Doctoral School in Medical Sciences

Under the title of manuscript

C.Z.U.: 616.282.7-006.385-07-089(043.2)

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DIAGNOSIS AND TREATMENT OF VESTIBULAR SCHWANNOMA

321.16 - OTORHINOLARYNGOLOGY

Summary of the Doctor of Medical Sciences thesis

Chisinau, 2025

The thesis was developed within the Department of Otorhinolaryngology of the Public Institution "Nicolae Testemitanu" State University of Medicine and Pharmacy and the Institute of Otolaryngology „O.S. Kolomiychenko" from Kiev, Ukraine.

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1. CONCEPTUAL REFERENCES OF RESEARCH

Vestibular schwannoma – acoustic neuroma (VS) is a benign tumor of the eighth pair of cranial nerves. It accounts for about 6% of all intracranial tumors and 80% of the tumors of the pontocerebellar angle [1, 2]. VS is well-known in specialized literature, which is confirmed by the more than 11,000 articles published in the PubMed database. Its level of study remains very high, with over 2000 articles published in the last 5 years [3]. The increased interest of researchers in this pathology is due to the evolution of VS which is not fully elucidated till nowadays. This is especially due to the unpredictable peculiarities of growth and clinical manifestation of this tumor. In some studies, it is shown that vestibular schwannoma, once diagnosed, may not show an increase in size over several years, and in some cases is discovered accidentally during anatomopathological examination [4-8]. In other studies, focused on the growth rate of acoustic neurinoma, in addition to lack of growth, even tumor regression was observed during monitoring [9-13]. Some tumors, however, may show very rapid growth and result in serious morbidity or even mortality if left untreated [13-17].

In the Republic of Moldova, during 2010 – 2019, 65 patients with VS, confirmedby histopathological examination, were surgically treated. Most of these patients experienced deafness as the main symptom, and about 1/3 of them had cofosis on the side of tumor localization. Approximately 2/3 of patients were diagnosed with VS > 20mm in size, and in over 1/2 cases the dimensions were > 30mm [18]. These data show a late diagnosis of VS, and the fact that hearing loss was the main symptom mentioned by patients marks the important role of the ENT doctor in detecting this tumor.

Taking into account the above-mentioned, we aimed to achieve the following **goal:** the clinical and paraclinical study of patients primarily diagnosed with vestibular schwannoma, in order to establish the peculiarities of tumor evolution and growth and to develop an algorithm for early diagnosis and treatment of this condition.

In order to achieve the purpose of the research, the following **objectives** were formulated:

1. Clinical diagnostic study of patients with vestibular schwannoma, in order to identify the most specific clinical diagnostic signs attesting to the evolution of the pathology.
2. Analysis of the results of MRI investigations in patients with vestibular schwannoma to establish the imaging peculiarities that show tumor evolution/growth.
3. Evaluation of changes in immunological markers in patients with vestibular schwannoma, in order to identify the most informative diagnostic and prognostic markers of tumor growth.
4. Developing an algorithm for early diagnosis and treatment of vestibular schwannoma.

General research methodology: In order to achieve the objectives proposed in the doctoral thesis, a prospective study of patients with VS was carried out, aiming to establish the evolution and factors that determine tumor growth. The prospective study included a group of patients with VS, divided into 2 Groups: the first Group, in which no tumor growth was observed, and the second Group, in which tumor growth was found. A comparative analysis of both clinical and laboratory data (imaging and immunological laboratory) was performed in these patients.

The current research study was approved by Ethics committee of the State University of Medicine and Pharmacy „Nicolae Testemițanu” (report nr. 1 from 19.06.2018).

Due to the low incidence of vestibular schwannoma and the small number of the population in the Republic of Moldova, the prospective study was carried out in the Department of Microsurgery and Otoneurosurgery of the Institute of Otolaryngology "O. S. Kolomiychenko" from Kyiv. The immunological analyzes were performed in the Pathophysiology and Immunology Laboratory of the same institution. The researches were carried out on the basis of the collaboration agreement between USMF "Nicolae Testemițanu" and the Institute of Otolaryngology "O. S. Kolomiychenko" from Kyiv, as well as the joint supervision agreement between these two institutions.

The approval of the Bioethics and Deontology Committee of the Institute of Otolaryngology "O.S. Kolomiychenko" in Kyiv, Ukraine (minute no. 22/19 of November 22, 2019) was positive.

Scientific novelty and theoretical significance of the results obtained: 1) the evolution of vestibular schwannoma was established based on the analysis of the results of the clinical and paraclinical examination in patients primarily diagnosed with VS. 2) The immunological results of cytokines and growth factors collected from patients with VS were analyzed. 3) The results of monitoring, by MRI examination, of patients with VS in whom tumor growth was not observed and those in whom the tumor was growing, were analyzed, with the determination of imaging aspects characteristic of tumor growth. 4) Certain clinical and immunological criteria have been established, which may be possible predictive markers of tumor growth. Thus, the doctoral thesis contributes with new information on the understanding of VS progression, the pace and nature of tumor changes, important in the development of new predictive models. The paper also provides new data on growth rates and tumor behavior, based on imaging characteristics resulting from contrast MRI examination, essential for evaluating treatment and adjusting therapeutic protocols. The application of clinical and immunological criteria for estimating the risk of tumor growth can substantiate the right decisions regarding the intervention, contributing to the development of personalized pathology management strategies.

The applicative value of the paper. In the applicative aspect, a diagnostic and treatment algorithm has been developed for patients with vestibular schwannoma, which can be integrated into a national clinical protocol. The translabirintic approach has also been introduced in VS surgery.

Keywords: vestibular schwannoma, acoustic neuroma, nuclear magnetic resonance, endothelial vascular growth factor, transforming growth factor 1β, immunoglobulin A, immunoglobulin M, carcinoembryonic antigen, translabirintic approach.

2. MATERIAL AND METHODS OF RESEARCH

2.1. General characteristic of the Research Methodology: Study lots, Stages and Design of the research

The paper is compartmentalized and exposes the results and analysis, obtained in 2 studies:

1. Prospective clinical and immunological study of patients with VS;
2. Case study: surgical treatment of VS by translabirintic approach.

The prospective study was conducted within the Department of Microsurgery and Otoneurosurgery of the "O. S. Kolomiychenko" Institute of Otolaryngology of the National Academy of Medical Sciences of Ukraine, based on a collaboration agreement between this institution and the "Nicolae Testemitanu" State University of Medicine and Pharmacy. Immunological analyses were performed in the Laboratory of Pathophysiology and Immunology of the same institute.

The case study included a summary of the first VS translabrintic approach intervention in the Republic of Moldova. This intervention was performed within the IMSP Neurosurgery Clinic "Diomid Gherman" Institute of Neurology and Neurosurgery. The study was conducted based on the collaboration agreement between the ENT Clinic of the "Timofei Mosneaga" Republican Clinical Hospital and the Neurosurgery Clinic of the "Diomid Gherman" Institute of Neurology and Neurosurgery.

The general group of patients included in the prospective study consisted of 47 patients. These were adult patients, aged 21 to 69 years, primarily diagnosed with VS and monitored by MRI examination over at least 6 months.

The general study group was divided into 2 Groups:

1. Group 1 of the study - 24 patients in whom no tumor growth was found;
2. Group 2 of the study - 23 patients in whom tumor growth was found.

Up to 40 patients in the general study group underwent immunological analysis, with determination of vascular endothelial growth factor (VEGF), transforming growth factor 1β (TGF-1β), immunoglobulin A (IgA), immunoglobulin M (IgM), and carcinoembryonic antigen (CEA) in blood serum. Taking into account that the immunological analysis was not performed in all patients in the general study group, their number varied according to each immunological factor. VEGF was determined in 38 patients, TGF-1β in 40 patients, IgA in 38 patients, CEA in 29 patients, and IgM in 18 patients. The immunological data obtained were compared with the reference values, provided by the reagent companies, as well as with the values in the control group, which included 10 completely healthy people. A comparative analysis between the 2 study Groups was also performed.

In order to determine the evolution of VS at the early stage, we performed an immunological analysis of VEGF, TGF-1β, IgA, IgM and CEA in patients with intracanalicular VSs (stage I). Thus, we selected 18 patients from the general study group, which were divided into 2 Groups. The data were compared with the control group consisting of 10 completely healthy people:

1. Group 1 of the study - 10 patients in whom no tumor growth was observed;
2. Group 2 of the study - 8 patients in whom tumor growth was found;
3. Control group - 10 completely healthy people.

The scheme of the researches carried out is shown in Figure 1.

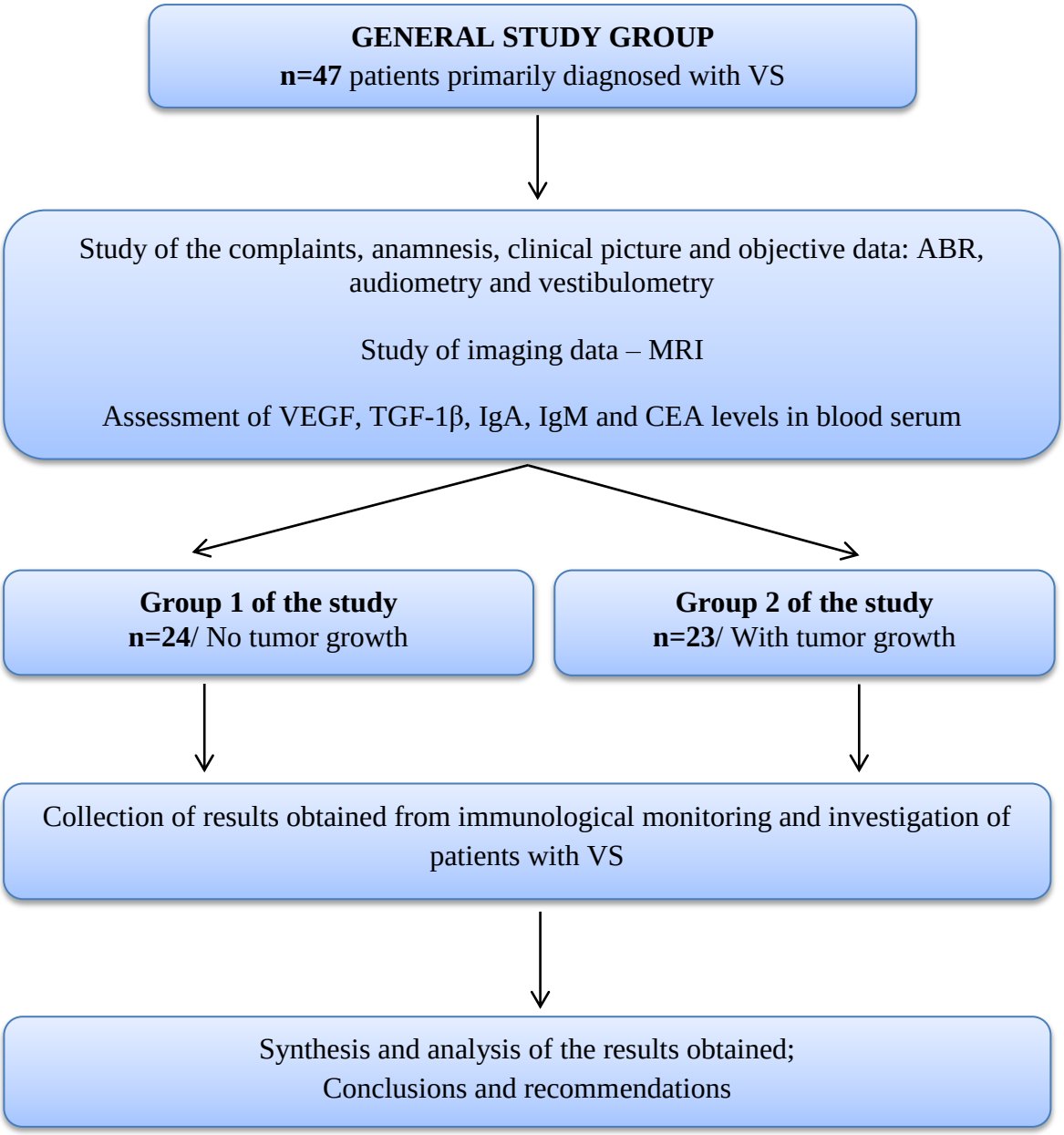


Figure 1. **Research design**

2.2. General characteristic of the study groups

The 47 patients included in the prospective study were diagnosed with VS of different degree, ranging in age from 21 to 69 years. The mean age was 51.36 years. The male/female ratio was 20 males to 27 females. In terms of location, 23 tumors were found on the left side and 24 tumors on the right side. Based on the tumor growth criterion, patients were divided into 2 Groups:

1. Group 1 of the study - 24 patients without tumor growth;
2. Group 2 of the study - 23 patients with tumor growth.

In the general study group, up to 40 patients underwent immunological analysis, evaluating VEGF, TGF-1β, IgA, IgM and CEA factors in blood serum. The immunological analysis was not performed in all patients in the general study group, the number varying according to each immunological factor: VEGF was determined in 38 patients, TGF-1β in 40 patients, IgA in 38

patients, CEA in 29 patients, and IgM in 18 patients. The immunological data obtained were compared with the reference values provided by the reagent companies and with the values in the control group, which was composed of 10 completely healthy people, a comparative analysis between the 2 study Groups being also performed. In order to determine the evolution of VS at an early stage, we performed an immunological analysis of patients with intracanalicular VSs (stage I), which included all growth factors and cytokines mentioned. This group of patients was composed of 18 cases, divided into 2 Groups:

1. Group 1 of the study - 10 patients without tumor growth;
2. Group 2 of the study - 8 patients with the growing tumor.

The control group included 10 completely healthy people, from whom blood samples were collected to determine the level of immunological factors analyzed.

