

# Stereotactic Radiotherapy for Vestibular Schwannoma

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**Mužević, Dario; Legčević, Jelena; Splavski, Bruno; Cayé-Thomasen, Per**

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## Stereotactic radiotherapy for vestibular schwannoma (Review)

Muzevic D, Legcevic J, Splavski B, Cayé-Thomasen P

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[Intervention Review]

## Stereotactic radiotherapy for vestibular schwannoma

Dario Muzevic<sup>1</sup>, Jelena Legcevic<sup>2</sup>, Bruno Splavski<sup>1</sup>, Per Cayé-Thomasen<sup>3</sup>

<sup>1</sup>Department of Neurosurgery, School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia. <sup>2</sup>Department of Methodological and Informatical Sciences, Faculty of Law, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia. <sup>3</sup>Department of Otorhinolaryngology Head and Neck Surgery, Gentofte University Hospital of Copenhagen, Hellerup, Denmark

**Contact address:** Dario Muzevic, Department of Neurosurgery, School of Medicine, Josip Juraj Strossmayer University of Osijek, Josipa Huttlera 4, Osijek, 31 000, Croatia. [dario.muzevic@me.com](mailto:dario.muzevic@me.com).

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### ABSTRACT

#### Background

Vestibular schwannomas (acoustic neuromas) are common benign tumours that arise from the Schwann cells of the vestibular nerve. Management options include observation with neuroradiological follow-up, microsurgical resection and stereotactic radiotherapy.

#### Objectives

To assess the effect of stereotactic radiotherapy compared to observation, microsurgical resection, any other treatment modality, or a combination of two or more of the above approaches for vestibular schwannoma.

#### Search methods

We searched the Cochrane Central Register of Controlled Trials; PubMed; EMBASE; CINAHL; Web of Science; CAB Abstracts; ISRCTN and additional sources for published and unpublished trials. The date of the search was 24 July 2014.

#### Selection criteria

Randomised controlled trials (RCTs) exploring the efficacy of stereotactic radiotherapy compared with observation alone, microsurgical resection or any other possible treatment or combination of treatments in patients with a cerebellopontine angle tumour up to 3 cm in diameter, presumed to be a vestibular schwannoma.

#### Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration.

#### Main results

No studies met the inclusion criteria for this review.

#### Authors' conclusions

There is no high quality evidence in the literature from RCTs to determine whether stereotactic radiotherapy is better than microsurgical resection or observation alone for patients with a vestibular schwannoma. In the absence of such evidence, the treatment method should be chosen on an individual basis, taking into consideration the patient's preferences, clinician experience and the availability of radiotherapeutic equipment. With the growing availability of radiotherapeutic equipment, randomised controlled trials should be undertaken to evaluate the role of stereotactic radiotherapy in comparison with other treatment options.

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## PLAIN LANGUAGE SUMMARY

### **Stereotactic radiotherapy for the treatment of vestibular schwannoma (acoustic neuroma)**

Vestibular schwannomas, also known as acoustic neuromas, are benign tumours of the eighth cranial nerve (responsible for hearing and balance). They can be treated by surgery or stereotactic radiotherapy (precisely delivered, focused brain irradiation), or just kept under observation because they may grow quite slowly or may not grow at all.

We searched the literature in order to find randomised controlled trials (RCTs) that compared stereotactic radiotherapy to other treatment methods. None of the studies we identified met the criteria for inclusion in this review.

There is currently no high quality evidence from RCTs to determine whether any of the treatment options for patients with a vestibular schwannoma have clear advantages over the others. Treatment therefore has to be selected on an individual basis, taking into account the patient's own preferences, clinician experience and the availability of radiotherapeutic equipment. Further research is needed to compare the efficacy and safety of all the different treatment options.

## BACKGROUND

### Description of the condition

Vestibular schwannomas, also known as acoustic neuromas, are benign tumours of Schwann cell origin that occur on the eighth cranial nerve. They represent 5% to 10% of all intracranial tumours (House 1974), and 80% to 90% of tumours of the cerebellopontine angle (Hart 1981).

The incidence of vestibular schwannoma is 2 per 100,000 person-years (Stangerup 2012), and the prevalence is estimated at 2 in 10,000 people (Lin 2005). Several centres have reported an increasing incidence of diagnosed vestibular schwannoma over recent years (Stangerup 2012). These tumours occur with about equal frequency in adult males and females, most frequently in patients between the ages of 30 and 60 years (Stangerup 2012). A minority of patients have central neurofibromatosis, with bilateral tumours.

