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# Paradoxal subtotal intended removal for Koos IV Vestibular Schwannoma: *est modus in rebus?*

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**Object:** Surgery is the first choice treatment for large (Koos IV) vestibular schwannomas. Postoperative facial and acoustic deficits are essentially due to the removal of the medial tumor capsule. Subtotal tumor removal may decrease these risks and tumor remnants may remain stable or shrink over time, or may be later treated by radiation. In this study, we describe the natural history of residual vestibular schwannoma and the clinical results after intended subtotal resection.

**Methods:** In the first step, we retrospectively evaluated all patients operated at our former institution for a vestibular schwannoma Koos grade IV between June 2009 and December September. Tumor volume was followed. Tumor recurrence was defined as a volume increase by >25% compared to baseline. Tumor regression was defined as a volume decrease by >0% and the others were considered as progression. Facial Function was defined as follows: “Good” (House-Brackmann 1-2), “Fair” (HB 3) and “Poor” (HB 4-6)

**Results:** thirty –eight cases with ages between 20 and 86 years old (mean 58 yoa) were included in the study. The mean preoperative tumor volume was 12,79 cm<sup>3</sup>. The mean volume of postoperative tumor remnant was 1,430 cm<sup>3</sup>. At last follow-up (mean 753,9 days after surgery) the mean tumor volume was 1,09 cm<sup>3</sup>. At the last follow-up (n=38), 3 cases (8%) showed tumor progression, twenty-two (58%) were stable and three (8%) with recurrence. Progression and recurrence were correlated with higher preoperative tumor volume, but not with postoperative residual volume (p=0,0004) and rate (p=0,0001)

For what concerns Facial Nerve: on preoperative thirty-seven patients had Good function and only one “Fair”. On the 1<sup>st</sup> follow up we found thirty cases of “Good” function, two of “Fair” and 6 with “Poor”. At last follow-up, only two patients had “Poor” function and three “Fair”. No statistical correlation was founded between residual volume and facial function (p=0,04) and residual rate and facial function neither (p<0,0001)

**Conclusion:** No statistical association was found between residual volume/rate and recurrence rate and with facial outcome neither. Intended subtotal removal leading to less postoperative deficits and recurrence rate, may therefore be a good treatment strategy as compared to radical resection

Vestibular schwannoma, Subtotal removal, Recurrence Rate, Facial Function

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# 1. INTRODUCTION

## HISTORY

Vestibular schwannomas (VS), benign tumours, which originate from the eighth cranial nerve, represent one of the hardest challenges for neurosurgeons.

### *DESCRIPTION OF VS AND PRIMITIVE SURGERY*

The earliest reference to VS dates back to 1777 when Eduard Sandifort, professor of anatomy in the Netherlands, found the first unilateral acoustic tumor during an autopsy[8-10]. For about two centuries thenceforth, diagnosing VS was only possible through autopsy because VS meant any possibility of survival.

It was only in 1894 that Sir Charles Balance, a British surgeon, managed to perform the first successful surgery on a cerebellopontine angle tumor; we are still not sure about the classification of the tumor, but perioperative findings and clinical presentation of that, probably traced us back to an acoustic neuroma. A brief description of the operation gives us an idea on quality of outcome of the period : « The finger had to be insinuated between the pons and the tumor to get it away ». The patient, a 49-year-old woman, survived with persistent cranial nerve deficits[11]. Surgery of vestibular schwannoma progressed, and new challenges started.

### *PROGRESS IN SURGERY : TOTAL VS PARTIAL REMOVAL*

In 1917, Harvey Cushing, a pioneer of neurosurgery who brought considerable development to CP surgery, published a monograph [11] of 30 surgically treated VS

patients with unprecedentedly low mortality rates. Still, he deemed a safe and complete removal of VS, with a good preservation of clinical function, was impossible [4]; so we had to accept an unsafe recurrence rate. Because of that, a debate started between Cushing and his pupil Walter Dandy. The last one considered recurrence rates published by his mentor too high. What's more, he affirmed that total removal, associated with lower mortality rates, could be reached beyond accurate capsular dissection [8].

Since then, mortality during VS removal ceased to be a variable to fear for neurosurgeons, and a new era of VS surgery began, prompting surgeons to a higher goal which hasn't fully reached: performing a complete resection, with a total preservation of the facial and vestibulo-cochlear nerves. In fact, incomplete resection means better clinical outcome, but many studies show an emphatic correlation among the volume of residual tumor and the incidence of recurrence[12].

In 1931, Sir Hugh Cairns of London performed the first total VS removal preserving the function of the facial nerve [4].

### *SURGICAL TECHNIQUES*

During the second part of the past century, new challenges have arisen while trying to reduce peri-operative tumor-related morbidity.

In order to improve surgical outcomes, new approaches are tested. The suboccipital approach, currently called the *retrosigmoid approach*, persist to be the standard track [10].

Others surgeon carried out techniques of intra-operative nerves' reconstruction, but this argument won't be discussed in this work.

The era of microsurgery for skull base started in the sixties [13], and affirmed itself for all types of VS toward the second half of the 20th century, when we get to the introduction of radiosurgery .

### THE CONTEMPORARY ERA: RADIOSURGERY VS MICROSURGERY

Many options exist for the management of patients with vestibular schwannomas; they include conservatory treatment through observation, microsurgical tumor removal, stereotactic radiosurgery or fractionated radiotherapy. In 2003 an important report was published among a 15-year experience of radiosurgery. Their conclusion was as follows:

*“For patients with large tumors (> 3cm in extracanalicular diameter) and those with progressive neurological deficits that require brainstem decompression, surgical resection is the preferred option [..]. For patients with small or medium-sized tumors, SRS has become a common treatment, with excellent reported long-term results. Patients must be comfortable with the concept of tumor control rather than tumor removal”*[14].

