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Intraoperative monitoring of cochlear nerve function during acoustic neuroma surgery with transtemporal approach: Warning signs as predictors of postoperative hearing loss

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Dedication:

I dedicate this work to my beloved mother

Table of Contents

1. Introduction

This study investigates the critical warning signs of intraoperative monitoring of cochlear nerve during transtemporal acoustic neuroma surgery. Accordingly, a brief overview on acoustic neuroma, its clinical presentation, management options and intraoperative monitoring of cochlear nerve during surgical resection will be given.

1.1 Acoustic neuroma

Acoustic neuroma is also called vestibular schwannoma, acoustic neurinoma, vestibular neuroma, and acoustic neurofibroma (Greene/Al-Dhahir 2019). The tumors mostly arise from the vestibular branch of the 8th cranial nerve, usually the inferior vestibular nerve (Khrais et al. 2008; Komatsuzaki/Tsunoda 2001 and Roosli et al. 2012). Acoustic neuroma occurs in a sporadic form or associated with neurofibromatosis type II (NF2), an autosomal-dominant genetic disorder. The damaged gene is located on chromosome 22q**.** The gene product, termed schwannomin or merlin, has a tumor-suppressing function. The mutation can be inherited; however, de novo mutations are common (Asthagiri et al. 2009). The prevalence of acoustic neuroma is 0.7-1.0 per 100,000 population. Increased quality and availability of diagnostic imaging may result in rising of the incidence of the acoustic neuroma. Incidentally discovered acoustic neuromas have been reported to be 2 in 10,000 (Lin et al. 2005).

Huang and his colleagues evaluated the symptoms and signs in 1,009 patients. Hearing loss was the most reported clinical sign in patients with acoustic neuroma. 85.8% of the represented patients were diagnosed to have hearing loss .Tinnitus was reported in 40.1% of the reviewed cases (Huang et al. 2013). Gradual hearing loss is the classic presentation of acoustic neuroma, however, about 4-20% of patients with acoustic neuroma represented with sudden hearing loss (Aslan et al. 1997 and Sauvaget et al. 2005)**.** Gradually progressive hearing loss results from mechanical compression exerted by the tumor on the cochlear nerve; compromising the vascular supply of the internal auditory artery or from biochemical changes in the inner ear (del Rio et al. 2006). Sudden hearing loss in acoustic neuroma may result from compression of the auditory nerve, impairment of vascular supply to the cochlea, or endolymphatic hydrops (Inoue et al. 2000). Hearing evaluation in acoustic neuroma patients can be done by pure tone audiometry and braistem auditory evoked potentials. In the past, hearing loss was confirmed in 95% of patients with acoustic neuroma using pure tone audiometry and only five percent of patient with acoustic neuroma have normal test, therefore, pure tone audiometry was considered to be the best initial screening test for the diagnosis of acoustic neuroma. The speech discrimination score was one of the most important sign of acoustic neuroma as the affected ear had reduced speech discrimination score which is usually out of proportion to the measured hearing loss. Nowadays, the audiologic characteristics of patients with acoustic neuroma are different. The implementation of magnetic resonance imaging (MRI) led to early detection of patients with a very small sized acoustic neuroma, these patients show minor amounts of hearing impairment (Van Dijk et al. 2000).

According to several published reports, a correlation between the amount of hearing loss and the size of tumor in patients with acoustic neuroma was found. The more the tumor growth rate, the worse the audiological findings (pure tone average as well as speech discrimination score) (Day et al. 2008; Kaye/Briggs 2001 and Massick et al. 2000).

Also a correlation between the configuration of hearing loss and the size of the tumor was observed. The patients with normal hearing or low-frequency hearing loss (rising type) had a small-sized tumor, while those with mid- or high-frequency hearing loss had a medium-sized tumor and those with global frequency hearing loss or total deafness had tumor size more than 2.5 cm (Day et al. 2008). Regarding auditory evoked potentials (AEP), they are potentials which can be generated in response to acoustic stimulation; seven waves are identified by roman letters I-VII. They were first analyzed and described in humans by Jewett and Williston in 1971 (Jewett and Williston 1971). Wave I arises from the cochlea and represents the nerve action potential of the cochlear nerve (Hashimoto et al. 1981; Moller/Jannetta 1982). Some authors mentioned that the anatomical generator of wave II is in the proximal parts of the cochlear nerve when it enters the brain stem (Moller et al. 1981; Moller/Jannetta 1982, 1983), other authors described wave II to be generated by the cochlear nucleus itself (Maurer 1993). Wave III is generated in the brain stem at the level of the superior olivery complex (Moller et al. 1995). The generator of wave IV cannot be clearly determined because it is created by overlaying tracts of the ipsi- and contralateral auditory pathway. The generator of wave V is potentially located at the level of the inferior colliculus (Hashimoto et al. 1981).

Usually, according to hearing, size and extension of the tumor, well-defined brainstem auditory evoked potential (BAEP) waves I, III, and V peaks are seen. There is a significant difference in inter-peak latencies of wave I to III and I to V on the affected side compared with those from the opposite ear (Grundy et al. 1981).The mean inter-aural latency difference of wave V in acoustic neuroma is 0.88 ms in patients with a clearly detected wave V and 1.26 ms patients with a poorly detected wave V (Aihara et al. 2014).

The BAEP test has the ability to detect 93% to 98% of patients with acoustic neuroma (Dornhoffer et al. 1994 and Josey et al. 1988). However, the reliability of BAEP testing in the diagnosis of acoustic neuroma is not always very high. The sensitivity of BAEP depends on the tumor extension. Hashimoto and his colleagues reported that BAEP was sensitive in detecting about 78% of small tumors with an extrameatal size of less than 15 mm (Hashimoto et al. 1991) whereas the sensitivity of BAEP was lower for intrameatal tumors (67%) (Wilson et al. 1992). Another study reported a sensitivity of 70% and specificity of 90% with small acoustic neuroma (Doyle 1999).

The other symptoms in acoustic neuroma may be due to vestibular nerve involvement, trigeminal nerve involvement, facial nerve involvement and tumor progression can lead to pressure on adjacent posterior fossa structures (Huang et al. 2013).

The vestibular nerve involvement occurred in 61 % of patients. Affected patients frequently complained of unsteadiness while walking (44.6 %), which was typically mild to moderate in nature and frequently fluctuated in severity. True spinning vertigo was uncommon and was reported to occur in 15.9 % of cases because these slow-growing tumors result in gradual rather than acute asymmetries in vestibular function. In this case, the central vestibular system can often compensate for the gradual loss of one side (Huang et al. 2013). Trigeminal nerve disturbances have been reported to occur in 53.5% of patients. Facial numbness, paresthesia, hypoesthesia and pain were the most frequently reported complaints (Huang et al.

2013). The facial nerve paresthesia was reported in 48.9 % of patients and the facial nerve paralysis in 21.1 % of patients (Huang et al. 2013). Facial paresis was the most frequent sign to be reported, while taste disturbances (due to Nervus intermedius impairment) were less often. Xerophthalmia, paroxysmal lacrimation and xerostomia can also be seen (Noonan et al. 2016).

1.2 Overview of the management strategy of acoustic neuroma

Treatment options include surgery, stereotactic radiotherapy and conservative management with observation. The choice between these options depends on several factors including the tumor size, the rate of growth, the age and the general condition of the patient.

1.2.1 Conservative management

Conservative management includes follow-up with audiometry and MRI every 6-12 months. There are important variables that should be evaluated if observation is considered as an option of the management. These variables are: hearing in both ears, surgical complications, the risk of hearing loss and paralysis of facial nerve as a consequence of surgery, size of the tumor and tumor growth rate and patients with neurofibromatosis type 2 (NF2) or bilateral tumors (Telian 1994).

Although conservative management in the cases of acoustic neuroma is available, it still remains controversial. Special consideration should be taken while selecting the patients who receive conservative management. Smouha and his colleagues performed meta-analysis aiming for the tabulation of the selection criteria for conservative therapy. They found that conservative therapy was recommended to older patients, those with concurrent medical risks and those with smaller tumors and better hearing ability (Smouha et al. 2005). The operative intervention should be reserved for patients with severe symptoms or because of brain stem compression (Al Sanosi et al. 2006). However, the decision regarding the management of small tumors will differ from center to center, some centers offer surgical resection for patients with small tumors and good preoperative hearing levels (Lin /Crane 2017).

1.2.2 Radiation therapy

There are two methods of radiation: stereotactic radiosurgery or gamma knife (Kopp et al. 2011). In comparison to the operative procedure, these procedures can be implemented without hospitalization (Pollock 2009). The choice of radiation therapy in the treatment of acoustic neuroma should be done with caution because of the potential occurrence of radiation-related neoplasia, which affects mainly young patients (Pollock 2009). Radiation therapy is indicated for acoustic neuroma with a maximum diameter of 30 mm (Bailo et al. 2016) and considered as an alternative for surgery in older patients or patients with a high perioperative risk.

Most of the currently available studies provide short term follow-up information regarding hearing status after radiation; however, Carlson and his colleagues studied the long term outcome up to 10 years of stereotactic radiosurgery for acoustic neuroma. They revealed progressive hearing deterioration in most patients (Carlson et al. 2013).

1.2.3 Surgical resection

Surgical resection is rather indicated mostly in persons under the age 65 of years with large or rapidly growing tumors, significant hearing loss and higher headache severity scores (Nellis et al. 2017). To excise acoustic neuroma, there are three surgical approaches commonly used: the middle fossa, the translabyrinthine and the suboccipital approach.

Middle cranial fossa (MCF) approach

The MCF approach is generally reserved for small tumors, which are mainly intrameatal, have less than 1 cm of cerebellopontine angle extension and for patients with good hearing. It is the only approach that enables the surgeon to visualize the lateral third of the internal auditory canal (IAC) with maintaining the possibility of hearing preservation (Doherty/Friedman 2006 and Jackler/Pitts 2008). The hearing preservation rate in this approach is ranging from 33% in large sized tumors to 76% in small sized tumors (Meyer et al. 2006). Higher hearing preservation rate was reported in intrameatal tumors with maximum 5mm extrameatal extension (Wang et al. 2013). Long term hearing preservation was reported in 70 % of patients with acoustic neuroma who were operated on via MCF approach (Friedman et al.

2003).The facial nerve course runs mostly across the anterior superior portion of the tumor. Consequently, it is in the way during tumor removal and is more vulnerable to injury (Hillman et al. 2010 and Sameshima et al. 2010). This approach provides only very limited exposure to the posterior fossa (Irving et al. 1998). The temporal lobe must be retracted with the risk of temporal lobe injury, usually in the form of an edema represented with drowsiness and speech disturbance (Sameshima et al. 2010).

Suboccipital (Retrosigmoid) approach

The suboccipital approach offers greater access to the cerebellopontine angle and it provides the best wide-field visualization of the posterior fossa while maintaining the option of hearing preservation (Ebersold et al. 1992 and Jackler/Pitts 2008). The hearing preservation rate in this approach is 17 to 88%, depending on the tumor extension and on the preoperative hearing quality (Samii/Matthies 1997). The suboccipital approach may require cerebellar retraction. Manipulation of the cerebellum has the risk for postoperative gait difficulties (Levo et al. 2004). The suboccipital approach may also provide a limited visualization of the fundus of the IAC. A higher recurrence rate and residual tumor were reported in suboccipital approach (Hillman et al. 2010).

Translabyrinthine approach

Indications of this approach include the lack of preoperative serviceable hearing and large tumors (Jackler/Pitts 2008). The translabyrinthine approach provides early identification of the facial nerve, therefore; the facial function is reported to be more frequently preserved (Sanna et al. 2004 b). It allows the removal of acoustic neuroma with minimal retraction of the cerebellum (Levo et al. 2004). Hearing loss is complete and unavoidable (Jackler/Pitts 2008).

During surgical resection of acoustic neuroma the cochlear nerve is susceptible to operative damage in various ways (Legatt 2002; Lüders 1988 and Zappia et al. 1996). These include direct operative trauma, especially during maneuvers, such as drilling into the internal auditory canal, tumor resection or traction (Abramson et al. 1985; Colletti et al. 1996; Colletti et al. 1997 and Moller 1996). Ischemic damage through occlusion, rupture or vasospasm can lead to vascular changes to the internal auditory artery. This is believed to induce postoperative hearing loss (Colletti et al. 1996; Colletti et al. 1997; Moller 1996; Mom et al. 2000 and Nadol et al. 1992;).