Commonly presenting symptoms include hearing loss, tinnitus and balance disturbance. Tumour progression can lead to brainstem compression, cranial neuropathies and hydrocephalus (Hansasuta 2011). The diagnosis is established with magnetic resonance imaging (MRI), which can demonstrate tumours as small as a few millimetres. As imaging technology has improved, more small tumours have been diagnosed.

Management options include observation, microsurgical resection and stereotactic radiotherapy (Hansasuta 2011; Varughese 2012).

Observation with neuroradiological follow-up is a management option for vestibular schwannoma, since many of these tumours grow slowly over years, or may not grow at all (Stangerup 2012).

The surgical resection of vestibular schwannoma has been a central feature of neurosurgical practice for more than 100 years (Ramsden 1995), from the pioneering attempts to achieve simple decompression, to the contemporary era, where the function of the eighth and adjacent cranial nerves may be preserved (Sampath 1998). However, while total tumour removal is possible with microsurgical resection in about 95% of patients, normal or near-normal facial nerve preservation is only possible in about 80% on average (Samii 1997), and hearing may be preserved in about 35% to 65% of patients (Battaglia 2006), although these numbers depend highly on tumour size, tumour localisation and the experience of the surgical team.

Stereotactic radiotherapy is a non-invasive technique that delivers high-dose irradiation to small, targeted tissue volumes. The use for vestibular schwannoma was first described by Leksell (Leksell 1971), and it represents an alternative to microsurgical resection in patients with small and moderate size tumours. It has been said that tumours up to 3 cm in diameter, when including the internal auditory canal in the measurement, can be successfully controlled in the majority of patients with this technique (Lederman 1997), although most studies reporting on the control of tumour growth include patients without documented tumour growth before the initiation of treatment.

There is no international consensus regarding the optimal treatment for vestibular schwannoma.

### Description of the intervention

Brain radiotherapy is a procedure in which beams of radiation are converged and targeted at a volume of tissue within the brain. Stereotaxis is an accurate targeting technique for intracranial structures that uses an external reference frame fixed to the head. Stereotactic radiotherapy therefore refers to the non-invasive destruction, by focused irradiation, of a particular intracranial target localised stereotactically.

In 1968, the first 'Leksell gamma unit', or 'gamma knife', was designed at the Karolinska Institute in Stockholm, Sweden. The unit evolved into the commercially available Leksell gamma unit, containing cobalt-60 sources located in a hemispherical array around a common focal point. Stereotactic radiotherapy has become an important treatment option for many patients with intracranial and spinal disorders (Sheehan 2009), ranging from arterial venous malformations to benign and malignant neoplasms (Yu 1997). Targets up to 3 cm in diameter are usually considered suitable for stereotactic radiotherapy.

A typical stereotactic radiotherapeutic procedure begins with the application of the stereotactic head frame under local anaesthesia. A magnetic resonance imaging (MRI) scan is then performed and a radiotherapeutic protocol designed to deliver the radiation dose to the defined target volume. The procedure is usually performed as an outpatient procedure and is well tolerated by the patient, with few patients developing major acute effects (Chao 2012).

### How the intervention might work

Stereotactic radiotherapy works by inducing radiation necrosis in the targeted tissue volume. The desired response is long-term growth control of the tumour (Niranjan 2004).

An observational study by Breivik and colleagues followed 237 patients with vestibular schwannoma for almost five years. One-hundred and thirteen patients received radiotherapy and 124 were managed conservatively. There was a significant reduction in tumour volume over time in the radiotherapy group and the need for additional treatment was reduced, compared to the observed patients, suggesting that vestibular schwannomas can be controlled by radiotherapy (Breivik 2013). As the technique has developed, cranial nerve complications following stereotactic radiotherapy have been significantly reduced by modifications in dose schedules (Noren 1993).

In comparison, a meta-analysis of observation as a management option included 26 studies with 1340 patients in total. Growth of the tumour was observed in 46% of patients, with a mean growth rate of 1.2 mm/year. Subsequent active treatment was required by only 18% of all patients (Yoshimoto 2005).

### Why it is important to do this review

We are unaware of any guidelines on the effectiveness and safety of stereotactic radiotherapy in comparison to observation or microsurgical resection as a management strategy. The best candidates for stereotactic radiotherapy are usually also ideal candidates for microsurgical resection (patients with easily resectable small to moderate size tumours). This dilemma is evident in everyday clinical practice, in centres which can offer stereotactic radiotherapy as an alternative treatment. Furthermore, it is still unclear whether some of these patients

can be managed by observation alone. The limited availability of radiotherapeutic equipment makes decision-making even more complex.