In this study we focused on surgical management of large vestibular schwannoma, Koos grade IV, for which actually a first surgical management has been demonstrated to be the most efficient way actually[15].



## EPIDEMIOLOGY AND PATHOLOGY

### EPIDEMIOLOGY

Schwannomas are benign tumors of peripheral nerves that can occur sporadically or in the context of several genetic tumor syndromes. We can find them in the context of schwannomatosis, Carney's complex or neurofibromatosis (bilateral vestibular schwannomas are pathognomonic for NF type 2 [16]). Schwannoma originates from schwann cells, a population of cells responsible for producing the myelin sheath enrolling peripheral neurons and apportioning them trophic support [17].

Vestibular schwannoma are the most common type of schwannoma and the most frequent tumor of the cerebello-pontine angle [18, 19], representing approximately 5-6% of all intracranial tumors [20]. They grow slowly, rarely menace survey, but have a negative effect on Quality of Life. When peripheral nerves enter the CNS, they stopped to be surrounded by schwann cells. Therefore Vestibular Schwannomas usually originate in the medial part of IAC, where vestibular nerves shift from peripheric to central myelin [19], displacing the nerves, but not destroying them [21]. Since they frequently remain undiagnosed, major studies are based prevalence in the autopsies of 157 patients; there, a frequency of 4.5% of sporadic central schwannoma with around 85% vestibular was discovered [16]. Studies have reported that the incidence of these tumors ranges from 0.6 to 1.9 per 100,000 population [19]. According to recent MRI studies, the incidence of asymptomatic VSs is 0.07 % or even 0.2 %; meanwhile, clinical incidence has been estimated to range from 0.2 to

5/100,000/year [4]. There are evidences of an increased incidence, probably due to a better access to non-invasive diagnostic tools as MRI and CT. They probably provide easier diagnosis and also earlier and fortuity discovery [18, 22].

## PATHOLOGY

Both sporadic and genetically acquired schwannomas are caused by defects in merlin. Merlin is a protein that inhibits the expression of growth factor receptor on the cell surface (like EGFR) [23] and defects in its expression cause hyperproliferation [16]. Noise exposure and radiation are the only environmental factors proven to increase the risk of VS, and may contribute to the increased incidence [19].

A history of chicken pox and the exposure to more than one cranial x-ray procedure were identified as potential risk factors [24], while tobacco use demonstrates an inverse relationship with VS [25] .

## ANATOMY

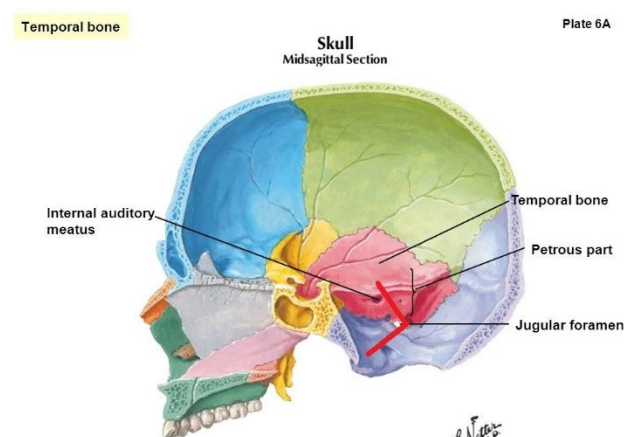


Figure 1[2]

Cerebellopontine angle is a V shaped anatomical space located at the basis of the cranium (figure 1). Anteriorly is delimited by the posterior surface of the petrous (temporal) bone; the pons and the cerebellum define the medial and latero-posterior limits and it is placed superior to the pyramids and inferior to the tentorium.

In this basin pass many neurovascular structures : the facial , trigeminal, abducent, vestibulocochlear nerve as nervous components ; the superior cerebellar and anterior inferior cerebellar arteries, a variable number of draining veins and the choroid plexus as vascular units. Other anatomic structures present are the flocculus and the middle cerebellar pedoncule. As one can

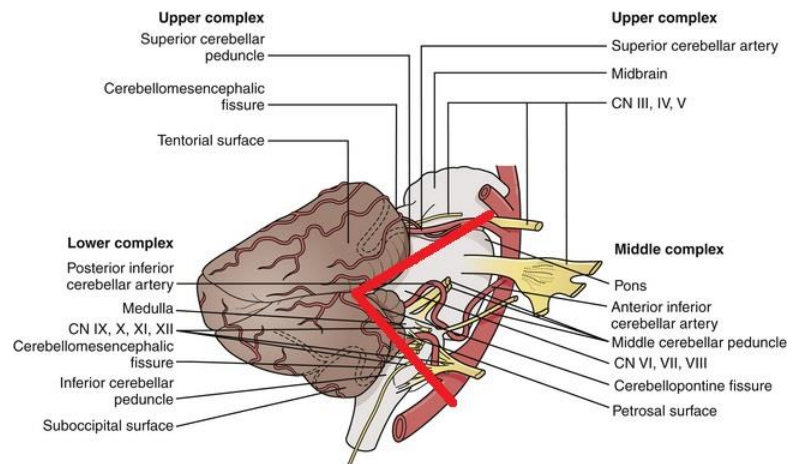


Figure 2[5]

see (figure 2), the nerves IX,X,XI lie in the lower part, although nerves VII and VII emerge from the internal auditory canal (IAC) in the middle part of CP angle. This topographic organisation of nerves in the IAC makes difficult the management of VS. Figure 3 clearly depicts how nerves VII and VIII (vestibular inferior, superior and cochlear) with nervus intermedius emerge from IAC, where they are accompanied by the labyrinthine artery [4, 26].

