Koos Grade IV Vestibular Schwannomas: Considerations on a consecutive series of 60 cases. Searching for the Balance Between Preservation of Function and Maximal Tumor Removal

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Abstract

Purpose

Koos Grade IV vestibular schwannomas (VS) (maximum diameter >3cm) compress the brainstem and displace the fourth ventricle. Microsurgical resection with attention to the right balance between preservation of function and maximal tumour removal is the treatment of choice.

Methods

Our series consists of 60 consecutive patients with unilateral VS, operated on from December 2010 to July 2019. All patients underwent microsurgical removal via the retrosigmoid approach. The adherence of VS' capsule to surrounding nervous structures and the excessive tendency of tumor to bleed during debulking, because of a redundant vascular architecture, was evaluated by reviewing video records. Microsurgical removal of tumor was classified as total (T), near-total (NT: residue<5%), subtotal (ST: residue 5-10%) or partial (P: residue>10%).

Results

Maximal mean tumor diameter was 3,97cm (SD±1,13; range 3,1-5,8cm). Preoperative severely impaired hearing or deafness (AAO-HNS Classes C-D) was present in 52 cases (86,7%). Total or NT resection was accomplished in 46 cases (76,7%), 65,8% in cases with and 95,4% without tight adhesion of capsule to nervous structures (p<0,001). Endoscopic-assisted microsurgical removal of VS in the IAC was performed in 23 patients: in these cases a T resection was obtained in 78,3% versus 45,9% of microsurgery only (p<0,001).

The capsule of VS was tightly adherent to nervous structures in 63,3% of patients, whereas hypervascular high-bleeding tumors represented 56,7%. Hearing preservation was possible in 2 out of 8 patients with preoperative class B hearing. At last follow-up, 34 patients (56,7%) had a normal postoperative FN outcome (HBI), 9 (15,0%) were HBII, 8 (13,3%) HBIII, and 9 (15,0%) HBIV. Total-NT resection of solid and low-bleeding VS, without tight capsule adhesion was associated with better FN outcome. Mortality was zero; permanent complications were observed in 2 cases (diplopia, hydrocephalus), transient in 9.

Conclusions

Microsurgery of Koos Grade IV VS seems to be associated with more than acceptable functional results, with high rate of T and NT removal of tumor. Long-term FN results seem to be worse in patients with cystic Koos Grade IV VS, in cases with tight capsule adherences to nervous structures and in high-bleeding tumors.

Introduction

Vestibular schwannomas (VS) are tumors arising from Schwann cells of the superior or inferior vestibular nerve. According to Koos' classification (25), Grade IV are *large and giant* VS (longitudinal diameter > 3cm), cause compression on the brainstem and may displace the fourth ventricle. Since the 1980s, their incidence has progressively declined due to broader and earlier access to MRI imaging (51–54): larger VS represented 40% of all tumors in the past and accounted only a few percent during the last decade. (40).

These giant tumors adversely affect patients, and the goal of treatment is to achieve oncological control while maintaining quality of life with facial or cochlear nerve preservation (32, 40, 57, 58). Microsurgical resection offers the best hope of achieving this goal. However, is still necessary to clarify if their frequent tendency towards hypervascularity and adhesion to neurological structures affects the functional outcome.

In this study, we retrospectively analyze the clinical and surgical data of a consecutive series of 60 patients with Koos IV VS operated on by retrosigmoid approach, highlighting the extent of tumor removal, postoperative nerve functions, and complications.

Materials And Methods

We reviewed 60 consecutive cases of Koos Grade IV VS out of 225 unilateral VS surgically treated in our Department between December 2010 and July 2019. General conditions and preoperative risk were assessed according to the American Society of Anesthesiology (ASA) classification (32). Two patients with neurofibromatosis type 2 affected by unilateral VS were included. Clinical data such as patients' age, sex, presenting symptoms and tumor size were recorded. Preoperative neuroimaging included temporal bone CT and contrast-enhanced MRI in all patients.

