List of Abbreviations

CPA: Cerebello-pontine angle

GTR: Gross total resection

IAC: Internal auditory canal

NF2: Type 2 neurofibromatosis

PTA: Total auditory loss (perte totale d'audition)

Retrosig: Retrosigmoidian surgical approach

SDS: Syllable discrimination threshold (seuil de détection des syllabes)

S/M: Schwannomin / merlin protein

Sub-occ: Sub-occipital approach

Translab: Translabyrinthine approach

VS: Vestibular schwannomas

VSTR: Vestibular schwannomas tumor remnants

Plan

Introduction

Vestibular schwannomas (VS), historically called acoustic neuromas, are histologically benign tumors arising from the Schwan-cells. Due to their histologically benign nature, the complex anatomy of the cerebello-pontine angle (CPA) and the morbidity and mortality related to surgery, the therapeutic management of vestibular schwannomas remains a major challenge.

History, Epidemiology of VS

History

VS were first described by Sandifort in 1777 as a neuroma or neurilemoma. It was only at the end of the 18th century, with the work of John Hunter, that the clinical symptomatology of these tumors began to be understood. At the end of the 19th century, the knowledge of the clinical presentation and evolution of the VS allowed physicians to make the diagnosis of VS not only during post-mortem examinations but also in live patients.

In 1895, Annandale was the first to successfully surgically remove a vestibular schwannoma in a 25 year-old pregnant woman, who afterwards gave birth under normal circumstances.

Epidemiology

VS represent 9% of brain tumors, 25% of posterior fossa tumors and are the most common tumor of the cerebello-pontine angle with 80% prevalence (1).

The incidence of VS is 2/100,000 per year, currently increasing as the initial size at diagnosis decreases. These changes in the epidemiology of the VS are described as a consequence of the multiplication of brain MR-scan investigations, leading to an increase of incidental radiological diagnosis without clinical symptoms (2, 3). The occurrence of VS is more common in women from 40 to 60 years of age.

VS are sporadic tumors in 95% of cases. But in 5% of cases, their occurrences are related to type 2 neurofibromatosis (NF2). In fact NF2 patients almost systematically

present an occurrence of VS. VS in NF2 patients are often bilateral, among the usual clinical features of neurofibroma and plexiform neuromas.

Pathology and pathophysiology of VS

Pathology

VS are extra-axial, benign tumors arising from the Schwann cells constituting the myelin sheath of the VIIIth nerve. The most common site of genesis of VS is the Obersteiner-Redlich zone, defined as the junction of the cranial nerve between the central and peripheral myelination.

Macroscopically, VS are usually described as a unilateral lonely firm yellow / brown tumor without a distinct capsule. These tumors drive back the vestibular nerve without invading it and push on the arachnoid sheath. The persistence of a thin arachnoid sheath around the tumor is described and used during surgery to help the dissection of the tumor (Figure 1).

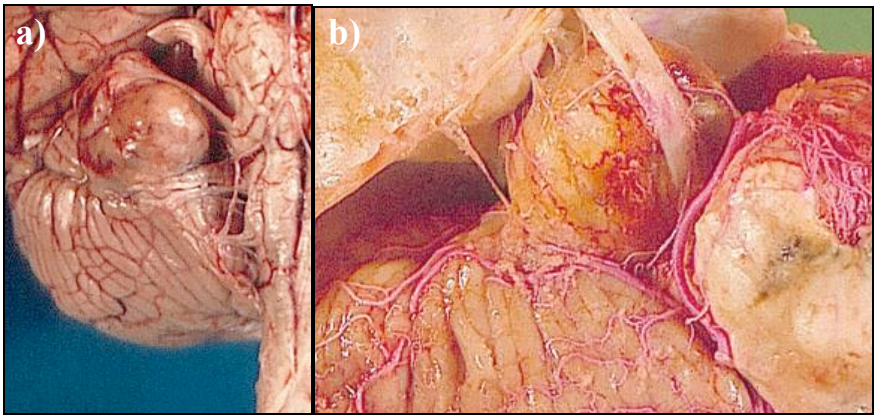


Figure 1: Macroscopical aspect of VS

a) Frontal anterior view of a VS in the right cerebello-pontine angle

b) Closer superior view of a VS in the left cerebello-pontine angle

Microscopically, 2 different types of structure coexist: the dense fibrillar tissue (Antoni A) composed of compact fusiform cells, reticulin and collagen and the faint reticular tissue (Antoni B), made of loose stellate round cells in stroma. Also, anuclear palissading cells called Verocay bodies can be observed in VS tumors (Figure 2).

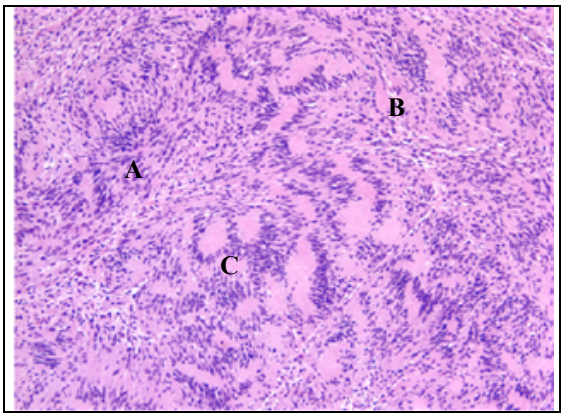


Figure 2: Microscopical aspect of VS
Magnification x50, hematoxylin-eosin-safron staining
A: Antoni A fibers, B: Antoni B fibers, C: Verocay bodies

Pathophysiology

Most of the recent understanding of pathophysiological mechanisms responsible for the genesis and growth of VS came from the study of NF2 patients.

NF2 gene is located on chromosome 22q12. This gene is expressed at high levels during embryonic development and in an adult's life, in the Schwann cells, the meningeal cells, the lens and the nerves.

This NF2 gene leads to the production of a protein called schwannomin/merlin (S/M). S/M is a 590 amino-acid protein, related to a family of cytoskeleton-to-membrane protein linkers and has been shown to interact with cell-surface proteins (Figure 3). These proteins are involved in cytoskeletal dynamics and in regulating ion transport as well as motility and growth of the Schwann cells by their interaction with CD44 and RhoGTPases. The NF2 gene acts as a tumor suppressor gene. Its alteration is the cornerstone of the Schwann cells proliferation and the genesis of VS, leading to the absence of expression, or the expression of a non-functional S/M protein by the Schwann cells.

In non-NF2 patients with a sporadic unilateral vestibular schwannoma, it has been shown that in 60% of cases a gene mutation leading to the production of a non-functional variant of S/M or the absence of its production is observed. In the remnant cases, it may be supposed that the expression of S/M is regulated by epigenetic factors and the action of protein cascades like caspases (4).

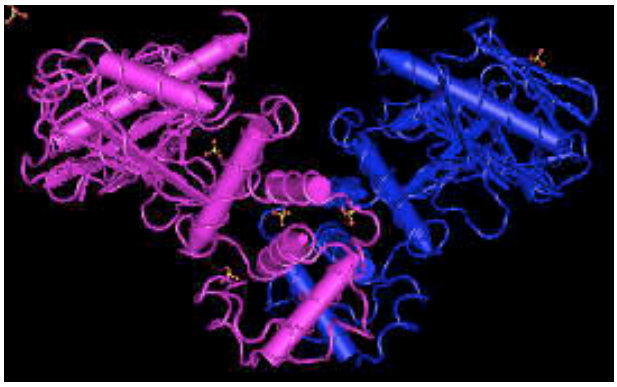


Figure 3: 3D modeling of the schwannomin/merlin (5)

Clinical presentation of VS

The clinical presentation was well described by Cushing and updated and summarized by Pertuiset in 1970 (1, 6). They described that typically the clinical presentation of VS is progressive and evolves gradually into 2 successive groups of clinical signs: the otological signs and then the neurological signs.

Otologic symptoms

The otologic symptoms are the first to occur. They are characterized by a unilateral perception hearing loss, tinnitus and vestibular signs.

Neurologic symptoms

Afterwards the neurologic signs appear. They are caused by the shift and mass effect induced by the VS on the brainstem. Neurological signs like ataxia, gait disturbance, facial function impairment and hydrocephalus may be noticed. Among the neurological signs, the search for cranial nerve impairment is critical and conditions the therapeutic management of VS. For example, V^{th} cranial nerve impairment will be searched for with the corneal reflex. Its impairment is the sign of an ocular risk with an increased risk of keratitis. VII^{th} cranial nerve impairment, which is important for the post-operative facial prognosis and surgery, is searched for and quantified using the House-Brackmaan scale (7)(Table I).

Table I: House-Brackmann classification for facial palsy

Grade	Definition
I	Normal symmetrical function in all areas
II	Slight weakness noticeable only on close inspection Complete eye closure with minimal effort Slight asymmetry of smile with maximal effort Synkinesis barely noticeable, contracture or spasm absent
III	Obvious weakness, but not disfiguring May not be able to lift eyebrow Complete eye closure and strong but asymmetrical mouth movement with maximal effort Obvious, but not disfiguring synkinesis, mass movement, spasm
IV	Obvious disfiguring weakness Inability to lift brow Incomplete eye closure and asymmetry of mouth with maximal effort Severe synkinesis, mass movement, spasm
V	Motion barely perceptible Incomplete eye closure, slight movement corner mouth Synkinesis, contracture, spasm usually absent
VI	No movement, loss of tone, no synkinesis, contracture, or spasm

However, usually, neurological symptoms tend to no longer be observed in most cases. In fact patients with ontological symptoms have complementary examinations. The sensitivity of auditory evoked potentials and the easy and early use of the MR-scan to investigate any unilateral perception hearing loss has led to the radiological diagnosis of small intracanalar VS of few millimeters in size, without the usual constellation of signs described in previous publications before the MR-scan era.