The goals of acoustic neuroma surgery have been shifted over the years because the safety profile of these surgeries improved and mortality rates became lower. As a result, hearing preservation and minimizing facial paresis are now considered to be main goals of the surgery. The current expectation is to achieve complete tumor resection with a serious intent to achieve good postoperative facial function together with preservation of preoperative existing hearing function (Vivas et al. 2018).

Several intraoperative monitoring techniques have been developed and evaluated aiming for the preservation of cochlear and vestibular nerves. EMG (Electromyography) has been frequently used for the monitoring of facial nerve and BAEP for the monitoring of cochlear nerve (Moller 1996; Yamakami et al. 2009 and Youssef/Downes 2009).

1.3 Intraoperative monitoring of cochlear nerve

Intraoperative monitoring of cochlear nerve function is mostly applicable in (1) smaller acoustic neuromas with well-preserved hearing, (2) non-schwannoma posterior fossa tumors (eg. meningeomas) or (3) microvascular decompression of posterior fossa cranial nerves (Moller et al. 1988).

There are two main methods for intraoperative monitoring of the cochlear nerve: the *far-field methods*, where the electrodes are placed on the scalp surface. The most common method of the far-field recording is the brainstem auditory evoked potential (BAEP) (Moller et al. 1988). In contrast, in *near-field methods*, the active electrode is placed near or actually on the cochlear nerve. The most commonly used near-field recording in surgical monitoring is the direct recording of the cochlear nerve action potential (CNAP). Transtympanic or tympanic recording of the cochlear microphonics is possible in combination with the auditory CNAP. BAEP and CNAP recordings together may help to increase the possibility of hearing preservation in small acoustic neuromas (Stanton et al. 1989).

Several limitations come with the use of BAEP in intraoperative monitoring. In a “far-field” technique, the auditory response is measured on the scalp, which is distant from the neural auditory response generator source (Phillips et al. 2010 and Simon, 2011)**,** noises and artifacts may interfere with the recording and mask the BAEP waves. Ultimately, this leads to increase the number of stimuli averages needed to obtain a wave of sufficiently high amplitude with significant time delay lasting up to several seconds (Colletti et al. 1996; Colletti et al. 1997 and James/Husain 2005; Yamakami et al. 2002 and Yamakami et al. 2003). Such a delay can negatively affect the application of the available data during the surgery (Colletti et al. 1998).

Furthermore, if fluid collection occurs in the mastoid and middle ear cavity, this will cause a conductive hearing loss leading to an amplitude reduction or even loss of the already minute waves recorded via far-field method (Nadol et al. 1992 and Yamakami et al. 2009).

BAEP recordings are prone to false-positive results. A waveform change in the form of wave loss or latency shift can occur as a result of traumatic injury of the nerve or ischemic insult of the blood supply. Waveform shifts can also occur due to other physiological or intraoperative processes such as anesthesia, hypothermia and irrigation (Simon 2011). The utility of BAEP depends on the quality of the response prior to or at the beginning of surgery. This depends on several factors such as tumor size as well as preoperative hearing status. Some patients do not have detectable BAEP while others have abnormal baseline BAEP (Stidham/ Roberson 2001). The disadvantage of using direct CNAP is related to the difficulty to localize the proximal portion of the cochlear nerve especially in cases with larger tumors and the presence of vessels around the cochlear nerve (Piccirillo et al. 2008). Moreover, the position of the electrode could shift with movements in the field during surgical manipulation (Simon 2011).

The role of IOM in the hearing preservation remains questionable because of the lack of studies that investigate hearing outcomes with and without intraoperative monitoring (Harper et al. 1992 and Youssef/Downes 2009). Some studies questioned the role of intraoperative BAEP in hearing preservation. Kveton reported hearing preservation in four of seven unmonitored patients and in four of nine monitored patients (Kveton 1990 b)***.*** However, Piccirillo and his colleagues reported better hearing preservation rate in patients operated with IOM rather than in patients without IOM (Piccirillo et al. 2008).

Variable BAEP patterns have been observed during surgery, such as completely stable, fluctuating or lost BAEP. These patterns depend in part on the surgical strategy and maneuvers. For example, if the surgeon exerts a certain stretch on the nerve-tumor border, this maneuver could cause definite BAEP loss and may result in complete loss of hearing (Matthies/ Samii 1997 b and Schmerber et al. 2004). It was also concluded that drilling of the posterior wall of the internal auditory canal and manipulation of the intrameatal part of cochlear nerve were the most critical surgical steps that cause about 37% of BAEP impairment (Hummel et al. 2016).

Several parameters are mentioned in the literature which represent warning signs guiding the surgeon during intraoperative monitoring using BAEP. Preservation of hearing is achieved in the majority of cases in which BAEP wave V was preserved after the tumor has been completely removed (Phillips et al. 2010 and Yamakami et al. 2009). Another author reported that waves I and V have the most powerful prognostic power as they have been consistently correlated with better postoperative hearing preservation rates (Simon 2011). Detecting waveform irregularities during intraoperative BAEP recording can still alert to potential cochlear nerve damage (Legatt 2002).

In an attempt to find the relationship between the intraoperative loss (either transient or permanent) of the BAEP waves and between the loss of hearing after the operation, Matthies and Samii (1997) recorded the intraoperative BAEP waves in patients who underwent acoustic neuroma surgery via suboccipital approach and reported that transient or permanent losses of waves V, I and III occurred at a rate of 21, 27 and 29% respectively, resulting in turn in postoperative hearing loss in 65 to 78% of the patients. They also mentioned that wave III was the earliest to disappear (Matthies/Samii 1997 b).

Hummel and her colleagues investigated the intraoperative BAEP quality in every step of the operation as well as in the postoperative period in 46 patients operated via a suboccipital approach. They categorized the intraoperative BAEP development into 3 types: *type A,* improved or stable BAEP quality during surgery; *type B*, deteriorated BAEP at the end of surgery and *type C,* sudden or slow loss of the BAEP waves. They correlated the end-operative BAEP types with the postoperative hearing status. They reported that the BAEP quality in the last phase (after 60%

tumor reduction) was the most important one for predicting the hearing outcome (Hummel et al. 2016).

However, most of the previous studies were performed on a small sample size and assessed the warning signs of postoperative hearing loss in suboccipital approach.

The question remains to be answered whether during transtemporal/middle fossa acoustic neuroma surgery certain BAEP signs, when observed and taken into consideration during the measurement, may lead to improve the outcome and increase the sensitivity and specificity of the procedure.

In order to reach better postoperative hearing preservation in patients with an acoustic neuroma, it is very important to identify the reliable warning sign of BAEP. Therefore, the aim of this work is to define those critical warning BAEP signs as a marker on the postoperative hearing outcome.

1.4 Aim of the Work

Objective of this study is to define the most important critical warning signs in BAEP in predicting the postoperative hearing loss. Different response parameters recorded intraoperatively during all stages of transtemporal removal of acoustic neuroma will be analyzed and evaluated regarding their ability to predict the postoperative hearing.

The questions to be answered:

1. What is the effect of the tumor extension on postoperative hearing outcome?
2. What are the critical warning signs of BAEP during intraoperative monitoring?
3. What is the difference between patients with postoperative hearing loss and patients with postoperative hearing preservation regarding the thresholds obtained during intraoperative direct recording of cochlear nerve?
4. What is the diagnostic ability of intraoperative significant BAEP signs and intraoperative direct recording of cochlear nerve as markers for postoperative hearing loss?

2. Subjects and Methods

2.1 Patients

This retrospective study included collection of the clinical data from 162 patients who underwent resection of acoustic neuroma via a transtemporal approach with IOM. BAEP was performed in all patients; while intraoperative direct recording of the cochlear nerve function was done in 131 patients (according to the surgeon's request). The study included patients operated from January 2011 to December 2017 at the Department of Otorhinolaryngology, plastic, aesthetic reconstructive head and neck surgery, University of Wuerzburg.

Inclusion criteria:

1. Patients who were diagnosed to have acoustic neuroma and were indicated for surgical resection using a transtemporal approach.
2. Presence of preoperative measurable hearing (at least) using Shelton's classification (Shelton et al. 1989) as described in Table 1: Shelton's classification

Table 1: Shelton's classification.

Class	Speech reception threshold (SRT)	discrimination score (SDS)
Good	< 30 dB	>70%
Serviceable	<50	>50%
Measurable	when any measurable hearing is present	

The patients in this study consisted of 82 men and 80 women. The tumor was located on the right side in 82 patients and on the left side in 80 patients.

The age at the time of surgery ranged from 16 to 79 years with a mean age of **52.17 years** (Figure 1).

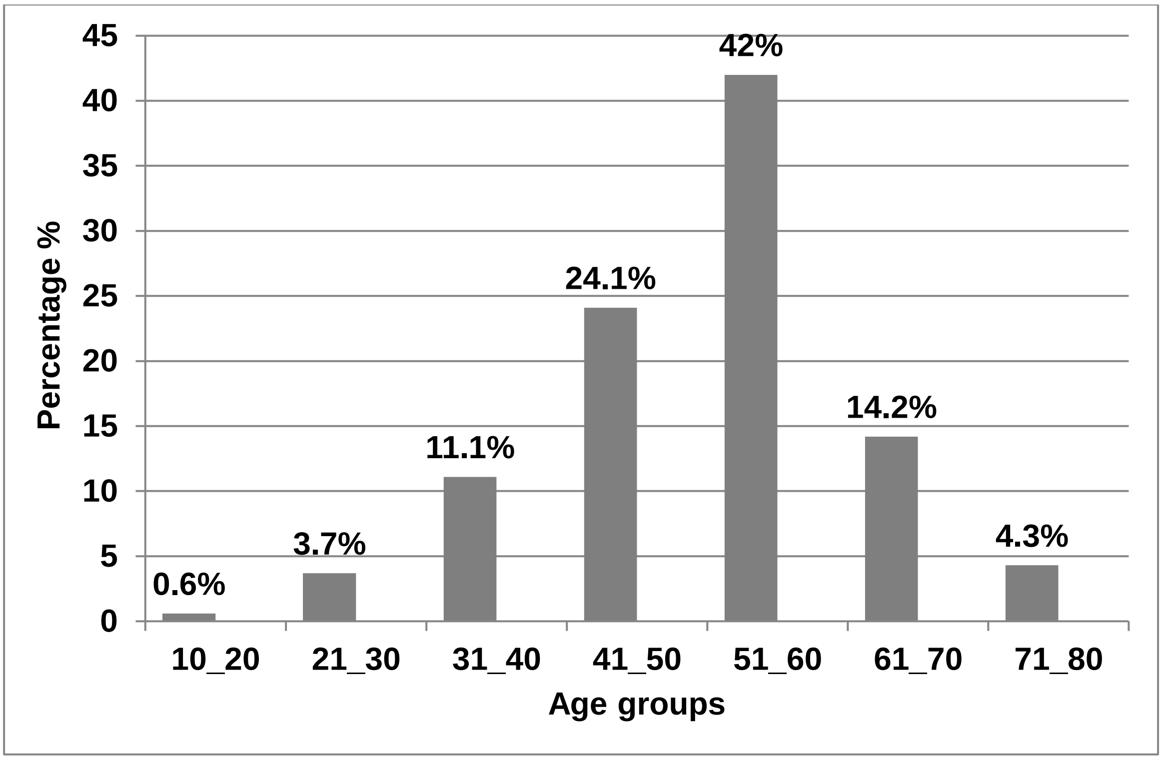


Figure 1: Age of patients at the time of the surgery (Percentage % of patients in each age group).

2.2 Methods

Each patient who underwent surgical resection of acoustic neuroma was subjected to a routine set of preoperative and postoperative investigations. These data served as variables in this study (Figure 2).

