23:24	51 62*	10 6	5 2	12 4	>20mm:18% >20mm:29%	no no
Myrseth 2005	3b	MS: 86 RS: 103	? ?	50 60*	20 12	1 1	2 10	>20mm:32% >20mm:17%	no no
Regis 2002	3b	MS: 110 RS: 100	M 35% M 46%	52 61	55 20	? 2	? 49	KoosIII:55%[d] KoosIII:34%	no no
Karpinos 2002	3b	MS: 23 RS: 73	6:17 23:50	45 62*	30 17	26 10	30 24	>40mm:17* >40mm:3%	26 14

a .Oxford CEBM grades of evidence for quality of study design

b. MS: microsurgery, RS: radiosurgery

c. percentage preserved, House-Brackmann grade 1-2

d. useful hearing: AAO-HNS class A-B or Gardner-Robertson grade I-II

e. Koos III: tumour occupying the cerebellopontine cistern without brainstem displacement

* significant ($p<0.05$)

Results

No randomized clinical trials on solitary vestibular schwannoma were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria. [10 11] Both studies are of level 2b according to the Oxford CEBM. The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery and of level 3b.[12-15] We identified no controlled studies involving fractionated stereotactical radiotherapy. (Appendix 2)

Four main quality items were assessed: selection of subjects, outcome measure, known confounders, statistical analysis. (Appendix 3) At the inception, in five out of six studies all patients were at the same stage of the disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The one exception is the study of Karpinos et al., which included recurrent tumours.[13] The indication for an intervention was clearly defined only in one study.[11] In the other studies just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patients' characteristics were quite similar in the study groups.(Table 1) Only the average age was higher in all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but the study of Pollock et al (2006). These are known risks to an uneventful outcome. If imbalance was present, the higher risk patients were in the

radiosurgery arms. There was minimal or no losses to follow-up in all but one study.[13] After summation of the number of items that downgrade the confidence in outcome (bold NO in appendix 3), four studies remained that showed trustworthy association between intervention and outcome. That is, were more likely to give unbiased results.

The outcomes are specified in Table 2. There was 1% mortality in two microsurgery arms.[14 15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation and better quality of life.

Table 2. Outcome of the six controlled studies on vestibular schwannoma; all comparing microsurgery (MS) and radiosurgery (RS):

author publ yr	therapy FU no.	follow-up (range)	mortal %	2nd ther. %	facial intact[a] %	% useful hearing[b]	other complic[c]	hosp. days	work resume%	QoL Tests[d]	QoL % Results
Pollock 2006	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 0	0 4	83 **98***	5 **63***	33 **11***	? ?	? ?	DHI, HS, HSQ	↓ =*
Myrseth 2009	MS 28 RS 60	≥ 2 yr	0 0	18 2	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 93	SF36, GBI	SF36= **GBI ↑***
Pollock 1995	MS 40 RS 47	3 yr median (2.1-4 yr)	0 0	0 0	78 **91***	14 **75***	38 **13***	9,5 **1.4***	? ?	ANSPQ	↓ 45 ↓ 26
Myrseth 2005	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	1 0	6 5	80 **95***	5 **32***	47 **4***	? ?	? ?	SF36, GBI	↓ =*
Regis 2002	MS 110 RS 97	≥ 3 yr	1 0	9 3	67 **100***	36 **50***	41 **8***	23 **3***	66 **99***	Pellet	↓ 39 **↓ 9***
Karpinos 2002	MS 18 RS 49	4yr median (0.3-7 yr)	0 0	0 4	60 **97***	40 44	48 **5***	2-16 **1-2***	88 94	none	- -

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as new trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d.. quality of life (QoL) from questionnaires as Dizziness Handicap Inventory, Headache Survey, Health Status Questionnaire, ShortForm36, Glasgow Benefit Inventory, Acoustic Neuroma Association Patient Questionnaire, Pellet Questionnaire;

* and bold: significantly better

Discussion

Both microsurgery and radiosurgery are equally highly effective in the treatment of vestibular schwannomas as demonstrated by numerous case series.[4] Appreciating a patients' individual preference, ideally counselling is based on the outcome of high-quality clinical trials. We searched for evidence and found that radiosurgery is best practice in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold-standard of evidence-based practice. Regarding vestibular schwannomas, however, we most probably

will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept blinded fate to decide for them to undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[16 17] The value of high-quality observational studies is validated by the remarkable similar results, which were witnessed when comparing specific treatments through both randomized and observational trials.[18-20] Such observational studies may provide trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for patients. Overall, these patients are more similar to the general disease population than those obeying to the strict inclusion and exclusion criteria of a randomised clinical trial. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. Based on Sign-50, this is the basic thought behind the assessment of quality of individual studies in appendix 3.

Selection of subjects

All retrieved controlled studies compared the same two interventions and consistently pointed to radiosurgery as being the best intervention for their research question. Some studies, however, provide more confidence to have unbiased results, as elucidated in appendix 3. A major scientific hazard of all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In five studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Only in the study by Karpinos et al. the source population differed due to inclusion of patients having had earlier surgery for the same disease.[13] In addition, this study had an inacceptable high loss to follow-up of over 20%. These two serious sources of bias prevented a favourable overall good quality judgment. In one studies pertinent bias rose, because of non-consecutive inclusion in the microsurgery arm. [14]

Only one study clearly defined the starting point of an intervention.[11], Nevertheless confounding by indication between the various studies appears unlikely, since major adverse events, like invalidating neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of an intervention. Therefore, the risk that such outcome occurs due to chance is not realistic and we assigned no relevance to defining the indication to intervene.

Outcome assessment

All but one study reported on the same clinical outcome measures, which are failure because a second intervention was needed, function preservation of the involved cranial nerves, more general complications and quality of life. The exception is the study by Karpinos et al, who did not report on quality of life. All used established classifications of facial motor function and useful hearing.

Only one group managed a blinded outcome measurement.[10] Taking into account that a troublesome outcome - when occurring - is quite clear-cut in this disease, not-blinded outcome measurement did not depreciate our trust that the reported outcome is true and caused by the specific intervention. Typically, repeated measurements increase this trust further.

Confounding variables

A previous treatment for the same disease evokes relevant bias, because of different base-line characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos et al., because the results from first and second intervention were not separated in their report.[13] Frail patients were in all but the study of Pollock et al. (2006) inclined to end up in the radiosurgery arm.[10] In general higher age, co-morbidity and larger tumours are drawbacks for a good outcome. In those studies showing significant imbalance of these variables the potential disadvantage, however, was at the side of radiosurgery, being already the best outcome in these (all) studies.[12 13 15] Therefore, we considered these imbalances as not relevant.

The overall assessment of study quality gave confidence in four studies, because no relevant biases were signalled. Quite importantly, all four consistently showed advantage for radiosurgery of significant magnitude, when directly compared in a controlled manner with microsurgical excision. (table 2)
One might argue that a weakness of some of the four trustworthy studies is the relative small numbers and short follow-up. However, patients' outcome in the assessed comparative studies is in accord with the long-term outcome in sizeable contemporary radiosurgery series as summarised in appendix 4. Radiosurgery for vestibular schwannoma is a day care with 2% (median) of patients requiring additional treatment; less than 1% (median) experienced some facial neuropathy and trigeminal neuropathy occurred in 5% (median). It has no direct mortality and the risk of incapacitating complications is negligible or not existing. The comprehensive review of Arthurs et al. showed that after microsurgery less than 2% requires additional treatment. Varying with tumour size the rates of facial nerve palsy are as high as 10-30%.[4] These numbers are of the same range in the comparative studies on tumours limited to a size of 3cm in table 2. Not mentioned in any detail by Arthurs et al. are other surgical morbidities, which are not trivial at all, being between 14-47% in the comparative studies. Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively.[21]
Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[22] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.[23] Distinctively, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S.

hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[21] If radiosurgery is not employed too enthusiastically due to its low threshold, but on proper indication, the risk of death by a radiation-induced tumour is not relevant in comparison to the (few) possible direct disasters of microsurgery. Undeniably, the mortality is much smaller and, if it occurs, it is many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of various health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[24-26] In addition, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table 2) Once an intervention is considered necessary, we conclude based on this systematic review of controlled studies, that radiosurgery is best practice for patients with solitary vestibular schwannoma up to 30 mm cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw and prof.dr. Cees J.J. Avezaat for them having initiated and stimulated evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data extraction. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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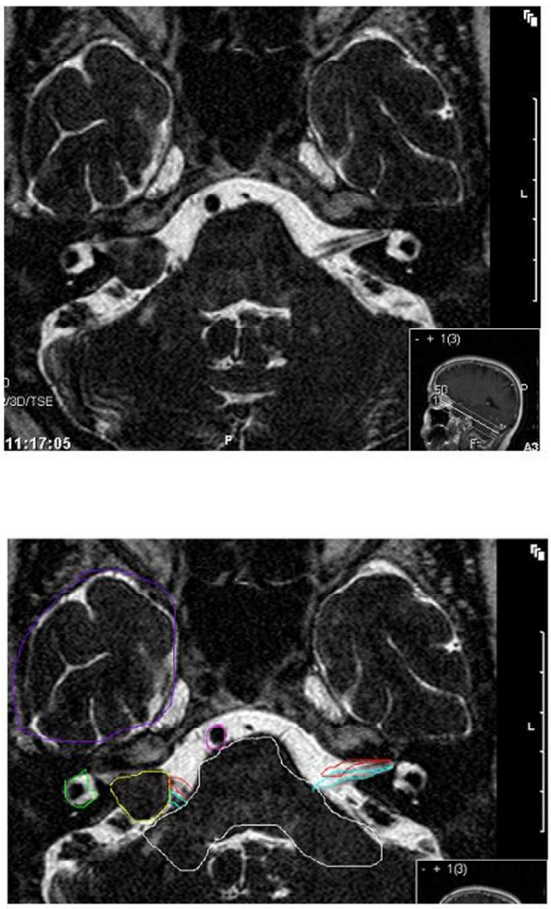

Figure 1. Axial T2 weighted MRI with a still discernible CSF-interface between tumour and brain. The largest diameter of the tumour in the CPA cistern is 14 mm.
Yellow: vestibular schwannoma, Green: labyrinth, Red: ipsi- and contralateral facial nerve
Blue: ipsi- and contralateral vestibulo-cochlear nerve, White: brainstem and cerebellar peduncle
Purple: caudal temporal lobe, Pink: basilar artery

135x210mm (120 x 120 DPI)

Search strategy: MEDLINE (PubMed)

01. "vestibular schwannoma" [All Fields]/
02. "acoustic neuroma" [All Fields]/
03. NOT neurofibromatoses [MeSH]
04. 1 or 2 not 3
05. management[All fields]/
06. "disease management"[MeSH]/
07. therapy [subheading]/
08. therapy [All Fields]
09. therapeutics[MeSH]/
10. treatment [All Fields]/
11. intervention [All Fields]
12. 5 or 6 or 7 or 8 or 9 or 11
13. "controlled trial" [All Fields]/
14. "controlled study" [All Fields]/
15. "clinical trial" [All Fields]/
16. 13 or 14 or 15
17. comparative [All Fields]/
18. comparison [All Fields]/
19. compared [All Fields]
20. 17 or 18 or 19
21. 16 or 20
22. 4 and 12 and 21

Appendix 3. Checklist on cohort studies based on SIGN 50 comparing microsurgery (MS) and radiosurgery (RS) for solitary vestibular schwannoma

authors and publication year	Pollock 2006	Myrseth 2009	Pollock 1995	Myrseth 2005	Regis 2002	Karpinos 2002
design	prospective consecutive predefined inclusion crit.	prospective consecutive predefined inclusion crit.	retrospective consecutive matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls	retrospective consecutive matched controls
allocation to treatment arm	preference patient	preference patient	preference patient and surgeon	preference patient	2 hospitals, preference by surgeon/patient	miscellaneous criteria by surgeon
same primary endpoint: intervention-associated morbidity	Yes	Yes	Yes	Yes	Yes	Yes
SELECTION OF SUBJECTS						
source population: adult, solitary VS<30mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	**No**
eligibility criteria: proven growth or predefined cisternal size	No	Yes	No	No	No	No
exclusion criteria NOT more strict for MS because of age and co-morbidity	Yes	No	No	No	No	No
participation rate NOT lower for MS because of specific RS referral	Yes	No	No	No	No	No
same baseline cranial nerve deficits	Yes	Yes	Yes	Yes	**No**	Yes
consecutive series and loss to follow up < 10%	Yes	Yes	Yes	Yes	**No**	**No**
adequate analysis drop outs	Yes	Yes	No	Yes	**No**	**No**
OUTCOME ASSESSMENT						
pre-specified endpoint	Yes	Yes	Yes	Yes	Yes	Yes
mortality addressed	Yes	Yes	No	Yes	Yes	Yes
blinded outcome measurement	Yes	No	No	No	No	No
same measure new cranial nerve deficit	Yes	Yes	Yes	Yes	Yes	Yes
same measure quality of life scores	Yes	Yes	Yes	Yes	Yes	**No**
repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	**No**
CONFOUNDING VARIABLES						
NOT substantial larger tumour size in MS arm	Yes	Yes	Yes	Yes	Yes	No
NOT substantial higher age in RS arm	No	Yes	No	No	No	No
NOT less fit patients in RS arm	Yes	No	No	No	No	No
one single intervention in each arm	Yes	Yes	Yes	Yes	Yes	**No**
STATISTICAL ANALYSIS						
statistical measure of precision	Yes	Yes	Yes	Yes	Yes	Yes
OVERALL ASSESSMENT						
number of relevant 'no'	0	0	0	0	3	6
overall judgment	++	++	+	+	-	-
NO commercial funding	Yes	Yes	Yes	Yes	Yes	Yes
confidence effect is due to intervention	Yes	Yes	Yes	Yes	No	No
outcome applicable to source population	Yes	Yes	Yes	Yes	No	No

