

**CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND  
EVIDENCE-BASED GUIDELINE ON THE ROLE OF RADIOSURGERY (SRS) AND  
RADIATION THERAPY IN THE MANAGEMENT OF PATIENTS WITH VESTIBULAR  
SCHWANNOMAS: UPDATES**

***Sponsored by:*** Congress of Neurological Surgeons (CNS) and the Section on Tumors

***Endorsement:*** Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS)

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**Running title:** Radiosurgery for Vestibular Schwannomas

***Abbreviations:***

GK: Gamma Knife

LINAC: Linear accelerator

MRI: Magnetic resonance imaging

NF2: Neurofibromatosis type

PTA: Pure tone average

SRS: Stereotactic radiosurgery

SRT: Stereotactic radiotherapy

VS: Vestibular schwannoma

## **ABSTRACT**

**Background:** Radiosurgery (SRS) is an established modality for treatment of adult patients with vestibular schwannomas (VS). The aim of this work is to provide an updated literature review on this topic.

**Objective:** To review the literature published since the last guideline on this topic.

**Methods:** OVID Medline and Embase were searched for the period January 1, 2015, to May 20, 2022, using search terms and search strategies to identify pertinent abstracts. These were then screened using published exclusion/inclusion criteria to identify full-text review articles. Evidence tables were constructed using data derived from full-text reviews and recommendations made from the evidence derived.

**Results:** From the total 1035 abstracts identified, 26 full-text articles met inclusion/exclusion criteria and were included in this update. Four new level III recommendations stemmed from this work. In adult patients with sporadic intracanalicular or <2cm VS, SRS should not be recommended as superior to observation alone for hearing preservation. In adult patients with sporadic VS treated with SRS, cochlear dose constraint should be considered as it provides better hearing preservation than no constraint. In the same population, single fraction SRS should be recommended rather than hypo-fractionated SRS (hfSRS: >1 and ≤5 fractions) as it results in decreased cranial nerve dysfunction. Finally, adult patients with sporadic VS undergoing SRS should be informed that SRS does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

**Conclusion:** Recent published literature provides new recommendations for the treatment of adult patients with VS with SRS.

## **SUMMARY OF RECOMMENDATIONS**

### **Unchanged Questions and Recommendations From the Prior Version of These Guidelines**

#### **SRS Technology**

##### Question

Is there a difference in outcome based on SRS equipment used: Gamma Knife (GK) versus linear accelerator (LINAC)-based SRS versus proton beam?

##### Target Population

This recommendation applies to all adults with VS who are candidates for SRS treatment.

##### Recommendation

There are no studies that compare two or all 3 modalities. Thus, recommendations on outcome based on modality cannot be made.

#### **Radiographic Follow-Up after SRS and Retreatment**

##### Question

What is the best time sequence for follow-up images after SRS?

##### Target Population

This recommendation applies to all adults with VS who underwent SRS treatment.

##### Recommendation

*Level III:* Follow-up imaging should be obtained at intervals after SRS based on clinical indications, a patient's personal circumstances, or institutional protocols. Long-term follow-up with serial MRIs to evaluate for recurrence is recommended. No recommendations can be given regarding the interval of these studies.

##### Question

Is there a role for retreatment?

##### Target Population

This recommendation applies to all adults with VS who show radiographic progression after SRS treatment.

Recommendation

*Level III:* When there has been progression of tumor after SRS, SRS can be safely and effectively performed as a retreatment.

**Neurofibromatosis Type 2 (NF2)**

Question

What are the indications for SRS in patients with NF2?

Target Population

This recommendation applies to all adults with VS who have a diagnosis of NF2.

Recommendation

*Level III:* SRS is a treatment option for patients with NF2 whose VS are enlarging and/or causing hearing loss.

**Questions and Recommendations Updated from the Prior Guidelines**

**SRS versus observation**

Question: In adult patients with imaging findings consistent with sporadic intracanalicular <2cm VS without tinnitus, does SRS provide better hearing preservation than observation?

Target Population: Adult patients with imaging findings consistent with sporadic intracanalicular <2cm VS without tinnitus.

Recommendation: Level III. In adult patients with sporadic intracanalicular or <2cm VS, SRS should not be recommended as superior to observation alone for hearing preservation. **SRS and cochlear dose constraint**

Question: In adult patients with imaging findings consistent with sporadic VS undergoing SRS does cochlear dose constraint provide better hearing preservation than no constraint?

Target Population: Adults with imaging finding consistent with sporadic VS undergoing SRS.

Recommendation: Level III. In adult patients with imaging findings consistent with sporadic VS undergoing SRS cochlear dose constraint should be considered as it provides better hearing preservation than no constraint. For single fraction SRS, a cochlear dose  $\leq 4\text{Gy}$  is associated with hearing preservation. Cochlear doses  $>4.2\text{Gy}$  are associated with higher risk of hearing loss. For fractionated SRT, cochlear dose  $< 35\text{Gy}$  is associated with hearing preservation.

### **SRS and Secondary Malignancies**

Question: In adult patients with imaging findings consistent with VS does single fraction SRS result in higher number of secondary malignancies compared to the rate expected in the overall population?

Target Population: Adults with imaging finding consistent with VS who have undergone single fraction SRS.

Recommendation: Level III. Adult patient with sporadic VS undergoing SRS should be informed that SRS does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

### **New Question and Recommendation Not Included in the Prior Guidelines**

#### **SRS technique**

Question: In adult patients with imaging findings consistent with VS does single fraction SRS provide better hearing preservation and/or other cranial nerve deficits than other radiation schemes, such as hypofractionation SRS (hfSRS) and/or conventional fractionated stereotactic radiotherapy (fSRT).

Target Population: Adults with imaging findings consistent with VS.

Recommendation: Level III. In adult patients with imaging findings consistent with sporadic VS single fraction SRS should be recommended rather than hypo-fractionated

SRS (hfSRS:  $>1$  and  $<5$  fractions) as it results in decreased cranial nerve dysfunction.

There is insufficient data to provide a recommendation about SRS versus fSRS with regard to radiographic control, hearing preservation, and/or other cranial nerve deficits.

## INTRODUCTION

### ***Goals and Rationale***

This clinical guideline has been created to improve patient care by outlining the appropriate information gathering and decision-making processes involved in the treatment of patients with VS. Neurosurgical care is provided in many different settings by many different providers. This guideline has been created as an educational tool to guide qualified physicians through a series of diagnostic and treatment decisions in an effort to improve the quality and efficiency of care.

### ***Objectives***

VS represent 8% of all primary brain neoplasms and approximately 16% of benign brain tumors<sup>1</sup>. The aim of this study is to provide an update on the topic of SRS and radiation therapy for adults patients with VS since the previous publication on this topic<sup>2</sup>, with literature search ending on December 31, 2014. In this update, four questions were developed to provide clinically relevant information on the role of SRS used in adult patients with VS. In particular, the first question addresses the role of SRS on hearing preservation compared to observation in adult patients with intracanalicular or <2cm VS. The second question assesses the role of cochlear sparing on hearing preservation. The third question focuses on identifying if SRS provides better hearing preservation and/or decreased other cranial nerve deficits compared to other radiation modalities. The final question focuses on the role of SRS on tumorigenesis.

## METHODOLOGY

As first step, the guidelines task force reviewed the questions from the 2018 publications and modified them to PICO (patient/intervention/comparison/outcome) format. With these as guidance the guidelines task force initiated a systematic review of the literature and evidence-based guideline update relevant to the treatment of patients with VS. Through objective evaluation of the evidence and transparency in the process of making recommendations, this evidence-based clinical practice guideline was developed for the diagnosis and treatment of adult patients with VS. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes. Additional information about the methods utilized in this systematic review is provided below.

### ***Literature Search***

The task force members identified search terms/parameter and a medical librarian implemented the literature search, consistent with the literature search protocol, using the OVID

Medline and Embase databases from 1/1/2015 to 5/20/2022 and limited to English language. Details of the strategies are noted in Appendix 1.

### ***Inclusion/Exclusion Criteria***

Articles were retrieved and included only if they met specific inclusion/exclusion criteria. These criteria were also applied to articles provided by guideline task force members who supplemented the electronic database searches with articles from their own files. To reduce bias, these criteria were specified before conducting the literature searches.

Articles that do not meet the following criteria were, for the purposes of this evidence-based clinical practice guideline, were excluded. To be included as evidence in the guideline, an article had to be a report of a study that:

- Appeared in a peer-reviewed publication or a registry report;
- Enrolled a minimum of 3 patients;
- Was of humans;
- Was published on or after January 1, 2015;
- Quantitatively presented results;
- Was not an in vitro study;
- Was not a biomechanical study;
- Was not performed on cadavers;
- Was published in English;
- Was not a systematic review, meta-analysis, or guideline developed by others

Systematic reviews or meta-analyses conducted by others, or guidelines developed by others were not included as evidence to support this review due to the differences in article inclusion/exclusion criteria specified compared to the criteria specified by the Guidelines Task Force.

The qualifying evidence derived from the searches was then collected and compared to the evidence already present in the 2018 publications, i.e., through the end of 2014, to determine if the recommendations could remain unchanged, needed updating, or if whole new recommendations were warranted.

### ***Assessment for Risk of Bias***

Our search generated a list of abstracts, which were screened, and those articles that addressed our identified questions underwent full independent review by the authors.

Reviewers were critical in their assessment, specifically with regard to the study design, prospective character, size of study population, and baseline characteristics between study groups which could account for survivorship bias, selection bias, and appropriate statistical analyses of reported data. Additional bias could stem by the fact that age might have a neurodegenerative effect on hearing. Thus, its effects are difficult to separate from those of the treatment used. Finally, clinical practice could bias how patients are treated. For example, in some centers asymptomatic patients with intra-canalicular VS may be treated upfront.

### ***Rating Quality of Evidence***

The quality of evidence was rated using an evidence hierarchy for each of four different study types: therapeutic, prognostic, diagnostic, and decision modeling. Additional information regarding the hierarchy classification of evidence can be located here: <https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology>.

### ***Revision Plans***

In accordance with the National Academy of Medicine's standards for developing clinical practice guidelines and criteria specified by the former National Guideline Clearinghouse, the task force will monitor related publications following the release of this document and will revise the entire document and/or specific sections if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations. In addition, the task force will confirm within five years from the date of publication that the content reflects current clinical practice and the available technologies for the evaluation and treatment for patients with VS.

## **RESULTS**

Based on review of the new literature starting on January 1 2015 through May 20, 2022 it was apparent that there was new data warranting update of three questions and recommendation wording from the prior guideline related to SRS versus observation, SRS and cochlear dose constraint, and SRS and secondary malignancies. There was also

additional data that warranted an additional new question addressing SRS techniques. The question for these four topics were revised to PICO format. There was no new literature that warranted an update or additional recommendations for the topics of SRS technology, radiographic follow-up and retreatment and NF2 and therefore the questions for these and their subsequent recommendations were left as they stood in the first version of the guidelines for VS.

