Evidence report for surgery vs. radiation therapy for treatment of vestibular schwannoma <30 mm in need of definitive treatment

Prepared by EBSCO Information Services

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Content

Part 1 - Scoping

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on June 19, 2019.

Results – Criteria Selection for Critical Appraisal

Population

Inclusion criteria

Adults with unilateral, small-to-medium-sized (<30 mm diameter) vestibular schwannoma for whom the medical care team has decided that definitive treatment is needed based on either unequivocal tumor growth as apparent on MRI scans and/or progressive or intractable symptoms that are amenable to definitive treatment.

Exclusion criteria

Adults with neurofibromatosis type 2 (characterized by near-universal development of bilateral vestibular schwannoma by 30 years of age), prior radiosurgery or microsurgery, large tumors (≥30 mm), or tumors causing brainstem compression or hydrocephalus.

Management Options:

Surgery

Surgery to remove the tumor

Radiation therapy

Radiation therapy delivers radiation to the tumor to halt its growth. This may include either stereotactic radiosurgery or stereotactic radiotherapy.[1]

[1] A recent systematic review aimed to compare the effects of single-fraction stereotactic radiosurgery vs. fractionated stereotactic radiotherapy; however, it found no controlled studies and included only case series (17 on single-fraction stereotactic radiosurgery and only 2 on fractionated stereotactic radiotherapy) from which no reliable conclusions could be drawn about relative effects (Persson 2017). Two recent systematic reviews considered 'radiation' a single entity and grouped together single-fraction stereotactic radiosurgery and fractionated stereotactic radiotherapy in comparing 'radiation' vs. surgery (Liu 2015; Papatsoutsos 2017); one of these systematic reviews noted that there is no clear advantage of one over the other (Liu 2015).

Outcomes

FAQ 1: What does the treatment involve?

Include a description of the treatment or procedure. Include frequency of dosing, duration of treatment, length of stay, and frequency and duration of monitoring as applicable.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 2: Will the treatment control the tumor?

Outcome of interest is tumor control based on no change or regression of tumor volume (diameter) during follow-up.

There are no randomized trials comparing surgery vs. radiation therapy in patients with vestibular schwannoma. This outcome will be assessed using cohort studies (ideally prospective) with adequate follow-up.

FAQ 3: Will the treatment make me feel better?

Outcome of interest is quality of life (general and/or disease-specific) at long-term follow-up.

There are no randomized trials comparing surgery vs. radiation therapy in patients with vestibular schwannoma. This outcome will be assessed using cohort studies (ideally prospective) with adequate follow-up.

FAQ 4: Will the treatment preserve my useful hearing?

Outcome of interest is preservation of useful hearing at long-term follow-up (among patients with useful hearing at time of diagnosis).

There are no randomized trials comparing surgery vs. radiation therapy in patients with vestibular schwannoma. This outcome will be assessed using cohort studies (ideally prospective) with adequate follow-up.

FAQ 5: Will the treatment preserve my facial nerve function?

Outcome of interest is good facial nerve function at long-term follow-up.

There are no randomized trials comparing surgery vs. radiation therapy in patients with vestibular schwannoma. This outcome will be assessed using cohort studies (ideally prospective) with adequate follow-up.

FAQ 6: Will I have tinnitus (ringing, clicking, or buzzing in the ears) after treatment?

Outcome of interest is post-treatment tinnitus.

There are no randomized trials comparing surgery vs. radiation therapy in patients with vestibular schwannoma. This outcome will be assessed using cohort studies (ideally prospective) with adequate follow-up.

FAQ 7: What are the risks?

Potential post-surgical complications to be considered include mortality, hearing loss following surgery, facial weakness following surgery, neurological deficit, cerebrospinal fluid leak, infection, and vascular complications. These outcomes will be assessed using observational studies.

Potential radiation-induced complications to be considered include facial weakness following surgery, hydrocephalus, radiation-induced malignancy, and declining hearing over time. These outcomes will be assessed using observational studies if there are available data; otherwise, descriptive responses will be used.

FAQ 8: How long does it take to recover?

Outcomes of interest are time to return to usual activity, time to return to work, and time to return to driving.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

Part 2 - Search and Selection

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve original study tracing from systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

FAQ Summary

Results

First-round searching – DynaMed Plus:

DynaMed Plus subsection	Relevant for FAQ(s)	Number of article citations	Number of unique references included
Vestibular schwannoma topic, Management section, Surgery and procedures subsection, Efficacy of microsurgery subsection, Comparing microsurgery to stereotactic radiation therapy subsection (June 21, 2019)	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	3	2 (Papatsoutsos 2018, Nuño 2019)
Vestibular schwannoma topic, Prognosis section, Quality of life subsection (June 21, 2019)	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6*	1	1 (Carlson 2015)
Vestibular schwannoma topic, Management section, Surgery and procedures subsection, Complications subsection (June 21, 2019)	FAQ4, FAQ5, FAQ6, FAQ7*	3	1 (Sughrue 2011)

* FAQs in addition to the FAQ most clearly dedicated to the subsection in consideration (e.g., FAQ7 for complications, FAQ3 for quality of life) are listed because literature may report certain outcomes as part of operationalizing the given construct.

Second-round searching – searches for intervention-specific systematic reviews:

Database	Search string	Relevant for FAQ(s)	Number of search results	Number of references included
PubMed, June 21, 2019	(vestibular schwannoma*[tiab] OR acoustic neuroma*[tiab]) AND (systematic[sb] OR "decision analysis"[tiab] OR "decision-analytic* model"[tiab] OR "decision analytic* model"[tiab]) AND ("2005/01/01"[PDAT] : "3000/12/31"[PDAT])	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	68	6 (Coughlin 2018, Papatsoutsos 2018*, Ahsan 2017, Liu 2015, Whitmore 2011, Sughrue 2009)

* Already identified in first-round searching

Third-round searching – original study tracing from systematic reviews:

Source	Tracing	Relevant for FAQ(s)	Number of search results	Number of references included
Liu 2015	Individual prospective cohort studies investigating microsurgery vs. stereotactic radiotherapy or radiosurgery	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	3	3 (Myrseth 2009, Pollock 2006, Régis 2002)
Papatsoutsos 2017	Individual prospective cohort studies investigating microsurgery vs. stereotactic radiotherapy or radiosurgery	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	3	3 (Di Maio 2009, Myrseth 2009*, Pollock 2006*)

* Already included via tracing of Liu 2015

Fourth-round searching – searches for original evidence reports:

Database	Search string	Relevant for FAQ(s)	Number of search results	Number of references included
PubMed, July 1, 2019	(vestibular schwannoma*[tiab] OR acoustic neuroma*[tiab]) AND (radiosurgery[tiab] OR radiation[tiab] OR radiotherapy[tiab]) AND (microsurgery[tiab] OR surgery[tiab] OR surgical[tiab]) AND prospective*[tiab] AND ("2014/04/01"[PDAT] : "3000/12/31"[PDAT])	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	29	0

Part 3 - Critical Appraisal of Evidence Reports

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.
-

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

FAQ Summary

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Characteristics and Results of Critically Appraised Studies/Sources

Below is a template for study summaries. At each major level, the intended content is a high-level statement (e.g., "Systematic review and meta-analysis of randomized controlled trials" for the item "Study design"). If there is a need to indicate additional relevant information, do so with a sub-bullet under the parent item. For instance, if downgrading once for "Risk of bias", one would comment "Serious concern" for the "Risk of bias" domain, and then using sub-bullets under the "Risk of bias" item, one would comment on the limitations that resulted in the serious concern. A template is included below, followed by an example summary.

AHSAN 2017
Ahsan SF, Huq F, Seidman M, Taylor A. Long-term Hearing Preservation After Resection of Vestibular Schwannoma: A Systematic Review and Meta-analysis. Otol Neurotol. 2017 Dec;38(10):1505-1511. PubMed

This systematic review was identified in second-round searching. It was not summarized because it evaluated long-term hearing preservation (FAQ4), an outcome for which we had pre-specified preferentially using prospective cohort studies, and this systematic review included only 10 retrospective studies.

CARLSON 2015
Carlson ML, Tveiten OV, Driscoll CL, Goplen FK, Neff BA, Pollock BE, Tombers NM, Castner ML, Finnkirk MK, Myrseth E, Pedersen PH, Lund-Johansen M, Link MJ. Long-term quality of life in patients with vestibular schwannoma: an international multicenter cross-sectional study comparing microsurgery, stereotactic radiosurgery, observation, and nontumor controls. J Neurosurg. 2015 Apr;122(4):833-42.

Relevant to FAQ3, FAQ4, FAQ5

- **Study design:** observational study
    - cross-sectional study using postal questionnaires to assess long-term quality of life among all patients with sporadic small- to medium-sized (< 3 cm) vestibular schwannomas who had microsurgery, radiosurgery, or observation between 1998 and 2008 at 2 academic referral centers
        - 79% response rate
- **Population:** all patients with sporadic small- to medium-sized (< 3 cm) vestibular schwannomas who had microsurgery, radiosurgery, or observation between 1998 and 2008 at 2 academic referral centers
- **Intervention:** microsurgery
- **Comparison:** radiosurgery
    - appeared to be limited to patients who had stereotactic radiosurgery modality (and to not include patients with stereotactic radiotherapy)

- **Study inclusion criteria:**
    - patients with neurofibromatosis Type 2, prior microsurgery or radiosurgery, tumors > 3 cm, or aged < 18 years were excluded

- **Number of studies:** 1
- **Number of participants:** 391
    - 391 patients included in relevant comparison of microsurgery (n = 144) vs. radiosurgery (n = 247)
- **Duration of follow-up:** mean 7.7 years for microsurgery group and 7.3 years for radiosurgery group (not significantly different)

- **Results:**
    - Note: A brief summary of Carlson 2015 has been prepared because it is a large and well-cited study so there may be an expectation of its inclusion in Part 3 with a brief description. However, because it used a retrospective cohort design and we pre-specified in our scoping document a preference for prospective cohort studies for the relevant FAQs it addresses (FAQs 3, 4, and 5), we did not assign certainty ratings, and we do not further assess it for Parts 4 or 5.

Effects of microsurgery vs. radiosurgery on hearing and facial function

Group	Proportion with ipsilateral serviceable hearing prior to treatment*†	Proportion with useful hearing preserved at last follow-up‡	Proportion with good facial function at last follow-up§
microsurgery	60%	14%	90%
radiosurgery	48%	40%	98%

* Defined as American Academy of Otolaryngology-Head and Neck Surgery Class A or B.
† Significant difference between groups in pairwise comparison (p = 0.021).
‡ Significant difference between groups in pairwise comparison (p < 0.001).
§ Good facial nerve function defined as House-Brackmann Grades I and II; significant difference between groups at last follow-up in pairwise comparison (p < 0.001) and no significant differences between groups in facial function prior to treatment. Consistent results with PANQOL facial questionnaire scores which also significantly favored radiosurgery compared to microsurgery.

Effects of microsurgery vs. radiosurgery on quality of life measures (all Low Certainty)
For these measures, the authors reported only mean (median; IQR) data for the individual groups (no estimates of between-group differences were provided, only p values for between-groups comparisons). We report the individual group values where the differences between groups were deemed significantly different, but we emphasize that actual reporting of estimates of between-group differences is strongly preferred. Where we present individual group values, they are presented as: mean (median; IQR).

10-item Patient-Reported Outcomes Measurement Information System short form (PROMIS-10) – no significant difference between groups in either physical or mental components
Penn Acoustic Neuroma Quality-of-Life (PANQOL) scale

- PANQOL total - microsurgery associated with significantly worse scores (p = 0.004)
    - microsurgery: 65 (67; 50–81)
    - stereotactic radiosurgery: 70 (71; 57–84)
- PANQOL components

- microsurgery associated with significantly worse scores in
  - PANQOL facial ($p < 0.001$)
    - microsurgery: 76 (75; 58–100)
    - stereotactic radiosurgery: 86 (100; 75–100)
  - PANQOL balance ($p < 0.001$)
    - microsurgery: 62 (63; 42–83)
    - stereotactic radiosurgery: 68 (71; 50–92)
  - PANQOL pain ($p = 0.018$)
    - microsurgery: 64 (75; 25–100)
    - stereotactic radiosurgery: 76 (100; 50–100)
- no significant differences in
  - PANQOL physical
  - PANQOL mental
  - PANQOL anxiety
  - PANQOL general
  - PANQOL hearing
  - PANQOL energy

Glasgow Benefit Inventory (GBI)

- GBI total - microsurgery associated with significantly worse scores ($p < 0.001$)
  - microsurgery: −12 (−11; −25 to 0)
  - stereotactic radiosurgery: 0 (0; −8 to 6)
- GBI components - microsurgery associated with significantly worse scores in
  - GBI general ($p < 0.001$)
    - microsurgery: −18 (−13; −38 to 0)
    - stereotactic radiosurgery: −1 (0; −13 to 8)
  - GBI social ($p = 0.027$)
    - microsurgery: 12 (0; 0–33)
    - stereotactic radiosurgery: 8 (0; 0–17)
  - GBI physical ($p < 0.001$)
    - microsurgery: −15 (−17; −33 to 0)
    - stereotactic radiosurgery: −5 (0; −17 to 0)

36-Item Short Form Health Survey (SF-36) - no significant difference between groups in either physical or mental components

COUGHLIN 2018

Coughlin AR, Willman TJ, Gubbels SP. Systematic Review of Hearing Preservation After Radiotherapy for Vestibular Schwannoma. Otol Neurotol. 2018 Mar;39(3):273-283. PubMed

This study was identified in second-round searching. It was not summarized because it evaluated long-term hearing preservation (FAQ4), an outcome for which we had pre-specified preferentially using prospective cohort studies, and of the 47 studies included in this systematic review, there were only 4 single-institution, single arm prospective studies and one two-institution study (juxtaposition of this study's discussion implies it is prospective, but this is not explicitly stated), and the systematic review does not give an indication which studies these were (precluding further consideration of these studies).

DI MAIO 2009
Di Maio S, Akagami R. Prospective comparison of quality of life before and after observation, radiation, or surgery for vestibular schwannomas. J Neurosurg. 2009 Oct;111(4):855-62. PubMed

Relevant to FAQ3, FAQ4, FAQ5, FAQ6

- **Study design:** observational study
  - prospective cohort study
  - response rate for SF-36 and custom questionnaires reported to be 77.7%
- **Population:** patients with unilateral vestibular schwannomas
  - patients had either observation, radiosurgery, or microsurgery
  - treatment recommended if
    - tumor growth was documented
    - patient was sufficiently symptomatic
    - tumor growth was sufficiently large at diagnosis
      - patients with larger vestibular schwannomas (> 3 cm in maximum diameter) were treated surgically
      - patients with small-to-medium-sized tumors and meeting treatment criteria above were referred to either surgery or radiation; only the outcomes specific to surgery patients with small-to-medium-sized tumors were extracted
- **Intervention:** microsurgery
  - microsurgery was performed by 1 neurosurgeon
- **Comparison:** radiosurgery
  - radiosurgery was delivered by team of 2 neurosurgeons and 3 radiation oncologists
  - type of radiosurgery was either fractionated stereotactic radiotherapy or LINAC stereotactic radiosurgery

- **Study inclusion criteria:** no additional

- **Number of studies:** 1
- **Number of participants:** 145
  - 145 patients considered for the microsurgery vs. radiation treatment comparison
    - 48 with radiation treatment
      - fractionated stereotactic radiotherapy (n = 23)
      - LINAC stereotactic radiosurgery (n = 25)
    - 97 with microsurgery among patients with tumors $\leq$ 3 cm in diameter
  - total number of patients in study was 264, with completed questionnaires from 229 patients (including additional observation group patients [n=47] and microsurgery patients with tumors > 3 cm in diameter [n = 37])
- **Duration of follow-up:** mean 31.8 months overall
  - mean 36.4 (range 1 to 84) months for radiosurgery group
  - mean 32.3 (range 3 to 72) months for microsurgery group patients with tumors $\leq$ 3 cm

- **Results and Certainty:**
  - comparing microsurgery vs. radiosurgery at baseline
    - microsurgery patients were significantly younger (48.6 [range 23.4 to 67.4] vs. 60.0 [range 19.3 to 80.3] years old, $p < 0.001$)

- no significant differences between groups in symptoms (including tinnitus, useful hearing, and dizziness) or quality of life measures

Effects of microsurgery vs. radiosurgery on tinnitus, useful hearing, dizziness, and facial weakness at last follow-up

Group	Proportion with outcome at last follow-up*†				Certainty (downgrade [applies to all 4 outcomes])
	tinnitus	useful hearing‡	dizziness	facial weakness§	
microsurgery (tumor ≤ 3 cm)	76.1% (54/71)	15.9% (11/69)	42.9% (30/70)	24.3% (17/70)	Very low (risk of bias [cohort study], imprecision)
radiosurgery	75.7% (28/37)	8.1% (3/37)	35.1% (13/37)	27.0% (10/37)	

* tinnitus, dizziness, and facial weakness outcomes were self-reported outcomes, assessed based on a custom questionnaire created by the study authors
† no significant difference between groups for any outcome below (no confidence intervals provided; only significance testing)
‡ reported to be based on American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria (speech reception threshold ≤ 50 dB; speech discrimination score ≥ 50%); corresponds to AAO-HNS Hearing Class A or B
§ defined as having "some element of facial weakness" based on custom questionnaire created by the study authors

