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Original article

Post-surgical vestibular schwannoma remnant tumors: What to do?☆

Reliquat tumoral post-chirurgical de schwannome vestibulaire : que faire ?

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ABSTRACT

Background. – Vestibular schwannomas (VS) are benign tumors of the vestibular nerve's myelin sheath. The current trend in VS surgery is to preserve at the facial function, even if it means leaving a small vestibular schwannoma tumor remnant (VSTR) after the surgery. There is no defined therapeutic management VSTR. The aim of this study was to assess the evolution of the VSTR to define the best therapeutic management and identify predictive factors of VSTR progression.
Methods. – Among the 256 patients treated surgically for VS in the Department of Neurosurgery at Angers University Hospital, 33 patients with a post-surgical VSTR were included in this retrospective study. For all surgical patients, the data collected were age at diagnosis, the Koos classification, the surgical access, the existence of a type 2 neurofibromatosis (NF2), the TR location and size on control MRI-scans. Patients had a bi-annual follow-up with clinical status and VSTR size assessment with MRI-scan. Survival analyzes were performed to determine the time and rate of VSTR progression, and identify factors of progression.
Results. – The mean follow-up of the population was 51 months. All VS remnant progression occurred between 38 and 58 months after surgery. In non-NF2 patients with first follow-up MRI-scan three months after surgery, 43% presented a spontaneous regression, 50% a stability and 7% a progression of the VSTR. In the same population with the 1-year MR-scan after surgery as baseline, 25% presented a spontaneous regression, 62.5% a stability and 12.5% a VSTR progression. These data are consistent with the data reported in the literature. The post-operative facial function impairment and an initial remnant $\geq 1.5\ cm^3$ were found to be significant risk factors of VS remnant progression in non-NF2 population in univariate analysis ($P = 0.048$ and 0.031) but not in multivariate analysis.
Conclusion. – In our experience, the best therapeutic management of the post-surgical VSTP in non-NF2 patients with no risk factor of progression is a simple clinical radiological follow-up otherwise complementary radiosurgery should be considered.

Mots clés :
Schwannome vestibulaire
Neurinome de l'acoustique
Reliquat tumoral
Radiochirurgie

RÉSUMÉ

Introduction. – Les schwannomes vestibulaires (SV) sont des tumeurs bénignes de la gaine du nerf vestibulaire. La tendance actuelle dans la prise en charge des SV est de conserver la fonction faciale, même si cela signifie laisser un reliquat tumoral (RT) en place lors de la chirurgie. Il n'existe pas de prise en charge thérapeutique définie de ce RT. Le but de cette étude est d'étudier l'évolution du RT afin de déterminer la meilleure prise en charge thérapeutique, ainsi que les facteurs pronostiques de progression du RT.
Patients et méthodes. – Nous avons réalisé une étude rétrospective portant sur 256 patients traités chirurgicalement pour SV dans le département de neurochirurgie du CHU d'Angers. Trente-trois patients

Abbreviations: GTR, gross total resection; IAC, internal auditory canal; NF2, type 2 neurofibromatosis; Retrosig, retrosigmoidian surgical approach; Translab, translabyrinthine approach; VS, vestibular schwannomas; VSTR, vestibular schwannomas tumor remnants.

☆ The preliminary results of this study was the subject of an oral communication at: Congress of the French Neurosurgical Society, Bordeaux, France, 22 Mars 2013; Congress of the French Speaking Association of Neuro-Oncologists, Bordeaux, France, 23 Mars 2013.

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porteurs d'un RT confirmé sur l'IRM de contrôle ont été inclus. Pour tous les patients chirurgicaux, les données recueillies étaient l'âge au moment du diagnostic, la classification de Koos de la lésion, la voie d'abord chirurgicale, l'existence d'une neurofibromatose de type 2 (NF2), l'emplacement du RT et la taille du RT sur les scanners de contrôle. Les patients ont eu un suivi bi-annuel avec bilan clinique et suivi de la taille du RT sur l'IRM de contrôle. Des analyses de survie ont été réalisées afin de déterminer le délai et le taux de reprise évolutive du RT, ainsi que les facteurs prédictifs de cette reprise évolutive.

Résultats. – La durée de suivi moyen de la population était de 51 mois. Toutes les reprises évolutives de RT de schwannome vestibulaire sont survenues entre 38 et 58 mois après la chirurgie. Chez les patients non NF2 avec comme IRM de référence celle faite 3 mois après la chirurgie, 43 % présentaient une régression spontanée, 50 % une stabilité et 7 % une progression du RT. Dans la même population comme IRM de référence celle faite 1 an après la chirurgie, 25 % présentaient une régression spontanée, 62,5 % une stabilité et 12,5 % une progression du RT. Ces résultats sont cohérents avec les données de la littérature. L'altération de la fonction faciale post-opératoire et un volume tumoral initial $\geq 1{,}5\,cm^3$ sont significativement associés à un risque de progression du RT de VS dans la population non NF2 en analyse univariée ($p = 0{,}048$ et $0{,}031$) mais pas dans l'analyse multivariée.

