CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE BASED GUIDELINE ON PATHOLOGIC METHODS AND PROGNOSTIC FACTORS IN VESTIBULAR SCHWANNOMAS

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

Endorsed by: Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)

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Abbreviations

LI: Labeling index

NF2: Neurofibromatosis 2

PCNA: Proliferating cell nuclear antigen

VEGF: Vascular endothelial growth factor

VS: Vestibular schwannoma

ABSTRACT

Target Population: Adults diagnosed with vestibular schwannomas (VSs).

Question 1

What is the prognostic significance of Antoni A versus B histologic patterns in VSs?

Recommendation

No recommendations can be made because of a lack of adequate data.

Question 2

What is the prognostic significance of mitotic figures seen in vestibular schwannoma specimens?

Recommendation

No recommendations can be made due to a lack of adequate data.

Question 3

Are there other light microscopic features that predict clinical behavior of vestibular schwannomas?

Recommendation

No recommendations can be made due to a lack of adequate data.

Question 4

Does the KI-67 labeling index predict clinical behavior of vestibular schwannomas?

Recommendation

No recommendations can be made due to a lack of adequate data.

Question 5

Does the proliferating cell nuclear antigen labeling index predict clinical behavior of vestibular schwannomas?

Recommendation

No recommendations can be made due to a lack of adequate data.

Question 6

Does degree of vascular endothelial growth factor expression predict clinical behavior of vestibular schwannomas?

Recommendation

No recommendations can be made due to a lack of adequate data.

INTRODUCTION

Rationale

With the diagnosis of vestibular schwannomas (VSs), the ability to prognosticate about the eventual outcome and disease control is challenging, given the complex set of circumstances in patients with recurrent or residual tumors. The present systematic review seeks to summarize the literature on these topics to provide clinical practice guidelines based on a robust systematic review of the literature and to identify gaps in our knowledge and suggest avenues for future study.

Objectives

The objectives of this paper are to determine what is known about the prognostic (ie, factors that predict recurrence or clinically aggressive behavior) significance of histopathologic features and immunohistochemical markers of VSs. To address these objectives, the information sought is divided into a set of key questions:

1. What is the prognostic significance of Antoni A versus B histologic patterns in vestibular schwannomas?
2. What is the prognostic significance of mitotic figures seen in vestibular schwannoma specimens?
3. Are there other light microscopic features that predict clinical behavior of vestibular schwannomas?
4. Does the KI-67 labeling index predict clinical behavior of vestibular schwannomas?
5. Does the proliferating cell nuclear antigen labeling index predict clinical behavior of vestibular schwannomas?
6. Does degree of vascular endothelial growth factor expression predict clinical behavior of vestibular schwannomas?

METHODS

Writing Group and Question Establishment

After establishing VS management as a priority for guideline development, the Joint Tumor Section of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, and the Guidelines Committee of the Congress of Neurological Surgeons selected a

multidisciplinary group of individuals to carry out this project. The entire group of individuals was screened for conflict of interest and then assembled into smaller groups by general components of management. These groups then agreed upon the main questions pertinent to these management components and shared them with the overall group for modification. The task force was divided into groups by management topic to evaluate the literature and write the guidelines.

Search Method

The task force group assigned to VS pathology collaborated with a medical librarian to search for articles published between January 1, 1990 and December 31, 2014. Two electronic databases, including PubMed and the Cochrane Central Register of Controlled Trials, were searched. Strategies for searching electronic databases were constructed using previously published search strategies to identify relevant studies (Figure 1 and Table 1).[1–8]

The task force group supplemented searches of electronic databases with manual screening of the bibliographies of all retrieved publications. The task force group also searched the bibliographies of recent systematic reviews and other review articles for potentially relevant citations. All articles identified are subject to the study selection criteria listed below. As noted above, the guideline committee also examines lists of included and excluded studies for errors and omissions.

Study Selection and Eligibility Criteria

A total of 688 citations were manually reviewed by the team with specific inclusion and exclusion criteria as outlined below. Two independent reviewers screened the abstracts to determine those worthy of full-text review. These two sets of data were compared for agreement by a third party. Inconsistencies were re-reviewed and disagreements were resolved by consensus. Citations that considered adult patients focusing on surgical treatment of VSs were considered. The following inclusions and exclusions were then applied:

- Investigated patients suspected of having VSs
- Patients ≥18 years of age
- Was of humans

- Published between January 1, 1990, and December 31, 2014
- Quantitatively presented results
- Was not an in vitro study (for novel molecular markers, in vitro studies were included on patient samples)
- Was not a biomechanical study
- Was not performed on cadavers
- Was published in English
- Was not a meeting abstract, editorial, letter, or a commentary
- Studies may include mixed pathology; however, the data pertaining to VSs were abstractable from the paper.
- >5 patients or patient samples

The authors did not include systematic reviews, guidelines, or meta-analyses conducted by other authors. These documents were developed using different inclusion criteria than those specified in this guideline. Therefore, they may include studies that do not meet the inclusion criteria stated above. The authors recalled these documents if their abstracts suggested that they might address one of the recommendations presented here, and the bibliographies were searched for additional studies.