From the total 1035 abstracts identified, 26 full-text articles met inclusion/exclusion criteria and were included in this update. Four new level III recommendations stemmed from this work. In adult patients with sporadic intracanalicular or <2cm VS, SRS should not be recommended as superior to observation alone for hearing preservation. In adult patients with sporadic VS treated with SRS, cochlear dose constraint should be considered as it provides better hearing preservation than no constraint. In the same population, single fraction SRS should be recommended rather than hypo-fractionated SRS (hfSRS: >1 and <5 fractions) as it results in decreased cranial nerve dysfunction. Finally, adult patients with sporadic VS undergoing SRS should be informed that SRS does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

### **Radiosurgery versus observation**

*Question: In adult patients with imaging findings consistent with sporadic intracanalicular or <2cm VS s without tinnitus, does radiosurgery provide better hearing preservation than observation?*

Recommendation: Level III. In adult patients with sporadic intracanalicular or <2cm VS s, radiosurgery should not be recommended as superior to observation alone for hearing preservation.

### *Summary of previous recommendations*

In the previously published guidelines on the role of radiosurgery versus observation to treat sporadic VSs in the adult population without radiographic progression, it was recommended that small tumors <2cm without tinnitus are observed, as observation does not have a negative impact on tumor growth or hearing preservation<sup>2</sup>. This was a Level

III recommendation based on the available data. The previous data included retrospective reviews, all of which were Class III evidence.

#### *Study selection and characteristics*

The initial search strategy included the review of 24 full text papers. From these, three articles were included in the final review for question 1 and included in the evidence Table 1 below. Data extraction included study design, class of evidence, total number of patients, study parameters, hearing outcome, and author's conclusions.

Ismail et al<sup>3</sup> published a retrospective review of a cohort of 247 patients with intracanalicular or < 2 cm VSs. One group (n = 140) underwent watchful-waiting management with a mean follow up of  $5.9 \pm 1.6$  years and the other group (n = 107) underwent stereotactic radiosurgery (SRS) treatment with mean follow up of  $7.1 \pm 1.9$  years. American Association of Otolaryngology Head and Neck Surgery Pure Tone Audiograms (AAOHNS PTA) and deterioration of Speech Discrimination Score (SDS) were used as primary outcome measures. Deterioration of hearing was noticed in all patients. AAOHNS PTA decreased significantly more in patients that underwent SRS (4.62 dB/year) versus 1.90 dB/year for watchful waiting group ( $p < 0.001$ ). The authors concluded that hearing outcomes are significantly better for patients undergoing watchful waiting. This is a retrospective study providing class III evidence.

Miller et al<sup>4</sup>, in a retrospective study reviewed 123 patients treated by observation (n = 89) or SRS (n = 34). They evaluated SDS, ASAOHNS PTA and Penn Acoustic Neuroma Quality of Life (PANQOL). Patients that were treated with SRS had worst hearing scores than patients in observation group. After radiation therapy their PANQOL improved. Both groups regressed to similar PANQOL total and hearing domain score at 400 weeks. It is unclear from the authors' conclusions whether SRS is recommended to improve PANQOL since both groups' outcome are similar at 400 weeks.

Milner et al<sup>5</sup>, aimed to assess audiological outcomes in 69 patients with growing VS (> 15% of tumor volume in 1 year). Twenty-four patients were in the watchful waiting

group and 46 underwent SRS treatment. Patients in the watchful waiting group experienced a slower growth rate than the patients in SRS group (21%/year vs 178%/year respectively). AAOHNS PTA deterioration and Gardner-Robertson class deterioration showed higher percentage of deterioration after SRS. The authors concluded that audiological deterioration was worst for patients that underwent SRS. However, the later had larger tumors ( $1749\text{mm}^3$  vs  $341\text{mm}^3$ ). The authors recommended that SRS should not be considered as an early treatment option if the sole aim is to attempt to preserve functional hearing.

### *Synthesis*

Based on the three retrospective single center reviews providing Class III evidence, a level III recommendation was made that radiosurgery for adult patients with sporadic intracanalicular or  $<2\text{cm}$  VS does not provide hearing preservation benefit superior to observation alone. Of note, another retrospective single center study provided data on hearing deterioration after SRS stratifying by volume size<sup>6</sup>. Since there was no direct comparison with observation, this was not included in the evidence table. The Authors concluded that smaller tumors have a better outlook at hearing preservation after SRS since 33% of patients with volume  $<1.2\text{cm}^3$  developed hearing deterioration after SRS compared to the 49% in the larger tumor cohort.

### **Radiosurgery and cochlear dose constraint**

*Question: In adult patients with imaging findings consistent with sporadic VSs undergoing radiosurgery does cochlear dose constraint provide better hearing preservation than no constraint?*

*Recommendation: Level III. In adult patients with imaging findings consistent with sporadic VSs undergoing radiosurgery cochlear dose constraint should be considered as it provides better hearing preservation than no constraint. For single fraction SRS, a 4Gy cochlear dose is associated with hearing preservation. Cochlear doses  $>4.2\text{Gy}$  are*

associated with higher risk of hearing loss. For fractionated SRT, cochlear dose < 35Gy is associated with hearing preservation.

### *Summary of previous recommendations*

In the previously published guidelines on the role of radiosurgery to treat sporadic VS in the adult population yielded a Level III recommendation that for single fraction SRS a dose <13Gy should be used to facilitate hearing preservation and minimize new onset or worsening of pre-existing cranial nerve deficits<sup>2</sup>. This level III recommendation was based on retrospective reviews, all of which were class III evidence. Due to new and emerging interest in determining specific doses delivered to the cochlea, in the current guidelines we examine the specific question of cochlear dose and its impact on hearing preservation.

### *Study selection and characteristics*

The initial search strategy included the review of 52 full text papers. From these 11 articles were included in the final review for question 2 and included in the evidence Table 2. Data extraction included study design, class of evidence, total number of patients, study parameters, treatment delivered, and author's conclusions.

Maksimowski et al<sup>7</sup> conducted a single institution retrospective study of 133 patients treated between 1998-2019 for VS with GKRS. They observed that all measures of radiation dose to the cochlea, such as maximum dose ( $p = 0.196$ ), average dose ( $p = 0.104$ ), and minimum dose ( $p=0.263$ ) were not associated with hearing loss. This class III evidence supports a level III recommendation.

Ju et al<sup>8</sup> conducted a single institution retrospective study of 41 patients with VS who underwent SRS to 18Gy in 3 fractions on the CyberKnife radiosurgery platform. Hearing preservation was excellent and was observed in over 90% of patients. Larger tumor volumes, higher cochlear doses, and lower cochlear volumes were associated with poorer hearing outcomes. This class III evidence supports a level III recommendation.

Frischer et al<sup>9</sup> conducted a large single institution retrospective study of 557 patients with VS who underwent SRS alone or combination microsurgery-SRS. They observed that the median dose to the cochlea was a predictor of Gardner Robertson hearing class at follow-up ( $p = 0.029$ ). Additionally, patients whose median cochlear doses exceeded 6Gy had higher rates of non-serviceable hearing at follow-up compared to those who had a median dose  $< 6$  Gy ( $p = 0.027$ ). This class III evidence supports a level III recommendation.

Patel et al<sup>10</sup> conducted a single institution retrospective study of 100 patients with VS, where 43 underwent SRS and 57 underwent fractionated radiation treatment (50.4 Gy in 28 fractions). In patients undergoing SRS, a cochlea dose of  $\geq 5$  Gy was a strong predictor of hearing loss with a sensitivity and specificity of 100% and 90%, respectively. In patients undergoing fractionated radiotherapy, a minimal cochlea dose  $\geq 35$  Gy was an excellent predictor of hearing loss with a specificity and sensitivity of 91% and 50%, respectively. This class III evidence supports a level III recommendation.

Van Linge et al<sup>11</sup> conducted a single institution retrospective comparative study with 611 patients collected from 5 institutions, where SRS (12 Gy in a single fraction) was compared to fractionated radiotherapy (54 Gy in 30 fractions) in patients who underwent primary treatment for VS. They observed that the volume of cochlea getting at least 90% of the prescription dose (V90 EQD<sub>2</sub>) was predictive of loss of functional hearing on univariate (HR: 1.01; 95% CI: 1.00-1.013;  $p = 0.027$ ) and multivariate (HR: 1.01; 95% CI: 1.00-1.02;  $p = 0.001$ ) analysis. This class III evidence supports a level III recommendation.

Chung et al<sup>12</sup> conducted a single institution retrospective study of 38 patients with VS, where 14 underwent SRS and 24 underwent fractionated radiotherapy. In patients who underwent SRS, those who developed decreased hearing preservation received a significantly higher minimum dose to the cochlea (7.41 vs. 4.24 Gy;  $p = 0.02$ ). Additionally, when the minimum cochlear dose exceeded 6 Gy, there was a significant risk of decreased hearing preservation (OR: 32;  $p = 0.02$ ). This class III evidence supports a level III recommendation.

Hasegawa et al<sup>13</sup> conducted a single institution retrospective study of 92 patients with VS. All patients underwent single fraction SRS to a dose of 12-13 Gy. The median mean dose to the cochlea was 4 Gy. On univariate and multivariate analysis (both  $p < 0.001$ ), increasing dose to the cochlea was associated with decreased hearing preservation. This class III evidence supports a level III recommendation.

Pan et al<sup>14</sup> conducted a single institution retrospective study of 93 patients with VS who underwent GK radiosurgery. They observed that the cochlea dose was a significant predictor of hearing preservation in patients with serviceable hearing following SRS. This class III evidence supports a level III recommendation.

Lin et al<sup>15</sup> conducted a retrospective study of 100 patients with VS who underwent single fraction SRS to 12-13 Gy. They observed that the only dosimetric predictor of hearing preservation was a mean cochlear dose  $< 4$  Gy ( $p = 0.02$ ). This class III evidence supports a level III recommendation.

Watanabe et al<sup>16</sup> conducted a retrospective study of 183 patients who underwent GKRS for VS. They observed that a mean cochlear dose  $> 4.2$  Gy ( $p = 0.03$ ) was associated with worse hearing preservation following treatment. This class III evidence supports a level III recommendation.

Mousavi et al<sup>17</sup> conducted a single center retrospective study in 254 patients. They reported that patients in the group with no subjective hearing loss had significantly higher rates of hearing preservation compared to patients with subjective hearing loss with similar cochlear dose. This class III evidence supports a level III recommendation.

### *Synthesis*

In 10 of the 11 studies summarized above class III evidence that dose constraint to the cochlea is associated with hearing preservation is provided. This leads to a level III recommendation that in adult patients with imaging findings consistent with sporadic VSs undergoing radiosurgery cochlear dose constraint should be considered as it provides better hearing preservation than no constraint. For single fraction SRS, a cochlear dose  $\leq 4$  Gy is associated with hearing preservation<sup>13,15</sup>. Cochlear doses  $> 4.2$  Gy are associated

with higher risk of hearing loss<sup>9,10,12,16</sup>. For fractionated SRT, cochlear dose  $\leq 35$ Gy is associated with hearing preservation. Only one of 11 studies provides contradictory class III evidence that maximum, average, and minimum doses to the cochlea are not associated with hearing loss following GKRS and is not deemed to alter the conclusions of the other eleven studies.

