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To cite this article: Jane Halliday, Scott A Rutherford, Martin McCabe & Gareth D Evans (2017): An update on the diagnosis and treatment of vestibular schwannoma, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2018.1399795

To link to this article: http://dx.doi.org/10.1080/14737175.2018.1399795

Accepted author version posted online: 01 Nov 2017.
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Abstract

Introduction: Vestibular schwannomas (VS) account for approximately 85% of tumors in the cerebello-pontine angle, with a lifetime incidence of approximately 1 in 1000. Most are sporadic, with approximately 5% related to the tumor predisposition syndrome Neurofibromatosis Type 2 (NF2). The mainstays of management strategies are: observation, surgery, radiosurgery/radiotherapy and, for patients with NF2 and rapidly growing tumors or deteriorating neurologic function the targeted therapy bevacizumab. While morbidity and mortality rates related to treatment of VS have improved dramatically over the last decades, there are still significant improvements that could be made, in particular with regards to long-term facial nerve and hearing outcomes.

Areas covered: The epidemiology and diagnosis of VS are discussed, followed by the different management strategies and outcomes of those for both sporadic and NF2 related tumors. An extensive literature review has been performed to inform this review article using PubMed and Google Scholar.

Expert commentary: The future direction of VS management lies in obtaining longer-term follow-up data for patients with treated VS, and in improved understanding of cellular pathways and targeted therapies.

Keywords: long-term outcomes, neurofibromatosis type 2, observation, radiosurgery, surgery, targeted therapy, vestibular schwannoma
1. Introduction

Vestibular schwannomas (VS) are benign tumors that arise from Schwann cells of the vestibular portion of the vestibulocochlear nerve inside the internal auditory canal (intracanalicular). As they grow they fill and extend beyond the internal auditory canal into the cerebello-pontine (CP) angle (extracanalicular). VS result from genetic abnormalities on chromosome of 22q12 (the Neurofibromatosis Type 2 (NF2) gene (coding for the tumor suppressor Merlin)). Approximately 5% of cases occur as part of the tumor predisposition syndrome NF2, and very rarely as part of the tumor predisposition syndrome Schwannomatosis [1] (caused by inactivating mutations in the tumor suppressor genes SMARCB1 and LZTR1). The remainder are thought to be sporadic due to acquired loss of NF2 gene function [2].

The most common presenting symptoms are progressive hearing loss (90%) and tinnitus (>60%). Imbalance, dizziness, vertigo, facial paraesthesia and headache secondary to hydrocephalus can occur with larger VS due to brainstem and trigeminal nerve compression. Up to 12% of patients can present with facial paraesthesia due to involvement of the trigeminal nerve, and up to 6% can present with facial nerve palsy; again these symptoms occur in patients with larger VS [3][4]

The lifetime risk of developing a VS is estimated at approximately 1 in 1000, including sporadic and NF2 related tumors [5][6]. The incidence appears to be increasing, thought largely due to the incidental diagnosis of asymptomatic lesions with the increasing use of magnetic resonance imaging (MRI) and, to a much lesser extent, computed tomography (CT) [7]. Linn et al [7] retrospectively analyzed 46,414 MRI scans performed for reasons other than suspected VS, and identified eight, suggesting that undiagnosed VS may be present in at least 0.02% of the population. Mean age of presentation is 50-55 years, with no significant difference in incidence by gender [5]. Over 90% of tumors are unilateral, equally affecting left and right, with bilateral VS almost exclusively occurring in patients with NF2. Environmental risk factors to developing VS continue to be studied. Radiation (ionizing or gamma rays) is however consistently identified [8], with conflicting data on the risk of mobile phones and noise exposure. The interphone study group have conducted one of the largest studies, undertaking a case-control study of 1105 patients with newly
diagnosed VS and 2145 controls, assessing mobile phone use by means of interviews. They found that regular mobile phone use conveyed no extra risk of developing VS to those who were not regular users, this included those who had used their phones for 10 years or more before the study was conducted [9]. Longer term data is still lacking.

Morbidity and mortality rates associated with the management of patients with VS have improved dramatically over the past decade. At the 1913 International Conference of Medicine in London mortality rates of greater than 50% were reported, with similarly high rates of morbidity in those who survived [10]. 104 years on from then mortality rates are now well under 1%, with similar significant improvements in morbidity rates too. Early detection, the development and use of operating microscopes and the use of intraoperative neurophysiological monitoring are thought to have been the largest contributors to this.

Once diagnosed there are a range of management options for VS management: 1. observation with serial MRI’s, 2. surgery, 3. radiosurgery/radiotherapy, and 4. targeted therapies. Treatment choice depends on the patient age, diagnosis of NF2, health status, symptoms, tumor size, patient preference and institutional and physician biases.

2. Diagnosis

The diagnosis of VS is often made incidentally, during the investigation of other complaints, or as a consequence of patients presenting with otological or neurological symptoms related to VS. These most commonly are hearing loss, and tinnitus. Otological symptoms almost always precede other neurological compromise. Hearing loss is sensorineural and typically progressive, thought to occur due to combination of compression of the cochlear nerve by the tumor and ischemia [11]. Despite their origin on the vestibular nerve it is rare for patients with VS to present with imbalance as their primary symptom. This is thought to occur due to compensation of the vestibular system to the gradual loss of function that typically occurs with VS, due to the slow growing nature of these tumors. Neurological symptoms include sensory trigeminal impairment, facial nerve impairment, headache and imbalance related to
brainstem compression and hydrocephalus. These symptoms as presenting symptoms are far rarer than otological symptoms.

