An update on unilateral sporadic small vestibular schwannoma

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Advances in neuroimaging have increased the detection rate of small vestibular schwannomas (VSs, maximum diameter < 25 mm). Current management modalities include observation with serial imaging, stereotactic radiosurgery, and microsurgical resection. Selecting one approach over another invites speculation, and no standard management consensus has been established. Moreover, there is a distinct clinical heterogeneity among patients harboring small VSs, making standardization of management difficult. The aim of this article is to guide treating physicians toward the most plausible therapeutic option based on etiopathogenesis and the highest level of existing evidence specific to the different cohorts of hypothetical case scenarios.

Hypothetical cases were created to represent 5 commonly encountered scenarios involving patients with sporadic unilateral small VSs, and the literature was reviewed with a focus on small VS. The authors extrapolated from the data to the hypothetical case scenarios, and based on the level of evidence, they discuss the most suitable patient-specific treatment strategies. They conclude that observation and imaging, stereotactic radiosurgery, and microsurgery are all important components of the management strategy. Each has unique advantages and disadvantages best suited to certain clinical scenarios. The treatment of small VS should always be tailored to the clinical, personal, and social requirements of an individual patient, and a rigid treatment protocol is not practical.
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TECHNOLOGICAL advances in neuroimaging have been responsible for changing the face of neurosurgery. This has certainly been true for VS, first described by Eduard Sandifort in the Netherlands in 1777.³ From what was considered a life-saving surgery (the finger extraction technique) done by Englishman Sir Charles Balance in 1894,⁸ VS treatment has evolved toward a more conservative management paradigm.

The common denominator for the evolution of VS treatment has been the focus on patients' quality of life.¹¹¹ In the 1990s, achieving tumor control while preserving facial and cochlear nerve function were the ideal goals of surgery. The management of VS has developed further over the past decade, with importance being given to

postoperative quality of life.^{18,21,61,84,111} This is even more pertinent to patients with small tumors (< 25 mm) or with minimal hearing deficits.^{21,61,111} Currently, the treatment options for managing small VS include conservative observation and serial imaging ("wait and scan"), stereotactic radiosurgery and microsurgery.

Formulating the best treatment strategy in patients with small tumors rests on the ability of the physician to understand specific patient and tumor characteristics and to be able to tailor the treatment options to the individual. The variability in the literature with respect to optimal treatment strategies for small VSs makes it even more challenging for the physician to formulate the most suitable plan. The main goal of this review is to outline the most suitable therapeutic option for different cohorts using hypothetical case scenarios and the highest level of evidence available. We list 5 hypothetical clinical situations and extrapolate from the reviewed literature pertinent to each clinical setting. Additionally, we discuss the proposed possible mechanisms of hearing loss in patients with small VSs.

Abbreviations used in this paper: AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; CPA = cerebellopontine angle; DPOAE = distortion products of otoacoustic emissions; GKS = Gamma Knife surgery; GRC = Gardner-Robertson Class; PTA = pure-tone average; SDS = speech discrimination score; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

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What Actually Creates the Treatment Dilemma?

Seth I. Rosenberg started his article on the natural history of acoustic neuroma⁸⁶ by quoting from the 1904 article by Fraenkel et al.:³¹ “An estimation of the size and character of the growth is nearly always a mere matter of speculation, based on tumor statistics, the rapidity of the clinical course, or associated constitutional conditions.” Apart from improvements in estimating tumor location and size, this statement holds true even after 100 years of scientific progress. One of the challenges a physician still has to overcome is that of making a therapeutic decision when a patient with a small VS comes to the clinic with a normal or serviceable hearing level. The parameters that are considered essential for planning the treatment strategy are listed in Table 1.

The factors that make the final decision a daunting task include variability in the data on the natural history of VS,^{68,86,118} mechanism of hearing loss,^{27,37,57,81,99} and treatment-specific hearing and facial function preservation rates.^{96,98,101} These inconsistencies are a major hindrance to the practice of evidence-based medicine. Meta-analyses of pooled data are fraught with considerable assumptions to simplify the nonuniform existent data and achieve statistical power and significance, which can greatly impact their conclusions.^{100,101,111,115} These studies should thus be interpreted with caution.

The aim of the current review is not to address statistical “treatment-specific analysis,” but rather highlight “case-specific” requirements and extrapolate from the literature in a simplified way for the treating physician.

Mechanism of Hearing Loss in VS

Considering the variability in the data regarding

TABLE 1: Essential parameters to be kept in mind while considering treatment options for small VS*

Parameter
pt age, occupation, SES
tumor location
status of hearing; PTA & SDS
status of CN V and VII function
tumor consistency
solid
cystic
mixed
tumor characteristics
calcification
microhemorrhages
fibrosis
necrosis
any comorbidities
expected impact of the treatment on QALYs
pt's personal preference

* CN = cranial nerve; pt = patient; QALY = quality-adjusted life year; SES = socioeconomic status.

the natural history of VS and the difficulty in predicting hearing outcomes in individual cases, we sought to briefly review the proposed mechanism for hearing loss in VS (Fig. 1).

In general, there are 4 patterns of hearing loss:^{21,27,37,38,51,57,71,72,81,99} 1) hearing deterioration in “growing” tumors, 2) hearing deterioration in “nongrowing” tumors, 3) early hearing loss, and 4) sudden hearing loss regardless of tumor growth.

