Role of electrophysiology in guiding near-total resection for preservation of facial nerve function in the surgical treatment of large vestibular schwannomas

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OBJECTIVE In large vestibular schwannoma (VS) surgery, the facial nerve (FN) is at high risk of injury. Near-total resection has been advocated in the case of difficult facial nerve dissection, but the amount of residual tumor that should be left and when dissection should be stopped remain controversial factors. The objective of this study was to report FN outcome and radiological results in patients undergoing near-total VS resection guided by electromyographic supramaximal stimulation of the FN at the brainstem.

METHODS This study was a retrospective analysis of a prospectively maintained database. Inclusion criteria were surgical treatment of a large VS during 2014, normal preoperative FN function, and an incomplete resection due to the strong adherence of the tumor to the FN and the loss of around 50% of the response of supramaximal stimulation of the proximal FN at 2 mA. Facial nerve function and the amount and evolution of the residual tumor were evaluated by clinical examination and by MRI at a mean of 5 days postoperatively and at 1 year postoperatively.

RESULTS Twenty-five patients met the inclusion criteria and were included in the study. Good FN function (Grade I or II) was observed in 16 (64%) and 21 (84%) of the 25 patients at Day 8 and at 1 year postoperatively, respectively. At the 1-year follow-up evaluation (n = 23), 15 patients (65%) did not show growth of the residual tumor, 6 patients (26%) had regression of the residual tumor, and only 2 patients (9%) presented with tumor progression.

CONCLUSIONS Near-total resection guided by electrophysiology represents a safe option in cases of difficult dissection of the facial nerve from the tumor. This seems to offer a good compromise between the goals of preserving facial nerve function and achieving maximum safe resection.

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KEY WORDS electromyography; CPA tumors; monitoring; vestibular schwannoma

A vestibular schwannoma (VS) is a benign, slow-growing tumor of the Schwann cells originating from the vestibular branch of the eighth cranial nerve, with an incidence of 12.4 tumors per million persons per year.27 Therapeutic options include an active wait-and-scan policy, stereotactic radiosurgery, and microsurgery. Although there is no general consensus for the treatment of small and medium-sized lesions, surgery still remains the preferred option for large tumors.

When surgery is indicated, preservation of good facial nerve (FN) function represents the most important goal. With large tumors, the possibility of developing facial palsy is higher than with smaller lesions.27 Many retrospective clinical studies have been carried out to define the prognostic factors influencing the early5 and long-term14 outcomes with respect to the FN. The size2,23 and characteristics of the tumor,20 the surgical observation and adherence of the FN,14 and electromyography (EMG) respons-
observations, tumor remnants thicker than 7.4 mm or with tumor control, as shown recently by Monfared et al., in their study, they observed a rate of VS regrowth that was 3 times higher in patients who underwent STR compared with those who underwent gross-total resection (GTR) or NTR. The authors did not explain in detail the reasons for having performed STR, apart from “the surgeon’s discretion considering intraoperative findings such as tumor adherence.”

The risk factors for tumor regrowth have largely been studied in other retrospective investigations: the extent of resection, the degree of adherence, and the volume of VS tumor. The extent of resection seems to be the most reported prognostic factor; when taking into consideration measurements based on postoperative MRI and not on surgical observations, tumor remnants thicker than 7.4 mm or with volume greater than 2.5 cm have a significantly higher rate of recurrence.

In our present study of cases in which VS surgery was guided primarily by electrophysiological responses rather than just surgical observation, we tried to identify the outcome with respect to FN function and the amount and evolution of the residual tumor when dissection of the VS from the FN was stopped to avoid FN dysfunction.

Methods

Study Design

This study was an analysis of data from medical records and a prospectively maintained database that includes all cases involving patients who undergo surgery for VS performed by the same neuro-otological team at our tertiary academic referral center. The study was approved by the local institutional review board (CPP Île-de-France VI). All patients provided written informed consent for inclusion in this study.

The inclusion criteria were surgical treatment of a large solitary VS (Stage III or IV) between January 2014 and December 2014 with electrophysiological monitoring, normal preoperative FN function, and interruption of dissection of the FN from the tumor because of loss of around 50% of the response of the nerve to a supramaximal stimulation (2 mA) at the brainstem associated with strong adherence of the tumor to the FN. This last criterion is based on an earlier study by the Mayo Clinic showing the usefulness of interrogating intraoperative FN function to predict which patients will ultimately have good facial nerve function. Patients suffering from neurofibromatosis Type 2 and patients operated on for a recurrent VS and/or with preoperative FN palsy were excluded. Four-channel FN monitoring (NIM3, Medtronic) was used for electromyography, and the response taken into consideration was the highest amplitude response of the 4 channels. The difference between electrode impedances was less than 1 Ω, and the FN was electrically stimulated by a monopolar probe with a 0.5-mm tip. Square current waves with 100-msec duration at 4-Hz frequency were applied as stimulation.