### **Radiosurgery technique**

*Question: In adult patients with imaging findings consistent with VSs (VS) does single fraction radiosurgery (SRS) provide better hearing preservation and/or other cranial nerve deficits that other radiation schemes, such as hypofractionation SRS (HfSRS) and/or conventional fSRT*

Recommendation: Level III. In adult patients with imaging findings consistent with sporadic VSs single fraction SRS should be recommended rather than hypo-fractionated SRS (HfSRS:  $>1$  and  $<5$  fractions) as it results in decreased cranial nerve dysfunction. There is insufficient data to provide a recommendation about SRS versus fSRS with regard to radiographic control, hearing preservation, and/or other cranial nerve deficits.

### *Summary of previous recommendations*

In the previously published guidelines on the role of radiosurgery technology to treat sporadic VS in the adult population treated with SRS and fSRT showed no difference in radiographic control and clinical outcome<sup>2</sup>. Therefore, recommendations were not given. This lack of recommendation was based retrospective reviews, all of which were Class III evidence. Based on new emerging interest in determining the role of hypofractionated SRS, defined as  $>1$  fraction and  $\leq 5$  fractions, in the current guidelines we separated this

radiation scheme from conventional single fraction SRS and created a new question addressing the technique.

### *Study selection and characteristics*

The initial search strategy included the review of 47 full text papers. From these, 10 articles were included in the final review for question 3 and included in the evidence Table 3 below. Data extraction included study design, class of evidence, total number of patients, study parameters, treatment scheme delivered, and author's conclusions.

Kuchler et al<sup>18</sup> reports on 149 patients treated with SRS/HfSRS (12Gy/1 fraction and 18Gy/3 fractions) compared to 87 patients treated with fractionated radiation therapy (fSRT, 57.6Gy/32 fractions) and 25 patients treated with fractionated proton therapy (FPT, 54Gy RBE/32 fractions). No statistical difference between treatment groups with regard to hearing preservation rates was observed. Facial and trigeminal nerve symptoms after RT were mild but the highest rates were observed in FPT patients. However, potential selection bias with larger tumor volumes treated by FPT could have influenced the results. This study provides class III evidence supporting level III recommendation.

Puataweepong et al<sup>19</sup> conducted a class III trial comparing outcomes of 20 patients treated with SRS (12Gy/1 fraction) and 100 patients treated with HSRT (18Gy/3 fractions). Treatment was delivered utilizing the CyberKnife radiosurgery platform. Among 28 patients with serviceable hearing in the HSRT group, 5 and 8-year hearing preservation rates were 87% and 65% respectively. No factor was significantly associated with hearing preservation rates on univariable and multivariable analyses. Rates of non-auditory complications were 4.3% in the SRS group and 15% in the HSRT group. Koos grade III and IV tumors were associated with higher risk of non-auditory complications. This study provides class III evidence supporting level III recommendation.

Diaz et al<sup>20</sup> conducted a class III trial evaluating 37 patients treated with SRS (12Gy/1 fraction) and 99 patients treated with hypoFSRT (39 patients receiving 18-21Gy/3 fractions and 60 patients receiving 25Gy/5 fractions). No significant difference in hearing

preservation or cranial nerve injury was observed with SRS versus hypoFSRT. This study provides class III evidence supporting level III recommendation.

Khattab et al<sup>21</sup> report a single institution retrospective study of 56 patients with VS who underwent single fraction SRS (12.5-16 Gy), 3-fraction SRS (7 Gy x 3), or 5-fraction SRS (4.5-5.5 Gy x 5). Significantly better audiologic outcomes were observed in multifraction vs. single fraction schemes ( $p = 0.009$ ), albeit with short follow up. Mean or maximum cochlear doses did not predict for changes in speech awareness threshold. This study provides class III evidence supporting level III recommendation.

Singh et al<sup>22</sup> conducted a phase III trial from a prospectively collected international database comparing 12 patients treated with SRS (12.25Gy/1 fraction) and 52 patients treated with fractionated SRS (fSRS, 18Gy/3 fractions or 25Gy/5 fractions) using the Cyberknife robotic system. No significant difference was seen in hearing preservation rates. fSRS was associated with higher likelihood of cranial nerve dysfunction. This study provides class II evidence supporting level II recommendation.

Udawatta et al<sup>23</sup> conducted a class III trial of 21 patients treated with SRS (12Gy/1 fraction), 33 patients treated with fSRT (50.4Gy/28 fractions) and 6 patients treated with HfSRS (25Gy/5fx). Hearing preservation rates 69.2% fSRT, 37.5% SRS and 100% HfSRT ( $p=0.025$ ). HfSRT showed better hearing preservation versus SRS or fSRT but was associated with significantly more non-auditory symptoms, i.e., other cranial nerve dysfunction. This trial did not report trigeminal and facial nerve outcomes and has a small number of patients. This study provides class III evidence supporting level III recommendation.

Tang et al<sup>24</sup> reported on 487 patients treated with single session (12.5Gy) and 74 patients treated with multisession SRS (6.7Gy/3 fractions over 3 consecutive days) using the GK system. Propensity score matching was used to compare the 2 groups with 29 patients from each group selected. There was a trend toward improved hearing preservation rates in the multi session group. On multivariate analysis the linear internal auditory canal length was the only significant predictor for hearing loss after multi session GKRS, odds ratio 0.3868. No significant differences were seen in trigeminal or facial nerve

complications between the two groups. This study provides class III evidence supporting level III recommendation.

Lo et al<sup>25</sup> performed a class III trial evaluating 136 patients treated with SRS (12Gy/1 fraction) and 17 patients treated with fSRT (50Gy/25 fractions). In the 49 patients with serviceable hearing treated with fSRT, hearing preservation was 55% at 3 years. On multivariable analysis, better pre-treatment ipsilateral pure-tone average was significantly associated with hearing preservation ( $p=0.04$ ). 10-year actuarial rates of RT induced trigeminal nerve dysfunction 25% after SRS and 12% after fSRT ( $p=0.01$ ). 10-year actuarial rates of RT induced facial nerve dysfunction 15% after both SRS and fSRT. This study provides class III evidence supporting level III recommendation.

Kessel et al<sup>26</sup> conducted a class III trial of 56 patients treated with SRS (12Gy/1 fraction) and 128 patients treated with fractionated (FSRT, 54Gy/30 fractions). The difference in hearing preservation was not significant ( $p=0.3$ ). No difference in facial nerve ( $p=0.5$ ) and trigeminal nerve ( $p=0.3$ ) dysfunction. This study provides class III evidence supporting level III recommendation.

Combs et al<sup>27</sup> performed a class III trial of 169 patients treated with SRS (13Gy/1 fraction) and 291 patients treated with FSRT (57.6Gy/32 fractions). No significant difference in hearing preservation, facial or trigeminal nerve dysfunction was noted between the SRS and FSRT groups.

### *Synthesis*

One study providing class II evidence<sup>22</sup> supported by another study providing class III evidence<sup>19</sup> provides evidence of decreased cranial nerve dysfunction other than acoustic with SRS compared to hypo-fractionated SRS (HfSRS:  $>1$  and  $\leq 5$  fractions). One study<sup>21</sup> provides class III evidence of better audiologic outcomes after HfSRS (3 or 5 fractions compared to single fraction SRS, albeit with short follow up. These three studies combined support a level III recommendation that in adult patients with imaging findings consistent with VSs single fraction SRS might result in decreased cranial nerve dysfunction compared to hypo-fractionated SRS (HfSRS:  $>1$  and  $\leq 5$  fractions). The

remaining 8 studies failed to provide evidence of consistent differences in outcome comparing SRS versus fSRT. Therefore, at the present time there is insufficient data to provide a recommendation about SRS versus fSRS in regards to radiographic control, hearing preservation, and/or other cranial nerve deficits. One recent study<sup>28</sup> reports on proton therapy indicating higher number of trigeminal and facial nerve deficits compared to SRS and/or fSRT. The possibility of selection bias with larger tumor volumes treated by proton therapy that could have influenced the results cannot be excluded.

### **Radiosurgery and Secondary Malignancies**

*Question: In adult patients with imaging findings consistent with VSs does single fraction radiosurgery result in higher number of secondary malignancies compared to the rate expected in the overall population?*

Recommendation: Level III. Adult patient with sporadic VSs undergoing radiosurgery should be informed that radiosurgery does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

#### *Summary of previous recommendations*

In the previously published guidelines on the topic of tumorigenesis after radiosurgery in adult patients with VS a level III recommendation based on clinical evidence III was issued stating that patients should be informed that there is a minimal risk of tumorigenesis after SRS<sup>2</sup>. Two papers met eligibility criteria for this topic. Hasegawa et al<sup>29</sup> reported on 440 patients treated with GK, including patients with NF2, with 1/440 developing a malignant transformation. Rowe et al<sup>30</sup> reported 1 cases of malignant transformation and 1 of new tumor formation (glioblastoma) in 146 VS treated in 118 patients. Compared to the national incidence in the UK, the predictive incidence would have been 2.5 cases over the same follow up period.

### *Study selection and characteristics*

The initial search strategy included the review of 16 full text papers. From these, 2 articles were included in the final review for question 4 and included in the evidence Table 4 below. Data extraction included study design, class of evidence, total number of patients, outcome and author's conclusions.

Wolf et al<sup>31</sup> performed a multi-center retrospective study with 1011 adult patients with VS treated with GK in 5 centers. The total number of patients studied including other pathologies equaled 4905 patients. The reported cumulative incidence of developing radiosurgery-associated malignancy, either new or a transformation of a benign tumor, was 0.045% over 10 years. The Authors concluded that the risk of developing a CNS tumor after SRS is similar to the risk in the general population. This study is the largest number of patient-years accumulated prospectively to estimate the incidence of malignant transformation and secondary malignancy in patients treated with GK radiosurgery since 1987 at five major radiosurgery centers. This class 3 evidence supports a level 3 recommendation.

Pollock et al<sup>32</sup> reported on 358 adult patients with VS treated with GK. No radiation induced tumors were identified in 11,262 patient-years (total patients N= 1142). Of 358 VS patients, 1 (0.3%) had malignant transformation. The authors concluded that risk of a radiation-induced tumor developing after SRS was 0.0% at 5 years, 0.0% at 10 years, and 0.0% at 15 years. This class III evidence supports a level III recommendation.

Additionally, 6 case reports were identified describing progression to a malignant peripheral nerve sheath tumor (MPNST) in adult patients with sporadic VS: 2/6 patients did not receive radiation<sup>33,34</sup>, 1/6 patient received fractionated radiation<sup>35</sup>, and 3/6 received SRS<sup>36,37,38</sup>. One additional case report described a glioblastoma occurring in a patient who had previously received SRS treatment for a sporadic VS<sup>39</sup>.