Vestibular schwannomas are histologically benign, slow-growing tumors that originate from the Schwann cells of the inferior vestibular nerve in most cases.⁴⁴ The location of the tumor's origin is described as the neurilemmal-neuroglial junction (Obersteiner-Redlich zone) within the internal auditory canal.^{48,67} Considering the origin of the tumor, the most obvious hypothesis for hearing loss is the mechanical and/or neurotoxic effect that a growing tumor might have on its neighboring neurovascular structures.^{57,81} The data, however, do not always show a linear correlation between the rate of tumor growth and deterioration of hearing.^{38,39,82,96,104}

Hearing Loss in Patients with Growing Tumors

The “mechanical effect” is thought to involve compression or stretching of the cochlear nerve (conduction block) or compromise of the vascular supply to the cochlea (through occlusion or spasm of the labyrinthine artery).⁸¹ This compromise of the vascular supply can be a result of an increase in intracanalicular pressure or due to direct compression caused by the laterally invading tumor.^{7,51} Compression of labyrinthine vessels has been shown to cause degeneration in the organ of Corti and the spiral ganglion (cochlear dysfunction).^{22,37,43,71} Of note, the progression of hearing loss in VS is most often gradual,^{39,96} although sudden deterioration is also possible.^{32,65}

Hearing Loss in Patients with Nongrowing Tumors

Another subset of VS patients develop hearing loss despite the lack of tumor growth on imaging.^{38,75} Obviously, the mechanical effect theory fails to explain this category of hearing loss. In these patients, neurotoxic injury, caused either by alterations in the biochemical properties of the inner ear fluid or through accumulation of tumor toxic metabolites, may be responsible for hearing loss. The perilymphatic space and endolymphatic space in the inner ear of patients with VS often stain positive for eosinophilic proteinaceous deposits.²⁶ The perilymphatic protein levels are reported to be 5–15 times higher than the levels found in the ears of healthy individuals.⁹³ This rich perilymphatic protein is believed to represent either a by-product of up-regulated genetic activity in the VS¹⁰⁹ or simply accumulation of serum proteins by the process of transudation.⁹³ The correlation between increased proteinaceous material and cochlear dysfunction is still not clear.

Early Hearing Loss

Efferent olivocochlear bundle dysfunction and alteration in biochemical properties of the inner ear fluid seem to be the most plausible causes of early hearing loss in VS patients. Gouveris et al.³⁷ compared DPOAE am-

Fig. 1. A schematic showing the possible mechanism of hearing loss in a small VS. a = fourth ventricle; b = efferent olivocochlear tract; c = labyrinthine artery (LA); d = vestibulocochlear nerve; e = proteinaceous deposits in the inner ear fluid due to tumor metabolism; IAF = inner ear fluid; OCB = olivocochlear bundle; OHC = outer hair cells.

plitudes between VS patients with normal, symmetrical hearing and VS patients with mild hearing loss. They reported that the early hearing loss in patients with VS was cochlear in origin, suggested by a consistent finding of decreased DPOAE amplitudes, indicating dysfunction of the outer hair cells. Although the authors did not provide the mean tumor size in their population, the concept of early hearing loss as cochlear in origin was striking. The possibility that a small intracanalicular tumor will impede cochlear blood flow to the level of causing outer hair cell dysfunction seems less likely. On the contrary, the proximity of the passing unmyelinated efferent olivocochlear tracts to the vestibular nerve suggests the etiology to be efferent auditory system dysfunction.⁸¹ The efferent olivocochlear bundle comprises medial fibers that innervate the outer hair cells and lateral fibers that synapse with the dendrites of the inner hair cells. The functions assigned to the efferent system of the ear include noise protection, improvement of signal-to-noise ratio, selective attention, adaptation, and frequency selectivity (through regulation of the micromechanical properties of outer hair cells).²⁰ Additionally, functionality in the 3D auditory world—localization of sound and speech restoration—is affected in efferent olivocochlear bundle dysfunction.²⁰

Animal studies suggest a hearing loss of up to 60 dB related to efferent auditory dysfunction.⁷³ Pennings et al.⁷⁵ followed 47 patients with purely intracanalicular tumors prospectively, without any intervention. At baseline, 12 patients already had PTA greater than 50 dB. This suggests that efferent auditory dysfunction alone may not be

responsible for early hearing loss and that alteration in the biochemical properties of the inner ear fluid might also play a role in the initial stages. Recently, van de Langenberg et al.¹⁰⁴ reported that in patients undergoing serial imaging, there was significantly greater deterioration of PTA over time in the ears in which labyrinthine signal hypointensity was seen on T2-weighted MR images than in those that showed a more isointense intense labyrinthine signal¹⁰⁴ ($p = 0.01$). Although nothing in the data suggested an explanation for this finding, the authors hypothesized that biochemical changes, including highly proteinaceous deposits and vascular compromise, might be the reason for the hypointensity.

Sudden Hearing Loss

Sudden hearing loss is also noted in some VS patients with documented rates between 3% and 23%.⁸⁸ The internal auditory artery or the labyrinthine artery (end artery) travels within the internal auditory canal, and it may be possible that vascular insult to it can result in sudden hearing loss.^{11,60} However, if only vascular insult was the cause, one would also expect to see vestibular symptoms and cochlear hearing loss, which is not always the case. Further, due to the anatomical distribution of the blood supply to the cochlea, vascular compromise should result in low-frequency hearing loss in these patients, whereas mostly higher-frequency loss is reported in such cases.^{51,52} Tumor characteristics, including accelerated tumor growth and an increased number of intratumoral hemorrhages, are thought to cause sudden hearing loss through

nerve compression and rapid accumulation of biochemical toxins.⁹⁹ A higher incidence of high- to mid-frequency hearing loss correlates well with the nerve compression theory,³² but otoacoustic emissions in such patients do not reflect purely retrocochlear hearing loss⁷¹ and suggest that both cochlear and retrocochlear components contribute to sudden hearing loss in such patients.