Yes: well covered or adequately addressed, increasing confidence that outcome is cause by the interventions

No: poorly or not addressed or not reported; cause for bias. Bold: possible relevant bias, decreasing confidence

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Appendix 4. Radiosurgery results; only contemporary series using low dose (≤ 13Gy), involving at least 100 patients and over 3 years of follow-up are presented. For comparison the radiosurgery results of the 4 high-quality controlled trials are integrated in the second part; mostly higher doses, lower numbers and shorter follow-up than in the case series, similar outcome however.

author, publ yr no. patients	margin dose[a] (range)	follow up (range)	stable %[b]	2[e] inter-vention %	n.V intact[c] %	n.VII intact[d]%	n.VIII intact[e] %
Friedmann, 2006[27] N=295	12.5 Gy median (10-22.5 Gy)	3.3yr mean N=63 >5yr	5yr: 90	1	99	99	?
Hempel, 2006[28] N=116	13 Gy median (10-14.5)	8.2yr mean (5.3 - 10,8)	96	3	94	100	54
Chopra, 2007[29] N=216	12 -13 Gy	5.7 yr median N=41 >8yr	10yr:: 91	1.4	10yr: 95	10yr: 100	10yr: 45
Regis, 2007[30] N=1000	12 Gy all	all > 3yr (3 – 12yr)	97	3	100	> 99	60
Fukuoka, 2009[31] N=152	12 Gy median (9-15 Gy)	all > 5yr	8yr: 92	?	97	100	71
Pollock, 1995[12] RS=47	16.3 mean (13-18 Gy)	3 yr median (2.1 – 4 yr)	94	0	86	91	75
Myrseth, 2005[15] RS=103	12.2 Gy mean. (10-20 Gy)	5.9yr mean (1 – 14.2 yr)	89	5	?	95	32
Pollock, 2006[10] RS=46	12.2 Gy mean	3.5yr mean (1 - 5,2 yr)	100	0	98	98	63
Myrseth, 2009[11] RS=60	12 Gy all	≥2 yr	98	2	?	100	68

a. minimum dose at the tumour margin
b. stable or smaller tumour volume
c. no loss sensitivity, no paraesthesias nor trigeminal neuralgia
d. preserved good facial function, House-Brackmann grade 1-2
e. preserved useful hearing: AAO-HNS class A -B or Gardner-Robertson grade I-II

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.1 and 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.1 and 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	append 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.2 and table1 +2 append 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.2 and Table1+2 append 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p.2 and append 3

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	table 2 append 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	append 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	append 2 p.5+6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	table1+2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	append 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	append 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	article summmary append 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.5 and 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.7
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ open

What intervention is best practice for vestibular schwannomas?
A systematic review of controlled studies.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001345.R2
Article Type:	Research
Date Submitted by the Author:	19-Jan-2013
Complete List of Authors:	Wolbers, John; Erasmus University Medical Centre, Neurosurgery Dallenga, Alof; Neurosurgery van Linge, Anne; Otorhinolaryngology Mendez Romero, Alejandra; Radiation Oncology
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical management, Ear, nose and throat/otolaryngology, Qualitative research
Keywords:	Vestibular Schwannoma, Excision, Radiosurgery, RADIOTHERAPY, NEUROSURGERY, Neurotology < OTOLARYNGOLOGY

Article summary

Article focus

- Search for best practice if an intervention for solitary vestibular schwannoma is considered necessary
- Systematic review of evidence from controlled intervention studies on the effectiveness of interventions for solitary vestibular schwannomas

Key messages

- The literature search yielded cohort studies comparing microsurgery and radiosurgery.
- Quality assessment showed four studies likely to give unbiased results.
- Radiosurgery consistently emerges as best practice for tumours smaller than 30 mm in cisternal diameter.

Strengths and limitations of this study

- All eligible studies compared the same interventions: microsurgical excision and radiosurgery
- All four trustworthy controlled studies pointed to the same intervention as best practise.
- Patients' outcomes in the assessed comparative studies are in accord with long-term outcomes in sizeable contemporary case-series.
- The conclusion is limited to solitary vestibular schwannomas smaller than 30 mm.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours.[1] A reliable register is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, usually slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological verification. The majority grows slowly or not at all; the average growth is 1 to 2 millimetres per year.[4 5] However, if the tumour grows, the rate in the first year is on average 5-10 mm.[6] There are no parameters known that predict which tumour will grow and to what extent.[7 8] The mild natural course and relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours an initial policy of watchful waiting by sequential MRI follow-up. However, if the tumour is sizeable and obliterates the cistern of the cerebellopontine angle (CPA) or grows substantial during follow-up, in principal an intervention is indicated. In most centres, the choice is between microsurgical resection for any tumour size and radiosurgery for small and

medium-sized tumours or stereotactic radiotherapy for tumours over 25-30 mm diameter. Numerous case series and non-systematic reviews have been summarised recently by Arthurs et al.[4] Understandably, due to inherent limitations of case series, these reviewers did not arrive at firm conclusions. In this study, we limit our search for best practice to comparative, controlled trials on interventions for vestibular schwannoma in a systematic and qualitative way.

Methods

PubMed / Medline and Embase were searched in November 2011 for controlled intervention studies on vestibular schwannomas. We imposed no restrictions on the kind of intervention or patient characteristics. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatoses) and (management OR therapy OR treatment OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). (Appendix 1) No language, publication status or other search restriction was imposed. The retrieved articles were screened by title and if necessary by abstract. Eventually thirteen full text articles were examined. The reference lists of studies meeting the eligibility criteria were checked. We also searched the Cochrane Central Register of Controlled Trials without finding further studies. The six eligibility criteria include controlled, intervention study, on newly-diagnosed, solitary, vestibular schwannoma reporting on clinical outcome. (Appendix 2)

The two neurosurgeons of our team assessed the risk of bias in the individual studies. The quality was assessed by judging criteria that were considered relevant by the team. The assessment is based on the Sign-50 quality criteria for cohort studies. These criteria are listed in Appendix 3. (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9] We abstracted the primary clinical outcome data: mortality, treatment failure (that is second intervention necessary), function of cranial nerves 7 and 8, other intervention-associated complications and the data on quality of life. These outcome measures are the most important to the patient. Secondary outcome measures, being duration of hospital stay and time off work were also addressed. Appendix 3 on risk of bias and table 2 on outcome measures served as a predefined format for data extraction. Disagreements between the two reviewers were resolved by consensus.

Table 1. Patients' pre-intervention characteristics; only sporadic vestibular schwannomas

Author publ yr	Intervention[a] included no	Male:Fem	age yr	n.trigem. deficit %	n. facial deficit %[b]	useful hearing %[c]	tumour size[d] mean mm	previous treatment %
Pollock 2006	MS: 36 RS: 46	19:17 27:19	48 54	0 0	0 0	61 65	14 12	no no
Myrseth 2009	MS: 28 RS: 60	12:16 36:24*	53 58	? ?	0 0	44 42	18 16	no no
Pollock 1995	MS: 40 RS: 47	18:22 23:24	51 62*	10 6	5 2	12 4	>20mm:18% >20mm:29%	no no
Myrseth 2005	MS: 86 RS: 103	? ?	50 60*	20 12	1 1	2 10	>20mm:32% >20mm:17%	no no
Regis 2002	MS: 110 RS: 100	M 35% M 46%	52 61	55 20	? 2	? 49	KoosIII:55%[d] KoosIII:34%	no no
Karpinos 2002	MS: 23 RS: 73	6:17 23:50	45 62*	30 17	26 10	30 24	>40mm:17* >40mm:3%	26 14

a. MS: microsurgery, RS: radiosurgery

b. percentage preserved, House-Brackmann grade 1-2

c. useful hearing: AAO-HNS class A-B or Gardner-Robertson grade I-II

d. Koos III: tumour occupying the cerebellopontine cistern without brainstem displacement

* significant ($p<0.05$)

Results

No randomized clinical trials on solitary vestibular schwannoma were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria. [10 11] The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery and of level 3b.[12-15] We identified no controlled studies involving fractionated stereotactical radiotherapy. (Appendix 2)

Four main quality items were assessed: selection of subjects, outcome measure, known confounders and statistical analysis. (Appendix 3) At the inception, in five out of six studies all patients were at the same stage of the disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The one exception is the study of Karpinos et al., which included recurrent tumours.[13] The indication for an intervention was clearly defined in only one study.[11] In the other studies, just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patient characteristics were quite similar in the treatment arms within the studies.(Table 1) Only the average age was higher in all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but the study of Pollock et al (2006). These are known hazards for a favourable outcome. If imbalance was present, the higher risk patients were in the radiosurgery arms. There was minimal or no loss to follow-up in all but one study.[13]

After summation of the number of items that downgrade the confidence in outcome (bold NO in appendix 3), four studies (the upper four of table 2) remained that showed trustworthy association between intervention and outcome.

The outcomes are specified in Table 2. There was 1% mortality in two microsurgery arms.[14 15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation and better quality of life.

Table 2. Outcome of the six controlled studies on vestibular schwannoma; all comparing microsurgery (MS) and radiosurgery (RS):

author publ yr	therapy FU no.	follow-up (range)	mortal %	2nd ther. %	facial intact[a] %	% useful hearing[b]	other complic[c]	hosp. days	work resume%	QoL Tests[d]	QoL % Results
Pollock 2006	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 0	0 4	83 **98***	5 **63***	33 **11***	? ?	? ?	DHI, HS, HSQ	↓ =*
Myrseth 2009	MS 28 RS 60	≥ 2 yr	0 0	18 2	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 93	SF36, GBI	SF36= **GBI ↑***
Pollock 1995	MS 40 RS 47	3 yr median (2.1-4 yr)	0 0	0 0	78 **91***	14 **75***	38 **13***	9,5 **1.4***	? ?	ANSPQ	↓ 45 ↓ 26
Myrseth 2005	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	1 0	6 5	80 **95***	5 **32***	47 **4***	? ?	? ?	SF36, GBI	↓ =*
Regis 2002	MS 110 RS 97	≥ 3 yr	1 0	9 3	67 **100***	36 **50***	41 **8***	23 **3***	66 **99***	Pellet	↓ 39 **↓ 9***
Karpinos 2002	MS 18 RS 49	4yr median (0.3-7 yr)	0 0	0 4	60 **97***	40 44	48 **5***	2-16 **1-2***	88 94	none	- -

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as new trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d.. quality of life (QoL) from questionnaires as Dizziness Handicap Inventory, Headache Survey, Health Status Questionnaire, ShortForm36, Glasgow Benefit Inventory, Acoustic Neuroma Association Patient Questionnaire, Pellet Questionnaire;

* and bold: significantly better

Discussion

Microsurgery and radiosurgery are equally effective interventions for vestibular schwannomas as demonstrated by numerous case series that were recently reviewed.[4] Whilst taking into account patients' individual preferences, ideally the choice of treatment should be based on high-quality evidence from well conducted clinical trials. We found evidence of greater clinical effectiveness of radiosurgery compared to microsurgery in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold-standard of evidence-based practice. Regarding vestibular schwannomas, however, we most probably

will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept chance to decide whether they would undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[16 17] Next to the value of well-conducted randomised trials, the value of high-quality observational studies is validated by the remarkable similar results, which were observed when comparing specific treatments through both randomized and observational trials. [18-20] Such observational studies may provide trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for patients. Overall, these patients are more similar to the general disease population than those complying with the strict inclusion and exclusion criteria of a randomised clinical trial. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. Based on Sign-50, this is the basic thought behind the assessment of quality of individual studies in appendix 3.

