

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

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## ABSTRACT

**Objective:** Largely, watchful waiting is the initial policy for patients with small-sized or medium-sized vestibular schwannoma, because of slow growth and relatively minor complaints, that do not improve by an intervention. If intervention (microsurgery, radiosurgery or fractionated radiotherapy) becomes necessary, the choice of intervention appears to be driven by the patient's or clinician's preference rather than by evidence based. 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 quality of the retrieved studies was assessed based on the Sign-50 criteria on cohort studies.

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

**Study selection:** Six eligibility criteria included a controlled intervention study on a newly diagnosed solitary, vestibular schwannoma reporting on clinical outcomes. Two prospective and four retrospective observational, controlled studies published before November 2011 were selected.

**Data analysis:** Two reviewers independently assessed the methodological quality of the studies and extracted the outcome data using predefined formats.

**Results:** Neither randomised studies, nor controlled studies on fractionated radiotherapy were retrieved. Six studies compared radiosurgery and microsurgery in a controlled way. All but one were confined to solitary tumours less than 30 mm in diameter and had no earlier interventions. Four studies qualified for trustworthy conclusions. Among all four, radiosurgery showed the best outcomes: there were no direct mortality, no surgical or anaesthesiological complications, but better facial nerve outcome, better preservation of useful hearing and better quality of life.

**Conclusions:** The available evidence indicates radiosurgery to be the best practice for solitary vestibular schwannomas up to 30 mm in cisternal diameter.

## INTRODUCTION

Vestibular schwannoma, also called acoustic neuroma, is not an uncommon benign brain

## ARTICLE SUMMARY

### Article focus

- Search for the 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.

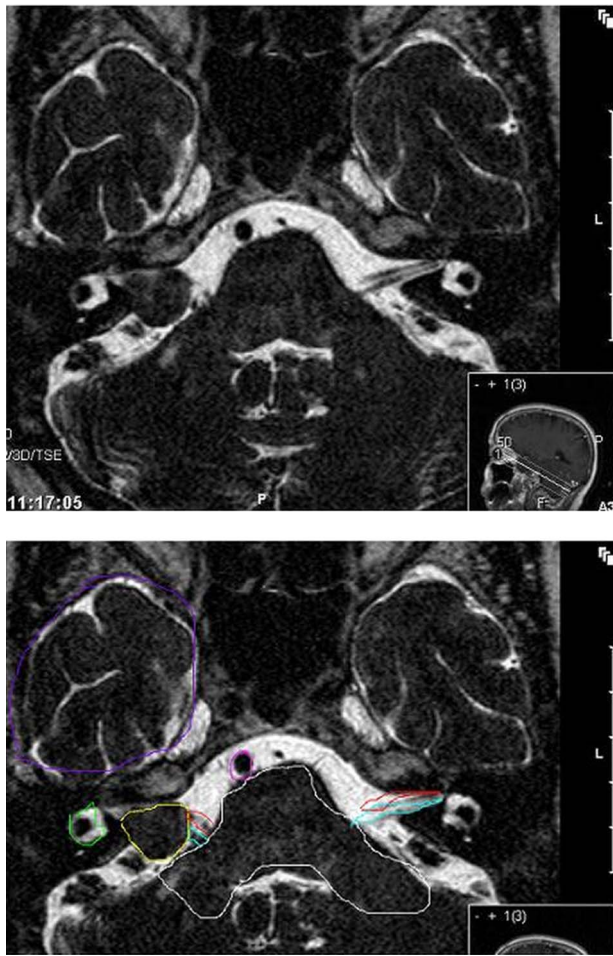
### Key messages

- The literature search yielded cohort studies comparing microsurgery and radiosurgery.
- Quality assessment showed four studies likely to give unbiased results.
- Radiosurgery consistently emerges as the 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 the best practice.
- Patients' outcomes in the assessed comparative studies are in accordance with long-term outcomes in sizeable contemporary case-series.
- The conclusion is limited to solitary vestibular schwannomas smaller than 30 mm.

tumour. It accounts for about 6% of all intracranial tumours.<sup>1</sup> 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.<sup>2</sup> Owing to its benign nature the prevalence accumulates to 200 per million.<sup>3</sup> The tumour originates from the Schwann cells of the vestibular section of the vestibulocochlear nerve at the borders of the central and peripheral myelin, usually slightly lateral to the rim of the internal auditory meatus. A vestibular schwannoma visualises characteristically at MRI (figure 1). In combination with symptoms like asymmetric hearing loss, tinnitus, vertigo or imbalance, the diagnosis is accepted without histological