To summarize, it would be reasonable to state that the exact mechanism of hearing loss in VS patients is likely to be multifactorial. Better understanding of the possible etiologies of hearing loss will help in guiding VS treatment choices, not only on the basis of tumor size and location, but also based on the intricate patterns of inner ear functioning in VS patients at the time of presentation.

In the section below, we present 5 distinct case scenarios and review the literature that is most applicable to formulating a management plan for each hypothetical patient.

Hypothetical Case Scenarios and Review of the Literature

Hypothetical Case 1

This patient is a 40-year-old man with a small VS (maximum diameter < 25 mm) that was discovered incidentally. The results of his audiometrical examination are within normal limits. Hearing preservation is his primary concern, as he works for a local music band and needs to have normal hearing to be successful. He inquires about the best option(s) for preserving his intact hearing status.

Advancements in neuroimaging have increased the rate of incidental detection of VS. In a recent Rotterdam-based population study, the most common brain lesions discovered incidentally by MRI were asymptomatic brain infarcts, followed by cerebral aneurysms and primary benign tumors.¹⁰⁵ The authors of the study reported the incidence of asymptomatic VS to be 1 in 500 individuals. A recent study of the Surveillance Epidemiology and End Results (SEER) US database identified the incidence rate of VS to be 1.1 per 100,000, with the mean age of detection being 53.1 years and the majority of lesions (84%) occurring in the Caucasian population.³⁴

Tumors That Will Grow if Left to Observation. To address the patient's concern about the chances of hearing preservation, knowledge about the chances of the tumor showing growth and the probable growth rate are important. Combining the results of 6 previous meta-analyses shows that tumor growth occurred in 29% to 54% of patients (mean 44.6%).^{4,9,89,95,101,113,118} A major drawback in the application of these results is that the mean follow-up time in these studies was only 3 years. A literature review of mostly Level 3 evidence yields impressive variability in growth rates (range 18%–73%).⁶⁸ There are very few prospective studies that report tumor growth in the patients followed with observation. Régis et al.⁸³ reported tumor growth in 77% of their patients (mean follow-up 5.3 years); Hajioff et al.,³⁹ in their 10-year follow-up prospective study (median duration of follow-up 121 months), reported tumor growth in 78% of patients (< 1 mm/year in 38% and > 1 mm/year in 40%); and Stangerup et al.⁹⁶ found that only 17% of intrameatal tumors became extrameatal and that

only 28.9% of extrameatal tumors showed growth (mean follow-up 3.6 years). It is difficult to develop a scientific rationale that would explain this variation. Régis et al.⁸³ pointed out that the definition of tumor growth was relatively personal. For example, Stangerup et al. considered a change in any tumor from intrameatal to extrameatal to be tumor growth, whereas Hajioff et al. defined significant growth as growth of more than 1 mm/year.

Tumor Growth Rates in Major Series. The inability to predict consistently whether a tumor will grow makes predicting the growth rate even more problematic. Tumor growth rate is a parameter about which there is general agreement with respect to treatment strategy decisions. A patient who has a tumor growth rate of more than 2–2.5 mm/year is at a significantly higher risk of hearing loss than a patient with less than 2.5 mm growth per year.^{38,39,75,101} This obviously does not account for patients who develop hearing loss without any significant tumor growth (as described earlier in this paper).

Recently, Sughrue et al.,¹⁰¹ in their systematic review of 34 published studies that included 982 patients (Level 3 evidence), found that in 75.32% of the patients tumor growth was greater than 2.5 mm/year, and the mean tumor growth was 2.9 mm/year. In contrast, a prospective study by the same group showed a growth rate of less than 2.5 mm/year in 83% of patients.⁹⁸ The authors of another recent prospective study documented the mean tumor growth in their population to be 2.1 mm/year.⁸³ A 2005 systematic review by Yoshimoto¹¹⁸ included 4 prospective studies in which only 29% of tumors showed growth. There is a striking difference between the growth rates documented by older meta-analyses and the 2.9 mm/year reported by Sughrue et al. in their 2010 review.¹⁰¹ Mean tumor growth rates of 1.8, 1.9, 1.9, 1.2, and 2 (mm/year) were reported in the meta-analyses published in 1998,⁸⁹ 2003,¹¹³ 2005,⁹⁵ 2005,¹¹⁸ and 2006,⁹ respectively.

Although there is variation in the literature, the results of prospective studies could be interpreted as suggesting that tumor growth is likely to be less than 2–2.5 mm/year in the majority of patients. Table 2 lists various factors that may have prognostic implications for VS growth patterns.^{2,5,13,28,39,41,59,62,68,101,104} But there is clearly a need for long-term prospective data documenting annual trends in tumor growth rates.

Hearing Preservation in Wait-and-Scan Group. The most recent meta-analysis, that of Sughrue et al. (2010),¹⁰¹ reviewed the literature on the natural history of untreated sporadic VS (tumor size < 25 mm). In 982 patients, the overall hearing preservation rate was 54%, with follow-

TABLE 2: Factors that may predict VS growth patterns

Predictors
significant growth (>2 mm/yr)
extension into the CPA
diameter >20 mm
sudden onset or short duration of sensory hearing loss
tinnitus, unsteadiness, & vertigo at presentation

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up ranging from 26 to 52 months. Meta-analyses in the past have documented hearing preservation in 49%–63% of patients with a mean follow-up of approximately 3 years.^{9,89,94,101,113,118} Sughrue et al. found that the hearing preservation rate was significantly higher for the group of patients demonstrating a tumor growth rate of 2.5 mm/year or less. Interestingly, the overall mean growth rate among 982 patients included in their meta-analysis was 2.9 ± 1.2 mm/year. It is worth mentioning a common finding among the majority of the wait-and-scan group studies, which is deterioration of PTA and SDS over years in almost all the patients presenting initially with some degree of hearing loss.^{39,75} Régis et al.,⁸³ in their cohort of 40 patients followed up for a mean of 43.8 months, reported useful hearing preservation rates of 75%, 52%, and 41% at 3, 4, and 5 years, respectively.