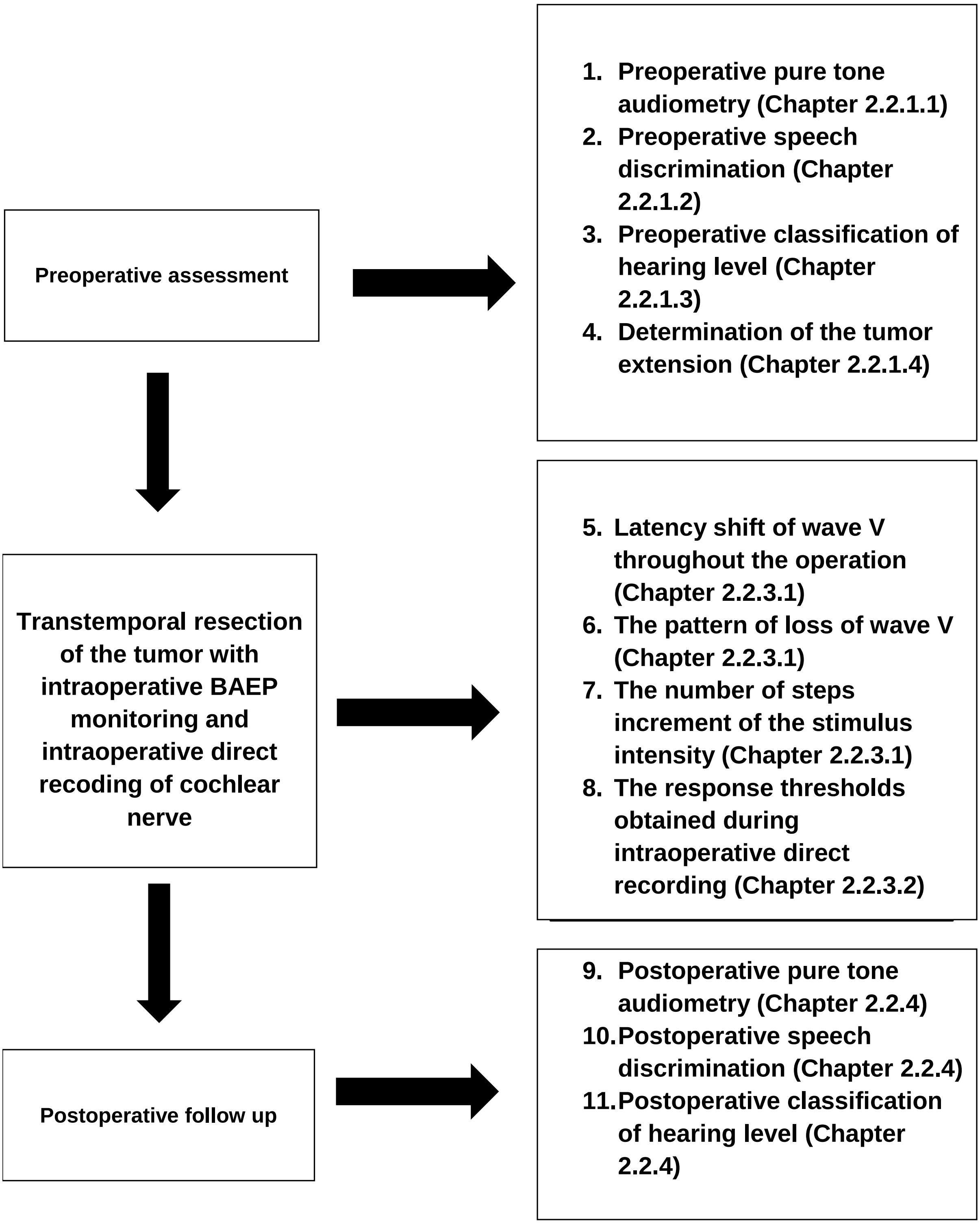


Figure 2: Study design and variables in this study.

2.2.1 Preoperative assessment

2.2.1.1 Preoperative pure tone audiometry (one day prior to surgery)

Audiological evaluation was done preoperatively one day prior to surgery in all patients to detect eventual changes in hearing and provide a baseline for the comparison with postoperative hearing status. Hearing thresholds with pure tone audiometry (PTA): include both air and bone conduction with masking of the opposite side. For the air conduction, pure tones in increasing intensity in the frequency range from 125 Hz to 8 kHz were presented to the patient using headphones and for the bone conduction, pure tones in increasing intensity in the frequency range from 500 Hz to 6 kHz were presented to the patients via a bone oscillator. Thresholds were determined when the patient perceives the sound 50% of the numbers of the application. Since the examiner relies on the patients´ response, it is considered a subjective procedure for the assessment of the hearing.

2.2.1.2 Preoperative speech audiometry

Speech recognition threshold (SRT)

Lists of 10 polysyllabic numbers (Freiburger Zahlen) were delivered to the patients through headphones at 20 dB sensation level. A series of lists (with 10 dB steps upwards or downwards) was applied until reaching the lowest level at which a person can identify 50% of the applied numbers.

Speech discrimination scores (SDS)

Lists of 20 monosyllabic words (Freiburger Einsilber) were delivered to the patients with head phones at 65 dB and 80 dBnHL and the SDS was calculated for each intensity level separately.

2.2.1.3 Classification of the hearing level

The hearing function was classified according to the American Academy of Otolaryngology - Head and Neck Surgery classification published in 1995 and according to the Gardner-Robertson Classification (Gardner/Robertson 1988).

American Academy of Otolaryngology-Head and Neck Surgery classification published in 1995 (AAO-HNS)

Patients fall into one of four categories (Figure 3).

- Class A (≥70 % Speech Discrimination Scores (SDS) and ≤ 30 dB average Pure Tone Threshold (PTT).
- Class B (≥ 50% SDS and 30- 50 dB PTT).
- Class C (≥ 50% SDS and > 50 dB PTT).
- Class D (< 50% SDS) patients' hearing is considered to be non-serviceable.

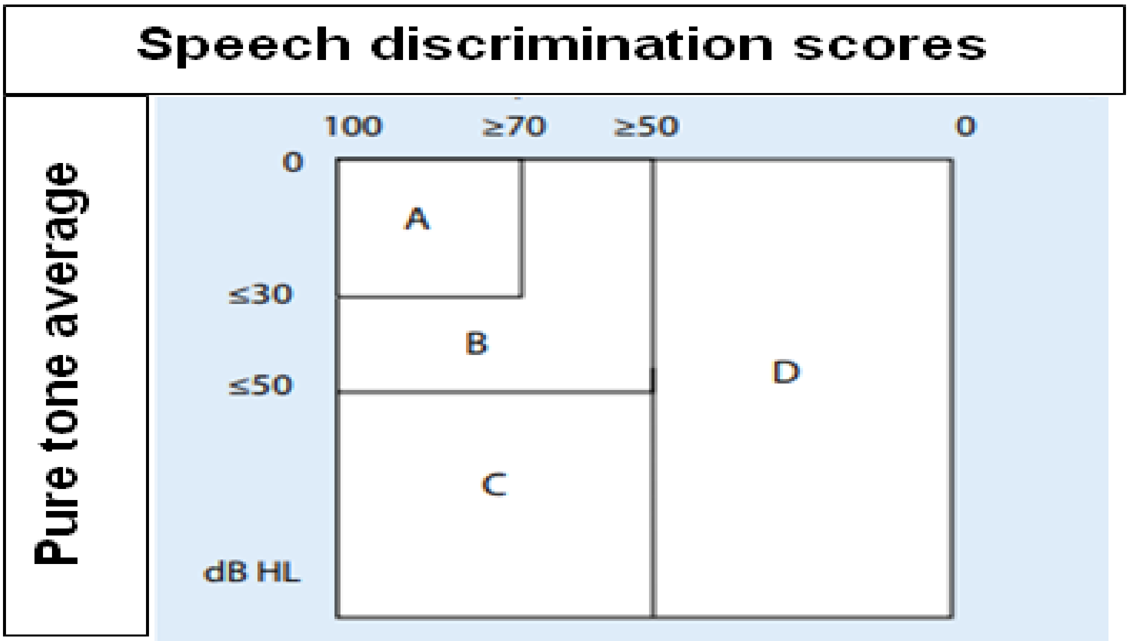


Figure 3: Hearing classes according to American Academy of Otolaryngology-Head and Neck Surgery classification, 1995 (Figure from Scheich et al., 2017. License number: 4758301316196).

Gardner-Robertson Classification:

Here, the hearing level is calculated from an average threshold level at 0.5, 1 and 2 kHz. According to this classification, patients are classified into 5 classes as illustrated in Table 2.

Table 2: Gardner-Robertson Classification (Gardner/Robertson 1988).

Class	Hearing	Pure tone average	Speech discrimination scores
1	Excellent	0 - 30 dB	70-100%
2	Serviceable	31- 50 dB	50-69%
3	Non- serviceable	51- 90 dB	5-49%
4	Poor	> 90 dB	1-4%
5	No hearing		0%

2.2.1.4 Tumor extension

The tumor extension was described according to Hannover classification of the tumor extension as follows: Class T1, purely intrameatal; Class T2, intra- and extrameatal; Class T3a, filling the cerebellopontine cistern; Class T3b, reaching the brain stem; Class T4a, compressing the brain stem; Class T4b, severely dislocating the brain stem and compressing the fourth ventricle (Samii/ Matthies 1997.)

2.2.2 Operation

All patients were operated using the transtemporal approach, described by House (1961). After opening the dura, most of the patients initially underwent a tumor debulking with the flexible CO_2 laser and finally, a complete resection of the tumor from the surrounding cranial nerves took place. An intraoperative BAEP monitoring and direct recording of cochlear nerve using ball electrode were derived.

2.2.3 Intraoperative monitoring of cochlear nerve

2.2.3.1 Intraoperative BAEP

The monitoring device is a 4-channel evoked potential system Nicolet (Viking system, Biomedical Madison, Wisconsin 5371). Intraoperative BAEP monitoring was done implementing the following test protocol:

Electrode montage:

Following general anesthesia and prior to draping and disinfection of the operation site, three intracutaneous needle electrodes (Modell Ambu Neuroline 720) were inserted subcutaneously and fixed with adhesive tape. The electrode impedence was kept below 5 kOhms. Active electrode was placed in the midline on the forehead (FPz) (10-20 EEG system) (Jasper 1958).The reference electrode was placed a little behind the ipsilateral mastoid (M1 or M2) to be out of the operation field and the ground electrode was placed on the contralateral mastoid (M1 or M2) (Figure 4 a-b).

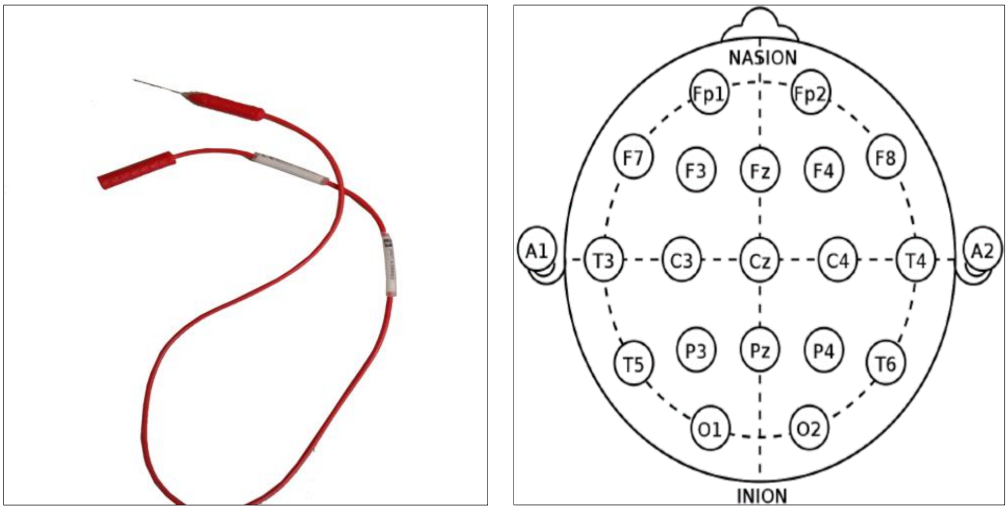


Figure 4: (a) Intracutaneous needle electrode used for intraoperative BAEP monitoring of cochlear nerve function (Photo: Mona Moharam) and (b) 10-20 EEG system for electrode placement on the scalp (Wikimedia Commons 2011).