This review is important to facilitate decision-making by clinicians and patients.

## OBJECTIVES

To assess the effect of stereotactic radiotherapy compared to observation, microsurgical resection, any other treatment modality, or a combination of two or more of the above approaches for vestibular schwannoma.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) evaluating the efficacy of stereotactic radiotherapy for vestibular schwannoma. We considered for inclusion all studies, irrespective of publication status or language.

#### Types of participants

Patients, irrespective of gender, age or race, with a cerebellopontine angle tumour up to 3 cm in diameter, presumed to be vestibular schwannoma. We excluded patients who had previously been treated surgically for vestibular schwannoma.

#### Types of interventions

Stereotactic radiotherapy (any protocol, dose or hardware).

We looked for the following comparisons:

- stereotactic radiotherapy versus microsurgical resection;
- stereotactic radiotherapy versus observation;
- stereotactic radiotherapy versus any other possible treatment or combination of treatments.

#### Types of outcome measures

##### Primary outcomes

- Proportion of patients in whom the tumour has not grown and whose symptoms (hearing loss, facial function, tinnitus, balance disturbance) have not deteriorated a) at 12 months, b) at two years, c) in the long term.

##### Secondary outcomes

- Tumour growth.
- Changes in hearing.
- Changes in facial function (assessed using a validated assessment instrument).
- Changes in tinnitus.
- Changes in balance disturbance.
- Quality of life.
- Reported side effects of stereotactic radiotherapy (early, intermediate and late), including the induction of secondary malignancies, peritumoral oedema, hydrocephalus and other cranial nerve neuropathies.

- Reported side effects of microsurgical resection (mortality, postoperative cranial nerve neuropathies, meningitis, cerebrospinal fluid leaks).
- Reported necessity for additional treatment in patients managed by observation.

### Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the search was 24 July 2014.

#### Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; ISRCTN; ClinicalTrials.gov; ICTRP, Google and Google Scholar.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))). Search strategies for major databases including CENTRAL are provided in [Appendix 1](#).

#### Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, we searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. We searched for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

### Data collection and analysis

#### Selection of studies

Two members of the review team independently selected papers and made decisions about eligibility, based on the analysis of the title, abstract or MeSH terms. We resolved all disagreements by discussion and consensus. We contacted the authors of the original papers to get additional data and clarify dubious issues.

#### Data extraction and management

We extracted the relevant data from the selected studies and recorded the data in customised forms. Two members of the review team performed the extraction, after determining the study eligibility. We discussed possible disagreements and if no consensus was reached, resolved them by the inclusion of the third author in the extraction process. We contacted authors of the original articles.

We extracted the following data:

- study design, setting and duration;
- participants;

- sample size;
- inclusion and exclusion criteria;
- details of the experimental intervention (protocol);
- details of the control intervention;
- outcome (the effect of treatment, defined as tumour growth control at the six-month to two-year follow-up);
- presence of ethical approval;
- funding sources;
- conclusions as reported by the authors.

#### Assessment of risk of bias in included studies

No studies were included in the current version of the review. Should studies be included in future updates, will undertake assessment of the risk of bias of the included trials independently by with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011)*:

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in Review Manager (RevMan 5) ([RevMan 2014](#)), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

#### Measures of treatment effect

If studies are included in future versions of review, we will analyse the data using RevMan 5. We will analyse binary data using odds ratio (with 95% confidence interval) and continuous outcomes by calculating means and standard deviations. We will pool scores as continuous variables either using weighted means or standardised means.

#### Unit of analysis issues

The unit of analysis will be the individual patient.

#### Dealing with missing data

Missing summary data will not be a reason to exclude a study from the review. If necessary, we will contact the authors of the original papers for more information on missing data.

#### Assessment of heterogeneity

We will test all included studies for clinical homogeneity. For studies considered to be clinically homogeneous, we will test the statistical heterogeneity using the Chi<sup>2</sup> test and the I<sup>2</sup> statistic. We will assume statistical significance of the Chi<sup>2</sup> test if the P value < 0.10. We will consider an I<sup>2</sup> statistic value greater than 50% to be substantial.

#### Assessment of reporting biases

Aside from within-study biases tested as described in [Assessment of risk of bias in included studies](#), we will assess between-study biases by comparing outcomes stated in protocols to those reported or, where protocols are not available, by comparing outcomes listed in the methods section to those reported in the results section.

#### Data synthesis

We could not perform data synthesis, as no studies are included in present version of the review. If studies can be included in the future updates, we will use RevMan 5 to perform meta-analysis, if we identify a sufficient number of studies ([RevMan 2014](#)). We will use a fixed-effect model for dichotomous data.