A prospective study from the University of California, San Francisco group (Sughrue et al. 2011⁹⁸) calculated the estimated time to hearing loss among 3 groups of patients—those with intracanalicular tumors, those with 0.1–1 cm extension into the CPA, and those with more than 1 cm extension into the CPA cistern. The estimated median time to hearing loss in these 3 groups was 11.6, 10.3, and 9.3 years, respectively. Further, the authors noted that the median time of hearing loss in patients with a tumor growth rate of more than 2.5 mm/year was 7 years as compared with 14.8 years in those with growth of less than 2.5 mm/year. Hajioff et al.³⁹ followed a cohort of 72 patients prospectively for a median of 121 months (range 80–271 months); 49% of the patients were advanced in age and 43% made a personal choice for observation. The authors noted that the patients' hearing deteriorated substantially even in cases of nongrowing tumors. The mean deterioration in PTA at 0.5, 1, 2, and 3 kHz was 36 dB, and the SDS deteriorated by a mean of 40%. The overall failure rate in their cohort was 40%, with three-fourths of the failures occurring during the first half of the study.

Another recent noncomparative prospective study followed 186 consecutive patients (median follow-up 43 months), all of which were initially allocated to conservative treatment.¹³ At the last follow-up, 40% of the patients required either radiosurgery or microsurgery and the median time to treatment was given as 26 months (SD 17.4 months). Serviceable hearing at 1–3 years and/or beyond 3 years was significantly decreased as compared with baseline hearing status.

Recently, Stangerup et al.⁹⁷ reported the results of their 932 VS cases managed with observation; 102 patients (11%) were observed for over 10 years and hearing preservation was seen in 46%. In this study, the author found that patients with 100% SDS at diagnosis have a 75% chance of maintaining good hearing even after 10 years of observation, which was in agreement with various other studies.

Some reproducible conclusions (Table 3) made from a review of literature regarding observation^{75,96,101,104} include the following: 1) Patients with an SDS of 100% at diagnosis have higher chances of long-term hearing preservation. 2) Hearing preservation rates are markedly higher for the patients with tumor growth of less than 2–2.5 mm/year. 3) Most tumors demonstrate growth within the first

TABLE 3: Factors predicting hearing outcomes in the observation and imaging group*

Category & Factor
factors predicting hearing loss
signal hypointensity in the affected labyrinth on T2-weighted MR images
established hearing loss at initial presentation
tumor growth >2.5 mm/yr
factors predicting better hearing outcomes
WRS Class 0 or 1 at initial presentation
initial hearing level up to 10 dB HL at 4000 Hz
tumor growth <2.5 mm/yr

* HL = hearing loss; WRS = word recognition score.

5 years of diagnosis. 4) Regardless of tumor growth, hearing deterioration is bound to happen without intervention.

Based on the current literature, a strategy of observation and serial imaging may be continued in a young or middle-aged patient who has normal findings on audiometric examination and a VS that has not demonstrated significant growth. However, if the tumor starts growing, the chance of losing serviceable hearing will increase. Is there a role for early intervention (SRS/MS) in these patients? The chances of hearing preservation in patients treated by means of SRS or microsurgery will be discussed subsequently under *Hypothetical Case 2*; this discussion will also clarify the role of early intervention in *Hypothetical Case 1*.

It is also worthwhile to mention that even in some academic centers of excellence, where the patients are sent constant reminders for follow-up, the percentage of patients lost to follow-up can be substantial. If we consider health care centers where following up is at the discretion of the patient only and regular follow-up is hindered by numerous factors including socioeconomic status and health insurance issues, it is quite worrisome to imagine the dropout rates from the observation subset of patients.

Hypothetical Case 2

This patient is a 40-year-old woman with a small VS (< 25 mm) and mild hearing loss (serviceable hearing).

Understandably, the patient wants to prevent any further hearing deterioration. She is open to any treatment modality that may stabilize her mild hearing loss or even improve her hearing.

The presence of any symptoms at presentation reflects some significant ongoing biological activity in the tumor causing anatomical and physiological compromise. The possible mechanisms^{57,81} through which functional compromise can take place include 1) mechanical compression, 2) neurotoxic effects mediated through either toxic by-products of tumor metabolism or alteration in the inner ear fluid biochemistry, and 3) efferent pathway dysfunction. As previously discussed, there is significant heterogeneity in the data with respect to tumor growth in the absence of treatment; given this heterogeneity, observation and serial imaging is not a reasonable strategy for

patients who present with some hearing loss but want to preserve a serviceable hearing level.