Unilateral hearing loss, tinnitus and vertigo are common presenting symptoms in patients attending Ear, Nose and Throat (ENT) clinics; VS as a cause of these symptoms is uncommon. It is estimated that up to 20% of patient presenting to ENT clinics have symptoms that could be attributed to a lesion in the CP angle [12]. For this reason, local guidelines have been created to guide clinicians as to when patients should be investigated for suspected VS. For example the ‘Oxford Guideline’ is to investigate in patients who have 15 dB asymmetry between mean thresholds of tested frequencies and unilateral tinnitus with normal hearing, and the ‘Northern Guideline’ to investigate those with 20 dB asymmetry between two contiguous frequencies and unilateral tinnitus [13]. Patients reporting symptoms that could be attributed to a CP angle lesion should undergo audiometry (pure tone and speech) as an initial screening laboratory test. Typically, patients with VS will have an asymmetrical sensorineural hearing loss, with the speech discrimination score typically much lower than the measured hearing loss. Brainstem-evoked response audiometry can be used as a further screening test, and prior to MRI imaging was the most accurate screening tool for suspected VS. However with a false negative rate as high as 30% with small vestibular schwannomas, and a 10% false positive rate it is no longer used as a first line investigation [14]. The gold standard imaging test is magnetic resonance imaging (MRI) with gadolinium contrast and fine sections through the internal auditory meatus. If a patient cannot tolerate MRI, high resolution CT scanning with and without contrast is an alternative although this will miss small intracanalicular tumors. Fast spin echo MRI has been investigated as a screening test; it is low cost compared to gadolinium MRI, non-invasive and has been found to have high sensitivity and specificity [15].

Patients with vestibular schwannomas and an underlying diagnosis of NF2 or schwannomatosis tend to present at a younger age and in NF2 with bilateral vestibular schwannomas (about 85% of NF2 are bilateral at presentation). The current clinical diagnosis of NF2 is based on the following [16]:

- Any one of: bilateral vestibular schwannomas before age 70 years or unilateral vestibular schwannoma before age 70 years and first-degree relative with NF2;
- Any two of: meningioma, non-vestibular schwannoma, neurofibroma, glioma, cerebral calcification, cataract and a first-degree relative with NF2 or unilateral vestibular schwannoma and negative LZTR1 testing;
- Multiple meningiomas and unilateral vestibular schwannoma or any two of the: non-vestibular schwannoma, neurofibroma, glioma, cerebral calcification, cataract;
- Constitutional or mosaic pathogenic NF2 gene mutation from the blood or by the identification of an identical mutation from two separate tumors in the same individual.

These criteria were recently changed to add an age limit as bilateral VS can occur by chance particularly after 70 years of age [17]. LZTR1 mutations have also been identified in 5 of 50 individuals with unilateral VS and two or more other schwannomas but no meningioma or other NF2 feature [14], thus the need to exclude LZTR1.

3. Management of Sporadic Vestibular Schwannoma

The principle of VS management is to reduce mass effect, as required for larger tumors, and maintain long term tumor control, while preserving facial nerve function, and hearing where possible. The management of patients with NF2-related VS differs from those patients with sporadic VS, and therefore will be discussed separately.

In a patient with very early onset apparently sporadic VS consideration needs to be given to the possibility of NF2 or LZTR1 related schwannomatosis. The chances of NF2 in an apparently sporadic VS under 20 years of age has been previously estimated to be 20% (half of these mosaic) and between 20-29 at 5% (only 1% chance of non-mosaic) [18]. More recently four of 106 people (3.8%) with a cranial schwannoma aged <25 years were identified with a germline LZTR1 mutation (3 were vestibular schwannomas and 1 was a non-vestibular schwannoma), and 9 (8.5%) had an NF2 mutation identified [19]. As such all patients with an apparently isolated VS under 30 years should be evaluated for NF2 and schwannomatosis including molecular testing.
The three major treatment options for patients with a sporadic vestibular schwannoma are surgery, radiation therapy, and observation (wait and watch policy).

### 3.1 Observation

Observation, i.e. a ‘watch and wait’ policy with serial MRI’s, is an accepted form of management of diagnosed small VS due to their typically slow growth, and the lack of significant symptoms and neurology with small VS. A typical ‘wait and watch’ scanning regime is as follows: initial scan at presentation; a first follow-up scan at 6 months (to detect the small proportion of more rapidly growing VS); further scans at 1 year intervals for a further 3 years; followed by further scans every 2 years for a minimum surveillance period of 10 years in total. The premise of continued watch and rescan is tumor stability, although very slowly growing tumors can continue to be monitored rather than actively treated if this is the patient’s preference.