Data Collection Process

The articles deemed relevant for full-text review were then reviewed, and the study design, topic evaluated, and conclusions were extracted. The items in the above-mentioned inclusion and exclusion criteria were applied before inclusion in the final dataset. For some questions, it became apparent that the data in the full-text articles were not able to provide meaningful support for any form of recommendation. These questions were dropped from the list of those that led to recommendations, and their topics were then moved for discussion in the "Conclusion and Key Issues for Future Investigations" section at the end of this article.

Assessment for Risk of Bias

The possibility of systematic bias in results was addressed by first stratifying the evidence based on the class of evidence quality, which highlights the limitations in this literature. Given the

sparsity of evidence for many of these questions, formal methods for studying publication bias such as funnel plots were not possible.

In addition, one obvious bias inherent to these studies is selection bias. For a patient to be in a pathology study, that patient, by definition, underwent microsurgical resection, which inherently biases the results toward larger and probably more aggressive tumors than would be seen in a cohort of all VSs. However, it is important to note that this bias is uniform across all studies of this type. Therefore, while individual practitioners may have skewed results by differences in case selection, there is no clear mechanism by which these biases are systematically distributed.

Classification System and Recommendation Formulation

The concept of linking evidence to recommendations has been further formalized by the American Medical Association (AMA) and many specialty societies, including the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Academy of Neurology (AAN). This formalization involves the designation of specific relationships between the strength of evidence and the strength of recommendations to avoid ambiguity. In the paradigm for prognostic evidence, evidence is classified based on the following 5 technical criteria: 1) Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease?, 2) Was patient follow-up sufficiently long and complete?, 3) Were objective outcome criteria applied in a "blinded" fashion?, 4) If subgroups with different prognoses were identified, was there adjustment for important prognostic factors?, 5) If specific prognostic factors were identified, was there validation in an independent "test set" group of patients?

Class I evidence, defined as studies which meet all 5 criteria, is used to support recommendations of the strongest type, defined as level 1 recommendations, indicating a high degree of clinical certainty. Studies which meet 4 or 5 criteria are designated as class II evidence. These are used to support recommendations defined as level 2, reflecting a moderate degree of clinical certainty. All other studies are considered class III evidence and support level 3 recommendations, reflecting unclear clinical certainty. A summary of these categories of evidence can be viewed at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RESULTS

Question 1: What is the prognostic significance of Antoni A vs B histologic patterns in vestibular schwannomas?

STUDY SELECTION AND CHARACTERISTICS

The task force identified 3 studies that were retrospective and specifically addressed some aspect of the question of whether Antoni A versus B versus A/B-type histology influenced prognosis in VS patients (Table 2).[9–11] In these studies, this determination was made based on subjective binary determinations of the pathologist and correlated with some type of clinical outcome.

RESULTS OF INDIVIDUAL STUDIES, DISCUSSION OF STUDY LIMITATIONS AND RISK OF BIAS

Two studies[9,10] found that the tumor pattern did not correlate with preoperative tumor growth rates. Another study[11] found that Antoni B type tumors were more likely to have preoperative facial palsy than Antoni A or Antoni A/B type tumors. None of these studies addressed postoperative outcomes based on these findings. The definition of these terms is vague and subjective, and therefore the reliability of these data is unclear. Misclassification bias is clearly possible. These studies are all retrospective; therefore, case selection bias, bias caused by a loss of data, and publication bias all play a role. Because of the limited number of studies, study bias is difficult to assess.

SYNTHESIS OF RESULTS

Antoni A versus B tumor patterns do not seem to predict growth rates, but these tumors may vary in their preoperative risk to the facial nerve. A single study showed Antoni B tumors might lead to risk to the facial nerve, which should be further explored in future research.[11] Presently, there are no data supporting using Antoni A versus B tumor patterns in prognostication of patients with VSs. It should be noted that this would be a difficult topic to study in a truly quantitative or semiquantitative manner that would realistically address this topic.

Presently, no meaningful recommendations can be made about this topic.

Question 2: What is the prognostic significance of mitotic figures seen in vestibular schwannoma specimens?

STUDY SELECTION AND CHARACTERISTICS

Three studies were identified that specifically addressed some aspect of the question of whether the presence of mitoses in the tumor specimen influenced prognosis in VS patients (Table 2). In 2 of these studies, the number or presence of mitoses were correlated with preoperative clinical behavior.[9,12] In 1 study,[13] mitoses were correlated with rates of growth of recurrent tumors.