Surgery

All patients were operated on in the supine position under general anesthesia through a translabyrinthine or retrosigmoid approach. For all patients, general anesthesia was induced with a mixture of sufentanil (0.15–1.3 μg/kg), propofol (2–3 mg/kg), and atracurium (0.5 mg/kg) before endotracheal intubation. In order to avoid confounding electrophysiological issues, anesthesia was maintained during the procedure with sevoflurane (1.5%–2.5%) and intravenous infusion of sufentanil (0.1–0.2 μg/kg/h), without any myorelaxant. FN dissection was performed after checking that myorelaxation was abolished with more than 90% train-of-four response. Body temperature was monitored and maintained between 36°C and 37°C with a warming blanket. Mean blood pressure was maintained between 65 and 75 mm Hg and end-tidal CO₂ between 30 and 35 mm Hg to preserve brain perfusion.

After opening the dura mater, the VS was initially debulked intratumorally with a tumor capsule preservation, the proximal segment of the FN at the brainstem always being rapidly identified. The FN was then stimulated supramaximally using a 2-mA stimulating current, and the peak response obtained from the channel having the greatest amplitude response was recorded as a baseline. Then, dissection of the FN proceeded laterally toward the porus with tumor reduction performed under constant visual observation of the FN. When the FN was hidden by the VS at the porus, the dura of the internal auditory canal (IAC) was opened, and the FN was identified at the fundus of the IAC after sectioning of the vestibular nerve. The dissection of the FN was then continued to the porus and to the cerebellopontine angle (CPA) while progressively reducing the amount of residual tumor. During this step, in case of an adherent FN, proximal supramaximal stimulation was regularly performed after each piece of tumor was removed and the dissection was interrupted if there was a loss of response that was close to 50% associated with adherence of the VS to the FN with interruption of the pial plane of the FN. Monitoring of the FN and all measurements were performed by the same technician. Since this method does not allow continuous monitoring of the loss of the response, cases in which there was an unintentional and unnoticed loss of response of more than 50% after one piece of tumor was removed were also included in this study. This method of dissection was only used in patients with an adherent FN; if the dissection was straightforward, this method was not used (because it necessitates repeated stimulation while dissecting), and GTR was performed.

Outcome Measures

Pathological examination confirmed VS in all cases. The Ki-67 index of the area of maximum proliferation (maximum Ki-67 index) was evaluated from the inflammatory infiltrates. Facial nerve function was assessed at Day 8 (when the maximum conduction block occurs) and...
at 1 year postoperatively, using the House-Brackmann scale. The FN function of patients who underwent NTR was compared with the FN function of patients who underwent GTR for Stage III and Stage IV tumors during the same period.

The amount of residual tumor was defined by an early MRI study performed a mean of 5 days postoperatively (range 1–20 days) with axial T1-weighted, high-resolution 3D T2-weighted, axial diffusion-weighted, 3D FLAIR, and 3D fat-saturated postcontrast T1-weighted imaging. MRI results were classified as no residual, linear enhancement, micronodular (maximum lesion diameter < 3 mm), and nodular residual (> 3 mm); in the case of nodular residual lesions, the volume was calculated using an Advantage Workstation (AW, GE Healthcare). Following the recommendations of the Acoustic Neurona Subtotal Resection Study, resection was classified as GTR when there was no visible tumor on MR images; NTR when imaging findings were linear enhancement, micronodular residual tumor, or nodule no larger than 0.5 cm; and STR when any larger tumor remnant was present. In addition, the presence of other abnormalities was recorded—for example, ischemia or hemorrhage in the adjacent cerebellum or brainstem on the basis of diffusion-weighted imaging or T1-weighted imaging (for ischemia and hemorrhage, respectively).

Evolution of the residual tumor was analyzed by MRI 1 year postoperatively using axial T1-weighted, 3D FLAIR, high-resolution 3D T2 (FIESTA), and 3D fat-saturated postcontrast T1-weighted images. If a nodular residual tumor was detected, its volume was calculated. In the case of early postoperative imaging abnormalities, signal changes were evaluated at 1 year after surgery and compared with the early MRI studies. All MRI studies were reviewed by the same neuroradiologist. Progression was defined as >20% increase in volume, and tumors that showed <20% reduction and <20% increase in volume were categorized as stable.