In a study of conservatively managed VS that included 386 patients, 59% of patients had an annual tumor growth rate of less than 1 mm per year [20], thus supporting a conservative wait and watch policy of management in appropriate patients. The Manchester group studied a group of 436 patients with VS, including patients with NF2. They found that two-thirds of VS did not grow, over an average follow-up period of 3.6 years. The mean growth rate for sporadic tumors was 1.1mm/year diameter, and for NF2 tumors 1.7mm/year [21]. Smouha et al performed a retrospective literature search of conservatively managed VS, including 21 studies. Across these studies with an average follow-up of 3.2 years, they found that 51% of tumors remained stable, 43% grew and 6% regressed without treatment. Only 20% of patients required treatment due to tumor and/or symptom progression. Tschudi et al [22], in their study of observed VS, found that growth in the first year following diagnosis was predictive of continued future growth. Patients identified at increased risk of further growth are those with a greater extracanalicular than intracanalicular component, extracanalicular component of diameter greater than 20mm, young age, and diagnosis of NF2 [21][23]. In keeping with these results Stangeruup et al, in their study of 729 patients with observed VS, found that 17% of intracanalicular tumors and 28.9% of extracanalicular tumors grew, all within the first 5 years after diagnosis. They did not find any correlation between sex and age and tumor growth rate [24].
Thus, observation is associated with the risk of tumor progression, and therefore the need to proceed with treatment. It is also associated with a risk of progressive hearing loss. Studies on the natural history of small vestibular schwannomas have helped to define the risk factors for further hearing loss. A study of hearing outcomes in conservatively managed vestibular schwannomas found that those patients with tumor growth rates of greater than 2.5mm per year had a significantly higher rate of hearing loss compared with those with growth rates less than that, 75% versus 32%, over a follow-up period ranging from 26 to 52 months [24]. Even slow growing tumors are therefore associated with hearing loss. As a consequence, if hearing preservation is important to a patient, this should be factored into the decision as to how appropriate it is to conservatively manage them. There is evidence that hearing preservation outcomes are improved in patients with pre-treatment serviceable hearing [25].

We can see from the literature that observation with serial scans is an acceptable management approach for patients with small tumors (<2cm), elderly patients in whom it is well recognized that treatment of VS is associated with higher morbidity and mortality rates than in younger patients, for those patients who prefer a conservative approach where possible, and for those patients with medical conditions that significantly increase the risk of operation. It is clearly less appropriate for patients with larger tumors with mass effect. Conservatively managed patients should be counselled that they may well require treatment at some point, and with regards to the potential risk of worsened hearing loss should they require future treatment. There is a role for more frequent interval scanning of patients identified at higher risk of further growth.

3.2 Surgery

The first recorded operation for VS removal was in 1884 by Sir Charles Balance [26], with recorded mortality rates of up to 84%. In the 1990s expert opinion was that surgery was the most appropriate form of treatment for all patients with VS, regardless of their size [27]. As we can see from the discussions earlier in the paper, opinion has shifted on the role of surgery for management of all VS. There does however, remain an extremely important role for surgical management of VS. The retrosigmoid and translabyrinthine surgical approaches predominate in the UK. Less frequently employed operations are the middle fossa, the extended middle fossa and
transotic approaches. Endoscopic tumor resection, while not widespread in use, is performed and reported, with some surgeons reporting its use for complete tumor resections in appropriately selected patients [28], and others for parts of tumor resection, for example of tumor in the internal auditory canal [29]. Subtotal resection, particularly for large VSs to preserve function, is an accepted deliberate surgical outcome [30]. However, evidence shows that patients who undergo subtotal resection have an almost 11-fold increased risk of recurrence than those who undergo total excision [31]. Thus those who have subtotal excision to preserve function must be observed closely, with treatment options of radiosurgery/radiotherapy and further surgery available if the residual demonstrates growth.

The translabyrinthine approach is typically performed as a joint procedure between neurosurgeons and ENT surgeons. The incision is typically retroauricular extending behind the mastoid tip. A mastoidectomy and labyrinthectomy gives exposure of the internal acoustic canal (IAC), and the dura of the middle and posterior fossa, allowing identification of the facial nerve by stimulation and visualisation, and the tumor. The main advantage of the translabyrinthine approach is that it allows early identification of the facial nerve. It also provides a good access to a wide range of tumor sizes, avoids the need for cerebellar retraction and is associated with low rates of post-operative CSF leaks and headache. Its major disadvantage is that it does not allow for preservation of hearing, thus making the ideal surgical group, for this approach, those patients with absent or non-serviceable hearing pre-operatively [32].

For the retrosigmoid approach a suboccipital craniotomy is performed, exposing the edges of the transverse and sigmoid sinuses. After dural opening the tumor is exposed by gentle retraction of the cerebellum. Drilling of the posterior lip of the IAC gives a 180° exposure of the IAC. After dividing the vestibular nerves the tumor is carefully dissected off the facial and cochlear nerves, and tumor debulking performed. Sometimes due to tumor size partial debulking has to be performed before the nerves can be clearly identified [32]. Removal of a wide range of sizes of tumor is possible via the retrosigmoid approach, and it offers the significant advantage of potential hearing preservation. The main disadvantages of the approach are reduced access to
the facial and cochlear nerves in the IAC, which increases the potential for nerve
damage and leaving residual tumor, and the need for cerebellar retraction, although
this is now minimized with microsurgical techniques. The approach is often preferred
by surgeons for tumors with significant mass effect and for those patients who have
serviceable hearing and wish to try and preserve this.

The middle fossa approach is not commonly used in UK practice now as it is limited
to small tumors of the IAC in patients in whom hearing preservation is important. It is
a less favored approach as it places the facial nerve between the surgeon and tumor,
thus placing the nerve at greater risk of damage [33], requires temporal lobe retraction
which increases the risk of seizures, and provides limited views of the cerebello-
pontine angle (CPA). It has been found however to have improved hearing outcomes
for patients with intracanalicular tumors compared with the retrosigmoid approach
[34].

Intra-operative monitoring, and improvements in this, allowing intraoperative
brainstem auditory evoked potential monitoring, direct cochlear nerve action potential
monitoring, and facial nerve electromyography, have been proven to improve the
functional outcomes of VS surgery, for both facial nerve function and hearing
preservation, for all approaches. Intra-operative monitoring helps surgeons to
anatomically identify nerves, thus increasing the possibility of preserving their
functional integrity [35]. Vasoactive drugs are being investigated for their potential
role in improving facial nerve and hearing outcomes after vestibular schwannoma
surgery. Studies have examined the use of nimodipine and hydroxyethyl starch, and
have found some benefit to treatment in terms of long term facial nerve outcomes [36]
and hearing preservation [37] after surgery. However, these results are not
consistently reproduced. A recent phase 3 trial examining the use of prophylactic
nimodipine after VS surgery showing no statistically significant effects of the
treatment [38]. More studies are required before the use of vasoactive treatments can
be clinically recommended.