Conclusion. – La prise en charge thérapeutique des RT post-chirurgicaux de SV la plus adaptée chez les patients non-NF2 sans facteur de risque de progression semble être un suivi clinico-radiologique simple, tandis qu'une radiochirurgie complémentaire nous semble être nécessaire dans les autres cas.

1. Introduction

Vestibular schwannoma (VS) is an histologically benign tumor arising from the schwannoma cell sheath of the vestibular portion of the VIII cranial nerve. VS is the most common tumor of the cerebellopontine angle, with an incidence of 2/100 000 per year, currently increasing as the initial size at diagnosis has decreased. These changes in the epidemiology of the VS have been reported as a consequence of the multiplication of brain MRI-scan investigations [1,2]. Typically, VS clinical symptoms begin with otologic symptoms characterized by unilateral perception hearing loss. If there is no subsequent treatment neurologic signs i.e. ataxia, gait disturbance, facial function impairment or hydrocephalus may then appear.

There are three main possibilities in the management of VS: a "wait-and-see" policy, consisting of a simple clinical follow-up with regular MRI-scan, primary radiosurgery or surgery. Decision management of VS is complex and will depend on a multitude of factors influencing the therapeutic approach.

VS localization in the cerebellopontine angle makes the surgery a technical challenge. The previous trend in therapeutic management was to treat VS surgically with a complete resection even at the cost of an impairment of the facial function. However, currently facial palsy is regarded as a severe handicap by the patient and is no longer considered an acceptable post-operative result. This attitude has led to a change of approach with the preservation of facial function as the first aim of surgery, before the complete resection of the VS [3–5].

Surgeons now prefer to leave a small remnant instead of risking the facial function of the patient by performing a complete resection [6], and this change of attitude in VS surgery is leading to an increase in the prevalence of post-operative vestibular schwannoma tumor remnants (VSTR), which makes the problematics of VSTR management a more frequent question.

There is no defined therapeutic approach towards this VS remnant. Some surgical teams recommend routine radiosurgery [7–12] while other teams have adopted a "wait-and-see" attitude [13–15], keeping radiosurgery for regrowth of the VS remnant [16,17].

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

2. Aims of the study

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

3. Methods

3.1. Patient population

All consecutive patients who underwent surgical treatment of VS in the Department of Neurosurgery at Angers University Hospital between 1977 and 1st May 2013 were included in the study. They all underwent 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 in the Koos classification [18,19], and no longer had a useful hearing capacity before surgery, with a Tokyo score of C or worse. The diagnosis was confirmed histologically in all cases.

3.2. Surgical technique

A multidisciplinary team, made up 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 translabyrinthine approach, allowing a more effective exposition of the internal auditory canal, was favored, except in patients with an ipsilateral partial hearing preservation, where the retrosigmoid approach was preferred in an attempt to preserve hearing. Facial nerve 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 weighed against the GTR of the tumor, and chose to leave a small tumor remnant to avoid any facial nerve lesions.

3.3. 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 when available, or with CT-scan by default.

The first consultation and clinico-radiological follow-up were performed three months after surgery. Therapeutic approach towards the VS remnant was then decided depending on the size of the residual tumor and the age of the patient.

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

MRI-scans were carried out with a 1.5 T Siemens Magnetom MRI-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 1 mm and a slice spacing of 0.8 mm. Assessment of the radiological follow-up was performed using the 3-plane radius of the tumor, data allowing 3D reconstruction, which was unfortunately not available for all patients.

3.4. Data collection and analysis

We performed 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 of May 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 data 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 as well as the secondary therapeutic decision that was made;
- facial nerve function before, after surgery and at the primary end-point using the House-Brackmann classification [20].

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 or with injection-enhanced sequence in CT-scan. The 3-plane tumor radii were measured on DICOM images using a multiplanar reconstruction mode [21].

Statistical analysis was then carried-out 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 performed in the search for the remnant recurrence factors with remnant progression defined as the primary event.

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

Among patients with VS, we must distinguish those 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 [22–24]. Therefore, to refine our analysis and to differentiate the potential therapeutic management approaches between NF2 and non-NF2 patients, we decided to continue our analysis with non-NF2 patients alone. The evolution of the NF2 patients will be discussed in a separate paragraph and due to the small number of patients, their results will not be considered in the discussion.

4. Results

4.1. Description of the population in the study

Among the 600 patients who were followed-up 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% (Fig. 1).