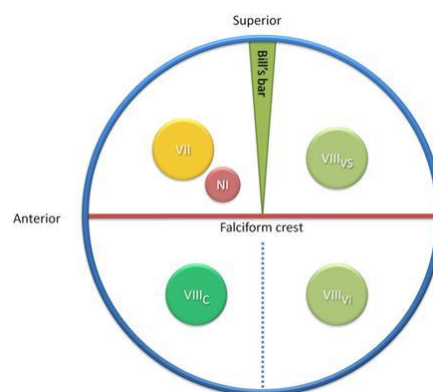


Figure 3[3]

## CLASSIFICATION

For a deeper understanding of this work, a series of grading systems and technical particularities regarding the world of Vestibular Schwannoma must be introduced.

Koos classification (figure 5) is the most

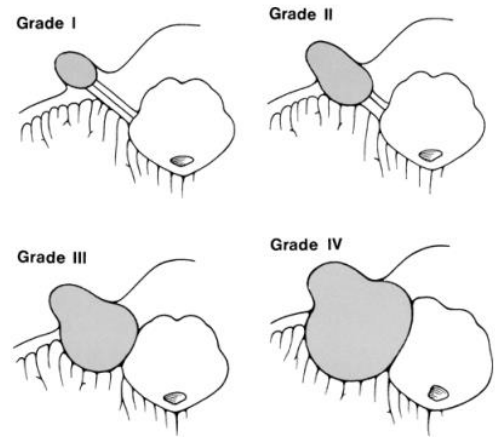


Figure 4[7]

significant for Vestibular Schwannoma. Grade I are considered the only intracanalicular tumors; they become Grade II when they extend into the cerebellopontine angle without touching the brainstem.

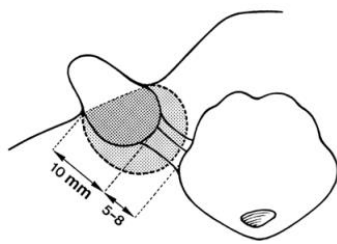


Figure 5[7]

Furthermore, we can divide grade II VS in IIa and IIb (figure 4) by simply calculating the extension from the porus acusticus into the CPA (IIa 0-10mm, IIb 11-18mm). Grade III VS are tumors that join the brainstem, yet not displacing it. Large tumors, grade IV (that we consider for this study) are tumors that cause a displacement of brainstem and nerves, with more effective clinical consequences [7].

What is more, facial nerve grading must be

House-Brackmann classification of facial nerve dysfunction

Grade	Characteristics
I. Normal	Normal function in all areas
II. Mild dysfunction	Gross Slight weakness noticeable on close inspection May have slight synkinesis Normal symmetry and tone at rest Motion Forehead: Moderate to good function Eye: Complete closure with minimal effort Mouth: Slight asymmetry
III. Moderate dysfunction	Gross Obvious but not disfiguring difference between the two sides Noticeable but not severe synkinesis, contracture, or hemifacial spasm Normal symmetry and tone at rest Motion Forehead: Slight to moderate movement Eye: Complete closure with effort Mouth: Slightly weak with maximum effort
IV. Moderately severe dysfunction	Gross Obvious weakness and/or disfiguring asymmetry Normal symmetry and tone at rest Motion Forehead: None Eye: Incomplete closure Mouth: Asymmetric with maximum effort
V. Severe dysfunction	Gross Only barely perceptible motion Asymmetry at rest Motion Forehead: None Eye: Incomplete closure Mouth: Slight movement
VI. Total paralysis	No movement

Figure 6[6]

The House-Brackmann scale, is an indicator of severity of peripheral palsy of the facial nerve (Bell's Palsy) and is divided into 6 grades of dysfunction (figure 6).

## CLINICS

Symptoms of acoustic neuroma derive from its topographic growth. They can be due to nerve involvement: cochlear (VIII) in the 95% of patients, with hearing loss and tinnitus; vestibular (VIII) in 61% through unsteadiness and more uncommonly spinning vertigo, trigeminal (V) paresthesia or hypesthesia and pain in 9% , and facial (VII) palsy, sometimes with taste disturbances in only 6% [27]. When a tumor grows, a cerebellar compression and a posterior fossa syndrome can also be, with symptoms such as ataxia, dysarthria, dysphagia. Rarely, due to slow growth, VS can lead to mortality by causing brainstem compression, cerebellar tonsil herniation or hydrocephalus.

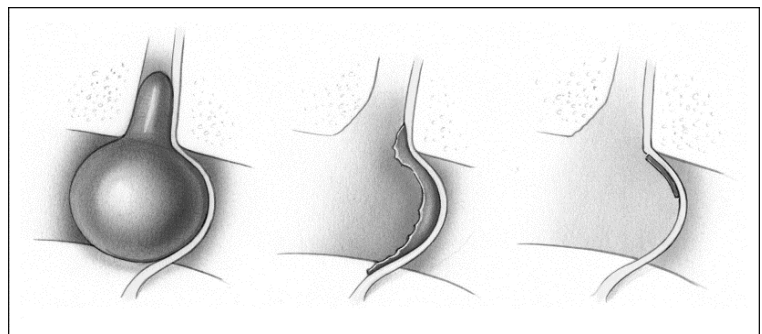
The most suggestive context for vestibular schwannoma is unilateral hearing loss or cranial nerve deficit (of the nerves we cited before). History and specific neurologic clinical examination (cranial nerves, audiometry etc.) must be well collected. The gold standard for diagnosis and care assessment for VS is a high definition CISS T1 gadolinium enhanced MRI [28, 29].

## RATIONALE AND AIM OF THIS STUDY

It has already been stated that studies prove that surgery is the best approach for large VS. The debate that remains vis-a-vis large vestibular schwannoma is either to pursue total resection or partial resection [1, 20, 30]?

“*Est modus in rebus*” (Orazio, Satire I, 1, vv106-107): between total and partial resection we can choose another paradoxal type of surgery: intended subtotal removal.