The outcomes of surgery for VS can be analyzed in terms of hearing outcomes, facial
nerve preservation, extent of tumor resection and of complications, namely CSF leak,
headache, major neurological complications and mortality.
3.2.1 Hearing preservation: Ansari et al [39], who undertook a literature review of outcomes of VS surgery that included 35 studies and a total of 5064 patients, found that hearing preservation rates were similar for intracanalicular tumors operated via middle fossa and retrosigmoid approaches (40.6% vs 44.3%, p = 0.492). Hearing preservation rates for tumors of less than 1.5cm were significantly better when operated via a middle fossa approach rather than a retrosigmoid approach (43.6% vs 64.3%; p < 0.001). For larger tumors of greater than 1.5cm hearing loss rates are significantly higher, but improved with retrosigmoid rather than middle fossa approaches (71.6% vs 82.7% hearing loss post-operatively).

3.2.2 Facial nerve function: Facial nerve function is graded by means of the House-Brackmann Scale [40]. In its simplified form grade 1 is normal, grade 2 slight weakness/asymmetry, grade 3 obvious weakness with movement but absence of disfigurement at rest and intact ability to close the eye, grade 4 obvious weakness with movement and disfigurement at rest and an inability to fully close the eye, grade 5 barely perceptible movement and grade 6 no movement.

Rates of facial nerve function have been examined in relation to factors such as tumor size and surgical approach. It has been found that tumor size is the most significant predictor of post-operative facial nerve outcomes. For example Surghru et al, in their extensive literature review [41], found that patients with operated tumors greater than 2cm in size had overall rates of preservation of facial nerve function of 67%, while those with operated tumors less than 2cm had overall rates of 90%. Bloch et al [42] examined facial nerve outcomes of 624 patients who underwent surgery for VS and similarly found that tumor size is the most significant predictor of post-operative facial nerve function. Their results suggested that surgical approaches, extent of resection and patient age are not independent predictors of post-operative facial palsy. This result does vary in the literature however, with, for example, Ansari et al [39] reporting a significant difference in post-operative rates of facial nerve dysfunction between the different surgical approaches for patients with tumors less than 1.5cm in diameter (3.3% via the middle cranial fossa approach, 7.2% via a retrosigmoid approach, and 11.5% via a translabyrinthine approach). For tumors, larger than 1.5cm there was no statistical significance in the rates of facial nerve dysfunction post-operatively for the different surgical approaches. For larger tumors facial nerve...
outcomes are improved with subtotal and near-total resections, where the decision to accept such an outcome is guided by a concern for facial nerve preservation [43].

3.2.3 Cerebrospinal Fluid (CSF) Leak: Patients who suffer post-operative CSF leak typically require re-operation and repair, and are at increased risk of developing meningitis. There is a significant variability in reported rates of CSF rates post VS surgery in the literature. Mangus et al [44] quoted rates of, on average 10% post-operative CSF leaks, and reported that there was no significant difference in rates of CSF leaks between retrosigmoid, translabyrinthine and middle fossa approaches in their series of 1,922 operated patients. In another study, post-operative CSF leaks are quoted as 8.5% and as occurring more frequently in patients operated via a translabyrinthine approach [41]. This finding is reflected in other studies too; it is suggested that the rate of this complication can be reduced by modification of technique [45].

3.2.4 Postoperative Headache: Postoperative headache is common after VS surgery, as high as 75% in the immediate post-operative period and 16.5% in the longer term (>6 months post operatively). Rates have been found to be highest in patients undergoing surgery from a retrosigmoid approach, particularly in the short term. There are numerous suggestions as to why this is, including the size of muscle incision and retraction and the presence of intracranial bone dust [46].

3.2.5 Residual tumor and recurrence rates: The decision to leave residual tumor is typically conscious to preserve facial nerve function where it would otherwise be felt to be at risk, or to simply decompress the brainstem in patients with significant comorbidity and/or to attempt to preserve hearing [4]. Recurrences are thought to occur where there have been small fragments of tumor left, or deliberate partial resection [47], although a recurrence rate of 0.3% for completely resected tumors has been reported by one author [48]. There is evidence of growth in a proportion of patients who have residual tumor, with a small proportion requiring further treatment in the form of surgery or SRS [43]. Bennett et al [49] studied the need and timing for post-operative imaging and concluded that initial imaging should be performed at 1 year post-op, with only those patients with enhancement, subtotal resections, or
neurofibromatosis type II needing serial imaging. This policy understandably varies between Neurosurgical Units.

3.2.6 Morbidity and Mortality: Mortality rates, once over 84% are now quoted as 0.2% [41]. Morbidity rates, in terms of major neurological complications such as stroke, injury to lower cranial nerves and/or trigeminal nerve, persistent cerebellar dysfunction and seizures, are reported at rates between 1.8–2.6% [39], and do not vary significantly between the different surgical approaches. Infection rates, namely of meningitis, are quoted at 4% [41]. These morbidity and mortality rates are relatively low, but even uncomplicated procedures represent a significant trauma to patients, with Pritchard reporting that one-third of patients were unable to work following surgery for at least six months. He calculated that the mean loss of income to patients undergoing VS surgery as £11,220. Post-operatively 75% of patients were anxious that they wouldn’t ‘ever be normal again’ and 39% reported depression.

