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EANO Guideline on the Diagnosis and Treatment of Vestibular Schwannoma

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Abstract

The level of evidence to provide treatment recommendations for vestibular schwannoma is low compared to other intracranial neoplasms. Therefore, the vestibular schwannoma task force of the European Association of Neuro-Oncology assessed the data available in the literature and composed a set of recommendations for health care professionals. The radiological diagnosis of vestibular schwannoma is made by magnetic resonance imaging. Histological verification of the diagnosis is not always required. Current treatment options comprise observation, surgical resection, fractionated radiotherapy and radiosurgery. The choice of treatment depends on clinical presentation, tumor size and expertise of the treating center. In small tumors, observation has to be weighed against radiosurgery, in large tumors surgical decompression is mandatory, potentially followed by fractionated radiotherapy or radiosurgery. Except for bevacizumab in neurofibromatosis type 2, there is no role for pharmacotherapy.

Introduction

This first EANO guideline on the diagnosis, treatment and follow-up of patients with vestibular schwannoma (VS) aims at guidance in an area where there is little evidence from controlled clinical trials, major variation of clinical practice across sites and countries, but urgent need for consensus and standard operating procedures. To facilitate future clinical research and to improve overall outcome for patients regarding both functional integrity of cranial nerves and long-lasting tumor control, consensus on standard operating procedures is demanded. To meet this goal, the European Association of Neuro-Oncology (EANO) assembled a task force of experts from various European countries reflecting the multidisciplinary approach to this disease to derive recommendations for diagnostic work-up and therapy.

Methods

The task force represents the clinical disciplines involved in diagnosis and treatment of patients with VS and was composed upon suggestions of the EANO board. Specialists representing, neurosurgery, ear, nose and throat surgery, radiation oncology, pharmacotherapy, neuroradiology, neuropathology, molecular pathology and molecular genetics were included. The topics of the guideline were distributed to groups of authors according to their clinical profession and scientific profile. The individual authors searched the Medline database from January 1990 to July 2018, the Cochrane Library from January 1990 until July 2018, as well as Embase-Ovid, Cancer Net and Science Citation Index (all January 1990 to July 2018). Sensitive and specific keywords as well as combinations of keywords were used. All types of clinical and basic science articles in all languages represented by the members of the EANO task force were considered. The main keywords were chemotherapy, facial, function, hearing, NF2, nerve, neurofibromatosis, observation,

outcome, radiosurgery, radiotherapy, schwannoma, sheath, surgery, tumor, vestibular, in various combinations.

In the consensus process with participation of all authors, the literature was evaluated and 174 papers were chosen for the final guideline. The scientific evidence was rated into classes I-IV and recommendations were labeled as level A-C, according to EFNS guidelines¹ (see table 1). When sufficient evidence for recommendations was not available, the task force offered advice as "good practice point".

Clinical presentation and epidemiology

VS, formerly termed as acoustic neuromas, represent the third most common intracranial non-malignant tumor entity after meningiomas and pituitary adenomas.¹ They are the most common extra-axial posterior fossa tumors in adults, comprising over 80% of tumors in the cerebellopontine angle.^{2,3} In most cases the tumors present unilaterally; bilateral VS are a hallmark of neurofibromatosis (NF) type 2 (see below).

Clinically, most patients present with unilateral sensorineural hearing loss (94%) and tinnitus (83%). The frequency of the vestibular symptoms vertigo and unsteadiness varies widely (17%-75% of patients), but they are likely underreported.⁴ Large tumors may cause trigeminal and facial neuropathies as well as brainstem compression and hydrocephalus.

According to the Central Brain Tumor Registry of the United States (US) from 2004 to 2010, the overall incidence of VS was 1.09 per 100,000/year.⁵ This incidence increased with age to a peak of 2.93 per 100,000/year in the age group 65 – 74 years without gender difference.

Worldwide there is substantial geographical variation in VS incidence: a recent analysis of the Surveillance, Epidemiology, and End Results database in the US including a total of 9,782 VS patients among 822 million person-years revealed the median annual disease incidence to be lowest among black and Hispanic and highest among Caucasian populations ($p < 0.001$).⁶ The

VS incidence in Denmark, Sweden, Finland and Norway varies widely by country, with highest incidence in Denmark.⁷ These differences in VS incidence may be due to genetic and environmental factors as well as different diagnostic practices. Improved screening protocols for asymmetrical hearing loss, better access to advanced imaging and improved resolution of magnetic resonance imaging (MRI) have led to an increased number of VS diagnoses and a decreased average tumor size at the time of diagnosis.⁸

Risk factors for VS have scarcely been investigated. A population-based case-control study of VS risk factors in the UK and Nordic countries, revealed an elevated elevated risk for VS in parous compared to nulliparous women.⁹ There was no relation to age at first birth or the number of children. Tumor risk was lower in current but not in ex-smokers. The underlying biological mechanisms, if any, underlying these observations remain unclear.