- **Quality of life outcomes – within group changes on SF-36 total as well as its composite physical and mental dimensions (no between-group differences reported)**
  - **Results**
    - at 2 years
      - microsurgery group associated with significant improvement from baseline in SF-36 total and mental dimension scores
      - no significant changes from baseline in radiosurgery group in any of the measures
    - at last follow-up
      - no significant changes from baseline for either group in any of the measures
  - **Certainty**
    - Very low
    - Downgrades for risk of bias (cohort study) and inconsistency (inconsistent results at 2 years vs. last follow-up)

LIU 2015
Liu W, Ni M, Jia W, Zhou D, Zhang Q, Jiang Y, Jia G. How to Address Small- and Medium-Sized Acoustic Neuromas with Hearing: A Systematic Review and Decision Analysis. World Neurosurg. 2015 Aug;84(2):283-291.e1. doi: 10.1016/j.wneu.2015.03.013. Epub 2015 Mar 17. PubMed

Relevant to FAQ2, FAQ4, FAQ7

- **Study design:** systematic review of prospective observational studies
    - for the comparison of radiosurgery and microsurgery, review authors limited to prospective studies and noted that they excluded 5 retrospective studies that had heterogeneous results and higher risks of bias
- **Population:** patients with vestibular schwannomas with tumors ≤ 3.0 cm in diameter or stages I, II, or III based on Koos classification and useful residual hearing; no major tumor-related symptoms other than hearing impairment and tinnitus
    - tumor size eligibility criteria in 3 included prospective studies comparing microsurgery vs. radiosurgery were < 3 cm, < 2.5 cm, and Koos stage II (tumor extension to external auditory canal, < 20 mm) & III (tumor extension to external auditory canal, < 30 mm or touching the brainstem without causing compression)
- **Intervention:** microsurgery
- **Comparison:** radiosurgery
    - radiosurgery approaches as defined by Liu 2015 included gamma knife, fractionated stereotactic radiotherapy, and linear accelerator radiosurgery
        - the term “radiosurgery” does not typically include radiotherapy, but the authors used this collective term in their review, and the authors noted that there is no clear advantage of one radiosurgery approach vs. another as justification for including all modalities in their review

- **Study inclusion criteria:**
    - inclusion criteria included retrospective studies, but review authors assessed them as not useful and excluded them to focus on the better-quality prospective studies
    - mean follow-up of > 2 years
    - > 20 cases
    - extractable data

- **Number of studies:** 3
    - the comparison of microsurgery vs. radiosurgery was limited to 3 prospective studies (Pollock 2006; Myrseth 2009; Régis 2002)
    - all 3 prospective cohort studies were included in the pooled analysis summarized below for the outcomes useful hearing preservation, tumor control rate, and complications
- **Number of participants:** 377
    - microsurgery = 174, radiosurgery group = 203
- **Duration of follow-up:** 24 months, 42 months, and 48 months in the 3 studies

- **Certainty and Results:**

Effects of microsurgery vs. radiosurgery on useful hearing preservation, tumor control rate, complications, and serious complications

Intervention	Pooled proportion with useful hearing at time of diagnosis*	Pooled proportion with useful hearing preserved*†	Pooled tumor control rate‡	Pooled compli-cations*§	Pooled serious compli-cations¶
microsurgery	65.5%	4.3%	94.3%	8.5%	2%
radiosurgery	50.7%	60.2%	97.0%	2%	1%

*Significant differences between groups (confidence intervals not reported; only p values).

† Proportion of patients with preservation of useful hearing at long-term follow-up among patients with useful hearing at time of diagnosis. Useful hearing defined as Gardner and Robertson Scale I or II or American Academy of Otolaryngology-Head and Neck Surgery class A or B.

‡ Defined as no change or regression of tumor volume (diameter) during follow-up.

§ Defined as $\geq$ 1 of following: facial nerve function worse than House-Brackmann grade of 1 or 2; cerebrospinal fluid leak, meningitis, or hydrocephalus that occurred after interventions; and survival with severe vertigo, unsteadiness, chronic headache, and tinnitus that was worse than when the status was diagnosed. Overall complications was reported as number with complications in each arm of each of 3 studies and as proportion in pooled analysis. It is not clear how authors calculated their pooled proportions. For example, pooled proportions for microsurgery and radiation therapy were reported as 8.5% and 2% respectively, but we calculated these to be 11.5% and 3.4% respectively based on numbers with Complications in each of the 3 studies and assuming all patients in study were included in this analysis as suggested by Table 2 (so it may be that denominators for this analysis did not include all patients in the 3 studies). In Table 3 footnote, the authors reported that the complications outcome showed significant difference but it was not entirely clear what comparison was being referred to (although it appeared to be the microsurgery vs. radiosurgery comparison) and it was not clear what data was used to evaluate whether the results were significant. To confirm this significant difference, the numbers with complications in each of the 3 studies was entered into RevMan using the number of patients in the study as the denominators and this pooled analysis showed a significant increase in complications with microsurgery compared to radiation therapy (risk ratio 3.29 [1.45, 7.45]; p = 0.004).

¶ Defined as life-threatening complications or death; only reported as proportion in pooled analysis, and not for each of the 3 includes studies.

- **Certainty by outcome**: Moderate for the comparison of proportion with useful hearing preserved; Very low for the comparison of tumor control rate, complications, and serious complications
    - **Risk of bias:** Serious concern for all outcomes (no randomization)
    - **Precision:** Serious concern for tumor control rate and for complications; Very serious concern for serious complications
    - **Directness:** no serious concerns
    - **Consistency:** no serious concerns
- **Other considerations: Increase in certainty for comparison of proportion with useful hearing preserved based on large effect size**
    - An additional prospective cohort study (Di Maio 2009) not included in the comparison of microsurgery vs. radiosurgery in Liu 2015 was included in Papatsoutsos 2018 (as 1 of the 3 prospective cohort studies contributing to the quality of life outcome) and it was briefly summarized in the Discussion section of Carlson 2015. It has been summarized in Part 3 (above). Of the outcomes from Liu

2015 summarized in the table directly above, only a hearing-related outcome was also reported in Di Maio 2009. However, the Di Maio 2009 hearing-related outcome cannot be integrated with the 'pooled proportion with useful hearing preserved' outcome reported by Liu 2015 because the Liu 2015 outcome restricts to patients with useful hearing at baseline but Di Maio 2009 only reported proportion with useful hearing at baseline and proportion with useful hearing at last follow-up (but not proportion with useful hearing at follow-up among those with useful hearing at baseline, or a way to calculate this). The hearing outcome reported in Di Maio 2009 showed no significant differences between groups. Di Maio 2009 did not report the tumor control rate outcome.

- Considerations about Liu 2015 including Régis 2002 are in Régis 2002 summary (below)

MYRSETH 2009

Myrseth E, Møller P, Pedersen PH, Lund-Johansen M. Vestibular schwannoma: surgery or gamma knife radiosurgery? A prospective, nonrandomized study. Neurosurgery. 2009 Apr;64(4):654-61. PubMed

Relevant to FAQ3, FAQ5, FAQ6, FAQ7

- **Study design:** observational study
  - prospective cohort study
- **Population:** patients with unilateral vestibular schwannomas with diameter ≤ 2.5 cm who were to have treatment either because documented tumor growth or tumor > 2 cm diameter
  - patients chose between microsurgery and radiosurgery
- **Intervention:** microsurgery
  - surgery was performed by team comprised of 1 or 2 neurosurgeons and 1 otosurgeon
- **Comparison:** radiosurgery
  - gamma knife radiosurgery
- **Study inclusion criteria**: vestibular schwannoma had to be *de novo* (not a recurrence) and could not be related to neurofibromatosis type 2

- **Number of studies:** 1
- **Number of participants:** 91
  - 3 patients in radiosurgery group withdrew from study before first follow-up exam and were excluded from analysis, leaving 88 patients analyzed
- **Duration of follow-up:** 2 years
  - all 88 patients completed follow-up at 2 years
    - 60 in radiosurgery group
    - 28 in microsurgery group
- **Results and certainty:**
  - note: hearing outcome not included in this summary, as it was captured by Liu 2015
  - comparing microsurgery vs. radiosurgery at baseline
    - no difference between groups on hearing ability, complaints, or any of the components of the SF-36 or Glasgow Benefit Inventory
    - all patients had normal (HB Grade 1) facial function
    - mean age non-significantly lower in microsurgery group (52.5 [range 26 to 73] vs. 57.5 [range 36 to 79]; p = 0.06)

Comparing microsurgery vs. radiosurgery on facial function and tinnitus at 2 years

	Facial function		
Group	**% (n/N) with good facial function at two years (House-Brackmann Grade 1 or 2)***	**% (n/N) with reduced facial function at two years (House-Brackmann Grade 2, 3, 4, 5, or 6)****	**Tinnitus (patient-reported as Y/N)*****
Microsurgery	82.1% (23/28)	46.4% (13****/28)	66.7% (40/60)
Radiosurgery	98.3% (59/60)	1.6% (1*****/60)	83.1% (23/28)
Certainty for comparison (reason for downgrade)	Low (risk of bias [cohort study])	Moderate (risk of bias [cohort study] but large effect size)	Very low (risk of bias [cohort study], imprecision)

*p value comparing these 2 proportions not reported in publication but calculated to be p = 0.0053.
**p value comparing groups at 2-years reported as p = 0.0009, although this p-value appeared to refer to a comparison of the distribution of House-Brackmann scores between groups, rather than comparison of proportion with any reduced facial function at 2 years. p-value comparing proportion with any reduced facial function at 2 years calculated to be p < 0.0001.
***reported as no significant difference between groups; number of patients assessed for tinnitus outcome not reported but assumed to be all included patients.
**** in 8 of 13 cases, effect was mild and classified as HB grade 2.
*****1 patient needed retreatment with surgery because of growing tumor and following surgery the patient had a complete palsy assessed as HB grade 5 at 2 years.

Quality of life outcomes at 2 years

- **Results**
  - SF-36
    - no significant within group changes from baseline to 2 years for either group in any of SF-36 components
    - between group differences not reported
  - Glasgow Benefit Inventory
    - Results text reported that for GBI "There was no significant difference between groups in any of the SF-36 or GBI paradigms at baseline. When comparing SF-36 paradigms at 1 or 2 years with baseline for each group, no significance or any trend toward a better or a worse outcome was found for either treatment group (Fig. 2). For GBI, there was a nonsignificant trend toward better scores in the GKRS [radiosurgery] group at 1 year. At 2 years, significant better outcomes in the GKRS group were found among the general, physical, and total scores; the latter 2 were positive in the GKRS group and negative in the microsurgical group (Fig. 3; Table 7)."
    - Discussion notes "QOL in the GKRS group was significantly better than for the surgical group 2 years after treatment when evaluated by the GBI questionnaire, but a significant difference was not found using the SF-36 questionnaire."
    - Results text and table 7 difficult to interpret (unclear whether reporting within- or between-group comparisons)
    - No significant differences in social component of GBI
- **Certainty**
  - Very low

- Downgrade for risk of bias (cohort study) and inconsistency (inconsistent results on SF-36 vs. Glasgow Benefit Inventory)

Perioperative complications

- **Results**
  - 4 cases in surgery group including
    - 2 cerebrospinal fluid leaks requiring reoperation
    - 1 asymptomatic small hematoma in the resection cavity found on the computed tomographic scan, and
    - 1 case of hoarseness resolving in a few weeks
  - no complications related to procedure in radiosurgery group

- **Certainty**
  - Very low
  - certainty downgrades for risk of bias (cohort study) and serious imprecision for each adverse event listed above

NUÑO 2019

Nuño M, Ugiliweneza B, Boakye M, Monfared A. Morbidity of Vestibular Schwannomas as Documented by Treating Providers. Otol Neurotol. 2019 Feb;40(2):e142-e149. PubMed

Relevant to FAQ7

- **Study design:** observational study
  - retrospective analysis of largest available database in the United States of patients having treatment for vestibular schwannomas
  - data recorded by treating providers for billing purposes
- **Population:** adults with vestibular schwannomas having microsurgery or radiosurgery for vestibular schwannomas between 2002 and 2012
  - size of tumor not reported
- **Intervention:** microsurgery
  - 60.5 % had microsurgery (n = 2,029)
- **Comparison:** radiosurgery
  - 39.5% had radiosurgery (n = 1,326)

- **Study inclusion criteria:** no additional

- **Number of studies:** 1
- **Number of participants:** 3,355
  - microsurgery = 2,029, radiosurgery = 1,326
- **Duration of follow-up:** mean 29.1 (SD 24.2) months before treatment and mean 39.2 (SD 30.5) months after treatment
- **Results and certainty:**
  - at time of diagnosis, microsurgery patients had significantly greater rates of following comorbidities
    - anemia (5.2% vs. 3.3%, p = 0.0107)
    - cardiac abnormalities (10.9% vs. 6.2%, p < 0.0001)

- hypertension (34.1% vs. 27.5% p < 0.0001)
- pulmonary abnormalities (7.9% vs. 5.1%, p = 0.0014)
- tobacco use (6.2% vs. 2.4%, p < 0.0001)
- any of above (or diabetes mellitus or hypothyroidism) (53.8% vs. 43.0%, p < 0.0001)

- 3-months before treatment, microsurgery patients had significantly greater rates of following symptoms
  - hearing loss (59.8% vs. 46.8%, p < 0.0001)
  - vertigo (26.2% vs. 18.1%, p < 0.0001)
  - tinnitus (20.0% vs. 16.7%, p = 0.0177)
  - facial weakness (3.2% vs. 1.7%, p = 0.0114)
  - fatigue (0.4% vs. 1.3%, p = 0.0035)
  - memory difficulty (0.3% vs. 0.8%, p = 0.0312)

Comparing microsurgery vs. radiosurgery on symptoms reported at 6 months post-treatment*

Variables	Type of treatment		Microsurgery vs. radiosurgery (p-values)	Certainty (reason for downgrade)
	microsurgery n (%) (n = 2,029)	radiosurgery n (%) (n = 1,326)		
Hearing loss	1,605 (79.1)	851 (64.2)	p < 0.0001	Very low (risk of bias [cohort study], indirectness†)
Tinnitus	94 (4.6)	50 (3.8)	p = 0.2284	Very low (risk of bias [cohort study], indirectness†)
Vertigo	306 (15.1)	125 (9.4)	p <0.0001	Very low (risk of bias [cohort study], indirectness†)
Disequilibrium	301 (14.8)	61 (4.6)	p <0.0001	Very low (risk of bias [cohort study], indirectness†)
Facial weakness‡	349 (17.2)	29 (2.2)	p <0.0001	Very low (risk of bias [cohort study], indirectness†)
Headache	300 (14.8)	120 (9.1)	p <0.0001	Very low (risk of bias [cohort study], indirectness†)
Fatigue	43 (2.1)	16 (1.2)	p = 0.0493	Very low (risk of bias [cohort study], indirectness†)
Depression	31 (1.5)	17 (1.3)	p = 0.5578	Very low (risk of bias [cohort study], indirectness†)
Memory difficulty	11 (0.5)	9 (0.7)	p = 0.6153	Very low (risk of bias [cohort study], indirectness†)
Eye problems	21 (1.0)	8 (0.6)	p = 0.1867	Very low (risk of bias [cohort study], indirectness†)
Difficulty swallowing	90 (4.4)	24 (1.8)	p <0.0001	Very low (risk of bias [cohort study], indirectness†)

* Consistent results at 3 months posttreatment

† All outcomes were downgraded for indirectness because size of tumor not reported

‡ Facial weakness was also measured at 12- and 24-months post-treatment, which showed increase in proportion of patients in both treatment groups over time: 19.4% vs. 3.28% at 12 months (p <0.0001) and 21.3% vs. 4.41% at 24 months (p <0.0001) for the microsurgery and radiosurgery groups, respectively.

Comparing microsurgery vs. radiosurgery on patient-level changes in morbidity from 6 months pre-treatment to 6 months post-treatment

	Microsurgery				Radiosurgery			
	Symptom status (6 months before compared to 6 months after)				Symptom status (6 months before compared to 6 months after)			
	Same	Better	Worse	Same	Same	Better	Worse	Same
Symptom, %*	(+, +)	(+, -)	(-, +)	(-, -)	(+, +)	(+, -)	(-, +)	(-, -)
Hearing loss	71.6	0	7.5	21.0	58.6	0	5.6	35.8
Tinnitus	3.0	23.9	1.6	71.5	2.3	19.2	1.5	77.0
Vertigo	6.4	25.9	8.7	59.0	4.0	17.4	5.4	73.2
Balance	1.7	2.9	13.1	82.3	1.6	3.4	3.0	92
Facial weakness	1.7	1.9	15.5	80.9	0.6	2.0	1.6	95.8
Headache	4.4	11.3	10.4	73.9	3.4	11.1	5.7	79.8
Fatigue	0.2	0.5	2.0	97.3	0.2	1.4	1.0	97.4
Depression	0.5	0.8	1.1	97.6	0.5	0.7	0.8	98.0
Memory difficulty	0.1	0.3	0.5	99.1	0.2	0.7	0.5	98.6
Eye problems	0.1	0.3	1.0	98.6	0	0.2	0.6	99.2
Difficulty swallowing	0.5	1.5	4.0	94.0	0.5	1.2	1.4	96.9

* Symptom present (+) and absent (-) at 6 months before and after treatment.