Complementary examinations

Audiometry

Both tonal and vocal audiometries are performed in the audiometric screening. A unilateral perception surdity associated with an early impairment of intelligibility is the main feature observed in VS.

The criteria to define and analyze this hearing loss and to guide the therapeutic management decision were defined in the Tokyo consensus. The Tokyo criteria use both the tonal and vocal audiometry to highlight the functional audition (8). The most common feature in tonal audiometry is an asymmetrical high-frequency sensorineural hearing loss (Figure 4).

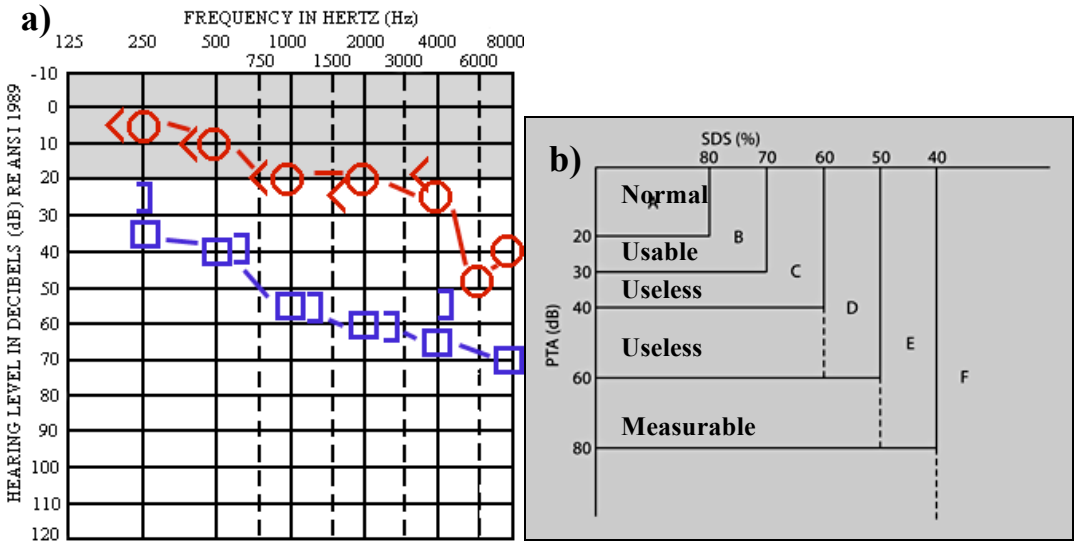


Figure 4: Audiometric investigations for VS diagnosis

a) Tonal audiometry in VS patient, courtesy of Prof. Timothy Hain.

b) Classification diagram of hearing according to the Tokyo consensus meeting.

PTA: Total auditory loss *SDS: Syllable discrimination threshold*

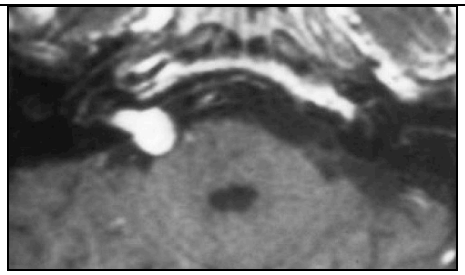
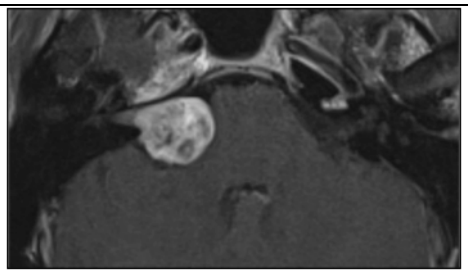
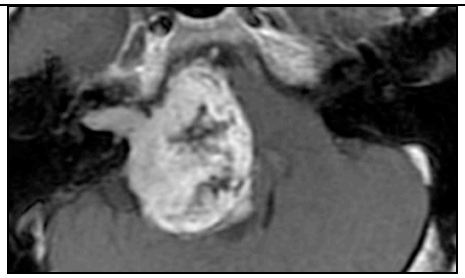
MR-scan

For the radiological diagnosis and evaluation of VS, the MR-scan has replaced the CT-scan and has been established as the gold standard, with a sensitivity and specificity up to 100%. The Koos classification is the most commonly used in diagnosis and therapeutic management of VS (9) (Table II).

The most commonly used sequences are T1-weighted sequences with and without gadolinium enhancement, T2 weighted sequences with High-resolution (CISS) and T2-FLAIR weighted sequences. The spatial resolution is sufficient with a slice thickness of 1mm and a slice spacing of 0.8 mm allowing 3D reconstruction.

The major role of the MR-scan in the diagnosis of VS should not exempt the use of a CT-scan with 3D reconstruction in bone window for the pre-surgical planning. This exam will allow physicians to assess the pneumatization of the mastoid bone, the procidence of the jugular bulb, which conditions the surgical approach, and the existence of a protrusion of the posterior canal, useful if the audition is to be preserved.

Table II: Koos classification of VS

Grade	Definition	MR-scan illustration
I	Intracanalar tumor	
II	Tumor spreading in the cerebellopontine angle without reaching the pons	
III	Tumor touching the pons, perhaps deforming it but without shifting it	
IV	Tumor deforming the pons and shifting the 4th ventricle	

Therapeutic management options

VS are benign tumors, which do not recur after complete removal. Their localization in the cerebello-pontine angle, their benign histological nature and the potential surgical morbidity and mortality due to the anatomical complexity of the cerebello-pontine angle make their treatment a technical challenge.

There are 3 main possibilities in management of VS: surgery, radiosurgery or a "wait-and-see" policy, consisting of a simple clinical follow-up with regular MR-scans.

Decision management of VS is complex, depending on a multitude of factors influencing the therapeutic attitude.

Historical management of VS tumors

The evolution of the therapeutic management of VS follows the evolution of Neurosurgery. 2 main periods can be described: the Neurosurgical period and the Otoneurosurgical period.

The Neurosurgical period

The Neurosurgical period took place in the first 60 years of the 20th century, with eminent figures like Cushing, Dandy and House. At this time, the goal of the surgery was to save the life of a bed-ridden patient in a life threatening condition due to large VS compressing the brainstem. The only therapeutic option was surgery with a sub-occipital approach. This surgical procedure was complex and had a mortality rate of 15.4% for partial resection with Cushing (1) up to 30% for complete resection with Dandy (10), and an almost systematic post-operative ipsilateral facial palsy.

The Otoneurosurgical period

The Otoneurosurgical period began at the end of the 1950s with the growing implication of Otologists in the diagnosis and treatment of VS. At this time, the diagnosis was refined and made at an early stage with a predominance of otological signs making VS patients “otological patients” rather than neurosurgical patients. This modification in the VS patient recruitment had a direct impact on the therapeutic objectives. VS surgery became more a functional surgery to avoid the appearance of neurological signs rather than a life-saving procedure, the primary therapeutic objective became the removal of the tumor with post-operative functional consequences. Otologists were the first to use peroperative microscopy (11) and they soon suggested transpetrous approaches.

Nowadays

The current trend in the therapeutic management of VS is the conservation of the facial function after surgery, before the complete resection of the tumor. For this, new approaches have been developed, with 2-stage surgery or planned sub-total surgery with

secondary radiosurgery (12, 13). Post-surgical mortality has become rare and post-surgical morbidity and facial palsy have decreased with the use of these techniques.

More recently, some surgical teams have even extended the indication of primary radiosurgery for large VS (14).

Surgery

Different surgical approaches have been described. Each technique has its advantages and disadvantages, and the preferential use of one technique is also dependent on the surgical team's experience.

Whatever the surgical approach used, there are several common techniques: operative microscope, microsurgical instrumentation, ultrasonic vacuum and continuous per-operative facial nerve monitoring.

Historically, the suboccipital approach was the first described and used by Cushing to perform the first VS resection. This surgical approach is currently suspended due to per- and post-operative complications caused by the seated position of the patient and the absence of visualization of the intracanalar portion of the tumor making a complete resection impossible.

Translabyrinthine approach

The translabyrinthine approach is one of the surgical approaches used nowadays. It was first described by Panse in 1904 and popularized by House with the publication of a group of 53 patients in 1964, with a sharp decrease in mortality and post-surgical facial palsy, with a 7% mortality rate and a normal facial function in 72% of cases in a group of 200 patients in 1968 (15, 16).

It is the elective surgical approach for large VS Koos III or IV, with an ipsilateral cophosis (Tokyo score C or worse) because this technique requires drilling the temporal bone and going through the cochlea and the semi-circular canals. Also, procidence of the jugular gulf and pneumatization of the mastoid bone should be assessed prior to surgery, an important procidence or a poor mastoid pneumatization may push the physician towards a retrosigmoid approach (17).