Tumor size was categorized according to the international criteria, measuring the volume and the largest extrameatal tumor diameter on post-contrast axial MRI. (23)

Preoperative audio-vestibular evaluation included pure tone audiometry and speech audiometry. Hearing level (HL) was assessed according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) classification. (7) HL Class A and B were categorized as good hearing, and hearing preservation was only attempted in these patients. Successful hearing preservation corresponded to Classes A, B and C (<50%).

Microsurgery via retrosigmoid approach was performed in all cases. Location of FN and its adherence to the tumor were evaluated by reviewing radiological images, surgical and video records. The course of the FN was classified according to its position in relation to the tumor: anterior (A), anterior-inferior (AI), anterior-superior (AS), and dorsal (D) (28,43). Based on operative reports and videos, tumors were classified as cystic (one or more cysts within the tumor), adherent and hypervascular. In detail, adherent VS were considered those without a clear perineural dissection plane between nervous structures (in particular, facial nerve and brainstem) and tumor capsule, in comparison to VS with well recognizable dissection plane (less adherent). Hypervascular VS had an unusual superficial and internal vascular

architecture and were complicated by high-rate bleeding during debulking and dissection, because of the rupture of multiple vessels present in the capsular and intracapsular portion of tumor.

The extent of tumor removal was calculated by means of manual segmentation and volumetry from pre- and postoperative MRI scans and was classified as total (T), near total (NT: thin strip of residual tumor; <5% of preoperative volume), subtotal (ST: strip of residual tumor; 5-10% of preoperative volume), partial (P: nodular residual tumor; >10% of preoperative volume).

Since October 2017, at the end of microsurgical resection, a 4-mm Flexible Video Endoscope (4-mm x 65-cm, Karl Storz, GmbH, Tuttlingen, Germany) has been inserted in the surgical cavity, handled by the surgeon (8,9), in order to detect eventual tumor residues in the internal auditory canal (IAC). Endoscopic-assisted microsurgical removal was performed in 23 patients out of 60.

FN function was assessed according to House-Brackmann (18) (HB) grading system and was evaluated preoperatively, at discharge and at final follow-up (³6 months).

The study was approved by the Internal Ethics Committee of the Hospital. A written consent for scientific treatment of personal data was obtained from any patient before surgery.

Operative technique

The retrosigmoid approach was used in all the surgical procedures, with the patient in lateral position. A 5-6 cm slightly curved incision was made 1-2 cm posterior to the mastoid process, exposing the lateral occipital bone and the superior and inferior nuchal lines. A retrosigmoid suboccipital craniotomy, 3cm in length and width, was performed, exposing the sigmoid sinus anteriorly and the transverse sinus superiorly. The retrosigmoid dura was incised in a semicircular fashion, and the lateral medullary cistern was opened and cerebrospinal fluid (CSF) was aspirated to obtain adequate cerebellar decompression. After cutting the dura along the “Tuebingen line” (2), covering the roof of IAC, the canal was opened with a 4mm extra-coarse diamond burr or by ultrasonic aspirator with dedicated bone tips. The tumor surface was exposed, possibly without retraction, and the rare but possible dorsal displacement of FN was investigated with monopolar stimulation. A V-cut was performed on the dorsal surface of tumor with microscissors or hand-held thulium laser, and debulking of tumor was obtained with microscissors, microcurettes, bipolar forceps, hand-held laser fiber, and ultrasonic aspirator. The tumor was then dissected from brainstem and cranial nerves during continuous facial nerve monitoring. In some cases of strong tumor adherence to surrounding structures, a millimetric remnant of tumor capsule was left, thus yielding a near-total resection. In few cases with tight tumor capsule adherences to FN and/or brainstem or excessive bleeding of tumor, a ST or P removal was performed. Accurate hemostasis, mastoid cells obliteration, and tight dura closure by pericranial graft, hemostatic materials and sealants were performed and a fitted titanium mesh -or the bone operculum- was placed on the craniectomy with miniscrews.

Intraoperative Neurophysiological Monitoring (IONM)

All the surgical procedures were performed with a FN monitoring system (Nimbus i-Care 100 intraoperative neurophysiologic monitoring; Newmedic Division of Hemodia, Labège, France), with electrodes inserted in orbicularis oris and orbicularis oculi muscles, to detect FN responsivity. The nerve stimulation was performed with monopolar (on tumor surface) or bipolar (close to the nerve) probes to locate the FN and verify its functional state.