In this population of 65 patients, 17 patients with a VSTR observed per-operatively by the surgeon did not have a radiologically confirmed GTR. This produces a concordance rate of 74% between the surgeon's appreciation and the MRI-scan check with an overestimation of the presence of a VSTR by the surgeon. In addition, one patient died of meningitis before the first checkup MRI-scan and one patient discontinued the study due to a transfer to another University hospital 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 check-up MRI-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 MRI-scan, 4 young patients with a large VSTR were referred immediately to radiosurgery and 33 patients underwent a simple follow-up. We also excluded 7 patients who had recently undergone surgery and had not undergone a MRI-scan check-up after the beginning of the clinico-radiological follow-up to allow the radiological assessment of VSTR evolution (Fig. 1, Table 1).

Therefore, in our study we included the 33 patients who had a per-operative VSTR confirmed on the first MRI-scan and who had undergone a basic follow-up.

4.2. Evolution of the "wait-and-see" population

Among patients with VS, patients with NF2 must be distinguished. In fact, their different pathophysiological features make them stand out from the non-NF2 population due to their clinical evolution, the number of lesions, their evolution and the different histology with hearing preservation as the main therapeutic goal [22–24]. Therefore, to refine our analysis and to differentiate the potential therapeutic management approaches between NF2

Table 1
Characteristics of the population.
Caractéristiques de la 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	5 (15%)
VSTR location	
CPA	19 (58%)
IAC	5 (15%)
Porus	9 (27%)
VSTR size at first checkup MRI-scan (cm^3)	0.75 ± 2.36
Follow-up duration (months)	60 ± 65.3
Mean pre-operative facial function	1 ± 0.2
Mean post-operative facial function	2.53 ± 2
Mean facial function at end-point date	2 ± 1.66

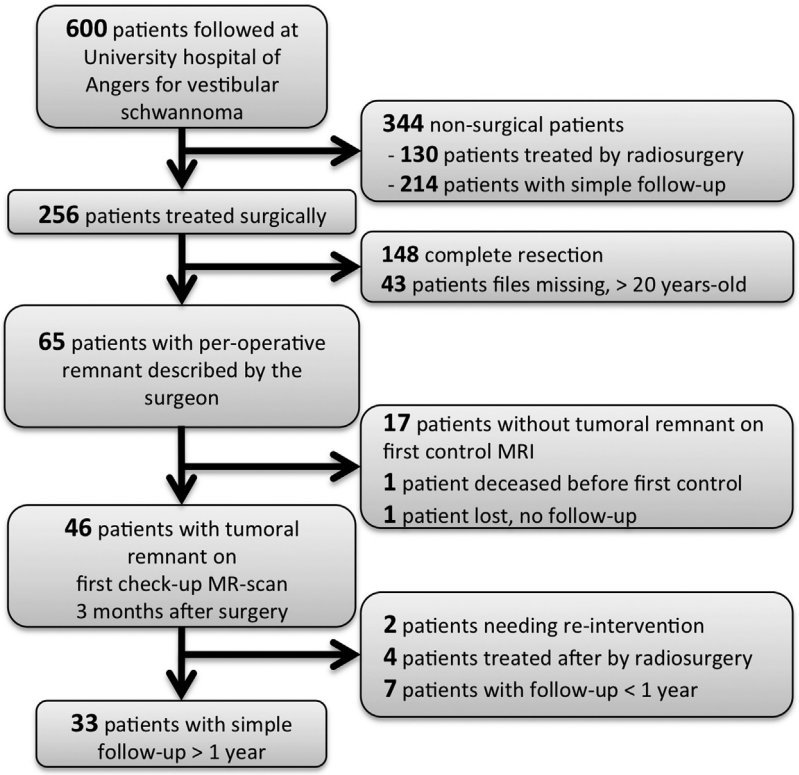

Fig. 1. Flow-chart of the population of VS patients followed-up at Angers University Hospital.
Diagramme de flux de la population de patients suivis pour un schwannome vestibulaire au CHU d'Angers.

and non-NF2 patients, we decided to continue our analysis with non-NF2 patients alone. The evolution of the NF2 patients will be discussed in a separate paragraph.

4.2.1. "Wait-and-see" non-NF2 patients with reference MRI-scan 3 months after surgery

Thirty non–NF2 patients had a radiological remnant on the MRI-scan 3 months after surgery and a follow-up of more than a year. In this population of 30 non-NF2 patients, with reference MRI-scan at 3 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 (Fig. 2).

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 2). No statistical difference was observed 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 2).

In multivariate analysis, the VS remnant size was significantly higher in the progression group versus the stable group ($p = 0.039$).

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

The delay between surgery and the first post-operative MRI-scan, usually done 3 to 12 months post-operatively, remains subject to debate. The main risk of an early post-operative MRI-scan is the confusion between a post-operative tumor remnant and post-operative scar tissue, which may lead to a false over estimation of the post-surgical remnant rate. To minimize this risk, we analyzed the same population of patients and the evolution of VS post-surgical remnant using the 1-year post-op MRI-scan as a reference.