Stimulus parameters:

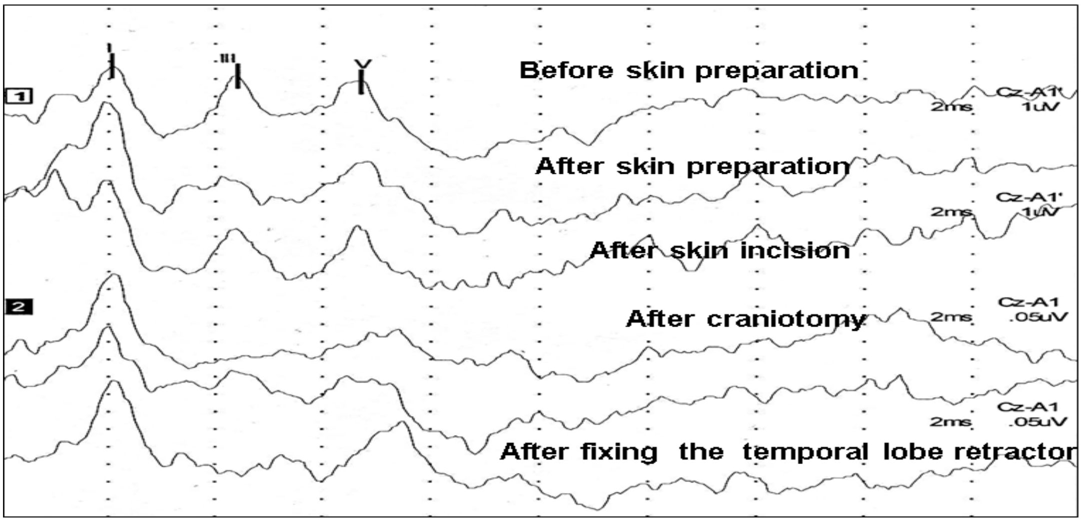
Rarefaction clicks, 0.1 ms in duration, presented at the lowest possible intensity where robust responses were observed, mostly starting at 70 dBnHL, a repetition rate of 20.1 Hz was used to elicit the BAEP. The stimuli were delivered to the ear via insert earphones and a 20 cm long silicone tube (Nicolet Biomedical Madison, Wisconsin 53711, Model Tip 300).The tube was connected to a foam ear tip placed in the external auditory canal. The ear tips of the suitable size were placed in the patients' ear and secured in place with a malleable ear-mold (silicone-based earmould, white/green, egger A / I, Otoplastik und Lasertehnik GmbH). This helped to keep the earphone in place and to prevent fluid entrance into the external ear canal.

Recording parameters:

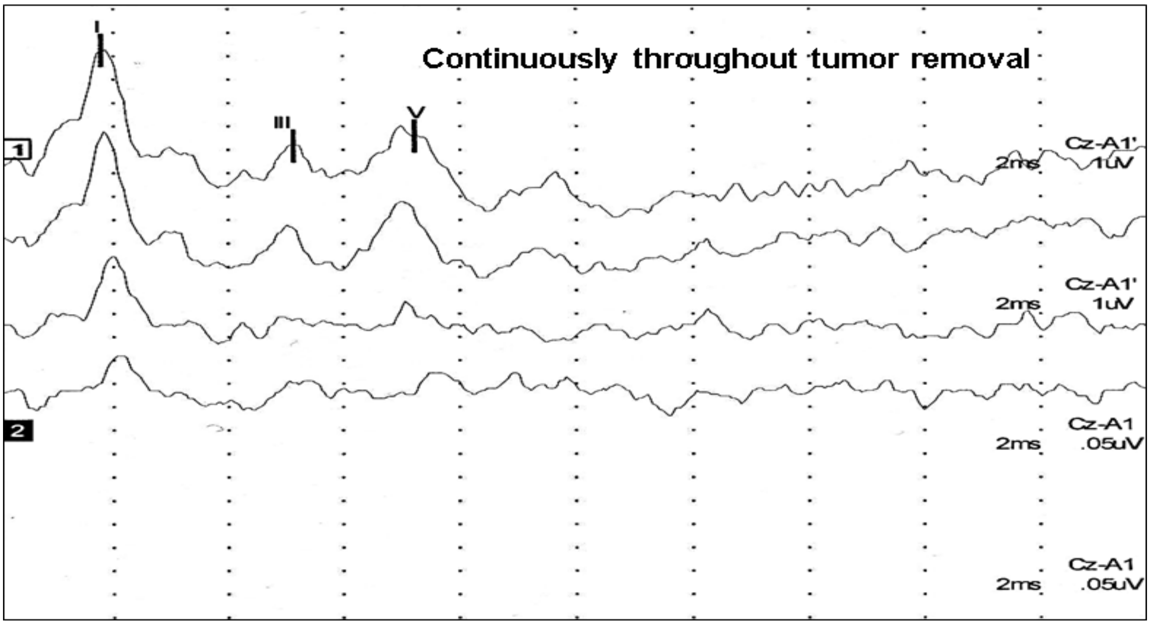
A total number of 500 sweeps were collected. The sweep duration was 20 msec. The low pass filter was set at 30 Hz and the high pass filter at 1500Hz. The amplifier gain was 100 000.

The recording was done during the following intraoperative stages (Figure 5 a-c):

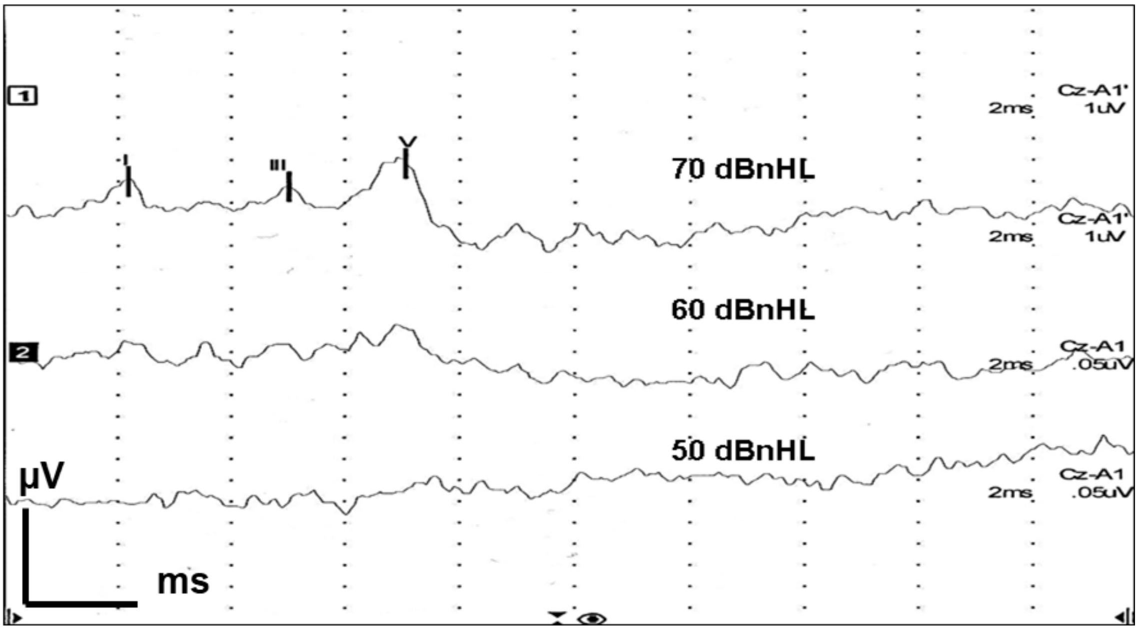
- Before skin preparation.
- Before making the skin incision (after skin preparation).
- After craniotomy.
- After fixing the temporal lobe retractor.
- After drilling to open the bony internal auditory canal to expose the tumor.
- Continuously throughout tumor removal.
- After tumor removal.
- After sealing of the internal auditory canal with a muscle graft.
- If needed, after suturing the skin incision.



(a)



(b)

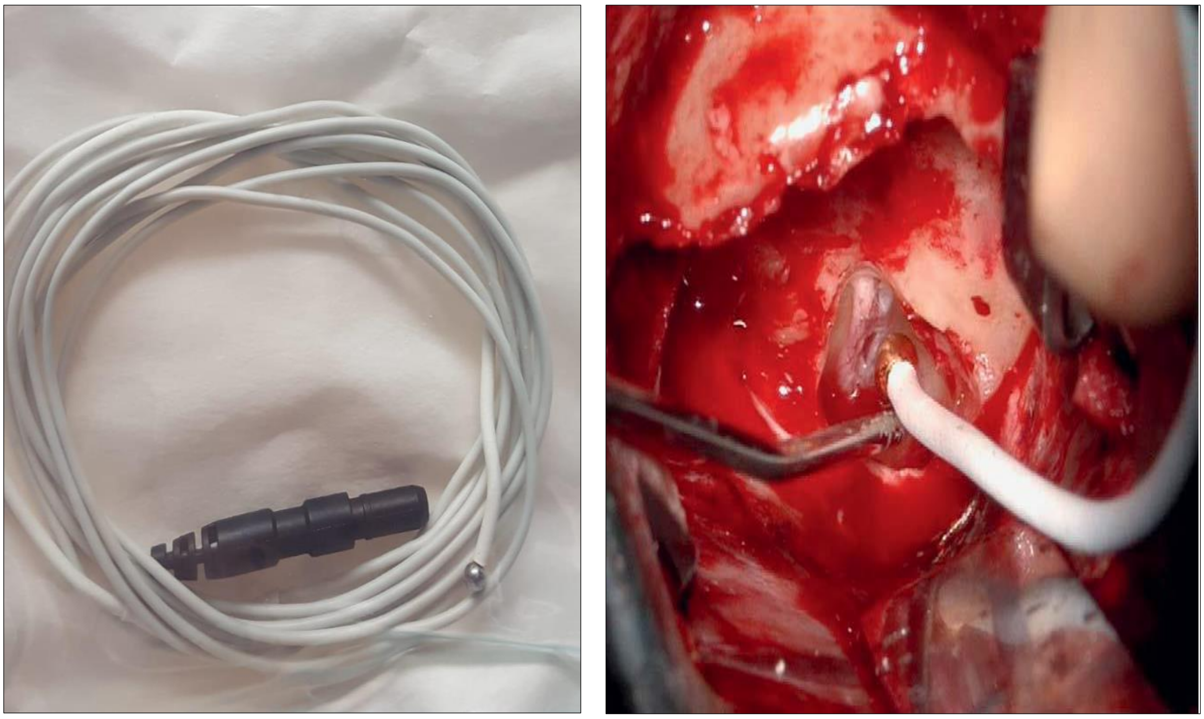


(c)

Figure 5: Intraoperative BAEP monitoring of cochlear nerve (a) after skin disinfection, after making the skin incision, after craniotomy, after fixing the temporal lobe retractor, (b) continuously throughout tumor removal (c) and after sealing of the internal auditory (Illustration: Mona Moharam).

2.2.3.2 Intraoperative direct recording of cochlear nerve function

Intraoperative direct recording of cochlear nerve is only possible after tumor excision and thus after exposure of the nerve. It was done using a ball electrode (Tyrek ® Roll with STERRAD ® Chemical Indicator) (Figure 6 a-b). The electrode was directly applied on cochlear nerve proximal to the resected tumor. The obtained responses with ball electrode during intraoperative direct recording of cochlear nerve were tracked down to thresholds (Figure 7).



(a) (b)

Figure 6: (a) Ball electrode used during intraoperative direct recording of cochlear nerve (Photo: Mona Moharam). (b) Insertion of the ball electrode directly on the cochlear nerve (Ehrmann- Müller et al. 2012, License number: 4753100389479).

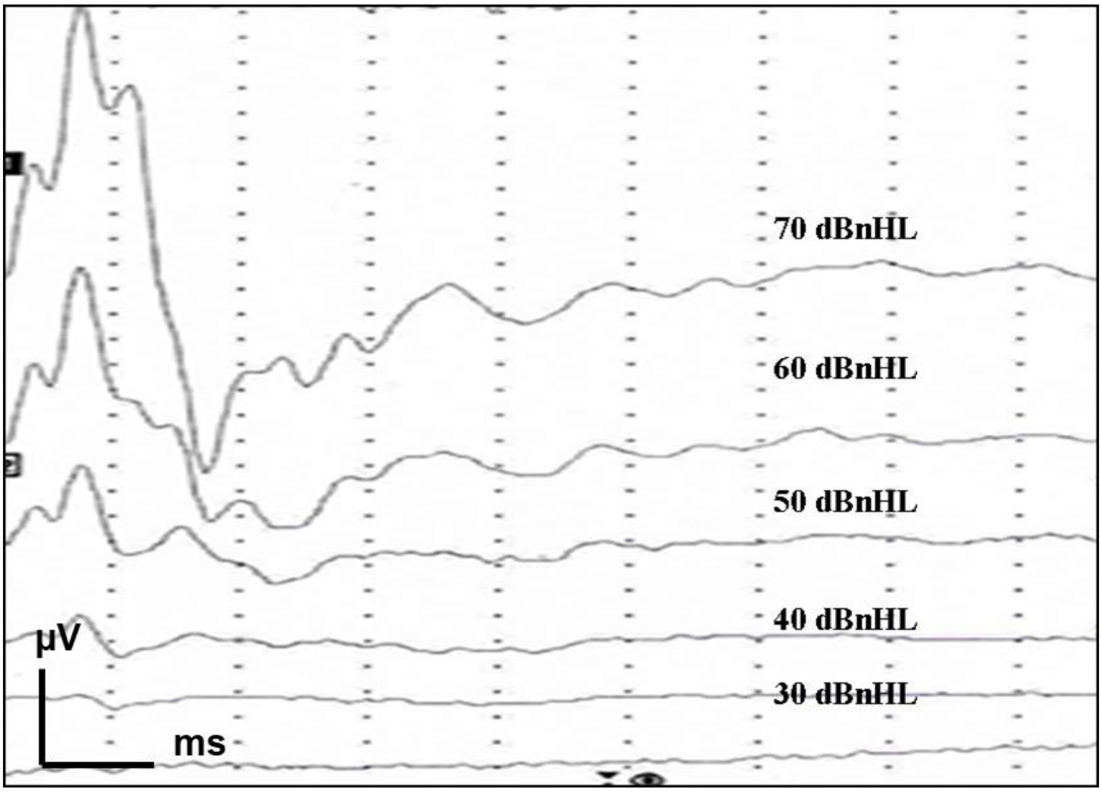


Figure 7: Intraoperative direct recording of cochlear nerve obtained with ball electrode. The response thresholds could be traced down to 50 dBnHL (Illustration: Mona Moharam).