3.3 Radiotherapy
A number of approaches are used for patients with VS; stereotactic radiosurgery, stereotactic radiotherapy and proton beam therapy. Stereotactic radiosurgery is considered for tumors up to 2.5cm in extracanalicular diameter, and stereotactic radiotherapy for tumors up to 3.5cm in extracanalicular diameter, although there is an increasing body of evidence to suggest they can be used in larger tumors [50]. All these methods have the goal of arresting tumor growth while minimising the risk to adjacent structures. Its use is not widespread in patients with larger tumors, symptoms secondary to mass effect, or those with brainstem compression.

3.3.1 Stereotactic radiosurgery (SRS) delivers a single conformal dose of radiation to a tumor by utilization of multiple convergent beams. This therefore minimizes injury to adjacent structures including the trigeminal and facial nerves. Gamma Knife radiosurgery (GKRS) uses 192 fixed Cobalt-60 sources to deliver highly focused gamma rays. The linear accelerator (LINAC) delivers highly focused x-rays by using a single source rotated about the target in radiation arcs. SRS usually uses a single isocentre prescription technique and requires targets with spherical shape and maximum diameter less than 3 cm [51]. For GKRS the marginal dose is delivered at
the 50% isodense line (the points in tissues that get the same doses), while for LINAC it is prescribed at the 90% isodense line [52].

Early users of SRS used treatment doses of up to 22Gy, which showed over 95% tumor control rates with up to 10 years of follow-up but had high rates of cranial nerve toxicity with hearing preservation rates of 40% at two years and trigeminal and facial nerve palsies in 33% of patients. Therefore this dose was reduced to 12-13Gy in most centres giving local control rates of 91-100% at 10 years and trigeminal or facial nerve complication rates of below 5% [53]. Those patients with post-treatment tumor growth are managed by observation, further radiotherapy or surgery. Surgery post SRS is more surgically challenging, associated with the need for subtotal resection to try and preserve facial nerve function and prevent other complications [54].

A study analyzing tumor control rates with SRS in relation to pre-treatment growth rates found that patients with pre-treatment growth rates of less than 2.5mm per year had control rates of 97% at an average of 43.5 months post treatment, while those with pre-treatment growth rates of greater than that had tumor control rates of 69% in the same follow-up period [55]. This finding certainly warrants closer observation and more regular follow-up imaging for patient with high pre-treatment tumor growth rates.

Hearing preservation rates, even with lower radiation doses, are reported to decline to approximately 25% at 10 years [56] [57]. A recent systemic review comparing Gamma Knife radiosurgery with microsurgical resection in VS eligible for both treatments demonstrated overall better outcome after Gamma Knife radiosurgery [58]. However, given that radiation can affect neurologic function even after many years while surgery results in immediate neurological deficit, the length of follow-up in the various studies does influence the incidence of neurologic impairment after radiation treatment. Longer-term data (>10years) on lower dose stereotactic radiosurgery are lacking, particularly relevant to younger patients treated by this method.

Post-radiation tumor expansion, otherwise known as pseudo progression, is well reported following SRS, at rates of up to 23%, onset at 6 months and typically regression by 24 months post treatment [59]. Tumor progression beyond this time is therefore likely to be treatment failure, and therefore further intervention should be considered only at this stage, unless there is a clinical need to intervene before due to mass effect. Delayed cyst formation has been reported in 2% of patients at a median
of 6 years after SRS that required surgical management [56]. Malignant transformation is rare, estimated at 0.3% after SRS [56]. There are no reported cases of radiation induced tumors at 5, 10 and 15 years post SRS [60].

3.3.2 Stereotactic photon radiotherapy
Fractionated stereotactic radiotherapy (FSRT) delivers focused doses of radiation given over a series of treatment sessions. The intent of this method of treatment is to control tumor growth while reducing radiation injury to critical neural structures such as the facial nerve. Its main advantage over SRS is for irregularly shaped tumors, where it allows a more homogeneous and less conformal dose deposition. It does not have a radiobiological advantage compared to SRS as the nature of VS (slow growing non-hypoxic tumors) means that there is no biological benefit from fractionation and a larger total dose of radiation is delivered. A large series of patients with VS treated with FSRT of 18Gy in 3 sessions, showed tumor control rates of 99% at 3 years and 96% at 5 years. Serviceable hearing preservation rate was 76%, there was no case of post-FSRT facial weakness and 1% of patients suffering permanent trigeminal dysfunction [61]. In another large series, patients received doses of 25Gy in five fractions or 30Gy in 10 fractions. Over an average follow-up of 5 years, 3% had progressive growth requiring surgical intervention, 1.6% had new facial weakness, 2.8% had new trigeminal paraesthesias and 0.9% had hydrocephalus. 0.5% of patients in the series had possible, but not confirmed, radiation-induced tumors.

A recent systematic review comparing SRS and FSRT that included 19 case series concluded that tumor control rates were similar between the two modalities, that the risk of facial and trigeminal nerve deterioration was less for patients treated by SRS and that there was no significant difference in preserved hearing between the two groups. The authors of this review acknowledged that in forming this comparison of treatments they could only identify 2 studies reporting on long-term tumor control after FSRT [62].