### *Synthesis*

The exposure to radiation in the range of 1- to 10Gy can result in sublethal DNA damage capable of inducing oncogenic mutation<sup>32</sup>. For this reason, the question of tumorigenesis

after radiosurgery for VS is of clinical importance for both onset of new tumors and/or malignant transformation of the treated tumor. In particular, malignant peripheral nerve sheath tumors (MPNST) have an estimated incidence of 0.017 per million people per year with 1 VN-MPNST for every 1041 VS<sup>39</sup>. A recent study by Havik et al<sup>40</sup> reported on genetic alterations associated with malignant transformation of sporadic VS in 4 tumors, two after GK radiation and two were radiation-naïve. The authors report no consistent mutational signature associated with ionizing radiation and suggest the existence of a pre-malignant VS genomic signature. Class III evidence from the papers included in this review support a level III recommendation that adult patient with sporadic VS undergoing radiosurgery should be informed that radiosurgery does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

*Recommendation:* Level III. Adult patient with sporadic VSs undergoing radiosurgery should be informed that radiosurgery does not result in an increased number of secondary malignancies compared to the rate expected in the overall population.

## **CONCLUSIONS**

Radiosurgery remains a heavily used therapeutic approach for treatment of adults with VS. This updates on the role of SRS for adult patients with VS yields to four new level III recommendations. These findings underscore the need to continue updating the guidelines every five years as recommended by the Academy of Medicine, previously Institute of Medicine.

## **KEY ISSUES FOR FUTURE INVESTIGATION**

The use of national and international registries documenting patients' selection, treatment and outcome might be helpful to further corroborate the current recommendations and perhaps add new evidence. With greater availability of proton centers, data for the VS adult population will accrue to help treating physician identifying the possible advantages and disadvantages over photon therapy. Finally, recognized barriers that might skew treatment need to be further explored.

### ***Conflicts of Interest***

All Guideline Task Force members were required to disclose all potential COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See Appendix V for a complete list of disclosures.

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### ***Disclaimer of Liability***

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. Each chapter is designed to provide an accurate review of the subject matter covered. This guideline is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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## Appendix I: Literature Searches

### *Search Strategies*

#### Ovid MEDLINE(R)

- 1 ((Stereotactic or stereotaxic) adj5 (radiotherap\* or radiation)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12210
- 2 Radiosurgery/ or RADIOSURG\*.ti,ab,kw. or RADIO-SURG\*.ti,ab,kw. 23970
- 3 (CYBERKNIFE\* or cyber-knife\* or cyber knife\*).mp. 1773
- 4 (gamma knife\* or linac or linear accelerator\*).ti,ab,kw. 14362
- 5 Radiotherapy/ and (stereotactic\* or stereotaxic\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 701
- 6 Radiotherapy, Intensity-Modulated/ 12455
- 7 (helical tomotherap\* or intensity modulated arc therap\* or intensity-modulated arc therap\* or intensity-modulated radiotherapy\* or volumetric modulated arc therap\* or volumetric-modulated arc therap\* or IMRT).ti,ab,kw. 15297
- 8 Radiation Dose Hypofractionation/ 1046
- 9 (HYPOFRACTIONAT\* or HYPO-FRACTIONAT\*).mp. 4903
- 10 or/1-9 54280
- 11 exp Neuroma, Acoustic/ 8763
- 12 ((vestib\* or acoustic) adj3 (neuroma\* or neurilemmoma\* or neurilemoma\* or neurinoma\* or tumor\* or tumour\* or schwannoma\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 11046
- 13 (acoustic nerve cancer\* or acoustic neurofibroma\* or acusticus neurinoma\* or auditory nerve neurinoma\* or ear schwannoma\* or angle tumor\* or angle tumour\* or cerebellopontine angle tumor\* or neurinoma of the acoustic nerve or neurosensory deafness\* or sensoryneural deafness\* or sensory neural deafness\*).ti,ab,kw. 1211
- 14 11 or 12 or 13 12489

15 limit 14 to english language 10469

16 Animals/ not Humans/ 4974929

17 15 not 16 10374

18 comment/ or editorial/ or letter/ or review/ or systematic review/ 5102112

19 17 not 18 8685

20 exp adolescent/ or exp child/ or exp infant/ 3849849

21 exp Adult/ 7797507

22 20 not 21 2052582

23 19 not 22 8366

24 limit 23 to dt=20150101-20220522 2297

25 in vitro techniques/ 387712

26 Culture Techniques/ 47809

27 Drug Evaluation, Preclinical/ 54481

28 Disease Models, Animal/ 383220

29 Xenograft Model Antitumor Assays/ 44247

30 24 not (25 or 26 or 27 or 28 or 29) 2275

31 10 and 30 494

# EMBASE

('radiosurgery'/exp OR radiosurg\*:ti,ab,kw,de OR 'radio-surgery':ti,ab,kw,de OR ((stereotactic OR stereotaxic) NEAR/5 (radiotherap\* OR radiation\*)) OR ('radiotherapy'/exp AND (stereotactic\* OR stereotaxic\*)) OR 'cyberknife'/exp OR 'cyberknife':ti,ab,kw OR 'cyber knife':ti,ab,kw OR 'gamma knife'/exp OR 'gamma knife':ti,ab,kw OR gammaknife:ti,ab,kw OR perfexion:ti,ab,kw OR 'linear accelerator'/exp OR 'linear accelerator':ti,ab,kw OR linac:ti,ab,kw OR 'intensity modulated radiation therapy'/exp OR 'intensity modulated radiation therapy':ti,ab,kw OR imrt:ti,ab,kw OR 'intensity modulated arc therapy':ti,ab,kw OR 'intensity modulated radiotherapy':ti,ab,kw OR 'intensity modulated photon radiotherapy':ti,ab,kw OR 'intensity modulated therapy':ti,ab,kw OR 'intensity-modulated radiation therapy':ti,ab,kw OR 'intensity-modulated radiotherapy':ti,ab,kw OR 'tomotherapy'/exp OR tomotherap\*:ti,ab,kw OR 'hypofractionation'/exp OR hypofractionat\*:ti,ab,kw,de OR 'hypo-fractionation':ti,ab,kw OR 'hypofractionated radiotherapy'/exp) AND ('acoustic

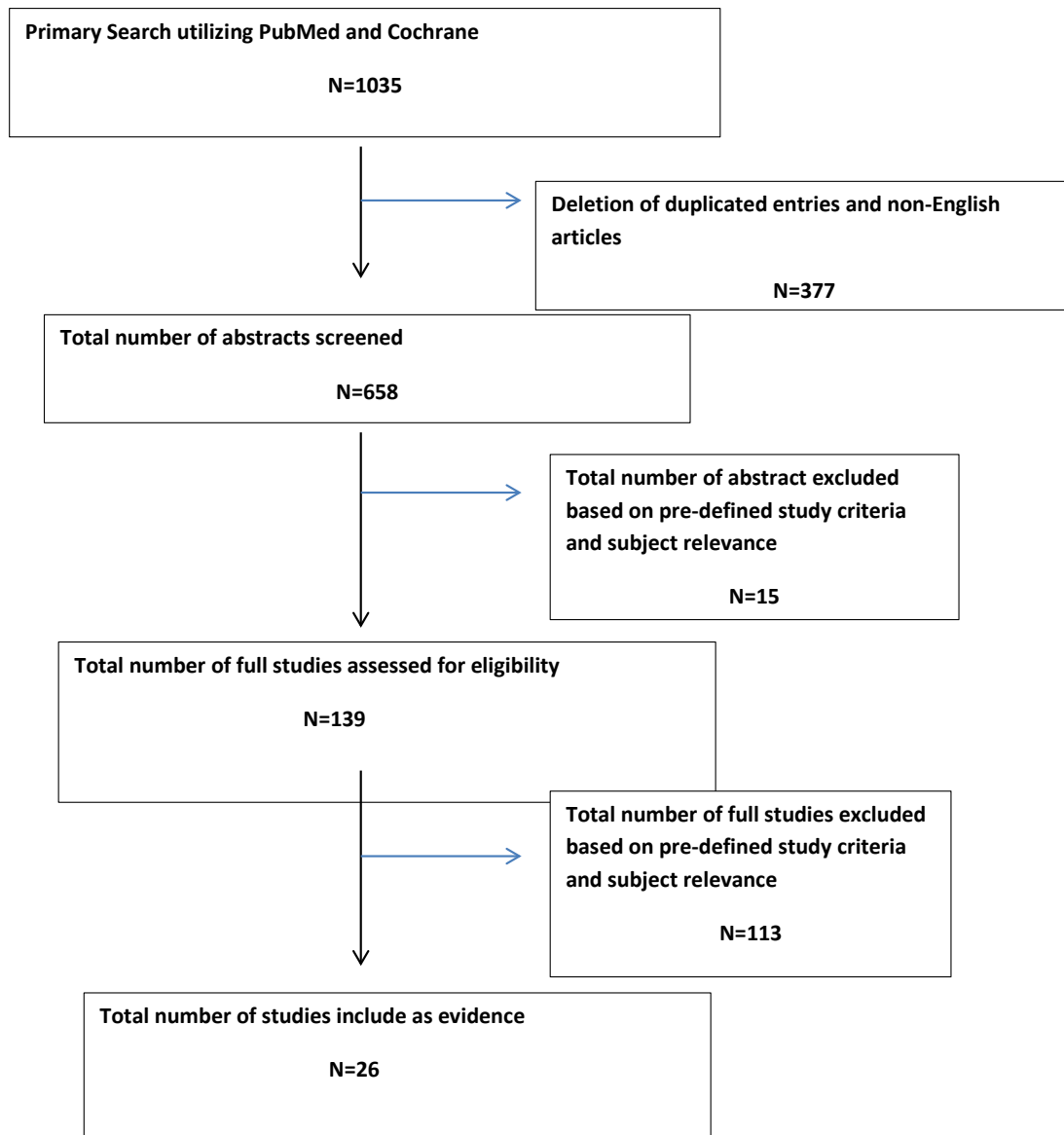
nerve cancer':ti,ab,kw OR 'acoustic nerve neurinoma':ti,ab,kw OR 'acoustic nerve tumor':ti,ab,kw OR 'acoustic nerve tumour':ti,ab,kw OR 'acoustic neurofibroma':ti,ab,kw OR 'acusticus neurinoma':ti,ab,kw OR 'auditory nerve neurinoma':ti,ab,kw OR 'ear schwannoma':ti,ab,kw OR 'angle tumor':ti,ab,kw OR 'angle tumour':ti,ab,kw OR 'neurinoma of the acoustic nerve':ti,ab,kw OR 'neurosensory deafness':ti,ab,kw OR 'sensoryneural deafness':ti,ab,kw OR 'sensory neural deafness':ti,ab,kw OR ((vestib\* OR acoustic) NEAR/3 (neuroma\* OR neurilemmoma\* OR neurilemoma\* OR neurinoma\* OR tumor\* OR tumour\* OR schwannoma\*)) AND [english]/lim NOT ('animal'/exp NOT 'human'/exp) NOT ('juvenile'/exp NOT 'adult'/exp) NOT ('letter'/exp OR 'editorial'/exp OR 'conference paper'/exp OR 'review'/exp) NOT ('case report'/exp NOT 'case control study'/exp) NOT (('acoustic nerve cancer':ti,ab,kw OR 'acoustic nerve neurinoma':ti,ab,kw OR 'acoustic nerve tumor':ti,ab,kw OR 'acoustic nerve tumour':ti,ab,kw OR 'acoustic neurofibroma':ti,ab,kw OR 'acusticus neurinoma':ti,ab,kw OR 'auditory nerve neurinoma':ti,ab,kw OR 'ear schwannoma':ti,ab,kw OR 'angle tumor':ti,ab,kw OR 'angle tumour':ti,ab,kw OR 'neurinoma of the acoustic nerve':ti,ab,kw OR 'neurosensory deafness':ti,ab,kw OR 'sensoryneural deafness':ti,ab,kw OR 'sensory neural deafness':ti,ab,kw OR ((vestib\* OR acoustic) NEAR/3 (neuroma\* OR neurilemmoma\* OR neurilemoma\* OR neurinoma\* OR tumor\* OR tumour\* OR schwannoma\*)) AND [english]/lim NOT ('animal'/exp NOT 'human'/exp) NOT ('juvenile'/exp NOT 'adult'/exp) NOT ('letter'/exp OR 'editorial'/exp OR 'conference paper'/exp OR 'review'/exp) NOT ('case report'/exp NOT 'case control study'/exp) AND 'conference abstract'/it) AND [01-01-2015]/sd NOT ('preclinical study'/exp OR 'animal experiment'/de OR 'in vitro study'/exp)