2.2.4 Postoperative hearing measurements

Postoperative pure tone audiometry, postoperative speech audiometry (within one week after the surgery, 3 months and 6 months postoperative) and postoperative classification of the hearing level.

2.3 Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (statistical package for social sciences) software version 25.

Descriptive statistics were done for parametric quantitative data by mean ± standard deviation, while they were done for categorical data by number and percentage.

Different statistical methods were performed to answer the questions of this study:

2.3.1 Determination of the effect of the tumor extension on the postoperative hearing status

Comparison between the patients with intrameatal tumor extension (T1) and extrameatal tumor extension (T2) regarding the postoperative hearing preservation rate using Chi square test (expected number per cell > 5) and Fisher's exact test (expected number per cell < 5). The level of significance is at **P value < 0.05**.

2.3.2 Determination of the critical warning signs of BAEP during intraoperative monitoring

In order to define the critical warning signs of BAEP during intraoperative monitoring, the following parameters were analyzed based on the greatest change of wave V compared to the baseline recording at the beginning of surgery prior to the skin incision. Wave V was selected since it is the most robust and stable one during the recording and is known to correlate better with the postoperative hearing compared to wave I which gives information only on the peripheral part of the auditory nerve (Simon. 2011)

The following parameters were evaluated:

A. Latency shift of the intraoperative recorded wave V.
B. The pattern of loss of the intraoperative recorded wave V.
C. Number of steps-increment of the stimulus intensity (stability of the intensity throughout the intraoperative recording).

Based on the previous parameters the patients were classified into ten groups:

Group (1): Patients with latency shift greater than 1 ms.

Group (2): Patients with latency shift 0 to 1ms. This group was used as a reference to group (1).

Group (3): Patients with transient loss of wave V.

Group (4): Patients with permanent loss of wave V

Group (5): Patients with constant wave V. This group was used as a reference to groups (3 and 4).

Group (6): Patients who needed one-step (10 dB) increment of the stimulus intensity to obtain clearly visible wave V.

Group (7): Patients who needed two-steps increment of the stimulus intensity (20 dB) to obtain clearly visible wave V.

Group (8): Patients who needed three-steps increment of the stimulus intensity (25 dB) to obtain clearly visible wave V.

Group (9): Patients who needed maximum intensity of the stimulus from the start to obtain clearly visible wave V.

Group (10): Patients who had clearly visible wave V at 70 dB without the need of increment of the stimulus intensity. This group was used as a reference to groups (6, 7, 8 and 9).

The frequency of postoperative hearing loss was calculated for the different groups and also among patients who had two parameters to determine the critical warning signs during intraoperative monitoring of acoustic neuroma. Analyses were done using Chi square test (expected number per cell > 5) and Fisher's exact test (expected number per cell < 5). The level of significance is at **P value < 0.05**.

2.3.3 Difference between patients with postoperative hearing loss and patients with postoperative hearing preservation regarding the thresholds obtained during intraoperative direct recording of cochlear nerve

Response thresholds recorded using the ball electrode were compared in patients who experienced postoperative hearing loss to those who showed postoperative hearing preservation using independent t- test.

The level of significance was at **P value < 0.05**.

2.3.4 Determination of the diagnostic ability of intraoperative significant BAEP signs and intraoperative direct recording of cochlear nerve as markers for postoperative hearing loss

Logistic regression analysis was used to test the diagnostic ability of the significant intraoperative BAEP signs as well as the diagnostic ability of intraoperative direct recording of cochlear nerve in predicting postoperative hearing loss. Logistic regression is used in the presence of a categorical dependent variable (binomial response) (Sperandei 2014).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPP) were calculated for each significant intraoperative BAEP sign, which had been statistically proven to increase the risk of postoperative hearing loss and for the response thresholds obtained during intraoperative direct recording of cochlear nerve. Additionally, the receiver operating characteristic curve (ROC) and area under the curve (AUC) were done. ROC and AUC are a visual representation of the relationship between the true-positive rates (sensitivity) and false-positive rates (1-specificity) of a given marker at different cut off points (Zweig/Campbell 1993). A marker with AUC=1 is considered to have a perfect diagnostic ability, while AUC=0.5 means that the marker has a poor diagnostic ability (Zweig/Campbell 1993). The main aim of creating the ROC curve is to define the optimal cut off, at which most of the examined individuals will be correctly diagnosed as diseased or not based on the used marker (Youden 1950).

3. Results

The total number of patients evaluated in this study was 162, however, a complete set of data was available for 146 patients.

3.1 Preoperative audiological findings (pure tone audiometry and speech discrimination scores)

As explained in the chapter (2.2.1.2) the hearing level and speech discrimination of the patients were determined preoperatively (Table 3). The pure tone average was considered as the average of the middle four frequencies (500 Hz, 1 kHz, 2 kHz and 4 kHz) (Choi/Park 2017).

Table 3: Descriptive statistics (Range, Mean and Standard Deviation (SD) of the pure tone average (PTA) and speech discrimination scores (SDS) preoperatively).

Preoperative audiological findings	Range Mean ± SD
Pure Tone Average (PTA)	(0-86) 34.79±19.54
Speech discrimination scores	(0-100) 80.92 ±26.77

3.2 Preoperative classification of the hearing level

3.2.1 American Academy of Otolaryngology-Head and Neck Surgery classification (1995)

The patients were classified according to the American Academy of Otolaryngology-Head and Neck Surgery classification (1995) into four hearing categories (A, B, C, and D). Number and percentage of patients in each class were calculated. 88 patients (54.3%) were in class A, 49 patients (30.3%) were in class B. Class C included 2 patients (1.2 %), while class D included 23 patients (14.2%) (Figure 8)

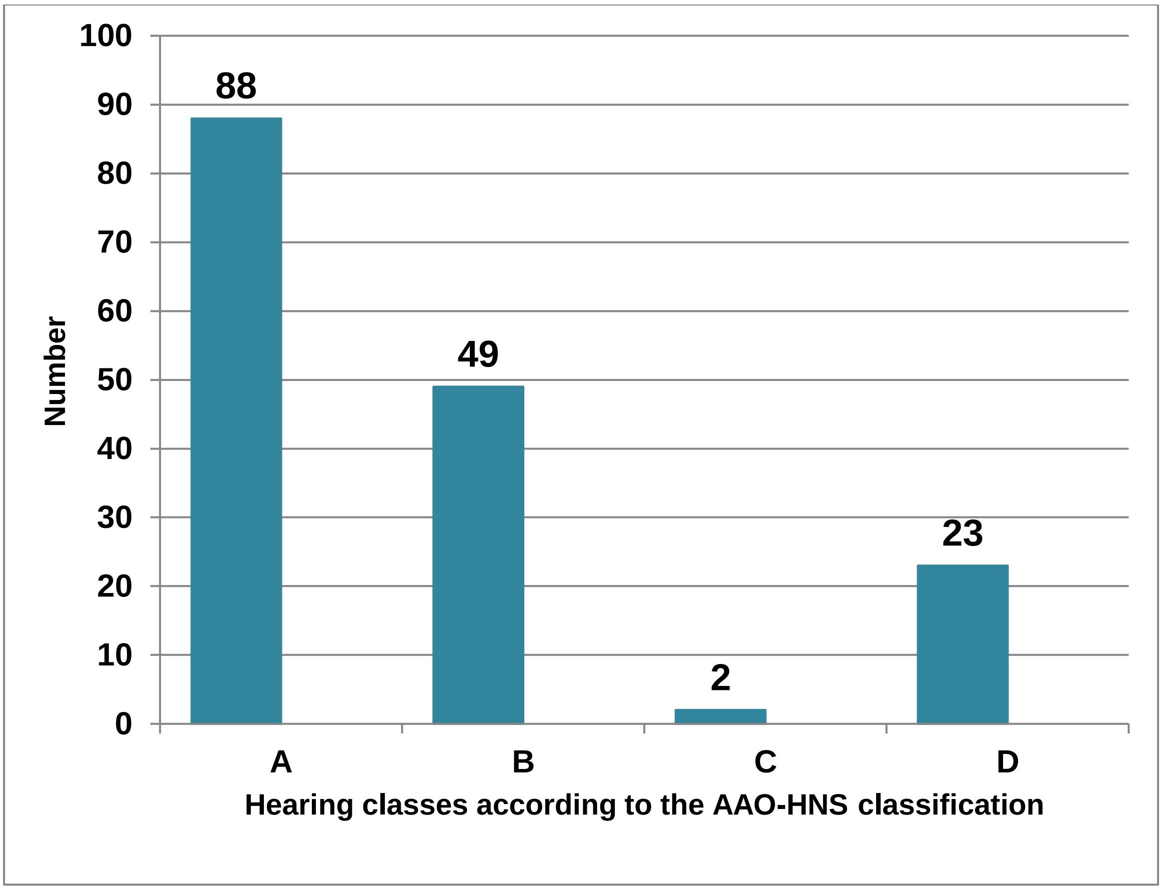


Figure 8: Distribution (numbers) of the patients' preoperative hearing according to the AAO-HNS classification.

3.2.2 Gardner-Robertson classification

The preoperative hearing was further classified using the Gardner-Robertson classification. 98 patients (60.5%) were in class 1 before surgery, 46 patients (28.4%) were in class 2. Class 3 included 18 patients (11.1 %); while there were no patients in classes 4 and 5 (Figure 9).

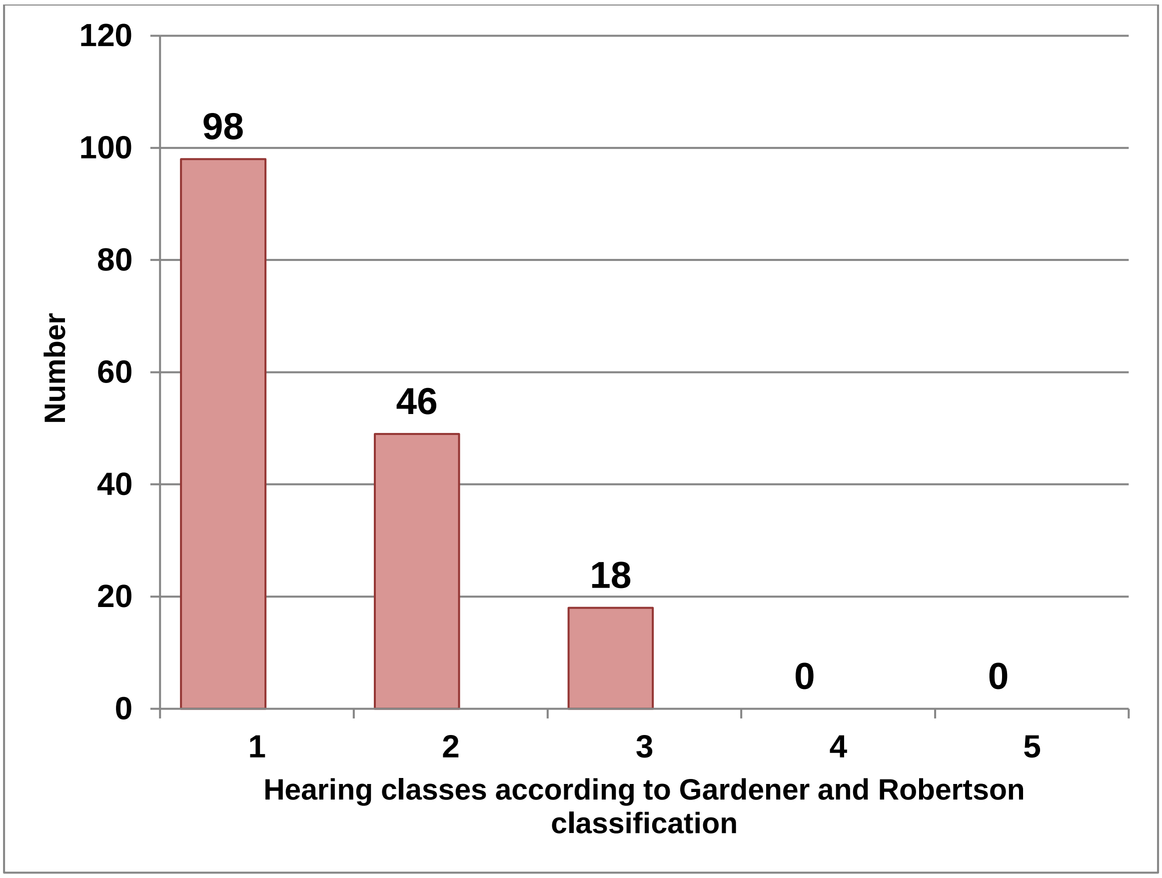


Figure 9: Distribution (numbers) of the patients' preoperative hearing according to Gardner and Robertson classification.