#### Subgroup analysis and investigation of heterogeneity

No subgroup analysis is planned.

#### Sensitivity analysis

If necessary, we will perform sensitivity analysis by comparing the primary analysis with analysis of the subgroup of studies that excludes those with unclear or high risk of bias.

## RESULTS

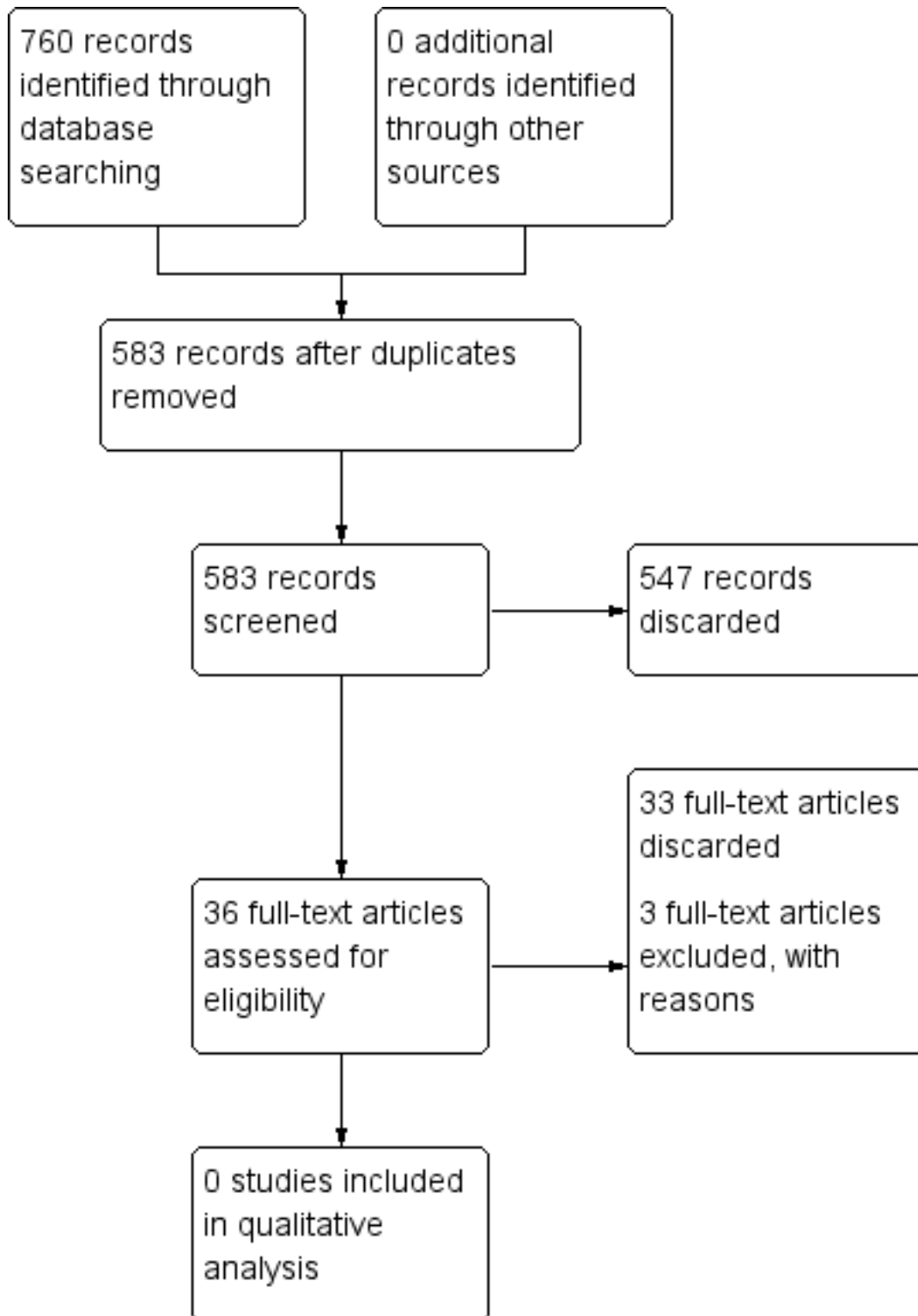
### Description of studies

#### Results of the search

Following a full search on 24 July 2014, we identified 760 studies. Other research sources provided no additional records. When we removed duplicates, 583 studies remained for further selection. Based on the title, abstract and keywords, we selected 36 studies as potentially relevant for the review and obtained them in full text ([Figure 1](#)). We discarded 33 of these studies, following review of the full text. We formally excluded three studies from the review (see [Excluded studies](#)). There are no studies awaiting assessment and we found no ongoing trials.