Planned near-total resection (figure 7) means a maximal enucleation of the tumor mass (nearest to the tumor capsule) that



does not attempt to separate the *Figure 7[1]*

tumor capsule from the highly vulnerable cisternal portion of the facial nerve. In fact, postoperative facial and acoustic deficits are primarily due to the removal of the medial tumor capsule; by intended subtotal tumor removal, there is potential for decreased risks and for tumor remnants to remain stable or shrink over time. In a wait-and-scan approach, when a recurrence was found, we considered an adjuvant radiochemical treatment.

This question has already been tackled by some experts and previous results of near-total resection showed a better outcome for facial nerve. It is, but it should be an improvement of tumor recurrence [1, 31, 32] For that reason, some suggest a threshold for VS resection for preservation of Facial function [20, 31] and others suggest a radio-surgical/radio-therapy intervention d'emblée after microsurgery [30, 33]. We describe

the natural history of residual vestibular schwannoma and clinical results after intended subtotal resection. We will demonstrate a more efficient approach on facial function and a non-improvement in recurrence rate after intended subtotal removal, eventually followed by radiotherapy where residual mass show volumetric progression.

## 2. PATIENTS AND METHODS

### TRIAL DESIGN

We retrospectively evaluate all patient operated for unilateral vestibular schwannoma stage IV Koos, between June 2009 and September 2015 at the Universitätsspital Basel, whose surgery was carried out by the same surgeon, Prof. Mariani. Clinical and neuroradiological data on preoperative, post-operative and follow-up of each patient were analysed.

Goal of this study, as cited at the end of the introduction, is to determine whether sub-total intended removal allows better clinical facial (VII) outcomes than total removal and lower recurrence rate than partial.

### PATIENTS

Only sporadic VS at first or second planned surgery were taken into this study. Totally 7 patients with large VS Koos IV have been excluded: 1 case for NF2, 2 for recurrence surgery, 2 because whose diagnosis was changed into meningioma and 2 because initially operated by others surgeons.

Finally 38 statistically equals and relevant patients, with no significant comorbidities, aged at surgery between 20.6 – 86.6 years [mean age 58 years], were selected. Female to male ratio is 1.37:1.

At surgery, only 3 patients (7.9%) were asymptomatic. The majority of them manifested several symptoms, all typical of a cerebellopontine angle tumor, including hypoacusis or anacusis (23 cases, 60.5%), imbalance (18 cases, 47.4%), vertigo (13



cases, 34.2%), ataxia (16 cases, 42.1%), tinnitus (8 cases, 21.1%), nystagmus (5 cases, 13.2%), headache (2 cases, 5.3%), facial dysesthesia (1 cases, 2.6%), and cerebellar dysarthria or diplopia (1 case each, 2.6%).

## SURGERY

All these patients underwent intended sub-total removal as their first intervention with microscopical stereotactic neurosurgery, through a standard retrosigmoidal approach. Intraoperative continuous neurophysiological neuromonitoring (electromyography for CN VI, VII, IX, X, XI, XII; brainstem auditory evoked potentials and direct cochlear nerve action potential monitoring for CN VIII; motor evoked potentials and somatosensory evoked potentials) and Neuronavigation (Brainlab) were performed for each patient.

For surgery the patient is placed in a semi-sitting position, the affected side of the head is up (figure 8).

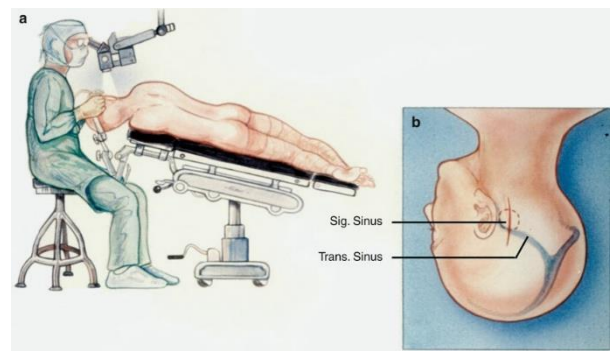


Figure 8[4]

Then we reach the cerebellopontine angle (figure 9) through a retrosigmoid approach:

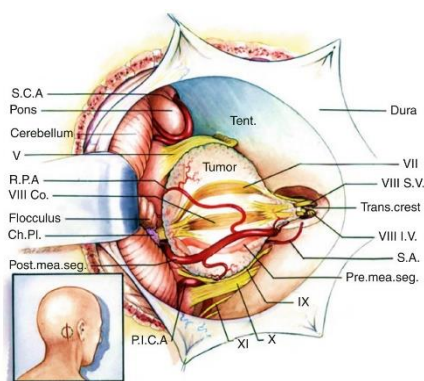


Figure 9[4]

a craniotomy is performed between the transverse and sagittal venous sinus. After internal debulking of the tumor, with a particular attention to neurovascular surrounding structures, the facial nerve was identified at its root entry zone. The internal acoustic meatus was drilled open for

removal of the intrameatal portion of the tumor and exposure of the distal portion of the facial nerve. The tumor was then maximally shelled out of its capsule, and the capsule itself was removed piecemeal to the extent that this was judged to be safe. That was made on the basis of tumor and nerves characteristics, as well as direct stimulation with a threshold of 0.2 mA (i.e., an EMG response from the nerve upon stimulation at any current below 0.2 mA was taken as evidence that the particular piece of tumor stimulated was too close to the nerve to be safely resected). In no case the anteromedial portion of the tumor capsule was dissected free from vulnerable transitional portion of the facial nerve located at the junction of its meatal and cisternal segments. In case of nerve discontinuity, we did not do any intraoperative reconstruction.