For this technique, the patient is placed in a dorsal decibitus position. Then the surgeon performs a retro-auricular incision, followed by a craniotomy by drilling the mastoid bone and the labyrinth. For the translabyrinthine drilling, the borders of the

craniotomy are the middle fossa's dura mater in cranial, 2cm after the bare sigmoid sinus in dorsal, the jugular gulf in caudal and the posterior face of the internal auditory canal in frontal. After opening the dura mater, the facial nerve is identified, the dissection of the VS begins with the cisternal portion with tumor volume regression allowing the physician to gradually continue the dissection of the VS from the facial nerve towards its apparent origin form the pons, and towards the internal auditory canal (18) (Figure 5).

The advantage of this technique is to offer a large exposure of the internal auditory canal and a good visualization of the facial nerve without retraction of the cerebellum, making this surgical approach the best option for a complete removal of the VS with optimal facial function preservation.

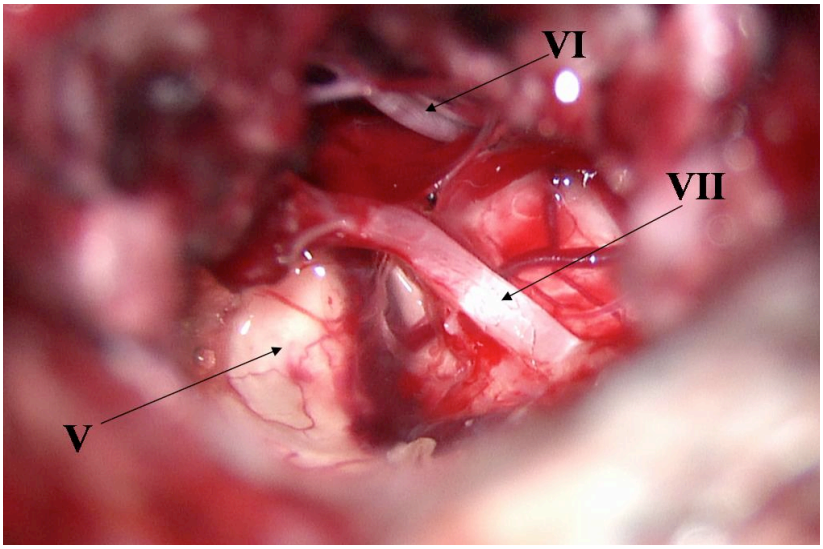


Figure 5: Cranial nerves and tumor exposure using the translabyrinthine approach

Retrosigmoid approach

The retrosetrosigmoid approach is the second most often used surgical approach for VS. This is a versatile approach, well known by most neurosurgeons, allowing a wide access to the cerebello-pontine angle. It allows access to the internal auditory canal with a trajectory parallel to the petrous bone.

It is the elective surgical approach for large VS with serviceable hearing, whereas a translabyrinthine approach would normally be considered appropriate (18).

For the procedure, the patient is placed in the park-bench position. First, the surgeon locates the cutaneous projections of the transverse sinus with the horizontal line crossing the inion, and the sigmoid sinus with the vertical line crossing the tip of the mastoid. Then, an S-shaped incision crossing the projection of the transverse sinus is

performed, followed by a retrosigmoidian craniotomy limited at the front by the sigmoid sinus and at the top by the transverse sinus, with careful obturation of the mastoid air cells to prevent cerebrospinal fluid leakage. The dura mater is open and a retractor gently placed on the cerebellum (Figure 6). The posterior lip of the internal auditory canal is then drilled to expose the intracanalar portion of the tumor (18, 19). Afterwards, the surgeon proceeds with the gentle removal of the VS, as described in the translabyrinthine approach, with continuous monitoring of the facial nerve.

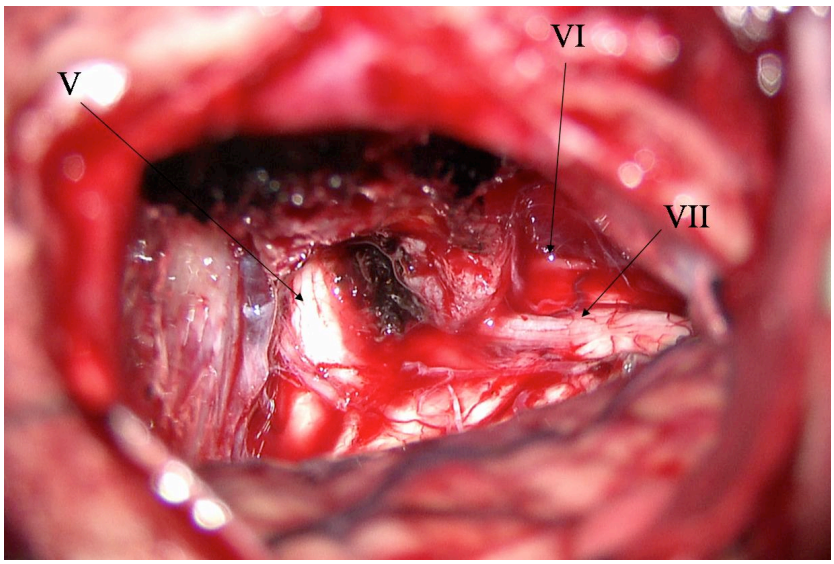


Figure 6: Cranial nerves and tumor exposure using the retrosigmoidian approach

The advantage of the retrosigmoidian approach compared to the translabyrithine approach is the possibility of hearing preservation at the price of an insufficient exposure of the internal auditory canal, thus making the GTR more difficult. This technique is described by Samii as providing sufficient access to the area and offering the possibility of complete tumor removal in a safe way with a very low complication rate and a good hearing preservation rate in small VS (20). However these results are discussed concerning the hearing preservation rate and, to our opinion, the surgeon should favor the translabyrinthine approach compared to the retrosigmoidian approach, to focus on an optimal resection of VS.

Radiosurgery

The use of radiosurgery is the most recent therapeutic advance in VS management. This technique was developed by Lars Leksell in 1951 and tested for the first time in the

treatment of trigeminal neuralgia (22). The first stereotatic radiosurgical treatment of VS was performed in 1969 (23).

The goal of radiosurgery is to stop the growth of the VS and preserve cochlear and other cranial nerve function. The long-term benefits of radiosurgery in VS control have established this technique as an important minimally invasive alternative technique to microsurgery for Koos I-III VS (24).

Prior to the procedure, a sterotactic frame is attached to the head of the patient and a MR-scan is done with a high resolution T2-weighted sequence to show the cranial nerves and the internal auditory components like the cochlea. Afterwards, a multidisciplinary team composed of a neurosurgeon, a radiation oncologist and a medical physicist does the radiosurgical dose planning. This planning is critical to allow an optimal dose to be delivered to the VS without harming the peripheral structures. Then, after the validation of the radiosurgical planning, the patient is installed in the Gamma-knife and the planned dose is delivered. Patients are observed for a few hours and are discharged from the hospital in less than 24 hours (24).

The main advantage of this technique is its non-invasive character, with a low risk of complication, allowing an ambulatory management of patients.

However, radiosurgery is not the recommended option for therapeutic management for patients with large VS, especially with neurological symptoms, because of the delay between the radiosurgery and its effect and the risk of a transient tumor swelling after radiosurgery that may worsen the symtomatology.

Despise these known risks, recent studies tends to suggest radiosurgery even for large VS with an acceptable control rate and hearing preservation, at the price of an increased regrowth and post-surgical morbidity compared to radiosurgery in smaller VS (14).

"Wait-and-see"

As VS are benign tumors with a slow progression, a late onset of clinical symptoms compared to the development of the tumor, and therapeutic options with potential side effects, the option of a simple follow-up may be discussed.

The goal of this attitude is to delay the therapeutic management if possible until the remaining days of life in the elderly, and to defer potential adverse effects of the treatment for as long as possible in young patients. The patient has a clinico-radiological follow-up, with regular clinical examination and MR-scan, every 6 months in our department.

With this “wait-and-scan” policy, Konziolka describes a growth rate of 70% at 5-years and 95% at 10-years after diagnosis (25). Huang reports a spontaneous regression rate of 3.8% with simple follow-up on a series of 1261 VS (26).

This makes a “wait-and-see” policy a viable alternative to surgery and radiation, especially in small VS koss I-II and the fortuitous VS discoveries on MR-scans.

Therapeutic management issues of post-surgical VS remnant

As we saw before the previous trend in therapeutic management of VS was to treat surgically with a complete resection even at the price of an impairment of the facial function. But nowadays, facial palsy is considered as a severe handicap by the patient and is no longer considered as an acceptable post-operative result. This attitude has led to a change of approach with the preservation of the facial function as the first aim of the surgery, before the complete resection of the VS (27-29).

Surgeons prefer to leave a small remnant instead of risking the facial function of the patient by performing a complete resection, and this change of attitude in VS surgery is leading to an increase in the prevalence of post-operative vestibular schwannoma’s tumor remnants (VSTR), which makes the problematic of VS remnant’ management a more frequent question.

There is no defined therapeutic attitude towards this VS remnant. Some surgical teams recommend systematical radiosurgery (12, 30-34) while other teams have adopted a “wait-and-see” attitude (35, 36).