## Appendix II: Rating Evidence Quality

### Classification of Evidence on Therapeutic Effectiveness and Levels of Recommendation

|                                                       |                                                                                                                                                                                                                             |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Class I Evidence<br>Level I (or A) Recommendation     | Evidence from one or more well-designed, randomized controlled clinical trial, including overviews of such trials.                                                                                                          |
| Class II Evidence<br>Level II (or B) Recommendation   | Evidence from one or more well-designed comparative clinical studies, such as non-randomized cohort studies, case-control studies, and other comparable studies, including less well-designed randomized controlled trials. |
| Class III Evidence<br>Level III (or C) Recommendation | Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed randomized controlled trials.                                                    |

### Appendix III: PRISMA Flowchart



## Appendix IV. Evidence Tables

**Table 1:** Radiosurgery versus observation in adult patients with intracanalicular or <2cm VSs without tinnitus

| Author/year                      | Study Description                                                                                                                                                                                                                                                                                                                                         | Data Class | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ismail et al <sup>3</sup> , 2022 | <p>Retrospective comparison review of two patients cohorts with intracanalicular or &lt; 2 cm VS</p> <p>Single institution</p> <p>247 patients:</p> <p>140 – watchful waiting, mean follow up 5.9 +/- 1.6 years</p> <p>107 – SRS, mean follow up 7.1 +/- 1.9 years</p> <p>SDS and AAOHNS PTA hearing threshold deterioration used as primary outcomes</p> | III        | <p>Data Summary:</p> <p>Mean tumor size increase:</p> <ul style="list-style-type: none"> <li>- watchful waiting: from 9.59 +/- 4.89 mm to 9.80 +/- 5.44 mm (p = 0.926)</li> <li>- SRS: 11.30 +/- 5.02 mm to 13.68 +/- 4.96 mm (p &lt; 0.001)</li> </ul> <p>Deterioration of hearing overtime:</p> <ul style="list-style-type: none"> <li>- watchful wait: Mean PTA decrease of 1.90 dB/yr</li> <li>- SRS: Mean PTA increase of 4.62 dB/yr (p &lt; 0.001)</li> </ul> <p>SDS available for 46 watchful wait patients and 47 for SRS patients</p> <p>SDS decline for SRS patients was 4.54%/year for watchful wait was 1.56%/yr</p> <p>Serviceable hearing preservation:</p> <ul style="list-style-type: none"> <li>- Watchful waiting: 16 (34.8%) at time of presentation and 11 (23.9%) after 5.7 years (p = 0.025)</li> <li>- SRS: 13 (27.7%) at presentation and 2 (4.3%) at the end of 6.9 years (p = 0.001)</li> </ul> |

|                                  |                                                                                                                                                                                                                                                                                        |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  |                                                                                                                                                                                                                                                                                        |     | <p>Author's Conclusions: Hearing outcomes of watchful waiting strategy are significantly better than those managed by SRS. Patients with &lt; 2cm VS will have better hearing outcomes if managed conservatively</p> <p>Comments</p> <p>Retrospective single institution study.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Miller et al <sup>2</sup> , 2019 | <p>Retrospective comparison of two patient cohorts with VS</p> <p>Single institution</p> <p>123 patients with VS included</p> <ul style="list-style-type: none"> <li>- SRS: 34 patients</li> <li>- Observation: 89</li> </ul> <p>Main outcome measures were PTA, SDS, PANQOL Score</p> | III | <p>Data Summary:</p> <p>Mean Tumor Size: Observation patients vs SRS was 16.2 mm vs. 7.7 mm respectively (<math>p &lt; 0.001</math>)</p> <p>Mean PTA at diagnosis was worse for SRS patients (50 +/- 20 dB) than observation group (36 +/- 20 dB)</p> <p>SDS at diagnosis was worse for SRS (42 +/- 32%) vs observation group (72 +/- 29%)</p> <p>PANQOL score was higher at baseline in observation group (532 +/- 115) than in the SRS group (455 +/- 120) (<math>p = 0.006</math>)</p> <p>SRS group had higher probability to progress to class D hearing compared to observation (HR 7.1, <math>p = 0.005</math>)</p> <p>Rate of change of PANQOL scores in SRS group improved in total at a rate of 23.92/yr (<math>p = 0.005</math>) and hearing 2.39/yr (<math>p = 0.04</math>) domain score when compared with observation</p> |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     | <p>Both groups regress to similar PANQOL total and hearing domain scores at 400 weeks</p> <p>Author's Conclusions:</p> <p>PANQOL scores were higher at baseline for observation group. Overtime they increased for SRS group and decreased for Observation group, resulting in equivalent scores for both groups at 400 weeks.</p> <p>Comments</p> <p>Retrospective review. Not clear what conclusions to deduct from this study.</p>                                                                                                                                                                           |
| Milner et al <sup>3</sup> , 2018 | <p>Retrospective comparison review patients with growing VS (&gt;15% tumor volume in 1 year) treated either with SRS or watchful waiting</p> <p>Single institution</p> <p>69 patients with growing VS:</p> <p>24 – Watchful waiting</p> <p>46 – SRS (GK 12 – 13 Gy marginal dose)</p> <p>Mean follow up: 69.6 months for SRS and 71.7 months for Watchful waiting cohort</p> <p>AAOHNS PTA hearing threshold deterioration and Gardner-Robertson class deterioration overtime were used as primary outcome measurements</p> | III | <p>Data Summary:</p> <p>SRS group: Tumor growth rate before treatment 178%/yr</p> <p>watchful wait group growth rate 21%/year</p> <p>Mean tumor size:</p> <p>SRS: 1749.4 mm<sup>3</sup> [range 12 – 9504 mm<sup>3</sup>]</p> <p>Watchful wait: 341.5 mm<sup>3</sup> [range 6 – 1785 mm<sup>3</sup>]</p> <p>AAOHNS PTA deterioration for SRS (mean = 32.5 dB) and watchful waiting (mean 26.8 dB) (t = 0.33, SE = 7.44, p=0.745).</p> <p>Gardner-Robertson class deterioration for SRS demonstrated in 13/43 patients (65.1%), for watchful wait 13/23 (56.5%) (Adj OR = 2.63, 95% CI 0.21 – 32.5, p = 0452)</p> |

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|  |  |  | <p>Functional hearing was maintained in 8 (53.3%) of watchful wait patients and 7 (25.9%) SRS patients (<math>X^2 = 3.15</math>, <math>df = 1</math>, <math>p = 0.075</math>)</p> <p>Mean rate of progression to loss of functional hearing was 23.1 months in SRS patients and 26.7 months in watchful waiting patients (Adj. HR 0.37, 95% CI 0.11 – 1.26, <math>p = 0.11</math>)</p> <p>Author's Conclusions:</p> <p>Audiological deterioration is greater amongst patients treated with SRS that had preserved hearing at diagnosis. Patients with lower AAOHNS PTA and functional hearing threshold at diagnosis are more likely to develop a deterioration in hearing threshold and functional hearing. SRS should not be advocated as an early treatment modality in growing VS if sole aim is to attempt to preserve functional hearing</p> <p>Comments</p> <p>Retrospective study with inherent biases such as SRS cohort was larger and had faster growing tumors.</p> |
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Abbreviations: RT = Radiation Therapy; VS = Vestibular Schwannoma; AAOHNS PTA = American Association of Otolaryngology – Head and Neck Surgery Pure Tone Audiograms; SDS = Speech discrimination score; Mo = months; SRS = Stereotactic RadioSurgery; PTA = Pure Tone Average; PANQOL = Penn Acoustic Neuroma Quality of Life;

\*\*volume  $1.2\text{cm}^3$ =diameter 1.32cm

**Table 2: Radiosurgery and cochlear dose constraint in adult patients with imaging findings consistent with sporadic VSs undergoing radiosurgery.**

| Author/year | Study Description | Data Class | Conclusion |
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| <p>Maksimoski et al<sup>7</sup>, 2021</p> | <p>Study Description:</p> <p>Retrospective study of patients with VS</p> <p>Patient Population:</p> <p>N = 133 patients with VS</p> <p>Treatment:</p> <p>All patients underwent GKRS</p> | <p>III</p> | <p>Results:</p> <p>All measures of radiation dose, such as maximum cochlear dose (p = 0.196), average cochlear dose (p = 0.104) and minimum cochlear dose (p = 0.263) were not associated with hearing loss.</p> <p>Author Conclusion:</p> <p>Maximum, average, and minimum doses to the cochlea are not associated with hearing loss following GKRS.</p> <p>Comments and Conclusions:</p> <p>Class III due to retrospective single center study. Maximum, average, and minimum doses to the cochlea are not associated with hearing loss following GKRS.</p> |
| <p>Ju et al<sup>8</sup>, 2019</p>         | <p>Study Description:</p> <p>Retrospective study in patients with VS</p> <p>Single center</p> <p>Patient Population:</p> <p>N = 41 patients with VS</p> <p>Treatment:</p>                | <p>III</p> | <p>Results:</p> <p>In 37/41 (90%) patients hearing was either preserved or improved following treatment. Higher cochlear radiation doses was associated with worse hearing outcomes.</p> <p>Author Conclusion:</p>                                                                                                                                                                                                                                                                                                                                            |