3.3.3 Proton beam therapy
Proton beam therapy delivers targeted high energy protons to target tissue, damaging the DNA of the cells they are targeting. Most of the damage is thought to be indirect through the production of oxygen radicals rather than by direct collision with protons.
All protons of a given energy have a certain range, meaning that very few penetrate beyond that distance, with the dose delivered to tissue being maximized over the last few millimetres of its range (called the Bragg peak) which minimizes the dose to surrounding tissues. There are few papers studying the use of proton beam therapy for treatment of VS. Weber et al conducted a study that included 88 patients treated by proton beam SRS, and a follow-up period of 5 years, giving a dose of 160-MeV protons in 2-4 convergent beams [63]. They treated tumors up to 35mm in diameter. 5-year tumor control rate was 93.6%, 33% of patients with pre-treatment serviceable hearing retained their hearing, and 5 year facial and trigeminal nerve function rates were 91.1% and 89.4% respectively. It is clear that further studies are required to explore this method more fully, including the effects of altering dose as has been performed in studies of gamma knife SRS. The shortage of proton beam facilities and extra costs may make this modality unworkable at present for VS treatment in many countries.

4. Neurofibromatosis Type 2 and Vestibular Schwannoma Management

Patients with VS secondary to NF2 require a different management strategy from those patients with sporadic VS, with the goal of management being preservation of function and quality of life. When tumors are detected the risks of treatment versus the risks of observation have to be carefully balanced. Strategies for managing patients with NF2 and VS are observation, surgery, stereotactic radiosurgery and radiotherapy and targeted therapies, particularly the VEGF inhibitor bevacizumab. The complexity of decision making for this group of patients is highlighted by their proven improved outcomes when managed in specialty treatment centres [64].

Functional preservation should be central to all management decisions for patients with VS and NF2, as well as restoration at the time of treatment. Cochlear implantation and auditory brainstem implantation are hearing restoration options where hearing preservation is not possible with any form of tumor management. Cochlear implantation provides significantly better outcomes than auditory brainstem implantation. The best long-term hearing outcomes for patients with surgically managed VSs occur in those who have restoration surgery in the same setting [65]. This has also been found for facial nerve outcomes where facial nerve continuity is
lost at the time of tumor resection; immediate reconstruction gives the best outcomes [4].

The indications for conversion from observation to treatment in patients with VS and NF2 are brainstem compression, deterioration in facial nerve function and deterioration in serviceable hearing [66]. Surgery, while still the most accepted form of intervention, is more complicated in patients with NF2. Pathologically VS in NF2 differ from sporadic VS in that they tend to be more lobular in shape (mainly due to multifocality) and grow more quickly [67]. They may also envelop adjacent cochlear and facial nerves (again due to multifocality) rather than displacing them as do sporadic VS, which makes finding cleavage planes more complex [68]. Schwannomas of the facial and cochlear nerves can also co-exist with the VS. Surgically this means that VS in NF2 patients are more difficult to remove, and the risks of facial nerve dysfunction and hearing loss post-operatively are higher than their sporadic VS counterparts. These higher risks are particularly important to consider, especially for patients with bilateral disease. A recent study [69] reporting the outcomes of translabyrinthine surgery for VS in NF2 achieved total tumor excision in 66%, near total excision in 24%, subtotal excision in 5% and partial removal in 5%, with a radiological recurrence rate of 13.9%. 83.6% of patients had facial nerve function of House-Brackmann (HB) score of 1-3, and 53.4% had a HB score of 1 post-operatively. 15% of patients required shunts for post-operative hydrocephalus, and 21% of patients reported worsened post-operative tinnitus. The mortality rate was 1.6%. Hearing rehabilitation was attempted in many patients, with fifty-six patients undergoing auditory brainstem implantation (ABI). It is clear from these outcomes, from centres specializing in the management of patients with NF2, that VS in NF2 are rather different from sporadic VS and require special consideration.

Radiosurgery and fractionated radiotherapy have a role in management of VS in NF2 patients, particularly for those who are high-risk surgical candidates, are more elderly or for those who refuse surgery. Outcomes for radiosurgery and fractionated radiotherapy vary in the literature for VS in NF2 as they do for sporadic VS. Tumor control rates for NF2 VSs are reported at 85, 81, and 81% at 5, 10, and 15 years, respectively, with tumor volume being a significant predictor of control [70]. In the same study serviceable hearing preservation rate was reported as 73% at 1 year and
48% at 5 years, facial palsy in 8% and trigeminal neuropathy in 4%. A larger study of 122 VS from 96 patients showed a complete tumor control rate of only 50% at 8 years [71]. There are significant concerns, particularly in younger patients requiring treatment, of increased risk of secondary malignancies, both with stereotactic radiosurgery [72] and radiotherapy [73]. Patients should be counselled appropriately. Surgery, at present, is favored over radiotherapy for patients with NF2 that have a VS requiring intervention [74].

Progress in cellular research has enhanced understanding with regard to pathways in which the NF2 gene product interacts, and this has led to the trial and subsequent use of targeted therapies in NF2 patients. Three of the most studied targeted therapies in NF2 and VS are bevacizumab, everolimus and lapatinib. While these have shown benefit to select groups of patients, as yet their use as a treatment remains limited.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), thought to be of benefit in the treatment of growing VS because it prunes and regularizes tumor vasculature or has a direct antibody effect on overexpressed VEGF, thus halting tumor growth. One of the first trials of bevacizumab was in 2009, when 6 of the 10 patients treated had hearing improvement or greater than 20% reduction in tumor volume [75]. The same group has subsequently analyzed the outcomes of 31 patients with NF2 and VS managed with bevacizumab and found that 88% of patients had stable or decreased tumor size at 3 years, 54% at 5 years. 90% of patients had stable or improved hearing after 1 year, and 61% at 3 years [76]. These findings have led to bevacizumab being funded in the UK by the National Specialized Commissioning Team (NSCT) (NHS England). To be treated patients must have a schwannoma that is growing by at least 4mm/year (or 60% by volume), in whom the potential benefits of treatment outweigh the risks (for example of hypertension and altered renal and liver function) [77]. Treatment must be decided by a patient’s NF2 “hub” centre (Cambridge, London, Manchester or Oxford) as well as by a partner centre, or in the case of children, by all four centres [78].