Despite being safe compared to surgery, radiosurgery is not without potential side effects and complications especially in a post-surgical cerebello-pontine angle, and its place as a systematic treatment of VS post-surgical remnant is widely discussed.

Objectives of the study

The objectives of this original study are to define the best therapeutic attitude towards post-surgical VS remnant tumors and to identify the factors of VS remnant progression.

Methods

Patient population

Every patient who underwent surgical treatment of VS in the Department of Neurosurgery of the University Hospital of Angers between 1977 and 1st May 2013 were included. All patients had a planned gross total resection (GTR). The surgical indication was the appearance of neurological symptoms or hydrocephalus. Most of the VS were stage III or IV on the Koos classification, and no longer had a useful hearing capacity before surgery, with a Tokyo score of C or worse (8, 9). The diagnostic was confirmed histologically in all cases.

Surgical technique

A multidisciplinary team, composed of a neuro-otologist and a neurosurgeon performed the surgical procedures. The primary surgical objective was the GTR and internal auditory canal decompression, with preservation of the facial function. The facial function was continuously checked during the intervention by facial nerve monitoring. The surgical procedure was halted when the facial nerve stopped responding to neurostimulation during surgery or when the surgeon estimated that the benefit/risk ratio regarding facial function preservation was weighted against the GTR of the tumor, and chooses to leave a small tumor remnant to avoid any facial nerve lesions.

Clinico-radiological follow-up

All patients benefited from a multidisciplinary follow-up by their neuro-otologist and neurosurgeon with regular consultations and control MR-scans.

The first MR-scan and first consultation were performed 3 months after surgery. Therapeutic attitude towards the VS remnant was then decided on depending on the size of the residual tumor and the age of the patient.

Follow-up was then at six months and then yearly after the first post-op consultation with clinical and MR-scan surveillance.

MR-scans were carried out with a 1.5 T Siemens Magnetom MR-scan. The chosen sequences were T1-weighted with and without gadolinium enhancement, T2 High-

resolution (CISS) and T2-FLAIR weighted, each with a slice thickness of 1mm and a slice spacing of 0.8 mm allowing for 3D reconstruction.

Data collection and Analysis

We did a retrospective study on patients treated or followed up for a VS in the Department of Neurosurgery of the University Hospital of Angers since its opening in 1977. The primary end-point for data collection and survival analysis was fixed at the 1st May of 2013.

All the files of patients treated surgically with a planned GTR and with a per-operative tumor remnant described by the surgeon were collected and analyzed. Patients with a per-operative tumor remnant and a "wait-and-see" therapeutic management of the VSTR were included for statistical analysis.

The following datas were collected:

- Age at diagnosis
- The initial VS size (in cm^3)
- Koos stage
- Existence of a cystic component
- Existence of a type 2 neurofibromatosis (NF2)
- Surgical access
- Per-operative tumor remnant size, estimated by the surgeon
- VSTR location
- VSTR size at each consultation during follow-up (in cm^3)
- Follow-up duration in months and the reason and the secondary therapeutic decision made.
- Facial nerve function before, after surgery and at the primary end-point using the House-Brackmann classification (7)

The volume of the VS initial size and the VS remnant size was calculated for each MR-scan using a contrast enhanced T1-weighted sequence with a slice thickness of 1mm and slice-spacing of 0.8 mm allowing for 3D reconstruction. The 3-plane tumor radii were measured on DICOM images using a multiplanar reconstruction mode (37).

Statistical analysis was then undertaken with two-sample T-tests, or ANOVA followed by a post-hoc test, for the descriptive and comparative analysis of the different subpopulations. A Cox-model and Kaplan-Meier survival analysis were undertaken in the search for the remnant's recurrence factors with remnant progression defined as the main event.

The regression of the VSTR was defined by the reduction by at least 25% of the VS volume between two successive MR-scans whereas progression was defined by an increase of at least 10% in volume.

The most appropriate timing of the post-surgical MR-scan checkup being subject to discussion (38), datas were analyzed and VSTR evolution assessed with a MR-scan reference done 3 months or 1 year after surgery.

Results

Description of the population in the study

Among the 600 patients followed in our Department of Neurosurgery for VS, 256 underwent surgery and 65 patients presented a per-operative VSTR described by the surgeon, meaning a GTR rate of 74.6% (Figure 7).

In this population of 65 patients, 17 patients with a VSTR observed per-operatively by the surgeon didn't have a radiologically confirmed GTR. This gives a concordance rate of 74% between the surgeon's appreciation and the MR-scan check with an overestimation of the presence of a VSTR by the surgeon. In addition, 1 patient died of meningitis before the first checkup MR-scan and 1 patient dropped out of the study due to a transfer to another University hospital to be closer to his home for post-operative surveillance and follow-up.

Among the 46 remaining patients with a per-operative VSTR confirmed on the first checkup MR-scan, three sub-populations with different therapeutic management approaches were defined: 2 young patients had a planned 2-staged GTR and underwent a

second surgical intervention just after the first checkup MR-scan, 4 young patients with a large VS remnant were referred immediately to radiosurgery and 33 patients underwent a simple follow-up. We excluded 7 patients who had recently undergone surgery and hadn't had a checkup MR-scan after the beginning of the clinico-radiological follow-up to allow the radiological assessment of VSTR evolution (Figure 5, Table III).

Therefore we included in our study the 33 patients who had a per-operative VSTR confirmed on the first MR-scan and underwent a simple follow-up.

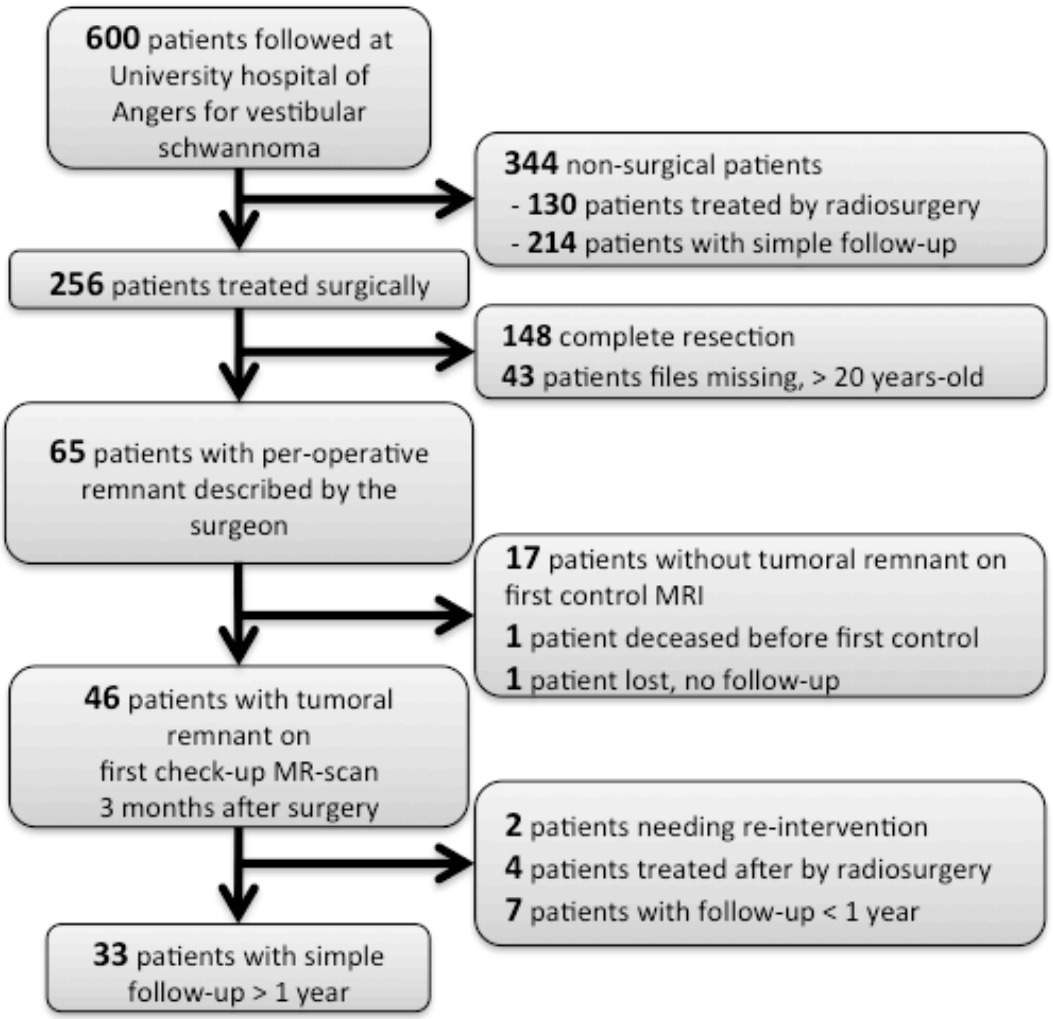


Figure 7: Flow-chart of the population of VS patients followed at the University Hospital of Angers

Table III: Characteristics of the population

	Population n= 33
Age at diagnosis (year)	52,4 ± 15,1
Initial volume before surgery (cm^3)	9,8 ± 6,4
Koos stage	
- *III*	11 (33 %)
- *IV*	22 (67 %)
Cystic component	8 (24 %)
NF2	3 (9,1 %)
Surgical access	
- *Translabyrinthine*	28 (85 %)
- *Retrosigmoidian*	3 (9 %)
- *Sub-occipital*	2 (6 %)
VSTR location	
- *CPA*	19 (58 %)
- *IAC*	5 (15 %)
- *Porus*	9 (27 %)
VSTR size at first checkup MR-scan	0,75 ± 2,36
Follow-up duration (months)	60 ± 65,3
Pre-operative facial function	1 ± 0,2
Post-operative facial function	2,53 ± 2
Facial function at end-point date	2 ± 1,66

Evolution of the "wait-and-see" population

Among patients with VS, we must distinguish patients with NF2. Indeed, their different pathophysiological features make them stand out from the non-NF2 population by their clinical evolution, the number of lesions, their evolution and the different histology (39-41). So, to refine our analysis and to differentiate the potential therapeutic management approaches between NF2 and non-NF2 patients, we decided to continue our analysis only with non-NF2 patients. The evolution of the NF2 patients will be discussed in a separate paragraph.