RESULTS OF INDIVIDUAL STUDIES, DISCUSSION OF STUDY LIMITATIONS, AND RISK OF BIAS

One study[9] found that mitoses did not correlate with preoperative tumor growth rates. Another study[12] found that mitoses did not correlate with preoperative hearing loss. Finally, Hwang et al[13] studied a group of patients with recurrent tumors and found that there was no correlation between the presence of mitoses and rates of growth at the time of recurrence (Table 2). The retrospective nature of these studies leaves them at risk for selection and publication bias, and unintentional data entry oversights and neglect. None of these studies addressed the postsurgical course of the patient after the specimen in question was resected. Therefore, it is unclear if these findings are predictive of future behavior of the tumor.

SYNTHESIS OF RESULTS

The limited studies available do not suggest that the presence of mitoses on light microscopy portends a poorer or different prognosis. No recommendations for against a relationship between mitoses and postoperative prognosis can be made.

Question 3: Are there other light microscopic features that predict clinical behavior of vestibular schwannomas?

STUDY SELECTION AND CHARACTERISTICS

Two studies addressed the prognostic significance of tumor cell density. One[9] studied the relationship between cell density and preoperative growth rate, and another[13] studied cell density and its relationship to growth rate of recurrent tumors before repeat surgery. Both studies assessed density in a semiquantitative manner using cell counting techniques.

Two studies addressed the prognostic significance of tumor microhemorrhage. One[12] studied the relationship between hearing loss, and another[14] studied extent of hemosiderin deposition and its relationship to tumor size.

Two studies were identified that correlated tumor vessel density with tumor progression leading up to surgery.[13,15] Another study[13] was found that addressed the relationship between nuclear pleomorphism and growth rate (Table 2).

RESULTS OF INDIVIDUAL STUDIES, DISCUSSION OF STUDY LIMITATIONS, AND RISK OF BIAS

Both studies that addressed cell density found that increased cell density was correlated with faster preoperative tumor growth. Postoperative tumor growth was not addressed. Intratumoral microhemorrhage was found to predict preoperative hearing loss[12] and to correlate with larger preoperative tumor size.[14] One study addressing tumor vessel density[15] found that increased tumor vessel density correlated with a faster preoperative tumor course. The other study[13] that studied specimens from recurrent VS patients found that faster growing recurrent tumors did not have a higher microvascular density than slower growing ones. The only study addressing pleomorphism did not find a significant difference between the groups.[13]

None of these studies addressed the postsurgical course of the patient after the specimen in question was resected. Therefore, it is unclear if these findings are predictive of future behavior of the tumor. The retrospective nature of these studies leave them at risk for selection and publication bias, and unintentional data entry oversights and neglect. Because of the limited number of studies, it is difficult to determine across study bias. In addition, these studies were performed in different manners to address different endpoints.

SYNTHESIS OF RESULTS

The limited literature in this area suggests a few interesting histopathologic features that correlate with worse preoperative behavior in some cases. For example, cell density and microhemorrhage have been linked to adverse clinical traits in two studies.[12,14] It is important, however, to note that none of these studies relates a histologic trait to a future clinical behavior, which is a fundamental trait of a clinical useful biomarker. Therefore, caution should be applied

before clinical use of any of these histologic features in decision making. Cell density and the presence of extensive microhemorrhage may correlate with worse preoperative behavior. Microvascular density and nuclear pleomorphism are of unclear significance. None of these factors have been studied in relation to postoperative prognosis.

Thus presently, no recommendations can be made regarding the relationship between light microscopic features and postoperative prognosis.

Question 4: Does the KI-67 labeling index predict clinical behavior of vestibular schwannomas?

STUDY SELECTION AND CHARACTERISTICS

Our searches identified 10 studies that addressed the relationship between KI-67 (MIB-1) LIs and the clinical behavior of VS tumors (Table 3). Four studies[10,14,16,17] examined the relationship between the KI-67 LI and preoperative tumor size. Four studies looked at the relationship between KI-67 LI and preoperative growth rate[18–20] or the rate of clinical progression.[17] Two studies compared the relationship between KI-67 LI and tumor growth rate of recurrent tumors.[13,21] Finally, 2 studies compared the KI-67 LI between neurofibromatosis 2 (NF2) and sporadic VS tumors.[22, 23]

RESULTS OF INDIVIDUAL STUDIES, DISCUSION OF STUDY LIMITATIONS, AND RISK OF BIAS

All 4 studies addressing the relationship between tumor size at time of surgery and KI-67 LI found no relationship between tumor size and the KI-67 LI.[10,14,16,17] Similarly, both studies on the topic found that NF2 tumors have a higher KI-67 LI than sporadic VSs.[22,23]

Charabi et al[17] found that elevated KI-67 LIs correlated with a shorter duration of preoperative symptoms. One study[19] found that KI-67 LI elevation correlated with faster preoperative tumor growth rate, while 2 found that they did not.[18,20] The 2 studies, which determined the relationship between tumor growth rate in recurrent VS cases, both found that KI-67 LI were related to growth rate. One[13] found that faster growing tumors undergoing repeat surgery had higher KI-67 LIs than slower-growing tumors undergoing repeat surgery. Another[21] found that tumors with

elevated KI-67 LIs had fast tumor doubling times compared to lower KI-67 LI tumors, and that there was a direct logarithmic relationship between tumor doubling times and KI-67 LIs.