**Figure 1. Study flow diagram.**



**Included studies**

After we analysed the full-text articles, we found that none of the studies met the inclusion criteria.

**Excluded studies**

See: [Characteristics of excluded studies](#).

We excluded two prospective studies because of the lack of randomisation ([Myrseth 2009](#); [Pollock 2006](#)). Both studies

compared stereotactic radiotherapy with microsurgical resection. In the study by Myrseth et al, patients were allowed to choose treatment, after receiving information about all treatment alternatives (Myrseth 2009). Patients in the study by Pollock et al also chose the treatment after discussion of the options (Pollock 2006). One study was a prospective randomised controlled trial comparing two radiosurgical modalities. It did not report the treatment outcomes required for a study to be included in the review (Régis 2009). It evaluated irradiation time, treatment time, treatment room occupation time, dose-planning parameters, dosimetry measurements on the patient's body, workflow, patient comfort and quality assurance procedures for patients with various intracranial pathologies, 79 of whom had acoustic neuromas. We contacted the authors of this study and they expect to publish data regarding the treatment outcome.

### Risk of bias in included studies

No studies met the inclusion criteria.

### Effects of interventions

No studies met the inclusion criteria.

## DISCUSSION

The wider availability of stereotactic radiotherapy has led to difficulty in choosing the optimal treatment for patients with vestibular schwannoma. While many papers and review articles report satisfactory tumour growth control and few side effects with this method (Arthurs 2011; Mendehall 2004), it is still unclear whether this treatment is superior to microsurgical resection. Furthermore, observation with neuroradiological follow-up may be an equally valid option. Prospective randomised controlled trials comparing all three treatment options are therefore clearly needed.

### Summary of main results

In the present version of the review, we were not able to include any studies, mainly due to lack of randomisation in otherwise well-designed trials (Myrseth 2009; Pollock 2006). A randomised controlled trial comparing two stereotactic radiotherapy techniques has not yet reported any clinical outcome data, however the publication of these data is planned (Régis 2009).

### Quality of the evidence

The main issue we identified with the studies considered for this review was the lack of randomisation. This may be because researchers consider it unethical to design such a trial, because individual patient considerations or preferences render randomisation very difficult or even impossible, because the treatment centres do not master the different treatment modalities equally well, or because the researchers themselves are biased towards one of the treatment options.

Furthermore, the studies we considered usually did not investigate the late side effects of stereotactic radiotherapy, such as the induction of secondary malignancies. This should be done in the assessment of all procedures using irradiation.

### Potential biases in the review process

At present, the only possible bias in the review process could be related to accidentally missing relevant studies. However, we performed an extensive literature search for this review, covering 16 international databases, and our search is up to date to July 2014, so we consider this is highly unlikely.

### Agreements and disagreements with other studies or reviews

There are three recent reviews of the literature on treatment modalities for vestibular schwannoma (Bassim 2010; Gauden 2011; Maniakas 2012). As in this review, no randomised controlled trials were identified. The main body of evidence comes from non-randomised trials or observational studies. Bassim et al concluded that the lack of uniform reporting criteria for tumour control, facial function and hearing preservation, as well as the variability in follow-up times, makes difficult to compare studies of radiation treatment for vestibular schwannoma; they recommend that consideration be given to using standardised reporting guidelines (such as those used in otology) for reporting vestibular schwannoma resection results (Bassim 2010). Gauden et al state that the most common quality of life measure used is the Short Form Questionnaire (SF-36), although it has not been validated for patients with vestibular schwannomas (Gauden 2011). The problem of selecting uniform outcome measures is also evident in our review (Characteristics of excluded studies). All studies emphasise the need for well-designed, randomised prospective research (Bassim 2010; Gauden 2011; Maniakas 2012), which is in concordance with our conclusions.

## AUTHORS' CONCLUSIONS

### Implications for practice

Stereotactic radiotherapy is increasingly used in the management of patients with vestibular schwannomas. However, there is no high quality evidence in the literature to determine whether this treatment option is in any way preferable to microsurgical resection or observation alone. In the absence of such evidence, the treatment method should be chosen on an individual basis, taking into consideration the patient's preferences, clinician experience and the availability of radiotherapeutic equipment.

### Implications for research

With the increased availability of radiotherapeutic equipment, randomised controlled trials should be designed to evaluate the role of stereotactic radiotherapy in comparison with other treatment options for patients with vestibular schwannoma. Since all treatment options are routinely used in everyday practice, there should be no ethical issues in designing such a randomised trial. Studies should be careful to define tumour dimensions, radiation dosage and outcome measurements.