"Wait-and-see" non-NF2 patients with reference MR-scan 3 months after surgery

In this population of 30 non-NF2 patients, three months after surgery, we observed a progression of the VSTR in 7% of the population, 50% with tumor remnant stability and 43% with spontaneous regression (Figure 8).

The average follow-up duration was 45 months for the patients with a spontaneous VSTR regression, 57 months for the stable group and 48 months for the progression group (Table IV). No statistical difference was shown between the different durations of follow-up (p=0,84).

Univariate analysis showed a significant association between an impaired facial function after surgery and the progression of the post-surgical VSTR in non-NF2 patients (p= 0,02 in univariate analysis). We also observed a strong association between large VS before surgery and a large VSTR with the risk of recurrence (both p= 0,06)(Table IV).

In multivariate analysis, the VS remnant size is significantly higher in the progression group versus the stable group (p=0,039). Despite this interesting result, there isn't a statistical association between VS remnant size and progression (p=0,097 in multivariate analysis).

Table IV: Univariate analysis and description of the evolution of VS TR in the non-NF2 "wait-and-see" population

	Regression n=13	**Stability n=15**	**Progression n=2**	**p value**
Age at diagnosis (year)	55,3 ± 12,3	48,9 ± 17,9	62 ± 22,6	*0,64*
Initial volume before surgery (cm^3)	7,4 ± 7,2	11 ± 6	14 ± 1,8	*0,06*
Koos stage				*0,67*
- III	5 (38 %)	6 (40 %)	-	
- IV	8 (62 %)	9 (60 %)	2 (100 %)	
Cystic component	3 (23 %)	3 (20 %)	1 (50 %)	*0,67*
Surgical access				*0,59*
- Translabyrinthine	12 (92 %)	13 (87 %)	2 (100 %)	
- Retrosigmoidian	1 (8 %)	1 (6,5 %)	-	
- Sub-occipital	-	1 (6,5 %)	-	
VSTR location				*0,17*
- CPA	5 (38 %)	11 (73 %)	1 (50 %)	
- IAC	4 (31 %)	1 (7 %)	-	
- Porus	4 (31 %)	3 (20 %)	1 (50 %)	
VSTR size at first checkup MR-scan	1,1 ± 3,1	0,1 ± 0,2	14 ± 1,8	*0,06*
Follow-up duration (months)	44,6 ± 26,7	56,6 ± 67,8	48 ± 14,1	*0,84*
Pre-operative facial function	1 ± 0	1,1 ± 0,3	1 ± 0	*0,16*
Post-operative facial function	2,7 ± 2,2	1,9 ± 1,6	5,5 ± 0,7	***0,02***
Facial function at end-point date	1,9 ± 1,9	1,7 ± 1,3	4 ± 2,8	*0,47*

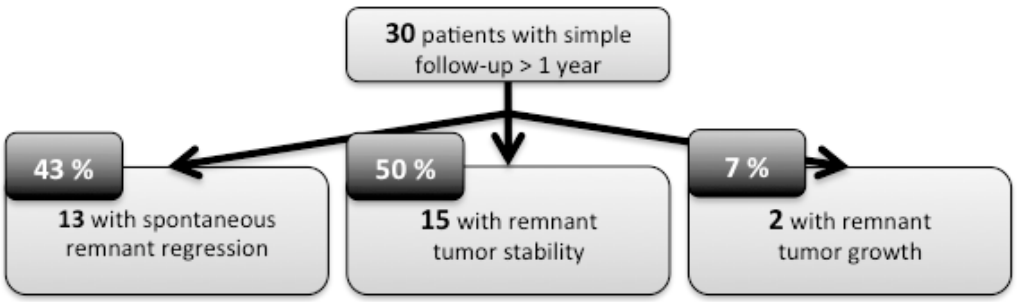


Figure 8: Description of the population of VS non-NF2 patients with a per-operative VSTR described by the surgeon. First checkup MR-scan 3 months after surgery

"Wait-and-see" non-NF2 patients with a reference MR-scan one year after surgery

The delay between surgery and the first post-operative MR-scan is subject to debate, usually done 3 to 12 months post-op. The main risk with an early post-operative MR-scan is the confusion with a post-operative tumor remnant and post-operative scar tissue, leading to a false underestimation of the GTR rate. To minimize this risk, we analyzed the population and the evolution of VS post-surgical remnant using the 1-year post-op MR-scan as a reference.

16 patients were included in this population. Compared to the population of NF2 patients with a first MR-scan 3 months after surgery, 9 patients had an insufficient follow-up duration and thus were excluded. Also, 5 patients were excluded and considered as GTR because of the complete regression of their VSTR remnant between the 3 months post-op MR-scan and the 1-year MR-scan.

In this population, we observed a progression of VSTR in 12.5% of the population, 62.5% with stability and 25% with spontaneous regression (Figure 9). The average follow-up duration was 43 months for the patients with a spontaneous VSTR regression, 65 months for the stable group and 37 months for the progression group (Table V).

In this group too, there is a significant association between post-surgical facial function and the VSTR's evolution in univariate analysis, confirmed in the multivariate analysis (p= 0,01 and p= 0,05) (Table V).

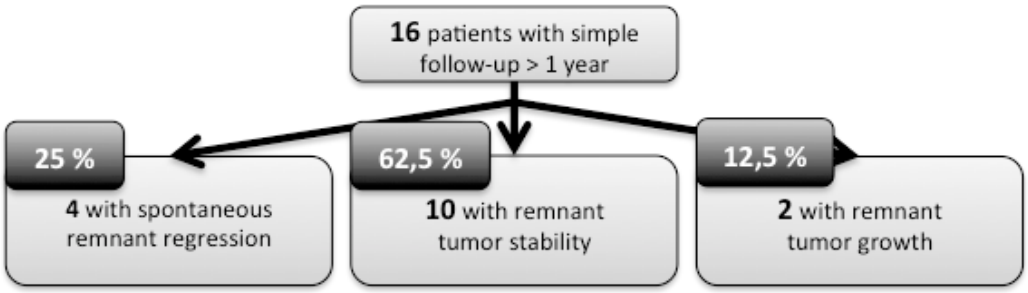


Figure 9: Description of the population of VS non-NF2 patients with a per-operative VSTR described by the surgeon. First checkup MR-scan 1 year after surgery

Table V: Univariate analysis and description evolution of VS TR in the non-NF2 "wait-and-see" population with first MR-scan at one year after surgery

	Regression n=4	**Stability n=10**	**Progression n=2**	**p value**
Age at diagnosis (year)	59,8 ± 3	47,3 ± 13,8	62 ± 22,6	*0,61*
Initial volume before surgery (cm^3)	9,6 ± 12,9	10,4 ± 5,5	14 ± 1,8	*0,14*
Koos stage				*0,21*
- III	2 (50 %)	5 (50 %)	-	
- IV	2 (50 %)	5 (50 %)	2 (100 %)	
Cystic component	2 (50 %)	1 (10 %)	1 (50 %)	*0,67*
Surgical access				*0,64*
- Translabyrinthine	4 (100 %)	8 (80 %)	2 (100 %)	
- Retrosigmoidian	-	1 (10 %)	-	
- Sub-occipital	-	1 (10 %)	-	
VSTR location				*0,50*
- CPA	1 (25 %)	8 (80 %)	1 (50 %)	
- IAC	2 (50 %)	-	-	
- Porus	1 (25 %)	2 (20 %)	1 (50 %)	
VSTR size at first checkup MR-scan	3,1 ± 5,6	0,1 ± 0,2	4 ± 5,6	*0,59*
Follow-up duration (months)	38 ± 20	65,6 ± 75,3	31 ± 7,1	*0,16*
Pre-operative facial function	1 ± 0	1,2 ± 0,4	1 ± 0	*0,16*
Post-operative facial function	3 ± 2,5	1,8 ± 1,4	5,5 ± 0,7	***0,01***
Facial function at end-point date	2,5 ± 2,3	1,8 ± 1,4	4 ± 2,8	*0,50*

NF2 patients

In this study, 3 NF2 patients were included, representing 9.1% of the population with a post-operative tumor remnant described on the first MR-scan.