These studies all used different methods for quantifying tumor growth rate. In addition, the method for determining KI-67 LIs were often different, varying between measuring the number of positive cells per high-powered field to a quantitative fraction of cells. The data were also studied using arbitrary cutoffs or correlation analysis in different studies, making it difficult to extrapolate and compare data from different studies. The retrospective nature of all but 1 of these studies leave them at risk for selection and publication bias and unintentional data entry oversights and neglect. There is only 1 study,[21] which looked at the KI-67 LI as a predictor of future behavior (ie, prognosis), and even then, only studied this in a subset of tumors that had recurred. Therefore, it is unclear if any of these findings are predictive of future behavior of the tumor.

SYNTHESIS OF RESULTS

In short, no recommendations can be made regarding the relationship of KI-67 and postoperative prognosis.

While it seems reasonable to hypothesize that tumors with greater fractions of dividing cells might behave more clinically aggressively, especially before surgery, the data are limited and more mixed on this topic than would be expected. Most importantly, there are few data that attempt to determine if a patient with elevated KI-67 is actually at greater risk of recurrence after surgery, which is the fundamental question a prognostic biomarker is expected to try to answer. The results of studies that relate KI-67 LIs to tumor behavior are mixed. It is unclear if tumors with higher KI-67 LIs are growing faster on imaging. In addition, there are only limited studies attempting to determine if having an elevated KI-67 LI puts a patient at risk for recurrence or more aggressive tumor behavior.

Question 5: Does the proliferating cell nuclear antigen labeling index predict clinical behavior of vestibular schwannomas?

STUDY SELECTION AND CHARACTERISTICS

The literature search identified three studies that addressed the relationship between PCNA LIs and the clinical behavior of VS tumors (Table 4). Two studies[9,19] correlated PCNA LIs with preoperative tumor growth rate. One study compared the PCNA LI between NF2 and sporadic VS tumors.[23]

RESULTS OF INDIVIDUAL STUDIES, DISCUSSION OF STUDY LIMITATIONS, AND RISK OF BIAS

One study[19] found that PCNA LI elevation (above the arbitrary cutoff of >40% positive cells) correlated with faster preoperative tumor growth rate. The other study compared the PCNA with preoperative growth rate and found a direct correlation between the LI data and growth rate.[9] Similar to their KI-67 LI results,[23] Antinheimo et al found that NF2 VS tumors had higher LIs than sporadic tumors. The retrospective nature of these studies leaves them at risk for selection and publication bias and unintentional data entry oversights and neglect. None of these studies attempted to determine the relationship between PNCA indices and postoperative outcomes. Therefore, it is unclear if any of these findings are predictive of the future behavior of the tumor.

SYNTHESIS OF RESULTS

As with KI-67, when studying PCNA, the authors were surprised to find a general lack of data trying to determine if these indices actually predict future tumor behavior. These studies are obviously more challenging to perform, but are essential to determine if clinicians should use these LIs in clinical decision making. Therefore, while it is reasonable to think that a higher cell proliferation index might suggest that a tumor may be biologically more aggressive in the period before surgery, there are essentially no data to suggest that these tests should guide clinical decision making. The limited data suggest that tumors with higher PCNA LI grow faster; however, whether this predicts future behavior is presently unclear. PCNA LIs are best viewed as experimental data at the present time as it is not certain what their relationship is to prognosis.

In short, no recommendations can be made regarding the use of PCNA in clinical practice.

Question 6: Does degree of vascular endothelial growth factor expression predict clinical behavior of vestibular schwannomas?

STUDY SELECTION AND CHARACTERISTICS

The literature searches identified 4 studies that addressed the relationship between VEGF levels and the clinical behavior of VS tumors (Table 5). Two studies[24,25] correlated VEGF levels with preoperative tumor growth rate. One study from a previously cited group[26] was sufficiently different in size from their previous study such that the data likely do not involve significant duplication of patients, and as such, was included. This study, compared VEGF levels between recurrent and/or previously irradiated tumors, and previously untreated tumors. One study compared VEGF levels between NF2 and sporadic VS tumors.[27]

RESULTS OF INDIVIDUAL STUDIES, DISCUSSION OF STUDY LIMITATIONS, AND RISK OF BIAS

Both studies relating preoperative growth rate and VEGF expression found that increased VEGF expression correlated well with increased growth rates. In addition, recurrent tumors and tumors that had previously been irradiated were found to have increased VEGF levels compared to previously untreated tumors in a subsequent study by 1 of these groups.[26]
Saito et al[27] found no difference in VEGF expression between NF2 VS tumors and sporadic tumors (Table 5).

None of these studies attempted to determine the relationship between VEGF and postoperative outcomes. Therefore, it is unclear if any of these findings are predictive of future behavior of the tumor. It is difficult to assess bias across studies in such a small sample size. One possible problem with these studies is that most tumors studied express VEGF to varying degrees, and it is not clear how reliable semiquantitative methods are at differentiating these expression patterns in stained tumor tissue.