3.3 Tumor extension

Tumor extension was described according to the Hannover classification of tumor extension as mentioned in the chapter (2.2.1.4 Tumor extension). Most of the patients in this study were in class T2 (52.5 %) and the rest were in class T1 (47.5%).

3.4 The relationship between preoperative and postoperative hearing

The hearing level of the patients was determined preoperatively, immediate postoperative (within one week after the operation), 3 months postoperative and 6 months postoperative (Figure 10).

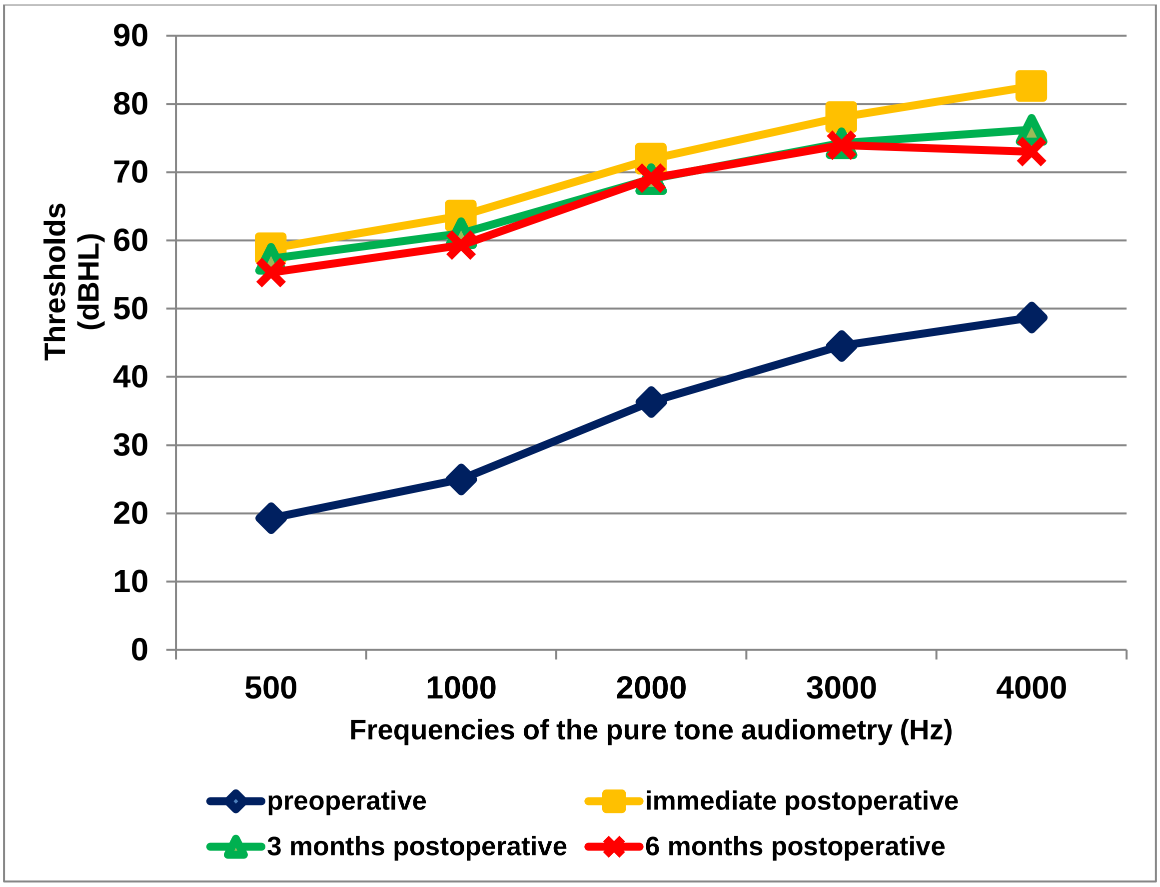


Figure 10: Mean values of the pure tone audiometry preoperative, immediate postoperative (within one week after the operation), 3 months and 6 months postoperative.

The speech discrimination scores of the patients were determined preoperatively, immediate postoperative (within one week after the operation), 3 months postoperative and 6 months postoperative (Figure 11 and Table 4).

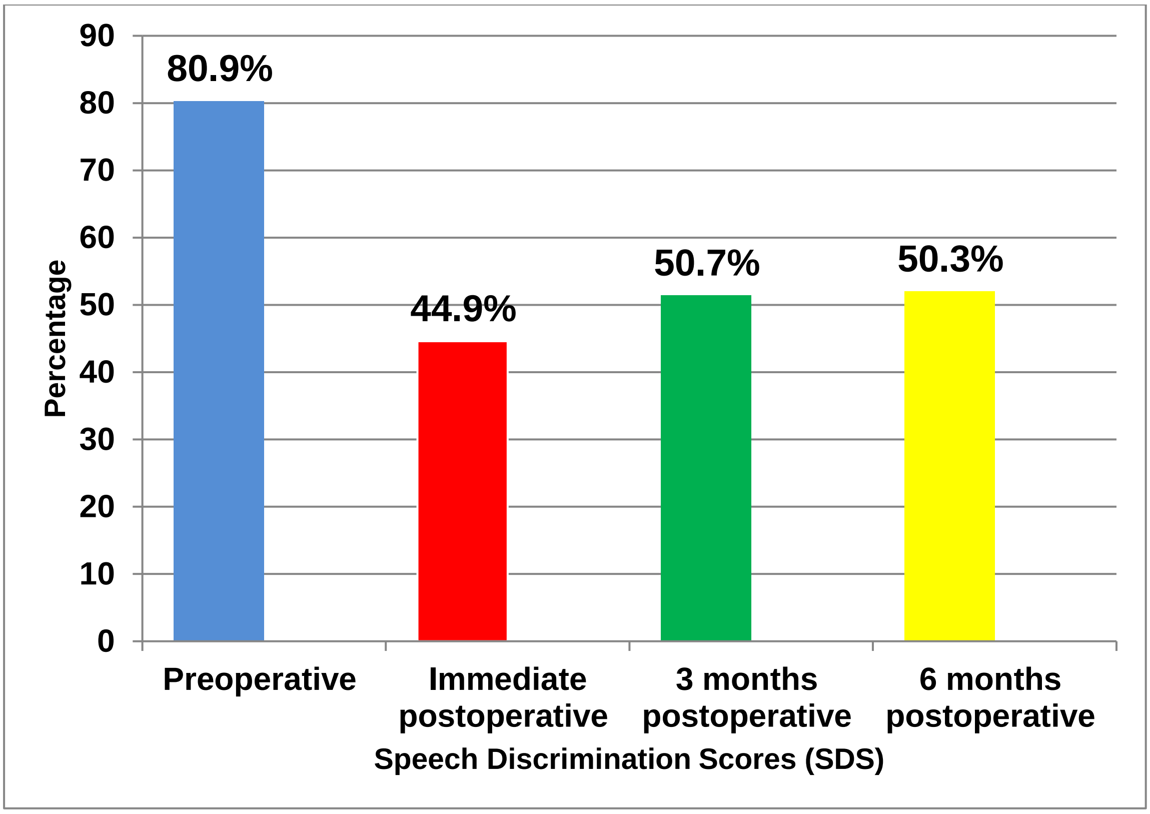


Figure 11: Speech discrimination scores (SDS) preoperative, immediate postoperative (within one week after the operation), 3 months and 6 months postoperative.

Table 4: Minimum, maximum, mean and standard deviation of the speech discrimination scores (SDS) preoperative, immediate postoperative (within one week after the operation), 3 months and 6 months postoperative.

	Minimum	Maximum	Mean	Standard deviation(SD)
Preoperative SDS	0	100	80.9	26.76
Immediate postoperative	0	100	44.9	41.82
3months postoperative	0	100	50.7	42.88
6months postoperative	0	100	50.3	43.01

Based on AAO- HNS classification, 88 patients were in class A preoperatively, 35 of them stayed in class A, while 14 shifted to class B, five patients to class C and 34 to class D. A total number of 49 patients were in class B preoperatively, one of them moved postoperatively to class A, while ten of the patients stayed in class B, ten patients shifted from class B to class C and 28 patients shifted to class D. Class C included two patients preoperatively, both of them moved to class D. Class D had 23 patient preoperatively, 16 of them stayed in the same class postoperatively, while one patient moved up to class A, two to class B and four to class C (Table 5).

Table 5: Distribution of the patients hearing (preoperative and postoperative) based on the AAO-HNS classification.

AAO-HNS classification	preoperative				Total
	A	B	C	D	
postoperative					
A	35(39.8%)	1(2%)	0(0%)	1(4.3%)	37
B	14(15.9%)	10(20.4%)	0(0%)	2(8.7%)	26
C	5(5.7%)	10(20.4%)	0(0%)	4(17.4%)	19
D	34 (38.6%)	28(57.1%)	2(100%)	16(69.6%)	80
Total	88	49	2	23	162

Based on Gardner-Robertson classification, 98 patients had excellent hearing preoperatively, 49 of them had postoperative excellent hearing, while 16 had a serviceable hearing. Ten patients had non-serviceable, two had poor hearing postoperative and 21 patients had no hearing. A total number of 46 patients had serviceable hearing preoperatively, one of them improved postoperatively to excellent hearing, nine stayed with serviceable hearing, 17 shifted to non-serviceable, one to poor hearing and 18 to non-hearing. The non-serviceable group included 18 patients preoperatively, one of them improved to serviceable hearing. Eight of them stayed in the same group, two patients and seven patients shifted downward to be in poor and non-hearing groups respectively (Table 6).

Table 6: Distribution of the patients hearing (preoperative and postoperative) based on the Gardner-Robertson classification.

Gardner Robertson classification	Preoperative					Total
	Excellent	Serviceable	Non-Serviceable	Poor	None	
Postoperative						
Excellent	49 (50%)	1(2.2%)	0(0%)	0(0%)	0(0%)	50
Serviceable	16(16.3%)	9(19.6%)	1(5.6%)	0(0%)	0(0%)	26
Non-Serviceable	10(10.2%)	17(37.0%)	8(44.4%)	0(0%)	0(0%)	35
Poor	2(2%)	1(2.2%)	2(11.1 %)	0(0%)	0(0%)	5
No hearing	21(21.4%)	18(39.1%)	7(38.9%)	0(0%)	0(0%)	46
Total	98	46	18	0	0	162

3.5 Hearing Preservation rate

In order to calculate the postoperative hearing preservation rate, the pre- and postoperative hearing results were compared. A patient is considered to have hearing preservation if he/she stayed in class (A or B) postoperatively, stayed in the same group or shifted to a higher group (Figure 12).