Comparing microsurgery vs. radiosurgery on proportion with complications* within 30 days of treatment

Complication†	Microsurgery (n = 2,028) (% with complication)	Radiosurgery (n= 1,346) (% with complication)	Certainty (reason for downgrade)
Any of specific complications below	28.5%	2.6%	Very low (risk of bias [cohort study], indirectness§)
Specific complications‡			
Wound infection	1.7%	0.1%	Very low (risk of bias [cohort study], indirectness§)
Venous thrombosis	0.8%	0.2%	Very low (risk of bias [cohort study], indirectness§)
Pulmonary embolism	0.4%	0%	Very low (risk of bias [cohort study], indirectness§)
Pneumonia	1.6%	0.4%	Very low (risk of bias [cohort study], indirectness§)
Mechanical ventilation	0.2%	0%	Very low (risk of bias [cohort study], indirectness§)
Hydrocephalus	3%	0.8%	Very low (risk of bias [cohort study], indirectness§)
Hematoma/seroma	2%	0.2%	Very low (risk of bias [cohort

			study], indirectness§)
Cerebrospinal fluid leak	4.4%	0%	Very low (risk of bias [cohort study], indirectness§)
Central nervous system	10.1%	0.3%	Very low (risk of bias [cohort study], indirectness§)
Acute myocardial infarction	0.3%	0.1%	Very low (risk of bias [cohort study], indirectness§)

* Complications were recorded by both treating physician and hospital auditor.
† Rates for complications reported in this table were not reported in Results text and were roughly estimated based on Figure 1. Total number of patients evaluated for complications in microsurgery and radiosurgery groups estimated based on proportion and number in each group with any complication. The following complications were significantly different between groups: venous thrombosis ($p < 0.05$); pulmonary embolism and pneumonia (both $p < 0.005$); wound infection, hydrocephalus, hematoma/seroma, cerebrospinal fluid leak, and central nervous system (all $p < 0.0005$); and any complication (listed as "Any of specific complications below" in the table; $p < 0.0001$).
‡ Methods listed 'facial paralysis' as an additional specific complication but this was not included in Figure 1 in Results.
§ All outcomes were downgraded for indirectness because size of tumor not reported.

PAPATSOUTSOS 2018

Papatsoutsos E, Spielmann PM. Self-Evaluated Quality of Life and Functional Outcomes After Microsurgery, Stereotactic Radiation or Observation-Only for Vestibular Schwannoma of the Adult Patient: A Systematic Review. Otol Neurotol. 2018 Feb;39(2):232-241. PubMed

Relevant to FAQ3

- **Study design:** systematic review of prospective and retrospective observational studies
  - review included studies evaluating pre-post comparisons in a single group as well as studies comparing groups (microsurgery, radiosurgery, or observation)
    - we limited to studies that compared microsurgery vs. radiosurgery
  - review included retrospective and prospective studies, but review authors focused on the prospective studies because of their higher quality of evidence
    - we limited to the prospective studies for this summary
  - no meta-analysis was performed
- **Population:** adults with sporadic vestibular schwannomas who had microsurgery or radiosurgery
  - maximum size of tumor for eligibility for inclusion of study in systematic review not reported as inclusion criteria; however, the 3 prospective studies that included both microsurgery and radiosurgery groups that we consider for this summary have each been confirmed to require tumor diameter < 3 cm (ie, Myrseth 2009 required tumor diameter $\leq$ 2.5 cm and Pollock 2006 and Di Maio 2009 each required tumor diameter < 3 cm)
- **Intervention:** microsurgery
- **Comparison:** stereotactic radiation therapy
  - eligibility criteria states that this group includes both stereotactic radiosurgery and fractionated stereotactic radiotherapy
- **Study inclusion criteria:**
  - evaluated quality of life outcome using a validated questionnaire
  - publication language either English or German

- **Number of studies:** 3
    - 10 prospective and 29 retrospective studies were included in the review but only the 3 prospective studies that included both microsurgery and radiosurgery groups were considered for this summary
- **Number of participants:** 375 (in 3 prospective studies comparing microsurgery vs. radiosurgery)
    - 5,525 patients in all studies included in review
- **Duration of follow-up:** mean 24 to 42 months

- **Results and certainty:**
    - results for quality of life in 3 prospective cohort studies that have compared microsurgery vs. radiosurgery (first bullet summarizes findings as reported in Papatsoutsos 2018; sub-bullet for each summarizes findings as extracted from full-text publication of each individual prospective cohort study [from Part 3 summaries])
        - Di Maio 2009 (n = 47) found improvement in SF-36 scores after microsurgery but no significant effect after radiosurgery at 24 months follow-up (only 24-month results and not last follow-up results [mean 36.4 months for radiosurgery group and mean 32.3 months for microsurgery group] reported in Papatsoutsos 2018)
            - Note: The full-text of Di Maio 2009 was also used to extract quality-of-life outcomes and the findings are included in the Di Maio 2009 summary. At 2 years, microsurgery group associated with significant improvement from baseline in SF-36 total and mental dimension scores, with no significant changes from baseline in radiosurgery group in SF-36 total or its physical or mental dimension scores. At last follow-up, there were no significant changes from baseline for either group in any of these 3 SF-36 measures.
        - Myrseth 2009 (n = 91) "found GBI [Glasgow Benefit Inventory] scores were significantly better for SRT compared with MS at 24 months, although no significant difference in SF-36 scores was seen between MS and SRT groups at baseline or in follow-up"
            - Note: The full-text of Myrseth 2009 was also used to extract quality-of-life outcomes and the findings are included in the Myrseth 2009 summary. Briefly, at 24 months there were no significant within group changes for either group on any of the 8 components of SF-36, but the radiosurgery group appeared to have better outcomes on 3 of the 4 components of the Glasgow Benefit Inventory (although methods and reporting were unclear).
        - Pollock 2006 (n = 82) was reported to find "significant deterioration in SF-36 scores after MS but not after SRT with a mean follow up of 42 months"
            - Note: The full-text of Pollock 2006 was also used to extract quality-of-life outcome and the findings are included in the Pollock 2006 summary. The radiosurgery group appeared to have significantly better outcomes on $\leq$ 1 of the 10 components of the Health Status Questionnaire (modified version of SF-36 quality of life questionnaire) at last follow-up (42 months) but the reporting was unclear.
    - certainty of overall body of evidence for quality-of-life outcome
        - very low with following downgrades

- risk of bias due to cohort design of studies reviewed
- serious inconsistency due to inconsistent results among the 3 prospective cohort studies evaluated (though issues with reporting clarity, different scales, inconsistent reporting of within- vs. between-group differences, and lack of confidence intervals being reported complicate assessment)

POLLOCK 2006

Pollock BE, Driscoll CL, Foote RL, Link MJ, Gorman DA, Bauch CD, Mandrekar JN, Krecke KN, Johnson CH. Patient outcomes after vestibular schwannoma management: a prospective comparison of microsurgical resection and stereotactic radiosurgery. Neurosurgery. 2006 Jul;59(1):77-85 PubMed

Relevant to FAQ3, FAQ5, FAQ6, FAQ7

- **Study design:** observational study
  - prospective cohort study
  - blinded independent observers determined tumor size, facial nerve function, and hearing preservation
- **Population:** patients with unilateral, unoperated vestibular schwannomas < 3 cm having microsurgery or radiosurgery based on patient preference after discussion of the treatment options
- **Intervention:** microsurgery
- **Comparison:** radiosurgery
  - stereotactic radiosurgery performed using Leksell Gamma Knife

- **Study inclusion criteria:** patients with neurofibromatosis type 2 or patients with recurrent tumors were excluded

- **Number of studies:** 1
- **Number of participants:** 82
  - 36 in microsurgery group
  - 46 in radiosurgery group
- **Duration of follow-up:** mean 42 months (range 12 to 62 months)
  - no patient withdrew from study

- **Results and Certainty:**
  - note: tumor control and hearing outcomes not included in this summary, as these are already captured by Liu 2015
  - comparing microsurgery vs. radiosurgery at baseline
    - no significant difference between groups on proportion with good hearing (American Academy of Otolaryngology-Head Neck Surgery Classification Class A or B), facial weakness (facial nerve outcomes were based on a blinded review of patient photographs), mean tinnitus score, tumor size, and all subscales of Health Status Questionnaire (modified version of SF-36 quality of life questionnaire)
    - no patient in either group had facial weakness

- 2 patients in microsurgery group (6%) and 1 patient in radiosurgery group (2%) had facial numbness
- mean age significantly younger in microsurgery group (48.2 years vs. 53.9 years, p = 0.03)

Comparing microsurgery vs. radiosurgery on facial function and tinnitus at last follow-up

	Facial function*		**Tinnitus (questionnaire assessing whether tinnitus reduces quality of life)*†**		**Certainty (reason for downgrade)**
Group	% with normal facial movement (House-Brackmann Grade 1)‡	% with normal or near normal facial movement (House-Brackmann Grade 1 or 2)§	Not at all	Not at all or slightly	
microsurgery	75% (27/36)	83% (30/36)	30% (11/36)	73% (26/36)	*Facial nerve function*: Low (risk of bias [cohort study])
radiosurgery	96% (44/46)¶	98% (45/46)	32% (15/46)	82% (38/46)	*Tinnitus*: Very low (risk of bias [cohort study], imprecision)

* Numerators and denominators not reported for facial function or tinnitus. Although report stated that no patient withdrew from study, Table 2 (QoL outcomes) shows numbers of patients available for analysis at last follow-up and not all patients are included (at least for QoL outcomes reported in Table 4), and this is consistent with their report that "Data available for evaluation included facial photographs (98%), audiograms (94%), and questionnaires (94%)." This degree of missingness amounts to approximately 5 patients' (0.06*82) data being unavailable for the questionnaires and approximately 2 patients' (0.02*82) data being unavailable for the facial photographs. To provide estimates of numerators and denominators, and because we do not know how many patients' data might have been unavailable in each group, we have performed calculations using the full denominator and the reported proportion for each group. Although patients lost to follow-up may fare worse than those who continue to follow-up, the degree of impact this would have would depend on the distribution of missing data between the groups and how those people fared, and overall, we consider this degree of missingness unlikely to have a large enough effect on the results to change overall patterns.

† No significant difference comparing distribution of scores between two groups (ie, significance test in publication not done on dichotomized data reported here).

‡ $p < 0.01$

§ $p = 0.04$

¶ the 2 patients with facial weakness in radiosurgery group developed it following surgical removal of tumor following failed radiosurgery

Quality of life outcomes at last follow-up

- **Results**
  - 10 components of Health Status Questionnaire evaluated
  - the authors report comparing groups and describe using statistical tests intended for comparison of two groups (e.g., Wilcoxon Rank-Sum test), and for some outcomes (e.g., the facial function and tinnitus outcomes above), they clearly did compare groups;

however, for quality of life, it appears only within-groups comparisons may be reported, but methodology and reporting was unclear for the quality of life outcomes (comparing Table 2 vs. the text in Results section, the latter clearly describing only within-groups comparisons)
    - Results text
        - radiosurgery group was reported to have had no decline in any of components compared to before surgery
        - microsurgery group was reported to have had decline in different components at different timepoints, with only bodily pain being statistically significant (p = 0.02) at final follow-up
    - Table 2
        - confusing and difficult to interpret in conjunction with the text of the Results section with respect to which components showed decline and whether the significance tests reported were for comparison to baseline or comparison between groups
        - placement of footnotes indicating significant differences at follow-up suggest differences are only for the radiosurgery group, unless the footnotes are for comparisons between the microsurgery and radiosurgery group
        - even if Table 2 does present between-groups comparisons, the only findings (of 10 outcomes assessed) that are statistically-significantly different at last follow-up are "Mental health" and "standardized mental component scale", and the authors only report *p* values and the means in each group, not mean difference estimates or confidence intervals; however, if these are between-group comparisons, the magnitude of difference is small and of questionable clinical relevance (mental health, 76.1 vs. 82.9; standardized mental component scale, 51.6 vs. 54.9)
- **Certainty**
    - Low
        - downgrades due to risk of bias (cohort study)
    - **Other considerations**: We have serious concerns about the quality of reporting for the quality of life outcomes in Pollock 2006 and how this impacts our certainty in the evidence from Pollock 2006 for quality of life.

Perioperative complications

- **Results**
    - microsurgery group
        - 5 patients (14%) had cerebrospinal fluid leaks (resolved with lumbar drain)
        - 1 patient had wound infection
        - 1 patient had deep vein thrombosis
        - 6 patients (17%) needed either tarsorrhaphy (5 patients) or gold weight placement (1 patient) for eye protection
    - radiosurgery group – none reported
- **Certainty**
    - Very low

- certainty downgrades for risk of bias (cohort study) and serious imprecision for each adverse event listed above

Additional treatment

- **Results**
  - microsurgery group – no patient needed further tumor treatment
  - radiosurgery group
    - 1 patient developed trigeminal neuralgia that was controlled with medications
    - 2 patients (4% had increasing ataxia that improved with placement of ventriculo-peritoneal shunt)
    - 2 patients (4%) had later resection 24 and 28 months after radiosurgery as a result of progressive tumor enlargement
- **Certainty**
  - Very low
  - certainty downgrades for risk of bias (cohort study) and serious imprecision for each adverse event listed above

RÉGIS 2002

Régis J, Pellet W, Delsanti C, Dufour H, Roche PH, Thomassin JM, Zanaret M, Peragut JC. Functional outcome after gamma knife surgery or microsurgery for vestibular schwannomas. J Neurosurg. 2002 Nov;97(5):1091-100. PubMed

Régis 2002 was considered for a summary because it is a cohort study which was reported to include a prospective design, and we had pre-specified using prospective cohort studies preferentially for FAQs 2, 3, 4, 5, and 6. Upon further examination of Régis 2002, it was found that only the radiosurgery group was evaluated prospectively and its results were compared with results from the microsurgery group which had previously been evaluated retrospectively. It is a judgment call for whether to include Régis 2002 among prospective cohort studies because only 1 of the 2 groups was prospectively evaluated. Régis 2002 was not included (or even mentioned) in Papatsoutsos 2018 systematic review of quality-of-life or in the Carlson 2015 Discussion section which summarized the 3 previous prospective cohort studies (ie, Di Maio 2009, Myrseth 2009, Pollock 2006). However, it was 1 of the 3 'prospective cohort studies' included in the comparison of microsurgery vs. radiosurgery in Liu 2015.

The results of Régis 2002 were consistent with those of the other two prospective cohort studies in Liu 2015 in finding that microsurgery provides worse hearing preservation than radiosurgery while maintaining a high rate of tumor control. Therefore, the inclusion vs. exclusion of Régis 2002 from Liu 2015 would be unlikely to impact the pooled results on hearing preservation and tumor control rate from Liu 2015.

In terms of quality-of-life, microsurgery patients had significantly worse results than radiosurgery patients in Régis 2002. Papatsoutsos 2018 included 3 prospective cohort studies and they had inconsistent results on quality of life and were not meta-analyzed; the inclusion of Régis 2002 would not affect the overall quality-of-life finding based on Papatsoutsos 2018.

Régis 2002 included a facial motor disturbance outcome and found that 47% of patients who had microsurgery had a new facial motor disturbance compared with 0% of patients who had radiosurgery. This is consistent with 2 of the 3 prospective cohort studies which showed significantly worse facial

function in the microsurgery group (Myseth 2009; Pollock 2006); the third prospective cohort study showed no significant difference between groups (Di Maio 2009).

Régis 2002 included a tinnitus outcome and found that 40% of patients had a new complaint of tinnitus after microsurgery vs. 50% after radiosurgery (not significant). The lack of a clear difference is consistent with the results of the 3 prospective cohort studies summarized elsewhere in this report that reported on this outcome (Di Maio 2009, Myrseth 2009, Pollock 2006).