In contrast to the data on growth of untreated tumors, the data available in the literature addressing tumor growth control following SRS demonstrate impressive consistency. The tumor control rate after SRS among the meta-analytical studies^{9,47,91,108,113–116} in the last decade (regardless of tumor size) range from 91% to 94.7%, with a mean of 93.4%. Even though microsurgical removal of small VSs is the most effective means of long-term tumor volume reduction, the associated morbidities and lesser rates of hearing preservation, make it a less popular treatment strategy among physicians and patients (details to be discussed later). Of note, stabilizing the tumor through SRS does not preclude the chances of hearing deterioration and there is a subset of patients who experience sudden hearing loss after SRS.^{30,40,49,56,69,78,84,85,103,106,112} Nevertheless, the chance of this phenomenon is less in patients in whom the median tumor dose does not exceed 13 Gy.^{19,45,52,58,69,108}

Radiobiology of VS

Ionizing radiation induces cell cycle arrest, necrotic cell death, or both in VS.¹¹⁷ The higher the number of tumor cells in the proliferative phase, the more radio-sensitive is the tumor.^{53,54} Ionizing radiation arrests the tumor cells in the proliferative phase such that the cell cycle checkpoint signaling (activated by DNA damaging agents) prevents the replication of damaged DNA as well as segregation of aberrant chromosomes, thus achieving tumor control.¹¹⁷ The radiation also induces double-strand DNA breaks, which leads to apoptosis.⁵² In addition to a low proliferative index, another factor causing radio-resistance is tumor hypoxia. Rapidly growing tumors will be more hypoxic due to inadequate angiogenesis and therefore may be more radio-resistant.⁶

Lee et al.⁵³ found that recurrent VSs removed through microsurgery, which were previously treated by Gamma Knife surgery, had lower a proliferation rate than those treated primarily by microsurgery ($p = 0.03$). This suggests that radiosurgery might be able to induce apoptosis in the cells with a high proliferative index and leave behind those with a low proliferative index. Surgical removal alone, especially subtotal resection, might leave behind a mixed population of tumor cells, and subsequently the cells with a high proliferative index might continue to grow.

On occasions, VSs may show a transient increase in size following SRS.^{64,77} This phenomenon is reported to occur in 17%–74% of patients undergoing SRS. It may be attributed secondary to radiation-induced tumor necrosis, chronic intratumoral bleeding, or biological response to ionizing radiation. A higher radiation dose has also been described as a possible risk factor for expansion.^{43,66,80} Additionally, the growth may also be associated with transient facial spasm and trigeminal nerve dysfunction.⁶⁴ This transient expansion is most evident within the 1st year of treatment, and in most cases the tumor volume eventually becomes significantly less than before treatment. Rarely, continued growth after transient expansion is noted. If the growth is persistent and becomes symptomatic, further SRS or microsurgery is usually recommended.

Chances of Hearing Preservation After SRS. Yang et al.,¹¹⁴ in their 2010 review, quantified data from 45 published studies to investigate hearing preservation rates after SRS. The overall hearing preservation rate (AAO-HNS Class 1 or 2, GRC 1 or 2) was reported to be 51% (mean follow-up 44.4 ± 32 months [SD]). This outcome appeared to be dose dependent. The studies that used a radiation dose of 13 Gy or less had a preservation rate of 60.5%, which was significantly higher than the studies in which the dose was larger than 13 Gy (50.4%). Some recent contemporary retrospective studies^{30,52,56,103} using mean tumor margin doses of less than 13 Gy have reported long-term hearing preservation rate ranging from 68% to 93.3%. Details of hearing outcome in the prospective studies are shown in Table 4. The hearing preservation rates in these studies range from 63% to 93% for patients with VSs smaller than 3 cm in maximum diameter. Additionally Niranjana et al.⁶⁹ followed 96 patients with intracanalicular tumors prospectively and found that serviceable hearing in 77.5% of the patients with AAO-HNS Grade 1 hearing preoperatively and in 64.5% in those with Grade 2 preoperatively (mean follow-up 42 months). Facial and trigeminal nerve function was preserved in 100% of the patients.

In 2010, Régis et al.⁸³ published the results of a prospective comparative study on intracanalicular VS, in which they compared patients treated with GKS with the wait-and-scan group. In the 34 patients treated by GKS, the useful hearing preservation rates at 3, 4, and 5 years were 77%, 70%, and 64% in comparison with 75%, 52% and 41% in the wait-and-scan group at the same follow-up points. Also, in that study the chance of maintaining functional hearing and avoiding further intervention was 79% at 2 years' follow-up and 60% at 5 years' follow-up in the GKS group compared with 43% and 14% in the wait-and-scan group.

Hearing Loss After SRS. Gamma Knife surgery for VS has occasionally been shown to cause hearing loss, especially within the first 12 months. Wackym et al.¹⁰⁶ prospectively evaluated 59 patients treated with SRS (mean follow-up 63.76 months). They found that limiting the cochlear dose of radiation to less than 4 Gy can significantly decrease the incidence of hearing loss. They noted a distinct pattern of hearing loss in their cohort of patients, similar to what was reported earlier by Lasak et al.⁵² It was consistent with a type of hearing loss resulting from radiation-induced injury to stria vascularis, characterized by a stria presbycusis-like pattern with hearing loss across all frequencies and relative preservation of speech discrimination ability. Other proposed mechanisms of hearing loss after SRS are damage to spiral ganglion neurons inside the modiolus and ischemic insult to the primary afferent and efferent nerve fibers within the internal auditory canal.⁵² Therefore, modulation of the radiation dose to the cochlea below 4 Gy and appropriate shielding techniques employed for protection of the cochlea are reasonable options that may help in decreasing the incidence of hearing loss after SRS.