, Intended near-total tumor resection was performed either in a single session (35 cases, 92,2%) or as a planned two-stage procedure (3 cases, 7,9%), depending on the size of tumor and the extent of its protrusion into the subarachnoid space of the cerebellopontine angle and its contact with, or displacement of, the cerebellum and brainstem. Two of the 38 cases in this series involved the intended near-total tumor resection of VS that had already been treated previously. In one case, there had been significant volumetric progression of the tumor after initial radio-surgical treatment in an outside hospital, and an intended near-total tumor resection was performed 5 years after radiosurgery. In the other case, volumetric progression was noticed, after subtotal surgical removal by another team and co-adjuvant radiosurgery, with a preoperative volume of 20.80cm<sup>3</sup> So, and an intended near-total resection was performed 8 months

after the initial operation: first surgery on 07.2011, with a residual volume 3.88 cm<sup>3</sup> and second on 11.2012 with a residual volume of 0.985cm<sup>3</sup>.

## RADIOLOGICAL FOLLOW-UP

VS volume based on preoperative, postoperative and follow-up MRI scans was measured with software tool “iPlan® RT planning software (Brainlab)”. Axial MRI sequences highly sensitive for Vestibular Schwannomas (CISS, T1-Gd) were analysed: single-slice tumor surface was personally delimited and supervised by two independent experts. For 3 follow-up MRI we have normal MRI, not CISS sequences. Mean number of follow up is 2.89 and average time between surgery and first follow-up was 72.79days; between surgery and last follow-up mean was 753.92days [10 - 2154 days]. 10 patient had only 1 post-operative follow up.

Based on radiologically findings, recurrence was defined as a volume increase by >25% compared to residual volume. An increase in tumor mass <25% and >0% was considered progression. Tumor regression was defined as a volume decrease by >0%.

## CLINICAL FOLLOW-UP

Clinical follow-up was realised contemporary at MRI follow-up and had the goal to evaluate Facial, Vestibular and Trigeminal nerves' function. It was realised by neurosurgeons of the Neurochirurgische Klinik in Basel.

For this study, facial Function is defined as “Good function” when HB 1 and 2, “Fair Function” when HB 3 and “Poor Function” HB 4,5 and 6.

In our database, the Cochlear portion of the VIII cranial nerve was defined as follow: “0” when hearing was potentially saveable (loss < 50%) and “1” when hearing was irretrievably lost (loss > 50%). During clinical follow-up, we did not evaluate Vestibular function.

Trigeminal function was classified in “1” or “0”: 1 when touched, and 0 when normal.

## DATA ANALYSIS

Patients data were recorded on Excel® secure documents. We used MedCalc®, SPSS® and Microsoft Excel® for statistical analysis and graphs production. For analysis, we performed Pearson correlation and Wilcoxon rank sum tests. A p-value < 0.05 was considered significant. For citation management we used Endnote®.

Ethics committee and institutional review board approval was obtained for prospective data collection and for the retrospective analysis and publication of clinical and radiographic data.

Research of the literature was made on pubmed.com using terms as “vestibular schwannoma surgery”, “large vestibular schwannoma management”, “subtotal/partial removal vestibular schwannoma”, “vestibular schwannoma Koos grade IV” and MeSH words “Vestibular Schwannoma” “subtotal/partial removal” “surgery”.

### 3. RESULTS

#### PREOPERATIVE

All tumors were considered large or very large ( $\geq 2$  cm in greatest diameter) and Koos grade IV with a displacement of brainstem and nerves. The mean tumor volume at surgery was  $12.79 \text{ cm}^3$ , range  $2.2 - 65.8 \text{ cm}^3$  with a SD of 11.32. Left to right ratio 1,1 : 1.

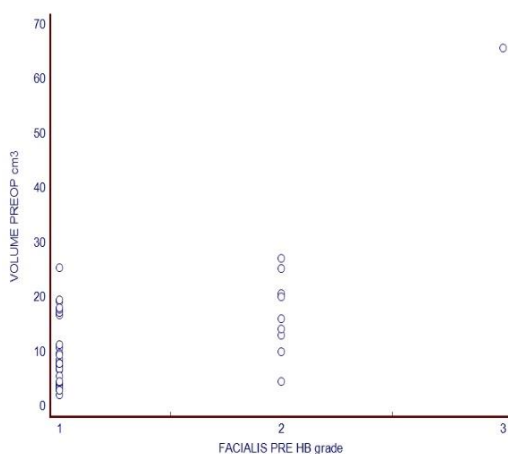
	Our study	Samii[27]
<i>Hypacusis or Anacusis</i>	60.5%	95%
<i>Imbalance</i>	47.4%	40%
<i>Vertigo</i>	34.2%	28%
<i>Ataxia</i>	42.1%	14%
<i>Tinnitus</i>	21.1%	51%
<i>Nystagmus</i>	13.2%	
<i>Headache</i>	5.3%	
<i>Facial dysesthesia</i>	2.6%	5.2%
<i>Dysarthria</i>	2.6%	
<i>Diplopia</i>	2.6%	1.8%

The patients in our study presented clinical features similar to those identified in Samii's major study of clinical presentation in 1000 cases of VS. Hypacusis/anacusis has been found in 23 cases (60,5%), imbalance in 18 cases (47,4%), vertigo in 13 cases (34,2%), ataxia in 16 cases (42,1%), tinnitus in 8 cases (21,1%), nystagmus in 5 cases (13,2%),

headache in 2 cases (5,3%), facial dysesthesia in only 1 case (2,6%) and cerebellar dysarthria and diplopia in one case each (2,6%).