SUGHRUE 2009
Sughrue ME, Yang I, Han SJ, Aranda D, Kane AJ, Amoils M, Smith ZA, Parsa AT. Non-audiofacial morbidity after Gamma Knife surgery for vestibular schwannoma. Neurosurg Focus. 2009 Dec;27(6):E4. PubMed

Relevant to FAQ7

- **Study design:** systematic review of observational studies
    - description of study design or quality of included studies not reported
    - appears to combine data from case studies, case series, and prospective cohort studies to calculate a pooled estimate
        - Table 1 shows that several studies included in the pooled analysis were single case series
        - Table 1 also shows that prospective cohort studies (eg, Régis 2002; Myrseth 2005) were included in pooled analysis
- **Population:** patients having radiosurgery for vestibular schwannomas with tumors < 2.5 cm in largest diameter
    - patients with neurofibromatosis type 2 were also included
- **Intervention:** single fraction Gamma Knife surgery
    - other forms of radiation were excluded
    - mixed radiosurgery modalities that were aggregated for analysis were not included
    - studies of patients having microsurgery as treatment were excluded
- **Comparison:** not applicable
-
- **Study inclusion criteria:** no additional

- **Number of studies:** 63
- **Number of participants:** 5,631
- **Duration of follow-up:** median 39.5 months for patients receiving ≤ 13 Gy and 36.5 months for patients receiving > 13 Gy
    - time point for assessment for complications was not reported but it is assumed that the complications reported were short-term/peri-operative complications and that the duration of follow-up mentioned above is for other long-term outcomes reported in included studies but not extracted for this systematic review

- **Results and certainty:**
    - Results
        - complications recorded in review were reported to all be “new morbidities, appearing after radiation treatment or exacerbations of symptoms present prior

to radiosurgery"; facial nerve and hearing morbidity outcomes not included in this review
        - Complication rates after radiosurgery
            - new non-cranial nerve VII or non-cranial nerve VIII cranial neuropathy in 2.4% (135/5,631); 95% CI 2.0% to 2.8%
                - trigeminal neuropathy (cranial nerve V neuropathy), manifested by "facial paresthesias or tingling" was reported to be "by far the most common neuropathy" (accounting for 2.30% of the reported 2.4% rate; cranial nerves VI and XII accounted for the remainder, at 0.03% and 0.08%, respectively)
            - hydrocephalus in 0.85% (48/5,631); 95% CI 0.6% to 1.1%
            - vertigo or balance disturbance in 1.49% (84/5,631)
            - tinnitus in 0.44% (25/5,631); 95% CI 0.3% to 0.7%
        - mortality reported to be an outcome in Methods, but no mortality results included in Results
        - 95% CIs are calculated (not reported in results)
    - Certainty
        - Very low
            - downgrade twice due to very serious concern for risk of bias
                - quality of studies not assessed and studies with very low reliability (eg, single case reports) were combined with more reliable studies (eg, prospective cohort studies)
            - downgrade due to serious concern for indirectness
                - patients with neurofibromatosis type 2 were included

SUGHRUE 2011
Sughrue ME, Yang I, Aranda D, Rutkowski MJ, Fang S, Cheung SW, Parsa AT. Beyond audiofacial morbidity after vestibular schwannoma surgery. J Neurosurg. 2011 Feb;114(2):367-74. PubMed

Relevant to FAQ7

- **Study design:** systematic review of observational studies
- **Population:** patients who had microsurgery for vestibular schwannoma
    - subgroup analysis based on tumor size (≤ 2.5 cm vs. > 2.5 cm) was performed and data extracted for this summary specific to tumor size ≤ 2.5 cm
    - identity, study design, or quality of included studies not reported but methods suggest that similar to Sughrue 2009, data from studies of varying reliability were combined to calculate a pooled estimate
- **Intervention:** microsurgery
- **Comparison:** not applicable

- **Study inclusion criteria:** morbidity and/or mortality rates were reported
    - patients with neurofibromatosis Type 2 were also considered
        - report does not mention proportion of studies/patients with neurofibromatosis Type 2
    - all radiotherapy and radiosurgery cases were excluded
    - audiofacial morbidities (eg, loss of facial nerve or hearing function) were not extracted

- **Number of studies:** 100
- **Number of participants:** 32,870
    - 7,667 patients had tumor size < 2.5 cm
- **Duration of follow-up:** mean 15.7 months (range 2.3 to 132 months)
    - publication did not report time point for assessment of the postsurgical complications summarized in article

- **Results and certainty:**
    - Results
        - microsurgery complications among patients with tumor size ≤ 2.5 cm
            - cerebrospinal fluid leakage
                - 6% (460/7,667)
                - 95% CI 6.1% to 7.6%
            - vascular complications
                - defined as any ischemic injury or intracranial hemorrhage that was attributed to surgical procedure
                - 0.7% (56/7667)
                - 95% CI 0.4% to 0.9%
            - neurological complications
                - defined as any postoperative neurological symptoms other than facial nerve palsy or hearing loss that was not explicitly stated to have been present preoperatively
                - 4.6% (355/7,667)
                - 95% CI 3.9% to 5.3%
            - infection rates
                - 1% (84/7,667)
                - 95% CI 0.7 to 1.3%
            - mortality
                - Mortality was only reported for the overall group (those with a vestibular schwannoma of any size). The overall mortality rate was 0.2% (66/32,870) with a 95% CI of 0.1% to 0.3%. Compared to tumors ≤2.5 cm, tumors >2.5 cm may have a higher rate of mortality (i.e., the overall estimate may be an upward-biased estimate compared to what the estimate would be if restricted to those with tumors ≤2.5 cm). However, given the event rate is still low in spite of this (which may be meaningful to patients), we include this outcome here.
    - Certainty
        - Very low
            - downgrade twice due to very serious concerns for risk of bias
                - quality of studies not assessed and studies with very low reliability (eg, single case reports) appear to have been combined with more reliable studies
            - downgrade due to serious concerns for indirectness
                - patients with neurofibromatosis type 2 were included

- Other considerations: overall rate of having > 1 significant complication were reported only for all patients combined (those with a vestibular schwannoma of any size) and because this rate is likely to be subgroup specific, this outcome was not extracted

WHITMORE 2011
Whitmore RG, Urban C, Church E, Ruckenstein M, Stein SC, Lee JY. Decision analysis of treatment options for vestibular schwannoma. J Neurosurg. 2011 Feb;114(2):400-13. PubMed

This systematic review was identified in second-round searching. It was not reviewed or summarized because of its methodology. It included 113 studies using different methodologies (eg, case series, retrospective cohort studies, prospective cohort studies) and derived summary estimates by combining them using a decision analytic framework that involves constructing a model that weights outcome estimates with utility estimates (with their primary intent being to estimate quality of life as a proportion from 0 to 1). Setting aside nuances involved in evaluating a decision analytic model, their pooling of various study types as above-noted is not in line with our scoping indicating preference for prospective data (for FAQs 2 through 6), and we have identified such prospective data as documented throughout Part 3. As such, the only possible utility of this study for this evidence report would be for outcomes pertinent to FAQ 7 (risks), where we did not specify a specific preference for prospective data (though prospective data are arguably still more desirable for risks). However, we have concerns about the authors' approach to synthesis that still lead us to conclude this report is unusable for FAQ 7 as well. Briefly, although the authors describe using a recognized meta-analysis package (metan from Stata), their presented results give us serious concern about the reliability of the results: for instance, for some outcomes, they provide a pooled estimate of the prevalence without any indication of the studies that contributed to the estimate (whereas in the same table, they do indicate the contributing studies for other outcome estimates) and for some purportedly pooled estimates (e.g., the "other" category, which itself is a bit of a "catchall" category), they present a pooled mean prevalence but say a confidence interval was not calculated. Especially given the availability of other data, we consider this report's quality and/or value to be too questionable for inclusion in this evidence report. This systematic review also concluded that microsurgery improved quality of life compared to radiosurgery, which was the opposite conclusion to that of more reliable studies. For example, Carlson 2015 (a large observational study) found a worsening in some quality of life measures with microsurgery compared to radiosurgery, and none of the 3 earlier cohort studies reviewed in the Discussion section of Carlson 2015 reported a quality of life benefit of microsurgery compared to radiosurgery. Finally, a 2017 systematic review found no quality-of-life benefit of microsurgery compared to radiosurgery (Papatsoutsos 2017).

Part 4 - Evidence Review

Methods

For each FAQ, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. Where evidence is very limited, or the FAQ is for descriptive summary, summary text will be provided.

Results

FAQ 1: What does the treatment involve?

Microsurgery

Descriptive Summary

The goal of surgery is to remove the tumor, though complete removal may not be possible in some cases. The surgery is done while the patient is under general anesthesia, and the tumor is either removed through a hole in the skull and removal of part of the inner ear ("translabyrinthine" approach) or through a hole in the skull ("suboccipital"/"rectosigmoid" and "middle cranial fossa" approaches). If removing the tumor with a translabyrinthine approach, hearing loss will result because of how the surgery is done. As such, this approach is usually only considered if people already have hearing problems or hearing loss that surgery is unlikely to help (regardless of approach). After having a form of surgery, the Congress of Neurological Surgeons recommends follow-up magnetic resonance imaging studies (MRIs) be obtained based on a patient's individual case, specifically whether there was gross total resection and whether any change in nodular enhancement is seen on follow-up imaging. For those who had gross total resection, a postoperative MRI may be obtained ≤1 year after surgery. For those who did not have gross total resection, they recommend more frequent surveillance MRIs and suggest an annual MRI for 5 years might be reasonable. They also recommend imaging surveillance plans should be adjusted for continued surveillance if any change in nodular enhancement is seen.

Radiation therapy

Descriptive Summary

The goal of radiation therapy is to stop the tumor's growth. The tumor's position is "mapped" using imaging studies. This "map" is used to direct radiation in at the tumor in a highly-focused way while minimizing exposure of healthy tissue. One type of radiation treatment ("stereotactic radiosurgery") does this in a single session. Another type of radiation treatment ("stereotactic radiotherapy") uses a smaller dose of radiation that is delivered over several sessions. Neither of these treatments require cutting or actual surgery. The "surgery" part of "stereotactic radiosurgery" only indicates that the treatment occurs in one session (like surgery does), whereas stereotactic radiotherapy occurs over several sessions. Both treatments can be done while the patient is awake, though the patient's head is held still with equipment and the scalp may be numbed. Stereotactic radiosurgery is used more commonly than stereotactic radiotherapy. After having a form of radiation treatment, the Congress of Neurological Surgeons recommends long-term follow-up with repeated MRIs to assess for recurrence, but they state no recommendations can be given regarding the interval for these studies. They also suggest imaging studies should be obtained in accordance with a patient's individual case (including if clinical indications arise) and any institutional protocols that may exist.

(Arthurs 2011, DynaMed 2019, Germano 2018, Johns Hopkins Medicine nd, Kutz 2018, Lin 2017, Mayo Clinic 2018)

FAQ 2: Will the treatment control the tumor?

Microsurgery vs. radiation therapy

Evidence Review Table

Tumor control rate was assessed using the results of a systematic review that pooled outcome data from 377 patients total from 3 prospective cohort studies (Régis 2002; Myrseth 2009; Pollock 2006) comparing microsurgery vs. radiosurgery in patients with tumors < 3.0 cm in diameter or stages I, II, or III based on Koos classification with mean follow-up of 2 to 3.5 years (Liu 2015).

Pooled effects of microsurgery vs. radiosurgery on tumor control rate based on systematic review and meta-analysis (Liu 2015)*

Intervention	Tumor control rate†	Certainty for comparison (reason for downgrade)
microsurgery	94.3%	Very low (risk of bias [no randomization], imprecision)
radiosurgery‡	97.0%	

* For 1 of the 3 studies included in the Liu 2015 pooled analysis comparing microsurgery vs. radiosurgery, only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design (Régis 2002). It is a judgment call whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the groups was prospectively evaluated. The results of Régis 2002 were consistent with those of the other 2 prospective cohort studies included in Liu 2015 in finding that radiosurgery provides a high rate of tumor control (comparable to microsurgery) and with significantly better hearing preservation. Thus, the inclusion (vs. exclusion) of Régis 2002 from Liu 2015 would be unlikely to impact the Liu 2015 pooled results on tumor control rate (or hearing preservation).
† Defined as no change or regression of tumor volume (diameter) during follow-up; no significant differences between groups (confidence intervals not reported; only p values).
‡ Radiosurgery approaches included gamma knife, fractionated stereotactic radiotherapy, and linear accelerator radiosurgery; authors noted that there is no clear advantage of one radiosurgery approach vs. another as justification for including all approaches in their systematic review.

The certainty of the overall body of evidence on tumor control rate was assessed as Very low with downgrades for risk of bias (because all three studies are cohort studies) and imprecision (sample size too small to be confident in absence of difference).

FAQ 3: Will the treatment make me feel better?

Microsurgery vs. radiation therapy

Evidence Review Table

Studies that reported on quality of life were identified from a systematic review that evaluated quality of life outcomes after microsurgery, stereotactic radiation (including either stereotactic radiosurgery or fractionated stereotactic radiotherapy), or observation-only in adults with vestibular schwannoma (Papatsoutsos 2018). Three prospective cohort studies that included both microsurgery and radiosurgery groups were identified from this systematic review and considered for this Evidence Report. The quality of life outcomes for each of these 3 studies were briefly summarized in the Results text of Papatsoutsos 2018, which we extracted for this systematic review's summary; we also extracted the quality-of-life outcomes directly from the full-text reports of each of the 3 individual prospective cohort studies in preparing their summaries.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting quality of life outcomes identified through systematic review*

Author year	Sample size	Maximum tumor diameter required for eligibility	Follow-up duration	Quality of life results	Certainty (downgrade)
Di Maio 2009	145	< 3 cm	radiosurgery: 36.4 months; microsurgery: 32.3 months	*At 24 months*, microsurgery group associated with significant improvement from baseline in SF-36 total and mental dimension scores, with no significant changes from baseline in radiosurgery group in SF-36 total or its physical or mental dimension scores. *At last follow-up*, there were no significant changes from baseline for either group in any of these 3 SF-36 measures.	Very low (risk of bias [cohort study] and inconsistency [inconsistent results at 24 months vs. final follow-up])

Myrseth 2009	88	< 2.5 cm	24 months	At 24 months there were no significant within group changes for either group on any of the 8 components of SF-36, but the radiosurgery group appeared to have better outcomes on 3 of the 4 components of the Glasgow Benefit Inventory (although methods and reporting were unclear). The discussion section of the article qualitatively mentions what appears to be between-group comparisons, but again notes inconsistency (possible benefit for Glasgow Benefit Inventory, but no difference for SF-36). Again, methods and reporting were unclear.	Very low (risk of bias [cohort study] and inconsistency [inconsistent results on SF-36 vs. Glasgow Benefit Inventory])
Pollock 2006	82	< 3 cm	42 months	The radiosurgery group appeared to have significantly better outcomes on $\leq$ 1 of the 10 components of the Health Status Questionnaire (modified version of SF-36) at last follow-up (although methods and reporting were unclear). The microsurgery group had "significant deterioration" in Papatsoutsos 2018's review, and review of full text of Pollock 2006 suggested decline in different components at different timepoints, with only bodily pain being significantly worse at final follow-up (again, however, methods and reporting were unclear). Although methods and reporting were unclear, even if tabulated results present between-group comparisons, then only 2 of 10 components of the Health Status Questionnaire were significantly different between the groups, and the magnitude of difference is of questionable clinical relevance.	Low (risk of bias [cohort study])

* One additional potentially eligible report (Régis 2002) that was not included in Papatsoutsos 2018 was identified through its inclusion in the Liu 2015 systematic review (which pooled results from 3 prospective cohort studies comparing microsurgery vs. radiosurgery for the outcomes of hearing preservation, tumor control, and complication rates, but did not include quality-of-life as an outcome). The full-text report of Régis 2002 was obtained and it was found that only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design. It is a judgment call whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively. Régis 2002 included a quality-of-life outcome and found that microsurgery patients had significantly worse quality-of-life results than radiosurgery patients. The 3 prospective cohort studies included in Papatsoutsos 2018 had inconsistent results on quality of life. Thus, the addition of Régis 2002 would not affect the 'bottom-line' finding of inconsistent results based on a summary of the 3 prospective cohort studies included in Papatsoutsos 2018.

The certainty of the overall body of evidence on quality of life was assessed as Very low with downgrades for risk of bias (two downgrades, because all 3 studies are cohort studies) and serious inconsistency (because of inconsistency of results within and between studies).

FAQ 4: Will the treatment preserve my useful hearing?

Microsurgery vs. radiation therapy

Evidence Review Table

Preservation of useful hearing was assessed using the results of a systematic review (Liu 2015) that pooled results from 3 prospective cohort studies (Régis 2002; Myrseth 2009; Pollock 2006) with mean follow-up of 2 to 3.5 years and 377 patients total that compared microsurgery vs. radiosurgery in patients with tumors < 3.0 cm in diameter or stages I, II, or III based on Koos classification.

Pooled effects of microsurgery vs. radiosurgery on preservation of useful hearing based on systematic review and meta-analysis (Liu 2015)*

intervention	design of studies pooled	pooled proportion with useful hearing† at time of diagnosis‡	pooled proportion with useful hearing† preserved‡§	Certainty for comparison (reason for downgrade)
microsurgery	prospective cohort¶	65.5%	4.3%	Moderate (risk of bias [no randomization] but increased certainty for large effect size)
radiosurgery**	prospective cohort¶	50.7%	60.2%	

* An additional prospective cohort study (Di Maio 2009) was not included in the Liu 2015 comparison of microsurgery vs. radiosurgery. It was included in Papatsoutsos 2018 (as 1 of the 3 prospective cohort studies comparing microsurgery vs. radiosurgery) and it was 1 of 3 prospective cohort studies comparing microsurgery vs. radiosurgery that were briefly summarized in the Discussion section of Carlson 2015. Di Maio 2009 reported a hearing-related outcome; however, its data cannot be integrated with the 'pooled proportion with useful hearing preserved' outcome reported by Liu 2015 because the Liu 2015 outcome restricts to patients with useful hearing at baseline but Di Maio 2009 only reported proportion with useful hearing at baseline and proportion with useful hearing at last follow-up (but not proportion with useful hearing at follow-up among those with useful hearing at baseline). The proportion with useful hearing at last follow-up outcome reported in Di Maio 2009 showed no significant differences between groups.
†Useful hearing defined as Gardner and Robertson Scale I or II or American Academy of Otolaryngology-Head and Neck Surgery class A or B
‡ Significant differences between groups: $p = 0.004$ comparing groups at time of diagnosis and $p < 0.001$ comparing groups in useful hearing preserved
§ Proportion of patients with preservation of useful hearing at long-term follow-up among patients with useful hearing at time of diagnosis
¶ For 1 of the 3 studies in the pooled analysis comparing microsurgery vs. radiosurgery, only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design (Régis 2002). It is a judgment call whether to include Régis 2002 among prospective cohort studies because only 1 of the groups was prospectively evaluated. The results of Régis 2002 were consistent with those of the other 2 prospective cohort studies pooled in Liu 2015 in finding that radiosurgery provides better hearing preservation (and a similarly high tumor control rate) compared to microsurgery. Thus, the inclusion (vs. exclusion) of Régis 2002 from Liu 2015 would be unlikely to impact the Liu 2015 pooled results on hearing preservation (or tumor control rate).
** Radiosurgery approaches included gamma knife, fractionated stereotactic radiotherapy, and linear accelerator radiosurgery; authors noted that there is no clear advantage of one radiosurgery approach vs. another as justification for including all approaches in their review.