Statistical Analysis

Values are reported as mean ± SD. Cases were dichotomized on the basis of postoperative FN function (good [House-Brackmann Grades I and II] vs impaired [grade ≥ III]) and residual tumor growth (no growth vs regrowth) and variables were assessed for prognostic value using the Mann-Whitney-Wilcoxon test (for quantitative variables) and Fisher exact test (for qualitative variables). Comparison of FN function between patients undergoing NTR and patients undergoing GTR was done with the chi-square test. For all comparisons, p < 0.05 was considered to be statistically significant.

Results

Patients

Twenty-five (24%) of 106 patients operated on for VS during the 12-month study period were included in this analysis (Table 1). The group included 14 men and 11 women, and their mean age was 57 ± 11 years (range 35–73 years). All 25 patients had large VSs (Stage III or IV). The mean maximum diameter of the VS in the CPA was 28 ± 5 mm (range 19–44 mm) and the mean tumor volume was 8.5 ± 5 cm³ (range 3.7–23.9 cm³). The tumors were categorized according to the largest diameter in the axial plane (or coronal if necessary) in the CPA on gadolinium-enhanced T1-weighted MRI sequences as follows: Stage I (extrameatal diameter 0 mm), Stage II (maximum extrameatal diameter ≤15 mm), Stage III (extrameatal diameter 15–30 mm), or Stage IV (extrameatal diameter >30 mm). The tumors were classified as Stage IV in 10 cases (40%) and Stage III in 15 cases (60%), corresponding to 19 Stage IV and 6 Stage III of the Koos classification.

During the same period of time, a GTR was performed in 29 Stage III and 17 Stage IV solitary VS. Compared with all patients operated on during the same period (n = 106), an NTR was performed in 34% and 37% of Stage III and Stage IV cases, respectively.

All but 4 patients were operated on through a translabyrinthine approach; the others were operated on through a retrosigmoid approach in an attempt to preserve hearing.

The mean baseline amplitude of the response using supramaximal stimulation after the first identification of the FN at the brainstem was 2782 ± 1970 μV (range 500–9000 μV) and this decreased to 1794 ± 1482 μV (range 300–7500 μV) at the end of the dissection (Table 1). The mean loss of amplitude response was 36% ±17% (range 10%–78%, Fig. 1). In five patients (Cases 4, 7, 18, 23, and 24), the loss of response was more than 50%.

The mean of the maximum Ki-67 index was 4.4% ±1.73% (range 3%–8%).

Facial Nerve Function

At Day 8 postoperatively, facial nerve function was assessed at House-Brackmann Grade I in 10 patients (40%), Grade II in 6 patients (24%), Grade III in 4 patients (16%), Grade IV in 3 patients (12%), and Grade V in 2 patients (8%) (Table 1). Overall, good FN function (Grade I or II) was seen in 64% of the patients. These results improved at the 1-year postoperative evaluation, which demonstrated House-Brackmann Grade I in 18 patients (72%), Grade II in 3 patients (12%), Grade III in 3 patients (12%), and Grade IV in 1 patient (4%). Overall, good FN function was achieved in 84% of patients. No severe FN paralysis (Grade V or VI) was seen 1 year postoperatively.

Regarding the prognostic factors, only patient age was significantly correlated with poorer FN function at 1 year after surgery (p = 0.04, Mann-Whitney-Wilcoxon test). There was a trend toward significance for the presence of ischemia on postoperative MRI (p = 0.06, Fisher exact test for proportion).

Patients suffering from Stage III (n = 29) and Stage IV (n = 17) VS undergoing GTR during the same period achieved good FN function (Grade I and II) in 34 cases (74%). The proportion of patients with good FN function did not differ significantly between these patients and the patients in our study (chi-square test, p = 0.33).

Radiological Results

The early postoperative MRI study (Fig. 2) showed no detectable residual tumor in 1 case (4%), linear thickening along the FN in 7 cases (28%), micronodular enhancement...
in 7 cases (28%), and a nodular residual in 10 cases (40%; mean volume 0.26 cm$^3$), corresponding to 1 GTR and 24 NTRs. Seven patients showed early ischemia—limited to the middle cerebellar peduncle in 5 cases and extending to the brainstem in 2 (Fig. 3). In 4 of these 7 cases, signal abnormality was still observed 1 year postoperatively. Of note, 4 of these 7 patients had FN function that was worse than House-Brackmann Grade II at 1 year after surgery ($p = 0.06$, Fisher exact test for proportion). No patient with MRI abnormalities in the cerebellum or the brainstem showed clinical neurological dysfunction.