Selection of subjects

All retrieved controlled studies compared the same two interventions and consistently pointed to radiosurgery as being the best intervention for their research question. Some studies, however, provide more confidence to have unbiased results, as elucidated in appendix 3. A major risk of bias of all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In five studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Only in the study by Karpinos et al. the source population differed due to inclusion of patients having had earlier surgery for the same disease.[13] In addition, this study had an unacceptably high loss to follow-up of over 20%. These two serious sources of bias prevented a favourable overall good quality judgement. In one study pertinent bias arose, because of non-consecutive inclusion in the microsurgery arm. [14]

Only Myrseth et al (2009) clearly defined the starting point of an intervention.[11] Nevertheless, confounding by indication between the various studies appears unlikely, since major adverse events, like disabling neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of an intervention. Therefore, the risk that an adverse outcome occurs due to chance instead of being related to the intervention is not realistic and we assigned no relevance to the potential confounder of being at various points in the disease progression (non-bold NO, appendix 3).

Outcome assessment

All but one study reported on the same clinical outcome measures, which are failure because a second intervention was needed, function preservation of the involved cranial nerves, more general complications and quality of life. The exception is the study by Karpinos et al, who did not report on quality of life. All used established classifications of facial motor function and useful hearing.

Only one group managed a blinded outcome measurement.[10] Taking into account that a troublesome outcome - when occurring - is quite clear-cut in this disease, non-blinded outcome measurement did not depreciate our trust that the reported outcome is true and caused by the specific intervention. Typically, repeated measurements increase this trust further.

Confounding variables

A previous treatment for the same disease induces relevant bias, because of different base-line characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos et al., because the results from first and second intervention were not separated in their report.[13] Frail patients were in all but the study of Pollock et al. (2006) inclined to end up in the radiosurgery arm.[10] In general higher age, co-morbidity and larger tumours are drawbacks for a good outcome. In those studies showing significant imbalance of these variables the potential disadvantage, however, was at the side of radiosurgery, which nevertheless produced the best outcome in all studies.[12 13 15] As these imbalances work in favour of microsurgery, we considered them not relevant (non-bold no's in appendix 3)

The overall assessment of study quality gave confidence in four studies, because no relevant biases were identified. Quite importantly, all four consistently showed a significant advantage for radiosurgery over microsurgical excision , when directly compared in a controlled manner. (table 2)

One might argue that a weakness of some of the four trustworthy studies is the relative small numbers and short follow-up. However, patients' outcome in the assessed comparative studies is in accord with the long-term outcome in sizeable contemporary radiosurgery series as summarised in appendix 4. Radiosurgery for vestibular schwannoma is a day case with 2% (median) of patients requiring additional treatment; less than 1% (median) experienced some facial neuropathy and trigeminal neuropathy occurred in 5% (median). It has no direct mortality and the risk of incapacitating complications is negligible or non-existing. The comprehensive review of Arthurs et al. showed that after microsurgery less than 2% of patients require additional treatment. The rates of facial nerve palsy are as high as 10-30%, varying with tumour size.[4] These numbers are of the same range in the comparative studies on tumours limited to a size of 3cm in table 2. Not mentioned in any detail by Arthurs et al. are other surgical morbidities, which are not trivial at all, being between 14-47% in the comparative studies. Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively.[21]

Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[22] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1

per 1000.[23] Distinctively, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S. hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[21] If radiosurgery is not employed too enthusiastically due to its low threshold, but on proper indication, the risk of death by a radiation-induced tumour is not relevant in comparison to the (few) possible direct disasters of microsurgery. Undeniably, the mortality is much smaller and, if it occurs, it is many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of various health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[24-26] In addition, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table 2) Once an intervention is considered necessary, we conclude based on this systematic review of controlled studies, that radiosurgery is best practice for patients with solitary vestibular schwannoma up to 30 mm cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw and prof.dr. Cees J.J. Avezaat for them having initiated and stimulated evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data extraction. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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Article summary

Article focus

- SearchQuest for best practice if an intervention for solitary vestibular schwannoma is considered necessary
- Systematic search forreview of evidence from controlled intervention studies on the effectiveness of interventions for solitary vestibular schwannomas

Key messages

- The literature search yielded Only observational cohort studies comparing microsurgery and radiosurgery were found.
- Quality assessment showed Ffour studies were more likely to give unbiased results.
- Consistently, Rradiosurgery consistently emerges as best practice for tumours smaller than 30 mm cisternal diameter.

Strengths and limitations of this study

- All eligible studies compared the same interventions: microsurgical excision and radiosurgery
- All four trustworthy controlled studies unanimously pointed to the same intervention as best practise.
- Patients' outcomes in the assessed comparative studies are in accord with long-term outcomes in sizeable contemporary case-series.
- The conclusion is limitedrestricted to solitary vestibular schwannomas smaller than 30 mm.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours.[1] A reliablesolid registerration is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, usuallymostly slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological verification. The majority may hardly or not grows slowly or not at allfor years; the average growth is 1 to 2 millimetres per year.[4 5] However,But if the tumour grows, the rate in the first year isseems on average 5-10 mm.[6] There are no parameters known that predict which tumour will grow and to what extent.[7 8]

The mild natural course and with relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours an initial starting policy of watchful waiting byusing

sequential~~regular~~ MRI follow-up. However, if the tumour is sizeable ~~in case of a sizeable tumour, that~~ and obliterates the cistern of the cerebellopontine angle (CPA) or grows ~~after~~ substantial ~~growth~~ during follow-up, in principal~~ly an indication for~~ an intervention is indicated~~evolves~~. In most centres, the choice is between microsurgical resection for any tumour size and radiosurgery for small and medium-sized tumours or stereotactic radiotherapy for tumours over 25-30 mm diameter. ~~In several reviews~~ Numerous case series and non-systematic reviews have been summarised recently by Arthurs et al.[4] Understandably, due to~~because~~ inherent ~~to the~~ limitations of case series, these reviewers did not arrive at firm conclusions~~clear statements~~. In this study, we ~~focus and~~ limit our search for best practice to comparative, controlled trials on interventions for vestibular schwannoma in a systematic and qualitative way.

Methods

PubMed / Medline and Embase were searched in November 2011 for controlled intervention studies on vestibular schwannomas. We imposed no restrictions on the kind of intervention or patient characteristics. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatoses) and (management OR therapy OR treatment OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). (Appendix 1) No language, publication status~~rate~~ or other search restriction was~~ere~~ imposed. The retrieved articles were screened by title and ~~by abstract~~ if necessary by abstract. Eventually thirteen full text articles were examined. The reference lists of studies meeting the eligibility criteria were checked~~screened~~. We also searched the Cochrane Central Register of Controlled Trials without finding further studies. The six eligibility criteria include controlled, intervention study, on newly-diagnosed, solitary, vestibular schwannoma reporting on clinical outcome. (Appendix 2)

The two neurosurgeons of our team ~~classified the study designs according to the Oxford Centre of Evidence-based Medicine (CEBM; http://www.cebm.net/index.aspx?o=1025), and~~ assessed the ~~quality (that is~~ risk of bias in the~~) of~~ individual studies. The quality was assessed by judging criteria that were considered relevant by the team. The assessment is based on the Sign-50 quality criteria for cohort studies. ~~The quality was assessed by judging factors that were considered relevant for the disease under study.~~ These criteria~~factors~~ are listed~~delineated~~ in Appendix 3. (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9] We abstracted the primary clinical outcome data: mortality, treatment failure (that is second intervention necessary), function of cranial nerves 7 and 8, other intervention-associated complications and the data on quality of life. These outcome measures are the most important to the patient. Secondary outcome measures, being duration of hospital stay and time off work ~~resume~~ were also addressed. Appendix 3 on risk of bias and table 2 on outcome measures served as a predefined format for data -extraction. Disagreements between the two reviewers were

resolved by consensus.

Table 1. Patients' pre-intervention characteristics; only sporadic vestibular schwannomas

Author publ yr	Intervention[a] included no	Male:Fem	age yr	n.trigem. deficit %	n. facial deficit %[b]	useful hearing %[c]	tumour size[d] mean mm	previous treatment %
Pollock 2006	MS: 36 RS: 46	19:17 27:19	48 54	0 0	0 0	61 65	14 12	no no
Myrseth 2009	MS: 28 RS: 60	12:16 36:24*	53 58	? ?	0 0	44 42	18 16	no no
Pollock 1995	MS: 40 RS: 47	18:22 23:24	51 62*	10 6	5 2	12 4	>20mm:18% >20mm:29%	no no
Myrseth 2005	MS: 86 RS: 103	? ?	50 60*	20 12	1 1	2 10	>20mm:32% >20mm:17%	no no
Regis 2002	MS: 110 RS: 100	M 35% M 46%	52 61	55 20	? 2	? 49	KoosIII:55%[d] KoosIII:34%	no no
Karpinos 2002	MS: 23 RS: 73	6:17 23:50	45 62*	30 17	26 10	30 24	>40mm:17* >40mm:3%	26 14

a. MS: microsurgery, RS: radiosurgery

b. percentage preserved, House-Brackmann grade 1-2

c. useful hearing: AAO-HNS class A-B or Gardner-Robertson grade I-II

d. Koos III: tumour occupying the cerebellopontine cistern without brainstem displacement

* significant ($p<0.05$)

Results

No randomized clinical trials on solitary vestibular schwannoma were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria. [10 11] ~~Both studies are of level 2b according to the Oxford CEBM.~~ The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery and of level 3b.[12-15] We identified no controlled studies involving fractionated stereotactical radiotherapy. (Appendix 2)

Four main quality items were assessed: selection of subjects, outcome measure, known confounders and~~,~~ statistical analysis. (Appendix 3) At the inception, in five out of six studies all patients were at the same stage of the disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The one exception is the study of Karpinos et al., which included recurrent tumours.[13] The indication for an intervention was clearly defined in only ~~in~~ one study.[11] In the other studies, just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patient~~s'~~ characteristics were quite similar in the ~~study groups~~ treatment arms within the studies.(Table 1) Only the average age was higher in all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but the study of Pollock et al (2006). These are known hazards~~risks~~ for~~to~~ a~~n uneventful~~favourable ~~-~~outcome. If imbalance was present, the higher risk patients were in the radiosurgery arms. There was minimal or no

losses to follow-up in all but one study.[13] After summation of the number of items that downgrade the confidence in outcome (bold NO in appendix 3), four studies (the upper four of table 2) remained that showed trustworthy association between intervention and outcome. That is, were more likely to give unbiased results.

The outcomes are specified in Table 2. There was 1% mortality in two microsurgery arms.[14 15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation and better quality of life.

Table 2. Outcome of the six controlled studies on vestibular schwannoma; all comparing microsurgery (MS) and radiosurgery (RS):

author publ yr	therapy FU no.	follow-up (range)	mortal %	2nd ther. %	facial intact[a] %	% useful hearing[b]	other complic[c]	hosp. days	work resume%	QoL Tests[d]	QoL % Results
Pollock 2006	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 0	0 4	83 **98***	5 **63***	33 **11***	? ?	? ?	DHI, HS, HSQ	↓ =*
Myrseth 2009	MS 28 RS 60	≥ 2 yr	0 0	18 2	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 93	SF36, GBI	SF36= **GBI ↑***
Pollock 1995	MS 40 RS 47	3 yr median (2.1-4 yr)	0 0	0 0	78 **91***	14 **75***	38 **13***	9,5 **1.4***	? ?	ANSPQ	↓ 45 ↓ 26
Myrseth 2005	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	1 0	6 5	80 **95***	5 **32***	47 **4***	? ?	? ?	SF36, GBI	↓ =*
Regis 2002	MS 110 RS 97	≥ 3 yr	1 0	9 3	67 **100***	36 **50***	41 **8***	23 **3***	66 **99***	Pellet	↓ 39 **↓ 9***
Karpinos 2002	MS 18 RS 49	4yr median (0.3-7 yr)	0 0	0 4	60 **97***	40 44	48 **5***	2-16 **1-2***	88 94	none	- -

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as new trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d.. quality of life (QoL) from questionnaires as Dizziness Handicap Inventory, Headache Survey, Health Status Questionnaire, ShortForm36, Glasgow Benefit Inventory, Acoustic Neuroma Association Patient Questionnaire, Pellet Questionnaire;

* and bold: significantly better

Discussion

Both mMicrosurgery and radiosurgery are equally highly effective interventions forin the treatment of vestibular schwannomas as demonstrated by numerous case series that were recently reviewed.[4] Whilst taking into accountAppreciating a patients' individual preferences, ideally the choice of treatmentcounselling is should be based on the outcome of high-quality evidence from well conducted clinical trials. We searched for evidence and found evidence of greater clinical effectiveness ofthat radiosurgery compared to microsurgery is best practice in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold-standard of evidence-based practice. Regarding vestibular schwannomas, however, we most probably will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept chanceblinded fate to decide whether they wouldfor them to undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[16 17] Next to the value of well-conducted randomised trials, tThe value of high-quality observational studies is validated by the remarkable similar results, which were observedwitnessed when comparing specific treatments through both randomized and observational trials. [18-20] Such observational studies may provide trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for patients. Overall, these patients are more similar to the general disease population than those complying withobeying to the strict inclusion and exclusion criteria of a randomised clinical trial. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. Based on Sign-50, this is the basic thought behind the assessment of quality of individual studies in appendix 3.