Sixty-one patients with the rapid required growth showed high rates of tumor control/shrinkage and hearing preservation when treated with bevacizumab. The toxicities of bevacizumab have been reported widely in older cancer populations. Significant rates of hypertension and proteinuria have been reported with increasing
cumulative bevacizumab doses in the NF2 population [79]. This finding raises some concern in a population of largely young patients on long-term bevacizumab treatment.

Everolimus is an oral inhibitor of mTOR complex 1 (mTORC1). The mTOR signaling pathway has been identified as a major mediator of the tumor suppressor activity of merlin and therefore is an attractive therapeutic target in NF2 [80]. Studies have revealed that loss of merlin activates mTORC1 signaling, which is proven to reduce the growth of merlin-deficient arachnoidal, menigioma, and schwannoma cells [81]. In addition, targeting mTORC1 may inhibit production of vascular endothelial growth factor (VEGF) and therefore reduce tumor angiogenesis [82]. Results so far are mixed. Karajannis et al in their study of 10 patients did not see a volumetric or hearing response to everolimus [83]. Similarly Goutagny et al [84] studied the response of 10 patients to everolimus, and found that 40% of patients had progressive disease and 50% had stable disease. There was a reduced annual growth rate from 67% per year pre-treatment to 0.5% per year during treatment, with resumed growth after treatment had stopped. More studies are clearly needed.

Lapatinib is an EGFR/ErbB2 inhibitor, and abnormal activation of these growth factor receptors in NF2 patients is thought to be important in tumor development in patients with NF2 [85]. It was found to have anti-tumor activity in pre-clinical trials [86] and a good safety profile, and has therefore been trialed on NF2 patients with VS. Matthias et al [85] in their study of 21 eligible patients found volumetric and audiological response rates of 23.5% and 30.8% respectively over a treatment course of 12 months. In responders, the reduction in VS volumes ranged from −15.74% to −23.9%. Therefore, Lapatinib shows promise, but again more studies are required.
5. Conclusion

Vestibular schwannomas account for 85-90% of tumors in the cerebello-pontine angle in adults. Most are sporadic, typically detected incidentally or during the investigation of hearing loss, tinnitus and headache while approximately 5% develop as part of the tumor predisposition syndrome NF2, and a much smaller number as a consequence of the tumor predisposition syndrome schwannomatosis. The incidence of incidentally diagnosed VS is increasing with increased scanning rates for often-unrelated problems. Audiometry and MRI scans with gadolinium are the gold standard investigations for patients with suspected vestibular schwannoma. In those in whom NF2 is suspected, genetic testing must be conducted.

Once detected there are a number of strategies for management of VS. These differ for sporadic and NF2 related tumors. For sporadic tumors recommended strategies include observation (two-thirds of VS have been found not to grow, over an average follow-up of 3.6 years [21]), surgery and radiosurgery/fractionated radiotherapy. Treatment is recommended for large tumors presenting with mass effect and small but growing tumors. Radiosurgery and radiotherapy are limited to tumors 3.5cm or less in diameter [87], but for eligible patients, tumor growth control rates are reported at 91-100% at 10 years with trigeminal or facial nerve complication rates of below 5%. Surgery has mortality rates of less than 0.2%, and facial nerve preservation rates of up to 90% [41]. It can be performed through a number of approaches, typically the translabyrinthine route for patients with reduced or non-serviceable hearing, and the retrosigmoid approach for those with serviceable hearing who wish to try and preserve this if possible [32]. The current treatment options and potential indications in sporadic VS and NF2 and are outlined in tables 1 and 2. Interestingly there are no significant differences between the different treatment modalities of VS and their impact on quality of life. Rather it is the diagnosis of VS that has been found to make the most significant difference to quality of life [88].

A national audit of UK practice in the management of patients with sporadic VS showed that 69% of patients with VS are observed, 19% of patients undergo surgery and 12% undergo radiotherapy [89]. There are differences in practices between units
however, a reflection perhaps of the absence of clear long-term data as yet as to the most beneficial intervention for patients that require treatment for their VS.

In the UK patients with NF2 and VS are managed through one of four NF2 centres based in Manchester, Oxford, London and Cambridge. Management strategies in this group of patients should focus on quality of life, rather than tumor treatment per se. They include observation, with different parameters for intervention than patients with sporadic tumors, surgery, radiosurgery/radiotherapy and targeted therapies, of which bevacizumab is commissioned for use in the UK at present due to its good safety profile and tumor and hearing response rates [76]. Studies are on-going as to the efficacy of other targeted therapies such as everolimus [83] and lapatinib [85]. Response rates to treatment, both surgery and radiosurgery/radiotherapy are worse for patients with NF2 than sporadic tumors, with higher rates of neurological dysfunction, tumor recurrence and mortality in this group of patients [69][70].

It is clear that at present there is no single best treatment for every patient with VS, either sporadic or related to NF2. Patients must be fully informed as to their treatment options, and decisions made on a case-by-case basis. Since the early reports of VS surgery, with mortality rates of over 50% [10], VS management has come a long way and continues to do so. While it is clear that surgery will remain an essential method of managing patients with VS, there is a growing role for non-surgical treatment and this is likely to continue into the future.