We always exposed distal and proximal FN with the feedback of IONM. The stimulation threshold was carefully monitored throughout the resection. If the threshold started to exceed 0,5 mAmp, especially in cases where no clear dissection plane, further tumor removal was not performed. The final threshold was recorded in every case.

Clinical follow-up

Clinical and radiological follow-up was scheduled at six months after operation and then once a year. Long-term FN outcome evaluation was performed at minimum six months after operation in 5 patients and after more than 1 year in 55 (final follow up: January 31, 2020), and categorized according to House-Brackmann grades I-VI (18).

Statistical analysis

Statistical analysis was performed by means chi-square test for categorical variables and Student's t-test for continuous ones, using the software MS Excel (Microsoft Corporation, Redmond, WA, USA). Statistical significance was set at $p < 0,05$.

Results

Characteristics of the patients and clinical presentation

Among the 60 cases of unilateral VS, 26 were males and 34 females. Mean age was 48,8±15,7 years (range 21-80). Mean maximal tumor diameter was 3,97cm (SD: ±1,13; range 3,1-5,8cm): the VS was large (>3cm of maximal diameter) in 25 patients (41,7%) and giant (>4cm) in 35 (58,3%). Preoperative mean ASA class was 2,08 (range 1-4). Fourteen tumors were cystic and 46 solid. Severely impaired hearing or deafness (AAO-NS Classes C-D) was present in 52 cases (86,7%), ataxia in 18 (30,0%), trigeminal symptoms in 20 (33,3%), facial palsy HBII to IV in 11 (18,3%). Preoperative patients data are summarized in Table 1. Follow-up period ranged between 6 and 113 months (mean 59,3±13,7 months; median 61 months).

In the cisternal segment, FN was AS in 26 cases (43,3%), A in 18 (30,0%) and AI in 16 (26,6%), in line with previously published data (28,43).

Adhesions of Tumor Capsule, Bleeding Rate and Extent of resection

Tumor capsule was tightly adherent to nervous structures in 38 patients (63,3%), whereas hypervascular tumors represented 56,7% of cases (34 patient). Among cystic VS, adherences of capsule to nervous structures were present in 85,7% of cases (12 out of 14) versus 56,5% (26 out of 46) of solid tumors (p<0.001).

Total or NT resection was accomplished in 46 cases (76,7%): 65,8% (25 patients) with and 95,4% (21) without tight adhesions of capsule to nervous structures (p<0,001).

Endoscopic-assisted microsurgical removal of tumor in the IAC was performed on 23 patients: in these cases a T resection was obtained in 78,3% (18 out of 23) versus 45,9% of those operated on with microsurgery alone (17 out of 37) (p<0,001); furthermore, T-NT removal was possible in 100% of cases (23 patients), versus 56,7% (21 out of 37 cases) (p<0.001). These data are summarized in Table 2.

Long-term Hearing and Facial Outcome

Hearing preservation was possible in 2 out of 8 patients with preoperative class B hearing: in both cases, the postoperative class of hearing level was unchanged.

FN anatomical and neurophysiological integrity was preserved in 54 cases (90,0%). In 11 cases a preoperative HB II-IV FN deficit was present postoperatively. At the last follow-up (Table 3), 34 patients (56,7%) had a normal postoperative FN function (HBI), 9 (15,0%) HBII, 8 (13,3%) HBIII, and 9 (15,0%) HBIV.

As expected, mean FN stimulation threshold at the end of surgery, was inversely correlated with extent of resection. In particular, T-NT: mean stimulation threshold was 0,24 mAmp; ST-P: mean stimulation threshold 0,57 mAmp (p<0,001).