Selection of subjects

All retrieved controlled studies compared the same two interventions and consistently pointed to radiosurgery as being the best intervention for their research question. Some studies, however, provide more confidence to have unbiased results, as elucidated in appendix 3. A major risk of bias scientific hazard of all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In five studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Only in the study by Karpinos et al. the source population differed due to inclusion of patients having had earlier surgery for the same disease.[13] In addition, this study had an ui nacceptably high loss to follow-up of over 20%. These two serious sources of bias prevented a favourable overall good quality judgement. In one studyies pertinent bias arose, because of non-consecutive inclusion in the microsurgery arm. [14]

Only Myrseth et al (2009)one study clearly defined the starting point of an intervention.[11] Nevertheless, confounding by indication between the various studies appears unlikely, since major adverse events, like disablinginvalidating neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of an intervention. Therefore, the risk that an adverse such outcome occurs due to chance instead of being related to the intervention is not realistic and we assigned no relevance to the potential confounder of being at various points in the disease progression (non-bold NO, appendix 3).defining the indication to intervene.

Outcome assessment

All but one study reported on the same clinical outcome measures, which are failure because a second intervention was needed, function preservation of the involved cranial nerves, more general complications and quality of life. The exception is the study by Karpinos et al, who did not report on quality of life. All used established classifications of facial motor function and useful hearing.

Only one group managed a blinded outcome measurement.[10] Taking into account that a troublesome outcome - when occurring - is quite clear-cut in this disease, nont-blinded outcome measurement did not depreciate our trust that the reported outcome is true and caused by the specific intervention. Typically, repeated measurements increase this trust further.

Confounding variables

A previous treatment for the same disease inducesevokes relevant bias, because of different base-line characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos et al., because the results from first and second intervention were not separated in their report.[13] Frail patients were in all but the study of Pollock et al. (2006) inclined to end up in the radiosurgery arm.[10] In general higher age, co-morbidity and larger tumours are drawbacks for a good outcome. In those studies showing significant imbalance of these variables the potential disadvantage, however, was at the side of radiosurgery, which nevertheless producedbeing already the best outcome in these (all) studies.[12 13 15] As these imbalances work in favour of microsurgeryTherefore, we considered them not relevant (non-bold no's in appendix 3).

The overall assessment of study quality gave confidence in four studies, because no relevant biases were identifiedsignalled. Quite importantly, all four consistently showed a significant advantage for radiosurgery of over microsurgical excision significant magnitude, when directly compared in a controlled manner with microsurgical excision. (table 2)

One might argue that a weakness of some of the four trustworthy studies is the relative small numbers and short follow-up. However, patients' outcome in the assessed comparative studies is in accord with the long-term outcome in sizeable contemporary radiosurgery series as summarised in appendix 4. Radiosurgery for vestibular schwannoma is a day carse with 2% (median) of patients requiring additional treatment; less than 1% (median) experienced some facial neuropathy and trigeminal neuropathy occurred in 5% (median). It has no direct mortality and the risk of incapacitating complications is negligible or non-t-existing. The comprehensive review of Arthurs et al. showed that after microsurgery less than 2% of patients requires additional treatment. Varying with tumour size Tthe rates of facial nerve palsy are as high as 10-30%, varying with tumour size.[4] These numbers are of the same range in the comparative studies on tumours limited to a size of 3cm in table 2. Not mentioned in any detail by Arthurs et al. are other surgical morbidities, which are not trivial at all, being between 14-

47% in the comparative studies. Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively.[21]

Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[22] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.[23] Distinctively, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S. hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[21] If radiosurgery is not employed too enthusiastically due to its low threshold, but on proper indication, the risk of death by a radiation-induced tumour is not relevant in comparison to the (few) possible direct disasters of microsurgery. Undeniably, the mortality is much smaller and, if it occurs, it is many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of various health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[24-26] In addition, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table 2) Once an intervention is considered necessary, we conclude based on this systematic review of controlled studies, that radiosurgery is best practice for patients with solitary vestibular schwannoma up to 30 mm cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw and prof.dr. Cees J.J. Avezaat for them having initiated and stimulated evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data extraction. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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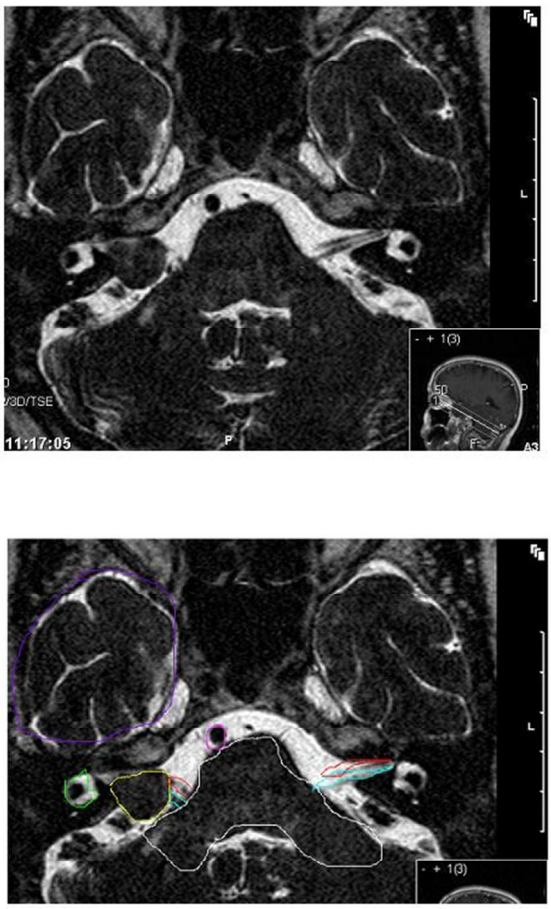
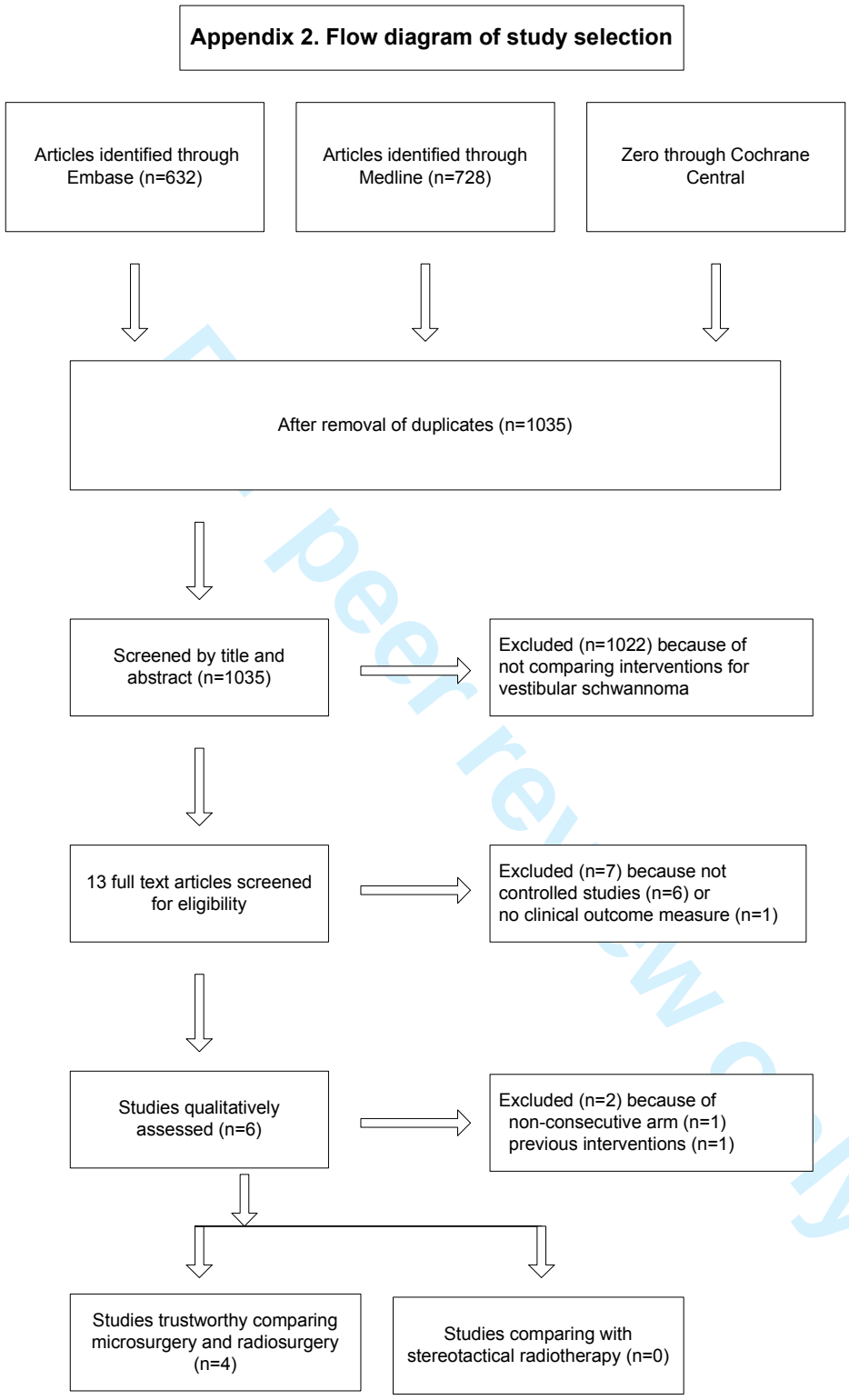


Figure 1. Axial T2 weighted MRI with a still discernible CSF-interface between tumour and brain. The largest diameter of the tumour in the CPA cistern is 14 mm.
Yellow: vestibular schwannoma, Green: labyrinth, Red: ipsi- and contralateral facial nerve
Blue: ipsi- and contralateral vestibulo-cochlear nerve, White: brainstem and cerebellar peduncle
Purple: caudal temporal lobe, Pink: basilar artery

135x210mm (120 x 120 DPI)

Appendix1. Example Search strategy: MEDLINE (PubMed)

01. "vestibular schwannoma" [All Fields]/
02. "acoustic neuroma" [All Fields]/
03. NOT neurofibromatoses [MeSH]
04. 1 or 2 not 3
05. management[All fields]/
06. "disease management"[MeSH]/
07. therapy [subheading]/
08. therapy [All Fields]
09. therapeutics[MeSH]/
10. treatment [All Fields]/
11. intervention [All Fields]
12. 5 or 6 or 7 or 8 or 9 or 11
13. "controlled trial" [All Fields]/
14. "controlled study" [All Fields]/
15. "clinical trial" [All Fields]/
16. 13 or 14 or 15
17. comparative [All Fields]/
18. comparison [All Fields]/
19. compared [All Fields]
20. 17 or 18 or 19
21. 16 or 20
22. 4 and 12 and 21



Appendix 3. Checklist on cohort studies based on SIGN 50 comparing microsurgery (MS) and radiosurgery (RS) for solitary vestibular schwannoma

authors and publication year	Pollock 2006	Myrseth 2009	Pollock 1995	Myrseth2005	Regis 2002	Karpinos 2002
design	prospective consecutive predefined inclusion crit.	prospective consecutive predefined inclusion crit.	retrospective consecutive matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls	retrospective consecutive matched controls
allocation to treatment arm	preference patient	preference patient	preference patient and surgeon	preference patient	2 hospitals, preference by surgeon/patient	miscellaneous criteria by surgeon
same primary endpoint: intervention-associated morbidity	Yes	Yes	Yes	Yes	Yes	Yes
SELECTION OF SUBJECTS						
source population: adult, solitary VS<30mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	**No**
eligibility criteria: proven growth or predefined cisternal size	No	Yes	No	No	No	No
exclusion criteria NOT more strict for MS because of age and co-morbidity	Yes	No	No	No	No	No
participation rate NOT lower for MS because of specific RS referral	Yes	No	No	No	No	No
same baseline cranial nerve deficits	Yes	Yes	Yes	Yes	**No**	Yes
consecutive series and loss to follow up < 10%	Yes	Yes	Yes	Yes	**No**	**No**
adequate analysis drop outs	Yes	Yes	No	Yes	**No**	**No**
OUTCOME ASSESSMENT						
pre-specified endpoint	Yes	Yes	Yes	Yes	Yes	Yes
mortality addressed	Yes	Yes	No	Yes	Yes	Yes
blinded outcome measurement	Yes	No	No	No	No	No
same measure new cranial nerve deficit	Yes	Yes	Yes	Yes	Yes	Yes
same measure quality of life scores	Yes	Yes	Yes	Yes	Yes	**No**
repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	**No**
CONFOUNDING VARIABLES						
NOT substantial larger tumour size in MS arm	Yes	Yes	Yes	Yes	Yes	No
NOT substantial higher age in RS arm	No	Yes	No	No	No	No
NOT less fit patients in RS arm	Yes	No	No	No	No	No
one single intervention in each arm	Yes	Yes	Yes	Yes	Yes	**No**
STATISTICAL ANALYSIS						
statistical measure of precision	Yes	Yes	Yes	Yes	Yes	Yes
OVERALL ASSESSMENT						
number of relevant 'no'	0	0	0	0	3	6
overall judgment	++	++	+	+	-	-
NO commercial funding	Yes	Yes	Yes	Yes	Yes	Yes
No relevant bias, outcome due to intervention	Yes	Yes	Yes	Yes	No	No
outcome applicable to source population	Yes	Yes	Yes	Yes	No	No