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|  | <p>CyberKnife SRS to 18 Gy in 3 fractions</p> |  | <p>18 Gy delivered in 3 fractions in patients with VS results in excellent hearing preservation.</p> <p>Comments and Conclusions:</p> <p>Class III due to retrospective single institution study with relatively small numbers of patients. fSRS is associated with excellent hearing preservation in patients with VS. Hearing outcomes are likely further improved by minimizing dose to the cochlea.</p> |
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| <p>Frischer et al<sup>9</sup>, 2019</p> | <p>Study Description:</p> <p>Retrospective study of patients with VS</p> <p>Patient Population:</p> <p>N = 557 patients with VS</p> <p>Treatment:</p> <p>N = 452 underwent SRS alone and N = 105 underwent microsurgery-SRS</p> | <p>III</p> | <p>Results:</p> <p>On multivariate analysis, median dose to the cochlea was a predictor of GR class at follow-up (<math>p = 0.029</math>). Patients whose median cochlear dose exceeded 6 Gy had a higher rate of nonserviceable hearing at last follow up compared to those who had a median cochlear dose <math>&lt; 6</math> Gy (<math>p = 0.027</math>).</p> <p>Author Conclusion:</p> <p>Minimizing cochlear doses appears to be beneficial for hearing preservation; however, intracanalicular tumors should not be undertreated in favor of lowering the cochlea dose.</p> <p>Comments and Conclusions:</p> <p>Large Retrospective study with mixed patient population SRS alone and SRS as after surgery. Cochlear median doses <math>&lt; 6</math> Gy appear to be associated with improved hearing outcomes.</p> |
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| <p>Patel et al<sup>10</sup>, 2019</p> | <p>Study Description:</p> <p>Retrospective study of patients with VS</p> <p>Patient Population:</p> <p>N = 100 patients</p> <p>Treatment:</p> <p>N = 43 underwent SRS and N = 57 underwent fractionated radiotherapy (50.4 Gy in 28 fractions)</p> | <p>III</p> | <p>Results:</p> <p>Patients who developed a decrease in their GR score and those who lost serviceable hearing following SRS/fractionated radiotherapy were noted to have significantly higher minimal doses to the cochlea.</p> <p>In patients undergoing SRS, a cochlea dose <math>\geq 5</math> Gy was an excellent predictor of hearing loss with a sensitivity and specificity of 100% and 90%, respectively.</p> <p>In patients undergoing fractionated radiotherapy, a minimal cochlea dose <math>\geq 35</math> Gy was an excellent predictor of hearing loss with a specificity and sensitivity of 91% and 50%, respectively.</p> <p>Authors Conclusion:</p> <p>Minimal dose to the cochlea with thresholds <math>&lt; 5</math> Gy and 35 Gy for SRS and fractionated radiotherapy, respectively may improve hearing preservation following radiation treatment for VS.</p> |
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|  |  |  | <p>Comments and Conclusions:</p> <p>Class III due to single institution retrospective design with small sample size. Cochlear dose thresholds of 5 Gy and 35 Gy for SRS and fractionated radiotherapy, respectively may be associated with improved hearing preservation following radiation treatment for VS.</p> |
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| Van Linge et al <sup>11</sup> , 2018 | <p>Study Description:</p> <p>Retrospective comparative study in patients with VS</p> <p>Single center</p> <p>Patient Population:</p> <p>N = 94 adult patients with VS</p> <p>Treatment”</p> <p>SRS in N = 67 patients to a dose of 12 Gy in a single fraction</p> <p>Fractionated Radiotherapy (fSRT) in N = 27 patients to 54 Gy in 30 fractions</p> | III | <p>Results:</p> <p>On both univariable and multivariable analyses, the volume of cochlea getting at least 90% of the prescription dose (V90 EQD<sub>2</sub>) was significantly associated with loss of functional hearing, increase in baseline GR class, and deterioration in PTA. No differences were observed by fractionation scheme.</p> <p>Authors Conclusion: Limiting the V90 to the cochlea may reduce progression of hearing loss</p> <p>Comments and Conclusions:</p> <p>Retrospective study comparing SRS to fractionated radiotherapy. Class III evidence due to retrospective nature, limited sample size, and patients all treated at a single institution. Limiting cochlea V90 may reduce hearing loss.</p> |
| Chung et al <sup>12</sup> , 2018     | <p>Study Description:</p> <p>Retrospective case control study of patients with VS</p> <p>Single center</p>                                                                                                                                                                                                                                            | III | <p>Results:</p> <p>In patients who underwent SRS, those who developed decreased hearing received a significantly higher minimum cochlear</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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|                                     | <p>Patient Population:</p> <p>N = 38 patients with VS</p> <p>Treatment:</p> <p>N = 14 patients underwent SRS (12 Gy x 1) or fractionated radiotherapy (N = 24, fSRT 50.4 Gy in 28 fractions)</p> |     | <p>dose (7.41 vs. 4.24 Gy; <math>p = 0.02</math>). When the minimum cochlear dose exceeded 6 Gy, there was a significant risk of decreased hearing preservation (OR: 32; <math>p = 0.02</math>)</p> <p>In patients who underwent fractionated radiotherapy, no differences in cochlear dose were observed for patients with decreased hearing.</p> <p>Author Conclusion:</p> <p>Higher minimum cochlea dose was predictive of decreased hearing preservation in patients undergoing SRS for VS.</p> <p>Comments and Conclusions:</p> <p>Class III due to small sample size and single institution retrospective nature. Higher minimum doses to the cochlea in patients undergoing SRS is predictive of worsened hearing preservation.</p> |
| Hasegawa et al <sup>13</sup> , 2018 | <p>Study Description:</p> <p>Retrospective study of patients with VS</p> <p>Patient Population:</p> <p>N = 92 patients with VS</p>                                                               | III | <p>Results:</p> <p>The median mean cochlear dose for all patients was 4 Gy. On univariable (<math>p &lt; 0.001</math>) and multivariable (<math>p &lt; 0.001</math>) analysis, mean</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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|                                | <p>Treatment:</p> <p>All underwent GKRS to a median margin dose of 12 Gy</p>                                                                                                                                       |     | <p>cochlear dose was associated with hearing preservation.</p> <p>Author Conclusion:</p> <p>Higher mean cochlear doses are associated with decreased hearing preservation.</p> <p>Comments and Conclusions:</p> <p>Class III due to single institution retrospective study. Increasing mean cochlear dose is associated with worse hearing preservation in patients with VS undergoing SRS.</p> |
| Pan et al <sup>14</sup> , 2017 | <p>Study Description:</p> <p>Retrospective study of patients with VS</p> <p>Patient Population:</p> <p>N = 93 patients with VS</p> <p>Treatment:</p> <p>Upfront GKRS in all patients to a margin dose of 12 Gy</p> | III | <p>Results:</p> <p>The dose to the cochlea was a statistically significant predictor of hearing preservation in patients with serviceable hearing following SRS.</p> <p>Authors Conclusion:</p> <p>Cochlea dose is a significant predictor of hearing preservation in patients with serviceable hearing following SRS.</p>                                                                      |

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|                                     |                                                                                                                                                                                                                     |     | <p>Comments and Conclusions:</p> <p>Class III due to small sample size and single institution retrospective design. Cochlea dose is a significant predictor of hearing preservation.</p>                                                                                                                                                                                                                                                                                                         |
| Lin et al <sup>15</sup> , 2017      | <p>Study Description:</p> <p>Retrospective Study of Patients with VS</p> <p>Patient Population:</p> <p>N = 100 patients with VS</p> <p>Treatment:</p> <p>All patients underwent single fraction SRS to 12-13 Gy</p> | III | <p>Results:</p> <p>Mean cochlear dose &lt; 4 Gy was the only significant dosimetric predictor of hearing preservation (p = 0.02)</p> <p>Authors Conclusion:</p> <p>The mean dose to the cochlea is the most crucial factor for hearing preservation following SRS for VS.</p> <p>Comments and Conclusions:</p> <p>Class III due to single institution retrospective design. Maintaining a mean cochlear dose of &lt; 4 Gy is associated with improved hearing outcomes following SRS for VS.</p> |
| Watanabe et al <sup>16</sup> , 2016 | <p>Study Description:</p> <p>Retrospective study of patients with VS</p>                                                                                                                                            | III | <p>Results:</p> <p>A mean cochlear dose of &gt; 4.2 Gy (p = 0.03) was associated with</p>                                                                                                                                                                                                                                                                                                                                                                                                        |

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|                                    | <p>Patient Population:</p> <p>N = 183 patients with VS</p> <p>Treatment:</p> <p>GKRS in all patients</p>                                                                                                                                                                                                        |     | <p>worse hearing preservation.</p> <p>Authors Conclusion:</p> <p>Mean cochlear dose &gt; 4.2 Gy is a significant predictor of hearing preservation.</p> <p>Comments and Conclusions:</p> <p>Class III due to single institution retrospective design. A mean cochlear dose of &gt; 4.2 Gy is associated with worse hearing preservation following GKRS for VS.</p>                                                                                                                                                                 |
| Mousavi et al <sup>17</sup> , 2015 | <p>Study Description:</p> <p>Retrospective study in patients with VS</p> <p>Single center</p> <p>Patient Population:</p> <p>N = 68 patients with GR Class I hearing; N = 25 had no subjective hearing loss and N = 43 has subjective hearing loss prior to GKRS</p> <p>Treatment:</p> <p>SRS to 12.5 Gy x 1</p> | III | <p>Results:</p> <p>No statistically significant difference between the two groups was observed for mean cochlear dose or median tumor margin dose. Patients in the group with no subjective hearing loss had significantly higher rates of hearing preservation. Median cochlear dose, median tumor marginal dose, and median maximum dose were not associated with worse hearing outcomes.</p> <p>Author Conclusion:</p> <p>At 2- to 3-years following GKRS, patients without subjective hearing loss or a PTA &lt; 15 dB had</p> |

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|  |  |  | <p>higher rates of hearing preservation.</p> <p>Comments and Conclusions:</p> <p>Class III due to single institution retrospective nature. Patients without subjective hearing loss or a PTA &lt; 15 dB had higher rates of grade I or II hearing preservation 2- to 3-years post GKRS.</p> |
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Abbreviations: ASHL: acute sensorineural hearing loss; EQD<sub>2</sub>: equivalent dose in 2 Gy fractions; GKRS: Gamma Knife Radiosurgery; GR: Gardner Robertson hearing scale; Gy: gray; HR: hazard ratio; PTA: pure tone average; OR: odds ratio; SAT: speech awareness threshold; SRS: stereotactic radiosurgery; VS: vestibular schwannoma

**Table 3.** Hearing preservation and /or other cranial nerve deficits after radiosurgery delivered as single fraction radiosurgery (SRS) and/or hypofractionation SRS (HfSRS) and/or conventional fSRT in adult patients with imaging findings consistent with VSs .