Sixteen non–NF2 patients had a radiological remnant on the MR-scan 1 year after surgery and a follow-up of more than a year after the MRI-scan reference. The number of patients was lower

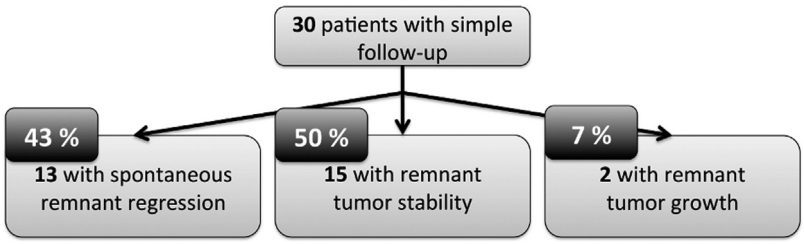

Fig. 2. Description of the population of VS non NF2 patients with a per-operative VSTR described by the surgeon. First check-up MRI-scan three months after surgery.
Description de la population de patients non NF2 opérés d'un schwannome vestibulaire avec un reliquat décrit en per-opératoire par le chirurgien. 1re IRM de contrôle à 3 mois.

Table 2
Univariate analysis and description of the evolution of VSTR in the non-NF2 "wait-and-see" population.
Analyse univariée et description de l'évolution de VSTR dans la population non-NF2 wait-and-see.

	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 approach				0.59
Translabyrinthine	12 (92%)	13 (87%)	2 (100%)	
Retrosigmoidian	1 (8%)	2 (13%)	–	
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 MRI-scan	1.1 ± 3.1	0.1 ± 0.2	14 ± 1.8	0.06
Mean follow-up duration (months)	44.6 ± 26.7	56.6 ± 67.8	48 ± 14.1	0.84
Mean pre-operative facial function	1 ± 0	1.1 ± 0.3	1 ± 0	0.16
Mean post-operative facial function	2.7 ± 2.2	1.9 ± 1.6	5.5 ± 0.7	0.02
Mean facial function at end-point date	1.9 ± 1.9	1.7 ± 1.3	4 ± 2.8	0.47

than the previous group with first MRI-scan 3 months after surgery. Nine patients had an insufficient follow-up duration and thus were excluded, and 5 patients were excluded and considered as GTR because of the absence of a remnant on 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 (Fig. 3). 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 3).

Also in this group, there was a significant association between post-surgical facial function and the VSTR evolution in univariate analysis (p= 0,01), confirmed in the multivariate analysis (p= 0.05) (Table 3).

4.2.3. NF2 patients

In the literature, NF2 patients are considered a specific entity among VS patients, with a specific medical history and specific management. In our study, 3 NF2 patients were included, representing 9.1% of the population with a post-operative tumor remnant shown on the MRI-scan at 3 months.

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 entire 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 was identified. Due to the small number of NF2 patients, they were not included in the discussion.

5. Survival analysis of VS remnant growth

5.1. Non-NF2 population

5.1.1. Overall survival curve

In the entire non-NF2 population ($n=30$), the average follow-up duration was 51 months and the median of 37 months. All VS remnant progression occurred between 38 and 58 months after surgery (Fig. 4).

5.1.2. Statistical analysis

Univariate analysis showed a significant risk of progression in patients with an initial tumor remnant volume $\geq 1.5\ cm^3$ or a post-operative facial nerve function score ≥ 4 on the House-Brackmann scale ($P=0.048$ and 0.031) (Fig. 5A and B). 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 VSTR progression.

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 ($P=0.82$).

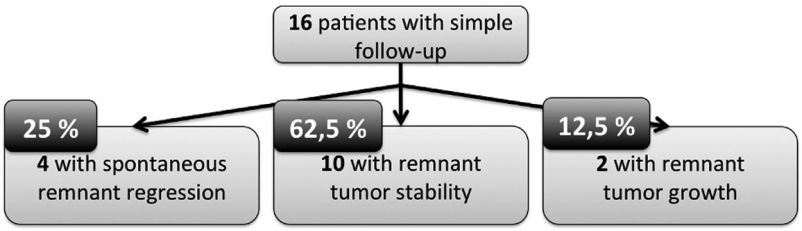

Fig. 3. Description of the population of VS non-NF2 patients with a per-operative VSTR described by the surgeon. First check-up MRI-scan one year after surgery.
Description de la population de patients non NF2 opérés d'un schwannome vestibulaire avec un reliquat décrit en per-opératoire par le chirurgien. 1re IRM de contrôle à 1 an.

Table 3
Univariate analysis and description evolution of VS TR in the non-NF2 "wait-and-see" population with first MRI-scan at one year after surgery.
Analyse univariée et description de l'évolution du reliquat post-chirurgical de schwannome vestibulaire dans la population non NF2 sous simple surveillance. IRM de référence 1 an après chirurgie.