The case study regarding the surgical treatment of VS by translabirintic approach was performed on a 60-year-old patient, diagnosed with VS of the second degree, surgically treated by this approach, on 09.12.2022 within the IMSP "Diomid Gherman" Institute of Neurology and Neurosurgery.

2.3. Research methods

Clinical methods: The complaints and anamnesis of vestibular schwannoma were thoroughly studied in all patients in the prospective study. It was determined what the first symptom of VS was and when it approximately appeared. It has been determined whether or not there are concomitant symptoms such as heavy-headedness, headache, vertigo, coordination disorder, imbalance, hypoaesthesia or paraesthesia in the head and face, tremor of the facial muscles, incomplete closure of the eye, facial muscle spasm, swallowing and speech articulation disorder, or whether there are other symptoms present in these patients.

ENT examination: All patients in the prospective study, taking into account the anamnesis and complaints mentioned, underwent the ENT examination. In these patients, the otomicroscopy examination was performed using the Zeiss OPMI Pico surgical microscope.

Paraclinical methods: The patients included in the prospective study, in addition to the clinical examination, underwent the following investigations:

- Audiometry;
- ABR;
- Vestibular testing;
- MRI examination of the internal auditory canal (IAC) and the cerebellopontine angle (CPA);
- Immunological analysis with determination of VEGF, TGF-1β, IgA, IgM and CEA.

2.4. Procedures of statistical analysis of results

In the analysis of the qualitative values of comparison between batches, Chi-Square tests were used: Pearson. For the analysis of quantitative comparison values between batches related to clinical-diagnostic data, including MRI, the Mann-Whitney U-test was applied. For the comparative quantitative analysis of immunological results, the Kruskal-Wallis test was used. In the case of small VS (stages 0 and 1), the comparative quantitative analysis of immunological results was performed using the ANOVA test. The correlation of comparative data between the two study groups was considered statistically significant for values with $p < 0.05$. Statistical data processing was performed using IBM SPSS Statistics 26.0.

3. CLINICAL AND IMMUNOLOGICAL STUDY OF PATIENTS WITH VESTIBULAR SCHWANNOMA

3.1. Anamnesis and symptomatology of patients diagnosed with vestibular schwannoma

The prospective study conducted within the Department of Microsurgery and Otoneurosurgery of the "A. I. Kolomiychenko" Institute of Otolaryngology of the National Academy of Medical Sciences of Ukraine, included 47 patients who, within the contrast MRI examination, were primarily diagnosed with VS. In order to determine the evolution of VS and to establish some potential criteria based on which tumor growth can be assumed, the patients included in the study underwent monitoring by repeatedly performing contrast MRI examination.

According to the House classification, of the total number of tumors diagnosed, 11 (23.4%, 95% CI [12.8-36.2]) were intracanalicular, 19 (40.4%, 95% CI [27.7-53.2]) were of Stage I, 11 (23.4%, 95% CI [10.6-36.2]) Stage II and VI (12.8%, 95% CI [4.3-23.4]) tumors were of Stage III (Table 1). Depending on the area 23 (48.9%, 95% CI [34-61.7]) tumors were on the right and 24 (51.1%, 95% CI [38.3-66]) were on the left. Of the total number of patients, 20 (42.6%, 95% CI [29.8-57.4]) patients were male and 27 (57.4%, 95% CI [42.6-70.2]) patients were female. The age of the patients was between 21 and 69 years. The mean age was 51.36 years (95% CI [47.8-54.93]), with a median of 54 years.

Depending on the tumor growth, the total number of patients was divided into 2 Groups: group 1 - 24 patients in whom no tumor growth was observed and group 2 - 23 patients in whom VS was increasing. In group 1, 8 (33.3%, 95% CI [14.8-54.2]) patients had intracanalicular VS, 12 (50%, C I95% [29.2-71.4]) patients had stage I VS, and 4 (16.7%, CI95% [4-32]) patients had stage I VS. In study group 2, 3 (13%, CI95% [0-29.2]) patients had intracanalicular VS, 7 (30.4%, C I95% [12.5-50]) patients had stage I VS, 7 (30.4%, 95% CI [12.5-50]) patients had stage II VS, and 6 (26.1%, CI95% [8.7-43.7]) patients had stage III VS (Table 1). According to the Chi-Square Pearson test, Stage III VS was observed only in study group 2 and had very high statistical significance p=0.005 (p < 0.01).

Table 1. **Number of patients with different VS stage in both study groups**

Tumor stage	**Lot 1, n=24 patients**		**Lot 2, n=23 patients**		
	n	**%**	**n**	**%**	
Stage 0 - intracanalicular	8	33.3	3	13	Test Chi-Square Pearson
Stage I ≤ 10mm	12	50	7	30.4	
Stage II ≤ 20mm	4	16.7	7	30.4	
Stage III ≤ 30mm	-	-	6	26.1	p < 0,01
Stage IV ≤ 40mm	-	-	-	-	
Stage V > 40mm	-	-	-	-	

First symptom. According to the history, the first symptom of VS occurrence in the patients included in the study (Table 2) was sensorineural hearing loss in 19 (40.5%) cases, tinnitus in 7 (14.9%) cases, and sensorineural hearing loss in association with tinnitus in 12

(25.5%) cases. In total, sensorineural hearing loss as the first symptom occurred in 31 (66%, 95% CI [51.1-78.7]) cases and tinnitus in 19 (40.4%, 95% CI [25.5-55.3] cases. Vertigo was present in 2 (4.3%, 95% CI [0-10.6]) cases, and postural instability and clogged ear sensation were present in one case (2.1%, 95% CI, [0-6.4]). In 5 cases it was not known what the first symptom of VS appearance was.

In the first group of patients, in whom no tumor growth was established, sensorineural hearing loss was present as the first symptom in 10 patients, tinnitus in 3 patients, hearing loss in association with tinnitus in 7 patients, and clogged ear sensation in one patient. In the second study group, in which tumor growth was established, sensorineural hearing loss as an initial symptom was determined in 9 cases, tinnitus in 4 cases, sensorineural hearing loss in association with tinnitus in 5 cases, vertigo as the first symptom of VS occurrence in 2 cases, and postural instability in only one case. In study group 1, 3 patients did not remember what the first symptom was, and 2 patients had normal hearing. In the second group, 2 patients did not know what the first symptom was, and 1 patient had normal hearing.

Table 2. **First symptom of VS appearance in both study Groups**

First symptom of VS appearance	**Lot 1, n=24 patients**		**Lot 2, n=23 patients**		
	n	**%**	**n**	**%**	
Hearing loss	10	42	9	39	Test Chi-Square Pearson p > 0,05
Tinnitus	3	12.5	4	17.4	
Hypoacusis & Tinnitus	7	29	5	21.7	
Vertigo	-	-	2	8.7	
Clogged ear sensation	1	4	-	-	
Postural instability	-	-	1	4.3	

Symptomatology. Depending on the tumor growth, hearing loss was present in 22 patients in study group 1 and 22 patients in study group 2, respectively. This was progressive in 2 patients (8.3%) in group 1 compared to 8 (34.8%) patients in group 2, who according to the Chi-Square Pearson test showed a statistically significant difference, p=0.02 (p<0.05). Sudden hearing loss on the same level was present in 2 patients (8.3%) in group 1 as opposed to 3 patients (13%) in group 2 of the study (p>0.05).

Headache was present in 20 (83.3%) of the total 24 patients in study group 1, as opposed to 17 (73.9%) of the total 23 patients in study group 2 (p>0.05). In 3 (12.5%) patients in study group 1 and 7 (30.4%) patients in study group 2 it was related to psychoemotional stress, and in 5 (20.8%) patients in group 1 and 7 (30.4%) patients in group 2 it was related to changes in atmospheric pressure.

Vertigo was present in an equal number of patients in both study groups: 16 (66.6%) patients in study group 1 and 16 (69.5%) patients in study group 2 (p>0.05). Vertigo associated with nausea was present in one patient (4.1%) in group 1 and unlike 4 (17.4%) patients in group 2 of the study (p>0.05).

Disturbed coordination was mentioned by 8 (33.3%) patients in group 1 and 10 (43.4%) patients in group 2, and the imbalance of 13 (54.1%) in group 1 and 9 (39.1%) patients in group 2 (p>0.05).

Hypoaesthesia or paraesthesia in the head and face was present in 7 (29.1%) cases in the group of patients without tumor growth and in 3 (13%) patients in the group in which VS growth was determined (p > 0.05).

Tremor of the facial muscles was present in 9 (37.5%) patients in group 1 and in 5 (21.7%) patients in group 2 (p > 0.05). In the group of patients without tumor growth, tremor in the cheek region was mentioned by one patient, eyelid tremor by 5 patients, and tremor of the cheek, eyelids, and lips from the VS localization was also mentioned by one patient. In the group of patients with VS eyelid tremor is increasing, it was present in 2 patients, tremor in the cheek and eyelid region was mentioned by 1 patient and tremor in both these two mentioned regions and in the lip region by 2 patients (Figure 2).

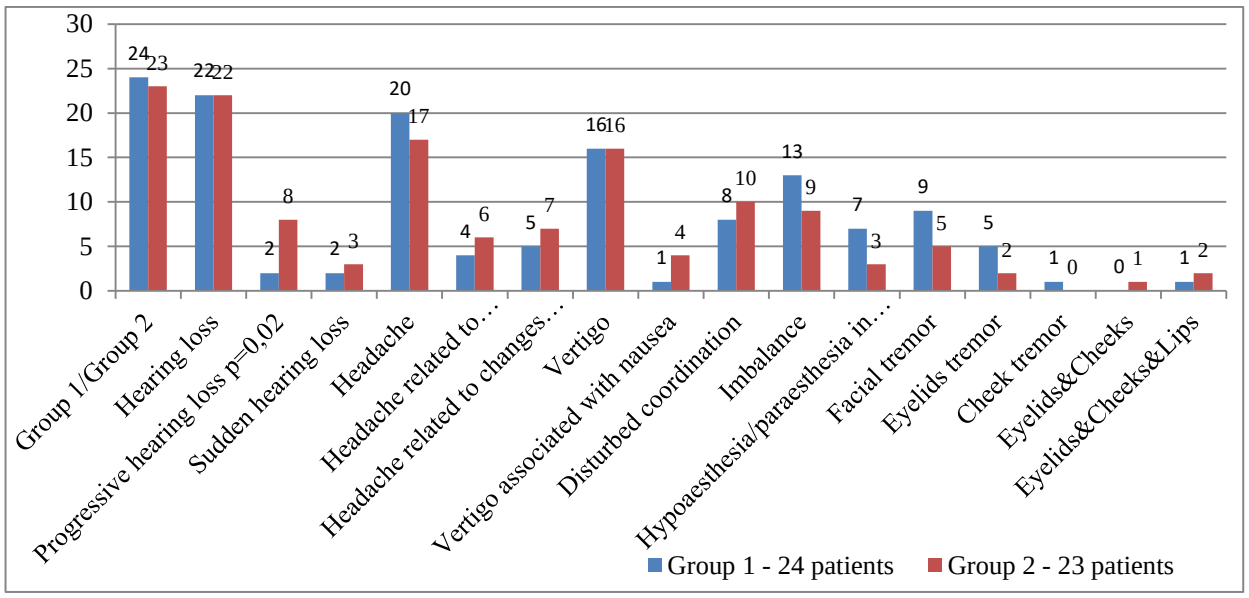


Figure 2. **Symptomatology of VS in groups 1 and 2 of the study depending on the absence or presence of tumor growth, abs.**

3.2. Clinical and paraclinical characteristics of patients diagnosed with vestibular schwannoma

Audiological examination. Following the tonal audiometry test and the voice audiometry test, sensorineural hearing loss was present in 44 (93.6%, 95% CI [85.1-100]) patients out of the total 47 patients included in the study. Depending on the tumor growth, according to the AAO-HNS classification, class A hearing loss was present only in patients in group 2 - 5 (10.6%) patients. Class B hearing loss was present in 4 (8.5%) patients in group 1 and in 7 (14.9%) patients in group 2. Class C hearing loss was present in 8 (17%) patients in group 1 and in 2 (4.2%) patients in group 2, and class D hearing loss was present in 5 (10.6%) patients in group 1 and in 6 (12.7) patients in group 2. Cofosis was present in 5 (10.6%) patients in group 1 and in 2 (4.2%) patients in group 2, and hearing within the normal range was present in 2 (4.2%) patients in group 1 and in 1 (2.1%) patient in group 2. Analysis of audiometric data did not reveal statistically significant differences between the two study groups (p > 0.05).

ABR examination. Recording of auditory evoked potentials showed an increase in the I-III and I-V interval in 26 (55.3%, 95% CI [40.4-70.2]) patients in the general study group: 10 (21.3%) patients in group 1 and 16 (34%) patients in group 2. In 11 (23.4%) cases, the wave

(through the entire complex I-V) at the time of registration was absent: in 7 (14.9%) cases in study group 1 (5 cases of profound hearing loss and 2 cases of confosis) and in 4 (8.5%) cases in study group 2 (2 cases of profound hearing loss and 2 cases of cofosis). No auditory evoked potentials were recorded in 10 (21.3%) patients, the primary diagnosis of VS being established from the start based on the MRI examination. ABR data did not have statistical significance between study groups ($p > 0.05$).