Among the NF2 population, 2 out of 3 patients presented a VS remnant progression, corresponding to a 66% progression rate, with one late progression observed 25 years after the first surgery. With these 2 VSTR progressions, NF2 patients represent half of the VSTR progression in the whole population of patients, despite the low prevalence of NF2 in the population.

Due to the small number of NF2 patients included, no statistical difference was shown between the NF2 and non-NF2 population and no risk factor of VSTR progression has been identified.

Survival analysis of VS remnant growth

Non-NF2 population

Overall survival curve

In the whole non-NF2 population, the average follow-up duration was 51 months. All VS remnant progression occurred between 38 and 58 months after surgery (Figure 10).

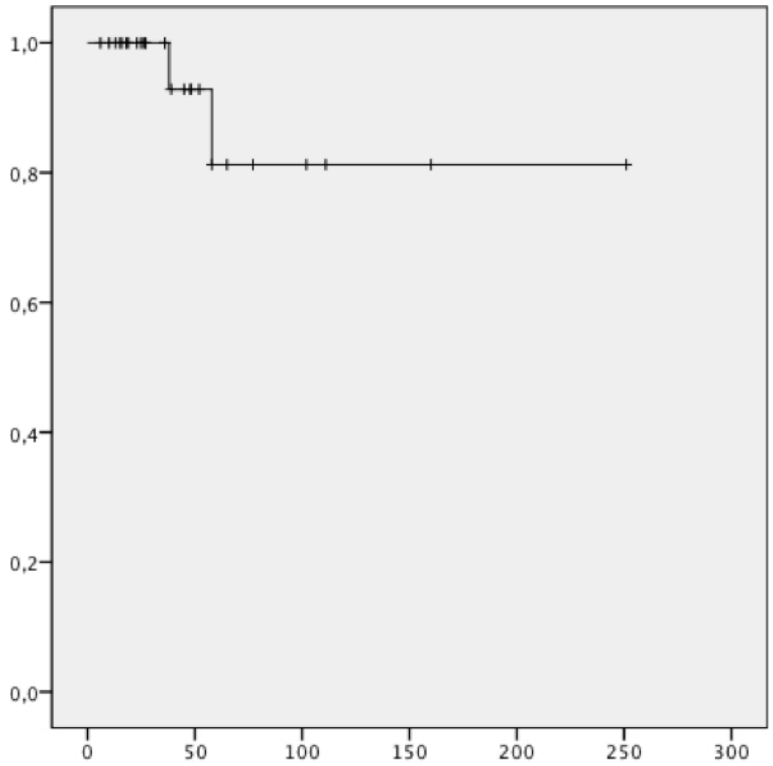


Figure 10: Survival curve for non-NF2 patients with VS remnant
x-axis: time in months after surgery, y-axis: probability of non-progression

Statistical analysis

Univariate analysis showed a significant risk of progression in patients with an initial tumor remnant volume ≥ 1.5cm^3 or a post-operative function score ≥ 4 on the

House-Brackmann scale (p=0,048 and p=0,031) (Figure 11). Neither the initial tumor volume, nor the existence of a cystic component, the Koos stage, the surgical approach, the initial VSTR size or location, or the pre-operative facial function were found to be a prognostic factor of recurrence.

Multivariate analysis did not show any significant difference because of the small number of patients in the population.

However, despite a lack of significance, we observed that all remnant progression occurred in Koos IV patients (p= 0,6) and no recurrences of remnants located in the internal auditory canal were observed (p= 0,82).

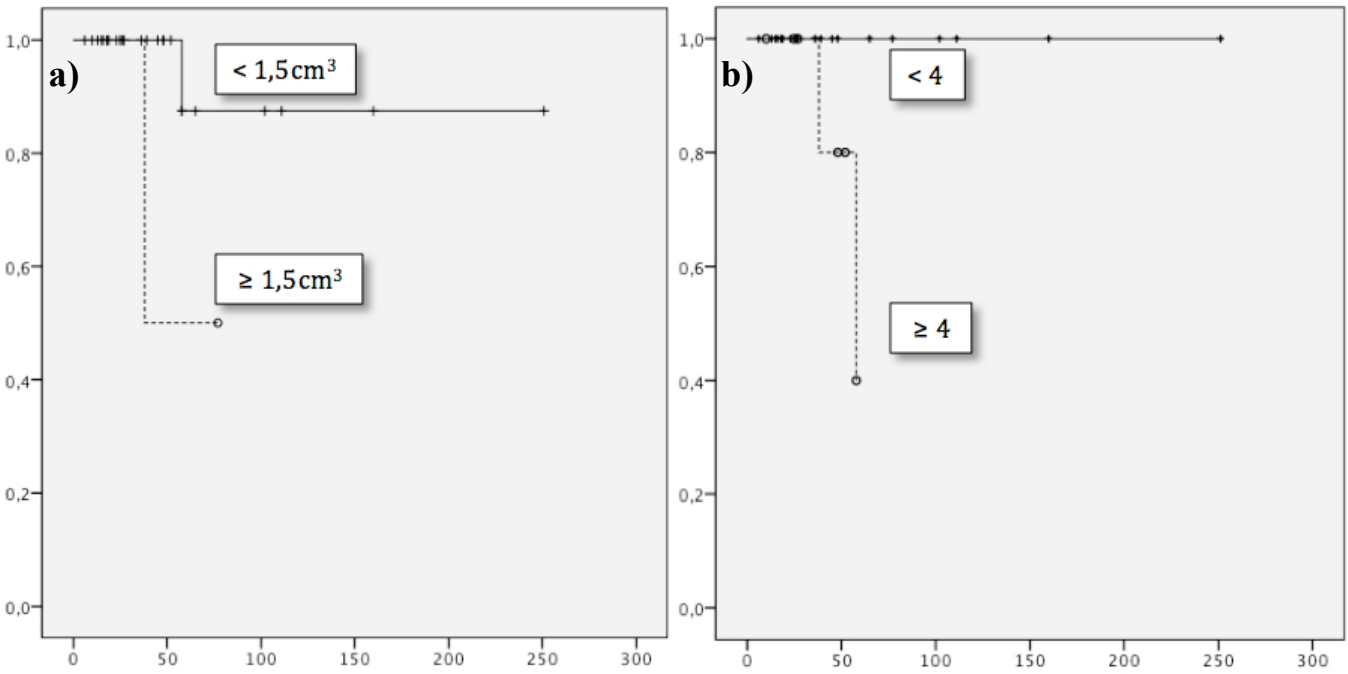


Figure 11: Kaplan-Meier stratification of VSTR non-progression survival curves
x-axis: time in months after surgery, y-axis: probability of non-progression, notches and circles: censored data

a) VS remnant volume with cut-off ≥ 1,5cm³
b) Postoperative facial function with cut-off ≥ 4

Comparison with non-NF2 population, first MR-scan 1 year post-op

In this population, the two significant VSTR main progressions occurred at 26 and 46 months after surgery (Figure 12).

Univariate analysis showed, as in the non-NF2 group, a significantly increased risk of tumor remnant progression in patients with a postoperative function score ≥4 (p= 0,021) (Figure 10).

However, in this group, the presence before surgery of VIIth nerve impairment with a score ≥ 2 is associated with a significant risk of progression (p= 0,001) (Figure 12). The initial VSTR size wasn't identified as a progression factor in this group (p= 0,193).