	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	–	2 (20%)	–	
VSTR location				0.5
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
Mean follow-up duration (months)	38 ± 20	65.6 ± 75.3	31 ± 7.1	0.16
Mean pre-operative facial function	1 ± 0	1.2 ± 0.4	1 ± 0	0.16
Mean post-operative facial function	3 ± 2.5	1.8 ± 1.4	5.5 ± 0.7	0.01
Mean facial function at end-point date	2.5 ± 2.3	1.8 ± 1.4	4 ± 2.8	0.5

5.1.3. Comparison with non-NF2 population, first MR-scan one year post-op

In this population ($n=16$), the two significant VSTR main progressions occurred at 26 and 46 months after surgery (Fig. 6A).

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 ($P=0.021$) (Fig. 6B).

However, in this group, the presence before surgery of VIIth nerve impairment with a score ≥ 2 is associated with a significant risk of progression ($P=0.001$) (Fig. 6C). The initial VSTR size was not considered a progression factor in this group ($P=0.193$).

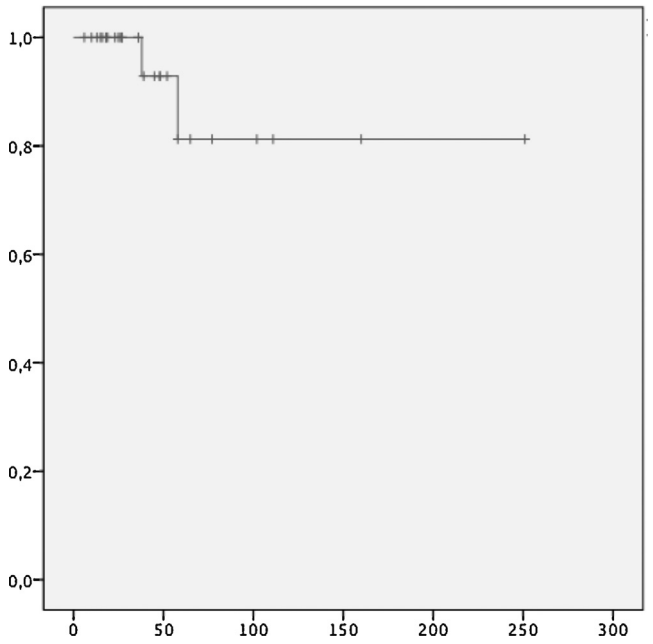

Fig. 4. Non-progression survival curve for non-NF2 patients with VS remnant. *x*-axis: time in months after surgery, *y*-axis: probability of non-progression.
Courbe de non-progression du reliquat tumoral chez les patients non NF2 porteur s'un reliquat tumoral post-chirurgical. Abscisse : temps en mois, ordonnée : probabilité de non progression du reliquat tumoral.

5.2. NF2 population

Two NF2 patients presented a VSTR, one at 48 months and one at 300 months (25 years) after surgery (Fig. 7).

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

However, in the survival analysis of the entire population, the existence of an NF2 was not found to be a significant risk factor of progression ($P=0.5$).

6. 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 approach 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 to focus on the natural history of VS post-surgical remnants and to establish the predictive factors of progression. This original study might shed new light on the optimal 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 who are 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 to follow-up during 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 routine radiosurgery for young people with major post-surgical VSTR. These strategies were chosen by the surgeons to minimize the recurrence rate, data regarding the VSTR progression rate and natural evolution under surveillance not currently available.

However, this study does not present an attrition bias, nor an evaluation bias. All patients, even those patients lost to follow-up in

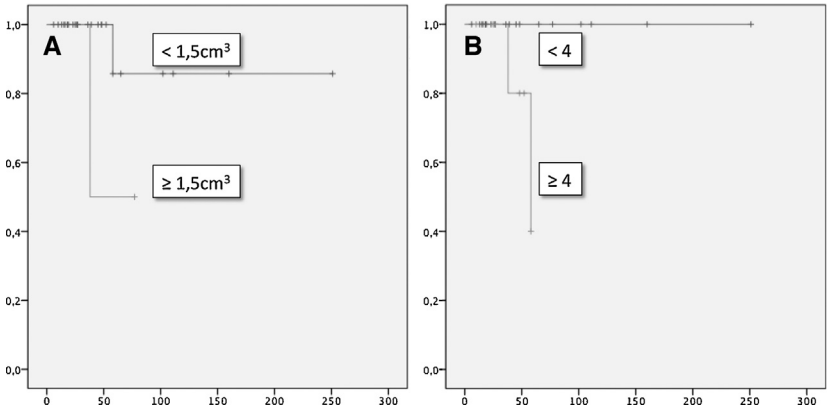

Fig. 5. Kaplan-Meier stratification of VSTR non-progression survival curves and first MR-scan three months after surgery. *x*-axis: time in months after surgery, *y*-axis: probability of non-progression, notches and circles: censored data. A. Stratification by VS remnant volume with cut-off ≥ 1.5 cm^3. B. Stratification by postoperative facial function with cut-off ≥ 4.