**Figure 1** Axial T2-weighted MRI with a still visible 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: ipsilateral and contralateral facial nerve; blue: ipsilateral and contralateral vestibulocochlear nerve; white: brainstem and cerebellar peduncle; purple: caudal temporal lobe; pink: basilar artery.

verification. The majority grows slowly or not at all; the average growth is 1–2 mm/year.<sup>4,5</sup> However, if the tumour grows, the rate in the first year is on an average 5–10 mm.<sup>6</sup> There are no parameters known that predict which tumour will grow and to what extent.<sup>7,8</sup>

The mild natural course and relatively minor symptoms—that do not improve by any intervention—justifies for small-sized and medium-sized 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 substantially during the 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-sized 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.*<sup>4</sup>

Understandably, owing to inherent limitations of case series, these reviewers did not arrive at firm conclusions.

In this study, we limit our search for the 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) (see online supplementary 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 13 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 included controlled, intervention study on a 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 enlisted in table 1) (<http://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, annexe C).<sup>9</sup> 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 randomised 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.<sup>10,11</sup> The search retrieved another four retrospective cohort studies with a matched control group, all comparing again microsurgery and radiosurgery.<sup>12–15</sup> We identified no controlled studies involving fractionated stereotactic radiotherapy (figure 2).

**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 <sup>10</sup>	Myrseth 2009 <sup>11</sup>	Pollock 1995 <sup>12</sup>	Myrseth 2005 <sup>15</sup>	Regis 2002 <sup>14</sup>	Karpinos 2002 <sup>13</sup>
Design	Prospective consecutive predefined inclusion criteria	Prospective consecutive predefined inclusion criteria	Retrospective consecutive matched controls	Retrospective consecutive matched controls	Retrospective non-consecutive matched controls	Retrospective consecutive matched controls
Allocation to treat 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<30 mm, no previous intervention	Yes	Yes	Yes	Yes	Yes	<b>No</b>
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 comorbidity	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	<b>No</b>	Yes
Consecutive series and loss to follow-up <10%	Yes	Yes	Yes	Yes	<b>No</b>	<b>No</b>
Adequate analysis drop outs	Yes	Yes	No	Yes	<b>No</b>	<b>No</b>
Outcome assessment						
Prespecified 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	<b>No</b>
Repeated outcome measurement	Yes	Yes	Yes	Yes	Yes	<b>No</b>
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

Continued

Table 1 Continued

Authors and publication year	Pollock 2006 <sup>10</sup>	Myrseth 2009 <sup>11</sup>	Pollock 1995 <sup>12</sup>	Myrseth 2005 <sup>15</sup>	Regis 2002 <sup>14</sup>	Karpinos 2002 <sup>13</sup>
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 judgement	++	++	+	+	-	-
No commercial funding	Yes	Yes	Yes	Yes	Yes	Yes
No relevant bias, outcome owing 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 caused 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 reviews are thought to be 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 exception is the study of Karpinos *et al*,<sup>13</sup> which included recurrent tumours. The indication for an intervention was clearly defined in only one study.<sup>11</sup> 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 comorbidity or high age was permitted in all but the study of Pollock *et al*.<sup>10</sup> 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.<sup>13</sup> 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 interventions and outcomes.<sup>10-12 15</sup> The outcomes are specified in table 3. There was 1% mortality in two microsurgery arms.<sup>14 15</sup> After radiosurgery, there was no mortality and no surgical or anaesthetic complications, but better facial function, better hearing preservation and better quality of life.

## DISCUSSION

Microsurgery and radiosurgery are equally effective interventions for vestibular schwannomas as demonstrated by numerous case series that were recently reviewed.<sup>4</sup> While 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 with that of microsurgery in medium-sized tumours.

Systematic reviews of randomised 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 randomised studies. Indeed, Myrseth *et al*<sup>11</sup> failed to go on with their randomised trials, because patients were reluctant to accept chance to decide whether they would undergo surgery or radiosurgery.<sup>11</sup> Next best evidence is obtained from well-designed non-randomised controlled trials.<sup>16 17</sup> 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 randomised and observational trials.<sup>18-20</sup> Such observational studies may provide trustworthy information on the risks of the intervention, on adverse events and ultimately on the quality of life of patients. Overall, these patients are more