## ACKNOWLEDGEMENTS

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## REFERENCES

### References to studies excluded from this review

#### Myrseth 2009 {published data only}

Myrseth E, Møller P, Pedersen PH, Lund-Johansen M. Vestibular schwannoma: surgery or gamma knife radiosurgery? A prospective, nonrandomized study. *Neurosurgery* 2009;**64**:654-61.

#### Pollock 2006 {published data only}

Pollock BE, Driscoll CLW, Foote RL, Link MJ, Gorman DA, Bauch CD, et al. Patient outcomes after vestibular schwannoma management: a prospective comparison of microsurgical resection and stereotactic radiosurgery. *Neurosurgery* 2006;**58**:77-83.

#### Régis 2009 {published data only (unpublished sought but not used)}

Régis J, Tamura M, Guillot C, Yomo S, Muraciotte X, Nagaje M, et al. Radiosurgery with the world's first fully robotized Leksell Gamma Knife Perfexion in clinical use: a 200-patient prospective, randomized, controlled comparison with the Gamma Knife 4C. *Neurosurgery* 2009;**64**:346-55.

### Additional references

#### Arthurs 2011

Arthurs BJ, Fairbanks RK, Demakas JJ, Lamoreaux WT, Giddings NA, Mackay AR, et al. A review of treatment modalities for vestibular schwannoma. *Neurosurgical Review* 2011;**34**(3):265-79.

#### Bassim 2010

Bassim MK, Berliner KI, Fisher LM, Brackmann DE, Friedman RA. Radiation therapy for the treatment of vestibular schwannoma: a critical evaluation of the state of the literature. *Otology & Neurotology* 2010;**31**(4):567-73.

#### Battaglia 2006

Battaglia A, Mastrodimos B, Cueva R. Comparison of growth patterns for acoustic neuromas with and without radiosurgery. *Otology & Neurotology* 2006;**27**:705-12.

#### Brevik 2013

Brevik CN, Nilsen RM, Myrseth E, Pedersen PH, Varughese JK, Chaudhry AA, et al. Conservative management or gamma knife radiosurgery for vestibular schwannoma: tumor growth, symptoms, and quality of life. *Neurosurgery* 2013;**73**(1):48-56.

#### Chao 2012

Chao ST, Thakkar VV, Bennett GH, Vogelbaum MA, Angelov L, Weil RJ, et al. Prospective study of the short-term adverse effects of gamma knife radiosurgery. *Technology in Cancer Research & Treatment* 2012;**11**(2):117-22.

#### Gauden 2011

Gauden A, Weir P, Hawthorne G, Kaye A. Systematic review of quality of life in the management of vestibular schwannoma. *Journal of Clinical Neuroscience* 2011;**18**(12):1573-84.

#### Handbook 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).

#### Hansasuta 2011

Hansasuta A, Choi CYH, Gibbs IC, Soltys SG, Tse VCK, Lieberman RE, et al. Multisession stereotactic radiosurgery for vestibular schwannomas: single-institution experience with 383 cases. *Neurosurgery* 2011;**69**(6):1200-9.

#### Hart 1981

Hart RG, Davenport J. Diagnosis of acoustic neuroma. *Neurosurgery* 1981;**9**(4):451-63.

#### House 1974

House WF, Hitselberg WE. Acoustic tumors. In: Vinken PJ, Bruyn GW editor(s). *Handbook of Clinical Neurology*. New York: Elsevier, 1974:666-92.

#### Lederman 1997

Lederman G, Lowry J, Wertheim S, Fine M, Lombardi E, Wronski M, et al. Acoustic neuroma: potential benefits of fractionated stereotactic radiosurgery. *Stereotactic and Functional Neurosurgery* 1997;**69**(1-4 Pt 2):175-82.

#### Leksell 1971

Leksell L. A note on treatment of acoustic tumors. *Acta Chirurgica Scandinavica* 1971;**137**:763-5.

#### Lin 2005

Lin D, Hegarty JL, Fischbein NJ. The prevalence of "incidental" acoustic neuroma. *Archives of Otolaryngology - Head and Neck Surgery* 2005;**131**(3):241-4.

#### Maniakas 2012

Maniakas A, Saliba I. Conservative management versus stereotactic radiation for vestibular schwannomas: a meta-analysis of patients with more than 5 years' follow-up. *Otology & Neurotology* 2012;**33**(2):230-8.