Stratification selon la méthode de Kaplan-Meier des courbes de non-progression du reliquat post-chirurgical de schwannome vestibulaire. IRM de référence 3 mois après la chirurgie. Abscisse : temps en mois, ordonnée : probabilité de non progression du reliquat tumoral. A. Stratification en fonction du volume du reliquat post-chirurgical de schwannome vestibulaire avec un cut-off ≥ 1,5 cm^3. B. Stratification en fonction de la fonction faciale en post-opératoire immédiat avec cut-off ≥ *4.*

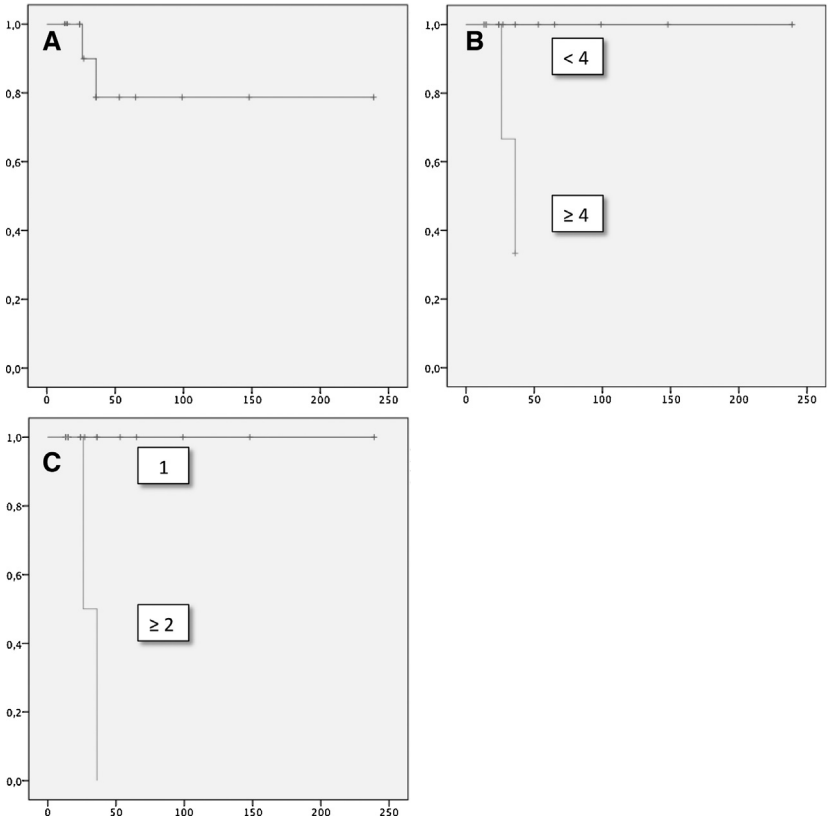

Fig. 6. Survival curves for non-NF2 patients with VSTR and first MRI-scan one year post-operatively. *x*-axis: time in months after surgery, *y*-axis: probability of non-progression. A. Overall survival curve. B. Stratification by post-operative function with cut-off ≥ 4. C. Stratification by pre-operative facial function with cut-off ≥ 2.

Courbes de survie de non-progression du reliquat tumoral chez les patients non-NF2 porteur s'un reliquat tumoral post-chirurgical. IRM de référence 1 an après la chirurgie. Abscisse : temps en mois, ordonnée : probabilité de non-progression du reliquat tumoral. A. Courbe de survie globale. B. Stratification en fonction de la fonction faciale en post-opératoire immédiat avec cut-off ≥ *4. C. Stratification en fonction de la fonction faciale en pré-opératoire immédiat avec* cut-off ≥ *2.*

the study, were included and the same surgeon performed a routine evaluation at regular time intervals.

7. Timing of the radiological assessment after VS surgery

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

The risk of an early MRI-scan check-up is to confuse VSTR with post-surgical scaring because of the similar 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 had the presence of the VSTR confirmed both per-operatively by the surgeon and radiologically on the control MRI-scan. This double confirmation minimizes the