| Author/Year                        | Study Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Data Class | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Kuchler et al <sup>18</sup> , 2022 | <p>Retrospective review<br/>Single institution</p> <p>Objective: Evaluate differences in tumor control, symptoms and quality of life after SRS/HfSRT (149 patients) vs. fractionated radiation therapy (fSRT) (87 patients) versus fractionated proton therapy (FPT) (25 patients)</p> <p>Median doses:<br/>SRS/fSRS 12Gy/1fx and 18Gy/3fx<br/>fSRT 57.6Gy/32 fx<br/>FPT 54Gy (RBE)/32 fx</p> <p>Median follow-up 38 months</p> <p>QOL assessment via questionnaire</p> <p>Median tumor volume:<br/>SRS/HfSRT 0.65ccm<br/>fSRT 1.59ccm<br/>FPT 3.93ccm</p> | III        | <p>Results:<br/>Hearing preservation rate 97% at 12 months and 87% at 60 months with no statistical difference between treatment groups (p=0.31).</p> <p>Facial and trigeminal nerve symptoms after SRS/fSRT were mild but with highest rates in FPT patients.<br/>Facial n: 6.9% after SRS/fSRT vs.27.8% after FPT.<br/>Trigeminal n: 10.8% after SRS/fSRT vs.20% after FPT.</p> <p>The majority of FPT patients who developed nerve related symptoms had large VS with brainstem contact (20%) or compression (60- 80%).</p> <p>In patients with SRS/HfSRT lower risk for facial and trigeminal nerve impairment was seen with fSRT versus SRS, but the difference was not statistically significant (p=0.66 and p =0.4 respectively)</p> <p>Authors conclusions:<br/>SRS/fSRS, fSRT and FPT show similar overall clinical and functional outcomes.<br/>Cranial nerve impairment rates vary, potentially due to selection bias with large VS in the fSRT and FPT group.</p> <p>Comments and conclusions:</p> |

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|                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |            | <p>Class III evidence due to retrospective study from single institution and due to cross-sectional study in a population treated over 10 years. Relatively small number of patients treated with proton therapy. The available data on FPT are biased as these patients had significantly larger lesions and were more symptomatic at time of treatment. No significant difference in outcomes was observed but higher rates of cranial nerve complications were observed in patients with large VS treated with fractionated therapy.</p>                                                                                                                                  |
| <p>Puataweepong et al<sup>19</sup>, 2022</p> | <p>Retrospective review<br/>Single institution<br/>Treatment delivered with CyberKnife</p> <p>Objective: Compare long-term clinical outcomes with SRS (23 patients) versus HfSRS (100 patients). SRS was used for patients with non-serviceable hearing and Koos grade I-III tumors. HfSRS was used for patients with serviceable hearing and Koos grade III-IV tumors.</p> <p>Median dose:<br/>SRS 12Gy/1fx<br/>HfSRS 18Gy/3fx</p> <p>Median tumor volume:<br/>SRS 0.92 cm<sup>3</sup> and HSRT 2.9 cm<sup>3</sup></p> <p>Median follow-up 72 months</p> | <p>III</p> | <p>Results:</p> <p>Among 28 patients with serviceable hearing in the HSRT group, the 5 and 8-year hearing preservation rates were 87% and 65% respectively. The median time to hearing deterioration was 71 months. No factor was significantly associated with hearing preservation rates on univariable and multivariable analyses.</p> <p>The rate of non-auditory complications was 4.3% in the SRS group and 15% in the HfSRS group. Koos grade III and IV was associated with non-auditory complications.</p> <p>Authors conclusions:<br/>fSRS delivered via CyberKnife may result in acceptable hearing preservation rates albeit with a higher incidence of non-</p> |

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|                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            | <p>auditory complications in Koos III/IV patients.</p> <p>Comments and conclusions: Class III evidence due to retrospective study from single institution. Patient numbers with serviceable hearing at time of treatment were small. There is a higher incidence of non-auditory complications in patients with Koos III/IV in the reported population.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>Soderlund<br/>Diaz et al<sup>20</sup>,<br/>2020</p> | <p>Retrospective review<br/>Single institution</p> <p>Objective: To assess outcomes after LINAC based radiosurgery (SRS) (37 patients) and fractionated radiosurgery (fSRS) (99 patients) and identify possible differences in outcomes</p> <p>SRS median dose 12Gy/1fx<br/>fSRS<br/>18-21Gy/3fx (39patients) or<br/>25Gy/5fx (60 patients)</p> <p>Median PTV volume 2.5cm<sup>3</sup> (range 0.6-10.8). PTV was significantly larger in the hypofSRS 5 fraction group with median volume of 3.9cm<sup>3</sup></p> <p>Median follow-up was 57 months (but was significantly shorter in the SRS group at 41 months p=&lt;0.001)</p> | <p>III</p> | <p>Results:<br/>Overall hearing preservation 35% (mean audiometric follow-up of 33 months). No significant difference in hearing preservation after SRS vs. fSRS (p=0.15)</p> <p>No difference in trigeminal nerve toxicity incidence was observed between SRS and fSRs (p=0.61). No difference was found between the treatment groups for facial nerve toxicity (p=0.35)</p> <p>Authors conclusions:<br/>Both SRS and fSRS are effective treatment options with no differences in hearing preservation or neurologic toxicity. SRS recommended for small to medium sized VS. fSRS is an alternative option including those with larger tumors. Dose fractionation for fSRS regimen is yet to be refined as patients treated with both 6Gy and 7Gy per fraction but analyzed together.</p> |

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|                                    |                                                                                                                                                                                                                                                                                                                      |     | <p>Comments and conclusions:<br/>Class III evidence due to being a retrospective study from single institution. Excellent long-term outcomes seen with 3-5 fraction fSRS. Further studies needed to refine optimal patient selection criteria for SRS versus fSRS and dose fractionation for fSRS requires further validation.</p>                                                                                                                                                                                                                                                                                                                                                                |
| Khattab et al <sup>21</sup> , 2019 | <p>Study Description:<br/>Retrospective study in patients with VS</p> <p>Patient Population:<br/>N = 56 patients with VS</p> <p>Treatment:<br/>Single fraction SRS in N = 12 patients (12.5-16 Gy)</p> <p>3-fraction SRS in N = 12 patients (7 Gy x 3)</p> <p>5-fraction SRS in N = 31 patients (4.5-5.5 Gy x 5)</p> | III | <p>Results:<br/>Multifraction SRS was associated with better audiologic outcomes compared to single fraction (<math>p = 0.009</math>). Both cochlear mean dose (<math>p = 0.85</math>) and cochlear max dose (<math>p=0.82</math>) were not associated with a change in speech awareness threshold (SAT).</p> <p>Authors Conclusion:<br/>Multifraction SRS may provide better hearing preservation than single fraction SRS in patients with VS</p> <p>Comments and Conclusions:<br/>Class III due to small number of patients and a retrospective, single institution cohort. Multifraction SRS may provide better hearing preservation in patients with VS compared to single fraction SRS.</p> |

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| <p>Singh et al<sup>22</sup>, 2019</p>    | <p>Multi institutional analysis with data obtained from a prospectively collected international database of VS patients treated with SRS and fSRS</p> <p>Objective: Compare clinical outcomes following SRS (12 patients) and fractionated stereotactic radiosurgery (fSRS) (52 patients).</p> <p>All patients were treated with CyberKnife robotic radiosurgery system</p> <p>Median # of fractions 3 (range of 1-5)</p> <p>Median prescription dose:<br/>1 fx 12.25Gy<br/>3 fx 18Gy<br/>5 fx 25Gy</p> <p>GTV median 1.09 cc (range 0.008–34.8)</p> <p>Median follow-up 30.4 months (range 7.5–107)</p> <p>Potential factors predictive of toxicity were estimated using the Kaplan-Meier method, Cox proportional hazard model and binary logistics regression with propensity score weighting</p> | <p>II</p>  | <p>Results:<br/>In regards to hearing loss, no statistically significant difference identified between SRS (0%) and fSRS (13.5%) (p=0.14) despite significantly longer median follow-up in the SRS group.</p> <p>fSRS was associated with a higher likelihood of toxicities (42.3% versus 8.3% for SRS; p=0.054), including trigeminal and facial nerve dysfunction.</p> <p>Author conclusions:<br/>Equivalent local control achieved but higher cranial nerve toxicity with fSRS.</p> <p>Comments and conclusions:<br/>Class II evidence from multi-center prospective data. Specifics regarding treatment planning unknown and may have varied amongst institutions. Follow up time was limited.</p> |
| <p>Udawatta et al<sup>23</sup>, 2019</p> | <p>Retrospective chart review<br/>Single institution</p> <p>Objective:<br/>Primary - To determine differences in preservation of serviceable hearing for patients treated with SRS (21 patients), fSRT (33 patients) or HfSRT (6 patients)</p> <p>SRS median dose 12Gy/1 fraction<br/>HfSRT median dose 25Gy/5fractions<br/>FSRT median dose 50.4Gy/28 fractions</p> <p>Median follow-up 31 months, but significantly shorter in the HfSRT group (median 9 months)</p>                                                                                                                                                                                                                                                                                                                               | <p>III</p> | <p>Results:<br/>Significant differences in hearing preservation rates as an effect of treatment type using Fisher exact test (p=0.025). Hearing retention rates 69.2% for FSRT, 37.5% for SRS and 100% for HfSRT patients.</p> <p>SRS cohort showed shorter time to hearing deterioration compared with FSRT and HfSRT cohorts.</p> <p>Authors conclusions:<br/>fSRT showed better hearing preservation versus SRS but</p>                                                                                                                                                                                                                                                                             |

|                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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|                                 | <p>The SRS cohort had a higher baseline incidence of non-serviceable hearing compared with other cohorts before RT (p=0.001)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |     | <p>was also associated with significantly more non auditory symptoms that can exert a negative impact on patient's quality of life. No radiation related symptoms seen in the HfSRT group however patient numbers were small and follow-up time-limited. Future studies needed to determine whether HfSRT can be used as a valid alternative to fSRT.</p> <p>Comments and conclusions: Class III evidence due to retrospective nature, and single institution study. Benefit of HfSRT limited by small patient numbers and limited follow-up. fSRT demonstrated better hearing preservation than SRS but with greater negative impact on quality of life.</p> |
| Tang et al <sup>24</sup> , 2018 | <p>Retrospective review<br/>Single institution</p> <p>Objective: To determine differences in hearing outcomes between single session (487 patients) and multisession (74 patients) GK radiosurgery (GKRS)</p> <p>Treatment<br/>Single session: Mean marginal dose 12.5Gy prescribed to the 45-60% isodose line</p> <p>Multi session: 3 sessions over 3 consecutive days with mean marginal dose per session of 6.7Gy prescribed to the 49- 70% isodose line</p> <p>Single session: Average tumor volume 3.03cm<sup>3</sup> (range: 0.24–9.4)<br/>All test session: Average tumor volume 2.81 cm<sup>3</sup> (range: 0.16–9.77)</p> <p>Follow-up: The mean follow-up for audiometry was 16 months in a single</p> | III | <p>Results:<br/>Hearing preservation rates were analyzed using both “&lt;20dB change in PTA” and GR class I or II criteria. No significant difference in hearing preservation rates were identified between the 2 groups (PTA: 69% versus 65.5%, p=0.08; GR class: 51.9% versus 45%, p=0.1015).</p> <p>There was a trend toward improved hearing preservation rates in the multi session group. The audiometric follow-up time in multi session groups was significantly longer than in single session group (21 versus 16 months, p=0.0385).</p> <p>On multivariate analysis the linear internal auditory canal</p>                                          |