**Table 2** Patients' preintervention characteristics; only sporadic vestibular schwannomas

Author publication year	Intervention included (no.)	Male: Female	Age (years)	n. trigeminal deficit %	n. facial deficit (%)†	Useful hearing (%)‡	Tumour size§ (mean mm)	Previous treatment (%)
Pollock 2006 <sup>10</sup>	MS: 36	19:17	48	0	0	61	14	No
	RS: 46	27:19	54	0	0	65	12	No
Myrseth 2009 <sup>11</sup>	MS: 28	12:16	53	?	0	44	18	No
	RS: 60	36:24*	58	?	0	42	16	No
Pollock 1995 <sup>12</sup>	MS: 40	18:22	51	10	5	12	>20 mm: 18%	No
	RS: 47	23:24	62*	6	2	4	>20 mm: 29%	No
Myrseth 2005 <sup>15</sup>	MS: 86	?	50	20	1	2	>20 mm: 32%	No
	RS: 103	?	60*	12	1	10	>20 mm: 17%	No
Regis 2002 <sup>14</sup>	MS: 110	M 35%	52	55	?	?	KoosIII: 55%§	No
	RS: 100	M 46%	61	20	2	49	KoosIII: 34%	No
Karpinos 2002 <sup>13</sup>	MS: 23	6:17	45	30	26	30	>40 mm: 17*	26
	RS: 73	23:50	62*	17	10	24	>40 mm: 3%	14

MS: microsurgery, RS: radiosurgery.

\*Significant ( $p < 0.05$ ).

†Percentage preserved, House-Brackmann grade 1–2.

‡Useful hearing: AAO-HNS class A–B or Gardner–Robertson grade I–II.

§KoosIII: tumour occupying the cerebellopontine cistern without brainstem displacement.

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 achieved 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 the 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*<sup>13</sup> the source population differed due to inclusion of patients having had earlier surgery for the same disease. 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.<sup>14</sup>

Only Myrseth *et al*<sup>11</sup> clearly defined the starting point of an intervention. 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 by 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.<sup>10</sup> 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 baseline characteristics and an inherent higher risk for adverse events. As mentioned already, this applied to the study of Karpinos *et al*,<sup>13</sup> because the results from first and second interventions were not separated in their report. Frail patients were in all but the study of Pollock *et al*<sup>10</sup> inclined to end up in the radiosurgery arm. In general higher age, comorbidity 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.<sup>12 13 15</sup> As these imbalances work in

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

Author publication ear	Therapy FU (no.)	Follow-up (range)	Mortality (%)	2nd ther. (%)	Facial intact* (%)	% useful hearing†	Other complications‡	Hospital days	Work resume (%)	QoL tests§	QoL (% results)
Pollock 2006 <sup>10</sup>	MS 36 RS 46	3.5 year mean (1–5.2 year)	0	0	83	5	33	?	?	DHI, HS, HSQ	↓ =*
Myrseth 2009 <sup>11</sup>	MS 28 RS 60	≥2 year	0	18	82	0	14	12.5	100	SF36, GBI	SF36= GBI ↑
Pollock 1995 <sup>12</sup>	MS 40 RS 47	3 year median (2.1–4 year)	0	0	78	14	38	2.5	93	ANSPQ	↓45 ↓26
Myrseth 2005 <sup>15</sup>	MS 86 RS 103	5.9 year mean (1–14.2 year)	1	6	80	5	47	9.5	?	SF36, GBI	↓
Regis 2002 <sup>14</sup>	MS 110 RS 97	≥3 year	1	9	67	36	41	1.4	?	Pellet	=* ↓39 ↓9
Karpinos 2002 <sup>13</sup>	MS 18 RS 49	4 year median (0.3–7 year)	0	0	60	40	48	3	88	None	– –

Bold: significantly better.

\*Percentage preserved, House-Brackmann grade 1–2.

†Percentage preserved, AAO-HNS class A–B or Gardner–Robertson grade I–II.

‡Percentage complications as new trigeminal deficit, haemorrhage, cerebrospinal fluid (CSF) leakage, meningitis, wound infection, CSF-shunt needed.

§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.