Pathogenesis

Inactivation of the *NF2* tumor suppressor gene is considered a major event in the tumorigenesis of conventional schwannoma. A recent whole exome sequencing study demonstrated that 77% of VS show evidence of genomic inactivation of *NF2* via loss of chromosome 22q or *NF2* gene mutation.¹⁰ *NF2* inactivation is the most highly recurrent genomic alteration in VS. Bi-allelic inactivation can be demonstrated by exome sequencing in 45% of cases whereas in 41% of cases only one hit either by heterozygous chromosome 22q deletion or *NF2* mutation is evident. In 14% of cases no genomic hit in *NF2* can be detected by exome sequencing. However, the consistent lack of the *NF2* gene product merlin in the tumor cells of VS suggests that in cases without evidence for genetic inactivation epi-genetic mechanisms of *NF2* silencing or mutational events in regions not covered by exome sequencing likely exist.¹¹ Another recent whole exome sequencing study reports concordant results regarding *NF2* alterations in VS.¹² However, there are discrepancies between both

studies regarding alterations in non-*NF2* genes. While one study found *ARID1A* (14%), *ARID1B* (18%), *DDR1* (11%), *TSC1* (9%), *TSC2* (7%), *CAST* (8%), *ALPK2* (8%), *LZTR1* (8%) and *TAB3* (3%) as additional genes recurrently altered in (vestibular) schwannomas, the other study did not find recurrent somatic mutations in these genes but in *CDC27* (11%) and *USP8* (7%).¹⁰ Therefore, further studies are required to clarify the role of non-*NF2* gene mutations in schwannoma pathogenesis.

RNA-sequencing revealed recurrent *SH3PXD2A-HTRA1* fusions on chromosome 10 in about 10% of VS associated with a male gender predominance and partly co-occurring with genetic *NF2* inactivation.¹⁰ Although the precise biochemical consequences of acquiring this fusion remain to be elucidated, activation of the *MEK-ERK* pathway seems to be involved.

Bi-allelic inactivation of *PRKARIA* by deletion and/or mutation is considered a major event in the pathogenesis of melanotic schwannoma.¹³ In addition, melanotic schwannomas frequently show monosomies of chromosomes 1, 2, 17 and 22q as well as variable whole chromosomal gains.^{14,15}

NF 2

VS are usually solitary tumors, however about 4-6% are associated with NF2, an autosomal dominant monogenic condition caused by pathogenic variants in the *NF2* gene on chromosome 22q.¹⁶⁻¹⁸ NF2 has a birth incidence of about 1 in 25,000-33,000 with a diagnostic prevalence of around 1 in 60-70,000.^{16,19} Rarely schwannomatosis caused by pathogenic variants in the *LZTR1* gene can cause isolated VS or VS that can be misdiagnosed as NF2.^{20,21} NF2 can be diagnosed when the criteria in table 2 are fulfilled or when a pathogenic mutation in the *NF2* gene is found in constitutional DNA or in two anatomically distinct tumors.^{17,18} Although NF2 usually presents with bilateral VS, it may present with unilateral VS with other NF2 features in up to 15% of patients.^{17,18,22-25} Furthermore *LZTR1* pathogenic variants can

also present with apparently isolated VS at young ages, particularly aged <25 years where of 106 patients with an apparently isolated VS, 9 patients (8.5%) had an *NF2* and 3 patients (2.9%) had *LZTR1* pathogenic variants. First affected individuals in a family and particularly those with unilateral presentation are often (30-35%) mosaic for the causative gene variant as this occurs during early embryogenesis and was not present in the gamete.^{21,25} *NF2* tumors are often multifocal caused by different clonal events and multiple second hits affecting the *NF2* gene in the internal auditory meatus with both roots of the vestibular nerve being affected throughout its course in the canal.^{26,27} This makes surgery and other interventions such as radiation treatment more difficult with higher rates of recurrence.²⁸ Radiation should be used with caution in young *NF2* patients because of the risk malignant transformation and secondary tumor induction.^{28,29} Although *NF2* is very variable in its course there are strong genotype-phenotype correlations with truncating variants in exons 2-13 associated with poorest life expectancy.³⁰ *NF2* can cause schwannomas throughout the central and peripheral nervous system and patients may also develop meningiomas and spinal ependymomas, the associated morbidity affects quality of life severely and reduces life expectancy.^{29,30}

When to consider NF2?