The certainty of the overall body of evidence on preservation of useful hearing was assessed as Moderate with double downgrade for risk of bias (because all three studies are cohort studies) but then an increase in certainty for the large effect size (risk ratio > 10).

FAQ 5: Will the treatment preserve my facial nerve function?

Microsurgery vs. radiation therapy

Evidence Review Table

Preservation of facial nerve function was not an included outcome in either systematic review of prospective cohort studies (Liu 2015; Papatsoutsos 2018). Therefore, this outcome has been summarized based on each of the 3 prospective cohort studies with long-term follow-up (> 2 years) that compared microsurgery vs. radiosurgery in patients with tumors < 3.0 cm.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting facial nerve function outcome*

Author year	Sample size	Maximum tumor diameter required for eligibility	Follow-up duration / outcome measurement time point	% (n/N) with good facial function†		Absolute difference (95% CI) for good facial function, MS vs. RS	% (n/N) with reduced facial function‡		Absolute difference (95% CI) for reduced facial function, MS vs. RS	Certainty (downgrade)
				MS	RS		MS	RS		
Di Maio 2009§	145	< 3 cm	RS: 36.4 months; MS: 32.3 months	NR	NR	N/A	24.3% (17/70)	27.0% (10/37)	-2.7% (-20.8% to 13.4%)	Very low (risk of bias [cohort study] and imprecision)
Myrseth 2009¶	88	< 2.5 cm	24 months	82.1% (23/28)	98.3% (59/60)	-16.2% (-3.9% to -34%)	46.4% (13/28)	1.6% (1/60)	44.8% (26.4% to 62.6%)	Moderate (risk of bias [cohort study] but large effect size)
Pollock 2006**	82	< 3 cm	42 months	83% (30/36)	98% (45/46)	-14.5% (-1.8% to -29.8%)	25% (9/36)	4% (2/46)	20.7% (5.5% to 37%)	Low (risk of bias [cohort study])

NR, not reported; MS, microsurgery; RS, radiosurgery

* One additional potentially eligible report (Régis 2002) was identified through its inclusion in the Liu 2015 systematic review (which pooled results from 3 prospective cohort studies comparing microsurgery vs. radiosurgery for the outcomes of hearing preservation, tumor control, and complication rates but did not include facial function as an outcome). The full-text report of Régis 2002 was obtained and it was found that only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design. It is a judgment call for whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively. Régis 2002 included a facial motor disturbance outcome and found that 47% of patients who had microsurgery had a new facial motor disturbance compared with 0% of patients who had radiosurgery. This is consistent with 2 of the 3 prospective cohort studies which showed significantly worse facial function in the microsurgery group (Myseth 2009; Pollock 2006); the third prospective cohort study showed no significant difference between groups (Di Maio 2009).

† Defined as House-Brackmann Grade 1 or 2 in Myrseth 2009 and Pollock 2006; this outcome was not reported in Di Maio 2009.

‡ Defined as House-Brackmann Grade > 1 in Myrseth 2009 and Pollock 2006 and as “some element of facial weakness” on patient self-reports on a custom questionnaire created by the study authors in Di Maio 2009.

§ No significant difference between groups.

¶ Significant differences between groups on percentage with good facial function ($p = 0.0053$) and percentage with reduced facial function ($p < 0.0001$).

** Significant differences between groups on percentage with good facial function ($p = 0.04$) and percentage with reduced facial function ($p < 0.01$).

The certainty of the overall body of evidence on facial nerve function was assessed as Very low with downgrades for risk of bias (because all three studies are cohort studies) and inconsistency (in effect estimates across studies and in risk estimates across studies).

FAQ 6: Will I have tinnitus (ringing, clicking, or buzzing in the ears) after treatment?

Microsurgery vs. radiation therapy

Evidence Review Table

Tinnitus was not an included outcome in either systematic review of prospective cohort studies (Liu 2015; Papatsoutsos 2018). Therefore, this outcome has been summarized based on each of the 3 prospective cohort studies with long-term follow-up (> 2 years) that compared microsurgery vs. radiosurgery in patients with tumors < 3.0 cm.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting tinnitus outcome*

Author year	Sample size	Maximum tumor diameter required for eligibility	Follow-up duration/outcome measurement time point	% (n/N) with tinnitus (yes/no)†		Absolute difference (95% CI) for tinnitus, MS vs. RS	Certainty (downgrade)
				MS	RS		
Di Maio 2009	145	< 3 cm	RS: 36.4 months; MS: 32.3 months	76.1% (54/71)	75.7% (28/37)	0.4% (-15.2% to 18.3%)	Very low (risk of bias [cohort study] and imprecision)
Myrseth 2009	88	< 2.5 cm	24 months	66.7% (40/60)	83.1% (23/28)	-15.5% (-31.6% to 5.2%)	Very low (risk of bias [cohort study] and imprecision)
Pollock 2006	82	< 3 cm	42 months	30% (11/36)	32% (15/46)	-2.1% (-21.2% to 18%)	Very low (risk of bias [cohort study] and imprecision)

MS, microsurgery; RS, radiosurgery

* One additional potentially eligible report (Régis 2002) was identified through its inclusion in the Liu 2015 systematic review (which pooled results from 3 prospective cohort studies comparing microsurgery vs. radiosurgery for the outcomes of hearing preservation, tumor control, and complication rates but did not include facial function as an outcome). The full-text report of Régis 2002 was obtained and it was found that only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design. It is a judgment call for whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively. Régis 2002 included a tinnitus (Y/N) outcome and found that 40% of patients had a new complaint of tinnitus after microsurgery vs. 50% after radiosurgery (not significant). The lack of a clear difference is consistent with the results of the 3 prospective cohort studies summarized above.

† No significant difference between groups in any of 3 studies.

The certainty of the overall body of evidence on tinnitus was assessed as Very low, with downgrades for risk of bias (because all three studies are cohort studies) and imprecision.

(In support of the downgrade for imprecision for the overall body of evidence, one can note that the studies themselves are small, Di Maio 2009 and Pollock 2006 have considerable imprecision, and Myrseth also has imprecision, albeit to a lesser extent than Di Maio 2009 and Pollock 2006. These studies together do not allay concerns over imprecision, and it is unlikely that formal pooling via meta-analysis would produce precise results.)

FAQ 7: What are the risks?

For complications, three different sources were considered:

1) retrospective analysis of the largest available database in the United States of patients having treatment for vestibular schwannomas (Nuño 2019);
2) systematic review that reported rates of overall complications and serious complications from a pooled analysis of 3 prospective cohort studies (Liu 2015); and
3) systematic reviews that evaluated complication risks following microsurgery (Sughrue 2011) or following radiation therapy (Sughrue 2009).

Each source had Very low certainty evidence with serious limitations, as described below. These descriptions are followed by an Evidence Review table for each source.

Source 1: Descriptive review

The retrospective analysis of the administrative database was judged to contain Very low certainty evidence with downgrade for risk of bias because it was a cohort study and downgrade for indirectness because it did not restrict inclusion to patients with tumors < 3 cm in diameter and tumor size was not reported (Nuño 2019). If a large proportion of patients diagnosed with vestibular schwannoma had tumors > 3 cm that may have positively biased the complication rate in the surgery group in this study (compared to if only patients with tumor diameter < 3 cm were included) because patients with larger tumors would probably be more likely to have complications from treatment. Other than the lack of reporting of tumor size and the retrospective cohort design, no other downgrades were identified, the reporting was clear, and multiple individual complications within 30 days of procedure were reported (as well as proportion with greater than or equal to 1 complication). Additionally, the authors reported that the complications data was recorded by both the treating physician and the hospital auditor and noted that they considered complications the most accurate part of their study data for this reason. Finally, the study design included both microsurgery and radiation therapy patients and included a statistical comparison of rate of complications between surgery and radiation therapy groups.

Source 1: Evidence Review Table

Comparing microsurgery vs. radiosurgery in proportion with complications within 30 days of treatment (Nuño 2019 retrospective database analysis)

Complication	Microsurgery (n = 2,028)	Radiosurgery (n= 1,346)	Certainty (reason for downgrade)
Any of specific complications below	28.5%	2.6%	Very low (risk of bias [cohort study*] and indirectness†)
Specific complications			

Wound infection‡	1.7%	0.1%	Very low (risk of bias [cohort study*] and indirectness†)
Venous thrombosis§	0.8%	0.2%	Very low (risk of bias [cohort study*] and indirectness†)
Pulmonary embolism¶	0.4%	0%	Very low (risk of bias [cohort study*] and indirectness†)
Pneumonia¶	1.6%	0.4%	Very low (risk of bias [cohort study*] and indirectness†)
Mechanical ventilation	0.2%	0%	Very low (risk of bias [cohort study*] and indirectness†)
Hydrocephalus‡	3%	0.8%	Very low (risk of bias [cohort study*] and indirectness†)
Hematoma/seroma‡	2%	0.2%	Very low (risk of bias [cohort study*] and indirectness†)
Cerebrospinal fluid leak‡	4.4%	0%	Very low (risk of bias [cohort study*] and indirectness†)
Central nervous system‡	10.1%	0.3%	Very low (risk of bias [cohort study*] and indirectness†)
Acute myocardial infarction	0.3%	0.1%	Very low (risk of bias [cohort study*] and indirectness†)

* surgery cohort had higher pre-treatment comorbidities including anemia, cardiac, and pulmonary conditions
† did not restrict inclusion to patients with tumors < 3 cm in diameter and tumor size not reported
‡ $p < 0.0005$
§ $p < 0.05$
¶ $p < 0.005$

Source 2: Descriptive review

The systematic review that reported rates of overall complications and serious complications from a pooled analysis of 3 prospective cohort studies was also judged to contain Very low certainty evidence (Liu 2015). In addition to a risk of bias downgrade, an additional downgrade was assigned for imprecision. The serious complications outcome was downgraded twice for imprecision because this outcome was reported by only a small proportion of patients so a valid estimate could not be made (1% of radiation therapy group and 2% of microsurgery group, with no significant difference between groups). This review was also of limited usefulness because it reported only 'Complications' and 'Serious complications' as outcomes, and not specific types of complications.

Source 2: Evidence Review Table

Pooled effects of microsurgery vs. radiosurgery on overall complications* and serious complications† (Liu 2015 systematic review with meta-analysis of 3 prospective cohort studies)

Outcomes	Microsurgery	Radiosurgery	Certainty (reason for downgrade)
Pooled overall complications	8.5%	2%	Very low (risk of bias [systematic review of cohort studies] and imprecision)
Pooled serious complications	2%	1%	Very low (risk of bias [systematic review of cohort studies] and imprecision)

*Overall complications defined as ≥ 1 of following: facial nerve function worse than House-Brackmann grade of 1 or 2; cerebrospinal fluid leak, meningitis, or hydrocephalus that occurred after interventions; and survival with severe vertigo, unsteadiness, chronic headache, and tinnitus that was worse than when the status was diagnosed. Overall complications was reported as number with complications in each arm of each of 3 studies and as proportion in pooled analysis. It is not clear how authors calculated their pooled proportions. For example, pooled proportions for microsurgery and radiation therapy were reported as 8.5% and 2% respectively, but we calculated these to be 11.5% and 3.4% respectively based on numbers with Complications in each of the 3 studies and assuming all patients in study were included in this analysis as suggested by

Table 2 (so it may be that denominators for this analysis did not include all patients in the 3 studies). In Table 3 footnote, the authors reported that the complications outcome showed significant difference but it was not entirely clear what comparison was being referred to (although it appeared to be the microsurgery vs. radiosurgery comparison) and it was not clear what data was used to evaluate whether the results were significant. To confirm this significant difference, the numbers with complications in each of the 3 studies was entered into RevMan using the number of patients in the study as the denominators and this pooled analysis showed a significant increase in complications with microsurgery compared to radiation therapy (risk ratio 3.29 [1.45, 7.45]; p = 0.004).
† Defined as life-threatening complications or death; only reported as proportion in pooled analysis, and not for each of the 3 includes studies.

Source 3: Descriptive review

These systematic reviews of complication rates following microsurgery (Sughrue 2011) or radiation therapy (Sughrue 2009) were both judged to contain Very low certainty evidence. In both reviews, the quality and design of the included studies was not assessed or reported and studies with very low reliability (eg, single case reports) appear to have been combined with more reliable studies (eg, prospective cohort studies) to calculate a single pooled estimate. Also, patients with neurofibromatosis type 2 were included in both, which resulted in a downgrade for indirectness. The individual complications reported were also limited in both, and neither included audio-facial outcomes (eg, loss of facial nerve or hearing function). Because different complications (with none in common) were reported for the review of radiation therapy patients (Sughrue 2009) and the review of microsurgery patients (Sughrue 2011), these systematic reviews do not allow for a comparison between microsurgery and radiation therapy for any specific complication. A final limitation is that neither of these systematic reviews reported time point for assessment for complications, but it is assumed that the complications reported were short-term/perioperative.

Source 3: Evidence Review Table

Effects of microsurgery vs. radiosurgery on specific complications (Sughrue 2009 and Sughrue 2011 systematic reviews of complications in radiation therapy and microsurgery groups respectively, with meta-analyses which pooled studies of varying designs including case studies, case series, and cohort studies)

Study/Complications reported	Number of studies	Number of patients	Microsurgery	Radiosurgery (Gamma knife surgery only) % (n/N)	Certainty (reason for downgrade)
*Sughrue 2009 (evaluated radiation therapy in patients with tumors < 2.5 cm in largest diameter)***	63	5,631			Very low (risk of bias [downgraded twice because quality of studies not assessed and studies with very low reliability (eg, single case reports) were combined with more reliable studies (eg, prospective cohort studies)] and indirectness [patients with neurofibromatosis type 2 were

					included]) -- *Certainty/downgrades applies to all Sughrue 2009 outcomes listed below*
• new non-cranial nerve VII or non-cranial nerve VIII cranial neuropathy**				2.4% (135/5,631) (95% CI 2.0% to 2.8%)	
• hydrocephalus				0.85% (48/5,631) (95% CI 0.6% to 1.1%)	
• tinnitus				0.44% (25/5,631) (95% CI 0.3% to 0.7%)	
Sughrue 2011 (evaluated microsurgery in patients with tumor size < 2.5 cm and > 2.5 cm in largest diameter; all outcomes below are for patients with tumor size < 2.5 cm except mortality which includes all patients)	100	7,667 (7,667 is # patients with tumor size < 2.5 cm among 32,870 patients total)			Very low (risk of bias [downgraded twice because quality of studies not assessed and studies with very low reliability (eg, single case reports) were combined with more reliable studies (eg, prospective cohort studies)] and indirectness [patients with neurofibromatosis type 2 were included]) – *Certainty/downgrades apply to all outcomes listed below*
• cerebrospinal fluid leakage			6% (460/7,667) (95% CI 6.1% to 7.6%)		
• vascular complications†			0.7% (56/7667) (95% CI 0.4% to 0.9%)		
• neurological complications‡			4.6% (355/7,667)		

			(95% CI 3.9% to 5.3%)		
• mortality			0.2% (66/32,870) (95% CI 0.1% to 0.3%)		additional downgrade for indirectness because mortality was only reported for the overall group (those with a vestibular schwannoma of any size) and that may upward-bias estimate compared to what the estimate would be if restricted to those with tumors ≤2.5 cm

*Complications in Sughrue 2009 were defined as "new morbidities, appearing after radiation treatment or exacerbations of symptoms present prior to radiosurgery"
** Trigeminal neuropathy (cranial nerve V neuropathy), manifested by "facial paresthesias or tingling" was reported to be "by far the most common neuropathy" (accounting for 2.30% of the reported 2.4% rate; cranial nerves VI and XII accounted for the remainder, at 0.03% and 0.08%, respectively)
† Defined as any ischemic injury or intracranial hemorrhage that was attributed to surgical procedure
‡ Defined as any postoperative neurological symptoms other than facial nerve palsy or hearing loss that was not explicitly stated to have been present preoperatively

Descriptive Summary: Risk of radiation-induced malignancy

Evidence for radiation-induced malignancy in the treatment of vestibular schwannoma is limited (Arthurs 2011, Germano 2018). The 2018 guideline on vestibular schwannoma from the Congress of Neurological Surgeons (Germano 2018) notes there are 13 cases of reported radiation-induced malignancy among patients with vestibular schwannoma who were treated with stereotactic radiosurgery, with the most common type possibly being peripheral nerve sheath tumor. Considering post-treatment malignant transformation of the vestibular schwannoma specifically, they cite one retrospective analysis of 440 patients, 347 of whom had stereotactic radiosurgery as initial treatment and 93 of whom had stereotactic radiosurgery after microsurgical resection. The median follow-up was 12.5 years and there was 1 malignant transformation of a vestibular schwannoma 66 months postoperatively. Due to the limitations in the available evidence, we concur with the approach adopted by the Congress of Neurological Surgeons, namely stating that there may be minimal risk of malignant transformation (without any quantitative representation at the summary level), but highlighting this is an uncertain statement (the Congress of Neurological Surgeons reflect their uncertainty by assigning a Level 3 rating to the recommendation concerning how to discuss this risk with patients, with a Level 3 rating being the lowest rating and "reflecting unclear clinical certainty").