Vestibular testing. Following the functional stimulation (caloric and rotational) and the recording of the experimental nystagmus by means of electronystagmography, different degrees of vestibular syndrome were highlighted. Thus, according to the tumor growth of VS, in the first study group, the vestibular syndrome grade I-II was present in 7 (14.9%) patients, grade II in 12 (25.5%) patients, grade II-III in 1 (2.1%) patient and grade III was present in 2 (4.2%) patients. Both labyrinthic hyporeflexia and reduced peripheral vestibular function were present in 1 (2.1%) patient at a time. In study group 2, the vestibular syndrome grade I was present in 2 (4.2%) patients, grade I-II in 2 (4.3%) patients, grade II in 11 (23.4%) patients, grade II-III in 3 (6.4%) patients and grade III in 2 (4.3%) patients. According to the Chi-Square Pearson test, vestibulometric data between study groups did not show a statistically significant difference ($p > 0.05$). However, the worsening of the vestibular syndrome showed a statistically significant difference $p = 0.01$ because it was found only in patients in study group 2 - 5 (10.6%) patients (Figure 3).

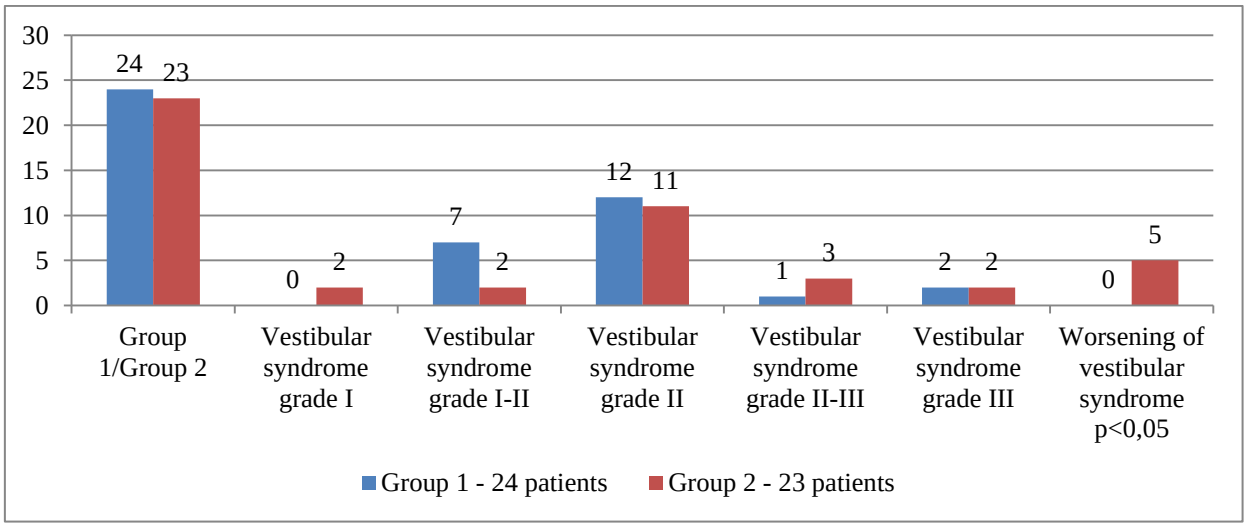


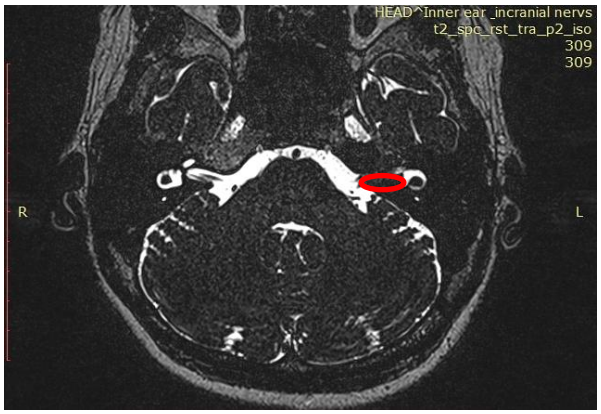
Figure 3. **Vestibulometry results depending on tumor growth in groups 1 and 2 of the study, abs.**

3.3. MRI examination data of patients with vestibular schwannoma

All patients included in the prospective study underwent monitoring by contrast MRI examination for a period of at least 6 months to 12 years. Tumor growth was caused by increasing tumor diameter by more than 2 mm in one size or 1 mm in two sizes over at least 6 months. Of the total 23 patients in study group 2 (with tumor growth), 5 were monitored for 6 months, 11 were monitored for one year, 3 were monitored for 3 years, 2 were monitored for 4 years, and one patient was monitored for 5 and 6 years.

The tumor growth rate in each patient in study group 2 was different. However, in the 11

patients who were monitored for one year, the tumor growth averaged 3.5 mm/year. Tumor growth from stage 0 (intracanalicular) to stage I was determined in 4 (8.5%) patients. Tumor growth from stage 0 to stage I, from stage I to stage II and from stage II to stage III was established in 2 (4.2%) patients (Figure 4). In the case of 7 patients, MRI images were not available for the study due to their lack. For these patients, only the diagnostic conclusions of the MRI examination were available: 5 cases from study group 1 and 2 cases from study group 2.



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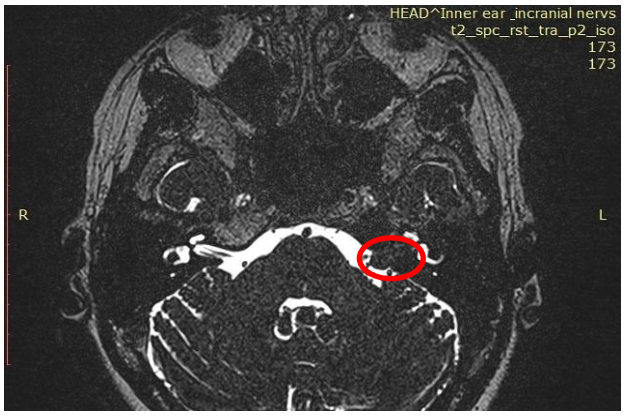

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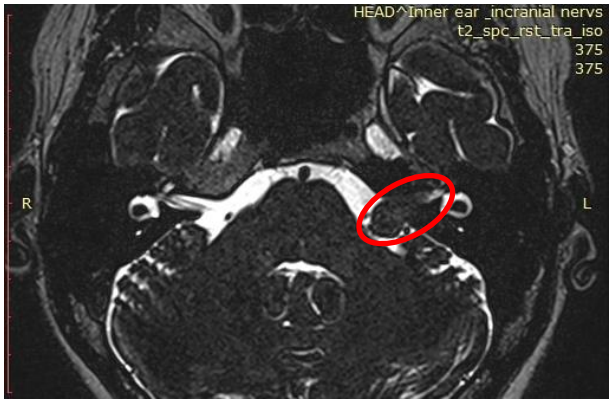


C

A – MRI 10.2017

B – MRI 04.2018

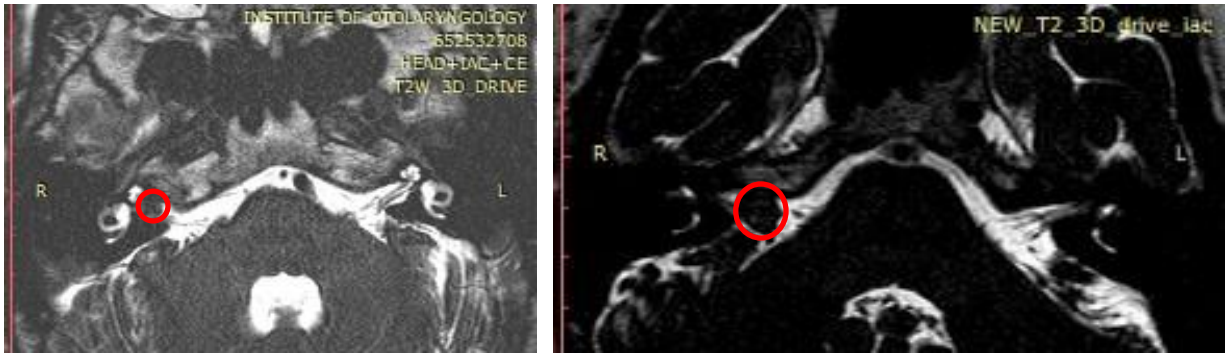
C – MRI 12.2019

Figure 4. **T2 MRI images in a patient in study group 2, diagnosed with left VS, in which tumor growth was established.**

Location of VS in IAC. Detailed analysis of images in different MRI sequences revealed the following: VS localization in the medial portion of the IAC was present in 34 (72.3%, 95% CI [59.6-85.1]) cases, in the lateral portion of the IAC in 21 (44.7%, 95% CI [31.9-59.6]) cases, and the IAC was completely occupied by the tumor in 17 (36.2%, 95% CI [23.4-48.9]) cases. In study group 1, the medial portion of the IAC was occupied by the tumor in 16 (34%) cases, the lateral portion of the IAC in 11 (23.4%) cases, and the IAC was completely occupied by the tumor in 8 (17%) cases. In study group 2, VS was present in the medial portion of the IAC in 18 (38.2%) cases, in the lateral portion of the IAC of the VS was present in 10 (21.3%) cases, and in one case it increased from side to medial with full occupation of the IAC. According to the Chi-Square Pearson test, a statistically significant difference between groups was not established ($p > 0.05$).

Location of intracanalicular VS in IAC. In study group I, in patients with intracanalicular VS, the tumor was present in the lateral portion of the IAC (near the inner ear) and in the medial portion of the IAC (near the CPA) in 2 (4.2%) cases, and the tumor completely

occupied the IAC in 3 (6.4%) cases (Figure 5). In study group 2, the tumor was located both in the lateral portion of the IAC and in the medial portion of the IAC in 1 (2.1%) case each, and in another case (2.1%) the tumor growth from the lateral portion of the IAC to the CPA was determined, completely occupying the IAC.

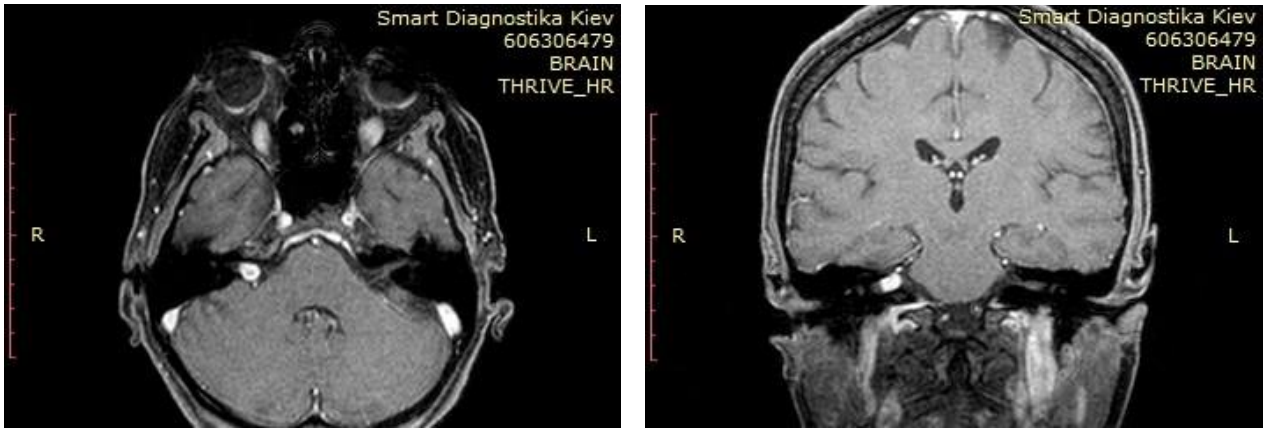


A B

Figure 5. **MRI images showing the location of VS in IAC: A & B - T2 images where VS is visualized in the medial and lateral portion of the IAC on the right.**

Medial dilation of the IACwas observed in 21 (44.7%, 95% CI [31.9-59.6]) patients in the general study group. In study group 1, in patients with intracanalicular VS, medial dilatation of the IAC (near CPA) was determined in one case (2.1%), in 6 (12.7%) cases in patients with stage I VS and in 2 (4.3%) cases it was present in patients with stage II VS. In study group 2, medial dilation of the IAC was detected in patients with stage II VS in 5 (10.6%) cases, stage II VS in 3 (6.3%) cases, and stage II VS was established in 4 (8.4%) cases (Figure 6). According to the Pearson Chi-Square test, these data were not statistically significant ($p > 0.05$).

Lateral dilation of theIAC was found in 5 (10.6%, 95% CI [2.1-21.3]) cases in the general study group: 2 (4.3%) cases of stage I VS in groups 1 and 2 of the study and one (2.1%) case of stage II VS in group 2 of the study. These data were also not statistically significant ($p > 0.05$).

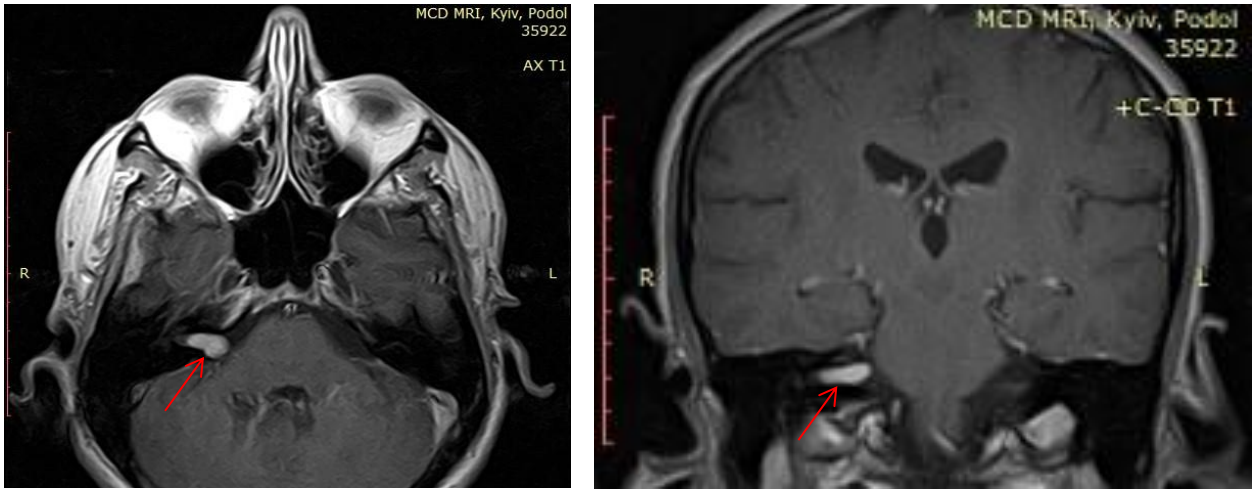


A B

Figure 6. **Contrast MRI images where the presence of VS with the medial dilation of the IAC is visualized: A - axial projection; B - coronal projection.**

Complete occupation of the IAC with dilatation in the medial portion (near the CPA). Full occupation of the IAC with pronounced dilation in the medial portion (near CPA), when the tumor is viewed on MRI images under the "trumpet" aspect, was detected in 7 (14.9%, 95% CI

[4.3-25.5]) cases in the general study group. This form of tumor was identified in 3 (6.4%) cases of stage I VS in study group 1 and in 2 (4.2%) cases of stage 1 and stage II VS in study group 2 (Figure 7).