NF2 should be considered when an individual presents with a unilateral vestibular or other sporadic schwannoma <30 years or meningioma <25 years.^{21,24,28} Germline pathogenic variants can be identified in 1-10% of cases. *NF2* should also be considered in older patients with two *NF2* related tumors although detection rates in germline are low mosaic *NF2* can be confirmed if an identical *NF2* pathogenic variant is found in both tumors.³¹

Diagnostic procedures

Imaging

Magnetic resonance imaging (MRI) is the method of choice for the identification of suspected VS, with contrast-enhanced T1-weighted scans considered to be the gold standard for the initial evaluation and postoperative assessment of recurrence or residual tumors.^{32,33} Computed Tomography (CT) has a complementary role in the evaluation of VS. It provides useful pre-operative information about the surgical anatomy of the skull base, especially the petrous bone.³⁴ The MRI protocol should include standard T1-and T2-weighted sequences, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery sequences (FLAIR). DWI imaging is useful to differentiate VS from arachnoid or epidermoid cysts. At least one T2-weighted sequence is mandatory to rule out a potential brainstem pathology mimicking VS symptoms such as multiple sclerosis or glioma. Axial sub-millimetric heavily T2-weighted sequence is the most important sequence in order to evaluate the vestibulocochlear nerve and its branches and depict the nerve as a linear hypointense structure surrounded by hyperintense CSF within adjacent cisterns (FIESTA, CISS or DRIVE).³⁵ There is a general agreement that MRI protocols should include axial T1-weighted sequences before and after gadolinium administration. Thin slice spin echo (SE) or TSE/FSE T1-weighted sequences or sub-millimetric T1-weighted 3D gradient echo (GRE) sequences can be used.^{34,36}

VS presents as a solid nodular mass with an intracanalicular component in the internal acoustic canal (IAC) that often results in its widening. Larger lesions can protrude into the cerebellar pontine cistern, whereas smaller lesions are often localized only inside the IAC or the labyrinth. The mass is usually isointense on T1-weighted imaging, with strong enhancement after gadolinium administration. On T2-weighted imaging, the lesion is heterogeneously hyperintense, while larger lesions may show scattered cystic degenerative changes and hemorrhagic areas (Figure 1). Calcifications are typically absent.

Despite the current debate about omitting the post-gadolinium T1-weighted sequences^{37,38}, T1-weighted MRI using gadolinium-based contrast is still considered the gold standard in the diagnostic work up of VS.^{32,33}

Histopathology

VS, formerly thought to originate from Schwann cells in the glial-Schwannian transitional zone of the vestibulocochlear nerve, do in fact arise anywhere along the eighth cranial nerve.³⁹ In about 80% of cases they are found in the vestibular portion and in about 20% of cases in the cochlear portion.⁴⁰ The diagnosis is made according to the WHO 2016 classification.⁴¹ The histological picture of conventional VS on hematoxylin/eosin-stained sections parallels that of schwannomas in other localizations and is specific enough for a morphological diagnosis in the vast majority of cases. Cellular Antoni A areas with interlacing bundles of spindle cells alternating with hypocellular, loose microcystic Antoni B areas are characteristic. Verocay bodies consisting of arrangements of palisading nuclei alternating with zones containing cell processes is another typical architecture of schwannomas. Immunohistochemically, VS are diffusely positive for S100B and SOX10. Cellular schwannoma and melanotic schwannoma are variants which may raise important differential diagnostic considerations. Cellular schwannoma is characterized by hypercellularity, predominance or exclusive presence of an Antoni A pattern without (well-formed) Verocay bodies.⁴² These tumors are considered benign and therefore the distinction from malignant peripheral nerve sheath tumors (MPNST) is important.^{15,43,44} Melanotic schwannoma is recognized by the WHO as a distinct entity that rarely may also affect cranial nerves.⁴⁵⁻⁴⁷ Melanotic schwannoma is grossly pigmented and expresses melanocytic markers like HMB45 or melan-A, raising a separate differential diagnosis including melanoma. The sub-variant of psammomatous melanotic schwannoma has a 50% association with the Carney-complex, an autosomal dominant clinical condition comprising myxomas and

hyperpigmentation and endocrine overactivity. In contrast to conventional or cellular schwannoma there is a 10% risk for malignant transformation in melanotic schwannoma.⁴⁸

Molecular pathology

Currently, molecular analyses do not have a role for the diagnosis, prognostication or for guiding therapy. Hotspot mutations in *GNAQ/GNA11*, *BRAF* and *pTERT* are helpful for differentiating melanotic schwannoma (wild type) from melanocytoma (often *GNAQ/GNA11* mutant) or cutaneous melanoma (often *BRAF*, *pTERT* mutant).^{14,49,50} Epigenetic analyses using genome wide methylation profiles emerge as a superb tool for differentiating biologically distinct tumor groups. Most VS form a distinctive methylation cluster compared to schwannomas from other localizations. Methylation profiles also separate (cellular) schwannomas from histological mimics.^{14,15} A reference set of conventional and melanotic schwannomas is included in the recently developed DNA methylation based brain tumor classifier tool.⁵¹ Additional studies are necessary to clarify whether *SH3PXD2A-HTRA1* fusion or any other molecular alteration in VS is of prognostic relevance.