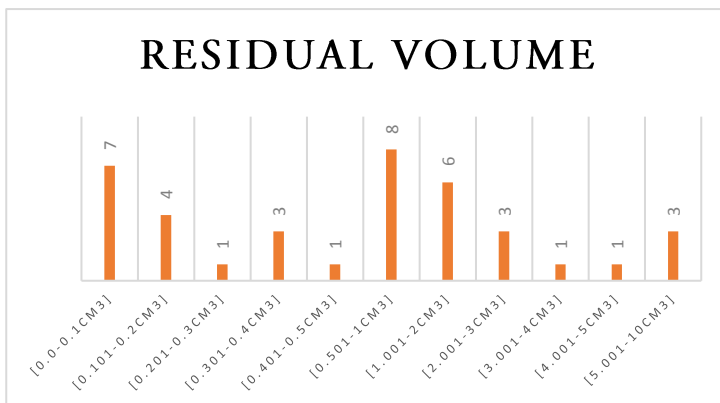
Preoperatively, for what concerns Facial Function: 37 patients (97.4%) had Good function (HB 1-2) and only 1 presented Fair facial function (HB 3). Hearing loss was considered as major ( $> 50\%$ ) and impossible to retrieve in 27 (71%) patients and minor ( $< 50\%$ ) and potentially retrievable in 11 patients (29%). Trigeminal function was conserved in 22 patient, and altered in 16.

Via statistical analysis, we investigated the presence of an association between size and clinical findings, and we highlighted a statistical significant association between tumor size and Facial Function, with a Pearson Coefficient of Correlation 0.662 ( $p < 0.0001$ ).



		HEARING PREOP	TRIGEMINUS PREOP	FACIALIS PREOP
<b>VOLUME</b>	Pearson	0,258	0,219	0,662
<b>PREOP</b>	P	0,1182	0,1859	<0,0001
	n	38	38	38

## 1<sup>st</sup> POSTOPERATIVE FOLLOW-UP



Residual tumor volume was between 0 – 8.35 cm<sup>3</sup>, mean 1.43 cm<sup>3</sup> with SD 2.04. Residual tumor rate was calculated considering volume and percentage (compared

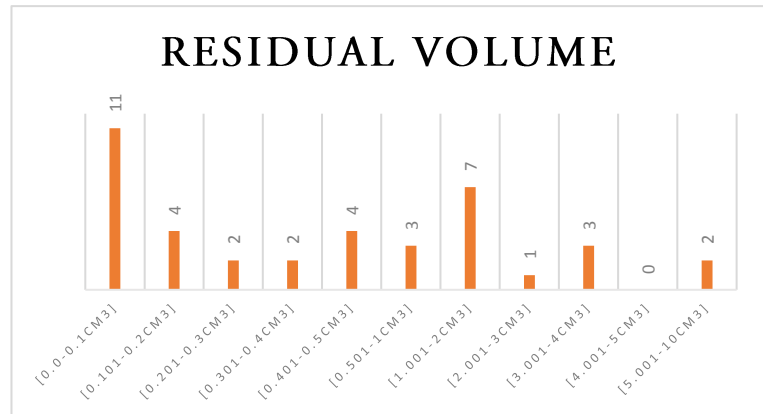
to initial mass). Residual rate interval was between 0 – 46%, mean 10.2% with SD 10.84.

Clinically, Facial outcome on first postoperative follow-up was as follows: 30 cases of “Good Function” HB1-2, 2 patients had “Fair Facial Function” HB3 and 6 had “Poor facial function” HB4-6.

Trigeminal function at 1st follow-up was conserved in 31 patients, and altered in 7. Hearing loss was found in 34 patients, with 4 preserving it.

## LAST POSTOPERATIVE FOLLOW-UP

At last follow-up (mean of 42 months) residual volume evolved positively with a decrease of mean dimension at  $1.09\text{cm}^3$   $[0.0-7.67\text{cm}^3]$  and SD of 1.73.



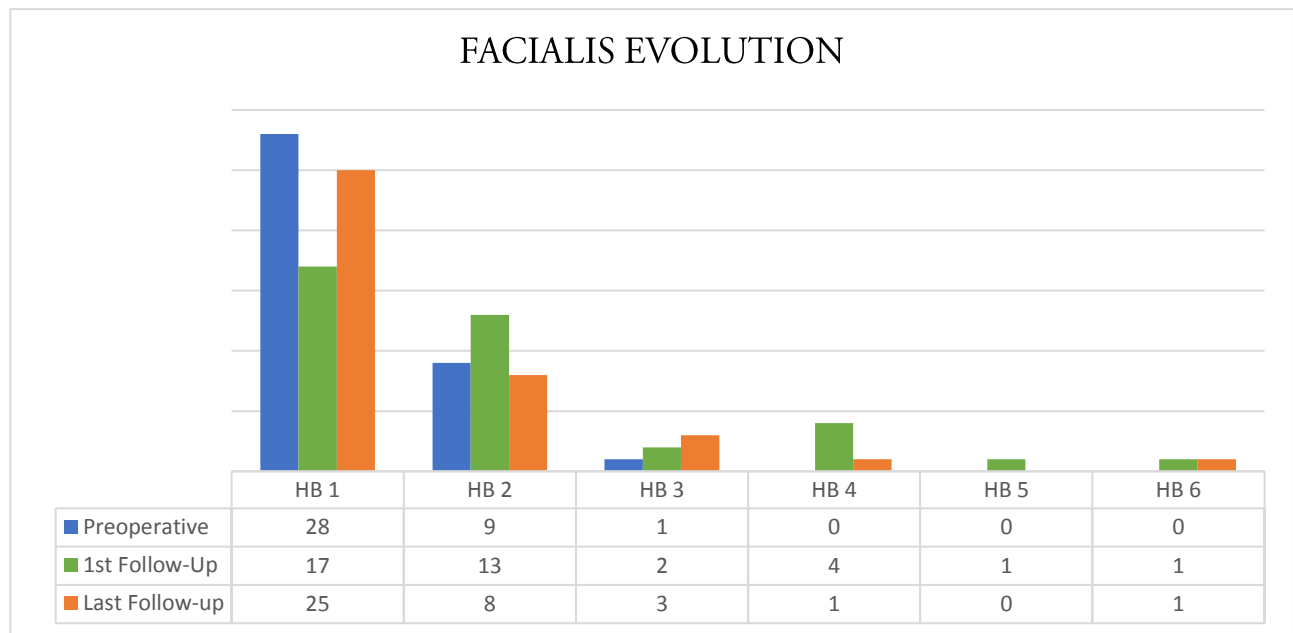
Facial Function was “Good” in 33 patients, “Fair” in 2 and “Poor” in 3. Hearing was finally lost in 36 cases and preserved in 2.