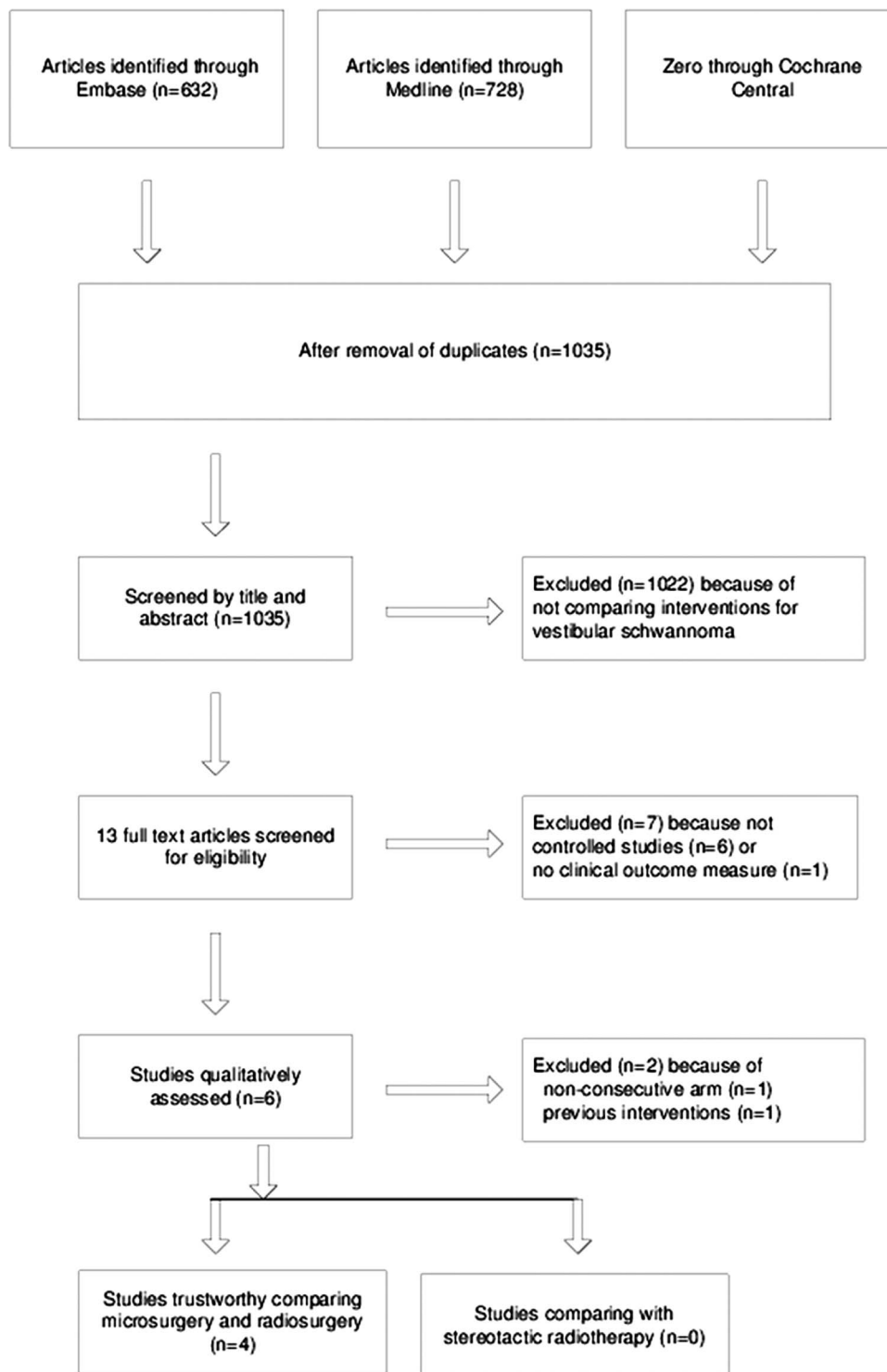
favour of microsurgery, we considered them not relevant (non-bold Nos in table 1).

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 accordance with the long-term outcome in sizeable contemporary radiosurgery series as summarised in online supplementary appendix 2.<sup>21–25</sup> 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 required additional treatment. The rates of facial nerve palsy are as high as 10–30%, varying with tumour size.<sup>4</sup> These numbers are of the same range in the comparative studies on tumours limited to a size of 3 cm 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% and 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.<sup>26</sup>

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 tumours have been reported worldwide.<sup>27</sup> Based on model calculations the probability of a malignant tumour after radiosurgery is estimated at 1 per 1000.<sup>28</sup> Distinctively, the hospital-based study mentioned herein before depicted 2643 surgeries in 265 US hospitals for vestibular schwannoma and showed a 3-month mortality of 0.5%.<sup>26</sup> If radiosurgery is not employed too enthusiastically owing 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 may do so many years later in a patient's life.

Looking for the 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.<sup>29–31</sup> In addition, the comparative studies showed deterioration in the 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 the best practice for patients



**Figure 2** Flow diagram of study selection.

with solitary vestibular schwannoma up to 30 mm in cisternal extension.

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