Yes: well covered or adequately addressed, increasing confidence that outcome is cause by the interventions

No: poorly or not addressed or not reported; cause for bias. Bold: possible relevant bias, decreasing confidence

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Appendix 4. Radiosurgery results; only contemporary series using low dose (≤ 13Gy), involving at least 100 patients and over 3 years of follow-up are presented. For comparison the radiosurgery results of the 4 high-quality controlled trials are integrated in the second part; mostly higher doses, lower numbers and shorter follow-up than in the case series, similar outcome however.

author, publ yr no. patients	margin dose[a] (range)	follow up (range)	stable %[b]	2[e] inter-vention %	n.V intact[c] %	n.VII intact[d]%	n.VIII intact[e] %
Friedmann, 2006[27] N=295	12.5 Gy median (10-22.5 Gy)	3.3yr mean N=63 >5yr	5yr: 90	1	99	99	?
Hempel, 2006[28] N=116	13 Gy median (10-14.5)	8.2yr mean (5.3 - 10,8)	96	3	94	100	54
Chopra, 2007[29] N=216	12 -13 Gy	5.7 yr median N=41 >8yr	10yr:: 91	1.4	10yr: 95	10yr: 100	10yr: 45
Regis, 2007[30] N=1000	12 Gy all	all > 3yr (3 – 12yr)	97	3	100	> 99	60
Fukuoka, 2009[31] N=152	12 Gy median (9-15 Gy)	all > 5yr	8yr: 92	?	97	100	71
Pollock, 1995[12] RS=47	16.3 mean (13-18 Gy)	3 yr median (2.1 – 4 yr)	94	0	86	91	75
Myrseth, 2005[15] RS=103	12.2 Gy mean. (10-20 Gy)	5.9yr mean (1 – 14.2 yr)	89	5	?	95	32
Pollock, 2006[10] RS=46	12.2 Gy mean	3.5yr mean (1 - 5,2 yr)	100	0	98	98	63
Myrseth, 2009[11] RS=60	12 Gy all	≥2 yr	98	2	?	100	68

a. minimum dose at the tumour margin
b. stable or smaller tumour volume
c. no loss sensitivity, no paraesthesias nor trigeminal neuralgia
d. preserved good facial function, House-Brackmann grade 1-2
e. preserved useful hearing: AAO-HNS class A -B or Gardner-Robertson grade I-II

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.1 and 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.1 and 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	append 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.2 and table1 +2 append 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.2 and Table1+2 append 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p.2 and append 3

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	table 2 append 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	append 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	append 2 p.5+6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	table1+2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	append 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	append 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	article summmary append 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.5 and 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.7
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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What intervention is best practice for vestibular schwannomas?
A systematic review of controlled studies.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001345.R3
Article Type:	Research
Date Submitted by the Author:	04-Feb-2013
Complete List of Authors:	Wolbers, John; Erasmus University Medical Centre, Neurosurgery Dallenga, Alof; Neurosurgery Mendez Romero, Alejandra; Radiation Oncology van Linge, Anne; Otorhinolaryngology
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical management, Ear, nose and throat/otolaryngology, Qualitative research
Keywords:	Vestibular Schwannoma, Excision, Radiosurgery, RADIOTHERAPY, NEUROSURGERY, Neurotology < OTOLARYNGOLOGY

Article summary

Article focus

- Search for best practice if an intervention for solitary vestibular schwannoma is considered necessary
- Systematic review of evidence from controlled intervention studies on the effectiveness of interventions for solitary vestibular schwannomas

Key messages

- The literature search yielded cohort studies comparing microsurgery and radiosurgery.
- Quality assessment showed four studies likely to give unbiased results.
- Radiosurgery consistently emerges as best practice for tumours smaller than 30 mm in cisternal diameter.

Strengths and limitations of this study

- All eligible studies compared the same interventions: microsurgical excision and radiosurgery
- All four trustworthy controlled studies pointed to the same intervention as best practise.
- Patients' outcomes in the assessed comparative studies are in accord with long-term outcomes in sizeable contemporary case-series.
- The conclusion is limited to solitary vestibular schwannomas smaller than 30 mm.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours.[1] A reliable register is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, usually slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological verification. The majority grows slowly or not at all; the average growth is 1 to 2 millimetres per year.[4 5] However, if the tumour grows, the rate in the first year is on average 5-10 mm.[6] There are no parameters known that predict which tumour will grow and to what extent.[7 8] The mild natural course and relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours an initial policy of watchful waiting by sequential MRI follow-up. However, if the tumour is sizeable and obliterates the cistern of the cerebellopontine angle (CPA) or grows substantial during follow-up, in principal an intervention is indicated. In most centres, the choice is between microsurgical resection for any tumour size and radiosurgery for small and

medium-sized tumours or stereotactic radiotherapy for tumours over 25-30 mm diameter. Numerous case series and non-systematic reviews have been summarised recently by Arthurs et al.[4] Understandably, due to inherent limitations of case series, these reviewers did not arrive at firm conclusions. In this study, we limit our search for best practice to comparative, controlled trials on interventions for vestibular schwannoma in a systematic and qualitative way.

Methods

PubMed and Embase were searched in November 2011 for controlled intervention studies on vestibular schwannomas. We imposed no restrictions on the kind of intervention or patient characteristics. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatoses) and (management OR therapy OR treatment OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). (Appendix 1) No language, publication status or other search restriction was imposed. The retrieved articles were screened by title and if necessary by abstract. Eventually thirteen full text articles were examined. The reference lists of studies meeting the eligibility criteria were checked. We also searched the Cochrane Central Register of Controlled Trials without finding further studies. The six eligibility criteria include controlled, intervention study, on newly-diagnosed, solitary, vestibular schwannoma reporting on clinical outcome.

The two neurosurgeons of our team appraised the articles for inclusion and assessed the risk of bias in the individual studies. The quality was assessed by judging criteria that were considered relevant by the team. The assessment is based on the Sign-50 quality criteria for cohort studies. (Our criteria are listed in Table1). (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9] We abstracted the primary clinical outcome data: mortality, treatment failure (that is second intervention necessary), function of cranial nerves 7 and 8, other intervention-associated complications and the data on quality of life. These outcome measures are the most important to the patient. Secondary outcome measures, being duration of hospital stay and time off work were also addressed. Table 1 on risk of bias and Table 3 on outcome measures served as a predefined format for data extraction. Disagreements between the two reviewers were resolved by consensus.

Results

No randomized clinical trials on solitary vestibular schwannoma were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria. [10 11] The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery.[12-15] We identified no controlled studies involving fractionated stereotactic radiotherapy. (Figure 2)

Figure 2. Flow diagram of study selection

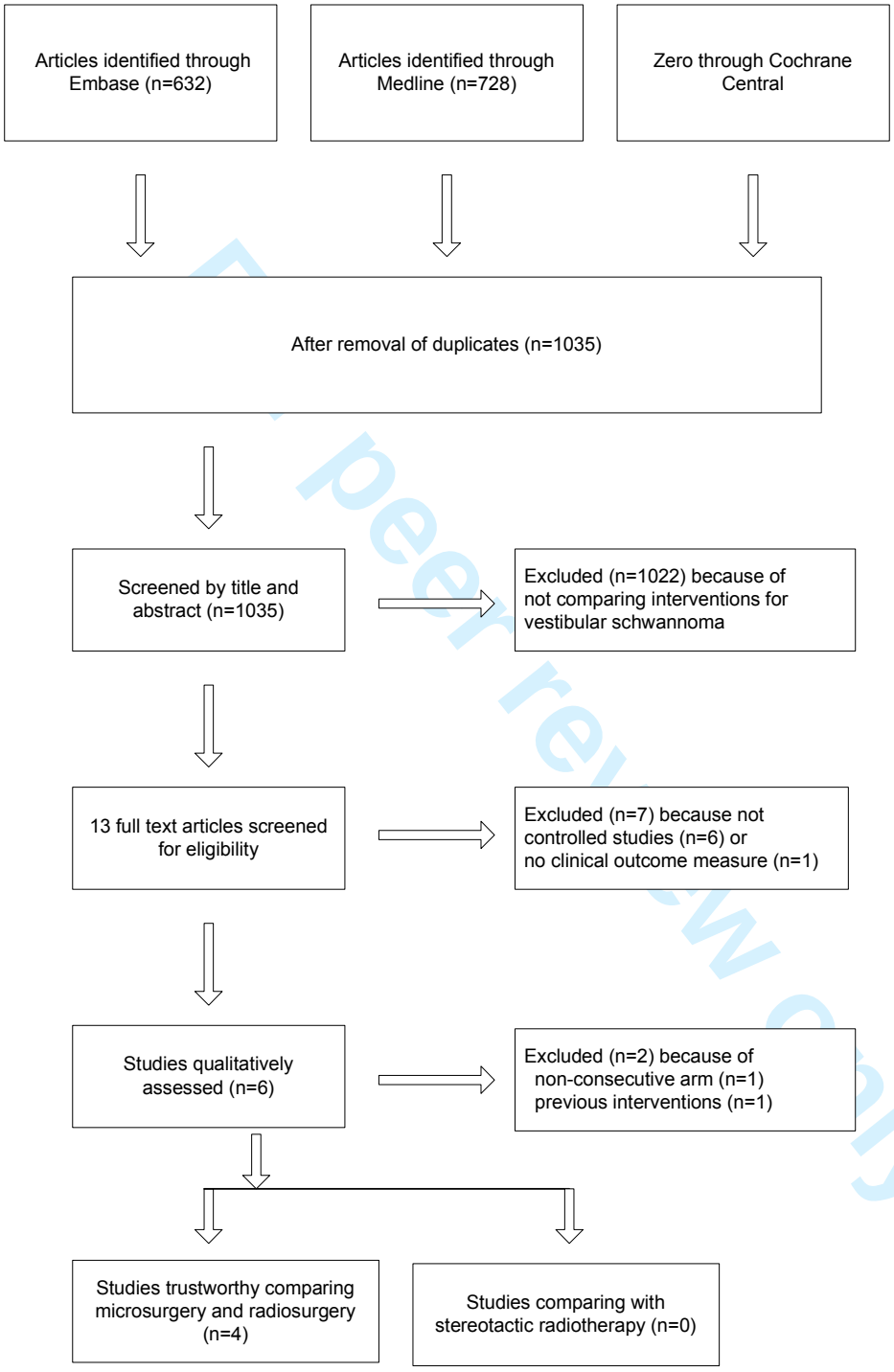

Table 1. Checklist on cohort studies based on SIGN 50 comparing microsurgery (MS) and radiosurgery (RS) for solitary vestibular schwannoma

authors and publication year	Pollock 2006[10]	Myrseth 2009[11]	Pollock1995[12]	Myrseth2005[15]	Regis 2002[14]	Karpinos 2002[13]
design	prospective consecutive predefined inclusion crit.	prospective consecutive predefined inclusion crit.	retrospective consecutive matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls	retrospective consecutive matched controls
allocation to treatment arm	preference patient	preference patient	preference patient and surgeon	preference patient	2 hospitals, preference by surgeon/patient	miscellaneous criteria by surgeon
same primary endpoint: intervention-associated morbidity	Yes	Yes	Yes	Yes	Yes	Yes
SELECTION OF SUBJECTS						
source population: adult, solitary VS<30mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	**No**
eligibility criteria: proven growth or predefined cisternal size	No	Yes	No	No	No	No
exclusion criteria NOT more strict for MS because of age and co-morbidity	Yes	No	No	No	No	No
participation rate NOT lower for MS because of specific RS referral	Yes	No	No	No	No	No
same baseline cranial nerve deficits	Yes	Yes	Yes	Yes	**No**	Yes
consecutive series and loss to follow up < 10%	Yes	Yes	Yes	Yes	**No**	**No**
adequate analysis drop outs	Yes	Yes	No	Yes	**No**	**No**
OUTCOME ASSESSMENT						
pre-specified endpoint	Yes	Yes	Yes	Yes	Yes	Yes
mortality addressed	Yes	Yes	No	Yes	Yes	Yes
blinded outcome measurement	Yes	No	No	No	No	No
same measure new cranial nerve deficit	Yes	Yes	Yes	Yes	Yes	Yes
same measure quality of life scores	Yes	Yes	Yes	Yes	Yes	**No**
repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	**No**
CONFOUNDING VARIABLES						
NOT substantial larger tumour size in MS arm	Yes	Yes	Yes	Yes	Yes	No
NOT substantial higher age in RS arm	No	Yes	No	No	No	No
NOT less fit patients in RS arm	Yes	No	No	No	No	No
one single intervention in each arm	Yes	Yes	Yes	Yes	Yes	**No**
STATISTICAL ANALYSIS						
statistical measure of precision	Yes	Yes	Yes	Yes	Yes	Yes
OVERALL ASSESSMENT						
number of relevant 'no'	0	0	0	0	3	6
overall judgment	++	++	+	+	-	-
NO commercial funding	Yes	Yes	Yes	Yes	Yes	Yes
No relevant bias, outcome due to intervention	Yes	Yes	Yes	Yes	No	No
outcome applicable to source population	Yes	Yes	Yes	Yes	No	No