SYNTHESIS OF RESULTS

While the existing literature shows potential for VEGF as a potential biomarker, no recommendations regarding the relationship of VEGF and postoperative prognosis can be made. As with much of the previous areas of study, appropriate data are lacking. Presently available data ask the question, “Are tumors that behaved badly also ones that express more VEGF?” The more important question, “Are tumors that express VEGF at higher levels deserving of different treatment?,” has yet to be studied. This limits the applicability of VEGF staining to clinical

practice at present. The limited data suggest that tumors with higher VEGF grow faster; however, whether this predicts future behavior is presently unclear. The finding that tumors that fail treatment have higher VEGF levels is an interesting observation that raises the possibility that treatment-failing tumors may be a selected group of high VEGF-expressing tumors. However, it is not possible to state whether this is a truly a prognostic reality without performing the inverse study where patients with high VEGF levels are followed to see if this predicts recurrence.

DISCUSSION

Taken together, the literature regarding prognostic factors that predict adverse behavior after a VS has been resected is essentially nonexistent. What little data there are focus largely on relationships between preoperative behavior and pathologic features, which while of academic interest, do not lend themselves to making firm recommendations regarding postoperative behavior. Therefore, we largely conclude that no firm recommendations for or against the relationship of any pathologic or molecular feature and future tumor behavior are warranted.

Our search identified a few areas for future study. Little microscopic evidence of elevated cell density and microhemorrhages may have some prognostic value in relation to tumor growth, but many other standard diagnostic characteristics used on frozen section, squash preparations, and hematoxylin–eosin-stained paraffin-embedded tissue preparations did not provide information. On an immunohistochemical level, PCNA LIs may help retrospectively in predicting preoperative tumor growth rate. Some words of caution when using PCNA (or other LIs) are worth mentioning. The data presented are older studies with PCNA, which has been replaced by Ki-67 in many settings. PCNA staining is known to be somewhat finicky and is highly sensitive to fixation methods and antigen retrieval protocols. Therefore, it is unclear how reliable interstudy comparisons are with these stains, and caution should be exercised before using these LIs for making clinical decisions, because the data are weak and the test fraught with methodologic problems.

On a molecular level, VEGF expression may also help in retrospectively predicting preoperative tumor growth rate. Because no clinically important recommendations can be made regarding cell density, tumor microhemorrhages, PCNA LIs, and VEGF, these findings, though interesting,

certainly do not mandate these assessments as being critical to patient management. In addition, the findings are in small and mostly retrospective studies, and all warrant validation in properly powered prospective studies.

In the literature reviewed, it was apparent that a wide variety of other molecules and tumor progression mechanisms are worthy of study in VSs (Table 6). For instance, matrix metalloproteinase-9, fibroblast growth factor-receptor, and p27 expression have been studied for links to VS patient prognosis. One study[28] analyzed matrix metaloproteinase-9 levels (found among several other molecules) and their relationship to preoperative tumor growth. Another[29] studied fibroblast growth factor-receptor levels compared to tumor growth. A final report[30] was found that studied a variety of apoptosis and cell cycle genes, and of them, linked only p27 expression changes to growth rate. While these studies are interesting avenues of future research, confirmatory studies in additional cohorts are needed as they are the result of multiple molecule analyses and suffer from the potential for false discovery, not to mention confounding by other prognostic variables.

CONCLUSION AND KEY ISSUES FOR FUTURE INVESTIGATIONS

Based on the literature obtained from these literature searches, one can conclude that there is much yet to be gleaned from the histologic, immunohistochemical, and molecular marker status of VSs in terms of determining functional prognosis, risk of recurrence, and response to surgical or nonsurgical therapy.

The exact utility of KI-67 and PCNA LIs in predicting future recurrence after surgery is essentially unknown and is in need of future study.

VEGF staining is an interesting area of future investigation as its exact utility is unclear at present. As mentioned above, it would be helpful to know whether tumors that behaved badly express more VEGF. Also, are VSs that express VEGF at higher levels deserving of different treatment? With the advent of reliable tumor banking and electronic database availability, one can imagine both questions could be addressed in a retrospective fashion. With these data in hand, a prospective study to validate whatever suspicions arise from those findings could then be planned.

Conflict of Interest (COI)

The Vestibular Schwannoma Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the companion introduction and methods manuscript (https://www.cns.org/guidelines/guidelines-management-patients-vestibular-schwannoma/chapter_1).

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are 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.

Disclosures

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Figure 1. Article flowchart.