6. Expert Commentary

One of the key weaknesses of VS management so far is the lack of long-term outcome data available for the different treatment modalities, in particular the non-surgical modalities such as radiosurgery and radiotherapy. This is particularly relevant to younger patients diagnosed with VS, in whom it would be extremely valuable to understand the long-term (10 year plus) outcomes for. Data on the role and outcomes of proton beam therapy is particularly lacking and further research should be directed towards this in the management of VS. There is also a wide variability in published outcomes for patients managed with non-surgical therapies; it would be helpful to
have a clearer understanding of why these differ to accordingly aid decision-making for patients.

Future research holds potential in two main avenues. One is further clinical research to help better define long term outcomes of the available treatment modalities, and to better understand and hopefully reduce the variability in reported outcomes that exist. The second avenue is further exploration of the cellular pathways that lead to VS occurrence and growth, for both sporadic VS and those related to tumor predisposition syndromes such as NF2 and Schwannomatosis. So far cellular research has enhanced understanding with regard to pathways in which the NF2 gene product interacts, and has led to the trial and subsequent use of targeted therapies in NF2 patients. It has, as we can see from the discussions above, a long way to go. Further research would be helpful in exploring if targeted therapies could be of value in sporadic VS too, as well as further exploring their use in NF2 patients with VS. Furthermore, an ability to predict which tumors hold growth potential and those that respond well to non-surgical therapies including targeted therapies would be of great value in the management of VS. It is, therefore, cellular research and targeted therapies that hold the most interest to us at present.

7. Five-year view

We believe that in 5 years we will have more long term data on non-surgical therapies, a greater understanding of cellular pathways that lead to development and growth of VS, and further targeted therapies, both for sporadic and NF2-related VS. We believe that there will be a continued improvement in outcomes for patients with VS, both in terms of long-term tumor control rates, and also the morbidity associated with treatments for this tumor.

8. Key issues

- The incidence of diagnosed VS is increasing worldwide.
- There is still a lack of clear consensus between units on the most appropriate management strategies for patients with VS, both sporadic and those related to tumor predisposition syndromes.
- Life expectancies are increasing.
• Long-term data for non-surgical management strategies are lacking, and there is still a significant variability in reported outcomes between different studies.

• Outcomes for patients with VS secondary to NF2 remain significantly worse than for those patients with sporadic tumors.

• Significant progress has been made on understanding cellular pathways that lead to development of VS, particularly for patients with NF2, which has led to the trial and use of targeted therapies. These are still at the early stages of use and investigation, and much work is still to be done to explore the uses and potential value of targeted therapies for patients with both sporadic and NF2-related VS.

Funding
This paper was not funded.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
References

Papers of special note have been highlighted as:
* of interest
** of considerable interest


* The outcomes of a large series of conservatively managed VS.


* An overview of the common surgical approaches for VS.


* Study highlights the difficulty of managing recurrent tumors after SRS. Consideration should be given to this when counselling patients and making decisions about treatment options.


** One of few papers outlining long-term outcomes of SRS for VS.


* A thorough overview of NF2.


30
**Outcomes of Bevacizumab treatment in a large UK-wide cohort of patients with NF2 and VS.**


**Investigated a very important subject; is there a difference in patient's quality of life with the different treatment options available?**

* A valuable overview of the spread and trends in UK practice of VS management.

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Potential Indications</th>
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| Observation “wait and watch” | - small stable tumors (<2cm)  
- elderly patients  
- high surgical risk due to co-morbidity  
- patient preference |
| Radiosurgery            | - small growing tumors (<2cm)  
- no brainstem compression  
- elderly patients/patients with significant co-morbidities with growing tumors that cannot undertake surgical risks  
- patient preference |
| Radiotherapy            | - small tumors (<2cm) with an irregular outline  
- no brainstem compression  
- patient desire for serviceable hearing preservation if possible |
| Surgery                 | - large (>2cm) tumors not suitable for observation or radiosurgery/radiotherapy  
- small growing tumors (<2cm)  
- brainstem compression  
- symptoms and signs secondary to mass effect  
- patient preference |

Table 1: Treatment options for patients with sporadic VS and potential indications for each.
<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Potential Indications</th>
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<tbody>
<tr>
<td>Observation “wait and watch”</td>
<td>- small tumours with no mass effect and no growth or slow growth</td>
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<tr>
<td></td>
<td>- patients with small tumours and serviceable hearing</td>
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<tr>
<td></td>
<td>- patient preference</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>- tumour growing by at least 4mm/year (or 60% by volume)</td>
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<td>- potential benefits of treatment outweigh the risks</td>
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<td>- agreement for appropriateness of treatment at ‘hub’ centre and partner centre for adults, all four ‘hub’ centres for children.</td>
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<tr>
<td>Surgery</td>
<td>- large tumours with brainstem compression</td>
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<tr>
<td></td>
<td>- rapidly growing tumours with a high risk of developing brainstem compression</td>
</tr>
<tr>
<td></td>
<td>- deterioration in facial nerve function</td>
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<tr>
<td></td>
<td>- deterioration in serviceable hearing</td>
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<tr>
<td>Radiosurgery/radiotherapy</td>
<td>- small tumours without mass effect but demonstrable growth</td>
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<tr>
<td></td>
<td>- more elderly patients with mild phenotype</td>
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<td></td>
<td>- patient is a high risk surgical candidate</td>
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<td></td>
<td>- patient preference</td>
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**Table 2:** Treatment options for patients with VS and NF2 and potential indications for each.