A B

Figure 7. **T1 MRI images with contrast, with full occupancy of the IAC and dilation in the medial portion near the CPA – trumpet sign: A - axial projection; B - coronal projection.**

Location of VS in CPA. The presence of VS in CPA was detected in 23 (48.9%, 95% CI [34.1-63.8]) cases: 8 (17%) cases in study group 1 - 5 cases (10.6%) with stage I VS and 3 (6.3%) cases with stage II VS, and 15 (31.9%) cases in study group 2 - 3 (6.3%) patients with stage I VS, 6 (12.8%) patients with stage II VS and 6 (12.8%) patients with stage III VS ($p > 0.05$).

Location of VS in IAC and CPA. Expansion of VS from the IAC (with its medial dilation) into CPA, when the tumor is viewed on MRI images in the form of "ice cream cone", was present in 10 (21.3%, 95% CI [10.6-34.0]) cases in the general study group. In study group 1, this aspect was detected in 3 (6.4%) cases: 1 (2.1%) case of stage I VS and 2 (4.2%) cases of stage II VS. In group 2, the appearance of the "ice cream cone" was present in 3 (6.4%) cases of stage II VS and in 4 (8.5%) cases of stage III VS (Figure 10). The Chi-Square test indicated that, statistically speaking, data on the location of VS in CPA, the "trumpet" or "ice-cream cone" appearance of the tumor was not statistically significant ($p > 0.05$).

Cystic appearance of VS. The cystic appearance of VS was present in 10 (21.3%, 95% CI [10.6-34.0]) cases of the total study. In group 1, cystic VS was detected in 2 (4.2%) patients with stage II VS. In group 2, the cystic aspect of VS was found in 2 (4.2%) patients with stage I VS, in 2 (4.2%) patients with grade II VS and in 4 (8.4%) patients with stage III VS (Figure 8, 9).

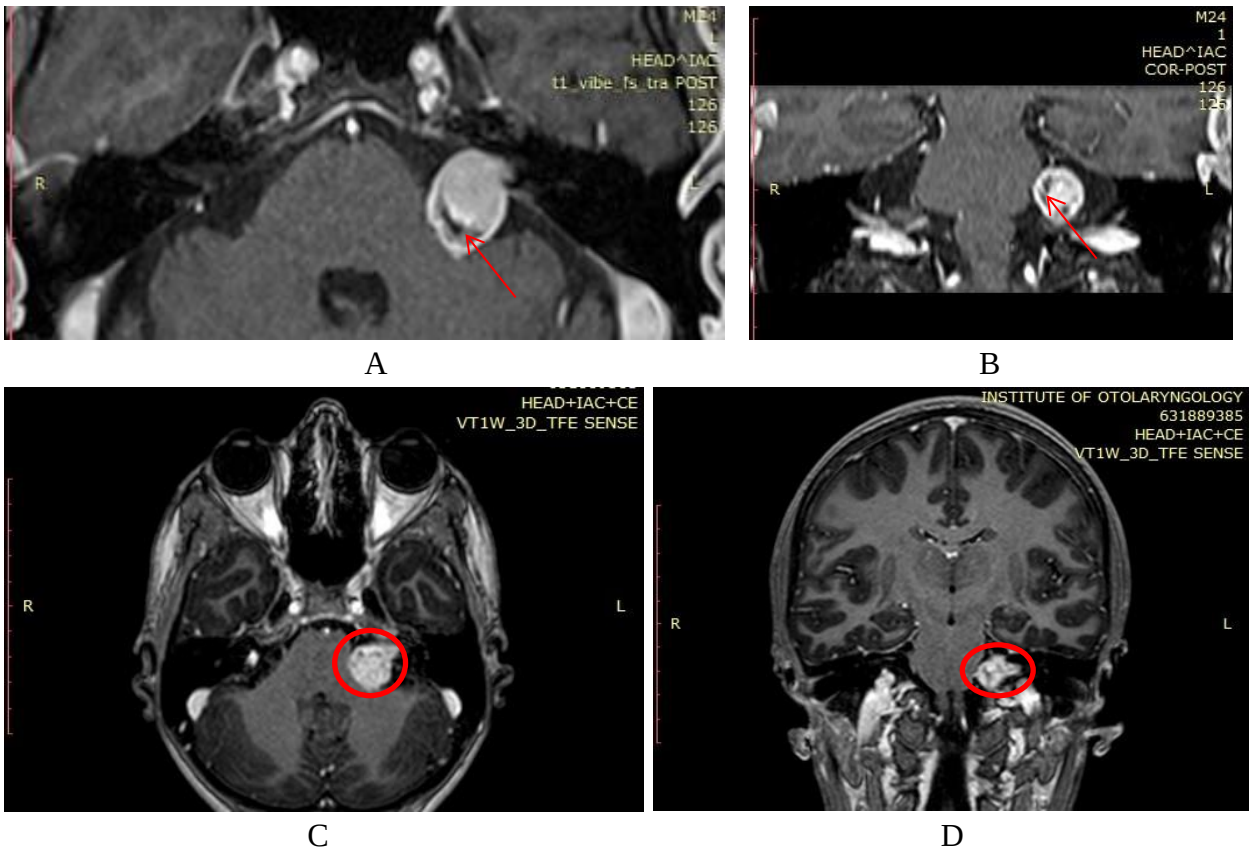


Figure 8. **T1 MRI images with contrast revealing: A, B - cystic appearance of the tumor in a patient with stage II VS; C, D - cystic type tumor under the aspect of "ice cream cone" in a patient with stage III VS.**

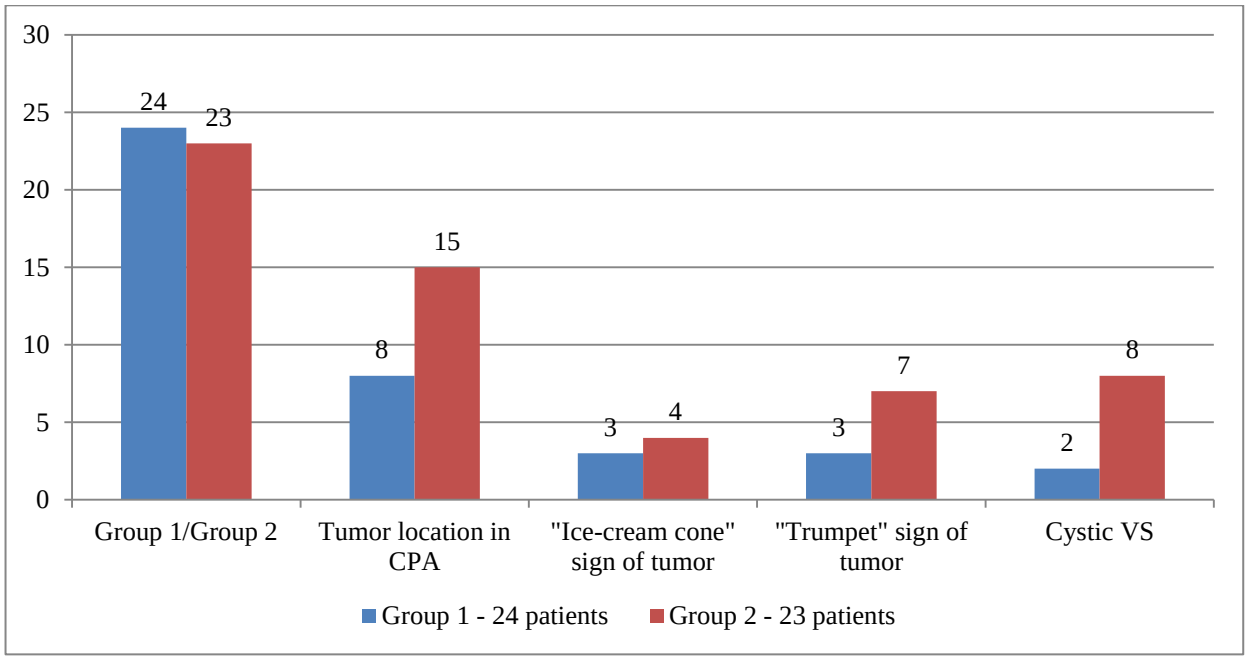


Figure 9. **Location and tumor appearance of VS on MRI images in patients in both study groups, abs.**

3.4. Evaluation of vascular endothelial growth factor, transforming growth factor 1β, immunoglobulins A, M and carcinoembryonic antigen in patients with vestibular schwannoma:

The immunological study included up to 40 patients diagnosed with VS. Considering that the immunological analysis was not performed in all patients in the general study group, their number varied according to each immunological factor: VEGF was determined in 38 patients, TGF-1β in 40 patients, IgA in 38 patients, CEA in 29 patients, and IgM in 18 patients. The control group consisted of 10 completely healthy people.

Vascular endothelial growth factor. According to the information provided by Euroimmun (Austria), the normal serum concentration of VEGF varies between 20-30 ng/ml. In our study, the serum concentration of VEGF in the control group was 26.3 ng/ml, 95% CI [17.09-35.50], while in the general study group it was, on average, 229.45 ng/ml, 95% CI [179.82-279.07]. The average of the VEGF values in study group 1 was 230.67 ng/ml, 95% CI [154.32-307.03], and in study group 2 it was 228.22 ng/ml, 95% CI [157.14-299.30]. Depending on the tumor stage, the mean serum VEGF value was: 237.41 ng/ml in patients with intracanalicular VS, 206.56 ng/ml in patients with stage I VS, 221.27 ng/ml in patients with stage II and 290.75 ng/ml in patients with stage III VS. According to the Kruskal-Wallis test, the difference between the control group and the study groups had very high statistical significance, ($p=0.000$). However, the comparative analysis between group 1 and group 2 of the study did not show statistically significant differences ($p > 0.05$).

Transforming growth factor 1 β. According to the data provided by DRG (Germany), the normal serum level of TGF-1β varies between 20-40 ng/ml. In the control group, the average of the serum concentration of TGF-1β was 58.6 ng/ml, 95% CI [36.42-80.77], while in the general study group the average was 89.35 ng/ml, 95% CI [67.45-111.25]. The average of the TGF-1β value in study group 1 was 71.43 ng/ml, 95% CI [39.90-102.96]. In study group 2, TGF-1β was 109.16 ng/ml, 95% CI [78.52-139.81]. The mean value of TGF-1β in the group of patients with intracanalicular VS was 92.34 ng/ml, in patients with stage I VS it was 87.93 ng/ml, in patients with stage II VS it was 70.05 ng/ml and in patients with stage III VS it was 117.23 ng/ml. From a statistical point of view, the Kruskal-Wallis test did not identify a statistically significant difference between the control group and the study groups ($p > 0.05$).

From the data obtained, it was observed that the serum levels of VEGF and TGF-1β were high at all tumor stages compared to the reference values or control values. The highest values of these factors are found in patients with stage III VS. Also, the level of VEGF in the blood serum was 8.72 times higher than the control values ($p < 0.01$), and the level of TGF-1β was 1.52 times higher than the control values. In group 2 of patients, where VS was increasing, the level of TGF-1β was 1.52 times higher than in group 1 of the study, where VS did not show tumor growth (Figure 10).