Yes: well covered or adequately addressed, increasing confidence that outcome is cause by the interventions

No: poorly or not addressed or not reported; cause for bias. Bold: possible relevant bias, decreasing confidence

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Four main quality items were assessed: selection of subjects, outcome measure, known confounders and statistical analysis. (Table 1) At the inception, in five out of six studies all patients were at the same stage of the disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The one exception is the study of Karpinos et al., which included recurrent tumours.[13] The indication for an intervention was clearly defined in only one study.[11] In the other studies, just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patient characteristics were quite similar in the treatment arms within the studies.(Table 2) Only the average age was higher in all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but the study of Pollock et al (2006). These are known hazards for a favourable outcome. If imbalance was present, the higher risk patients were in the radiosurgery arms. There was minimal or no loss to follow-up in all but one study.[13] After summation of the number of items that downgrade the confidence in outcome (bold NO in Table 1), four studies remained that showed trustworthy association between intervention and outcome. [10-12 15] The outcomes are specified in Table 3. There was 1% mortality in two microsurgery arms.[14 15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation and better quality of life.

Table 2. Patients' pre-intervention characteristics; only sporadic vestibular schwannomas

Author publ yr	Intervention[a] included no	Male:Fem	age yr	n.trigem. deficit %	n.facial deficit %[b]	useful hearing %[c]	tumour size[d] mean mm	previous treatment %
Pollock 2006[10]	MS: 36 RS: 46	19:17 27:19	48 54	0 0	0 0	61 65	14 12	no no
Myrseth 2009[11]	MS: 28 RS: 60	12:16 36:24*	53 58	? ?	0 0	44 42	18 16	no no
Pollock 1995[12]	MS: 40 RS: 47	18:22 23:24	51 62*	10 6	5 2	12 4	>20mm:18% >20mm:29%	no no
Myrseth 2005[15]	MS: 86 RS: 103	? ?	50 60*	20 12	1 1	2 10	>20mm:32% >20mm:17%	no no
Regis 2002[14]	MS: 110 RS: 100	M 35% M 46%	52 61	55 20	? 2	? 49	KoosIII:55%[d] KoosIII:34%	no no
Karpinos 2002[13]	MS: 23 RS: 73	6:17 23:50	45 62*	30 17	26 10	30 24	>40mm:17* >40mm:3%	26 14

a. MS: microsurgery, RS: radiosurgery

b. percentage preserved, House-Brackmann grade 1-2

c. useful hearing: AAO-HNS class A-B or Gardner-Robertson grade I-II

d. Koos III: tumour occupying the cerebellopontine cistern without brainstem displacement

* significant ($p<0.05$)

Table 3. Outcome of the six controlled studies on vestibular schwannoma; all comparing microsurgery (MS) and radiosurgery (RS):

author publ yr	therapy FU no.	follow-up (range)	mortal %	2nd ther. %	facial intact[a] %	% useful hearing[b]	other complic[c]	hosp. days	work resume%	QoL Tests[d]	QoL % Results
Pollock 2006[10]	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 0	0 4	83 **98***	5 **63***	33 **11***	? ?	? ?	DHI, HS, HSQ	↓ =*
Myrseth 2009[11]	MS 28 RS 60	≥ 2 yr	0 0	18 2	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 93	SF36, GBI	SF36= **GBI ↑***
Pollock 1995[12]	MS 40 RS 47	3 yr median (2.1-4 yr)	0 0	0 0	78 **91***	14 **75***	38 **13***	9,5 **1.4***	? ?	ANSPQ	↓ 45 ↓ 26
Myrseth 2005[15]	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	1 0	6 5	80 **95***	5 **32***	47 **4***	? ?	? ?	SF36, GBI	↓ =*
Regis 2002[14]	MS 110 RS 97	≥ 3 yr	1 0	9 3	67 **100***	36 **50***	41 **8***	23 **3***	66 **99***	Pellet	↓ 39 **↓ 9***
Karpinos 2002[13]	MS 18 RS 49	4yr median (0.3-7 yr)	0 0	0 4	60 **97***	40 44	48 **5***	2-16 **1-2***	88 94	none	- -

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as new trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d.. quality of life (QoL) from questionnaires as Dizziness Handicap Inventory, Headache Survey, Health Status Questionnaire, ShortForm36, Glasgow Benefit Inventory, Acoustic Neuroma Association Patient Questionnaire, Pellet Questionnaire;

* and bold: significantly better

Discussion

Microsurgery and radiosurgery are equally effective interventions for vestibular schwannomas as demonstrated by numerous case series that were recently reviewed.[4] Whilst taking into account patients' individual preferences, ideally the choice of treatment should be based on high-quality evidence from well-conducted clinical trials. We found evidence of greater clinical effectiveness of radiosurgery compared to microsurgery in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold standard of evidence-based practice. Regarding vestibular schwannomas, however, we most probably will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept chance to decide whether they would undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[16 17] Next to the value of well-conducted randomised trials, the value of high-quality observational studies is validated by the remarkable similar results, which were observed when comparing specific treatments through both randomized and observational trials. [18-20] Such observational studies may provide

trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for patients. Overall, these patients are more similar to the general disease population than those complying with the strict inclusion and exclusion criteria of a randomised clinical trial. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. Based on Sign-50, this is the basic thought behind the assessment of quality of individual studies in Table 1.

Selection of subjects

All retrieved controlled studies compared the same two interventions and consistently pointed to radiosurgery as being the best intervention for their research question. Some studies, however, provide more confidence to have unbiased results, as elucidated in Table 1. A major risk of bias of all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In five studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Only in the study by Karpinos et al. the source population differed due to inclusion of patients having had earlier surgery for the same disease.[13] In addition, this study had an unacceptably high loss to follow-up of over 20%. These two serious sources of bias prevented a favourable overall good quality judgement. In one study pertinent bias arose, because of non-consecutive inclusion in the microsurgery arm. [14]

Only Myrseth et al (2009) clearly defined the starting point of an intervention.[11] Nevertheless, confounding by indication between the various studies appears unlikely, since major adverse events, like disabling neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of an intervention. Therefore, the risk that an adverse outcome occurs due to chance instead of being related to the intervention is not realistic and we assigned no relevance to the potential confounder of being at various points in the disease progression (non-bold NO, Table 1).

Outcome assessment

All but one study reported on the same clinical outcome measures, which are failure because a second intervention was needed, function preservation of the involved cranial nerves, more general complications and quality of life. The exception is the study by Karpinos et al, who did not report on quality of life. All used established classifications of facial motor function and useful hearing.

Only one group managed a blinded outcome measurement.[10] Taking into account that a troublesome outcome - when occurring - is quite clear-cut in this disease, non-blinded outcome measurement did not depreciate our trust that the reported outcome is true and caused by the specific intervention. Typically, repeated measurements increase this trust further.

Confounding variables

A previous treatment for the same disease induces relevant bias, because of different base-line characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos et al., because the results from first and second intervention were not separated in their report.[13] Frail patients were in all but the study of Pollock et al. (2006) inclined to end up in the radiosurgery arm.[10] In general higher age, co-morbidity and larger tumours are drawbacks for a good outcome. In those studies showing significant imbalance of these variables the potential disadvantage, however, was at the side of radiosurgery, which nevertheless produced the best outcome in all studies.[12 13 15] As these imbalances work in favour of microsurgery, we considered them not relevant (non-bold no's in Table 1)

The overall assessment of study quality gave confidence in four studies, because no relevant biases were identified. Quite importantly, all four consistently showed a significant advantage for radiosurgery over microsurgical excision, when directly compared in a controlled manner. (Table 2)

One might argue that a weakness of some of the four trustworthy studies is the relative small numbers and short follow-up. However, patients' outcome in the assessed comparative studies is in accord with the long-term outcome in sizeable contemporary radiosurgery series as summarised in Appendix 2. Radiosurgery for vestibular schwannoma is a day case with 2% (median) of patients requiring additional treatment; less than 1% (median) experienced some facial neuropathy and trigeminal neuropathy occurred in 5% (median). It has no direct mortality and the risk of incapacitating complications is negligible or non-existing. The comprehensive review of Arthurs et al. showed that after microsurgery less than 2% of patients require additional treatment. The rates of facial nerve palsy are as high as 10-30%, varying with tumour size.[4] These numbers are of the same range in the comparative studies on tumours limited to a size of 3cm in Table 2. Not mentioned in any detail by Arthurs et al. are other surgical morbidities, which are not trivial at all, being between 14-47% in the comparative studies. Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively.[21]

Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[22] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.[23] Distinctively, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S. hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[21] If radiosurgery is not employed too enthusiastically due to its low threshold, but on proper indication, the risk of death by a radiation-induced tumour is not relevant in comparison to the (few) possible direct disasters of microsurgery. Undeniably, the mortality is much smaller and, if it occurs, it is many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of various health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[24-26] In addition, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table 3) Once an intervention is considered necessary, we conclude based on this systematic review of controlled studies, that radiosurgery is best practice for patients with solitary vestibular schwannoma up to 30 mm in cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw and prof.dr. Cees J.J. Avezaat for them having initiated and stimulated evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data extraction. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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Article summary

Article focus

- Search for best practice if an intervention for solitary vestibular schwannoma is considered necessary
- Systematic review of evidence from controlled intervention studies on the effectiveness of interventions for solitary vestibular schwannomas

Key messages

- The literature search yielded cohort studies comparing microsurgery and radiosurgery.
- Quality assessment showed four studies likely to give unbiased results.
- Radiosurgery consistently emerges as best practice for tumours smaller than 30 mm in cisternal diameter.

Strengths and limitations of this study

- All eligible studies compared the same interventions: microsurgical excision and radiosurgery
- All four trustworthy controlled studies pointed to the same intervention as best practise.
- Patients' outcomes in the assessed comparative studies are in accord with long-term outcomes in sizeable contemporary case-series.
- The conclusion is limited to solitary vestibular schwannomas smaller than 30 mm.

Introduction

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain tumour. It accounts for about 6% of all intracranial tumours.[1] A reliable register is available in Denmark, since almost all patients with a vestibular schwannoma are referred to one specialist clinic. The incidence approaches 20 per million per year. [2] Due to its benign nature the prevalence accumulates to 200 per million.[3] The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the border of central and peripheral myelin, usually slightly lateral to the rim of the internal auditory meatus. The MRI image of a vestibular schwannoma is characteristic (Figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological verification. The majority grows slowly or not at all; the average growth is 1 to 2 millimetres per year.[4 5] However, if the tumour grows, the rate in the first year is on average 5-10 mm.[6] There are no parameters known that predict which tumour will grow and to what extent.[7 8] The mild natural course and relatively minor symptoms - that will not improve by any intervention - justifies for small and medium-size tumours an initial policy of watchful waiting by sequential MRI follow-up. However, if the tumour is sizeable and obliterates the cistern of the cerebellopontine angle (CPA) or grows substantial during follow-up, in principal an intervention is indicated. In most centres, the choice is between microsurgical resection for any tumour size and radiosurgery for small and

medium-sized tumours or stereotactic radiotherapy for tumours over 25-30 mm diameter. Numerous case series and non-systematic reviews have been summarised recently by Arthurs et al.[4] Understandably, due to inherent limitations of case series, these reviewers did not arrive at firm conclusions. In this study, we limit our search for best practice to comparative, controlled trials on interventions for vestibular schwannoma in a systematic and qualitative way.