At this stage we had enough data to look into the presence of a correlation between tumor residual rate/volume and clinical outcome of facial, vestibulo-cochlear and trigeminal nerves; only the last one was significantly concerned at the last follow up.

		FACIALIS	HEARING	TRIGEMINUS	LAST TO FIRST
		LAST	LAST	LAST	RATE
RESIDUAL RATE	Pearson	-0,113	0,204	0,273	-0,162
	P	0,5011	0,2197	0,0967	0,3325
	n	38	38	38	38
RESIDUAL VOLUME	Pearson	-0,163	0,164	0,386	-0,035
	P	0,3267	0,3256	0,0168	0,8369
	n	38	38	38	38

## INTENDED SUBTOTAL REMOVAL AND FACIAL OUTCOME

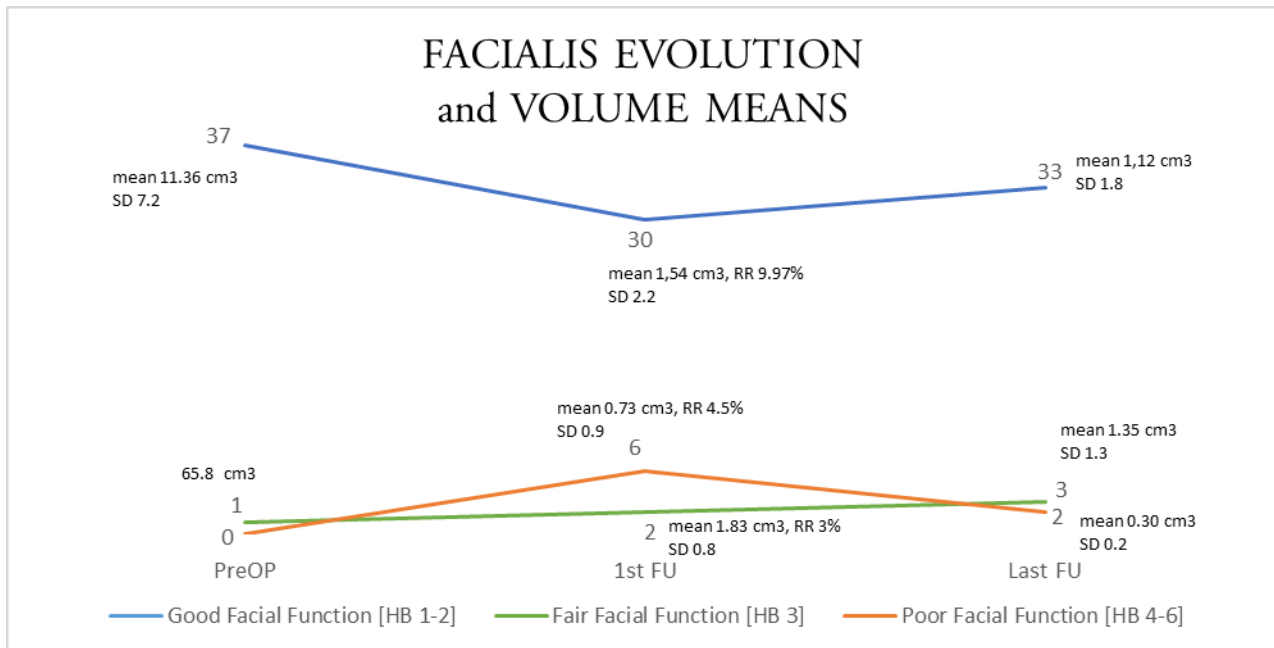
Evaluating Facial Nerve outcome in details it becomes increasingly clear that after subtotal removal, facial function decreases gradually from preoperative to first and last follow-up. There is an increase in the number of patients with “Fair” and “Poor” Facial function. Fortunately this situation evolves positively as shown in the graph below.



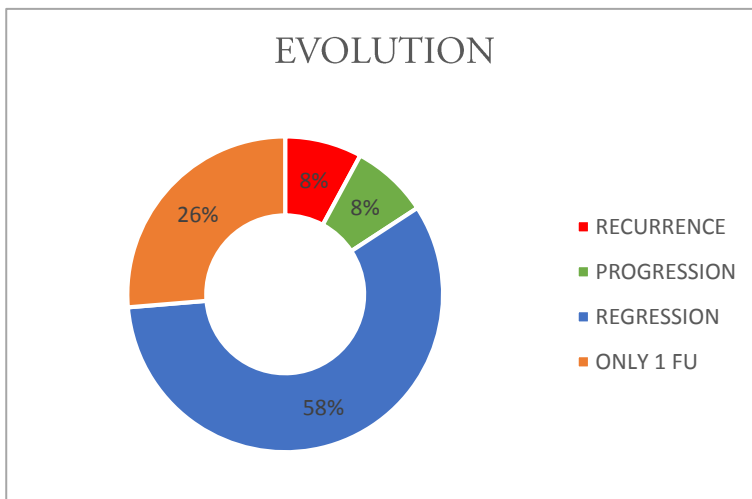
Secondly, we searched for a possible explication for facial outcome. In the next graph we outline our findings: on 1<sup>st</sup> follow-up, the mean of residual volume is lower in patients with “Poor facial function” ( $0.73\text{cm}^3$ ) than in patients with “Good facial function” ( $1.54\text{cm}^3$ ). The same is for residual rate, where the mean is lower in patient with “Poor” (4.5%) and “Fair” (3%) Facial function than in patients with “Good” function (9.97%). That can be explained with the fact that we went closer to Facial



Nerve to remove a larger tumor mass, but no significant correlation was found between them.