#### Mendehall 2004

Mendehall WM, Freidman WA, Amdur RJ, Antonelli PJ. Management of acoustic schwannoma. *American Journal of Otolaryngology* 2004;**25**(1):38-47.

#### Niranjan 2004

Niranjan A, Gobbel GT, Kondziolka D, Flickinger J, Lunsford LD. Experimental radiobiological investigations into radiosurgery: present understanding and future directions. *Neurosurgery* 2004;**55**(3):495-505.

#### Noren 1993

Noren G, Greitz D, Hirsch A, Lax I. Gamma knife surgery in acoustic tumors. *Acta Neurochirurgica (Wien)* 1993;**58**:104-7.

**Ramsden 1995**

Ramsden RT. The bloody angle: 100 years of acoustic neuroma surgery. *Journal of the Royal Society of Medicine* 1995;**88**(8):464P-8P.

**RevMan 2014 [Computer program]**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

**Samii 1997**

Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): the facial nerve-preservation and restitution of function. *Neurosurgery* 1997;**40**:684-94.

**Sampath 1998**

Sampath P, Rhines LD, Goel R, Long DM. Cranial nerve preservation in vestibular schwannoma (acoustic neuroma) surgery. *Critical Reviews in Neurosurgery* 1998;**8**:86-96.

**Sheehan 2009**

Sheehan J, Pouratian N. Stereotactic radiosurgery: quo vadis?. *Neurosurgical Focus* 2009;**27**(6):E1.

**Stangerup 2012**

Stangerup SE, Cayé-Thomasen P. Epidemiology and natural history of vestibular schwannomas. *Otolaryngologic Clinics of North America* 2012;**45**(2):257-68.

**Varughese 2012**

Varughese JK, Breivik CN, Tore WL, Morten LJ. Growth of untreated vestibular schwannoma: a prospective study. *Journal of Neurosurgery* 2012;**116**(4):706-12.

**Yoshimoto 2005**

Yoshimoto Y. Systematic review of the natural history of vestibular schwannoma. *Journal of Neurosurgery* 2005;**103**(1):59-63.

**Yu 1997**

Yu C, Luxton G, Apuzzo M, MacPherson D, Petrovich Z. Extracranial radiation doses in patients undergoing gamma knife radiosurgery. *Neurosurgery* 1997;**41**(3):553-60.

**CHARACTERISTICS OF STUDIES**
**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
<a href="#">Myrseth 2009</a>	ALLOCATION Not randomised
<a href="#">Pollock 2006</a>	ALLOCATION Not randomised
<a href="#">Régis 2009</a>	ALLOCATION Randomised PARTICIPANTS Patients with cerebellopontine tumours, presumed to be acoustic neuromas INTERVENTIONS Patients received gamma knife radiotherapy with Gamma Knife PerfeXion or Gamma Knife 4C equipment OUTCOMES Treatment outcome data not reported