Methods

PubMed ~~/ Medline~~ and Embase were searched in November 2011 for controlled intervention studies on vestibular schwannomas. We imposed no restrictions on the kind of intervention or patient characteristics. We performed Boolean searches using the following keywords ("vestibular schwannoma" OR "acoustic neuroma" NOT neurofibromatoses) and (management OR therapy OR treatment OR intervention) and ('controlled trial' OR 'controlled study' OR 'clinical trial') or (comparative OR comparison OR compared). (Appendix 1) No language, publication status or other search restriction was imposed. The retrieved articles were screened by title and if necessary by abstract. Eventually thirteen full text articles were examined. The reference lists of studies meeting the eligibility criteria were checked. We also searched the Cochrane Central Register of Controlled Trials without finding further studies. The six eligibility criteria include controlled, intervention study, on newly-diagnosed, solitary, vestibular schwannoma reporting on clinical outcome.

The two neurosurgeons of our team appraised the article for inclusion and assessed the risk of bias in the individual studies. The quality was assessed by judging criteria that were considered relevant by the team. The assessment is based on the Sign-50 quality criteria for cohort studies. (Our~~These~~ criteria are listed in ~~Appendix 3~~Table1). (www.ahrq.gov/clinic/epcix.htm: AHRQ Publication No. 02-E016, April 2002, http://www.sign.ac.uk/guidelines/fulltext/50/annexc.html: checklist and notes on cohort studies, annex C)[9] We abstracted the primary clinical outcome data: mortality, treatment failure (that is second intervention necessary), function of cranial nerves 7 and 8, other intervention-associated complications and the data on quality of life. These outcome measures are the most important to the patient. Secondary outcome measures, being duration of hospital stay and time off work were also addressed. Table 1~~Appendix 3~~ on risk of bias and Table ~~2~~3 on outcome measures served as a predefined format for data extraction. Disagreements between the two reviewers were resolved by consensus.

Results

No randomized clinical trials on solitary vestibular schwannoma were found. Only two studies – both comparing microsurgical excision with radiosurgery – showed up that had a controlled, prospective design with predefined inclusion criteria. [10 11] The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery ~~and of level 3b~~.[12-15] We identified no controlled studies involving fractionated stereotactic~~al~~ radiotherapy. (~~Appendix 2~~Figure 2)

Figure 2. Flow diagram of study selection

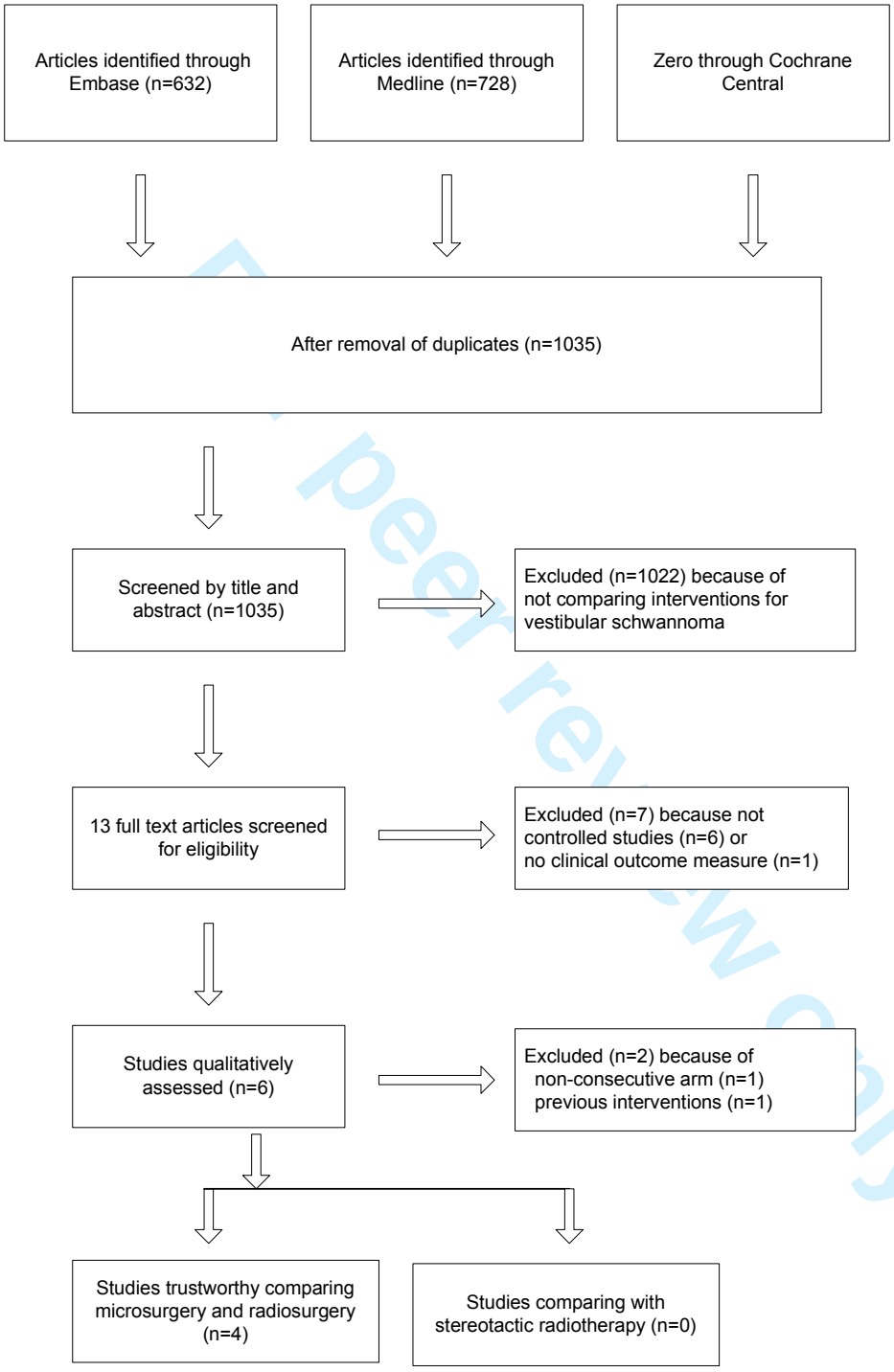

Table 1. Checklist on cohort studies based on SIGN 50 comparing microsurgery (MS) and radiosurgery (RS) for solitary vestibular schwannoma

authors and publication year	Pollock 2006	Myrseth 2009	Pollock 1995	Myrseth2005	Regis 2002	Karpinos 2002
design	prospective consecutive predefined inclusion crit.	prospective consecutive predefined inclusion crit.	retrospective consecutive matched controls	retrospective consecutive matched controls	retrospective not consecut. matched controls	retrospective consecutive matched controls
allocation to treatment arm	preference patient	preference patient	preference patient and surgeon	preference patient	2 hospitals, preference by surgeon/patient	miscellaneous criteria by surgeon
same primary endpoint: intervention-associated morbidity	Yes	Yes	Yes	Yes	Yes	Yes
SELECTION OF SUBJECTS						
source population: adult, solitary VS<30mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	**No**
eligibility criteria: proven growth or predefined cisternal size	No	Yes	No	No	No	No
exclusion criteria NOT more strict for MS because of age and co-morbidity	Yes	No	No	No	No	No
participation rate NOT lower for MS because of specific RS referral	Yes	No	No	No	No	No
same baseline cranial nerve deficits	Yes	Yes	Yes	Yes	**No**	Yes
consecutive series and loss to follow up < 10%	Yes	Yes	Yes	Yes	**No**	**No**
adequate analysis drop outs	Yes	Yes	No	Yes	**No**	**No**
OUTCOME ASSESSMENT						
pre-specified endpoint	Yes	Yes	Yes	Yes	Yes	Yes
mortality addressed	Yes	Yes	No	Yes	Yes	Yes
blinded outcome measurement	Yes	No	No	No	No	No
same measure new cranial nerve deficit	Yes	Yes	Yes	Yes	Yes	Yes
same measure quality of life scores	Yes	Yes	Yes	Yes	Yes	**No**
repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	**No**
CONFOUNDING VARIABLES						
NOT substantial larger tumour size in MS arm	Yes	Yes	Yes	Yes	Yes	No
NOT substantial higher age in RS arm	No	Yes	No	No	No	No
NOT less fit patients in RS arm	Yes	No	No	No	No	No
one single intervention in each arm	Yes	Yes	Yes	Yes	Yes	**No**
STATISTICAL ANALYSIS						
statistical measure of precision	Yes	Yes	Yes	Yes	Yes	Yes
OVERALL ASSESSMENT						
number of relevant 'no'	0	0	0	0	3	6
overall judgment	++	++	+	+	-	-
NO commercial funding	Yes	Yes	Yes	Yes	Yes	Yes
No relevant bias, outcome due to intervention	Yes	Yes	Yes	Yes	No	No
outcome applicable to source population	Yes	Yes	Yes	Yes	No	No

Yes: well covered or adequately addressed, increasing confidence that outcome is cause by the interventions

No: poorly or not addressed or not reported; cause for bias. Bold: possible relevant bias, decreasing confidence

++ All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.

+ Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.

- Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter.

Four main quality items were assessed: selection of subjects, outcome measure, known confounders and statistical analysis. (Table 1~~Appendix 3~~) At the inception, in five out of six studies all patients were at the same stage of the disease having minor symptoms, tumour size limited to 30 mm extension into the CPA and no earlier intervention. The one exception is the study of Karpinos et al., which included recurrent tumours.[13] The indication for an intervention was clearly defined in only one study.[11] In the other studies, just having a vestibular schwannoma seemed sufficient to initiate an intervention, be it excision or radiosurgery. Baseline patient characteristics were quite similar in the treatment arms within the studies.(Table ~~1~~2) Only the average age was higher in all radiosurgery arms. Specific allocation to the radiosurgery arm because of co-morbidity or high age was permitted in all but the study of Pollock et al (2006). These are known hazards for a favourable outcome. If imbalance was present, the higher risk patients were in the radiosurgery arms. There was minimal or no loss to follow-up in all but one study.[13] After summation of the number of items that downgrade the confidence in outcome (bold NO in ~~appendix 3~~Table 1), four studies remained that showed trustworthy association between intervention and outcome. [10-12 15] The outcomes are specified in Table ~~2~~3. There was 1% mortality in two microsurgery arms.[14 15] After radiosurgery, there was no mortality and no surgical or anaesthetic complications, better facial function, better hearing preservation and better quality of life.

Table ~~1~~2. Patients' pre-intervention characteristics; only sporadic vestibular schwannomas

Author publ yr	Intervention[a] included no	Male:Fem	age yr	n.trigem. deficit %	n. facial deficit %[b]	useful hearing %[c]	tumour size[d] mean mm	previous treatment %
Pollock 2006	MS: 36 RS: 46	19:17 27:19	48 54	0 0	0 0	61 65	14 12	no no
Myrseth 2009	MS: 28 RS: 60	12:16 36:24*	53 58	? ?	0 0	44 42	18 16	no no
Pollock 1995	MS: 40 RS: 47	18:22 23:24	51 62*	10 6	5 2	12 4	>20mm:18% >20mm:29%	no no
Myrseth 2005	MS: 86 RS: 103	? ?	50 60*	20 12	1 1	2 10	>20mm:32% >20mm:17%	no no
Regis 2002	MS: 110 RS: 100	M 35% M 46%	52 61	55 20	? 2	? 49	KoosIII:55%[d] KoosIII:34%	no no
Karpinos 2002	MS: 23 RS: 73	6:17 23:50	45 62*	30 17	26 10	30 24	>40mm:17* >40mm:3%	26 14

a. MS: microsurgery, RS: radiosurgery

b. percentage preserved, House-Brackmann grade 1-2

c. useful hearing: AAO-HNS class A-B or Gardner-Robertson grade I-II

d. Koos III: tumour occupying the cerebellopontine cistern without brainstem displacement

* significant ($p<0.05$)

Table ~~2~~3. Outcome of the six controlled studies on vestibular schwannoma; all comparing microsurgery (MS) and radiosurgery (RS):

author publ yr	therapy FU no.	follow-up (range)	mortal %	2nd ther. %	facial intact[a] %	% useful hearing[b]	other complic[c]	hosp. days	work resume%	QoL Tests[d]	QoL % Results
Pollock 2006	MS 36 RS 46	3.5 yr mean (1-5.2 yr)	0 0	0 4	83 **98***	5 **63***	33 **11***	? ?	? ?	DHI, HS, HSQ	↓ =*
Myrseth 2009	MS 28 RS 60	≥ 2 yr	0 0	18 2	82 **100***	0 **68***	14 **0***	12,5 **2.5***	100 93	SF36, GBI	SF36= **GBI ↑***
Pollock 1995	MS 40 RS 47	3 yr median (2.1-4 yr)	0 0	0 0	78 **91***	14 **75***	38 **13***	9,5 **1.4***	? ?	ANSPQ	↓ 45 ↓ 26
Myrseth 2005	MS 86 RS 103	5.9 yr mean (1-14.2 yr)	1 0	6 5	80 **95***	5 **32***	47 **4***	? ?	? ?	SF36, GBI	↓ =*
Regis 2002	MS 110 RS 97	≥ 3 yr	1 0	9 3	67 **100***	36 **50***	41 **8***	23 **3***	66 **99***	Pellet	↓ 39 **↓ 9***
Karpinos 2002	MS 18 RS 49	4yr median (0.3-7 yr)	0 0	0 4	60 **97***	40 44	48 **5***	2-16 **1-2***	88 94	none	- -

a. percentage preserved, House-Brackmann grade 1-2;

b. percentage preserved, AAO-HNS class A-B or Gardner-Robertson grade I-II;

c. percentage complications as new trigeminal deficit, haemorrhage, CSF leakage, meningitis, wound infection, CSF-shunt needed;

d.. quality of life (QoL) from questionnaires as Dizziness Handicap Inventory, Headache Survey, Health Status Questionnaire, ShortForm36, Glasgow Benefit Inventory, Acoustic Neuroma Association Patient Questionnaire, Pellet Questionnaire;

* and bold: significantly better

Discussion

Microsurgery and radiosurgery are equally effective interventions for vestibular schwannomas as demonstrated by numerous case series that were recently reviewed.[4] Whilst taking into account patients' individual preferences, ideally the choice of treatment should be based on high-quality evidence from well-conducted clinical trials. We found evidence of greater clinical effectiveness of radiosurgery compared to microsurgery in medium-sized tumours.