One-year follow-up MRI studies were performed in 23 cases; 2 patients were clinically evaluated for their FN function but did not have a MRI scan. MRI did not show any growth of the residual tumor in 15 (65%) of 23 cases (Fig. 4). In 6 (26%) of 23 cases, residual tumor that had been evident on early MRI studies (a linear in 2 cases, as micronodular lesions in 2 cases, and as nodular lesions in 2 cases) was found to have regressed (Fig. 5), and in only 2 (9%) of 23 cases (1 with nodular and 1 with micronodular residual tumor in the early MRI studies) was progression of the remnant observed (Fig. 6). Comparison of the 3 cases of residual tumor progression with the other cases showed no significant difference with respect to maximum Ki-67 index (Mann-Whitney-Wilcoxon test).

**Discussion**

Accumulated surgical experience often allows the complete removal of large VSs with functional preservation of the FN. This remains the best treatment because it is definitive. In contrast, to obtain normal postoperative facial function, partial surgeries have been advocated since the reports of Harvey Cushing. Based on recent and extensive literature analysis, it appears that NTR is optimal in cases in which the facial nerve is threatened (strong adhesion.

### TABLE 1. Summary of results for our study population

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pt Age (yrs)</th>
<th>Tumor Size (mm$^3$)</th>
<th>Tumor Vol (cm$^3$)</th>
<th>Stage</th>
<th>Supramax Stim Response (μV)$\dagger$</th>
<th>Loss of Response (%)</th>
<th>Max Ki-67 Index (%)‡</th>
<th>Day 8 HB§</th>
<th>MRI Findings</th>
<th>1-Yr Resid Tumor Evolution</th>
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FU = follow-up; HB = House-Brackmann grade; pt = patient; resid = residual; supramax stim = supramaximal stimulation; − = absent; + = present.

* Tumor size is the maximum extrameatal diameter of the tumor.
† Early EMG response represents the supramaximal stimulation at 2 mA after the identification of the FN in the CPA. Last EMG response represents the response obtained when the dissection was stopped.
‡ Ki-67 index of the area of maximum proliferation.
§ Results of FN function are categorized according to the House-Brackmann classification.
¶ Values in parentheses are residual tumor volume, for nodular tumors only.
with disappearance of the plane between the nerve, pia mater, and tumor. In this way, the patient should be able to retain normal facial function with a very small tumor remnant, which could require additional treatment by stereotactic radiosurgery. (It should be noted that there may be a higher risk of FN palsy after stereotactic radiosurgery following incomplete resection.)

In the present study, we aimed to evaluate whether the use of electrophysiology could help to maximize the extent of resection while preserving good postoperative FN function in the case of surgical difficulties when dissecting the FN from the tumor. The value of supramaximal stimulation of the FN as a prognostic factor for early and long-term FN function has been recognized in other retrospective and prospective studies. Since this stimulation allows depolarization of all of the nerve fibers, the responses give a more precise status of the FN than stimulation at threshold. We can speculate whether a 50% loss of response is an appropriate value. In their study, Schmitt et al. have shown that a drop of more than 69% was predictive of poor postoperative FN function. We have used a 50% cutoff. It is possible that adopting a 30% drop as the criterion for stopping dissection of the VS from the FN could improve our results even more, especially in older patients. In this study, using a 50% cutoff, we have documented Grade I or II FN function in 64% of patients at Day 8 and 84% at 1 year after surgery.

We have to consider some difficulties with respect to the use of the supramaximal response during surgery. First of all, the range of response is wide, because it depends on the concentration of endplates near the recording electrodes, and this varies from patient to patient. Then, in patients with large tumors, the FN is not immediately accessible at the brainstem, and some minor damage could be done during the debulking or during dissection of the tumor from the brainstem before identification of the FN. To overcome this drawback, Fukuda et al. proposed transcranial stimulation of the FN rather than stimulation at the brainstem to obtain an earlier response; but with this method, the value obtained is only one-fifth of what is routinely obtained with direct stimulation of the FN at the brainstem, limiting the stimulation to a few axons.