Statistical analysis demonstrated a significant correlation between good FN outcomes (HB I-II) and the following conditions (Table 4):

i. solid tumors: 80,4% (37 out of 46) versus 42,9% of cystic (6 out of 14) (p<0,01);
ii. presence of preoperative trigeminal symptoms: 80,0% (16 out of 20) versus 67,5% (27 out of 40) (p<0,001);
iii. presence of preoperative ataxia: 77,8% (14 out of 18) versus 69,0% (29 out of 42) (p<0,001);
iv. absence of tight tumor capsule adhesions: 95,4% (21 out of 22) versus 57,9% (22 out of 38) (p<0,001);

v. low-bleeding VS: 95,1% (25 out of 26) versus 59,2% (18 out of 34) (p<0,001);
vi. endoscopic-assisted microsurgery: 86,9% (20 out of 23) versus 62,2% with microsurgery only (23 out of 37) (p<0,001).
vii. T-NT tumor removal: 80,4% (37 out of 46) versus 42,9% of ST-Partial removal (6 out of 14) (p<0,01).

Other variables tested (age, sex, course and position of FN in the cisternal portion, large or giant size) had not significant correlations with the long-term FN outcome.

Postoperative complications and long-term follow up

Mortality rate was zero. One patient had a permanent diplopia for abducens nerve paralysis. One patient developed triventricular hydrocephalus 11 days after surgery, successfully treated with ventriculo-peritoneal shunt.

Postoperative transient complications were observed in 9 patients, without correlation with preoperative ASA class: CSF-leak followed by wound infection in 3 (successfully treated with antibiotics), transient diplopia in 2, cerebellar mutism, cerebellar infarction, dysphagia and pneumonia (resolved with antibiotics) in 1 each.

At a mean follow-up of 59,3 months, a recurrence/re-growth of residue was observed in 8 cases (13,3%) operated on with ST or P resection (5 ASA Class 2 and 3 Class 3): in 2 of them a second surgery was necessary for large cystic transformation, 2 and 4 years after the first operation, respectively. In the other 6 cases, the initial growth of tumor ceased at MRI controls performed once a year.

Discussion

A recent study, Troude et al. (56) analyzed the predictive factors of short-term and long-term FN function after VS resection by either translabyrinthine or retrosigmoid approach (no inter-approach difference was studied). In the short-term -i.e., at discharge and at 1-month follow up-, FN function was best anticipated by preoperative facial function, intraoperative cochlear preservation and extrameatal tumor diameter. Such association had already described by Nutik (34), whose review of 108 consecutive cases reported that anatomic preservation of FN was inversely related to tumor size and improved as the series progressed -thus stressing the importance of experience in VS microsurgery. When the nerve was anatomically preserved, satisfactory postoperative outcome was inversely related to tumor size. Chiluwal et al. (6) found that T1-T3a tumor extension (according to Hannover classification) was significantly associated with better functional outcome than T3b at 3-months follow up. In the long term, according to Troude et al. (56), FN function is best anticipated by postoperative early FN outcome; in the same multivariate analysis, a previous surgery negatively affected facial outcome. Furthermore, in univariate analyses, additional predictive factors were identified as surgeon's experience and tumor remnant volume. As the extent of resection did not seem to condition FN outcome per se, the authors concluded -and so do we- that maximal safe resection is the best operative strategy for patients harboring large VS.

Analyzing the FN results in detail we observed better outcome (HBI-II) in 43 cases (71,7%), especially in the following conditions (Table 4): solid tumors (80,4% versus 42,9%, p<0,01); presence of preoperative trigeminal symptoms (80,0% versus 20,0%, p<0,001); presence of preoperative ataxia (77,8% versus 69,0%, p<0,001); absence of tight tumor capsule adhesions (95,4% versus 57,9%, p<0,001); low-bleeding tumor (95,1% versus 59,2%, p<0,001); use of endoscopically assisted microsurgery (86,9% versus 62,2%, p<0,001); T-NT tumor removal (80,4% versus 42,9%, p<0,01).

Although great emphasis is currently placed on preserving nerve functions after VS resection, FN injury still represents a relatively common postsurgical complication. Even when careful FN dissection is performed, an anatomically intact nerve does not necessarily predict a normal facial function. Despite anatomical knowledge and experience, finding its proximal portion may be difficult especially in the case of large tumors. In our practice we usually adopt the following steps: 1. intracapsular tumor debulking; 2. identification of FN and, in smaller tumors, cochlear nerve by means of intraoperative neurophysiological monitoring techniques; 3. nerve dissection from the tumor capsule trying to preserve the arachnoid plane; 4. bimanual dissection of tumor capsule from FN and, in selected cases, cochlear nerve (24).