Descriptive Summary: Risk of more difficult surgery following radiation treatment if additional treatment is needed

If someone needs surgery after radiation treatment, there is evidence that the surgery is likely to be more complicated than if surgery had been performed as the initial treatment (DynaMed 2019, Hadjipanayis 2018). However, if additional treatment is needed after initial treatment with radiation, re-treatment with radiation is considered an acceptable option (Germano 2018).

FAQ 8: How long does it take to recover?

Microsurgery

Descriptive Summary

Surgery often requires a hospital stay of 2-6 days, with the exact time varying from patient to patient. After discharge from the hospital, there is often a recovery period of 4 to 6 weeks, but for some this may last up to 12 weeks. You may be advised to avoid strenuous activities during this period. You may be referred to a physical therapist for something called “vestibular rehabilitation” to help with issues you might have with balance and/or dizziness. Patients may need to wait 3 weeks or more before they can drive and 4 to 12 weeks before returning to work. However, all timelines should be individualized between the patient and the health care team.

Radiation therapy

Descriptive Summary

Radiation treatment may require a short hospital stay (up to 2 days), but if a stay is required, it is typically shorter for any given person than the stay would be for surgery. For many patients, radiation treatment can be done on an outpatient basis, with the treatment taking anywhere from 10 to 15 minutes for stereotactic radiotherapy and 30 to 120 minutes for stereotactic radiosurgery. Recovery time is quick for radiation treatment: There is often no recovery time or need to take time off from work. Some people receiving stereotactic radiotherapy opt to get treatment as they are coming from or heading to work.

(Acoustic Neuroma Association nd, Dartmouth-Hitchcock nd, Hansen 2018, Klutz 2018, Mayfield Clinic 2018, Mayo Clinic 2017, NYU Langone Health nd, University of Kansas Health System nd, University of Maryland Medical Center nd)

Part 5 - Evidence Synthesis

Methods

Evidence synthesis process

Synthesis methods will be based on the most appropriate methods matching the available evidence. We will systematically consider synthesis methods with the following questions:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

State "Yes" or "No". Provide justification if "No".

If "Yes", leave the statement below that reads "If 'Yes', what method is the best approach?" and select the best method from those listed. Delete everything else. If another method not listed is deemed appropriate, provide justification.

If "No", leave the statement below that reads "If 'No', what method is best to represent the evidence synthesis?" and select the best method from those listed. Delete everything else. If another method not listed is deemed appropriate, provide justification.

If "Yes", what method is the best approach?

Pick one of the following and justify:

(1) meta-analysis already done

(2) meta-analysis created from the evidence results

(3) median of sufficiently-valid results, stating cutoff for validity

(4) median of all results

If "No", what method is best to represent the evidence synthesis?

Pick one of the following and justify:

(1) range of all results

(2) range of sufficiently valid results

(3) descriptive summary without quantitative representation (e.g., consistency in direction, but inconsistency in magnitude)

(4) statement of inconsistency too limiting for single synthesized conclusion

Where evidence is very limited, or the FAQ is for descriptive summary, such that summary text was provided instead of Evidence Review Tables, the Descriptive Evidence Summary will be noted

Results

FAQ 1: What does the treatment involve?

Microsurgery

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

The goal of surgery is to remove the tumor, though complete removal may not be possible in some cases. The surgery is done while the patient is under general anesthesia, and the tumor is removed through a hole in the skull. The location of the hole in the skull may be described in the phrasing of the approach, such as “suboccipital” approach if the hole is behind the ear or “translabyrinthine” approach which includes removal of part of the inner ear. If removing the tumor with a translabyrinthine approach, hearing loss will result because of how the surgery is done. As such, this approach is usually only considered if people already have hearing problems or hearing loss that surgery is unlikely to help (regardless of approach).

For some patients, depending on the specific surgery and imaging results before the surgery, there are different recommendations for follow-up magnetic resonance imaging (MRI) studies, but most people will have at least 1 follow-up MRI. For patients who had gross total resection, a postoperative MRI may be obtained within 1 year after surgery. For patients who did not have gross total resection (ie, some tumor left behind), more frequent MRIs are recommended, and an annual MRI for 5 years might be reasonable.

Radiation therapy

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

The goal of radiation therapy is to stop the tumor’s growth. The tumor’s position is “mapped” using imaging studies. This “map” is used to direct radiation to the tumor in a highly-focused way while minimizing exposure of healthy tissue. One type of radiation treatment (“stereotactic radiosurgery”) does this in a single session. Another type of radiation treatment (“stereotactic radiotherapy”) uses a smaller dose of radiation that is delivered over several sessions. Neither of these treatments require cutting or actual surgery. The “surgery” part of “stereotactic radiosurgery” only indicates that the treatment occurs in one session (like surgery does), whereas stereotactic radiotherapy occurs over several sessions. Both treatments can be done while the patient is awake, though the patient’s head is held still with equipment and the scalp may be numbed. Stereotactic radiosurgery is used more commonly than stereotactic radiotherapy. After having radiation treatment, long-term follow-up with repeated MRIs is recommended to assess for recurrence.

(Arthurs 2011, DynaMed 2019, Germano 2018, Johns Hopkins Medicine nd, Kutz 2018, Lin 2017, Mayo Clinic 2018)

FAQ 2: Will the treatment control the tumor?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	0
Second-round (Systematic review searches)	68	1 (Liu 2015)
Third-round (Original study tracing)	Not applicable	
Fourth-round (Original article searches)	29	0

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate			
Low			
Very low	Liu 2015		
Unusable			
Not applicable			

Microsurgery vs. radiation therapy

Part 4 Results for FAQ2:

Tumor control rate was best estimated using the results of a systematic review that pooled outcome data from 3 prospective cohort studies comparing microsurgery vs. radiation therapy in 377 patients with tumors < 3.0 cm in diameter (or stages I, II, or III based on Koos classification) and mean follow-up of 2 to 3.5 years. (Liu 2015)

The Liu 2015 systematic review found Low certainty evidence of a pooled tumor control rate of 94.3% for microsurgery and 97.0% for radiation therapy. In the pooled analysis and in all 3 of the individual studies, both the radiation therapy group and microsurgery group had a high rate of tumor control, with no clear evidence of a difference. The certainty of the overall body of evidence on tumor control rate was assessed as Very low with downgrades for risk of bias (all 3 studies are cohort studies) and serious imprecision.

Evidence Synthesis Process for FAQ2:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

The Liu 2015 systematic review and meta-analysis provided a pooled estimate of tumor control rate in 3 prospective cohort studies. Its pooled results showed that patients with vestibular schwannomas < 3.0 cm in diameter have high tumor control rates regardless of whether they have radiation therapy or microsurgery. At a mean follow-up of 2 to 3.5 years, patients who have radiation therapy have a tumor control rate of about 94%; patients who have microsurgery have a tumor control rate of about 97%. (Very low certainty)

Although a meta-analysis already done is the best method for synthesis, we present here both quantitative and qualitative syntheses given the advantages and disadvantages of both.

Quantitative synthesis:

Out of 1,000 people with vestibular schwannoma, about 940 to 970 (94% to 97%) may have good control of the tumor at 2 to 4 years after treatment, regardless of whether they choose radiation treatment or surgery. (Very low certainty)

Qualitative synthesis:

Most patients may have good tumor control at 2 to 4 years after treatment, regardless of whether they have radiation treatment or surgery. (Very low certainty)

FAQ 3: Will the treatment make me feel better?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	2 (Carlson 2015, Papatsoutsos 2018)
Second-round (Systematic review searches)	68	0
Third-round (Original study tracing)	Traced Liu 2015* and Papatsoutsos 2018 systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery, yielding Di Maio 2009, Myrseth 2009, Pollock 2006, and Régis 2002	
Fourth-round (Original article searches)	29	0

* Liu 2015 did not include a quality of life outcome, so it does not appear in earlier rounds of searching for this FAQ, but we still traced Liu 2015 for prospective cohort studies investigating radiation therapy and microsurgery to see if these studies reported additional outcomes that were not considered by Liu 2015. Thus, we show tracing of Liu 2015 in third-round searching.

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate			
Low			
Very low	Papatsoutsos 2018		Di Maio 2009, Myrseth 2009, Pollock 2006 (prospective cohort studies)
Unusable			
Not applicable			Carlson 2015* (retrospective cohort study), Régis 2002† (retro- and prospective cohort study)

* We prespecified preference for prospective data for this FAQ, and Carlson 2015 is retrospective. Therefore, we do not consider this study in Parts 4 or 5.

† One additional potentially eligible report (Régis 2002) not included in Papatsoutsos 2018 was identified via its inclusion in Liu 2015. On evaluating the full text of Régis 2002, we discovered only the radiosurgery group was evaluated prospectively, with its results being compared to a microsurgery group that had previously been evaluated using a retrospective design. It is a judgment call whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively (and we prespecified preference for prospective data for this FAQ). Régis 2002 included a quality-of-life outcome and found patients receiving microsurgery had significantly worse quality-of-life results than patients receiving radiosurgery. The 3 prospective cohort studies included in Papatsoutsos 2018 had inconsistent results on quality of life; thus, Régis 2002 would not affect the 'bottom-line' finding of inconsistent results based on Papatsoutsos 2018. Therefore, we did not formally assess certainty for Régis 2002.

Microsurgery vs. radiation therapy

Part 4 Results for FAQ3:

Studies that reported on quality of life were identified from a systematic review that evaluated quality of life outcomes after microsurgery, stereotactic radiation (including either stereotactic radiosurgery or fractionated stereotactic radiotherapy), or observation-only in adults with vestibular schwannoma (Papatsoutsos 2018). Three prospective cohort studies that included both microsurgery and radiation therapy groups were identified from this systematic review and considered for this Evidence Report. A full summary of each of these 3 prospective cohort studies was prepared, which included data on quality of life outcomes, summarized below.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting quality of life outcomes identified through systematic review*

Author year	Sample size	Follow-up duration	Quality of life results	Certainty (downgrade)
Di Maio 2009	145	radiation treatment: 36.4 months; microsurgery: 32.3 months	*At 24 months*, microsurgery group associated with significant improvement from baseline in SF-36 total and mental dimension scores, with no significant changes from baseline in radiosurgery group in SF-36 total or its physical or mental dimension scores. *At last follow-up*, there were no significant changes from baseline for either group in any of these 3 SF-36 measures.	Very low (risk of bias [cohort study] and inconsistency [inconsistent results at 24 months vs. last follow-up])
Myrseth 2009	88	24 months	At 24 months there were no significant within group changes for either group on any of the 8 components of SF-36, but the radiosurgery group appeared to have better outcomes on 3 of the 4 components of the Glasgow Benefit Inventory (although methods and reporting were unclear).	Very low (risk of bias [cohort study] and inconsistency [inconsistent results on SF-36 vs. Glasgow Benefit Inventory])
Pollock 2006	82	42 months	The radiosurgery group appeared to have significantly better outcomes on $\leq$ 1 of the 10 components of the Health Status Questionnaire (modified version of SF-36) at last follow-up (although methods and reporting were unclear). The microsurgery group had "significant deterioration" in Papatsoutsos 2018's review, and review of full text of Pollock 2006 suggested decline in different components at different timepoints, with only bodily pain being significantly worse at final follow-up (again, however, methods and reporting were unclear).	Low (risk of bias [cohort study])

*all 3 studies had eligibility requirement of maximum tumor diameter < 3 cm

The certainty of the overall body of evidence on quality of life was assessed as Very low with downgrades for risk of bias (all 3 studies are cohort studies) and serious inconsistency (within and between studies).

Evidence Synthesis Process for FAQ3:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

No

If "No", what method is best to represent the evidence synthesis?

(4) statement of inconsistency too limiting for single synthesized conclusion

A single synthesized conclusion cannot be drawn because of the inconsistent findings of the 3 prospective cohort studies. In 2 of the studies with a combined 170 patients, the radiation therapy group appeared to have more favorable outcomes than microsurgery group on $\geq$ 1 quality of life outcome/component at final follow-up (Myrseth 2009; Pollock 2006). In the third study with 145 patients, the microsurgery group appeared to have more favorable outcomes than the radiation therapy group (at 2 years, but not at final follow-up). Additionally, there was a considerable degree of concern over the quality of reporting of methods and outcomes, and in several cases, only within-group differences were reported. Compared to baseline reports of improvement, no effect and worsening were noted across quality of life measures.

We do not have adequate research on how radiation treatment or surgery compare to each other in terms of a person's quality of life. We cannot state clearly if treatment improves or worsens quality of life.

FAQ 4: Will the treatment preserve my useful hearing?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	1 (Carlson 2015)
Second-round (Systematic review searches)	68	3 (Ahsan 2017, Coughlin 2018, Liu 2015)
Third-round (Original study tracing)	Traced Liu 2015 and Papatsoutsos 2018 systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery, yielding Di Maio 2009, Myrseth 2009, Pollock 2006, and Régis 2002*	
Fourth-round (Original article searches)	29	0

* Papatsoutsos 2018 did not include a hearing outcome, so it does not appear in earlier rounds of searching for this FAQ, but we still traced Papatsoutsos 2018 for prospective cohort studies investigating radiation therapy and microsurgery to see if these studies reported additional outcomes that were not considered by Papatsoutsos 2018. Thus, we show tracing of Papatsoutsos 2018 in third-round searching. However, tracing of Papatsoutsos 2018 only added Di Maio 2009 as a potential additional study (compared to those already included and accounted for by Liu 2015, namely Myrseth 2009, Pollock 2006, and Régis 2002). Di Maio 2009 also ultimately proved inapplicable and less informative compared to the data in Liu 2015 (see Part 3 recap).

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate	Liu 2015		
Low			
Very low			
Unusable			
Not applicable	Ahsan 2017*, Coughlin 2018*		Carlson 2015* (retrospective cohort study), Di Maio 2009† (prospective cohort study)

* We prespecified preference for prospective data for this FAQ. Carlson 2015 is retrospective, Ahsan contains only retrospective studies, and Coughlin 2018 has an overwhelming majority of retrospective studies and gives no way to differentiate which studies were not retrospective. We therefore do not consider these studies in Parts 4 or 5.

† Di Maio 2009 reported a hearing-related outcome; however, its data cannot be integrated with the data reported by Liu 2015, because Liu 2015 restricts to patients with useful hearing at baseline but Di Maio 2009 only reported proportion with useful hearing at baseline and proportion with useful hearing at last follow-up (but not proportion with useful hearing at follow-up among those with useful hearing at baseline, as Liu 2015 did). Given preservation of useful hearing is the key hearing goal of definitive treatment for vestibular schwannoma, we consider Liu 2015's operationalization of the hearing outcome to be more informative for evidence review and evidence synthesis, and we do not consider Di Maio 2009 for this FAQ in Part 5 (we include a brief footnote about it in Part 4).

Microsurgery vs. radiation therapy

Part 4 Results for FAQ4:

Useful hearing preserved was assessed using the results of a systematic review (Liu 2015) that pooled results from 3 prospective cohort studies (Régis 2002; Myrseth 2009; Pollock 2006) with mean follow-up of 2 to 3.5 years and 377 patients total that compared microsurgery vs. radiation therapy in patients with vestibular schwannomas < 3.0 cm in diameter (or stages I, II, or III based on Koos classification). The outcome of useful hearing preserved was defined as the proportion of patients with useful hearing at long-term follow-up among patients with useful hearing at time of diagnosis.

Pooled effects of microsurgery vs. radiosurgery on useful hearing preserved based on systematic review and meta-analysis (Liu 2015)*

Intervention	**Pooled proportion with useful hearing* preserved†**	**Certainty for comparison (reason for downgrade)**
microsurgery	4.3%	Moderate (risk of bias [no randomization] but increased certainty for large effect size)
radiosurgery‡	60.2%	

* Useful hearing was defined as Gardner and Robertson Scale I or II or American Academy of Otolaryngology-Head and Neck Surgery class A or B. Pooled proportion with useful hearing at time of diagnosis was 65.5% for microsurgery and 50.7% for radiation therapy (p = 0.004).

† p < 0.001 for comparison of treatments for preservation of useful hearing

‡ Radiosurgery as defined by the authors included gamma knife radiosurgery, linear accelerator radiosurgery, and fractionated stereotactic radiotherapy. The term “radiosurgery” does not typically include radiotherapy, but the authors used this collective term in their review, and the authors noted that there is no clear advantage of one radiosurgery approach vs. another as justification for including all modalities in their review.

Evidence Synthesis Process for FAQ4:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

The Liu 2015 systematic review found Moderate certainty evidence of useful hearing preserved in 4.3% of patients receiving microsurgery and 60.2% of patients receiving radiation therapy at a mean follow-up of 2 to 3.5 years. Both in the pooled analysis and in all 3 of the individual studies pooled, radiation therapy had a higher rate of useful hearing preserved compared to microsurgery.