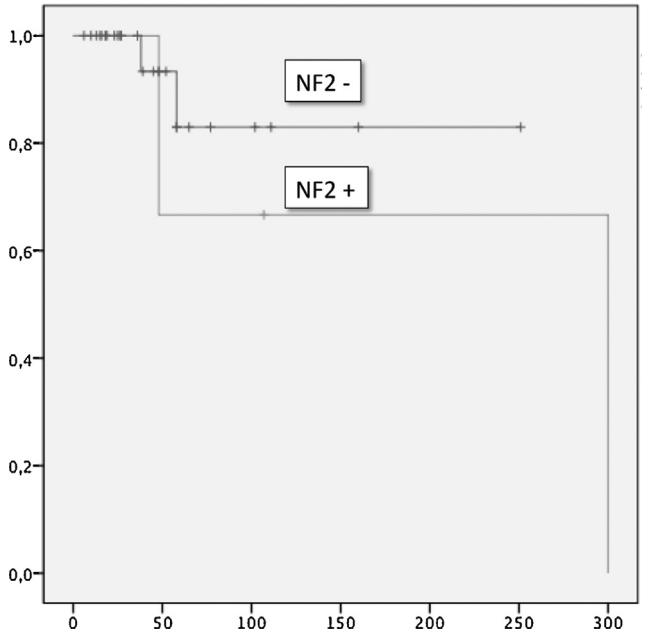

Fig. 7. Survival curves for VSTR non-progression in the whole population, stratified by the presence of an NF2. *x*-axis: time in months after surgery, *y*-axis: probability of non-progression, notches and circles: censored data.
Stratification de la probabilité de non-progression du reliquat post-chirurgical de schwannome vestibulaire en fonction de la présence ou non d'une NF2. Abscisse : temps en mois, ordonnée : probabilité de non progression du reliquat tumoral.

risk of confusion between a VSTR and a post-surgical scar in our study.

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 MRI-scan after surgery is a loss of information about early VSTR evolution. In our study, five patients with VSTR presented a complete spontaneous regression of their tumor remnant during the first year. This data could 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 experience, the 3-month post-op MRI-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.

8. Comparison of VS remnant evolution and progression rate with the literature

In non-NF2 patients with the first MRI-scan three 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 via radiosurgery [8].

Considering this patient population, its seems more appropriate to adopt a "wait-and-see" attitude instead of a routine radiosurgical treatment of VS surgical remnant, the benefit/risk balance being clearly in favor of a simple follow-up.

With one year post-op MRI-scan as reference, only 16 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 slightly higher than the previous rates found in the literature [8,25]. The population reduction explained in the results may be, in our estimation, the primary explanation for the increase of the progression percentage.

In our experience, 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.

9. Predictive factors of VS remnant growth

This original study is the first, to our knowledge, to assess 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 the "wait-and-see" policy should be given priority for non-NF2 patients, we decided to continue our investigation and attempt to establish predictive factors for recurrence.

In the entire population, we observed that almost all VS remnant progression occurred three to five years after surgery. The data of our retrospective study is in agreement with the literature [15,26]. However, with a median follow-up of 37 months, we cannot fully predict the long term risk of VS remnant progression. Thus, this explains why numerous cases of very late progression of VS remnants have been reported in the literature.

In each population the immediate post-operative facial function impairment ≥ 4 based on the House-Brackmann grading scale was statistically associated with a progression of the remnant. When examining the patient's file, this was explained by an altered per-operative facial function, leading the surgeon to end the intervention prematurely to preserve the facial function. This means leaving an unplanned VS remnant in size and location, with unsatisfactory surgery in the surgeon's opinion. The unplanned size of the VS remnant may be an explanation of the statistical association between post-operative facial function alteration and VS remnant progression, as the size of the remnant is a known factor of secondary progression.

In non-NF2 patients, the initial VS remnant volume also appears to be a statistically significant progression predictor, with a cut-off point at 1.5 cm^3, inferior to the 2.5 cm^3 cut-off point previously described by Vakilian et al. [27]. This predictive factor may be explained by the less efficient devascularization of large tumor remnants.

All recurring VS remnants 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. However, the Koos stage and therefore the initial volume of the VS was not found to be a statistically significant predictive factor, as described in previous studies [5,28,29].

Also, no significant progression was found with VS remnants located in the internal auditory canal (IAC), consistent with the literature, where no progression of VS located in the IAC was observed [15,30].

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 patient population.

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 also observed 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 were not statistically significant.

10. 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 clinical-radiological follow-up. The goal is to avoid routine radiosurgical treatment of VS remnants. Only the few remnants that will progress over time in the population presenting a low progression rate will be retained. 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 an effective technique providing a minimally invasive treatment at low risk for primary VS management [10,31–36]. However, for post-surgical VS remnants, its indications remain unclear. Nevertheless, even if it is a minimally invasive treatment, radiosurgery may have side-effects and complications. Ito et al. described 36% of transient facial palsy and 8.6% of severe permanent facial palsy and 14% of total hearing loss in patients with partially preserved hearing [28,37]. In clinical practice, radiosurgery in treatment of VS remnants is acceptable only if its benefits surpass its potential risks compared to other therapeutic options.

Re-operation is considered less often, due to its technicality, with an major risk of complications higher than the two previous therapeutic options with cranial nerve impairment and cerebro-spinal fluid leakage. Ramina et al. reported in their study of VS re-operation 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 [38]. One option to be considered in this category is the 2-staged surgery for large VS, that can improve facial outcome and diminish the morbidity [39].

We suggest therapeutic management for patients with radiologically confirmed VS remnants depending on the criteria highlighted in this study (Fig. 8).