Systematic reviews of randomized clinical trials – preferably double blinded - are considered the gold standard of evidence-based practice. Regarding vestibular schwannomas, however, we most probably will have to do without randomized studies. Indeed, Myrseth et al. failed to go on with their randomized trial, because patients were reluctant to accept chance to decide whether they would undergo surgery or radiosurgery.[11] Next best evidence is obtained from well-designed non-randomized controlled trials.[16 17] Next to the value of well-conducted randomised trials, the value of high-quality observational studies is validated by the remarkable similar results, which were observed when comparing specific treatments through both randomized and observational trials. [18-20] Such observational studies may provide

trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life for patients. Overall, these patients are more similar to the general disease population than those complying with the strict inclusion and exclusion criteria of a randomised clinical trial. Such high quality of observational studies is obtained by studying the same intervention by the same outcome measures in well-matched patient population without dropouts. Based on Sign-50, this is the basic thought behind the assessment of quality of individual studies in Table 1~~appendix 3~~.

Selection of subjects

All retrieved controlled studies compared the same two interventions and consistently pointed to radiosurgery as being the best intervention for their research question. Some studies, however, provide more confidence to have unbiased results, as elucidated in Table 1~~appendix 3~~. A major risk of bias of all observational studies is that the compared groups are substantially unequal in their initial susceptibility to the outcome. In five studies selection bias is reasonably controlled, since the compared groups are very similar except for the interventions under study. Only in the study by Karpinos et al. the source population differed due to inclusion of patients having had earlier surgery for the same disease.[13] In addition, this study had an unacceptably high loss to follow-up of over 20%. These two serious sources of bias prevented a favourable overall good quality judgement. In one study pertinent bias arose, because of non-consecutive inclusion in the microsurgery arm. [14]

Only Myrseth et al (2009) clearly defined the starting point of an intervention.[11] Nevertheless, confounding by indication between the various studies appears unlikely, since major adverse events, like disabling neurological deficits, do not occur in the natural history of vestibular schwannomas smaller than 30 mm. It is very implausible that any of the major adverse events occur in the absence of an intervention. Therefore, the risk that an adverse outcome occurs due to chance instead of being related to the intervention is not realistic and we assigned no relevance to the potential confounder of being at various points in the disease progression (non-bold NO, Table 1~~appendix 3~~).

Outcome assessment

All but one study reported on the same clinical outcome measures, which are failure because a second intervention was needed, function preservation of the involved cranial nerves, more general complications and quality of life. The exception is the study by Karpinos et al, who did not report on quality of life. All used established classifications of facial motor function and useful hearing.

Only one group managed a blinded outcome measurement.[10] Taking into account that a troublesome outcome - when occurring - is quite clear-cut in this disease, non-blinded outcome measurement did not depreciate our trust that the reported outcome is true and caused by the specific intervention. Typically, repeated measurements increase this trust further.

Confounding variables

A previous treatment for the same disease induces relevant bias, because of different base-line characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos et al., because the results from first and second intervention were not separated in their report.[13] Frail patients were in all but the study of Pollock et al. (2006) inclined to end up in the radiosurgery arm.[10] In general higher age, co-morbidity and larger tumours are drawbacks for a good outcome. In those studies showing significant imbalance of these variables the potential disadvantage, however, was at the side of radiosurgery, which nevertheless produced the best outcome in all studies.[12 13 15] As these imbalances work in favour of microsurgery, we considered them not relevant (non-bold no's in Table 1~~appendix 3~~)

The overall assessment of study quality gave confidence in four studies, because no relevant biases were identified. Quite importantly, all four consistently showed a significant advantage for radiosurgery over microsurgical excision, when directly compared in a controlled manner. (Table 2)

One might argue that a weakness of some of the four trustworthy studies is the relative small numbers and short follow-up. However, patients' outcome in the assessed comparative studies is in accord with the long-term outcome in sizeable contemporary radiosurgery series as summarised in Appendix 2. Radiosurgery for vestibular schwannoma is a day case with 2% (median) of patients requiring additional treatment; less than 1% (median) experienced some facial neuropathy and trigeminal neuropathy occurred in 5% (median). It has no direct mortality and the risk of incapacitating complications is negligible or non-existing. The comprehensive review of Arthurs et al. showed that after microsurgery less than 2% of patients require additional treatment. The rates of facial nerve palsy are as high as 10-30%, varying with tumour size.[4] These numbers are of the same range in the comparative studies on tumours limited to a size of 3cm in Table 2. Not mentioned in any detail by Arthurs et al. are other surgical morbidities, which are not trivial at all, being between 14-47% in the comparative studies. Major adverse events like mortality and discharge to long-term care may occur after microsurgery in about 0.5% and 1.2%, respectively.[21]

Not addressed in the comparative studies is the risk of secondary cancer after radiation for a benign tumour causing mortality. Indeed, radiation-associated tumours do occur after sufficient follow-up of 5-20 years. So far, 12 cases of radiosurgery-associated malignant tumour have been reported worldwide.[22] Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.[23] Distinctively, the hospital-based study mentioned before depicted 2643 surgeries in 265 U.S. hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.[21] If radiosurgery is not employed too enthusiastically due to its low threshold, but on proper indication, the risk of death by a radiation-induced tumour is not relevant in comparison to the (few) possible direct disasters of microsurgery. Undeniably, the mortality is much smaller and, if it occurs, it is many years later in a patients' life.

Looking for best practice, one should realise indeed that the results of various health-related quality of life studies after surgery called for modesty. Deterioration of the well-being of the patient proved difficult to avoid, even in elective surgery of relatively small tumours.[24-26] In addition, the comparative studies showed deterioration in quality of life as high as in 30-45% of patients operated on. (Table ~~2~~3) Once an intervention is considered necessary, we conclude based on this systematic review of controlled studies, that radiosurgery is best practice for patients with solitary vestibular schwannoma up to 30 mm in cisternal extension.

Acknowledgements. The authors gratefully acknowledge Dr. K.H. (Bernard) Pauw and prof.dr. Cees J.J. Avezaat for them having initiated and stimulated evidence-based practice in our Working Party on cerebellopontine angle tumours.

Contributors: All authors participated in the conception, design and interpretation of data. JW and AD conducted literature searches and data extraction. JW prepared the initial draft and led the preparation of the manuscript. All authors were involved in drafting and reviewing the manuscript and approved the final version.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None

Data sharing statement: No additional data is available

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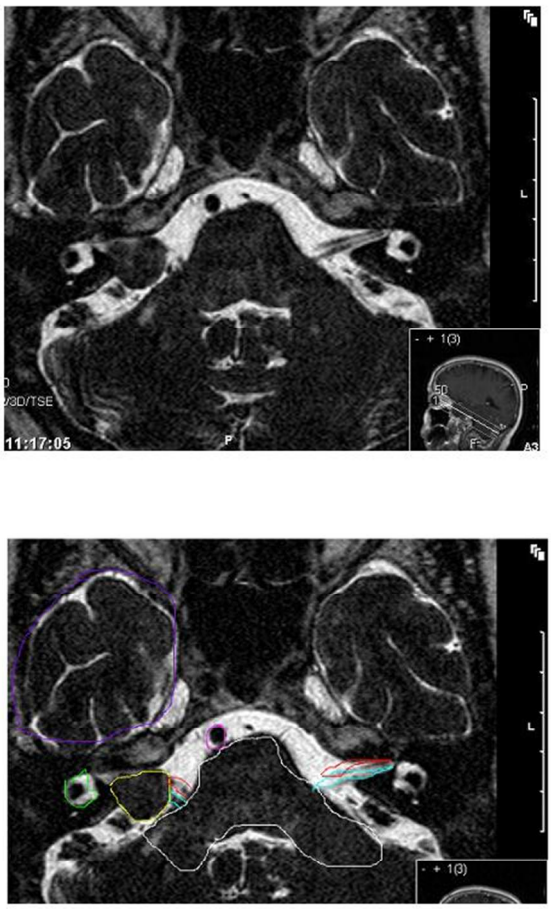

Figure 1. Axial T2 weighted MRI with a still discernible CSF-interface between tumour and brain. The largest diameter of the tumour in the CPA cistern is 14 mm.
Yellow: vestibular schwannoma, Green: labyrinth, Red: ipsi- and contralateral facial nerve
Blue: ipsi- and contralateral vestibulo-cochlear nerve, White: brainstem and cerebellar peduncle
Purple: caudal temporal lobe, Pink: basilar artery

135x210mm (120 x 120 DPI)

Appendix1. Example Search strategy: PubMed

01. "vestibular schwannoma" [All Fields]/
02. "acoustic neuroma" [All Fields]/
03. NOT neurofibromatoses [MeSH]
04. 1 or 2 not 3
05. management[All fields]/
06. "disease management"[MeSH]/
07. therapy [subheading]/
08. therapy [All Fields]
09. therapeutics[MeSH]/
10. treatment [All Fields]/
11. intervention [All Fields]
12. 5 or 6 or 7 or 8 or 9 or 11
13. "controlled trial" [All Fields]/
14. "controlled study" [All Fields]/
15. "clinical trial" [All Fields]/
16. 13 or 14 or 15
17. comparative [All Fields]/
18. comparison [All Fields]/
19. compared [All Fields]
20. 17 or 18 or 19
21. 16 or 20
22. 4 and 12 and 21

Appendix 2. Radiosurgery results; only contemporary series using low dose (≤ 13Gy), involving at least 100 patients and over 3 years of follow-up are presented. For comparison the radiosurgery results of the 4 high-quality controlled trials are integrated.

author, publ yr no. patients	margin dose[a] (range)	follow up (range)	stable %[b]	2[e] inter-vention %	n.V intact[c] %	n.VII intact[d]%	n.VIII intact[e] %
Friedmann, 2006[27] N=295	12.5 Gy median (10-22.5 Gy)	3.3yr mean N=63 >5yr	5yr: 90	1	99	99	?
Hempel, 2006[28] N=116	13 Gy median (10-14.5)	8.2yr mean (5.3 - 10,8)	96	3	94	100	54
Chopra, 2007[29] N=216	12 -13 Gy	5.7 yr median N=41 >8yr	10yr:: 91	1.4	10yr: 95	10yr: 100	10yr: 45
Regis, 2007[30] N=1000	12 Gy all	all > 3yr (3 – 12yr)	97	3	100	> 99	60
Fukuoka, 2009[31] N=152	12 Gy median (9-15 Gy)	all > 5yr	8yr: 92	?	97	100	71
Corresponding radiosurgery results of the 4 comparative studies (mostly higher doses, lower numbers and shorter follow-up than in the case series above): similar outcome however.							
Pollock, 1995[12] RS=47	16.3 mean (13-18 Gy)	3 yr median (2.1 – 4 yr)	94	0	86	91	75
Myrseth, 2005[15] RS=103	12.2 Gy mean. (10-20 Gy)	5.9yr mean (1 – 14.2 yr)	89	5	?	95	32
Pollock, 2006[10] RS=46	12.2 Gy mean	3.5yr mean (1 - 5,2 yr)	100	0	98	98	63
Myrseth, 2009[11] RS=60	12 Gy all	≥2 yr	98	2	?	100	68

a. minimum dose at the tumour margin
b. stable or smaller tumour volume
c. no loss sensitivity, no paraesthesias nor trigeminal neuralgia
d. preserved good facial function, House-Brackmann grade 1-2
e. preserved useful hearing: AAO-HNS class A -B or Gardner-Robertson grade I-II

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.1 and 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.1 and 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	append 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.2 and table1 +2 append 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.2 and Table1+2 append 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p.2 and append 3

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	table 2 append 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	append 3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	append 2 p.5+6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	table1+2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	append 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	append 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	article summmary append 3
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p.5 and 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.7
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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