Therapeutic strategies

Observation

Observing VS with serial MRI scanning and audiological monitoring without any tumor-directed treatment is considered appropriate for incidental, asymptomatic VS (evidence class III, recommendation level C).⁵² Compliance of patients has to be taken into account, since non-compliance could lead to a failure of follow up.⁵³ The task of observational management is to monitor tumor growth and hearing function to obtain data for a potential decision for therapy. There are hardly any clinical parameters which reliably predict growth in a newly diagnosed tumor. There are studies reporting age, sex, hearing loss, imbalance, initial size,

tumor location, and even sidedness as predictors of future growth, but these are mostly single studies at low evidence levels which were not reproduced.⁵⁴ The proportion of growing tumors at follow-up varies considerably with reported ranges from 30-70% over different periods of time, the variation most likely being due to methodological issues.^{55,56} On average, approximately 50% of tumors may be expected to grow over a five-year period.^{54,57,58} Series employing quantitative measurements of VS growth with long term follow up have shown a mean maximum diameter growth of 2.9 mm/year (maximum diameter).⁵⁹ Two recent studies found that 50% of patients lost functional hearing during a 3-4 year period.^{60,61} A full speech discrimination score was considered a good predictor for preservation of functional hearing.⁶¹

Four non-randomized studies compared outcomes from observation and stereotactic radiosurgery (SRS) showing better tumor control after SRS (evidence class II, recommendation level B).^{53,62-64} Some studies reported less hearing loss in patients with SRS whereas in others hearing outcome and complaints were not different.^{53,62-64} Two studies compared either conservative management, surgery or SRS using various quality of life questionnaires after 5-7 years of follow-up.^{65,66} Both reports showed that patients with conservative management only, responded more favorably in the questionnaires than those who were treated up front. In addition, hearing and facial nerve outcomes were better in observed patients; the latter only in comparison with surgery. However, in nearly all observed patients the tumors had stayed stable in size, which may represent a relevant bias but also indicates the importance of thoughtful indication to treat.

Surgery

Surgical management of VS should take into account tumor size and morphology at time of diagnosis as well as the patient's symptoms, comorbidities and preferences.⁶⁷ There are various classification systems for tumor size which support decision making.⁶⁸⁻⁷⁰ Of those, the Koos classification system is the most commonly used (see table 3).⁶⁹ In large VS (Koos

grade IV), surgery is considered as the primary treatment to remove a symptomatic lesion or potentially life threatening mass effect.⁶⁹ Surgery may also be considered for smaller tumors, if cystic degeneration is present or if cure is primary goal of treatment (evidence class IV, good practice point).⁷¹⁻⁷³

The choice of surgical approach depends on hearing status, tumor characteristics, patient's preferences and surgeon's expertise. The experience of the surgical team is an important factor affecting the outcome, suggesting that VS should be treated in high volume centers (evidence class IV, good practice point).⁷⁴⁻⁷⁶ Surgery related mortality is 0.5 percent in large series.⁷⁷ The probability of hearing preservation in patients with normal hearing (Gardner Robertson class A, see table 4) was >50-75% immediately after surgery, as well as after 2 and 5 years, and >25 – 50% after 10 years.^{78,79} Factors influencing preservation of serviceable hearing after microsurgery are tumor size < 1 cm, presence of a distal internal auditory canal CSF fluid fundal cap as well as good preoperative hearing function.⁷⁸ The risk of persisting facial palsy is between 3% and 46%.^{80,81} It depends on tumor size and the occurrence of an immediate paresis.⁸⁰ To improve the rate of functional preservation, intraoperative monitoring is mandatory for surgery of VS and should include somatosensory evoked potentials and electromyographic monitoring of the facial nerve comprising direct electrical stimulation and free-running electromyography (EMG) (evidence class III, recommendation level B). Facial motor evoked potentials are currently being evaluated.^{74,82} Intraoperative facial nerve monitoring leads to improved functional outcome and can be used to accurately predict favorable facial nerve function after surgery.⁷⁴ Brainstem auditory evoked responses should also be used when hearing preservation is attempted (evidence class III, recommendation level B).^{78,83,84} In case of large lesions, EMG of the lower cranial nerves is recommended (evidence class IV, good practice point).