Functional FN results.

The safe resection of VS depends on a thorough understanding of the microanatomy of these lesions. According to Roosli et al. (42), VS may arise anywhere along the course of the axons of cochleo-vestibular nerve from the glial-Schwann sheath junction up until their terminations within auditory and vestibular end organs. This variable origination may play a role in the relation of VS with arachnoidal plan: epiarachnoid or subarachnoid. Epiarachnoid tumors are defined by the absence of an arachnoid membrane on the tumor surface after moving the arachnoid fold (double layers of the arachnoid membrane) towards the brainstem. In contrast, subarachnoid VS are characterized by arachnoid membrane remaining on the tumor surface after moving the arachnoid fold. Kohno et al. (24) used intraoperative views and light and electron microscopy to confirm the existence of an arachnoid membrane after the arachnoid fold had been moved: they observed that the majority of VS are subarachnoid tumors, with epiarachnoid variant being considerably less common. Thus, according to Kohno et al. (24), there are 3 planes for possible tumor dissections: A. subarachnoid; B. subperineural (subcapsular); C. intracapsular.

According to Sasaki et al., (48) subperineural plane is the ideal cleavage plane for preservation of FN and cochlear nerve functions during VS microsurgery. Therefore, the layers we encounter starting from the surface of tumor are: 1. Arachnoid membrane; 2. FN and cochlear nerve; 3. perineurium/nerve fibers of vestibular nerve of origin of VS (14,33,41), and bimanual dissection is an essential part of the technique (24,29,36,44).

Surgical dissection for larger, vascularized and adherent VS.

Carlson et al. (3) described the genetic alterations observed in a series of sporadic VS, in order to identify if more clinically aggressive variants possess different genetic alterations compared to the more indolent.

To date, few studies attempted to profile genome-wide alterations in sporadic VS. Using high-throughput deep sequencing, “two-hit” alterations in the NF2 gene were identified in every tumor and were not present in peripheral blood supporting that all events were somatic. (3) Type of NF2 gene alteration and accessory mutations outside the NF2 locus may predict phenotypic expression and clinical course.

Several mechanisms may underly the hypervascular and adherent nature of large and giant VS and may present targets for future therapy. For the enlargement of any solid tumor, including schwannomas, angiogenesis is essential: vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) are considered to be potent mediators of tumor angiogenesis and growth pattern. (4,14,39,59) Moller et al. (33) observed that tumor concentration of MMP-9 correlates with VS growth rate. Uesaka et al. (59) performed immunohistochemical studies for VEGF and VEGFR-1 mRNA on 36 VS and confirmed that these proteins, especially in recurrent tumors, are prominently expressed. (59) A relationship among vascularization, adhesions and tumor size is quite reasonable, probably through MEK/ERK effectors, oncogenic gene miR-21 and mTOR pathways (63). The adhesion to nerve structures seems to develop through the downstream effectors that induce the synthesis of metalloproteinase of extracellular matrix. (33)

According to Peris-Celda et al. (38), large tumors are significantly more frequent among younger patients at diagnosis suggesting a more aggressive tumor biology. In their study the authors found that more than 17% of 1304 VS patients had a tumors size >3cm and more than 7% >4. On comparing VS >4cm with the rest of the cohort, they observed a statistically significant difference in terms of mean age at diagnosis: 52,3 years for VS smaller than 4 cm versus 42,4 years for larger tumors (p<0,001). (38)

The large and vascularized VS represent a unique microsurgical challenge, especially those with the capsule adherent to nervous structures, namely to brainstem and FN. Many Authors reported incomplete surgical removal, with the need of close long-term follow up for detecting possible recurrences.

Large and bleeding VS. Adherence of capsule to nervous structures.