Hearing Outcomes After Microsurgery. Recently, Sughrue et al.¹⁰⁰ performed a systematic review to highlight the hearing preservation rates after microsurgical re-

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TABLE 4: Summary of results of prospective studies comparing microsurgery and radiosurgery in small VSs (< 3 cm)*

Study & Details
<p>Régis et al., 2002</p> <p>no. of pts: SRS 97, MS 110 tumor size: Koos Stage II & III FU: 4 yrs functional hearing preservation (GRC 1 or 2) in pts w/ GRC 1 hearing preop: SRS 70%, MS 37.5% (overall functional hearing preservation rate [GRC 1 or 2]: SRS 40%, MS 5%, $p < 0.0001$) intact facial motor function postop: SRS 100%, MS 53%, $p = 0.00005$ ocular problems postop: 27% in SRS group vs 83% in MS group ($p < 0.0001$)† hypesthesia: SRS 4%, MS 29%, $p = 0.0009$ no return to work: SRS 1%, MS 34%, $p = 0.00016$ change in daily life postop: SRS 9%, MS 39%, $p = 0.00017$ % of pts suffering from postop tinnitus, vertigo, & imbalance: no statistically significant difference btwn SRS & MS groups</p>
<p>Pollock et al., 2006</p> <p>no. of pts: SRS 46, MS 36 tumor size: <3 cm FU: mean 42 mos (range 12–62 mos) AAO-HNS Class A or B hearing preservation at last FU: SRS 63%, MS 5%, $p < 0.001$ AAO-HNS Class A preservation at last FU: SRS 50%, MS 0%, $p < 0.01$ HB Grade 1 facial movement preservation at last FU: SRS 96%, MS 75%, $p < 0.01$ Dizziness Handicap Inventory score: SRS 8.4%, MS 16.5%, $p = 0.02$ % of pts w/ postop tinnitus & headache & associated changes in QOL: no statistically significant difference btwn SRS & MS groups QOL: significantly better overall QOL in SRS group than MS group at 3 mos, 1 yr, & 3 yrs</p>
<p>Myrseth et al., 2009</p> <p>no. of pts: SRS 60, MS 28 tumor size: <25 mm FU: 2 yrs GRC 1 hearing preservation: SRS 68%, MS 0%, $p = 0.0009$ HB Grade 1 facial nerve function preservation: SRS 98.3%, MS 53.6%, $p = 0.0009$ QOL: measured by GBI at 2 yrs, significantly better in SRS group than MS group % of pts w/ postop tinnitus, vertigo, & unsteadiness: no statistically significant difference btwn SRS & MS groups</p>
<p>Sughrue et al., 2010‡</p> <p>no. of pts followed prospectively in the MS group: 204 (tumor diameter <3 cm in 129) FU: median 10.2 yrs AAO-HNS Class A or B hearing preservation at 10 yrs: SRS 93%, MS 68% HB Grade 1 or 2 facial nerve function preservation at 10 yrs: SRS 100%, MS 76% freedom from any tumor growth in first 10 yrs: SRS (<13 Gy) 82%, MS 89% freedom from need for add'l therapy: SRS 96%, MS 91% freedom from any tumor growth in first 20 yrs: MS 86% (20-yr data not available for SRS)</p>

* add'l = additional; FU = follow-up; GBI = Glasgow Benefit Inventory; HB = House-Brackmann; MS = microsurgery; QOL = quality of life.

† Also reported by Tamura et al.

‡ Sughrue et al. compared their data collected prospectively for patients undergoing microsurgery with their previously published data on radiosurgery in young patients.

section of VS. In the selected 49 published articles, which included 998 patients, an overall hearing preservation rate of 52% was reported. Interestingly, the breakdown of the results according to tumor diameter revealed hearing preservation in the different subgroups as follows: 64% in patients with tumors less than 1 cm in diameter; 61% in those with tumors 1–1.5 cm in diameter; 32% in those with tumors 1.5–2 cm in diameter; and 37% in those with tumors 2–2.5 cm in diameter ($p < 0.0001$). A very significant drop in hearing preservation was observed when the tumor di-

ameter increased beyond 1.5 cm. Comparison of the largest systematic reviews of pooled data to date shows that hearing preservation rates achieved by microsurgery in patients with tumors less than 1.5 cm in size are similar to those observed in the literature for SRS. Nonetheless, the results of these systematic reviews are based largely on Level 3 or 4 evidence and should be interpreted cautiously. The prospective comparative studies that compare the results of small VSs treated with SRS or microsurgery at a single institution provide probably the best available evidence from

which conclusions can be drawn (Table 4), suggesting that SRS is the best management strategy, considering CN VII and VIII preservation rates and postprocedural quality of life. Moreover, similar results have been demonstrated by other retrospective studies.^{46,63,78,79,84,113} That being said, the results of a prospective nonrandomized comparative study (Level 2 evidence) are contrary to the aforementioned one.²⁴ At almost 3 years' follow-up, there was no statistically significant difference across the various health dimensions pertaining to quality of life (SF-36 questionnaire) for the observation, SRS, and microsurgery groups. Similar results were reported in a multicenter cross-sectional study with a maximum follow-up of no more than 5 years.¹⁴ One must remember that long-term follow-up data (> 10 years) in an SRS group are still not widely available.

Koos et al.⁵⁰ reported remarkable results in their group of patients with small VSs treated by microsurgery. Good hearing (using the 50/50 rule) was maintained in 100% of patients with Koos Stage 1 tumors and in 87% of patients with Koos Stage 2 tumors. Of patients presenting initially with House-Brackmann Grade 1 or 2 facial nerve function, 88% had House-Brackmann Grade 1 function 18 months postoperatively. These results have not been widely reproducible.