Goal of surgery should be the total or near-total resection, since residual tumor volume correlates with rate of recurrence (evidence class III, recommendation level B). A series of

116 patients with VS that were treated by gross total resection (GTR), near total resection (NTR) or subtotal resection (STR) yielded recurrence rates of 3.8%, 9.4% and 27.6% respectively.⁸⁵ The mean time to recurrence was 22 months, ranging from 6 to 143 months. In a recent study of 103 sporadic VS who underwent NTR or STR, patients with STR experienced recurrences over 13 times more often than those treated with NTR.⁸⁶ In a retrospective study with 111 incomplete excisions (NTR and STR), the 7 patients who showed evidence of tumor regrowth had all undergone STR.⁸⁷ Several further series also showed a considerably greater risk of regrowth with increasing residual tumor volumes.⁸⁸⁻⁹⁰ For large VS, the lower risk of recurrence after gross total resection should be weighed against the higher risk for facial nerve dysfunction and lower rates of hearing preservation, since there seem to be a relationship between tumor volume and functional outcome.^{91,92}

For these cases, partial resection followed by stereotactic radiosurgery (SRS, see below) has become increasingly popular.⁹³⁻⁹⁶ With this combined approach, the results reported so far show superior outcome regarding facial nerve function and hearing preservation when compared to total resection, with comparable tumor control rates. However the studies still are small and retrospective (evidence class IV, good practice point).^{93,96} After intentional near total or subtotal resection, a watch and scan policy is warranted as only a minority of remnants do progress, however the risk increases with the size of the remnant.⁹⁶ In cases of recurrences after radiosurgery, both reoperation and radiosurgical retreatment are possible. However, the functional risk for the facial nerve upon surgery is higher after previous irradiation and a very meticulous, conservative dissection technique might be necessary (evidence class IV, good practice point). In VS recurring after surgery, radiosurgery may be used preferentially because the risk of damage to the facial nerve is lower than with a second operation (evidence class III, recommendation level C).⁹⁷⁻¹⁰⁰

The following approaches are commonly used:

The suboccipital retrosigmoid (retromastoid) approach is favored by neurosurgeons and is particularly indicated for tumors located primarily in the cerebellopontine cistern or tumors with significant mass effect. It allows removal of tumors of various sizes and offers the possibility of hearing preservation. It provides excellent visualization of the brainstem, cranial nerves and relevant vascular structures, but requires some cerebellar retraction and allows only limited access to the fundus of the internal auditory canal.^{101,102} The procedure can be performed with the patient in either a (semi-)sitting or a horizontal positioning. Although there are some small retrospective studies reporting on superior functional outcome associated with the semisitting position, current data does not support favoring a particular positioning technique (class IV, good practice point).¹⁰³⁻¹⁰⁵

The translabyrinthine approach, usually performed by ENT surgeons, can be used to remove tumors of all sizes. A labyrinthectomy will result in complete loss of function of the inner ear and is therefore not suitable for patients seeking hearing preservation. The approach provides access to the internal auditory canal after labyrinthectomy and exposure of the facial nerve within the Fallopian canal. The approach has the advantage of excellent tumor access without the need of occipital or temporal lobe retraction.¹⁰⁶ It offers superior visualization of the entire facial nerve from brain stem to its entry into the labyrinthine portion of the Fallopian canal.¹⁰⁷

The middle fossa approach may be considered for patients with small tumors, who would like to preserve residual hearing. Suitable access requires temporal craniotomy above the zygoma and dissection of dura up to the arcuate eminence.

This approach requires careful patient selection. Tumor extending to the fundus and extending below the transverse crest is more difficult to remove than tumors where there is a CSF cap filling the lateral end of the IAC.^{108,109} Endoscope assisted resection has been reported as an aid for far lateral tumor dissection.^{110,111} Post-operative hearing outcome improves with

smaller tumors and optimal tumor size is less than 1 cm intracranial tumor diameter.¹¹² This approach has the potential disadvantage of increased facial nerve manipulation because of the anterosuperior course of the facial nerve through the internal auditory canal especially for those tumors that arise from the inferior vestibular nerve.¹¹³

Altogether, there are no sufficient data supporting the superiority of any approach in terms of radical tumor resection and nerve function preservation.¹¹⁴ Therefore, no recommendation can be made and the approach should be chosen upon the experience of the treating center.

Radiosurgery and Radiotherapy

Stereotactic radiosurgery (SRS) defines delivery of high dose irradiation with high conformity and precision in a single fraction and is commonly used for small to medium sized VS. SRS can be performed using a Cobalt-60 based GammaKnife or linear accelerator techniques like the CyberKnife using doses from 11 to 14 Gray (Gy).^{81,115-117} The definition of a hypofractionated schedules of up to five fractions as “radiosurgery” remains controversial in Europe. In case of larger tumors, fractionation is mandatory. For these cases, fractionated radiotherapy (RT) or hypofractionated stereotactic radiotherapy (SRT) using up to 10 fractions are increasingly used. There are no data providing an outcome based comparison of GammaKnife or linear accelerator techniques.⁵²

Five prospective studies without randomization (evidence class II) have revealed that SRS is superior to microsurgery for patients with VS <3 cm in terms of preserving facial nerve and hearing function.^{81,116,118-120} As upper limit for radiosurgery a mass effect on the brainstem (Koos IV) is considered, there is no clear definition by diameter or volume alone (evidence class IV, good practice point).