Although a meta-analysis already done is the best method for synthesis, we present here both quantitative and qualitative syntheses given the advantages and disadvantages of both.

Quantitative synthesis:
Out of 1,000 people with vestibular schwannoma who had useful hearing prior to treatment and receive radiation treatment, about 600 (60%) may still have useful hearing at 2 to 4 years after treatment. (Moderate certainty)

Out of 1,000 people with vestibular schwannoma who had useful hearing prior to treatment and receive surgery, about 40 (4%) may still have useful hearing at 2 to 4 years after treatment. (Moderate certainty)

Quantitative synthesis:
Many people who have radiation treatment may still have useful hearing 2 to 4 years after treatment if they had useful hearing prior to treatment. This seems less likely with surgery, and there is a risk of hearing loss. (Moderate certainty)

FAQ 5: Will the treatment preserve my facial nerve function?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	1 (Carlson 2015)
Second-round (Systematic review searches)	68	0
Third-round (Original study tracing)	Traced Liu 2015 and Papatsoutsos 2018 systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery, yielding Di Maio 2009, Myrseth 2009, Pollock 2006, and Régis 2002*	
Fourth-round (Original article searches)	29	0

* Neither Liu 2015 nor Papatsoutsos 2018 included facial nerve function as an individual outcome (Liu 2015 includes adverse facial nerve outcomes as a complication), so neither appears in earlier rounds of searching for this FAQ; however, we still traced both systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery to see if these studies reported additional outcomes that were not considered by these systematic reviews. Thus, we show tracing of these systematic reviews in third-round searching.

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate			
Low			Myrseth 2009 (prospective cohort study), Pollock 2006 (prospective cohort study)
Very low			Di Maio 2009 (prospective cohort study)
Unusable			
Not applicable			Carlson 2015* (retrospective cohort study), Régis 2002† (retro- and prospective cohort study)

* We prespecified preference for prospective data for this FAQ, and Carlson 2015 is retrospective. Therefore, we do not consider this study in Parts 4 or 5.

† One additional potentially eligible report (Régis 2002) was identified via inclusion in Liu 2015. On reviewing the full text of Régis 2002, we found that only the radiosurgery group was evaluated prospectively, with its results being compared with those of the microsurgery group which had been previously evaluated with a retrospective design. It is a judgment call whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively. Régis 2002 included a facial motor disturbance outcome and found that 47% of patients who had microsurgery had a new facial motor disturbance compared with 0% of patients who had radiosurgery. This is consistent with 2 of the 3 prospective cohort studies which showed significantly worse facial function in the microsurgery group (Myseth 2009; Pollock 2006); the third prospective cohort study showed no significant difference between groups (Di Maio 2009). We did not formally assess certainty of outcomes in Régis 2002.

Microsurgery vs. radiation therapy

Part 4 Results for FAQ5:

Preservation of facial nerve function was not an included outcome in either systematic review of prospective cohort studies (Liu 2015; Papatsoutsos 2018). Therefore, this outcome has been summarized based on each of the 3 prospective cohort studies with long-term follow-up (2 to 3.5 years) that compared microsurgery vs. radiosurgery in patients with tumors < 3.0 cm.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting facial nerve function outcome at long-term follow-up (range 24 to 42 months)

Author year	Sample size	% (n/N) with good facial function*		% (n/N) with reduced facial function†		Certainty (downgrade)
		Microsurgery	Radiation therapy	Microsurgery	Radiation therapy	
Di Maio 2009‡	145	Not reported	Not reported	24.3% (17/70)	27.0% (10/37)	Very low (risk of bias [cohort study] and imprecision)
Myrseth 2009§	88	82.1% (23/28)	98.3% (59/60)	46.4% (13/28)	1.6% (1/60)	Moderate (risk of bias [cohort study] but large effect size)
Pollock 2006¶	82	83% (30/36)	98% (45/46)	25% (9/36)	4% (2/46)	Low (risk of bias [cohort study])

*Defined as House-Brackmann Grade 1 or 2 in Myrseth 2009 and Pollock 2006; this outcome was not reported in Di Maio 2009.
† Defined as House-Brackmann Grade > 1 in Myrseth 2009 and Pollock 2006 and as "some element of facial weakness" on patient self-reports on a custom questionnaire created by the study authors in Di Maio 2009.
‡ No significant difference between groups in proportion with reduced facial function. Absolute risk differences and confidence intervals are presented in Part 4.
§ Significant differences between groups on percentage with good facial function (p = 0.0053) and percentage with reduced facial function (p < 0.0001). Absolute risk differences and confidence intervals are presented in Part 4.
¶ Significant differences between groups on percentage with good facial function (p = 0.04) and percentage with reduced facial function (p < 0.01). Absolute risk differences and confidence intervals are presented in Part 4.

The certainty of the overall body of evidence on facial nerve function was assessed as Very low with downgrades for risk of bias (all 3 studies are cohort studies) and inconsistency (in effect estimates across studies and in absolute risk estimates across studies).

Evidence Synthesis Process for FAQ5:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

No

If "No", what method is best to represent the evidence synthesis?

(2) range of sufficiently valid results

The relevant studies reported preservation of facial nerve function as proportion of patients with "good facial function" and/or as proportion of patients with "reduced facial function", at long-term follow-up after microsurgery or radiation therapy. Because these constructs are similar and because only the "reduced facial function" outcome was reported by all 3 studies, we have focused on that outcome.

For the proportion of patients with "reduced facial function" outcome, a single synthesized conclusion cannot be drawn because of the range of findings of the 3 prospective cohort studies. In 2 of the 3 studies, a substantially lower proportion of patients in the radiation therapy group had reduced facial function compared to the microsurgery group (2% vs. 46% in Myrseth 2009; 4% vs. 25% in Pollock 2006). However, in the third study, there were no significant or clinically important differences between groups (although a slightly higher proportion in the radiation therapy group had reduced facial function, 27% vs. 24%) (Di Maio 2009). Therefore, to offer a conservative conclusion (to avoid false precision), a single synthesized result may not be the best summary, and we instead present a range of sufficiently valid results from the above studies.

Although a meta-analysis already done is the best method for synthesis, we present here both quantitative and qualitative syntheses given the advantages and disadvantages of both.

Quantitative synthesis:

Out of 1,000 people with vestibular schwannoma who receive radiation treatment, about 20 to 270 (2% to 27%) may have reduced function of their face at 2 to 4 years after treatment. (Very low certainty)

Out of 1,000 people with vestibular schwannoma who receive surgery, about 240 to 460 (24% to 46%) may have reduced function of their face at 2 to 4 years after treatment. (Very low certainty)

Qualitative synthesis:

After treatment with radiation, some patients may have reduced function of their face at 2 to 4 years after treatment. This may occur just as often or much more often with surgery. (Very low certainty)

FAQ 6: Will I have tinnitus (ringing, clicking, or buzzing in the ears) after treatment?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	0
Second-round (Systematic review searches)	68	0
Third-round (Original study tracing)	Traced Liu 2015 and Papatsoutsos 2017 systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery, yielding Di Maio 2009, Myrseth 2009, Pollock 2006, and Régis 2002*	
Fourth-round (Original article searches)	29	0

* Neither Liu 2015 nor Papatsoutsos 2018 included tinnitus as an outcome, so neither appears in earlier rounds of searching for this FAQ; however, we still traced both of these systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery to see if these studies reported additional outcomes that were not considered by these systematic reviews. Thus, we show tracing of these systematic reviews in third-round searching.

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate			
Low			
Very low			Di Maio 2009, Myrseth 2009, Pollock 2006 (prospective cohort studies)
Unusable			
Not applicable			Régis 2002* (retro- and prospective cohort study)

* One additional potentially eligible report (Régis 2002) was identified via inclusion in the Liu 2015 systematic review. On evaluating the full text of Régis 2002, we found that only the radiosurgery group was evaluated prospectively, and its results were compared with those of the microsurgery group which had previously been evaluated using a retrospective design. It is a judgment call whether to include Régis 2002 among prospective cohort studies because the 2 groups were not studied contemporaneously and only 1 of the 2 groups was evaluated prospectively. Régis 2002 included a tinnitus (Y/N) outcome and found that 40% of patients had a new complaint of tinnitus after microsurgery vs. 50% after radiosurgery (not statistically significant). The lack of a clear difference is consistent with the results of the 3 prospective cohort studies summarized above. We did not formally assess certainty of outcomes in Régis 2002.

Microsurgery vs. radiation therapy

Part 4 Results for FAQ6:

Tinnitus was not an included outcome in either systematic review of prospective cohort studies (Liu 2015; Papatsoutsos 2018). Therefore, this outcome has been summarized based on each of the 3 prospective cohort studies with long-term follow-up (2 to 3.5 years) that compared microsurgery vs. radiosurgery in patients with tumors < 3.0 cm.

Prospective cohort studies including both microsurgery and radiosurgery groups and reporting tinnitus outcome at long-term follow-up (range 24 to 42 months)*

Author year	**Sample size**	**% (n/N) with tinnitus (yes/no)***		**Certainty (downgrade)**
		Microsurgery	Radiation therapy	
Di Maio 2009	145	76.1% (54/71)	75.7% (28/37)	Very low (risk of bias [cohort study] and imprecision)
Myrseth 2009	88	66.7% (40/60)	83.1% (23/28)	Very low (risk of bias [cohort study] and imprecision)
Pollock 2006	82	30% (11/36)	32% (15/46)	Very low (risk of bias [cohort study] and imprecision)

* No significant difference between groups in any of 3 studies

The certainty of the overall body of evidence on tinnitus was assessed as Very low, with downgrades for risk of bias (because all 3 studies are cohort studies) and imprecision.

Evidence Synthesis Process for FAQ6:

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

No

If "No", what method is best to represent the evidence synthesis?

(2) range of sufficiently valid results

None of the 3 prospective cohort studies comparing microsurgery vs. radiosurgery found a clear difference in the rate of tinnitus at long-term follow-up (2 to 3.5 years). Overall sample sizes were small, and the rate of tinnitus for either treatment option ranged from about 30% (30% for microsurgery, 32% for radiation therapy) to about 80% (76% for microsurgery, 83% for radiation therapy). As no study demonstrated a clear difference in the rate of tinnitus, one should not overinterpret any apparent difference in point estimates. We judged expressing the ranges as such was more appropriate than any attempt to provide a single quantified estimate, as the former better reflects the uncertainty that exists in the evidence.

Although a meta-analysis already done is the best method for synthesis, we present here both quantitative and qualitative syntheses given the advantages and disadvantages of both. For the qualitative synthesis, we incorporate very basic quantitative representation given the difficulty in expressing the range of possibilities (30% to 83%).

Quantitative synthesis:

Out of 1,000 people with vestibular schwannoma, about 300 to 830 (30% to 83%) may have ringing, buzzing, or clicking in their ears at 2 to 4 years after treatment, regardless of whether they choose radiation treatment or surgery. (Very low certainty)

Qualitative synthesis (primarily qualitative):

People may have ringing, buzzing, or clicking in their ears at 2 to 4 years after treatment. Whether someone chooses radiation treatment or surgery may not make a difference in whether this happens. How often this occurs is not very clear, but it may be somewhere between 3 in 10 people and 8 in 10 people. (Very low certainty)

FAQ 7: What are the risks?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	7	2 (Nuño 2019, Sughrue 2011)
Second-round (Systematic review searches)	68	3 (Liu 2015, Sughrue 2009, Whitmore 2011)
Third-round (Original study tracing)	Traced Liu 2015 and Papatsoutsos 2017* systematic reviews for prospective cohort studies investigating radiation therapy and microsurgery, yielding Myrseth 2009 and Pollock 2006	
Fourth-round (Original article searches)	29	0

* Papatsoutsos 2018 did not include complications as an outcome, so it does not appear in earlier rounds of searching for this FAQ, but we still traced Papatsoutsos 2018 for prospective cohort studies investigating radiation therapy and microsurgery to see if these studies reported additional outcomes that were not considered by Papatsoutsos 2018. Thus, we show tracing of Papatsoutsos 2018 in third-round searching.

Part 3 Critical Appraisal:

Certainty	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate			
Low	Liu 2015		
Very low	Nuño 2019, Sughrue 2009, Sughrue 2011		Myrseth 2009, Pollock 2006 (prospective cohort studies)
Unusable	Whitmore 2011*		
Not applicable			

* Concerns over methods and reliability of results resulted in us classifying this as unusable. See Part 3 for details.

Part 4 Results for FAQ7:

Descriptive Summary of sources considered

For complications, three different sources were considered:

1) retrospective analysis of the largest available database in the United States of patients having treatment for vestibular schwannomas (Nuño 2019);
2) systematic reviews that evaluated complication risks following microsurgery (Sughrue 2011) or following radiation therapy (Sughrue 2009); and
3) systematic review that reported rates of overall complications and serious complication from a pooled analysis of 3 prospective cohort studies (Liu 2015).

The certainty of evidence was considered Very low for each of these sources because all had important limitations/downgrades in addition to downgrade due to study design, as described below.

The primary limitation of the retrospective analysis is that it did not restrict inclusion to patients with tumors < 3 cm in diameter and tumor size was not reported (Nuño 2019). If a large proportion of patients diagnosed with vestibular schwannoma had tumors > 3 cm, that might have positively biased the complication rate in the surgery group in this study (compared to only including patients with tumor diameter < 3 cm), because patients with larger tumors would probably be more likely to have complications from treatment. There were no other limitations of this study identified, as further described in Part 4.

The primary limitation of the systematic reviews of complication rates following microsurgery (Sughrue 2011) or radiation therapy (Sughrue 2009) is that the quality and design of the included studies was not assessed or reported, and studies with very low reliability (eg, single case reports) appear to have been combined with more reliable studies (eg, prospective cohort studies) to calculate a single pooled estimate. Also, patients with neurofibromatosis type 2 were included in both, which resulted in downgrades for indirectness.

The primary limitation of the systematic review that reported rates of overall complications and serious complications from a pooled analysis of 3 prospective cohort studies was imprecision (Liu 2015). The serious complications outcome (defined as life-threatening complications or death) was downgraded twice for imprecision because of the low event rate (1% of radiation therapy group and 2% of microsurgery group, with no significant difference between groups). This review was also of limited usefulness because it reported only “Complications” and “Serious complications” as outcomes, and not specific types of complications. Due to these issues, we deemed this source to be of limited usefulness to inform synthesis statements regarding risks, so it was not considered further for Part 5.

The risks summarized below include mortality (reported only in Sughrue 2011, and only for microsurgery group), pooled overall complications (reported by Liu 2015 and Nuño 2019 for both groups in each), and various specific complications (reported by Nuño 2019 for both groups and with review and comparison of complications reported by Sughrue 2011 and Sughrue 2009).

Mortality

The only source that reported on mortality as a complication was the Sughrue 2011 systematic review, which reported a mortality rate of 0.2% (95% CI of 0.1% to 0.3%) following microsurgery in an analysis of studies of patients with a vestibular schwannoma of any size. (Very low certainty)

Evidence Synthesis Process for mortality

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

The only available data on mortality as a complication of microsurgery is from a systematic review with meta-analysis already done.

No source reported on mortality as a complication following radiation therapy.

Out of 1,000 people with vestibular schwannoma who have surgery, 2 (0.2%) may die. We do not have adequate research to know whether this is higher, lower, or the same as people who have radiation treatment. (Very low certainty)

Overall complications

An outcome of overall complications was reported by Liu 2015 and Nuño 2019, but it was defined differently in the two studies. Nuño 2019 defined overall complications as any of following: wound infection, venous thrombosis, pulmonary embolism, pneumonia, mechanical ventilation, hydrocephalus, hematoma/seroma, cerebrospinal fluid leak, central nervous system, or acute myocardial infarction. Liu 2015 defined overall complications as ≥ 1 of following: facial nerve function worse than House-Brackmann grade of 1 or 2; cerebrospinal fluid leak, meningitis, or hydrocephalus that occurred after interventions; and survival with severe vertigo, unsteadiness, chronic headache, and tinnitus that was worse than when the status was diagnosed.

The rate of overall complications reported in the two studies was as follows:

- microsurgery group
  - 28.5% in Nuño 2019
  - 8.5% in Liu 2015
- radiation therapy group
  - 2.6% in Nuño 2019
  - 2% in Liu 2015

Both Nuño 2019 and Liu 2015 found a significant difference in overall complications between groups.

Evidence Synthesis Process for overall complications

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

No

Although the estimates for the radiation therapy group are fairly compatible, the estimates for the surgery group show considerable inconsistency, and we favor reflecting this via a range of sufficiently valid results rather than attempting to provide a single quantified estimate.

If "No", what method is best to represent the evidence synthesis?

(2) range of sufficiently valid results

Out of 1,000 people with vestibular schwannoma who have surgery, about 85 to 285 (8.5% to 28.5%) may have a complication of any kind. (Very low certainty)

Out of 1,000 people with vestibular schwannoma who have radiation treatment, about 20 to 26 (2% to 2.6%) may have a complication of any kind. (Very low certainty)

Specific complications

Nuño 2019 reported Very low certainty evidence on 9 specific complications and found a significantly higher rate in the microsurgery group for 7 out of 9 complications. The rates for specific complications in each group are reported below. Specific complications with significantly higher rate in microsurgery group are bolded. Omitted from the table is the composite outcome "central nervous system complications"; its components were not clearly defined (thus making this outcome less informative).