	VEGF	TGF-1β
Growth –	230,649	71.4324
Growth +	228,221	109.1695
Control	26.3	58,6

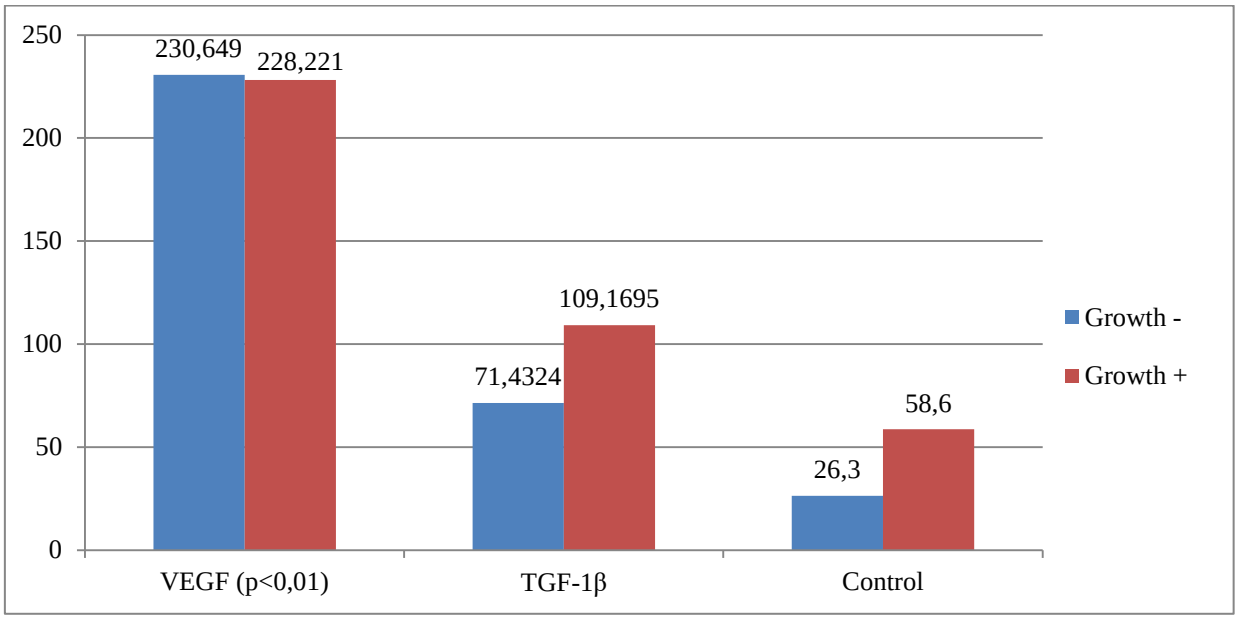


Figure 10. **Serum levels of VEGF and TGF-1β according to VS evolution, ng/ml.**

Immunoglobulin A. The serum concentration of IgA according to the information provided by the company OO «Хема медика» (Russian Federation) varies between 0.5-2.5 g/l. In the control group, the average of the IgA values was 1.8 g/l, 95% CI [1.59-2], while in the general study group the average was 2.99 g/l, 95% CI [2.68-3.30]. The average of the IgA values in study group 1 was 3.13 g/l, 95% CI [2.69-3.56], and in study group 2 it was 2.85 g/l, 95% CI [2.37-3.33]. Depending on the tumor stage, the serum level of IgA in patients with intracanalicular VS was 3.58 g/l, and in patients with stage I and II VS it was 2.75 g/l, while in patients with stage III VS it was 3.14 g/l (Table 10). The Kruskal-Wallis test demonstrated a statistically significant difference between the control group and the study groups, p=0.005. However, the comparative analysis of both study groups showed approximately equal values ($p > 0.05$).

Immunoglobulin M. The serum level of IgM was analyzed according to the data presented by the company OO «Хема медика» (Russian Federation), which indicates a reference range of 0.6-1.8 g/l. In the control group, the average serum IgM level was 1.5 g/l, 95% CI [1.08-1.91]. Comparatively, in the general study group, the average of the serum concentration of IgM was 6.4 g/l, 95% CI [4.09-8.71]. The average of the IgM values in study group 1 was 4.96 g/l, 95% CI [2.68-7.23], and in study group 2 it was 7.84 g/l, 95% CI [3.46-12.22]. The serum level of IgM in patients with intracanalicular VS was 6.73 g/l, in patients with stage I VS it was 4.2 g/l, in patients with stage II VS it was 8.11 g/l, and in patients with stage III VS it was 5.92 g/l. According to the Kruskal-Wallis test, the higher values of IgM in the study groups compared to the control group had a very high statistical significance (p=0.001). However, the comparison test in pairs between the study groups was not statistically significant ($p > 0.05$). Despite this, the level of IgM in study group 2 was 1.58 times higher than that in study group 1.

The analysis of the data presented in the table shows statistically significant changes ($p < 0.01$) in the serum concentration of IgA, in particular, of IgM in all groups of patients with different tumor stage, compared to the control group. The serum level of IgM in the general study group was at least 3 times higher than that in the control group or than the reference values (Figure 11).

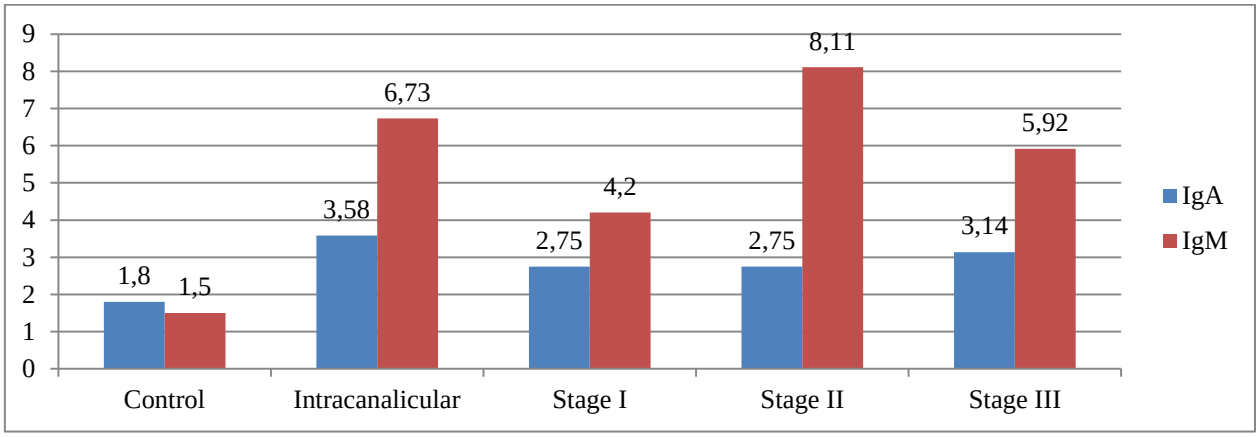


Figure 11. **The serum level of IgM and IgA in patients with different stages of VS compared to the control group ($p<0.01$), g/l.**

Carcinoembryonic antigen. According to CanAg (Sweden), serum CEA values vary between 0-10 ng/ml. In the control group, their average was 2.92 ng/ml, CI95% [1.45-4.38]. In the general study group, the average of the serum level of the CEA was 2.53 ng/ml, CI95% [1.77-8.71]. The serum values of CEA in patients with intracanalicular VS were on average 3.83 ng/ml, in patients with stage I VS it was 1.98 ng/ml, in patients with stage II VS it was 2.52 ng/ml, and in patients with stage III VS it was 3.22 ng/ml. The average of the serum concentration of CEA in study group 1 was 2.14 ng/ml, CI95% [1.10-3.18], and in study group 2 it was 2.85 ng/ml, CI95% [1.68-4.02]. Given that serum CEA values in the control group were higher than in the study groups, the Kruskal-Wallis test did not establish a statistically significant importance of the data presented ($p > 0.05$).

In order to determine the evolution of VS at the early stage, an immunological analysis of VEGF, TGF-1β, IgA, IgM and CEA was performed in patients with intracanalicular VS (stage I). 18 patients were selected from the general study group, which were divided into 2 Groups, and the data were compared with the control group consisting of 10 completely healthy persons:

1. Group 1 of the study - 10 patients in whom no tumor growth was determined;
2. Group 2 of the study - 8 patients in whom an increase in tumor was observed;
3. Control group - 10 completely healthy people.

Vascular endothelial growth factor. The average of the serum level of VEGF in the group of patients with stage 0 and 1 VS was 216.5 ng/ml, 95% CI [125.41-307.58], while in the control group it was 26.3 ng/ml, 95% CI [17.09-35.50]. In 15 cases from the study group, the VEGF values exceeded the average of the control group. Depending on the tumor stage, the average serum VEGF values in patients with intracanalicular VS were 228.66 ng/ml, 95% CI [64.19-393.13], and in patients with stage I VS it was 210.41 ng/ml, 95% CI [82.48-338.37]. According to the ANOVA test, the VEGF difference between the control group and the study groups had very high statistical significance ($p < 0.01$), while the comparative analysis between

group 1 and group 2 of the study was not statistically significant ($p > 0.05$).

Transforming **growth factor 1 β. In the** control group, the average of the serum concentration of TGF-1β was 58.6 ng/ml, 95% CI [36.42-80.77], compared to the general study group in which the average was 84.48 ng/ml, 95% CI [46.28-122.68]. In 12 cases from the study group, the serum level of TGF-1β exceeded the average from the control group. The average value of TGF-1β in the group of patients with intracanalicular VS was 78.3 ng/ml, C I95% [2.52-159,12], and in patients with stage I VS it was 87.58 ng/ml, 95% CI [36.77-138,38]. The ANOVA test used to assess the differences between groups did not establish statistically significant differences between the control groups and/or between the study groups ($p > 0.05$).

Immunoglobulin A. In the control group, the average of the IgA was 1.8 g/l, 95% CI [1.59 -2], compared to the general study group, where the average was 2.9 g/l, 95% CI [2.41-3.38]. The IgA values in the general study group exceeded the average of the control group in 12 cases. The serum level of IgA in patients with intracanalicular VS had a average of 3.67 g/l, 95% CI [3.39-3.95], and in patients with stage I VS it was 2.51 g/l, C I95% [1.89-3.13]. The ANOVA test revealed a statistically significant difference between the control group and the study groups ($p < 0.01$). Depending on the tumor growth, the difference between both study groups was also statistically significant ($p<0.05$).

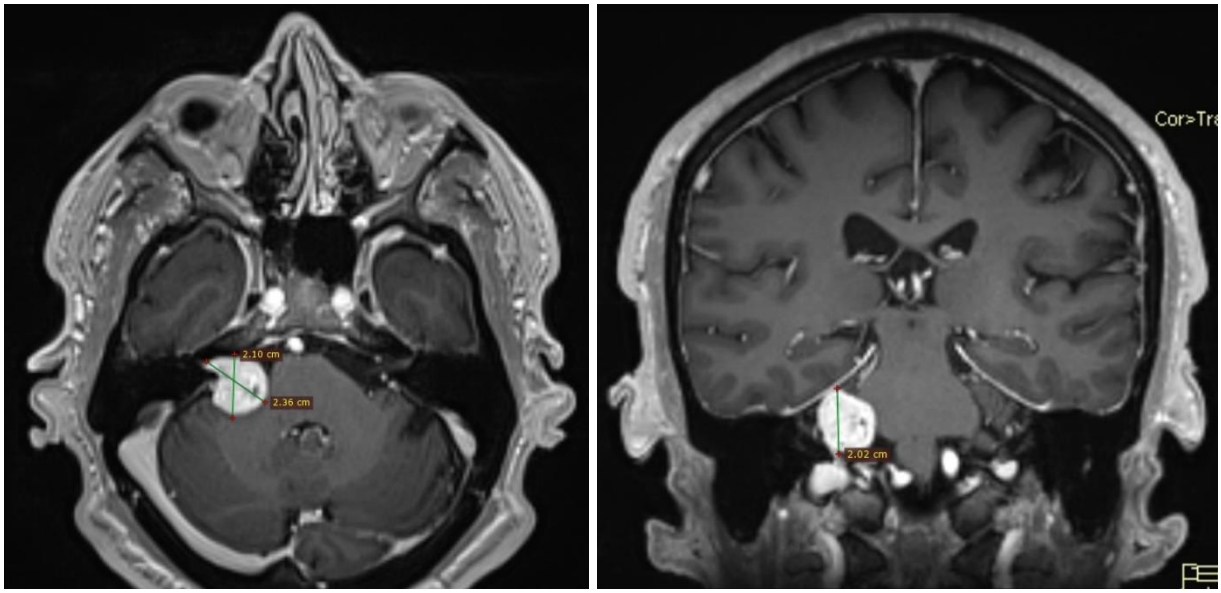
Immunoglobulin M. Given the small number of cases in which immunological analysis of IgM was performed: 3 patients out of a total of 18, it was not possible to perform a statistical analysis for this cytokine.

Carcinoembryonic antigen. In the control group, the average of the CEA was 2.92 ng/ml, 95% CI [1.45-4.38]. In the general study group, the average CEA was 2.85 ng/ml, 95% CI [1.32-4.38]. The serum values of CEA in patients with intracanalicular VS were on average 5.25 ng/ml, 95% CI [2.07-8.42], and in patients with stage I VS were 2.32 ng/ml, 95% CI [0.65-3.98]. Because serum CEA values in the control group were higher than in the study groups, the ANOVA test did not indicate statistical significance ($p > 0.05$).

The data presented in this chapter of the paper suggest that for all the tumor stages analyzed, the serum levels of VEGF and TGF-1β were significantly higher compared to the reference or control values. Specifically, the values of VEGF in the blood serum exceeded 8.72 times the control values ($p < 0.01$), and the TGF-1β was 1.52 times higher compared to the control values. In patients with stage III VS of the tumor, TGF-1β was 1.52 times higher than in patients without tumor growth. The serum concentrations of IgA and IgM showed statistically significant changes ($p < 0.01$) in all groups of patients with different tumor stage compared to the control group [20]. The serum level of IgM was at least 3 times higher than in the control group or reference values. In the group of patients with small VS (intracanalculary and stage I), a statistically significant increase in IgA was established compared to the control group ($p < 0.01$) and a significant difference compared to the group with tumor growth compared to the group where VS was in stagnation ($p < 0.05$).

3.5. Surgical treatment of vestibular schwannoma by translabirintic approach - case study

The first VS translabirintic approach intervention in the Republic of Moldova was performed at the IMSP "Diomid Gherman" Institute of Neurology and Neurosurgery on 09.12.2021 in a 60-year-old patient diagnosed with **vestibular schwannoma of the IAC and CPA on the right, of the third degree** (Figure 12).