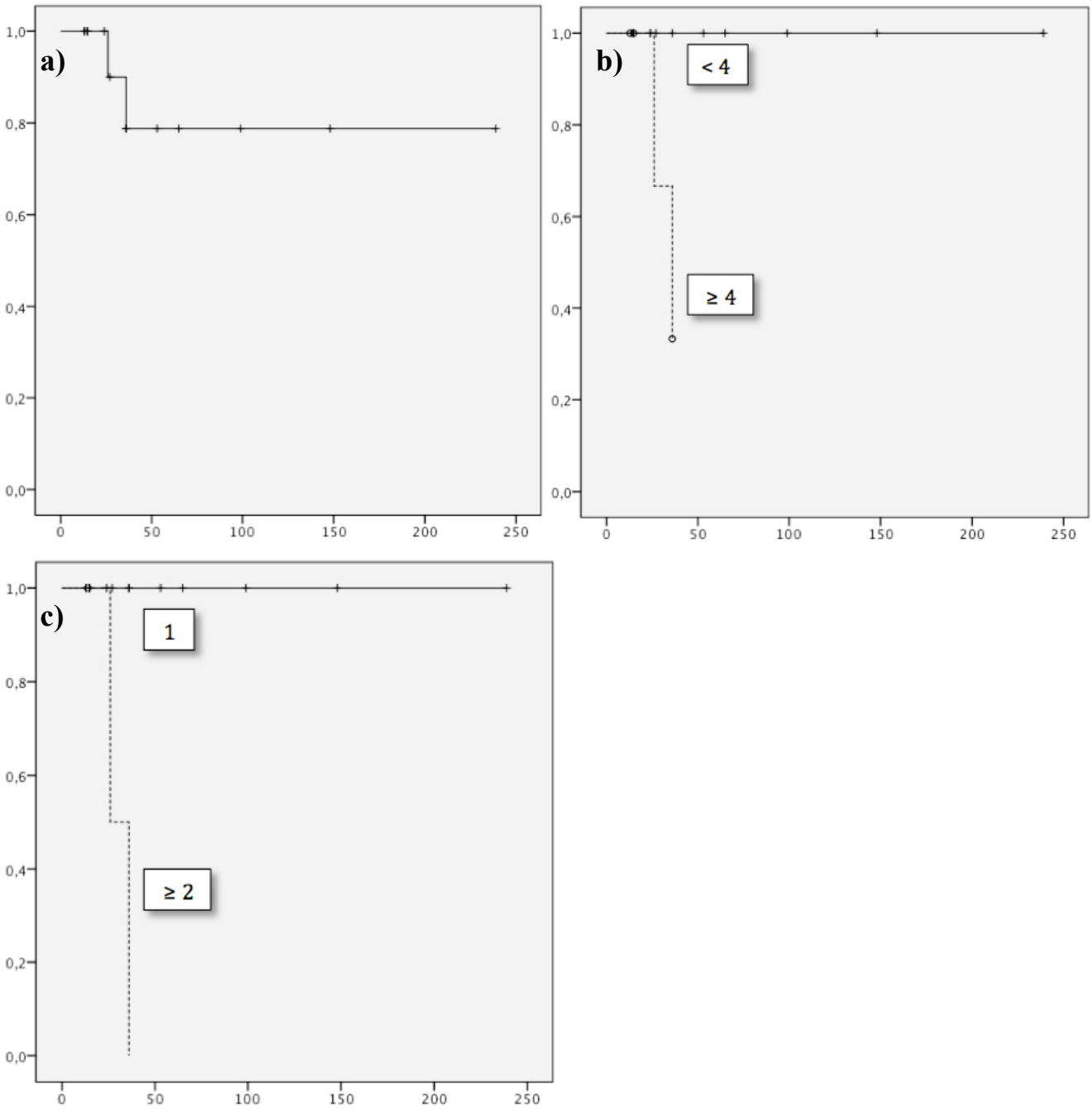


Figure 12: Survival curves for non-NF2 patients with VSTR and first MR-scan one year post-op

x-axis: time in months after surgery, y-axis: probability of non-progression

- ***a) Overall survival curve***
- ***b) Post-operative function with cut-off ≥ 4***
- ***c) Pre-operative facial function with cut-off ≥ 2***

NF2 population

2 NF2 patients presented a VSTR, one at 48 months and one at 300 months (25 years) after surgery (Figure 13).

Due to the small number of NF2 patients included, survival analysis was not done on this population because of the predictable lack of significance.

However, in the survival analysis of the whole population, the existence of an NF2 was not found to be a significant risk factor of progression (p= 0,5).

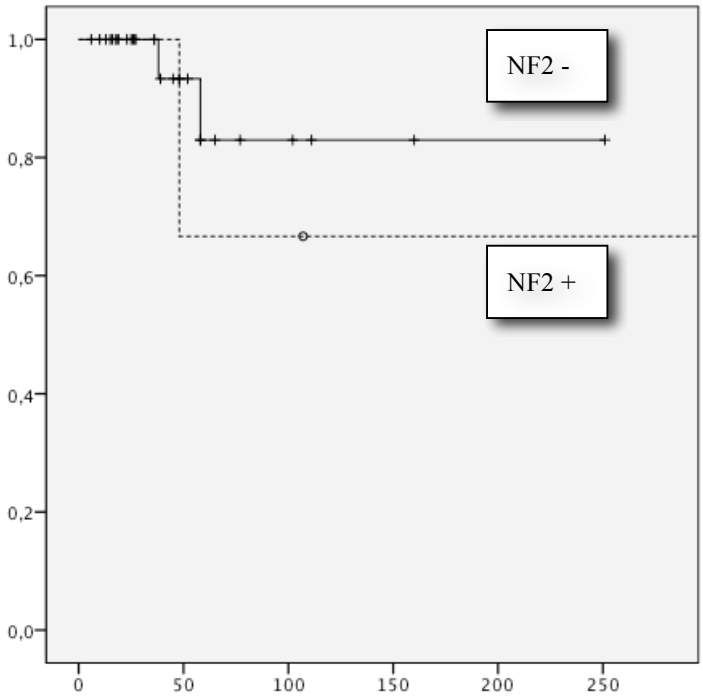


Figure 13: Survival curves for VSTR non-progression in the whole population, stratified by the presence of an NF2

x-axis: time in months after surgery, y-axis: probability of non-progression, notches and circles: censored datas

Discussion

The therapeutic management of post-surgical VS remnants is a crucial debate in an era where the preservation of the facial function at all costs leads to an increase in their prevalence.

The management of post-surgical VS requires physicians to identify predictive factors of progression and to characterize the different sub-populations. The aim is to choose the best therapeutic attitude for each patient with the most appropriate benefit/risk ratio, its particularities and its individuality among the VS patient population.

Our study is, to our knowledge, the first one to focus on the natural history of VS post-surgical remnants and to bring out the predictive factors of progression. Our original study might shed new light on the best therapeutic attitude towards post-surgical VS remnants. We suggest following up the results with a post-surgical VS remnant assessment that may help to select patients at a high risk of progression.

The main limitation of this study is its retrospective analysis, posing the problem of non-homogenous follow-up, missing data and patients lost from the study. VS prevalence is low among the general population, making a prospective study long and difficult to undertake to reach the statistical level required to demonstrate the existence of predictive factors in VSTR progression between multiple variables.

This study also presents a selection bias, with 2-stage surgery chosen by the surgeons for younger people and systematic radiosurgery for young people with big post-surgical VSTR. These strategies were chosen by the surgeons to minimize the recurrence rate, data about VSTR progression rate and natural evolution under surveillance not being available at this time.

However, this study doesn’t present an attrition bias, nor an evaluation bias. All patients, even those lost from the study, were included in this study and the same surgeon performed a systematic evaluation at regular time intervals.

Timing of the radiological assessment after VS surgery

The most appropriate timing for an MR-scan assessment of the existence of VSTR after surgery is subject to question between early and delayed post-surgical checkups.

The risk of an early MR-scan checkup is to confuse VSTR with post-surgical scaring because of the same gadolinium enhancement pattern. This distinction is critical for our study because of the spontaneous regression of the post-surgical scar, which can be confused with the spontaneous regression of a VSTR.

In our study, all VSTR patients included had the presence of a VSTR both confirmed per-operatively by the surgeon and described in the surgical report, and on the first MR-scan 3 months after surgery. This double confirmation makes the confusion of post-surgical scaring for spontaneous VSTR regression in our study unlikely.

Despite its interest in reducing the risk of confusion between post-surgical scaring and VSTR, the disadvantage of the use of a 1-year post-op MR-scan after surgery is a loss of information about early VSTR evolution. In our study, 5 patients with VSTR presented a complete spontaneous regression of their tumor remnant during the first year. This data would have been ignored and would have led to a false increase of the GTR of VS and a lowering of the VSTR spontaneous regression rate, if only the data based on the 1-year post surgical MR-scan had been considered.

In our opinion, the 3-month post-op MR-scan should be given priority for VSTR confirmation and the follow-up should be given priority for the per-operative and radiological confirmation of the existence of a VSTR making the risk of a false positive unlikely.

Comparison of VS remnant evolution and progression rate with the literature

In non-NF2 patients with the first MR-scan 3 months post-op, the progression rate was 7%. This result is inferior to the 10% recurrence rate found in a recent study, which excluded NF2 patients and treated all post-surgical VS remnants with radiosurgery (12).

Considering the non-NF2 population, its seems more appropriate to adopt a “wait-and-see” attitude instead of a systematic radiosurgical treatment of VS surgical remnant, the benefit/risk balance being clearly in favor of a simple follow-up.

With 1 year post-op MR-scan as reference, only 22 patients had sufficient follow-up to be included, making this population less representative and the statistical significance poorer.

In this case, we found a progression rate of 12%, equivalent to the overall population characteristics and similar to previous rates found in the literature. We think that the shrinking of the population may be the principal explanation for the increase of the progression percentage.

In our opinion, the therapeutic management of post-surgical VS in non-NF2 patients should be a “wait-and-see” policy, the progression rate being equivalent or lower than in patients treated systematically with radiosurgery. Due to their high progression rate, post-surgical VS remnants in NF2 patients should be treated with radiosurgery.

Our population of NF2, despite its small size, accounts for half of the VSTR progression observed and has a 66% progression rate. The usual progression rate of VSTR for VS patients is 14.6%, higher than the usual progression rate found in the general population of NF2 patients (12, 31, 40, 42, 43). In the literature, NF2 patients are a specific entity among VS patients, with a specific medical history and specific management, hearing preservation being in their case the main objective due to the high prevalence of bilateral localizations.

Thus, despite the lack of scientific evidence found in the literature, it would seem logical to give preference to systematic radiosurgical treatment for VTSR in NF2 patients to minimize the progression risk and preserve the hearing for as long as possible.

Predictive factors of VS remnant growth

This original study is the first, to our knowledge, to study the natural history of VS post-surgical remnants, to define the best therapeutic attitude and the factors of VSTR progression with the characterization of sub-populations at a high risk of recurrence. After demonstrating that radiosurgery should be given priority in the NF2 population and a

"wait-and-see" policy for non-NF2 patients, we decided to continue our investigation and try to bring out predictive factors for recurrence.