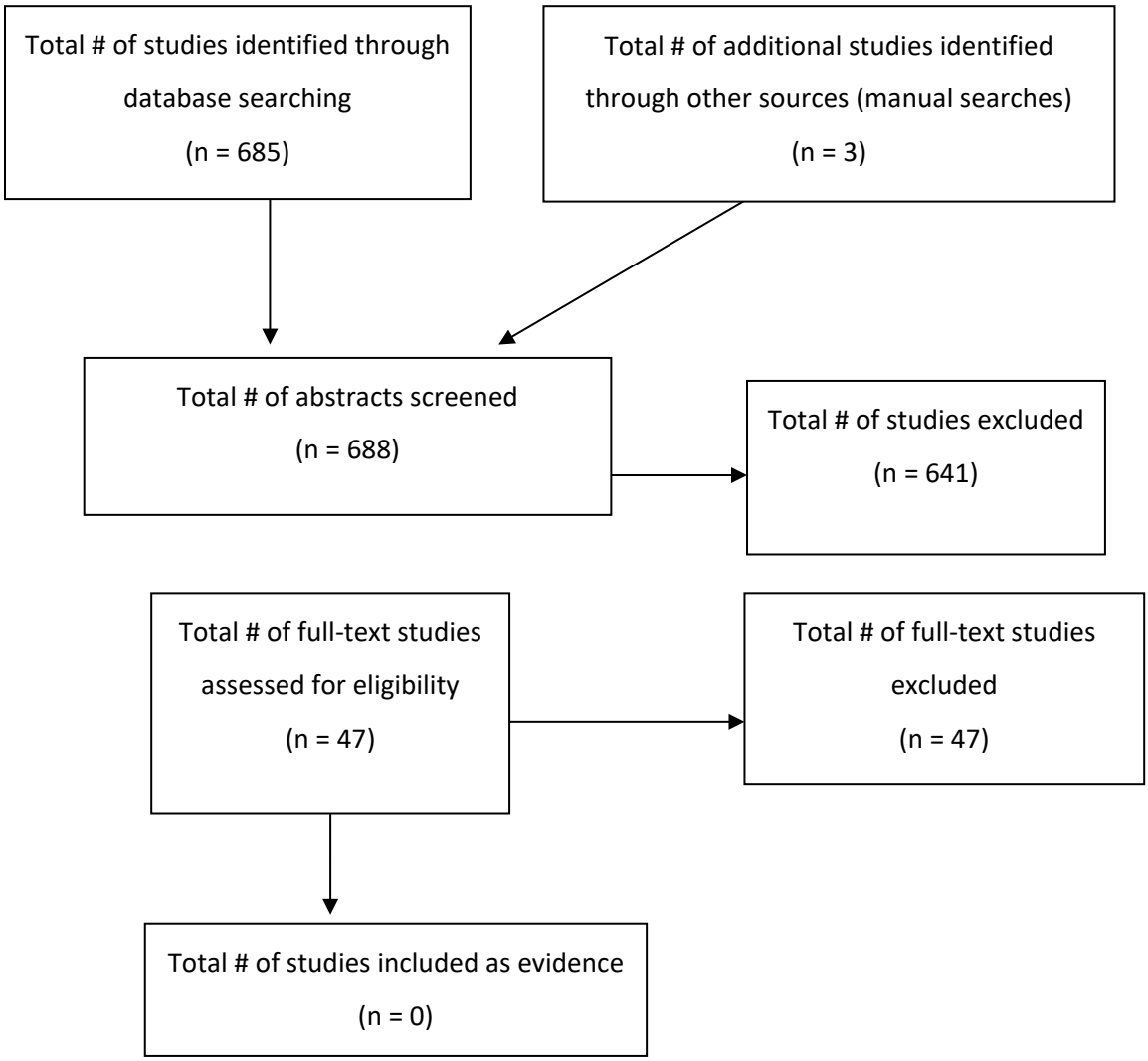

Table 1. Primary search strategies

PUBMED (NLM), searched on April 13, 2015:
Step 1: Neuroma, Acoustic [MeSH]
Step 2: (vestibular[Title/Abstract] OR vestibulocochlear[Title/Abstract] OR acoustic[Title/Abstract]) AND (neuroma*[Title/Abstract] OR neurilemmoma*[Title/Abstract] OR neurilemoma*[Title/Abstract] OR neurinoma*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR schwannoma* [Title/Abstract])
Step 3: Step 1 OR Step 2
Step 4: Ki-67 Antigen[MeSH] OR Tumor markers, biological [MeSH] OR Gene expression regulation, neoplastic [MeSH] OR Genes, p53 [MeSH] OR Vascular endothelial growth factor A [MeSH] OR Vascular endothelial growth factor receptor-1 [MeSH] OR Karyotyping [MeSH] OR Comparative genomic hybridization [MeSH] OR Vimentin [MeSH] OR S100 proteins [MeSH]
Step 5: Ki-67 Antigen [NM] OR Tumor markers, biological [NM] OR Vascular endothelial growth factor A [NM] OR Vascular endothelial growth factor receptor-1 [NM] OR Vimentin [NM] OR S100 proteins [NM] OR MIB-1 antibody [NM]