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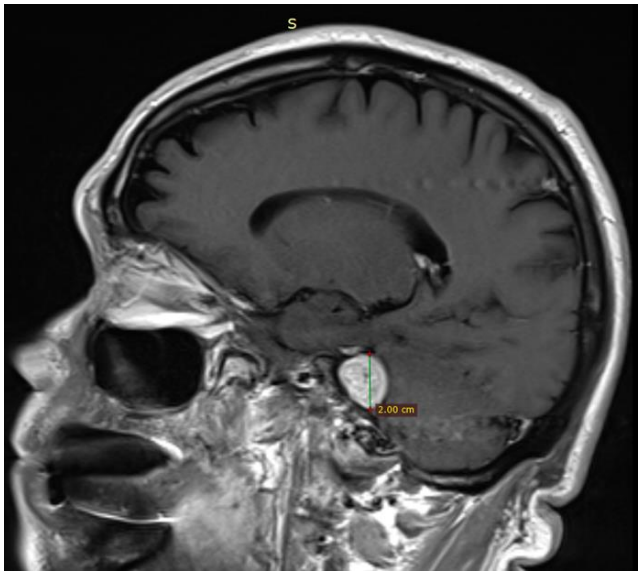


C

Figure 12. **Volumetric formation at the level of CPA and IAC on the right: A - axial projection; B - coronal projection; C - sagittal projection.**

Symptomatology: The patient, at the time of the examination, had the following complaints: deafness of the right ear, moderate deafness of the left ear, permanent tinnitus in the right ear of high frequency, which was aggravated by fatigue; periodic vertigo; permanent headache of moderate intensity, which was also aggravated by physical and emotional overload and which was influenced by changes in atmospheric pressure; imbalance and coordination disorder while walking, especially in the dark.

Intraoperatively, the incision was performed in the form of a crescent in the retroauricular area on the right, with elevation of the subcutaneous tissue up to the periosteum. The periosteum was incised at a 90º angle with its detachment from the mastoid surface. An extended mastoidectomy was performed on the right with exposure of the dura mater at the level of the

middle and posterior cranial fossa. The trajectory of the facial nerve canal in the mastoid segment was determined. The sigmoid sinus was exposed up to the level of the jugular bulb and, respectively, the delimitation of the semicircular canals - lateral, posterior and superior. Labyrinthectomy was performed by cutting the semicircular canals - lateral, posterior and superior (Figure 13).

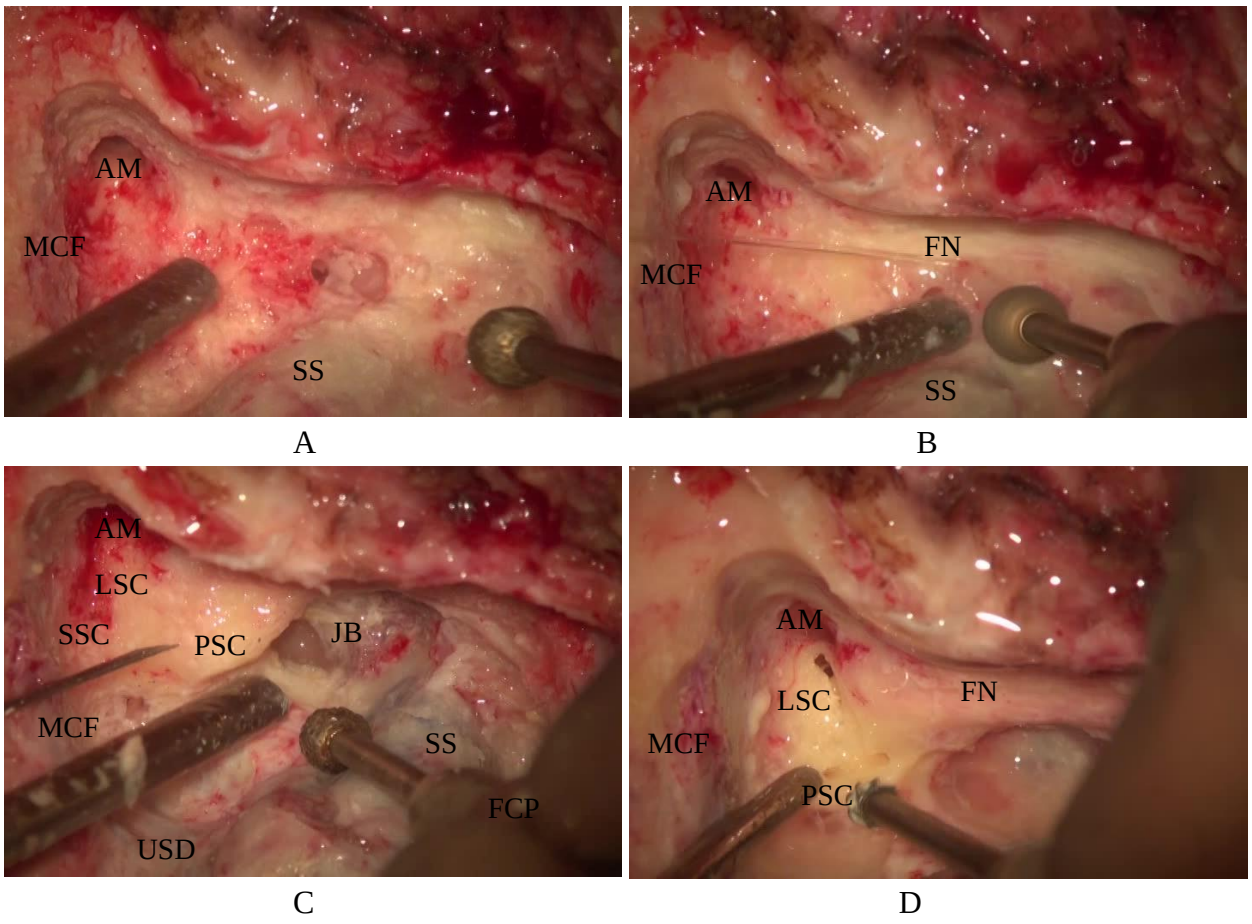


Figure 13. **Microscopic image showing the mastoidectomy with: A - opening of the mastoid antrum (AM), sigmoid sinus exposure (SS) and of the dura mater at the level of the middle cranial fossa (MCF); B - exposure of the facial nerve channel (FN) in the mastoid segment; C - exposure of the lateral semicircular channels (LSC), posterior (PSC), superior (SSC) and of the jugular vein bulb (JB); D - opening of the lateral and posterior semicircular channels.**

IAC were visualized and delimited from both its lateral and upper and lower sides. Incision of the dura mater was performed at the level of the IAC and CPA and ablation of the tumor from the IAC was performed, after which it was subtotally removed from the CPA. Subsequently, a suture was applied to the dura mater, the anvil was removed and the tympanic box was obliterated with temporal muscle fragments, and the postoperative defect was filled with fat fragments collected from the abdominal area. Wound suturing was performed on layers, subcutaneously, applying an active drainage tube (Figure 14).

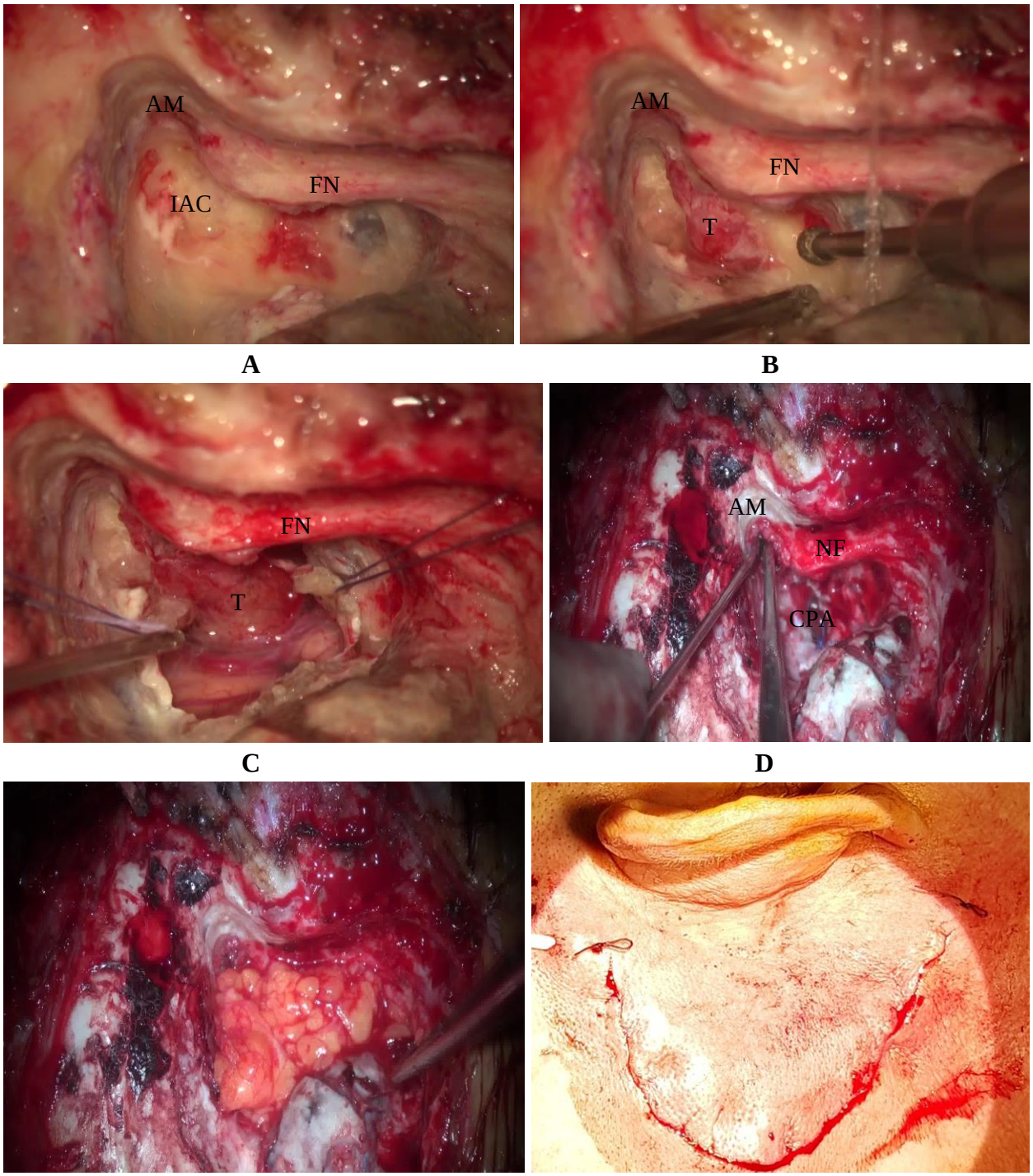
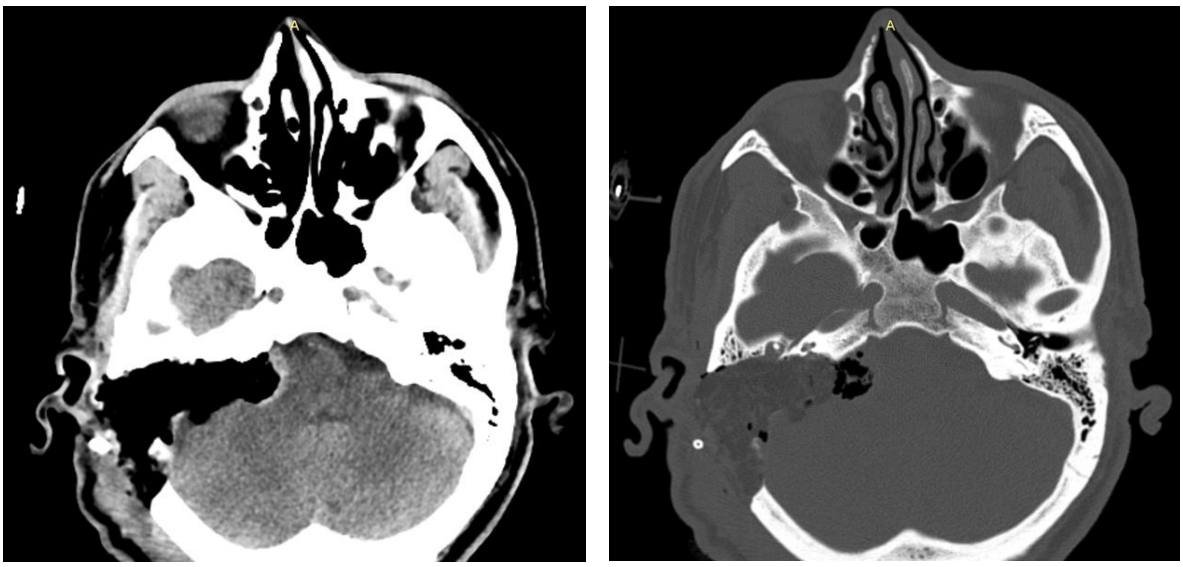


Figure 14. **Microscopic image showing: A – internal auditory duct; B – tumor (T) at the level of IAC; C – tumor at the level of CPA; D – CPA after complete removal of the tumor and obliteration of the middle ear with temporal muscle fragments; E – filling of the postoperative defect with fat tissue fragments; F – wound sutured with the presence of the active drainage tube.**

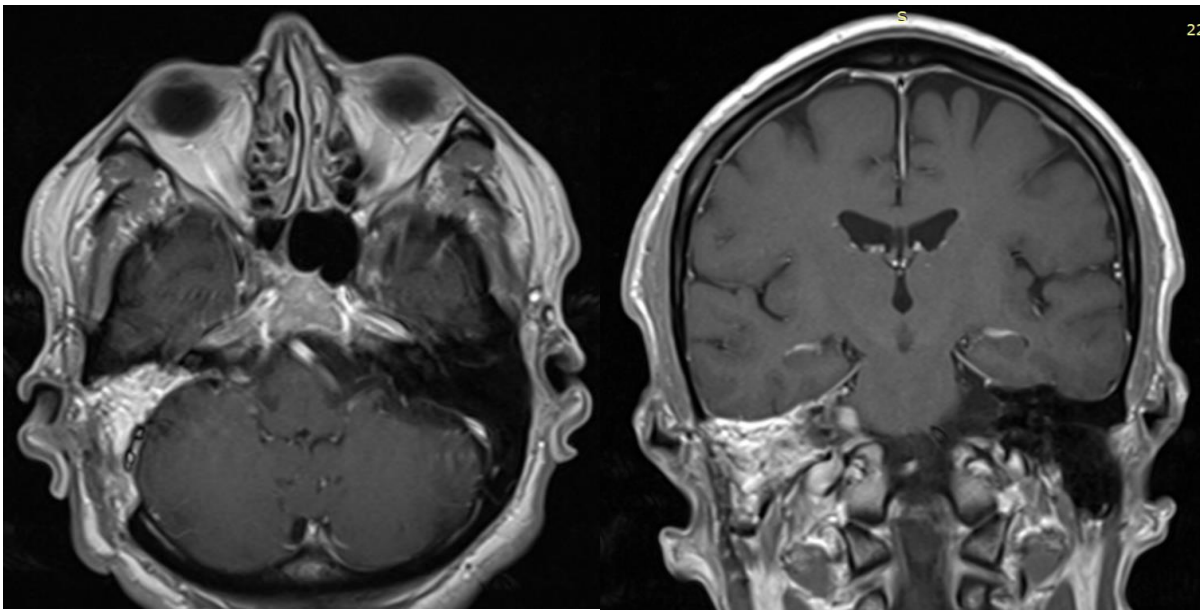
The intervention was performed under permanent monitoring of facial nerve function with the help of neuromonitoring. The postoperative patient's condition had a favorable evolution. A control computed brain tomography was performed at the 2nd postoperative day, which confirmed the volume of the performed surgical intervention, with no complications detected (Figure 15).