In the whole population, we observed that almost all VS remnant progression occurred 3 to 5 years after surgery, except for one NF2 patient who presented a progression 25 years after surgery. This data is coherent with the literature (36, 44).

In each population the immediate post-operative facial function impairment ≥4 on the House-Brackmann grading scale was a significant progression factor. This may be explained by the fact that an altered per-operative facial function may lead the surgeon to end the intervention prematurely. This means leaving an unplanned VS remnant in size and location, with an unsatisfactory surgery in the surgeon's opinion.

In non-NF2 patients, the initial VS remnant volume also appears to be a statistically significant progression predictor, with a cut-off at 1.5 cm^3, inferior to the 2.5cm^3 cut-off previously described by Vakilian (45). This predictive factor may be explained by the less efficient devascularization of large tumor remnants.

All recurring VS remnant were primary grade IV on the Koos classification, suggesting a potential statistical association between the initial size of the VS and the risk of recurrence. But the Koos stage and thus the initial volume of the VS weren't found to be a statistically significant predictive factor, as described in previous studies (29, 46, 47).

The NF2 didn't appear to be a significant tumor remnant progression factor with a p=0.5, despite the fact that 2 out of 3 patients presented a VS progression. However, despite the lack of significance which may be explained by the low prevalence of NF2 patients in the population and the low number of NF2 patients included in this study, we think that NF2 is a significant risk factor for progression and that NF2 and non-NF2 patients are 2 distinct populations with different pathological findings, clinical presentations, history and outcomes (41, 48).

NF2 patients need specific management of their VS with hearing preservation being the first goal of therapeutic management (39, 40). Systematic radiosurgery should be given priority in these patients due to a high tumor remnant progression rate, and the limited side effects in a population were hearing preservation is crucial.

Also, no significant progression was found with VS remnants located in the IAC, being consistent with the literature, where no progression of VS located in the IAC was observed (36, 49).

Due to lack of statistical significance, the initial VS remnant volume was not found to be a predictive factor of progression in the population with the first MR-scan at one year after surgery. Instead, we found a significantly increasing risk of recurrence with the alteration of pre-operative facial function even with a small impairment (House-Brackmann score ≥2), which can be interpreted more as a statistical association than a cause-effect link in this population.

In conclusion, NF2 patients have a different evolution to non-NF2 patients and show a higher rate of progression.

Post-operative facial function impairment and the initial VS remnant volume are found to be significant predictive factors of progression in the non-NF2 population.

We observed also that all growing VS remnants were initially Koos grade IV and no VS remnant progression was observed on VS remnants located in the internal auditory canal, but these results weren't statistically significant.

Post surgical VS remnants: therapeutic management proposal

Three therapeutic options are available for the management of post-surgical VS remnants: a "wait-and-see" attitude, radiosurgery and surgery.

A "wait-and-see" attitude is based on a regular clinico-radiological follow-up. The goal is to avoid systematical radiosurgical treatment of VS remnants and to keep it only for the few remnants that will progress over time in the population presenting a low progression rate. The inconvenient of this therapeutic management is the delay in treating the progression and the increased difficulty of treating an important remnant tumor instead of a small post-operative remnant.

Radiosurgery is considered as an efficient technique providing at low risk a minimally invasive treatment for primary VS management (32, 50-55). But, for post-surgical VS remnants, its indications remain unclear. However, even if it is a minimally invasive treatment, radiosurgery may have side effects and complications like VIIth and VIIIth nerve lesions (46, 56). In clinical practice, radiosurgery in treatment of VS remnants

is acceptable only if its benefits surpass its potential risks compared to other therapeutic options.

Reoperation is considered less often, due to its technicality, with an important risk of complications higher than the two previous therapeutic options, with cranial nerve impairment and cerebro-spinal fluid leakage. Ramina and al. reported in their study of reoperation of VS that 7% of cases had facial nerve lesions, 13% had transient bulbar nerve palsy and 20% had cerebro-spinal fluid leakage in a group of 15 patients (57).

We suggest for patients with radiologically confirmed VS remnants a therapeutic management depending on the criteria highlighted in this study (Figure 13).

MR-scans remain the radiological exam of choice to check the evolution of post-surgical tumor remnants, with T1 with and without gadolinium enhancement, T2 High-resolution and T2-FLAIR weighted, each in 3D acquisitions. The poor correlation between the surgeon and the MR-scan checks, to determine the existence of a post-operative remnant, make the first checkup MR-scan the best check with a sensitivity and a specificity up to 100% (58).

The first MR-scan 1 year after surgery may allow us to minimize the risk of confusing a post-surgical scar for a VS remnant despite losing information about the early regression of post-surgical VS remnants. However, we chose to do the first MR-scan 3 month after surgery to allow early detection of post-surgical complications, and appreciate early VS remnant regression, as did Roche et al. (34).

For NF2 patients presenting a high progression rate and needing special management to preserve both hearing and facial functions, we suggest using complementary radiosurgery on the VS remnant.

In the non-NF2 population, patients with an impaired facial function with a score ≥4 on the House and Brackmann grading scale and patients with a VS remnant size ≥1.5cm^3 had a statistically increased risk of progression. Therefore, we suggest for these sub-populations of non-NF2 patients at risk of progression a complementary radiosurgical treatment.

For patients with a VS remnant, all progression occurred between 3 and 5 years after the first surgery. This suggests that a close follow-up during the first 6 years after surgery is needed, and can be more widely spaced after this critical period of surveillance (Figure 14).

In our therapeutic management proposal, we suggest treating non-NF2 patients with an impaired post-operative facial function with radiosurgery. This choice of treating patients with an already impaired facial function with radiosurgery may be questionable because of the risk of aggravation. But in our study, because of a statistically significant risk of VS remnant growth in this population, we considered the benefit/risk ratio in favor of the radiosurgery treatment.

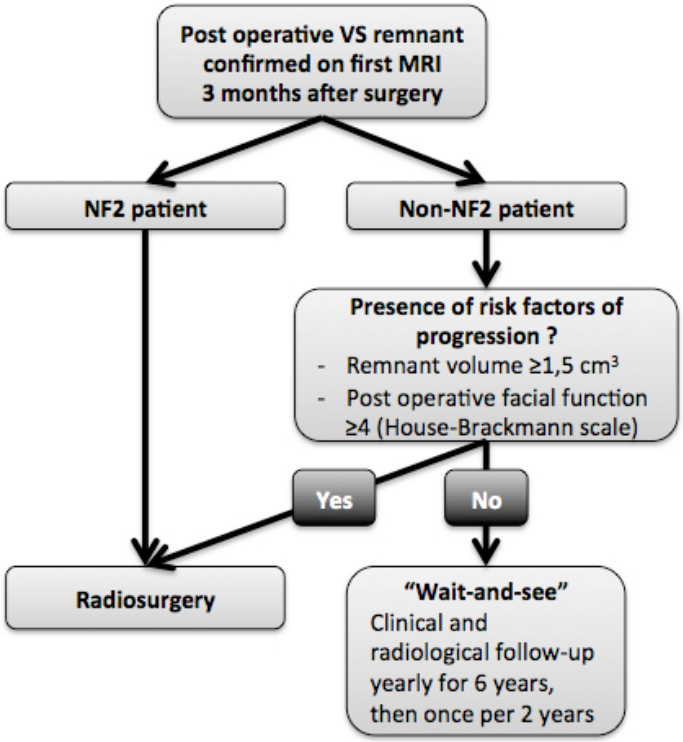


Figure 14: Therapeutic management proposal for VS post-surgical remnant

Spontaneous remnant regression: myth or reality?

The existence of spontaneous regression of post-surgical VS remnants is subject to question. Only a few studies report its existence and its radiological behavior (35, 59). It is often attributed to a post-surgical scar.

In our study, apparently spontaneous regression of post-operative remnants occurred in 39% of the overall population and 43 % in the non-NF2 population with a first MR-scan 3 months after surgery.

The regression of the post-operative remnant seems to occur shortly after surgery. In our study, spontaneous regression of VS remnants happened in the first year after surgery in 60% of cases. This means that an important part of this population is excluded in the one-year post-op analysis and in studies based on 1-year post-surgery MR-scans.

Distinctions between a VS remnant and a post-surgical scar can be confusing. However, each VS remnant included in our study was described per-operatively by the surgeon and the tumor remnant location on first checkup MR-scan matched to the remnant described by the surgeon. This tends to go against the hypothesis of a post-surgical scar and false detection of VS remnants.

The mechanisms of the VS remnant regression remain unclear. One main explanation may be the devascularization of the remnant tumor during surgery, as described by Hahn (35).

Conclusion

NF2 patients presented a high progression rate.

Initial VS remnant size $\geq$ 1.5 cm^3 and immediate post-operative facial function impairment with House-Brackmann score $\geq$ 4 are statistically associated with a significant risk of VS remnant progression in non-NF2 patients.

In our opinion, the best therapeutic management of VS post-surgical remnants in non-NF2 patients with no predictive factor of progression is a simple clinico-radiological follow-up whereas, patients with a least one of the predictive factors of progression may benefit from radiosurgery.

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List of Figures

List of Tables

Table of Contents