**APPENDICES**
**Appendix 1. Search strategies**

<b>CENTRAL</b>	<b>PubMed</b>	<b>EMBASE (Ovid)</b>
#1 MeSH descriptor Neuroma, Acoustic explode all trees	#1 "Neuroma, Acoustic"[Mesh]	1 exp acoustic neurinoma/
#2 (vestibular or vestibulocochlear or acoustic) and (neuroma* or	#2 ((vestibular OR vestibulocochlear OR acoustic[Title/Abstract])) AND (neuroma* OR neurilemmoma* OR neurilemoma* OR neurinoma* OR tumour* OR tumor* OR schwannoma*[Title/Abstract])	2 ((vestibular or vestibulocochlear or acoustic) and (neuroma* or neurilemmoma* or neurilemoma* or neurinoma* or tumor* or tumour* or schwannoma*)).tw.
neurilemmoma* or neurilemoma* or neurinoma* or tumor* or	#3 (#1 OR #2)	3 1 or 2
tumour* or schwannoma*)	#4 "Radiosurgery"[Mesh]	4 exp radiosurgery/
#3 (#1 OR #2)	#5 radiosurg*[Title/Abstract]	5 "radiosurg*".tw.
#4 MeSH descriptor Radiosurgery explode all trees	#6 "Radiotherapy"[Mesh]	6 exp radiotherapy/
#5 radiosurg*	#7 (radiother* or irradiat*[Title/Abstract])	7 (radiother* or irradiat*).tw.
#6 MeSH descriptor Radiotherapy explode all trees	#8 "Surgical Procedures, Operative"[Mesh]	8 exp surgical technique/
#7 radiother* or irradiat*	#9 "Stereotaxic Techniques"[Mesh]	9 exp stereotactic procedure/
#8 MeSH descriptor Surgical Procedures, Operative explode all trees	#10 (surgery or stereotactic* or stereotaxi* or "gamma knife" or cyberknife or linac[Title/Abstract])	10 (surgery or stereotactic* or stereotaxic* or "gamma knife" or cyberknife or linac).tw.
#9 MeSH descriptor Stereotaxic Techniques explode all trees	#11 ((#6 OR #7) AND (#8 OR #9 OR #10))	11 (6 or 7) and (8 or 9 or 10)
#10 surgery or stereotactic* or stereotaxi* or "gamma knife" or	#12 (#4 OR #5 OR #11)	12 4 or 5 or 11
cyberknife or linac	#13 "Neuroma, Acoustic/surgery"[Mesh]	13 3 and 12
#11 ((#6 OR #7) AND (#8 OR #9 OR #10))	#14 "Neuroma, Acoustic/radiotherapy"[Mesh]	14 exp acoustic neurinoma/su [Surgery]
#12 (#4 OR #5 OR #11)	#15 (#13 AND #14)	15 exp acoustic neurinoma/rt [Radiotherapy]
	#16 (#14 OR #15)	16 14 and 15
		17 13 or 16
<b>CINAHL (EBSCO)</b>	<b>Web of Science (Web of Knowledge)</b>	<b>ISRCTN (mRCT)</b>
S1 (MH "Neuroma, Acoustic+")	#1 TS=((vestibular or vestibulocochlear or acoustic) and (neuroma* neurilemmoma* or neurilemoma* or neurinoma* or tumor* or tumour* or schwannoma*))	((acoustic or vestibular or vestibulocochlear) and
S2 TX (vestibular or vestibulocochlear or acoustic) AND	#2 TS=radiosurg*	(neuroma* or neurinoma* or neurilemmoma* or neurilemoma* or neurinoma* or tumor* or tumour*)) and (radiosurg* or "gamma knife" or cyberknife or linac)
TX (neuroma* or neurilemmoma* or neurilemoma* or tumor* or tumour* or schwannoma)	#3 WC=Radiology, Nuclear Medicine & Medical Imaging	
S3 (S1 or S2)	#4 TS=(radiother* or irradiat*)	
S4 (MH "Radiosurgery+")		

(Continued)

S5 TX radiosurg*	#5 WC=surgery
S6 (MH "Radiotherapy+")	#6 TS=(surgery or stereotactic* or stereotaxic* or "gamma knife" or cyberknife of linac)
S7 TX radiother* or irradiat*	
S8 (MH "Surgery, Operative+")	#7 (#3 or #4) and (#5 or #6)
S9 (MH "Stereotaxic Techniques+")	#8 #2 or #7
S10 TX surgery or stereotactic* or stereotaxi* or "gamma knife" or cyberknife or linac	#9 #1 and #8
S11 (S6 or S7) AND (S8 or S9 or S10)	
S12 S4 or S5 or S11	
S13 S3 and S12	
S14 (MH "Neuroma, Acoustic+/SU")	
S15 (MH "Neuroma, Acoustic+/RT")	
S16 (S14 and S15)	
S17 S13 or S16	

## CONTRIBUTIONS OF AUTHORS

Conceiving, designing and co-ordinating the review: Dario Muzevic (DM), Bruno Splavski (BS)  
 Designing search strategies and undertaking searches: Cochrane Ear, Nose and Throat Disorders Group Trials Search Co-ordinator  
 Screening search results and retrieved papers against inclusion criteria: DM, BS, Jelena Legcevic (JL)  
 Appraising quality of papers: DM, BS, JL  
 Extracting data from papers: DM, BS, JL  
 Writing to authors of papers for additional information: BS  
 Data management for the review and entering data into RevMan 5: DM, BS, JL  
 Analysis and interpretation of data: BS, DM, Per Cayé-Thomasen (PCT)  
 Providing a clinical perspective: BS, PCT  
 Writing the review: DM, BS, JL, PCT  
 Providing general advice on the review: BS, JL, PCT  
 Performing previous work that was the foundation of the current review: DM

## DECLARATIONS OF INTEREST

Dario Muzevic: none known.  
 Jelena Legcevic: none known.  
 Bruno Splavski: none known.  
 Per Cayé-Thomasen: none known.

## SOURCES OF SUPPORT

### Internal sources

- None, Other.

**External sources**

- None, Other.

**INDEX TERMS****Medical Subject Headings (MeSH)**

\*Radiosurgery; Neuroma, Acoustic [\*surgery]

**MeSH check words**

Humans