A B

Figure 15. **Computed tomography images showing: A - postoperative defect; B - obliteration of the postoperative defect with adipose tissue.**

Postoperative facial nerve paralysis was absent. On the 3rd postoperative day, the drain tube was removed. The patient was discharged on 20.12.2021 in satisfactory condition. 3 months after the surgery, a contrast brain MRI examination was performed, which revealed the postoperative defect, but no signs of relapse of VS in the CPA region on the right. The MRI examination at one year postoperatively also confirmed the absence of VS in the right CPA (Figure 16).



A **B**

Figure 16. **MRI images with CPA visualization at 1 year postoperatively C - axial projection; D - coronal projection.**

Currently, the patient is in a satisfactory condition and is monitored by the ENT doctor and the neurosurgeon [21].

The clinical and paraclinical study we conducted and the case study were the basis for developing an algorithm for early diagnosis and treatment of VS (Figure 17).

According to the proposed algorithm, the patient, in case of referral to the family physician/ENT with complaints of hearing loss and/or tinnitus, undergoes an ENT examination by

otoscopy/otomicroscopy. If during this examination the tympanic membrane and external auditory duct have a common appearance, then the patient is subjected to pure tone audiometry. The establishment of a unilateral sensoneural hearing loss, bilateral asymmetric hearing loss with an asymmetry o more than 20dB in 2 adjacent frequencies or more than 15dB in the frequency interval 2000-8000Hz, also unilateral tinnitus, serves as the first indicator of vestibular schwanoma, which requires the mandatory performance of a 1.5-3T contrast brain MRI to visualize the internal auditory canal and the pontocerebellar angle, respectively to establish the presence or absence of a tumor formation at this level [22-24].

Vestibular schwannoma, once diagnosed, begins to be monitored by performing the second brain MRI with contrast of 1.5-3T over 6 months. If the tumor is found to be of the same size, then monitoring is continued by performing MRI examination annually for 5 years, then every 2 years for 4 years, thereafter every 5 years throughout life [25].

However, in case of an increase in VS size of more than 3mm/year, especially with worsening of hearing loss, vestibular symptoms or other symptoms/signs specific to tumor growth, a multidisciplinary approach with patient involvement is necessary to decide the treatment tactics [26].

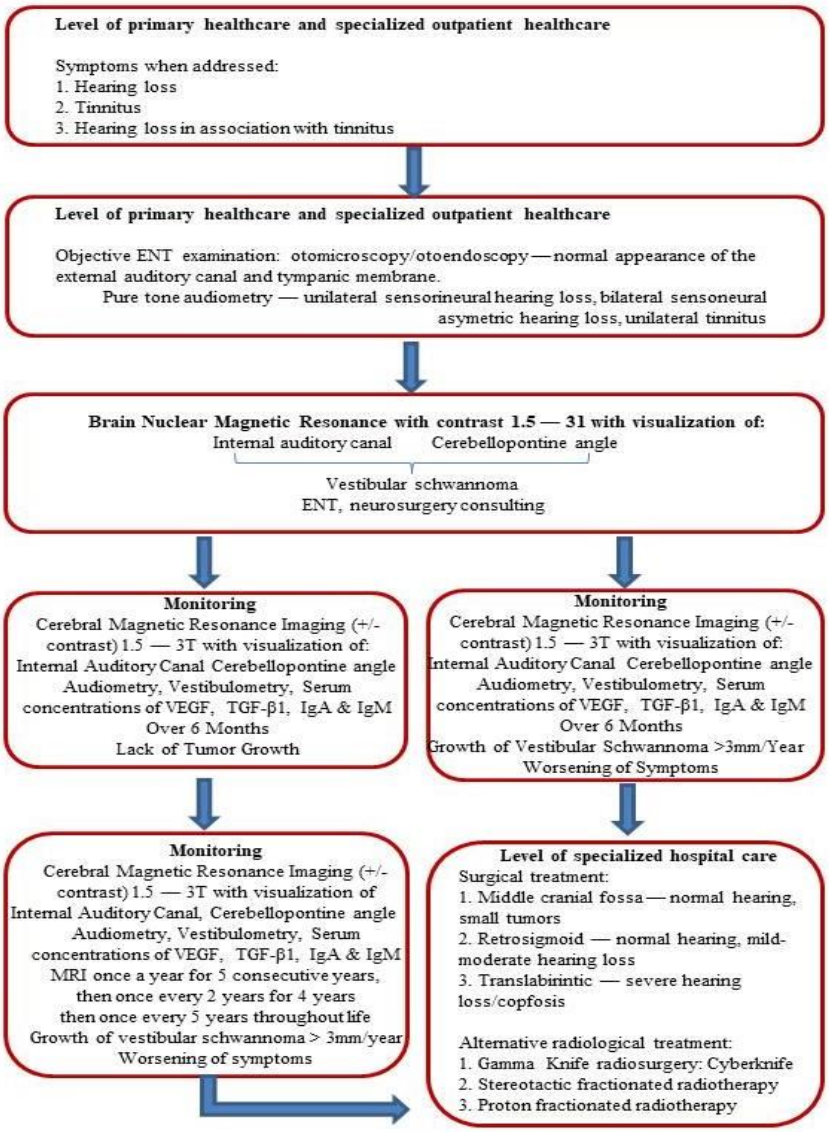


Figure 17. Diagnostic and treatment algorithm of vestibular schwannoma.

GENERAL CONCLUSIONS

1. Progressive hearing loss and worsening of vestibular syndrome in patients with vestibular schwannoma have been associated with tumor growth ($p<0.05$), which substantiates their usefulness as predictive clinical factors of vestibular schwannoma growth.
2. The analysis of the results of the MRI examination in patients with vestibular schwannoma revealed that the large size of the tumor ($p<0.01$), as well as the cystic type tumor, the one with medial dilation of the internal auditory duct and/or the one that extends into the pontocerebellar angle (under the aspect of "ice cream cone" or "trumpet"), were most commonly associated with the growing vestibular schwannoma, which attests to the predictive value of tumor growth of these imaging indicators.
3. The immunological study identified the possibility of using the serum level of IgA and IgM, as well as VEGF as diagnostic markers of vestibular schwannoma, with VEGF being significantly higher in the study group compared to the control group and reference values (about 8 times, $p<0.001$), and immunoglobulins showing similar trends. Of all the immunological indices studied, only IgA has demonstrated the ability to predict tumor growth in the case of small tumors.
4. Effective management of vestibular schwannoma requires a comprehensive systemic approach to diagnosis, monitoring and treatment - complex clinical examination, MRI/MRI examination with contrast and evaluation of the immunological status in dynamics, by an interdisciplinary group of specialists (otorhinolaryngologist, imagist and neurosurgeon) who, in cooperation with the patient, will ensure the early diagnosis of this pathology, optimal treatment and a favorable prognosis.

PRACTICAL RECOMMENDATIONS

Scientific and didactic recommendations:

1. Inclusion of the topic addressed in the continuing medical education program of ENT doctors to raise awareness of these specialists regarding the diagnosis, management and treatment of vestibular schwannoma.
2. Inclusion of the topic addressed in the residency program of the family medicine to familiarize the resident doctors in this field with the principles of diagnosis of vestibular schwannoma.
3. Development of a national clinical protocol regarding the early diagnosis, management and treatment of vestibular schwannoma.

Clinical recommendations:

1. Mandatory referral by ENT physicians of patients with unilateral sensoneural hearing loss; bilateral asymmetric hearing loss; unilateral tinnitus to MRI examination with 1.5-3T contrast, in order to establish or exclude the diagnosis of vestibular schwannoma.
2. ENT physician monitoring of patients with vestibular schwanoma at an interval of 6 months from the initial diagnosis, then 1 time per year 5 consecutive years, thereafter every 2 years for 4 years, and thereafter every 5 years throughout life.
3. Taking into account the possibility of monitoring and the existence of different treatment options, each case of vestibular schwanoma needs to be discussed individually between the ENT doctor, neurosurgeon and patient, especially when we find an increase in tumor.

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LIST OF SCIENTIFIC PUBLICATIONS AND PRESENTATIONS of Mr. Buracovschi Marin, PhD graduate, Department of Otorhinolaryngology, made for his doctoral thesis in medical sciences on the theme:
”Diagnosis and treatment of vestibular schwannoma”, doctoral program 321.16 – otorhinolaryngology, "Nicolae Testemițanu" State University of Medicine and Pharmacy from the Republic of Moldova

SCIENTIFICAL PUBLICATIONS

- **Articles in scientific journals abroad:**

✓ **articles in ISI, SCOPUS and other international databases**

1. Borysenko O., Melnykov O., Prilutskaya A., **Buracovschi M**. Immunological Analysis of Vestibular Schwannoma Patients. In: Journal of International Advanced Otology. 2023; 19(1):1-4. doi: 10.5152/iao.2023.22581 (**IF: 1,3**).

✓ **Articles in international scientific collections**

2. **Buracovschi M.**, Sandul A., Borysenko O., Zapuhlîh G., Moraru V., Glavan I. Vestibular schwannoma – a retrospective study in the Republic of Moldova. In: ORL.ro. 2022; 56(3). doi**:** 10.26416/ORL.56.3.2022.6922.
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- **Articles in accredited national scientific journals:**

✓ **articles in category B journals**

5. **Buracovschi M.**, Borysenko O., Zapuhlîh G., Vetricean S., Moraru V. Translabyrinthine approach in acoustic neuroma surgery – case report. In: Mold J Health Sci. 2024; 11(2):74-80. doi.org/10.52645/MJHS.2024.2.10.
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✓ **Summaries/abstracts/theses in the works of national and international scientific conferences**

7. **Buracovschi M.**, Vetricean S., Borysenko O., Papp A., Zapuhlîh G., Moraru V. Abordul translabirintic în chirurgia schwanomului vestibular din Republica Moldova. În: *Materialele celei de a 3-a Conferință a Asociației Internaționale a Mării Negre de Otologie și Neurootologie. Sovata;* 2023, p. 19.
8. **Buracovschi M.**, Zapuhlîh G., Borysenko O., Vetricean S., Buracovschi N. Aspecte evolutive ale neurofibromatozei de tip 2 – studiu de caz. În: *Materialele Forumului ORL.ro cu genericul „Ear and hearing care for all”. București;* 2023.
9. Borysenko O., **Buracovschi M.** „Wait and Scan” evaluation of vestibular schwannoma: a comparative study between growth and no growth tumors. În: *Materialele celui de al 13-a Congres al Otorinolaringologilor din Ucraina. Odesa;* 2021, p. 166.

10. Borysenko O., Mishanchuk N., Skorohoda A., Bobrov A., **Buracovschi M.** Functional and structural modifications of cranial nerves during monitoring of I-III stage vestibular schwannoma patients. În: *Materialele celui de al 13-a Congres al Otorinolaringologilor din Ucraina. Odesa;* 2021, p.13.
11. Melnikov O., Borysenko O., Prilutskaya A., Papp O., **Buracovschi M.** Concentration changes of immunoglobulins M, G, E in blod serum of I-IV stage vestibular schwannoma patients after surgery and radiotherapy. În: *Materialele celui de al 13-a Congres al Otorinolaringologilor din Ucraina. Odesa;* 2021, p.83.
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16. **Buracovschi M.**, Sandul A., Borysenko O., Zapuhlîh G., Moraru V., Buracovschi N. „Wait & Scan" în evidența pacienților cu neurinom de acustic. În: *Materialele Congresului consacrat aniversării a 75-a de la fondarea Universității de Stat de Medicină şi Farmacie „Nicolae Testemiţanu". Chişinău;* 2020, p. 470.
17. **Buracovschi M.**, Sandul A., Borysenko O., Zapuhlîh G., Moraru V., Glavan I. Acoustic neuroma – retrospective study in Republic of Moldova. În: *Materialele Conferinței Tradiționale Anuale a Societății Otorinolaringologilor din Ucraina. Odesa;* 2019, p. 135.