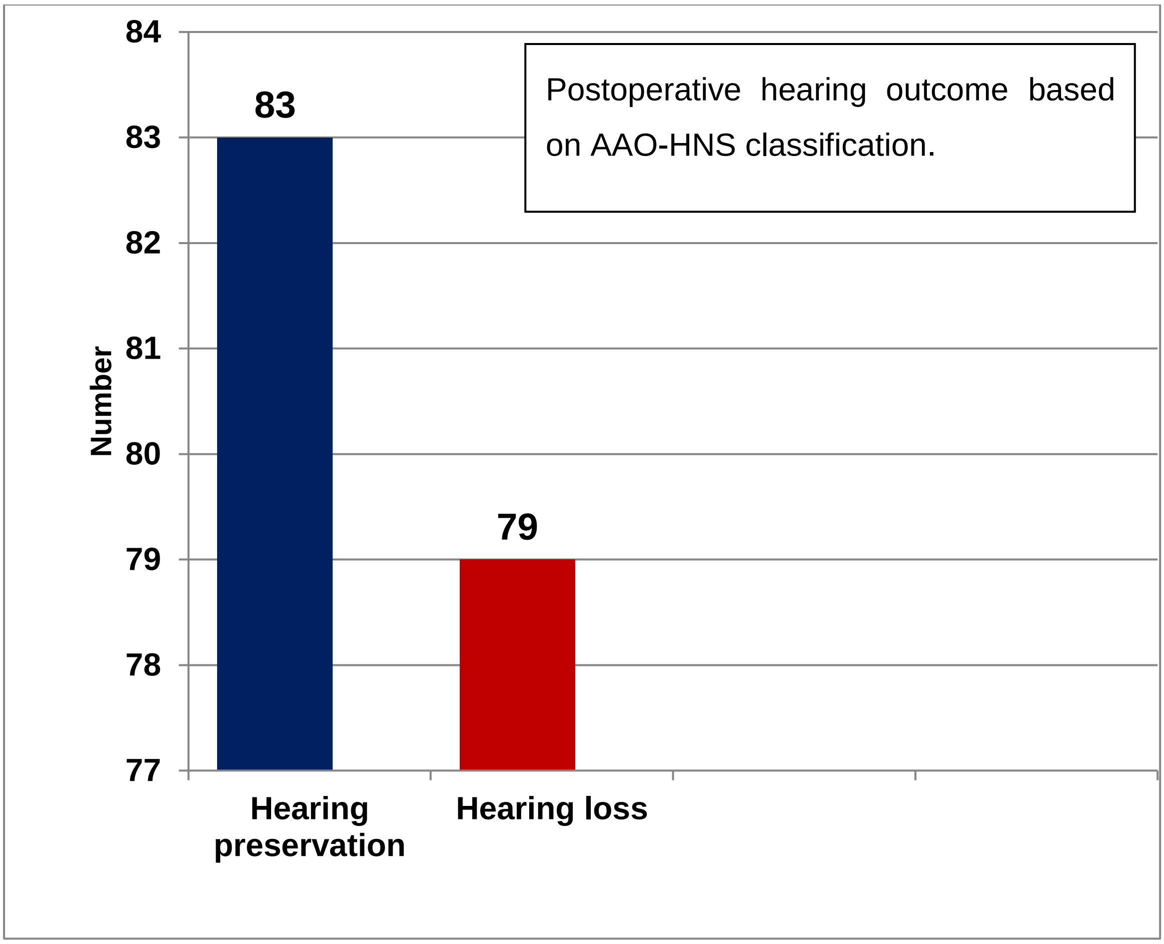


Figure 12: Number of patients with postoperative hearing preservation and the number of patients with postoperative hearing loss based on AAO-HNS classification.

The total hearing preservation rate based on AAO-HNS classification was **51.23 %.**

According to Gardner-Robertson classification. A patient is considered to have postoperative hearing preservation if he/she classified to be in class 4 or a higher class (Figure 13).

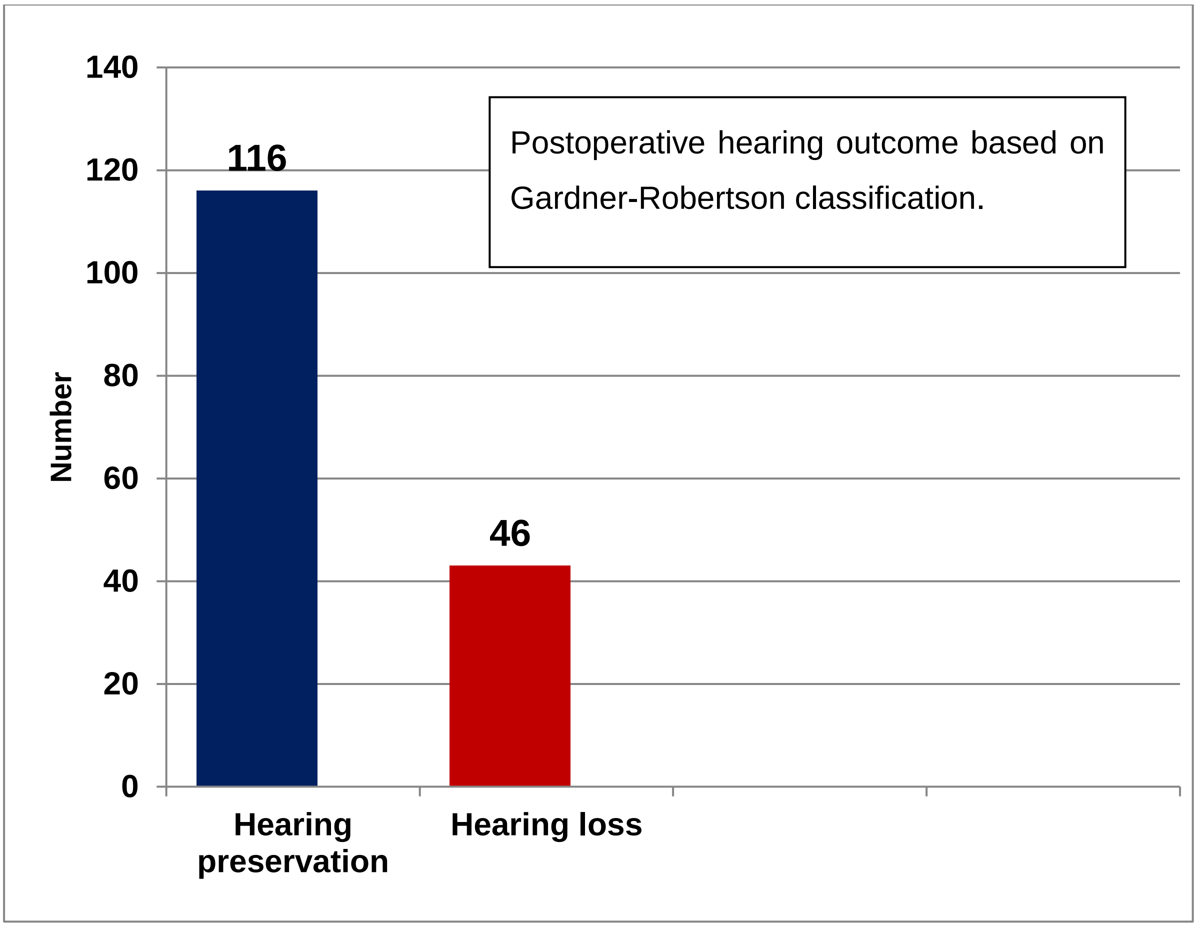


Figure 13: Number of patients with postoperative hearing preservation and the number of patients with postoperative hearing loss based on Gardner-Robertson classification.

The total hearing preservation rate based on Gardner-Robertson classification was **71.6 %.**

3.6 Effect of the tumor extension on the hearing preservation rate

Tumor extension was graded according to the Hannover classification for the tumor size into (T1) with intrameatal tumor extension and (T2) with extrameatal tumor extension. The hearing preservation was calculated in each category based on both the AAO-HNS classification (Figure 14) and Gardner-Robertson (Figure 15). Although a tendency to preserve hearing in patients with T1 is present, however, this tendency did not reach a statistically significant difference.

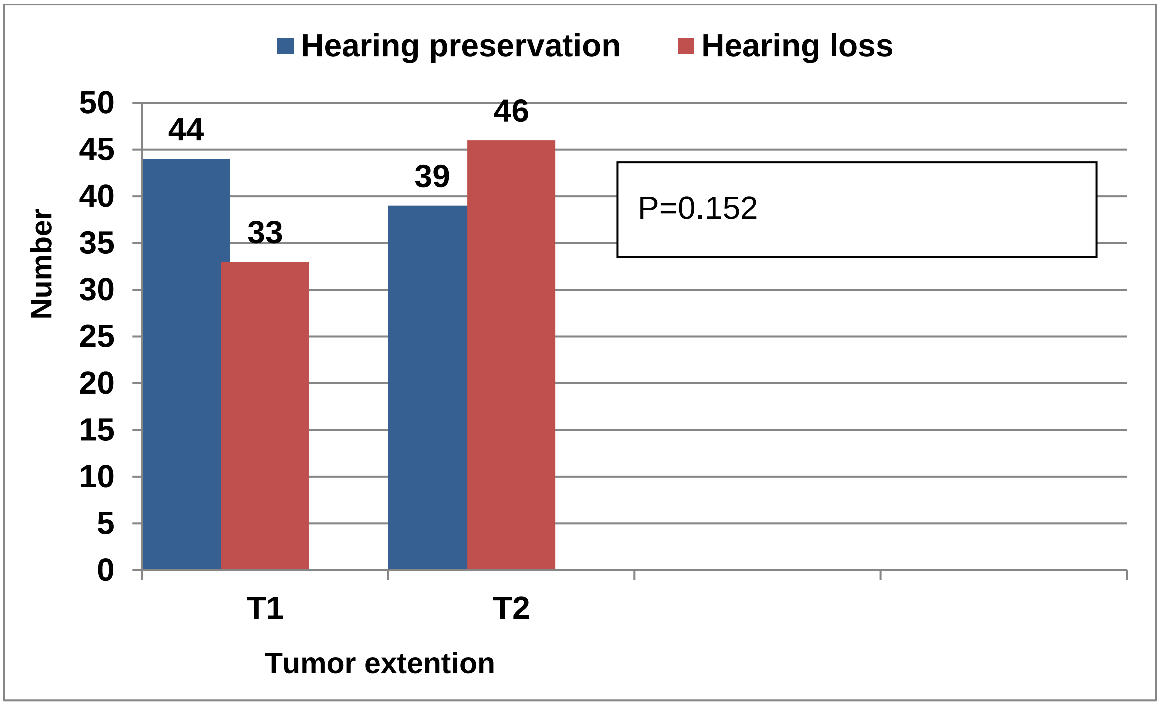


Figure 14: Comparison between the patients with intrameatal tumor extension (T1) and extrameatal tumor extension (T2) regarding the postoperative hearing preservation rate based on the AAO-HNS classification.

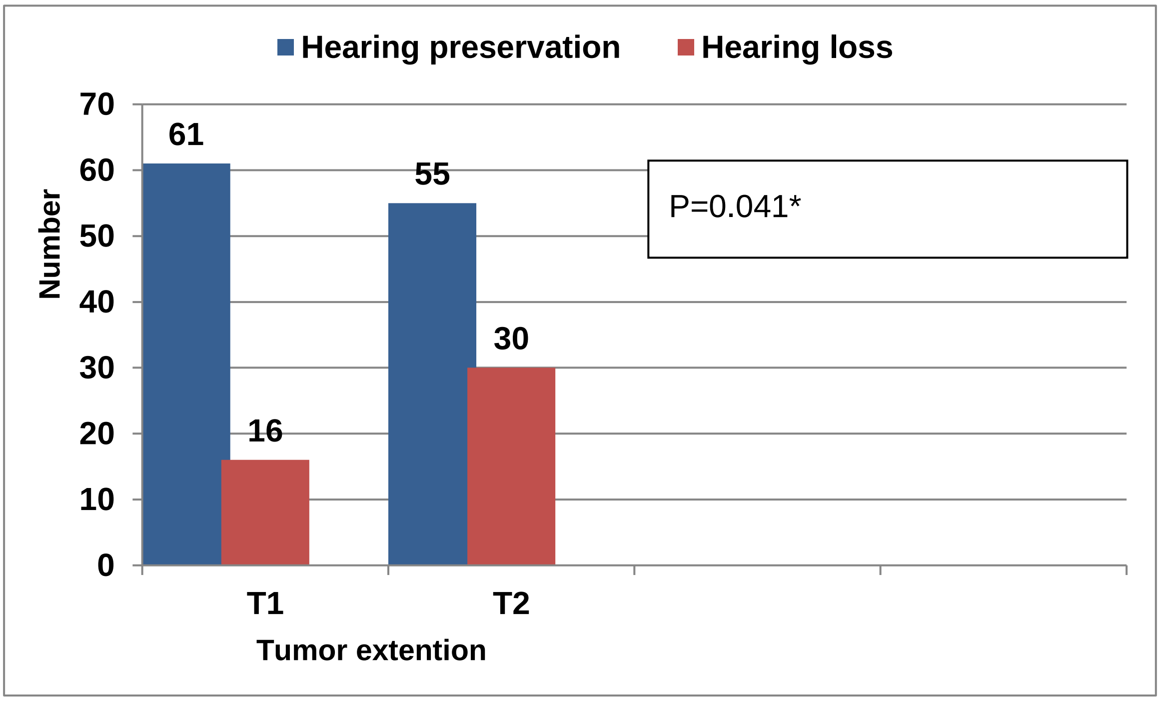


Figure 15: Comparison between the patients with intrameatal tumor extension (T1) and extrameatal tumor extension (T2) regarding the postoperative hearing preservation rate based on the Gardner-Robertson classification.