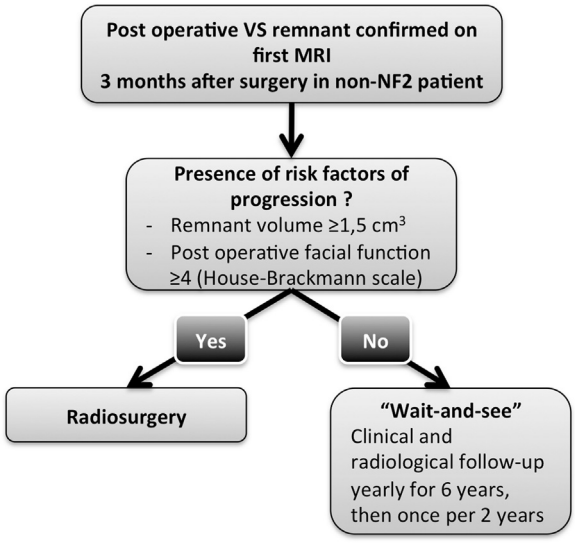

Fig. 8. Therapeutic management proposal for VS post-surgical remnant in non-NF2 patients.
Proposition de prise en charge thérapeutique des patients non NF2 porteurs d'un reliquat post-chirurgical de schwannome vestibulaire.

MRI-scans remain the radiological exam of choice to monitor 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 MRI-scan checks to determine the existence of a post-operative remnant makes the first check-up MRI-scan the best check with a sensitivity and a specificity up to 100% [40].

The first MRI-scan one year after surgery may permit 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 perform the first MRI-scan three months after surgery to allow early detection of post-surgical complications, and monitor early VS remnant regression, as in the series reported by Roche et al. [12].

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

For patients with a VS remnant, all progression occurred between three and five years after the first surgery. This suggests that a close follow-up during the first six years after surgery is needed, and can be more widely spaced after this critical period of surveillance (Fig. 8).

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 due to the risk of aggravation. Nevertheless, 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.

11. Spontaneous remnant regression: myth or reality?

The existence of spontaneous regression of post-surgical VS remnants is subject to question. Only a few studies have reported its existence and radiological behavior [14,41]. It is often attributed to a post-surgical scar.

In our study, 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 three 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-operative analysis and in studies based on 1-year post-surgery MRI-scans.

Distinction between a VS remnant and a post-surgical scar can be confusing, requiring authors to be cautious about the interpretation of the rapid disappearance of contrast-enhanced lesion located in the surgical site. However, we think that we can safely affirm that no confusion was made between VS remnant and post-surgical scar in this study, since each VS remnant was described per-operatively by the surgeon and the tumor remnant location on first check-up MRI-scan exactly matched the remnant described by the surgeon, as shown in Fig. 9.

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 et al. [14].

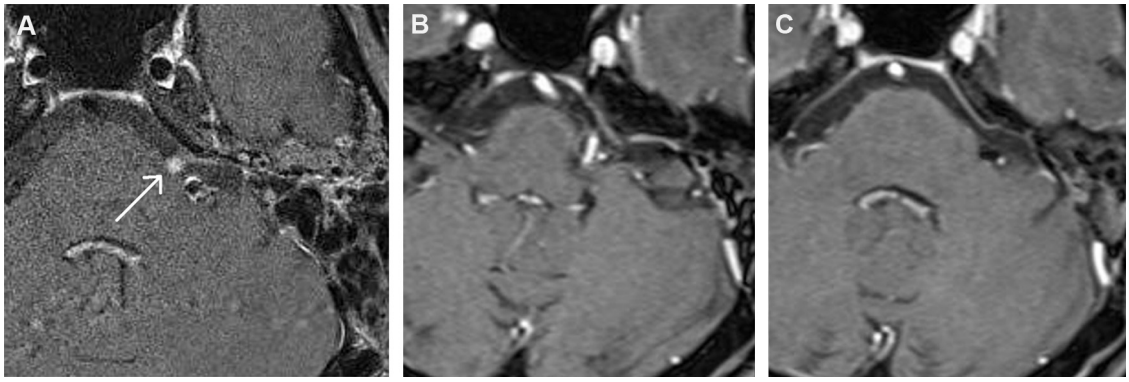

Fig. 9. Vestibular schwannoma remnant spontaneous regression. Illustrative case of a 50-year-old patient. A. Vestibular schwannoma remnant on control MR-scan one year after surgery. B and C. Complete regression of the vestibular schwannoma remnant on MR-scan two years after surgery.
Régression spontanée d'un reliquat tumoral de schwannome vestibulaire. Cas illustratif d'une patiente de 50 ans. A. reliquat tumoral visible sur l'IRM post-opératoire à 1 an. B et C. Régression complète du reliquat tumoral sur l'IRM de contrôle 2 ans après la chirurgie.

12. Conclusion

Initial VS remnant size $\geq 1.5\ cm^3$ and immediate post-operative facial function impairment with House-Brackmann score ≥ 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 clinical-radiological follow-up whereas, patients with a least one of the predictive factors of progression may in fact benefit from radiosurgery.

13. Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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