To summarize, if a young or middle-aged patient presents with serviceable hearing loss, following a wait-and-scan strategy is unlikely to do any good with respect to the ongoing active tumorigenesis and the patient's hearing status. Considering the chances of stabilizing or improving hearing status, freedom from future treatment at 10 years' follow-up, and the quality of treatment, the literature suggests that such patients may benefit the most from SRS. Since data for 20-year follow-up are not widely available for SRS (as opposed to microsurgery), one would have to clearly inform patients of the potential long-term failures that have not yet been well described.

Hypothetical Case 3

This patient is 40-year-old woman with a small VS (< 25 mm) and a serviceable hearing level. The patient works as a newscaster or a professional model, and therefore, apart from hearing preservation, her primary concern is to maximize the chances of preservation of normal facial movement.

Facial Nerve Outcomes After Microsurgery. A recent systematic review addressing facial nerve outcomes after microsurgery examined data from 79 articles pertaining to a total of 11,873 patients.¹⁰² Although the inclusion criteria were not specific for tumor size, the authors were able to compare the facial nerve preservation rates in 2 subgroups: studies with a mean tumor size < 20 mm (90%) and studies with a mean tumor size > 20 mm (67%). A previous meta-analysis done in 2003 yielded similar results.¹¹³ In the studies representing Class II evidence for treatment of small VSs, the postoperative rate of facial nerve preservation ranged from 53% to 76% (Table 4), remarkably worse than the results reported in systematic reviews that largely represent data from retrospective case series.¹⁰² It is evident that smaller VSs treated with microsurgery have better hearing and facial nerve preservation rate than larger VSs (Fig. 2). Class II or higher evidence

for intracanalicular VS managed through microsurgery is lacking. Recently, Noudel et al.⁷⁰ conducted a systematic review that included 35 studies of microsurgical resection of intracanalicular VS. They reported that the average hearing preservation rate (AAO-HNS Classes A and B or GRC I and II) for intracanalicular VS was 58% with a retrosigmoid approach and 62% with a middle fossa approach. Interestingly, facial nerve preservation (House-Brackmann Grade 1 or 2) was as high as 91% in the retrosigmoid approach group as compared with 77% in the middle fossa approach group, although the difference was not statistically significant ($p > 0.05$).

Facial Nerve Outcomes After SRS. Recently, Yang et al.¹¹⁶ quantified the existing data to evaluate facial nerve preservation after SRS, and the results correlated with what one would intuitively expect. The authors reported an overall facial nerve preservation rate of 96.2%; for the population with tumors of less than 1.5 cm³ in volume, the rate was 99.5%. They also found that reduction of the radiation dose to less than 13 Gy was associated with significant improvement in facial nerve preservation rates. In all but one of the comparative prospective studies, facial nerve preservation rates were much higher in the SRS treatment groups than in the microsurgery groups. The one exception was the study by Di Maio and Akagami,²⁴ who reported no statistically significant difference in the incidence of facial weakness between the microsurgery and SRS groups.

To summarize, in a young or middle-aged patient who presents with serviceable hearing and in whom preservation of facial function is crucial (for example, in someone who works as a newscaster or professional model), the literature suggests the superiority of SRS over observation or microsurgery.

Hypothetical Case 4

This patient is a 40-year-old man with a small VS (< 25 mm) and with a nonserviceable hearing level. He wants the best chance to stabilize or restore hearing function and emphasizes his desire to choose an intervention that will provide him with best quality of life.

Currently the data in the literature are equivocal with respect to the choice between microsurgery and SRS for patients with small VSs who present with a nonserviceable hearing level. In patients who have already lost serviceable hearing it is worthwhile to consider tumor control and treatment-related morbidity factors that influence quality of life. In patients presenting with profound hearing loss, comparative prospective studies have not found any statistically significant difference among those undergoing SRS and those undergoing microsurgery in terms of quality of life.³⁶ Whitmore et al.¹¹¹ recently reported the results of a comprehensive quantitative, statistically driven study designed to determine which treatment modality yields the best quality of life at 5- and 10-year follow-up in patients with VSs smaller than 25 mm in diameter who present with some residual hearing. Even though the study was limited by the assumptions the authors had to make to come up with the best possible comparative model, it provided useful insights into treatment-related morbidity

FIG. 2. Contrast-enhanced T1-weighted MR images demonstrating small VSs with diameters of 1 cm (**left**) and 2 cm (**right**). Systematic review of mostly Class 3 evidence suggests that the chances of facial nerve preservation after microsurgery is significantly higher in tumors 1.5 cm or less in diameter than in those with a diameter of more than 1.5 cm.

parameters and their influence on postoperative quality of life. The authors concluded that at 5 years posttreatment, patients who underwent radiosurgery had a better quality of life than those treated with either microsurgery or managed with observation. At 10 years, quality of life in both the radiosurgery and microsurgery groups was significantly better than in the observation group, but there was no statistically significant difference in the quality of life between the SRS and microsurgery groups. The authors also found that hearing loss had a greater overall negative impact on quality of life than other morbidities, including facial weakness and numbness. This finding was also documented by a previous prospective study²⁴ (Level 2 evidence). Some studies have also shown that disabling imbalance has the maximum negative impact among complications involving CN VII and VIII (that is, audiotfacial complications, including facial nerve palsy and hearing loss) and nonaudiotfacial complications. In these studies, microsurgical resection was associated with the alleviation of the disability and improvement in quality of life for the majority of patients.⁵⁵