Total or NT resection was feasible in 46 of our 60 cases (76,7%), which is in line with other reports in the literature (16,19,20,46,52). In particular, T or NT resection was accomplished in 65,8% of cases with and 95,4% without tight adhesions of capsule to nervous structures (p<0,001). In 23 patients of our series operated on with flexible endoscopic-assisted microsurgical removal of tumor in the IAC a T resection was obtained in 78,3% (18 out of 23) versus 45,9% of cases with microsurgery only (p<0,001), whereas, T-NT removal was possible in all the 23 patients operated on with endoscopic-assisted microsurgery versus 56,7% of those operated on with microsurgery only (21 out of 37 cases) (p<0,001) (Table 2).

A relatively large group of cystic tumors (14 out of 60 cases: 23,3%) was also observed among our Grade IV VS. According to several Authors (12,15,16,30) cystic VS did not show signs of greater adherence intraoperatively nor did they significantly affect the postoperative outcome. However, in the present series we observed in 12 out of 14 cystic cases (85,7%) tight adherences of capsule to nervous structures, in

comparison to 56,5% (26 out of 46) of solid tumors (p<0,001). In addition, a better FN outcome (HBI-II) was obtained in solid tumors: 80,4% versus 42,9% of cystic (p<0,01).

In our patients, the clinical presentation featured signs of hearing impairment, balance disturbances, preoperative FN deficit, and headache; facial paresthesias and other trigeminal symptoms were also noted by 33,3% of patients, which has been occasionally reported in case of giant tumors (49,50). In particular, FN outcome seems to be better (HBI-II) in patients with preoperative trigeminal symptoms, 80,0% versus 20,0% (p<0,001), and in those with preoperative ataxia, 77,8% versus 60,0% (p<0,001). The reasons of the better outcome of FN in patients with preoperative trigeminal impairment and ataxia remain unclear.

Although hearing loss is one of the most common signs at presentation (41,7% of cases (1), as far as hearing is present preoperatively, attempts should be made –when possible- to accomplish hearing preservation (11,52). As far as large and giant VS are concerned, hearing has been reportedly preserved in 21,4-50% (11,31,60,61) and 66,7% (45) of cases, respectively. Preoperative severely impaired hearing (AAO-HNS hearing Class C) was present in 30 cases (50,0%) of our series and hearing preservation was achieved only in 2 out of 8 patients with preoperative AAO-HNS hearing Class B (Table 3).

The rate of total tumor resection, as reported in the literature, ranges between 28,6% (64) and 95,5% (26) with a recent meta-analysis showing an overall T resection rate of 77% (52). Two case series are reported, wherein total resection could be accomplished in all of the cases (45,50). However, the postoperative facial function preservation rate is quite different in the two studies, being 45% in Silva et al (50) and 75% in Samii et al. (45). The preservation of FN functional state is of paramount importance in VS surgery and it is accomplished, as reported in the literature, in 32,9-83,3% of cases (16,19,26,45, 62,65), with a meta-analysis demonstrating FN preservation in 60% of cases (52). The highest value of FN function preservation rate was reported by Zhang et al. (18) in a cohort of patient who underwent subtotal resection instead of radical extirpation.

Grade IV VS represent a surgical challenge: a risk/benefit ratio must be for obtaining a satisfactory extent of resection against a good postoperative functional outcome, in order to find the right balance between preservation of functions and maximal tumour removal (52).

Increasingly popular is the concept of the planned less-than-total resection performed for FN preservation (52). According to some authors (22,56,66) outcome might be improved in selected cases by a combined surgical and radiosurgical treatment. Zumofen et al. (66) reported HBI-II postoperative rate of 89%, with no need for salvage surgery after Gamma Knife had been administered onto planned tumor residues. However, Iwai et al. (22) found that optimal FN outcome (HBI-II postoperative rate of 95%) could be jeopardized by the need for salvage surgery after Gamma Knife in case of large tumor remnants (at least 6cm^3). Such findings underline that radiosurgery is not an enemy of microsurgery (13,56), even if surgical removal should be attempted with the objective of maximal safe tumor eradication.