Specific complications	Microsurgery (n = 2,028)	Radiosurgery (n= 1,346)
Wound infection	**1.7%**	**0.1%**
Venous thrombosis	**0.8%**	**0.2%**
Pulmonary embolism	**0.4%**	**0%**
Pneumonia	**1.6%**	**0.4%**
Mechanical ventilation	0.2%	0%
Hydrocephalus	**3%**	**0.8%**
Hematoma/seroma	**2%**	**0.2%**
Cerebrospinal fluid leak	**4.4%**	**0%**
Acute myocardial infarction	0.3%	0.1%

Complications reported in Sughrue 2009 or Sughrue 2011 were cross-checked against those reported in Nuño 2019 (above). Two complications were considered useful to supplement Nuño 2019, with the rest being considered non-useful as described below:

- Outcomes deemed useful to supplement data from Nuño 2019
    - for the microsurgery group, "vascular complications" were reported as 0.7% in Sughrue 2011, with the outcome defined as "any ischemic injury or intracranial hemorrhage that was attributed to the surgical procedure"
    - for the radiosurgery group, new non-cranial nerve VII or non-cranial nerve VIII cranial neuropathy was reported in 2.4% of participants in Sughrue 2009, with trigeminal neuropathy (manifested by paresthesias or tingling in the face) being by far the most common (accounting for 2.3% or the 2.4% rate; cranial nerves VI and XII accounted for the remainder, at 0.03% and 0.08%, respectively)
- Outcomes deemed not useful to supplement data from Nuño 2019
    - only 2 specific complications reported in Nuño 2019 were also reported in either Sughrue 2009 or Sughrue 2011 and results were consistent for both
        - hydrocephalus in radiation therapy group
            - 0.85% in Sughrue 2009
            - 0.8% in Nuño 2019
        - cerebrospinal fluid leak in microsurgery group
            - 6% in Sughrue 2011
            - 4.4% in Nuño 2019
    - for the microsurgery group, 1 complication reported in Sughrue 2011 was defined similarly but not identically to complications reported in Nuño 2019
        - "neurological complications" was reported in 4.6% in Sughrue 2011 and "central nervous system complications" was reported in 10.1% in Nuno 2019
            - because it is not clear how these differ, and because there is no comparative rate of neurological complications for radiation therapy group, only the Nuño 2019 outcome is reported below (Nuño 2019 also

offers the more conservative estimate of the 2 sources, i.e., the higher estimate given this is a risk)

- for the radiotherapy group, Sughrue 2009 also reported on tinnitus (reporting a 0.44% rate), but we did not consider this as a risk given it has typically been considered as a long-term outcome (which we address in FAQ6)

Evidence Synthesis Process for overall complications

Is it useful and appropriate to present the synthesis of evidence results as a single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

Estimates from studies already done

Out of 1,000 people who have vestibular schwannoma and receive surgery:

- **about 44 (4.4%) may have fluid from inside the brain leak out**
- **about 30 (3%) may have fluid buildup in their brain**
- **about 20 (2%) may get a pocket of blood or fluid near where the surgery was done**
- **about 17 (1.7%) may get a wound infection**
- **about 16 (1.6%) may get pneumonia**
- **about 8 (0.8%) may get a blood clot, with 4 (0.4%) getting the blood clot in the lung**
- **about 7 (0.7%) may have bleeding or blockage of blood flow that can cause injury to the area or a stroke**
- **about 2 (0.2%) may have to go on a breathing machine for a certain period of time after the surgery**
- **about 3 (0.3%) may have a heart attack**

(Very low certainty)

Out of 1,000 people who have vestibular schwannoma and receive radiation treatment:

- **about 24 (2.4%) may develop a problem with a nerve near the brain, most likely resulting in numbness or tingling in the face**
- **about 8 (0.8%) may have fluid buildup in their brain**
- **about 4 (0.4%) may get pneumonia**
- **about 2 (0.2%) may get a pocket of blood or fluid near where the treatment occurs**
- **about 2 (0.2%) may get a blood clot, with 0 (0%) getting the blood clot in the lung**
- **about 1 (0.1%) may have a heart attack**
- **about 1 (0.1%) may get a wound infection**

(Very low certainty)

Radiation treatment-specific risks answered descriptively

Below, we present descriptive summaries regarding two radiation treatment-specific risks of interest: The risk of malignancy caused by the radiation treatment, and the risk of a more complicated surgery after having radiation treatment if re-treatment is needed and surgery is selected as the treatment modality.

Descriptive Summary: Risk of radiation-induced malignancy

Evidence for radiation-induced malignancy in the treatment of vestibular schwannoma is limited (Arthurs 2011, Germano 2018). The 2018 guideline on vestibular schwannoma from the Congress of Neurological Surgeons (Germano 2018) notes there are 13 cases of reported radiation-induced malignancy among patients with vestibular schwannoma who were treated with stereotactic radiosurgery, with the most common type possibly being peripheral nerve sheath tumor. Considering post-treatment malignant transformation of the vestibular schwannoma specifically, they cite one retrospective analysis of 440 patients, 347 of whom had stereotactic radiosurgery as initial treatment and 93 of whom had stereotactic radiosurgery after microsurgical resection. The median follow-up was 12.5 years and there was 1 malignant transformation of a vestibular schwannoma 66 months postoperatively. Due to the limitations in the available evidence, we concur with the approach adopted by the Congress of Neurological Surgeons, namely stating that there may be minimal risk of malignant transformation (without any quantitative representation at the summary level), but highlighting this is an uncertain statement.

Although evidence is limited, the risk of getting a cancer from radiation treatment appears very low.

Descriptive Summary: Risk of more difficult surgery following radiation treatment if additional treatment is needed

If someone needs surgery after radiation treatment, there is evidence that the surgery is likely to be more complicated than if surgery had been performed as the initial treatment (DynaMed 2019, Hadjipanayis 2018). However, if additional treatment is needed after initial treatment with radiation, re-treatment with radiation is considered an acceptable option (Germano 2018).

If you need to have additional treatment later due to the schwannoma coming back or growing again, having surgery is likely to be more difficult than if you had surgery for your first treatment. However, you may also be able to have radiation treatment again. You can discuss this further with your health care team.

FAQ 8: How long does it take to recover?

Pre-Synthesis Efforts: Not applicable

Microsurgery

Descriptive Summary

Surgery often requires a hospital stay of 2-6 days, with the exact time varying from patient to patient. After discharge from the hospital, there is often a recovery period of 4 to 6 weeks, but for some this may last up to 12 weeks. You may be advised to avoid strenuous activities during this period. You may be referred to a physical therapist for something called “vestibular rehabilitation” to help with issues you might have with balance and/or dizziness. Patients may need to wait 3 weeks or more before they can drive and 4 to 12 weeks before returning to work. However, all timelines should be individualized between the patient and the health care team.

Radiation therapy

Descriptive Summary

Radiation treatment may require a short hospital stay (up to 2 days), but if a stay is required, it is typically shorter for any given person than the stay would be for surgery. For many patients, radiation treatment can be done on an outpatient basis, with the treatment taking anywhere from 10 to 15 minutes for stereotactic radiotherapy and 30 to 120 minutes for stereotactic radiosurgery. Recovery time is quick for radiation treatment: There is often no recovery time or need to take time off from work. Some people receiving stereotactic radiotherapy opt to get treatment as they are coming from or heading to work.

(Acoustic Neuroma Association nd, Dartmouth-Hitchcock nd, Hansen 2018, Klutz 2018, Mayfield Clinic 2018, Mayo Clinic 2017, NYU Langone Health nd, University of Kansas Health System nd, University of Maryland Medical Center nd)

Reference list

Beispiel Literaturnachweis

ACOUSTIC NEUROMA ASSOCIATION ND
Acoustic Neuroma Association. Treatment Options – Overview. Last updated/reviewed date not providence. Accessed June 26, 2019. Available at https://www.anausa.org/learn-about-acoustic-neuroma/treatment-options/overview.

AHSAN 2017
Ahsan SF, Huq F, Seidman M, Taylor A. Long-term Hearing Preservation After Resection of Vestibular Schwannoma: A Systematic Review and Meta-analysis. Otol Neurotol. 2017 Dec;38(10):1505-1511. PubMed

ARTHURS 2011
Arthurs BJ, Fairbanks RK, Demakas JJ, Lamoreaux WT, Giddings NA, Mackay AR, Cooke BS, Elaimy AL, Lee CM. A review of treatment modalities for vestibular schwannoma. Neurosurg Rev. 2011 Jul;34(3):265-77; doi: 10.1007/s10143-011-0307-8. Epub 2011 Feb 9. PubMed

CARLSON 2015
Carlson ML, Tveiten OV, Driscoll CL, Goplen FK, Neff BA, Pollock BE, Tombers NM, Castner ML, Finnkirk MK, Myrseth E, Pedersen PH, Lund-Johansen M, Link MJ. Long-term quality of life in patients with vestibular schwannoma: an international multicenter cross-sectional study comparing microsurgery, stereotactic radiosurgery, observation, and nontumor controls. J Neurosurg. 2015 Apr;122(4):833-42. PubMed

COUGHLIN 2018
Coughlin AR, Willman TJ, Gubbels SP. Systematic Review of Hearing Preservation After Radiotherapy for Vestibular Schwannoma. Otol Neurotol. 2018 Mar;39(3):273-283. PubMed

DARTMOUTH-HITCHCOCK ND
Dartmouth-Hitchcock. Your Surgery & Hospitalization: What to Expect. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.dartmouth-hitchcock.org/acoustic-neuroma-clinic/your-surgery-what-to-expect.html.

Dartmouth-Hitchcock. Recovery at Home and Taking Care of Yourself. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.dartmouth-hitchcock.org/acoustic-neuroma-clinic/recovery-at-home.html.

DI MAIO 2009
Di Maio S, Akagami R. Prospective comparison of quality of life before and after observation, radiation, or surgery for vestibular schwannomas. J Neurosurg. 2009 Oct;111(4):855-62. PubMed

DUNN 2018
Dunn IF, Bi WL, Mukundan S, Delman BN, Parish J, Atkins T, Asher AL, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Imaging in the Diagnosis and Management of Patients With Vestibular Schwannomas. Neurosurgery. 2018 Feb 1;82(2):E32-E34. doi: 10.1093/neuros/nyx510. PubMed. The full guideline is available at The full guideline can be found at https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_5.

DYNAMED 2019
DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T1549311276720, Vestibular schwannoma; [updated 2019 Jun 10, cited 2019 June 26]. Available from https://www.dynamed.com/topics/dmp~AN~T1549311276720. Registration and login required. Registration and login required.

GERMANO 2018
Germano IM, Sheehan J, Parish J, Atkins T, Asher A, Hadjipanayis CG, Burri SH, Green S, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Radiosurgery and Radiation Therapy in the Management of Patients With Vestibular Schwannomas. Neurosurgery. 2018 Feb 1;82(2):E49-E51. doi: 10.1093/neuros/nyx515. PubMed. The full guideline is available at https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_7.

HADJIPANAYIS 2018
Hadjipanayis CG, Carlson ML, Link MJ, Rayan TA, Parish J, Atkins T, Asher AL, Dunn IF, Corrales CE, Van Gompel JJ, Sughrue M, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on Surgical Resection for the Treatment of Patients With Vestibular Schwannomas. Neurosurgery. 2018 Feb 1;82(2):E40-E43. doi: 10.1093/neuros/nyx512. PubMed. The full guideline is available at https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_8.

HANSEN 2018
Hansen M, Gantz BJ. Acoustic neuroma. Last reviewed/updated April 2018. Accessed June 26, 2019. Available at https://www.umms.org/ummc/health-services/hearing-balance/services/acoustic-neuroma.

JOHNS HOPKINS MEDICINE ND
Johns Hopkins Medicine. Radiosurgery. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/radiosurgery.

Johns Hopkins Medicine. Stereotactic radiosurgery. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/stereotactic-radiosurgery.

Johns Hopkins Medicine. Acoustic Neuroma (Vestibular Schwannoma). Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.hopkinsmedicine.org/health/conditions-and-diseases/brain-tumor/vestibular-schwannoma.

Johns Hopkins Medicine. Translabyrinthine Craniotomy. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/brain_tumor/treatment/surgery/translabyrinthine-craniotomy.html.

Johns Hopkins Medicine. Keyhole Brain Surgery (Minimally-Invasive Retro-Sigmoid Craniotomy). Last reviewed/updated date not provided. Accessed June 26, 2019. Available at

https://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/brain_tumor/treatment/surgery/key-hole-retro-sigmoid-craniotomy.html.

KUTZ 2018
Kutz JW. Acoustic Neuroma Treatment & Management. Last reviewed/updated April 10, 2018. Accessed June 26, 2019. Available at https://emedicine.medscape.com/article/882876-overview.

LIN 2017
Lin EP, Crane BT. The Management and Imaging of Vestibular Schwannoma. AJNR Am J Neuroradiol. 2017 Nov;38(11):2034-2043. doi: 10.3174/ajnr.A5213. Epub 2017 May 25. PubMed

LIU 2015
Liu W, Ni M, Jia W, Zhou D, Zhang Q, Jiang Y, Jia G. How to Address Small- and Medium-Sized Acoustic Neuromas with Hearing: A Systematic Review and Decision Analysis. World Neurosurg. 2015 Aug;84(2):283-291.e1. doi: 10.1016/j.wneu.2015.03.013. Epub 2015 Mar 17. PubMed

MAYFIELD CLINIC 2018
Mayfield Clinic. Suboccipital surgery for acoustic neuroma. Last reviewed/updated May 2018. Accessed June 26, 2019. Available at https://mayfieldclinic.com/pe-acousticsurgery.htm.

MAYO CLINIC 2017
Mayo Clinic. Acoustic neuroma: Diagnosis & treatment. Last reviewed/updated March 5, 2017. Accessed June 26, 2019. Available at https://my.clevelandclinic.org/health/diseases/16400-acoustic-neuroma/management-and-treatment.

MAYO CLINIC 2018
Mayo Clinic. Acoustic neuroma: Diagnosis & treatment. Last reviewed/updated August 10, 2018. Accessed June 26, 2019. Available at https://www.mayoclinic.org/diseases-conditions/acoustic-neuroma/diagnosis-treatment/drc-20356132.

MYRSETH 2009
Myrseth E, Møller P, Pedersen PH, Lund-Johansen M. Vestibular schwannoma: surgery or gamma knife radiosurgery? A prospective, nonrandomized study. Neurosurgery. 2009 Apr;64(4):654-61. PubMed

NUÑO 2019
Nuño M, Ugiliweneza B, Boakye M, Monfared A. Morbidity of Vestibular Schwannomas as Documented by Treating Providers. Otol Neurotol. 2019 Feb;40(2):e142-e149. PubMed

NYU LANGONE HEALTH ND
NYU Langone Health. Stereotactic Radiosurgery for Acoustic Neuroma. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://nyulangone.org/conditions/acoustic-neuroma/treatments/stereotactic-radiosurgery-for-acoustic-neuroma.

PAPATSOUTSOS 2018
Papatsoutsos E, Spielmann PM. Self-Evaluated Quality of Life and Functional Outcomes After Microsurgery, Stereotactic Radiation or Observation-Only for Vestibular Schwannoma of the Adult Patient: A Systematic Review. Otol Neurotol. 2018 Feb;39(2):232-241. PubMed

POLLOCK 2006
Pollock BE, Driscoll CL, Foote RL, Link MJ, Gorman DA, Bauch CD, Mandrekar JN, Krecke KN, Johnson CH. Patient outcomes after vestibular schwannoma management: a prospective comparison of microsurgical resection and stereotactic radiosurgery. Neurosurgery. 2006 Jul;59(1):77-85 PubMed

RÉGIS 2002
Régis J, Pellet W, Delsanti C, Dufour H, Roche PH, Thomassin JM, Zanaret M, Peragut JC. Functional outcome after gamma knife surgery or microsurgery for vestibular schwannomas. J Neurosurg. 2002 Nov;97(5):1091-100. PubMed

SUGHRUE 2009
Sughrue ME, Yang I, Han SJ, Aranda D, Kane AJ, Amoils M, Smith ZA, Parsa AT. Non-audiofacial morbidity after Gamma Knife surgery for vestibular schwannoma. Neurosurg Focus. 2009 Dec;27(6):E4. PubMed

SUGHRUE 2011
Sughrue ME, Yang I, Aranda D, Rutkowski MJ, Fang S, Cheung SW, Parsa AT. Beyond audiofacial morbidity after vestibular schwannoma surgery. J Neurosurg. 2011 Feb;114(2):367-74. PubMed

UNIVERSITY OF KANSAS HEALTH SYSTEM ND
University of Kansas Health System. Vestibular Schwannoma. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.kansashealthsystem.com/care/conditions/vestibular-schwannoma.

UNIVERSITY OF MARYLAND MEDICAL CENTER ND
University of Maryland Medical Center. Acoustic Neuroma. Last reviewed/updated date not provided. Accessed June 26, 2019. Available at https://www.umms.org/ummc/health-services/hearing-balance/services/acoustic-neuroma.

WHITMORE 2011
Whitmore RG, Urban C, Church E, Ruckenstein M, Stein SC, Lee JY. Decision analysis of treatment options for vestibular schwannoma. J Neurosurg. 2011 Feb;114(2):400-13. PubMed