Several retrospective cohort studies evaluated SRS using GammaKnife with at least 100 patients, 2 years follow up and objective audiometric assessment. One linear accelerator series with over 100 patients included and 2 years follow up did not report functional hearing outcome.¹¹⁵ Pioneer series of SRS included patients treated with very high dose regimens. Contemporary SRS series using GammaKnife with tumor marginal doses between 12 and 14 Gy revealed 5-year tumor control rates of 90-99%, hearing preservation rates of 41-79%, facial nerve preservation rates of 95-100% and trigeminal preservation rates of 79-99%. Numerous authors have found that the key predictor for functional hearing preservation is the quality of hearing at time of radiosurgery.¹²¹⁻¹²⁶ A recent review revealed a relevant decline in hearing after SRS, even in patients with normal hearing function (Gardner Robertson grade 1).⁷⁸ The probability to preserve hearing was >75-100% after two years, >50-75% after five years and >25 -50% after 10 years. After 5 and 10 years, the rates of hearing preservation were similar to patients having microsurgery.⁷⁸ However, it has to be considered that the latter data are based on selected surgical cases with a special attempt to preserve hearing.

The maximum dose at the modiolus of the cochlea has been reported to be a negative predictor for functional hearing preservation with a threshold around 4 Gy.^{122,123,127-130} However, these series comprise small retrospective cohorts of patients. Cochlear dose is likely to be one of many variables associated with hearing preservation. The recommendation is to use SRS with a dose of 11-14 Gy at the margin and 11-12 Gy when the risk of hearing loss is a critical issue (evidence class III, recommendation level C).⁵²

There are no randomized, prospective studies comparing SRS and SRT. Six non-randomized studies found that the functional hearing preservation is similar but the rate of facial palsy and trigeminal nerve dysfunction seems higher with SRT than SRS.¹³¹⁻¹³⁸

There is little data about the incidence of malignant VS after radiation of spontaneous, non-NF2 VS. The spontaneous risk of malignancy was addressed in a large retrospective

study using the Surveillance Epidemiology and End Results (SEER) database. The incidence of malignant peripheral nerve sheath tumors (MPNST) of the eighth cranial nerve with no history of prior radiation was 0.017 per 1 million persons/year. When compared with the incidence of benign VS, 1041 VSs were present for every 1 MPNST arising from the eighth cranial nerve. There is no evidence that spontaneous MPNST is a feature of NF2 as opposed to NF1, nonetheless around half of MPNST reported after radiation treatment are in NF2 patients.¹³⁹ This baseline rate of malignancy should be considered when estimating the risk of malignant transformation following stereotactic radiosurgery for VS.¹⁴⁰ In a retrospective single center review, Pollock et al did not find any radiation-induced tumors in 11,264 patient-years of follow-up after SRS.¹⁴¹ In a review by Maducdoc et al. only eight cases with malignant transformation after surgery or SRS were found, four of these patients had surgery only.¹⁴²

Numerous studies have reported about transient enlargement of VS occurring within 3 years after radiosurgery.¹⁴³⁻¹⁴⁷ This MR change observed in up to 30% of the patients is related to the therapeutic effect of SRS and is termed pseudoprogession. It is not a predictor of failure.¹⁴³⁻¹⁴⁷ We recommend clinical and radiological observation within this time frame performing annual MRI scans (expert opinion, good practice point).

Systemic treatment options

Local therapies are the mainstay for the treatment of VS. There is no level I evidence of for any systemic treatment and even level II evidence for the treatment with the anti-vascular endothelial growth factor antibody bevacizumab is disputable and only valid for schwannomas arising in patients with NF 2. In the sequence of therapies, a safe surgical resection and radiotherapy are considered as superior. Thus, systemic, medical treatment options have been generally used in locally pretreated patients, potentially limiting efficacy and more importantly interfering with the ability to assess efficacy.

Bevacizumab has been successfully used for patients with progressive VS associated with NF2.¹⁴⁸ Patients experienced an improvement of hearing and objective (>20% reduced tumor volume) radiographic responses.¹⁴⁹ In NF 2 patients with progressive VS a prospective, multi-institutional, uncontrolled phase II study with 14 patients using 7.5 mg/kg bevacizumab administered every 3 weeks revealed a hearing improvement in 36% of patients, and no patient with a hearing decline in the trial period of 12 months.¹⁵⁰ Volumetric assessments demonstrated a partial radiographic response of volume reduction of 20% or more in 43% (6/14 patients) making bevacizumab a potential treatment option for NF2 patients (evidence class II, recommendation level B).