Large tumor size often hinders safe and effective gross total resection (6,57). In the series of Tos et al. (53-55), HB I-II function was achieved in 97% of medium-sized, 87% of large and 66% of giant tumors. Similar findings were reported by Ojemann (37) in his series of 410 patients, although the size categories were different: normal FN function was achieved in 98% of small, 96% of medium sized (1-1,9 cm), 75% of medium large (2-2,9 cm), 56% of large (3-4 cm) and 56% of giant tumors (> 4 cm). In their cohort of 45 large VS, Hoshide et al. (16) reported a HBI-II rate of 83% after total or near-total resection in each of their cases. In a recent meta-analysis of large VN, a 60% HBI-II rate was reported (52). Furthermore, a cystic consistency has been independently associated with poorer FN outcomes (13,35). Tumor size being comparable, cystic VS shows a tendency towards poorer early FN results (13). Our results seem in line with such features, as T or NT resection was achieved in 82,9% and HBI-II was reported in 59% of cases in the whole series.

Complications

Mortality rate did not occur in our series, whereas permanent complications have been observed in 2 cases (abducens nerve paralysis and obstructive hydrocephalus). Nine patients had postoperative transient complications, without correlation with preoperative ASA class.

At a follow-up ranging from 6 to 113 (mean 59,3), a recurrence/re-growth of residue was observed in 8 cases (13,3%) operated on with ST or P resection. In 2 of them a second surgery was necessary for large cystic transformation, whereas in other 6 cases the initial growth of tumor ceased at yearly MRI controls.

Similar rates are in line with the literature (19-21,26,45,47,57,58,61,62) and confirm that the retrosigmoid approach is safe and feasible to remove even giant lesions (20,26,45,47,50,57). The translabyrinthine approach has been traditionally advocated for this kind of tumors, with arguably good results in terms of extent of resection (rates of total resection being approximately 90%), postoperative facial outcome (HBI-III close to 75%) and perioperative complications (CSF leaks present in nearly 2% of cases) (5,10,16,27,47). On the other hand, perioperative complication rates as high as 14,3% have also been reported (16). Even if translabyrinthine approach is a feasible alternative, the results of our series contribute to support the use the retrosigmoid approach.

Surgical resection represents the ideal treatment for large and giant VS. It significantly and positively impacts on the patients' quality of life (52,58) and should be considered even in the case of elderly ones.

Conclusions

Searching for the right balance between preservation of functions and maximal tumour removal of Koos Grade IV VS, from the analysis of the international literature and from the data of our personal limited experience, satisfactory results can be obtained adopting the following strategy:

1. T or NT resection should be the primary objective of surgery, especially in ASA Class ≤2 patients, with encouraging FN outcome;

2. The judicious resection should be preferred in ASA Class ≥3, in cystic, adherent and bleeding tumors, especially if the capsule of VS is firmly adherent to FN and/or brainstem;
3. The use of endoscopy for removal of tumor in the IAC is associated with higher rate of T-NT removal of tumor and better FN outcome.

The acceptable rate of postoperative complications confirms that the retrosigmoid approach is safe and feasible to remove even large and giant VS.

Declarations

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Conflicts of interest/Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material

None

Code availability

None

Ethics statement

The study involves human participants: for this reason, it has been reviewed and approved by local Ethics committee of the Hospital (Lazio1, ASLRoma1). A written consent for scientific treatment of personal data was obtained from any patient before surgery. No potentially identifiable human images or data are presented in this study.

Consent to participate

We confirm that the manuscript has been read and approved by all named authors; there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Consent for publication

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with

respect to intellectual property. Moreover, the authors affirm that human research participants provided informed consent regarding publishing their personal data. Authors are responsible for correctness of the statements provided in the manuscript.