Step 6: Patholog* [TIAB] OR Neuropatholog* [TIAB] OR Histopatholog* [TIAB] OR Immunohistochemi* [TIAB] OR “frozen section” [TIAB] OR MIB-1 [TIAB] OR MIB 1 [TIAB] OR P53 [TIAB] OR “gene expression” [TIAB] OR PI3K/AKT/mTOR [TIAB] OR VEGF-A [TIAB] OR Karyotyping [TIAB] OR Cytogenetic* [TIAB] OR CGH [TIAB] OR Vimentin [TIAB] OR S100 [TIAB]
Step 7: Step 4 OR Step 5 OR Step 6
Step 9: Step 3 AND Step 7
Step 10: Step 9 AND English [Lang]
Step 11: (animal [MeSH] NOT human [MeSH]) OR cadaver [MeSH] OR cadaver* [Titl] OR comment [PT] OR letter [PT] OR editorial [PT] OR addresses [PT] OR news [PT] OR “newspaper article” [PT] OR case reports [PT]
Step 12: Step 10 NOT Step 11
Step 13: Step 12 AND ("1990/01/01"[PDAT] : "2014/12/31"[PDAT])
Cochrane, searched on April 13, 2015:
Step 1: MeSH descriptor: [Neuroma, Acoustic]: explode all trees
Step 2: ((vestibular or vestibulocochlear or acoustic) and (neuroma* or neurilemmoma* or neurilemoma* or neurinoma* or tumor* or schwannoma*)):ti,ab,kw
Step 3: Step 1 OR Step 2

Step 4: MeSH descriptor: [Ki-67 Antigen] explode all trees
Step 5: MeSH descriptor: [Tumor markers, biological] explode all trees
Step 6: MeSH descriptor: [Gene expression regulation, neoplastic] explode all trees
Step 7: MeSH descriptor: [Genes, p53]
Step 8: MeSH descriptor: [Vascular Endothelial Growth Factor A] explode all trees
Step 9: MeSH descriptor: [Vascular Endothelial Growth Factor Receptor-1] explode all trees
Step 10: MeSH descriptor: [Karyotyping] explode all trees
Step 11: MeSH descriptor: [Comparative genomic hybridization] explode all trees
Step 12: MeSH descriptor: [Vimentin] explode all trees
Step 13: MeSH descriptor: [S100 proteins]
Step 14: (Patholog* or Neuropatholog* or Histopatholog* or Immunohistochemi* or "frozen section" or MIB-1 or MIB 1 or P53 or "gene expression" or PI3K/AKT/mTOR or VEGF-A or Karyotyping or Cytogenetic* or CGH or Vimentin or S100):ti,ab,kw
Step 15: Step 4 OR Step 5 OR Step 6 OR Step 7 OR Step 8 OR Step 9 OR Step 10 OR Step 11 OR Step 12 OR Step 13 OR Step 14
Step 16: Step 3 AND Step 15
Step 17: Filtered 1990-12/31/2014
Summary of Primary Search Combined from 2 database searches, total of 841 candidate articles

2 **Table 2.** Relationship of histologic findings and prognosis

Author, Year	Study Description	Data Class	Conclusion
Sughrue et al, 2011	Retrospective case series of 274 VS cases correlating preoperative hearing loss with histopathologic features	III	Extensive microhemorrhage and/or fibrosis predicts preoperative hearing loss
Kwiek et al, 2003	Retrospective pathology review of 91 VS cases studying pathologic findings and relating them to preoperative facial paralysis	III	Antoni B predominant tumors were more likely to present with preoperative facial paralysis than Antoni A or Antoni A/B tumors
Hwang et al, 2002	Retrospective case series of 29 recurrent VSs with histopathologic findings studied in patients with rapid vs delayed recurrence	III	Cellularity and nuclear pleomorphism were higher in 15 patients showing rapid regrowth of their tumors than 14 patients with slower regrowth. Mitosis and microvascular proliferation did not differ between these groups
Gomez-Brouchet et al, 2001	Retrospective case series of 30 VS cases studying pathologic findings	III	There was a correlation between amount of hemosiderin deposits and tumor size
Labit-Bouvier et al, 2000	Retrospective case series review of 69 VS cases studying pathologic findings and relating them to preoperative clinical course	III	Vessel density was correlated with faster a preoperative clinical course, Inflammatory infiltrates were correlated with a slower clinical course.

Author, Year	Study Description	Data Class	Conclusion
Kawamoto et al, 1995	Retrospective pathology review of 32 VS cases studying hyalinization, presence of Antoni A/B histology, mitotic figures, and cell density	III	Cell density correlated with preoperative growth rate. Number of mitoses, extent of hyalinization of vessel, Antoni A/B presence all did not affect preoperative growth rate.
Aguiar et al, 1995	Retrospective pathology review of 105 VS cases studying histologic features of VSs	III	Tumor cell type (Antoni A vs B) did not influence tumor size or KI-67 mitotic rate

3 VS, vestibular schwannoma.

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Table 3. Relationship of KI-67 labeling index and prognosis