Other pathways have been addressed based on preclinical or immunohistochemical target expression.¹⁵¹ Again, patients studied had VS in the context of NF2. Neither epidermal growth factor receptor (EGFR) pathway inhibition using erlotinib nor ErbB2 (and EGFR) pathway blockade applying lapatinib has been associated with relevant radiographic responses or impact on the hearing function.^{152,153} The mechanistic target of rapamycin (mTOR) signaling cascade has also been proposed for the treatment of NF2 related tumors since the mTOR pathway is considered a key driver of tumor growth in merlin (NF2)-deficient tumors. Similarly, a small (n=10 patients), single-institution trial study of the mTOR complex 1 inhibitor everolimus was not associated with tumor shrinkage or hearing improvement.¹⁵⁴

Supportive Care

There are almost no data about the value of supportive care in VS patients. Therefore, only expert opinion based recommendations are possible (good practice point).

Care should focus on clinical symptoms and treatment complications. Trigeminal and facial neuropathies, as well as brainstem compression or hydrocephalus could be symptoms of large

VS as well as treatment complications. Patients with facial nerve palsy can have various types of ocular complications like lagophthalmus, which can lead to exposure keratopathy, corneal breakdown, ulcers, and even perforation. Patient management should be based on the severity of the ocular findings and ranges from symptomatic treatment like moistening eye drops to surgical reanimation of the facial nerve via hypoglossal facial nerve anastomosis and symptomatic plastic measure for the eye or face.¹⁵⁵⁻¹⁵⁸ Patients with facial nerve palsy who present at earlier stages can benefit from conservative treatment. Therapy with corticosteroids is frequently administered in this case, however, evidence for this treatment is lacking. Decreased hearing can be supported by various hearing aid. We refer the reader to specific reviews about multidisciplinary treatment and rehabilitation of facial palsy and lower cranial nerve deficits as possible complications of surgical therapy.¹⁵⁹⁻¹⁶¹

Quality of life

Tumor size seems to be a predictor for quality of life (QoL) in VS patients.^{65,162,163} Several retrospective studies addressed the question, which treatment modality provides the best QoL but led to inconsistent results. Observation, resection, radiosurgery and radiotherapy were compared using different study designs.^{65,116,162,164-169} Although there are significant discrepancies between these studies, it might be concluded that QoL in patients with VS cannot be predicted based on management strategy alone. As expected, poor QoL is more likely in patients with large, symptomatic tumors that were resected.^{65,162,163}

Monitoring and Follow up

Follow up after treatment as well as with conservative management requires a program of MRI scanning, audiometry and outpatient consultation. There are plenty of retrospective data describing tumor growth in different situations over time (see above), however, prospective

data focusing on control intervals are rare. We support annual MRI follow up for five years in patients with untreated tumors, thereafter the follow up intervals can be prolonged.³³ There are also recommendations for a size dependent follow up with a recommendation of six month intervals in large tumors.¹⁶⁹ In a prospective collection of 196 patients, no onset of growth was found in intracanalicular tumors which were stable for five years after diagnosis.⁵⁷ In another large prospectively followed cohort of extra-and intracanalicular tumors, 7.2 % exhibited growth after a stable period of five years following diagnosis.¹⁷⁰ Thus, even if the likelihood of growth declines with time, imaging albeit at larger intervals is recommended for untreated tumors.

Based on these data, we recommend annual follow up intervals with MRT and audiometry in patients with conservatively treated, radiated and incompletely resected VS for five years. In case of stable tumor size, the intervals can be doubled thereafter (recommendation level: good practice point). In patients with gross total tumor resection, MRI controls postoperatively and after 2, 5 and 10 years are sufficient (expert opinion, recommendation level good practice point).

Specific recommendations:

VS in general:

Many tumors are managed in single departments or institutions offering one particular treatment. Since there are several therapeutic options possible, especially in medium sized tumors, we recommend discussion of patients with VS in multidisciplinary tumor boards. Besides treatment decisions, follow up including pseudoprogression can be evaluated by specialists from all disciplines involved (expert opinion, good practice point).

If surgery is indicated, surgical treatment at a high volume center is recommended, since surgical experience affects outcome, (evidence class IV, good practice point).

Sporadic unilateral VS

- Small asymptomatic tumor (Koos I-II)

Management of sporadic, non-NF2 related unilateral VS should depend on symptoms and signs, and on the size of the tumor. In small, asymptomatic tumor with regular cranial nerve function, observation is the management of choice. The data available provide evidence level III and recommendation level C.

As an alternative to observation, SRS can be performed to stop tumor growth and preserve long term nerve function. However, there still is a small risk of deterioration of nerve function or QoL. There is evidence level II and recommendation level B for SRS in asymptomatic patients.

If long term preservation of nerve function is the primary aim of management, even surgery can be chosen; however, the risk of any functional deterioration is considerable ranging up to 50 percent (evidence class III). Therefore, we recommend not to perform surgery in these patients (recommendation level C).