Author's individual contributions

L.M.: study design, study conception, data extraction, data analysis, manuscript writing

A.C.: data extraction, data analysis, statistical analysis

F.B.: data extraction, data analysis, literature analysis

C.G.S.: data extraction, data analysis, radiological measurement

E.C.: data extraction, data analysis, radiological measurement

G.C.: data extraction, data analysis, literature analysis

R.R.: data analysis, statistical analysis, critical review of the manuscript

A.S.: critical review of the manuscript, study supervision

A.Z.: critical review of the manuscript, study supervision

CONFLICT OF INTEREST

We wish to confirm that there are no known **conflicts of interest** associated with this manuscript and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and **approved by all named authors**; there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We warrant that the article is the **authors' original work**, has not received prior

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Sincerely,

On behalf of the Authors,

Luciano Mastronardi

References

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Tables

Table 1. Characteristics of the patients and clinical presentation

Characteristic of patients	*Sex*	26 M 34 F
	Mean age (SD)	48,8 yrs, range 21-80
	Mean ASA class of risk	2,08, range 1-4
	Presenting symptoms, n. of cases (%)	AAO-HNS class C/D 52 (86,7%)
		Ataxia 18 (30%)
		Trigeminal disturbances 20 (33,3%)
		AAO-HNS B 8 (13,3%), C 30 (50%), D 22(36,7%)
		Facial palsy HBII 9 (15%), HBIII 1 (1,7%), HBIV 1 (1.7%)
Characteristics of tumors	*Mean maximal size*	3,97cm (SD±1,13), range 3,1-5,8cm
	Morphology	14 cystic (23,3%)
		46 solid (76,7%)

Table 2. Adhesions of Tumor Capsule, Bleeding Rate and Extent of resection

Tumor capsule adhesion and tumor morphology			
	Cystic: 14 cases	Solid: 46 cases	Chi-test
Presence of tight adhesions: 38 cases (63,3%)	**12 (85,7%)**	26 (56,5%)	p<0.001
Absence of tight adhesions: 22 cases (36,7%)	2 (14,3%)	20 (43,5%)	
Extent of resection, capsule adhesions and technical equipment			
	Resection Total/NT: 46 cases	Resection ST/Partial: 14 cases	
Presence of adhesions (38)	25 (65,8%)	**13 (34,2%)**	p<0.001
Absence of adhesions (22)	**21 (95,4%)**	1 (4,6%)	
	Total removal	NT – ST – P removal	
Endoscope-assisted: 23 cases	**18 (78,3%)**	5 (21,7%)	p<0.001
Microscope only: 37 cases	17 (45,9%)	20 (54,1%)	

Table 3. Preoperative and postoperative facial and cochlear nerve function

	Preoperative	Postoperative
Facial nerve function – HB grade		
HBI	49 (81,7%)	34 (56,7%)
HBII	9 (15%)	9 (15,0%)
HBIII	1 (1,7%)	8 (13,3%)
HBIV	1 (1,7%)	9 (15,0%)
Cochlear nerve function – AAO-HNS grade		
A	0	0
B	8 (13,3%)	2 (3,3%)
C	30 (50,0%)	3 (5,0%)
D	22 (36,7%)	55 (91,7%)

Table 4. Long-term facial outcome

Anatomical and functional facial nerve preservation rate: 90% (54/60 cases)			
HBI: 34 (56,7%)	HBII: 9 (15%)	HBIII: 8 (13,3%)	HBIV: 9 (15%)
			Student's t-test
Mean stimulation threshold at the end of surgery	T+NT removal: 0,24 mAmp	ST+P removal: 0,57mAmp	p<0.001
		Postoperative HBI-II rate (43 cases)	*Chi-square test*
Tumor morphology	*Solid*	80,4% (37/46)	p<0.01
	Cystic	42,9% (6/14)	
Trigeminal symptoms	*Present*	80,0% (16/20)	p<0.001
	Absent	67,5% (27/40)	
Preoperative ataxia	*Present*	77,8% (14/18)	p<0.001
	Absent	69,0% (29/42)	
Tumor capsule adhesions	*Present*	57,9% (22/38)	p<0.001
	Absent	95,4% (21/22)	
Bleeding	*High*	59,2% (18/34)	p<0.001
	Low	95,1% (25/26)	
Use of Flexible Endoscopy	*Used*	86,9% (20/23)	p<0.001
	Not used	62,2% (23/37)	

Grade of tumor removal	*T-NT*	80,4% (37/46)	p<0.01
	ST-Partial	50,0% (6/14)	