## INTENDED SUBTOTAL REMOVAL AND RECURRENCE RATE



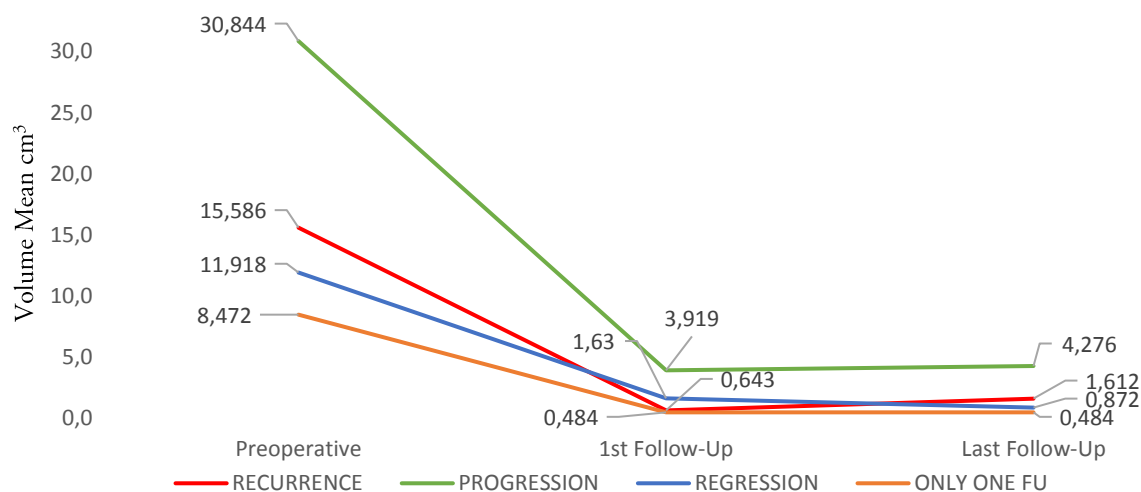
At the end of our radiological follow-up through MRI, we found: 22 cases of REGRESSION (58%) where tumor reduction was  $> 0\%$ ; 3 cases of PROGRESSION (8%)

with an increase of volume  $< 25\%$  and 3 cases of RECURRENCE (8%) defined as tumor expansion  $> 25\%$ . Unfortunately, at the end of our data collection, 10 patients benefited of only 1 follow-up, and more time would be necessary in order to evaluate their evolution and improve our statistical accuracy.

We looked for links between evolution and Volume Mean on preoperative, postoperative and at the last follow-up. None of these data were statistically relevant, but we can suspect a correlation between preoperative tumor volume mean and recurrence/progression rate. Cases with progression or recurrence had indeed a higher preoperative mean than those with regression or those who benefited of only 1 follow-up.

In opposite, patients with recurrence tend to have a lower mean of residual volume, meaning that recurrence rate is not related to residual volume. For what concern residual rate, patients who had a recurrence presented a mean of 4.65%, those with regression 13.14% and finally patients with progression 13.98%, excluding an association between recurrence rate and residual rate.

## TUMOR EVOLUTION and VOLUME MEAN



In this last paragraph of statistical analysis, we look for statistical association between residual rate/volume and recurrence/progression and Facialis Function at last follow-up.

The null hypothesis was ruled out with Wilcoxon test depending on the assumed distribution, with statistical significance defined as  $p \leq 0.05$ . The strength of association between paired variables was tested with Z statistic test.

- Association between Residual Volume ( $\text{cm}^3$ ) and Last-to-first rate (%) was excluded with Z 3.54,  $p=0.0004$ .
- Association between Residual Rate (%) and Last-to-first rate (%) was excluded too with Z 3.86,  $p=0.0001$
- We didn't find an association between Residual Volume ( $\text{cm}^3$ ) and Facialis Last (HB1-6) with Z 1.99,  $p=0.04$
- And last, an association between Residual Rate (%) and Facialis Grade at Last FU (HB 1-6) was excluded too with Z 4.66,  $p<0.0001$

## 4. DISCUSSION AND CONCLUSIONS

Vestibular schwannomas (VS) are benign tumours originated from the eight cranial nerve and they represent one of the hardest challenges for neurosurgeons.

Near-total intended removal has to be proved as a useful approach and data analysis ultimately confirms our initial hypothesis: recurrence rate seems not to be related to volume nor to rate of residual tumor.

Moreover, despite the existence of an early postoperative relationship between Facial Nerve Function and residual rate, its final outcome is not influenced by a higher rate of sub-total removal; we could not find a significant statistical connection between residual volume or rate and recurrence rate, nor between residual rate or volume and facial outcome. These considerations offer perspectives for a new era in the treatment of Large Vestibular Schwannoma.

Nevertheless, there are indeed some limits in this study.

First of all, surgical experience highly influences the success of VS surgery, especially intended sub-total removal. Secondly, the number of subjects in the study was at the limit of statistical significance and about one fourth of patients have not had more than one follow-up. Third, patients that showed signs of progression but not recurrence haven't yet been followed for a significant time of follow up; therefore it was not possible to draw conclusions.

In our last and more complete article, written by Dr. Daniel Zumofen soon to be published on *Neurosurgery*, we submitted a better statistical analysis showing how “the extent of resection was significantly lower ( $p=0.010$ ), and the residual tumor

volume significantly higher both at the first ( $p=0.017$ ) and at the last follow-up ( $p=0.00001$ ), in tumors whose remnants showed volumetric progression, compared to those whose remnants either remained stable or regressed” and “we found that initial tumor volume does not determine the facial nerve functional outcome”[34]

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