Author, Year	Study Description	Data Class	Conclusion
de Vries et al, 2012	Retrospective case series of 67 VS cases with KI-67 staining correlated with preoperative growth rate	III	KI-67 LI did not correlate with preoperative growth rate
Cafer et al, 2008	Retrospective case series review of 59 VS cases with KI-67 staining	III	KI-67 LI did not correlate with preoperative tumor size
Diensthuber et al, 2004	Retrospective case series of 22 VS cases with KI-67 staining correlated with preoperative growth rate	III	KI-67 LI did not correlate with preoperative growth rate
Bedanvanija et al, 2003	Retrospective case series review of 34 VS cases with KI-67 staining correlated with preoperative growth rate	III	Tumors with KI-67 LI >2.5% had higher preoperative growth rate than tumors with lower LIs
Hwang et al, 2002	Retrospective case series of 29 recurrent VSs with KI-67 LIs studied in patients with rapid vs delayed recurrence	III	KI-67 LIs were higher in 15 patients showing rapid regrowth of their tumors than 14 patients with slower regrowth
Gomez-Brouchet et al, 2001	Retrospective case series of 30 VS cases with KI-67 staining	III	KI-67 LI did not correlate with preoperative tumor size
Charabi et al, 1996	Prospective study of 124 VS cases comparing duration of symptoms in low, medium and high proliferative KI-67 cases	III	High KI-67 proliferative rate (>10 positive cells/HPF) predicted duration of preoperative symptoms, no relation with tumor size
Yokoyama et al, 1996	Retrospective case series of 58 VS cases with KI-67 staining	III	There was a direct, logarithmic correlation between KI-67 LI, and tumor doubling time in tumors that recurred after surgery

Author, Year	Study Description	Data Class	Conclusion
Aguiar et al, 1995	Retrospective case series review of 105 VS cases with KI-67 staining	III	KI-67 LI did not correlate with preoperative tumor size. LIs are higher in NF2 patients
Antinheimo et al, 1995	Retrospective case series review comparing KI-67 staining in 26 NF2 and 27 sporadic VS cases	III	KI-67 LI higher in NF2 tumors than sporadic tumors

6 HPF, high-powered field; LI, labeling index; NF2, neurofibromatosis 2; VS, vestibular schwannoma.

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Table 4. Relationship of proliferating cell nuclear antigen labeling index and prognosis

Author, Year	Study Description	Data Class	Conclusion
Bedavanija et al, 2003	Retrospective case series of 34 VS cases with KI-67 staining correlated with preoperative growth rate	III	Tumors with PCNA LI >40% had higher preoperative growth rate than tumors with lower LIs
Antinheimo et al, 1995	Retrospective case series comparing PCNA staining in 26 NF2 and 27 sporadic VS cases	III	PCNA LI higher in NF2 tumors than sporadic tumors
Kawamoto et al, 1995	Retrospective case series of 32 VS cases with PCNA staining	III	There is a direct positive correlation between postoperative growth rate and PCNA LI

LI, labeling index; NF2, neurofibromatosis 2; PCNA, proliferating cell nuclear antigen; VS, vestibular schwannoma.

Table 5. Relationship of vascular endothelial growth factor expression and prognosis

Author, Year	Study Description	Data Class	Conclusion
Koutsimpelas et al, 2012	Retrospective case series of VEGF staining in 182 sporadic VS cases	III	VEGF levels higher in recurrent, and previously irradiated tumors than untreated cases
Koutsimpelas et al, 2007	Retrospective case series of VEGF staining in 17 sporadic VS cases	III	VEGF staining level and VEGF mRNA levels correlate with tumor volume and growth rate
Saito et al, 2003	Retrospective case series comparing VEGF staining in 10 NF2 and 10 sporadic VS cases	III	VEGF staining present in most cases and not different between NF2 and sporadic tumors
Caye-Thomasen et al, 2003	Retrospective case series of VEGF staining in 18 sporadic VS cases	III	Semiquantitative VEGF staining correlated with preoperative tumor growth rate, but not symptom duration or tumor size

mRNA, messenger RNA; NF2, neurofibromatosis 2; VEGF, vascular endothelial growth factor; VS, vestibular schwannoma.

Table 6. Relationship of other molecular markers and prognosis

Author, Year	Study Description	Data Class	Conclusion
MMP-9			
Moller et al, 2010	Retrospective case series studying MMP-9 staining in 34 VS patients	III	MMP-9 staining significantly correlated with preoperative tumor growth rate
FGF-R			
O'Reilly et al, 2004	Retrospective case series studying FGF-R expression in 30 patients with sporadic VS	III	FGF-R overexpression was more common in faster-growing tumors, though correlation with growth rate was not significant
p27			
Seol et al, 2005	Retrospective case series of molecular markers in patients with rapidly growing recurrent VS	III	p27 deletion was more common in aggressive recurrences. p53, Bax, bcl-2, Fas, Fas-L, and caspase-3 studies did not differ between the groups

FGF-R, fibroblast growth factor receptor; MMP-9, matrix metalloproteinase-9; VS, vestibular schwannoma.

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