Based on the current review of the literature, in patients presenting with a nonserviceable hearing level, SRS does not seem to provide any additional advantage over microsurgery. There is no significant difference in the quality of life; incidence of nonaudiotfacial complications, including tinnitus, vertigo, and unsteadiness; and tumor control among the 2 treatment modalities, although there is a trend toward better results in patients complaining of imbalance in the microsurgery group. Some authors have reported comparable results of facial nerve preservation with microsurgical excision (especially for tumors less than 1.5 cm in diameter).^{24,87,102} Certainly, surgical experience is an important factor that needs to be taken into account when analyzing and comparing outcomes of surgical treatment of small VS. At the hands of some experienced surgeons, facial nerve outcomes are excellent in patients treated for small VS, and it is worthwhile

to consider microsurgery as a safe alternative in patients with nonserviceable hearing.^{24,87,102}

Also, in a patient whose hearing status is out of the equation, the small but real risk of radiation-induced malignancy may be considered (especially if the patient is young).^{23,90} Additionally, Di Maio et al.²⁴ showed in their prospective study that patients in the observation and radiation groups may have a greater psychological burden associated with harboring a tumor than those treated with surgery. Therefore, when improvement in hearing status is unlikely, microsurgery is certainly a valid treatment option.

Hypothetical Case 5

This patient is a 65-year-old man (or other adult with significant comorbidities), with a small VS (< 25 mm) and serviceable hearing loss. He seeks advice regarding the best possible way to stabilize the hearing loss and maintain an optimal quality of life for the coming years.

There seems to be a general consensus on the treatment strategy for these patients in the literature. If the patients' symptoms are minimal, the support for observation with serial imaging is immense. There is a great chance in this age group that active treatment may not be necessary.^{39,110} Furthermore, in the studies that address long-term follow-up for conservatively managed cases, patients 65 years or older represent a substantial percentage in the cohort.^{12,39} For patients in this age group who are symptomatic or in whom rapid tumor growth (> 2.5 mm/year) is documented, SRS seems to provide the best audiotfacial outcomes and postoperative quality of life (Table 4). The nonaudiotfacial postoperative morbidities, such as dysequilibrium, vertigo, and tinnitus, can usually be managed by appropriate rehabilitative services.

Special Considerations

Sudden Hearing Loss in Small VS

The percentage of cases in which patients present

with sudden hearing loss is relatively low (0.8%–3.7%).¹⁵ The chances of restoration of sudden hearing loss in VS patient through radiosurgery are not well documented. Most of the authors studying sudden hearing loss describe their treatment protocol as a combination of microsurgery and medical management with corticosteroid agents and vitamin B₁₂.^{32,42,88} Friedman et al.³² reported measurable hearing preservation after microsurgery in 73% of their patients with VSs less than 2 cm in diameter who presented with sudden hearing loss. Even though there remains a small chance of measurable-to-complete recovery with just observation or with medical therapy alone, microsurgery may provide the best chance of stabilizing or improving hearing in patients with small VSs presenting with sudden hearing loss.^{11,32,42,65,88}

Cystic Small VS

Cystic lesions account for approximately 4%–15% of all VS cases.^{22,76} They are characterized by rapid growth and therefore may result in a shorter duration of symptoms related to the vestibulocochlear and facial nerves and may also be seen in certain cases of small VS. Management of small VS with a cystic component is contentious.^{10,16,17,22,33,74,92,94,107} There is a severe lack of comparative data (even Level 3 or 4 evidence) to support the superiority of surgery or SRS or radiotherapy as a treatment strategy. Treatment of these lesions by means of either microsurgery or SRS is challenging and fraught with risks. Enlargement of the cyst following radiation, even after several years, has been noted to occur, and in some cases emergent surgical decompression may be required to avoid permanent cranial neuropathy.^{22,35,74,92} Results of surgery, however, are also known to be unfavorable for cystic VS, and surgical treatment is associated with higher rates of morbidity.^{10,17,33,94,107} At this point, the data in support of SRS or radiation therapy for treatment of cystic VS are too scant to even consider these treatments as reasonable alternatives to surgery.⁹² That being said, SRS and radiotherapy as well as surgery would have to be evaluated with better study designs and longer follow-up.

Syndrome-Associated Small VSs

Apart from being sporadic, VSs are known to develop in patients with neurofibromatosis Type 2. They may be unilateral or bilateral. Various studies have highlighted their unpredictable and unique natural history, growth patterns, and treatment response.^{1,25,29} Discussion of neurofibromatosis Type 2 is beyond the scope of this article.

Limitations of this Review

Comprehensive systematic analyses currently existing in the literature have a restricted clinical applicability due to the numerous inconsistencies, selection biases and lower level of evidence. For this reason, this review also has its limitations in suggesting a standard algorithm based on the limited higher form of evidence, even though every effort was made to customize answers to patient-specific requirements based on the level of evidence existing in the literature.

Conclusions

Even after more than 100 years since the first VS surgery, the controversy in treatment strategy remains. More large-scale prospective randomized trials may help us to better understand the “best” therapeutic option for certain patient scenarios. To achieve statistical significance for comparing outcomes for observation, radiosurgery and microsurgery for small vestibular schwannomas, a cohort of over 900–1000 patients followed for over 10 years is required. The logistics of obtaining the required sample size is challenging. Due to the paucity of high-level evidence to compare the treatment groups, proponents of each option will presumably stick with their current preference. We have attempted to extrapolate from the literature to specific patient scenarios. The existing evidence suggests that the treatment of small VS should always be tailored to the individual patient rather than being a generalized treatment protocol. We hope that our case-specific review may serve as a guide for neurosurgeons, neuro-otologists, and radiation oncologists treating this ever-increasing patient population and may encourage focused prospective randomized trials.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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