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|                               | <p>session group and 21 months in the multi session group.</p> <p>Propensity score matching was used to compare the 2 groups -29 patients from each group were selected for study. Patient's age, tumor volume, pre-GKRS pure-tone average and radiographic follow-up were not significantly different between the 2 groups (<math>p&gt;0.05</math>)</p>                                                                                     |     | <p>(IAC) length was the only significant predictor for hearing loss after multi session GKRS; odds ratio 0.3868.</p> <p>No significant difference seen in trigeminal or facial nerve complications between the 2 groups.</p> <p>Authors conclusions:<br/>Multi session GKRS is a safe and effective treatment option but hearing preservation rates were not superior to single session GKRS.<br/>Patients with longer IAC length may benefit from multi session treatment in terms of hearing preservation.</p> <p>Comments and conclusions:<br/>Class III evidence due to retrospective study and single institution. Follow-up period limited. No significant difference in hearing outcomes between the two groups.</p> |
| Lo et al <sup>25</sup> , 2018 | <p>Retrospective review<br/>Population-based study</p> <p>Objective: Evaluate long-term outcomes and toxicities of SRS (136 patients) and fSRT (17 patients)</p> <p>SRS dose 12Gy/1fx<br/>FSRT dose 50Gy/25fx<br/>FSRT used for tumors &gt;3cm and for patients with serviceable hearing (Gardner–Robertson classes I and II)</p> <p>Mean tumor volume: SRS 2.cm<sup>3</sup> and FSRT 3.6cm<sup>3</sup></p> <p>Median follow-up 7.7years</p> | III | <p>Results:<br/>In the 49 patients with serviceable hearing treated with FSRT, hearing preservation was 55% at 3 years and 29% at 7 years. In multivariable analysis, better pretreatment ipsilateral pure-tone average was significantly associated with hearing preservation (<math>p=0.04</math>).</p> <p>10 year actuarial rates of RT induced trigeminal nerve dysfunction were 25% after SRS, compared with 12% after FSRT (<math>p=0.01</math>).</p>                                                                                                                                                                                                                                                                 |

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |     | <p>10-year actuarial rates of RT induced facial nerve dysfunction were 15% after both SRS and FSRT.</p> <p>Authors conclusions:<br/>Both SRS and SRT provide excellent long-term local control however SRS was associated with higher rates of trigeminal nerve dysfunction. Even with FSRT, hearing preservation declined steadily with long-term audiometric follow-up.</p> <p>Comments and conclusions:<br/>Class III evidence due to retrospective review of population based study and the small number of patients treated with FSRT. Long-term hearing preservation rates decline despite the use of FSRT.</p> |
| Kessel et al <sup>26</sup> , 2016 | <p>Retrospective review<br/>Single institution<br/>Surveys assessing symptoms and quality of life sent to patient with a return rate of 76%.</p> <p>Objective: To assess hearing preservation and QOL outcomes for VS patients treated with SRS (56 patients) and fSRT (128 patients)</p> <p>Treatment:<br/>SRS median dose 12Gy/1 fraction<br/>Fractionated fSRT median dose 54Gy/30 fractions</p> <p>Median PTV volume 1.96 ml (range at 0.09-41.1 ml)</p> <p>Median follow-up: 7.5 years (range 0-14.4 years). Of patients who returned the survey, median follow-up was 9.6 years.</p> | III | <p>Results:<br/>In SRS group the median hearing preservation was 36.3 months (range 2.3-13.7 years). Hearing worsened in 30%.</p> <p>In fSRT group median hearing preservation was 48.7 months (range 0-13.8 years). The difference in hearing preservation was not significant between SRS and FSRT (p=0.3).</p> <p>No difference in facial and trigeminal nerve dysfunction was noted between the SRS and FSRT groups (facial nerve p=0.5 and trigeminal nerve p=0.1).</p>                                                                                                                                          |

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|                                  |                                                                                                                                                                                                                                                                                                                                                                            |     | <p>The survey response results correlated well with information documented in patient charts for facial and trigeminal nerve toxicity but significant differences noted in reporting of hearing impairment.</p> <p>Authors conclusions:<br/>Patient self-reported outcome during follow-up is of high value. fSRT can be offered independent of tumor size whilst SRS should be reserved for treatment of smaller lesions.</p> <p>Comments and conclusions:<br/>Class III evidence due to this being a retrospective study from a single institution. Patient self-reported outcomes were valuable but the questionnaire requires further validation. No significant difference in hearing preservation was noted between the two groups.</p> |
| Combs et al <sup>27</sup> , 2015 | <p>Retrospective review<br/>Pooled results from 3 large centers</p> <p>Objective: To evaluate local control, hearing preservation and cranial nerve toxicity for patients treated with SRS (169 patients) or fSRT (291 patients)</p> <p>SRS median dose 13Gy/1fx<br/>fSRT median dose 57.6Gy/32fx</p> <p>Median tumor diameter 15 mm</p> <p>Median follow-up 67 months</p> | III | <p>Results:<br/>Long-rank test used to evaluate intergroup differences in outcome. Loss of useful hearing was 14% for fSRT and 16% for SRS group. For patients treated with SRS <math>\leq 13</math>Gy hearing deterioration was 13%.</p> <p>No difference in trigeminal and facial nerve toxicity between SRS and fSRT groups.</p> <p>Authors conclusions:<br/>When chosen diligently based on tumor volume, pre-</p>                                                                                                                                                                                                                                                                                                                        |

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|  |  |  | <p>treatment characteristics and volume-dependent dose-prescription), both treatments may be considered equally effective.</p> <p>Comments and conclusions:<br/>Class III evidence due to retrospective study with pooled results from 3 centers. No significant difference in outcomes between the 2 groups.</p> |
|--|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Abbreviations: SRS= stereotactic radiosurgery; fx= fraction, fSRS= fractionated stereotactic radiosurgery ( $\leq 5$  fx); fSRT=fractionated stereotactic radiotherapy ( $>10$  fx); HfSRT= hypo-fractionated stereotactic radiotherapy ( $>5$ fx and  $\leq 10$ fx)

**Table 4:** Radiosurgery and secondary malignancies in adult patients with imaging findings consistent with VSs.

| Author/year                     | Study Description                                                                                                                                                                                                                                     | Data Class | Conclusion                                                                                                                                                                                                                                                                                                                                                                        |
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| Wolf et al <sup>35</sup> , 2018 | <p>Study Description:<br/>Retrospective multi-center study of patients with VS</p> <p>Patient Population:<br/>N = 1011 patients with VS<br/>Total N= 4905</p> <p>Treatment:<br/>All patients underwent GKRS</p> <p>Participating Centers:<br/>N=5</p> | III        | <p>Results:<br/>The cumulative incidence of developing radiosurgery-associated malignancy, either new or a transformation of a benign tumor, is 0,045% over 10 years.</p> <p>Author Conclusion:<br/>The risk of developing a CNS tumor after SRS is similar to the risk of the general population.</p> <p>Comments and Conclusions:<br/>Class III due to retrospective study.</p> |

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| Pollock et al <sup>31</sup> , 2017 | <p>Study Description:<br/>Retrospective single center study of patients with VS</p> <p>Patient Population:<br/>N = 358 patients with VS</p> <p>Treatment:<br/>All patients underwent GKRS</p> | III | <p>Results:<br/>No radiation induced tumors were identified in 11,262 patient-years (total patients N= 1142).<br/>Of 358 VS patients, 1 (0.3%) had malignant transformation.</p> <p>Author Conclusion:<br/>The risk of a radiation-induced tumor developing after SRS was 0.0% at 5 years, 0.0% at 10 years, and 0.0% at 15 years.</p> <p>Comments and Conclusions:<br/>Class III due to retrospective single center study.</p> |
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Abbreviations: GKRS: Gamma Knife Radiosurgery

#### Appendix V. Conflicts of Interest

| <b>Task Force Member</b>             | <b>Disclosure</b>                      |
|--------------------------------------|----------------------------------------|
| <i>Julie Honaker PhD, AuD</i>        | Nothing to Disclose                    |
| <i>Ben Allen Strickland, MD</i>      | Nothing to Disclose                    |
| <i>Eric J. Lehrer, MD</i>            | Servier Pharmaceuticals, Novocure Inc. |
| <i>Sheryl Green, MBBCh</i>           | Nothing to Disclose                    |
| <i>John P. Marinelli MD</i>          | Medtronic                              |
| <i>Christopher S. Graffeo MD, MS</i> | Nothing to Disclose                    |

|                                              |                                                                                                             |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| <i>Isabelle M. Germano, MD, MBA</i>          | Brianlab                                                                                                    |
| <i>Mateo Ziu, MD</i>                         | Omniscient Neurotechnology America Ltd; GT Medical Technologies, Inc                                        |
| <i>Walavan Sivakumar, MD</i>                 | Stryker Corporation                                                                                         |
| <i>Sherwin Tavakol, MD</i>                   | IRRAS USA, Inc.; Globus Medical, Inc.                                                                       |
| <i>Lucas Paul Carlstrom, MD, PhD</i>         | Kuros Biosciences USA, Inc                                                                                  |
| <i>Jamie J. Van Gompel, MD</i>               | Medtronic, Cadence                                                                                          |
| <i>Ian Dunn, MD</i>                          | Nothing to Disclose                                                                                         |
| <i>Jeffrey J. Olson, MD</i>                  | Verastem, Inc., Research Grant American Cancer Society, Editorial Consultant; Azurity Pharmaceuticals, Inc. |
| <i>Ghazal S. Daher MD</i>                    | Nothing to Disclose                                                                                         |
| <i>Matthew L. Carlson, MD</i>                | Cochlear Americas, Advanced Bionics, Stryker Corporation; iotaMotion, Inc.; Stryker Corporation             |
| <i>Neil S. Patel, MD</i>                     | Cochlear Americas, Zeiss, Viridian Therapeutics, IotaMotion, Inc.                                           |
| <i>Michael Sughrue, MD</i>                   | Omniscient Neurotechnology America Ltd                                                                      |
| <i>Constantinos G. Hadjipanayis, MD, PhD</i> | Stryker Corporation; Integra LifeSciences Corporation; Omniscient Neurotechnology America Ltd               |
| <i>Jeffrey Jacob, MD</i>                     | Stryker Corporation; KLS; Synthes                                                                           |