- Small tumor with impaired hearing (Koos I-II)

If patients with small tumors became symptomatic with vestibular and /or auditory symptoms, therapy should be discussed to avoid further deterioration. In these cases, SRS offers a better rate of hearing preservation and a lower risk for facial paresis than surgery (recommendation level C).

- Small tumor with complete hearing loss (Koos I-II)

In these patients, aim of therapy can be cure or tumor control while preserving facial nerve function. All options can be justified in these cases. Observation is usually the first option, since there is no function endangered for a long period of time (evidence class III, recommendation level C). SRS or surgery carry a low risk of facial nerve damage and may provide long term control or cure, respectively. Besides facial nerve function, SRS carries a lower risk profile than surgery making SRS the first option, if tumor control is regarded sufficient by the patient (evidence class II; recommendation level B).

- Medium sized tumors (Koos III-IV, < 3 cm)

Most patients with medium-sized tumors present with vestibular or cochlear symptoms. Facial paresis is rare and might even be a hint for a facial schwannoma. Due to the symptomatic burden and considerable tumor volume, therapy should be performed. Surgery or radiosurgery can be recommended at a very similar level (recommendation level C). The risk profile of SRS is lower than of surgery, however, surgery can offer complete removal of the tumor. Altogether, this situation should be meticulously discussed with the patients and all options explained. Also subtotal resection to preserve function might be an option, if subsequent SRS of a growing tumor rest can be provided (good practice point).

- Large tumor with brain stem compression (Koos IV > 3 cm)

These patients typically suffer from 8th cranial nerve symptoms for a long time. A considerable number of these patients present with additional symptoms like facial nerve paresis or gait ataxia. Primary goal of therapy is decompressing the brain stem and stretched cranial nerves, what makes surgery the only option. Since there are no prospective studies for this clinical situation, recommendation level is good practice point. Surgery in large tumors is accompanied by a considerable risk for loss or deterioration of cranial nerve function. For this

reason, tumor mass reduction by incomplete resection, followed by SRS or observation is a valid option (evidence class IV, good practice point).

NF2 with uni- or bilateral VS

Patients with NF2 suffer from bilateral VS or unilateral VS and other intracranial and/or spinal tumors (see table 1). The high incidence of newly developing tumors, the fast tumor growth and early tumor regrowth as well as the lack of a cure makes patient management challenging.¹⁷¹ Generally, observation and follow up should use shorter intervals compared to spontaneous VS particularly in younger patients. Follow up intervals of 6-12 months are recommended (evidence level IV, recommendation level good practice point). In most patients, several consecutive therapies have to be performed to preserve cranial nerve and brain stem function. Bilateral VS may lead to intense brain stem compression making surgical decompression mandatory. If incomplete resection is performed to preserve 7th and/or 8th cranial nerve function, residual tumors may be treated by SRS, in small tumor rests observation may be appropriate. In inevitable recurrent situations, therapy depends on the clinical condition of the patient, cranial nerve symptoms, tumor size, and therapies performed earlier. Re-surgery and re-SRS commonly need to be performed depending on the respective risk profile (good practice point). Prospective data show positive effects of bevacizumab on hearing and tumor growth (evidence class II), making bevacizumab a good treatment option (recommendation level B).¹⁷²⁻¹⁷⁴ Due to impaired hearing function, auditory rehabilitation is of utmost importance for these patients. There are no prospective data on general management, surgery or SRS especially for NF2 patients, allowing only recommendation as good practice points.

Key recommendations are summarized in table 5.

Research Outlook

This guideline presents the recommendations derived from the current state of the literature.

To generate progress in the area of VS management, we recommend to focus on the following issues:

The value of surgery versus SRS is difficult to evaluate in a prospective manner.

Randomization is conceivable only in medium and small sized tumors and we suspect that patients will be reluctant to undergo randomization. An improved multidisciplinary communication in tumor boards might help to solve this problem.

Since considerable late effects on hearing have been encountered, more information about the long time effects of SRS is needed by extending clinical and radiological follow up in VS patients more than 10 years.

According to other putative benign intracranial tumors like meningiomas, molecular profiling of VS should be intended on a broad scientific basis (i) to learn more about the reasons for clinically different growth behavior within a distinct WHO grade I tumor entity and (ii) to define targets for a tailored pharmacotherapy.

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Figure Captions:

Figure 1 – Intracanalicular and cisternal VS (Koos III). Axial 3D heavily T2-weighted sequence (DRIVE) (a) shows a VS expanding from the internal porus acusticus into the cerebellopontine-angle cistern. Coronal T2-weighted image (b) depicts slight mass effect on middle cerebellar peduncle. Cystic degenerative changes seen on T2 are well evident on axial (c) and coronal (d) T1- weighted images after Gadolinium (arrows).