FN damage could occur because of an undetected injury during the translabyrinthine approach, and this could

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**FIG. 1.** Scattergram with columns showing the decrease in response following supramaximal stimulation of the facial nerve (along the y-axis) with the facial nerve function at 1 year. HB = House-Brackmann grade.

**FIG. 2.** Early postoperative MRI. Axial T1-weighted contrast-enhanced fat-saturated images showing representative examples of linear enhancement (linear on the FN) (A), a micronodular residual (3 mm) (B), and a nodular residual (C).

**FIG. 3.** Early postoperative axial MR images showing an ischemic lesion with high diffusion-weighted signal (A) and decreased apparent diffusion coefficient (B).
lower the basal value of the response at supramaximal stimulation, and use of the stimulation bur during the approach could further reduce this complication. Moreover, it is remarkable to note that 3 of the 4 patients who experienced long-term unsatisfactory FN function had localized ischemia in the early and late postoperative MRI despite minimal drop-off in supramaximal response (32% ± 15%, range 21%–49%). These postoperative modifications can be explained by difficulties in tumor/brainstem dissection, and more probably by minor venous or arterial ischemia of the brainstem and/or cerebellum affecting the FN nucleus in the brainstem. Apart from these inconveniences, the use of supramaximal stimulation of the FN to guide incomplete resection seems to be a viable option. In addition to being retrospective, previous studies on incomplete resection of VS lacked guidelines to identify the moment when dissection should be stopped: only strong adherence was advocated, but this is subjective and also depends on the surgeon’s experience. So using the response to proximal supramaximal stimulation could guide the surgeon in the case of strong adherence so as to minimize the amount of residual tumor. When comparing the results for patients who underwent NTR with those who underwent GTR, no statistically significant difference was found in FN function 1 year after surgery, so we believe that we have not improved the “overall” FN function of patients undergoing VS resection, but only of those in whom the FN was strongly adherent. In this particular situation, a real control group is not advisable or ethical because, to achieve it, we would have to continue dissecting the FN with a higher risk of postoperative FN palsy to achieve a GTR in randomly selected cases.

The use of early postoperative MRI allows an estimation of the amount of residual tumor that is much more reliable than that achieved with surgical observation as has already been demonstrated by other authors. Moreover, early MRI could also be useful in detecting complications. Regarding the evolution of the residual tumor, in our study we observed growth in only 1 case of linear or micronodular enhancement at 1 year after surgery, and this result is consistent with other retrospective studies with longer follow-up. Moreover, 24% of residual tumors showed regression on 1-year-postoperative MRI, suggesting devascularization of the tumor remnant; indeed, all of the residual tumors were located in the CPA, and the possibility of revascularization in such a position is lower than in the IAC or at the brainstem surface. This regression can also be partly related to the postoperative dura and scar tissue enhancements, especially when imaging studies are performed relatively late. Indeed, in our study, the regressions were more frequent when the initial postoperative MRI study was late. This finding, in line with previous studies, suggests that MRI should be carried out in the first 3 days to avoid the nonspecific enhancement in postoperative field that can be present even 3 months after surgery. When nodular enhancement is present, volume

FIG. 4. Example of stable residual tumor. Preoperative (A), early postoperative (B), and 1-year postoperative (C) axial T1-weighted contrast-enhanced fat-saturated MR images.

FIG. 5. Example of regression of the residual tumor. Preoperative (A), early postoperative (B), and 1-year postoperative (C) axial T1-weighted contrast-enhanced fat-saturated MR images.
measurement is more reliable for assessing residual tumor than linear measurement, as demonstrated by Vakilian et al.\textsuperscript{28} Of course, all patients who undergo incomplete resection need to be followed for a longer period of time because regrowth of the residual tumor, even if unlikely, could occur more than 1 year after surgery. Furthermore, the proliferative activity of the tumor itself has been analyzed by other authors, showing that a Ki-67 index of more than 1.6\textsuperscript{29} or 2.28\textsuperscript{20} could be associated with an aggressive residual tumor; in such cases, patients could perhaps benefit from further immediate postoperative stereotactic radiosurgery.

**Conclusions**

The use of electrophysiology seems to be a reliable tool to guide dissection of the FN from an adherent VS. In our experience with the use of this parameter as a guide for terminating a dissection, the amount of residual tumor was small, with postoperative MRI showing GTR or NTR (residual tumor < 0.5 cm\textsuperscript{3}) in almost all patients. A longer follow-up is needed to evaluate the potential subsequent regrowth of the residual tumor.

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Dr. Sterkers reports a consultant relationship with Medtronic.

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