- **Invention patents, patents, registration certificates, materials for invention salons**

18. **Buracovschi M.**, Borodin S., Vetricean S., Borysenko O., Fedirko V. Implementarea abordului translabirintic în chirurgia tumorilor de conduct auditiv intern și unghi pontocerebelos. Certificat de inovator nr. 6236, 2024.04.01.
19. **Buracovschi M.**, Borysenko O., Zapuhlîh G., Vetricean S. Implementarea abordului translabirintic în chirurgia neurinomului de acustic. Certificat de inovator nr. 6237, 2024.04.01
20. **Buracovschi M.**, Sandul A., Borysenko O. Algoritmul de diagnostic și tratament al neurinomului de acustic. Certificat de inovator nr. 6238, 2024.04.01.
21. **Buracovschi M.**, Sandul A., Borysenko O., Vetricean S., Zapuhlîh G. Elaborarea criteriilor optimale de diagnostic şi tratament în neurinomul de acustic. Chirurgia neurinomului de acustic prin abord translabirintic - premieră în Republica Moldova. Certificat de înregistrare a drepturilor de autor nr.7984, 15.08.2024.
22. **Buracovschi M.**, Borysenko O., Zapuhlîh G., Vetricean S. Implementarea abordului translabirintic în chirurgia schwanomului vestibular. Expoziția internațională de inovație și transfer tehnologic EXCELLENT IDEA 2024, medalie de argint.

• **Participation with communications at scientific forums:**

✓ **International**

23. Forumul ORL.ro, ediția a 17-a cu genericul ”ORL și specialitățile de graniță”, 7-8 martie 2025, București, România;
24. 3rd Black Sea Countries Otology and Neurootology Congress, 7-10 iunie 2023, Sovata, România;
25. Forumul ORL.ro, ediția a 15-a cu genericul ”Ear and hearing care for all!”, 3-4 martie 2023, București, România;
26. 13th Congress of Ukrainian Otorhinolaryngologists, 19-22 septembrie 2021, Odesa, Ucraina;
27. 7th Congress of the Ukrainian Association of Neurosurgeons, 16-18 septembrie 2021, Odesa, Ucraina;
28. 7th Congress of Neurosurgeons of Ukraine, 11-18 mai 2021, Side, Turcia;
29. 2nd Black Sea Countries Otology Neurootology Congress, 23-25 octombrie 2020, Turcia;
30. The Traditional Annual Spring Conference of The Ukrainian Scientific Medical Society of Otorhinolaryngologists ”MODERN RESEARCH, SURGICAL AND THERAPEUTIC APPROACHES IN OTORHINOLARYNGOLOGY”, 20-21 mai 2019, Odesa, Ucraina;

✓ **national**

31. Sedința Asociației Științifico-Practice a Otorinolaringologilor din Republica Moldova, 1 decembrie 2023, Chișinău;
32. Săptamâna medicală balcanică, ediția a XXXVII-a „Perspective ale Medicinei Balcanice în Era Post-Covid 19”, 7-9 iunie 2023, Chișinău;
33. Școala de Vară de Otorinolaringologie, ediția a. 2022, cu genericul „Împreună pentru un act educațional de calitate”, 25 iulie 2022, Chișinău;
34. Ședința Societății Neurochirurgilor din Republica Moldova, 25 martie 2022, Chișinău;
35. Ședința Societății Neurochirurgilor din Republica Moldova, 24 ianuarie 2020, Chișinău;
36. Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemițanu”, 21-23 octombrie 2020, Chișinău;
37. Conferința națională cu participare internațională „Actualități în diagnosticul și tratamentul afecțiunilor ORL”. 17 mai 2019, Chișinău;
38. Conferința națională cu participare internațională „Actualități în diagnosticul și tratamentul afecțiunilor otologice”, 29 martie 2019, Chișinău;
39. Conferința consacrată Zilelor Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”, 17 octombrie 2019, Chișinău;
40. Ședința Societății ORL din Republica Moldova, 16 noiembrie 2018, Chișinău;
41. Conferința consacrată Zilelor Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”, 18 octombrie 2018, Chișinău, Moldova.

ADNOTARE

Buracovschi Marin, „Diagnosticul și tratamentul schwanomului vestibular”, teză de doctor în științe medicale, Chișinău, 2025

Structura tezei. Teza este expusă pe 91 pagini text de bază și include: introducere, 5 capitole, concluzii generale și recomandări metodice. Lucrarea citează 218 resurse bibliografice și este ilustrată cu 24 de figuri, 10 tabele și 3 anexe. Rezultatele obținute sunt publicate în 17 lucrări științifice.

Cuvinte cheie: schwanom vestibular, neurinom de acustic, rezonanță magnetică nucleară, factor vasculo-endotelial de creștere, factor transformator de creștere 1β, imunoglobulina A imunoglobulina M, antigen carcino-embrionar, abord translabirintic.

Scopul cercetării: studiul clinic și paraclinic al pacienților diagnosticați primar cu schwanom vestibular, pentru a stabili particularitățile evoluției și creșterii tumorale și pentru a elabora un algoritm de diagnostic precoce și tratament al acestei afecţiuni.

Obiectivele cercetării. 1) Studiul clinico-diagnostic al pacienților cu schwanom vestibular, pentru a identifica cele mai specifice semne clinico-diagnostice care atestă evoluția patologiei. 2) Analiza rezultatelor investigațiilor RMN la pacienții cu schwanom vestibular pentru a stabili particularitățile imagistice ce denotă evoluția/creșterea tumorală. 3) Evaluarea modificărilor markerilor imunologici la pacienții cu schwanom vestibular, pentru a identifica cei mai informativi markeri diagnostici și de pronostic ai creșterii tumorii. 4) Elaborarea unui algoritm de diagnostic precoce și tratament al schwanomului vestibular.

Noutatea și originalitatea științifică. A fost stabilită evoluția schwanomului vestibular pe baza analizei rezultatelor examenului clinic și paraclinic la pacienții diagnosticați primar cu tumora dată. Au fost analizate: rezultatele imunologice ale citokinelor și factorilor de creștere colectate de la acești pacienți; rezultatele monitoringului, prin examen RMN, cu determinarea unor aspecte imagistice caracteristice creșterii tumorale. Au fost stabilite anumite criterii atât clinice, cât și imunologice, care pot fi posibili markeri predictivi ai creșterii tumorale.

Rezultatele obținute care contribuie la soluționarea unei probleme științifice. Rezultatele obținute au stat la baza elaborării unui algoritm de diagnostic și tratament al schwanomului vestibular, care va permite diagnosticarea precoce și managementul cât mai corect a acestei patologii.

Semnificația teoretică. Lucrarea de doctorat contribuie cu noi informații privind înțelegerea progresiei schwanomului vestibular, ratele de creștere și comportamentul tumoral, ritmul și natura schimbărilor tumorale, importante în dezvoltarea de noi modele predictive. Aplicarea criteriilor clinice și imunologice pentru estimarea riscului de creștere tumorală poate fundamenta luarea deciziilor corecte privind tactica de tratament, contribuind la dezvoltarea unor strategii personalizate de management a patologiei.

Valoarea aplicativă. În aspect aplicativ, a fost elaborat un algoritm de diagnostic și tratament pentru pacienții cu schwanom vestibular, care va putea fi integrat într-un protocol clinic național. De asemenea, abordul translabirintic a fost introdus în chirurgia schwanomului vestibular.

Implementarea rezultatelor științifice. Rezultatele cercetării, inclusiv algoritmul de diagnostic și tratament al schwanomului vestibular, au fost implementate în cadrul Clinicii de Otorinolaringologie a IMSP Spitalul Clinic Republican „Timofei Moșneaga”, iar abordul translabirintic în chirurgia schwanomului vestibular a fost implementat în cadrul Clinicii de Neurochirurgie a IMSP Institutul de Neurologie și Neurochirurgie „Diomid Gherman”.

ANNOTATION

Buracovschi Marin, „Diagnosis and treatment of vestibular schwannoma”,
PhD thesis in medical sciences, Chișinău, 2025

Thesis structure. Thesis is presented on 91 pages of basic text and includes an introduction, 5 chapters, synthesis of the obtained results, general conclusions, practical recommendations, bibliographic index with 218 titles and 3 appendices. The illustrative material contains 10 tables and 24 figures. The obtained results are published in 17 scientific papers.

Key words: vestibular schwannoma, acoustic neuroma, nuclear magnetic resonance, endothelial vascular growth factor, transforming growth factor 1β, immunoglobulin A, immunoglobulin M, carcinoembryonic antigen, translabirintic approach.

The aim of the research: the clinical and paraclinical study of patients primarily diagnosed with vestibular schwannoma, in order to establish the peculiarities of tumor evolution and growth and to develop an algorithm for early diagnosis and treatment of this condition.

Research objectives. 1) Clinical diagnostic study of patients with vestibular schwannoma, in order to identify the most specific clinical diagnostic signs attesting to the evolution of the pathology. 2) Analysis of the results of MRI investigations in patients with vestibular schwannoma to establish the imaging peculiarities that show tumor evolution/growth. 3) Evaluation of changes in immunological markers in patients with vestibular schwannoma, in order to identify the most informative diagnostic and prognostic markers of tumor growth. 4) Developing an algorithm for early diagnosis and treatment of vestibular schwannoma.

Scientific novelty and originality of the research. The evolution of vestibular schwannoma was established based on the analysis of the results of the clinical and paraclinical examination in patients primarily diagnosed with this pathology. The immunological results of cytokines and growth factors collected from patients and the results of monitoring, by MRI examination, were analyzed. Certain clinical and immunological criteria have been established, which may be possible predictive markers of tumor growth.

The obtained results that contribute to the solution of a scientific problem. The obtained results were the basis for the development of an algorithm for the diagnosis and treatment of vestibular schwannoma, which will allow an early diagnosis and a correct management of this pathology.

Theoretical importance. The doctoral thesis contributes with new information on the understanding of vestibular schwannoma progression, the pace and nature of tumor changes, important in the development of new predictive models. The application of clinical and immunological criteria for estimating the risk of tumor growth can substantiate the right decisions regarding the intervention, contributing to the development of personalized pathology management strategies.

Applicative value. A diagnostic and treatment algorithm has been developed for patients with vestibular schwannoma, which can be integrated into a national clinical protocol. The translabirintic approach has been introduced in vestibular schwannoma surgery.

Implementation of the scientific results. The results of the research, including the diagnosis and treatment algorithm of vestibular schwannoma, were implemented in the Otorhinolaryngology Clinic of IMSP Republican Clinical Hospital "Timofei Moșneaga", and the translabyrinthine approach in vestibular schwannoma surgery was implemented in the Neurosurgery Clinic of IMSP Institute of Neurology and Neurosurgery "Diomid Gherman".

АННОТАЦИЯ

Бураковски Марин, «Диагностика и лечение вестибулярной шванномы», диссертация доктора медицинских наук, Кишинев, 2025 г.

Структура диссертации. Диссертация представлена на 91 страницах основного текста и включает: введение, 5 глав, общие выводы и методические рекомендации. Работа цитируется на 218 библиографических ресурсах и иллюстрирована 24 рисунками, 10 таблицами и 3 приложениями. Полученные результаты опубликованы в 17 научных статьях.

Ключевые слова: вестибулярная шваннома, акустическая невринома, ядерный магнитный резонанс, сосудисто-эндотелиальный фактор роста, трансформирующий фактор роста 1β, иммуноглобулин А, иммуноглобулин М, карцино-эмбриональный антиген, транслабиринтный доступ.

Цель: клиническое обследование пациентов с первичной вестибулярной шванномой для установления особенностей эволюции/роста опухоли и разработки алгоритма ранней диагностики и лечения этой патологии.

Цели исследования. 1) Клинико-диагностическое исследование больных вестибулярной шванномой для выявления наиболее специфических признаков развитии этой патологии. 2) Анализ результатов МРТ-исследований с целью установления признаков указывающих рост опухоли. 3) Оценка изменений иммунологических маркеров с целью выявления наиболее информативных признаков роста опухоли. 4) Разработка алгоритма ранней диагностики и лечения вестибулярной шванномы.

Научная новизна и оригинальность. Эволюцию вестибулярной шванномы установили на основании анализа результатов клинического обследования пациентов, у которых впервые была диагностирована данная опухоль. Были проанализированы: иммунологические результаты цитокинов и факторов роста; результаты МРТ-исследования с определением аспектов, характерных для роста опухоли. Установлены определенные ммунологические признаки эволюции/роста опухоли.

Полученые результаты, способствующие решению научной проблемы. Полученные результаты послужили основой для разработки алгоритма диагностики и лечения вестибулярной шванномы, который позволит провести раннюю диагностику и наиболее правильное лечение данной патологии.

Теоретическая значимость. Кандидатская диссертация дает новую информацию относительно понимания прогрессирования вестибулярной шванномы, скорости и характера опухолевых изменений, что важно для разработки новых прогностических моделей. Применение клинико-иммунологических критериев оценки риска опухолевого роста может обосновать принятие правильных решений относительно тактики лечения, способствуя разработке персонализированной стратегии ведения этой патологии.

Прикладная ценность. В плане применения разработан алгоритм диагностики и лечения пациентов с вестибулярной шванномой. Также транслабиринтный доступ был внедрен в хирургии вестибулярной шванномы.

Внедрение научных результатов. Результаты исследования, в том числе алгоритм диагностики и лечения вестибулярной шванномы, внедрены в Клинике оториноларингологии Республиканской клинической больницы «Тимофей Мошняга», а транслабиринтный подход в хирургии вестибулярной шванномы был внедрен в Клинике нейрохирургии Института неврологии и нейрохирургии «Диомид Герман».

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DIAGNOSIS AND TREATMENT OF VESTIBULAR SCHWANNOMA

321.16 - OTORHINOLARYNGOLOGY

Summary of the Doctor of Medical Sciences thesis

Aprobat spre tipar: 05.02.2025
Hârtie ofset. Tipar ofset.
Coli de tipar.: 2,0

Formatul hârtiei 60x84 1/16
Tiraj: 50 ex.
Comanda nr.9

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