3.7 Critical warning signs of BAEP during intraoperative monitoring (intraoperative BAEP changes and hearing outcome)

To define the critical warning signs of BAEP during the intraoperative monitoring, the following parameters were analyzed based on the greatest change of wave V compared to the baseline recording at the beginning of surgery prior to the skin incision.

A. Latency shift of the intraoperative recorded wave V.
B. The pattern of loss of the intraoperative recorded wave V.
C. Number of steps-increment of the stimulus intensity (stability of the intensity throughout the intraoperative recording)

Based on the previous parameters, the patients were classified into ten groups (Table 7).

Table 7: Number and percentage of patients in different groups.

Group number	Description		Number and % of Patients
Group (1)	Latency shift of the intraoperative recorded wave V	>1ms	62 (42.5%)
Group (2)		0-1ms (Reference group)	84 (57.5%)
Group (3)	Pattern of loss of the intraoperative recorded wave V	Transient loss of wave V	20 (13.8%)
Group (4)		Permanent loss of wave V	42 (28.9%)
Group (5)		Constant wave V (Reference group)	84 (57.3 %)

Group (6)	Number of steps-increment of of the stimulus intensity (stability of the intensity throughout the intraoperative recording)	One (10 dB)	34 (23.3%)
Group (7)		Two (20 dB)	14 (9.6%)
Group (8)		Three (25 dB)	49(33.6%)
Group (9)		Always at max.	10 (6.8%)
Group (10)		No need of increment of the stimulus (Reference group)	39 (27.6%)

Postoperative hearing loss within each of the previously mentioned groups was analyzed according to AAO-HNS classification (Figure 16). Group 4 (permanent loss of wave V) had the largest percentage of patients with postoperative hearing loss (90.5%). The percentage of postoperative hearing loss in group 4 was compared to that in patients with constant wave V (group 5) during the whole operation (34.5%) using Chi-square and Fisher exact test. The percentage of postoperative hearing loss was statistically significant higher in patients with permanent loss of wave V (group 4) ($p<0.001$). Group 8 (needed three-steps increment of the stimulus intensity to obtain clear waves), also had a statistically significant higher frequency of postoperative hearing loss (81.6%) compared to the percentage of postoperative hearing loss in the patients who had clear response without a need to increase the intensity (43.6%) in group 9 (p<0.001). On the other hand, the percentages of postoperative hearing loss were 51.6% in group 1 who experienced latency shift >1ms, 50% in group 3 who experienced transient loss of wave V, 23.5% in group 6 who experienced one-step increment of the stimulus intensity and 50 % in group 7 who experienced two-steps increment of the stimulus intensity, no statistically significant difference was observed between the groups 1, 3, 6 and 7 and their corresponding reference groups regarding the percentage of postoperative hearing loss (p > 0.05).

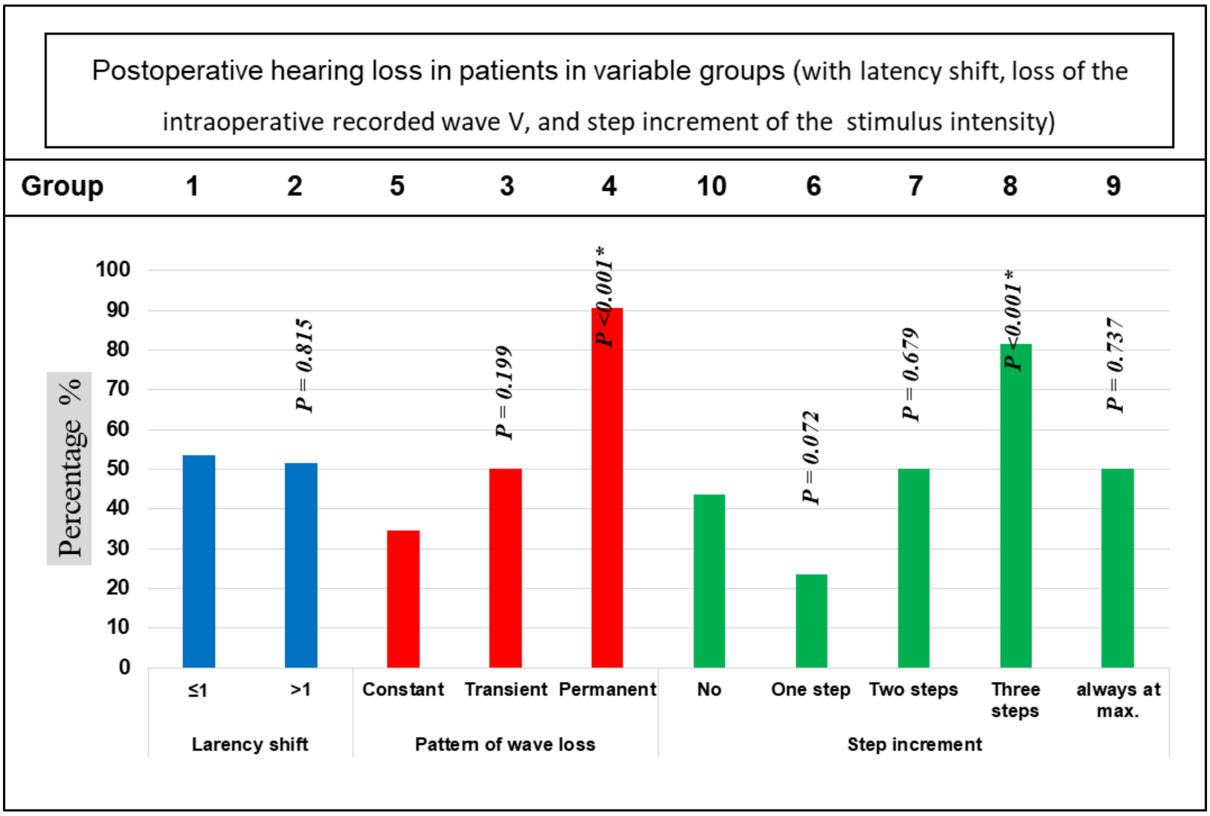


Figure 16: The percentage of postoperative hearing loss with latency shift, loss of the intraoperative recorded wave V, and step increment of the stimulus intensity.

In summary, permanent intraoperative loss of wave V and the need of three-steps increment of the stimulus intensity were associated with a statistically significant higher frequency of postoperative hearing loss. The presence of latency shift >1 ms was not associated with a significant higher percentage of postoperative hearing loss.

Some patients in this study had two intraoperative BAEP signs. To find out if the presence of two intraoperative BAEP findings had influenced the percentage of postoperative hearing loss, we compared the percentage of the patients who had two intraoperative BAEP findings and had postoperative hearing loss with the patients who had only one intraoperative BAEP finding and had hearing loss postoperatively.

To compare the percentage of post-operative hearing loss in patients with more than one finding to those with one finding, we used Chi square test and Fisher's exact test. The comparison is done after excluding the latency shift.

Statistical analysis of patients with transient loss of wave V in combination with one, two or three steps-increment of the stimulus intensity showed the following (Figure 17):

A: comparison of the percentage of postoperative hearing loss in patients with transient loss of wave V in combination with one-step increment of the stimulus intensity with patients who had transient loss of wave V or one-step increment of the stimulus intensity showed no statistically significant difference (p=0.294).

B: comparison of the percentage of postoperative hearing loss in patients with transient loss of wave V in combination with two-steps increment of the stimulus intensity with patients who had transient loss of wave V or two-steps increment of the stimulus intensity showed no statistically significant difference (p=0.0600).

C: comparison of the percentage of postoperative hearing loss in patients with transient loss of wave V in combination with three-steps increment of the stimulus intensity with patients who had transient loss of wave V or three-steps increment of the stimulus intensity showed no statistically significant difference (p=0.055).

D: comparison of the percentage of postoperative hearing loss in patients with transient loss of wave V in combination with being always at maximum intensity with the patients who had transient loss of wave V or being always at maximum intensity showed no statistically significant difference (p=0.483).

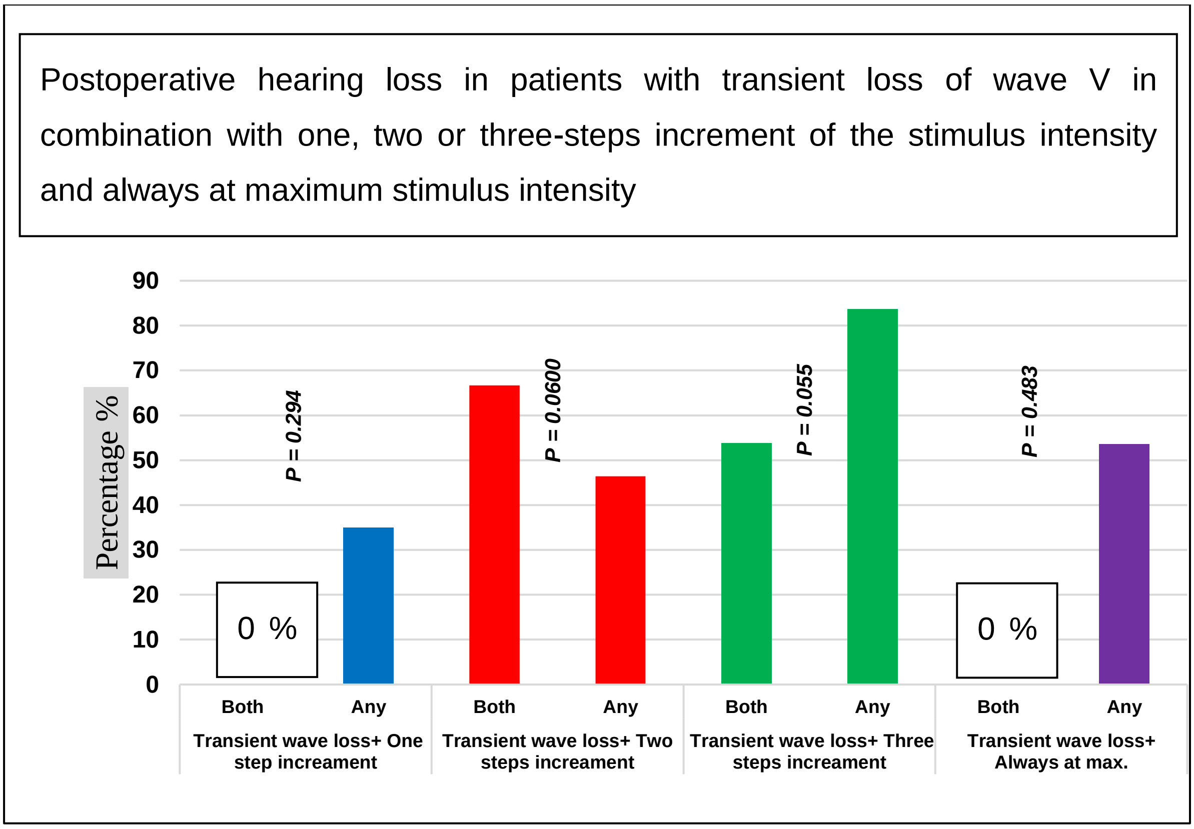


Figure 17: The percentage of postoperative hearing loss in patients with transient loss of wave V in combination with other parameters (one, two or three steps-increment of the stimulus intensity and always at maximum intensity).

The statistical comparison of patients with permanent loss of wave V and one, two, three-steps increment of the stimulus intensity or being always at maximum stimulation intensity showed the following (Figure 18):

A: comparison of the percentage of postoperative hearing loss in patients with permanent loss of wave V in combination with one-step increment of the stimulus intensity with patients who had permanent loss of wave V or one-step increment of the stimulus intensity showed a non-statistically significant difference (p=1.0).

B: comparison of the percentage of postoperative hearing loss in patients with permanent loss of wave V in combination with two-steps increment of the stimulus intensity with patients who had permanent loss of wave V or two-steps increment of the stimulus intensity showed a non-statistically significant difference (p=1.0).

C: comparison of the percentage of postoperative hearing loss in patients with permanent loss of wave V in combination with three-steps increment of the stimulus intensity with patients who had permanent loss of wave V or three-steps increment of the stimulus intensity showed a statistically significant difference (p= 0.030).

D: comparison of the percentage of postoperative hearing loss in patients with permanent loss of wave V in combination with being always at maximum intensity with patients who had permanent loss of wave V or being always at maximum intensity showed a non-statistically significant difference (p=1).

Frequency of postoperative hearing loss in patients with permanent loss of wave V in combination with one, two or three-steps increment of the stimulus intensity and always at maximum intensity

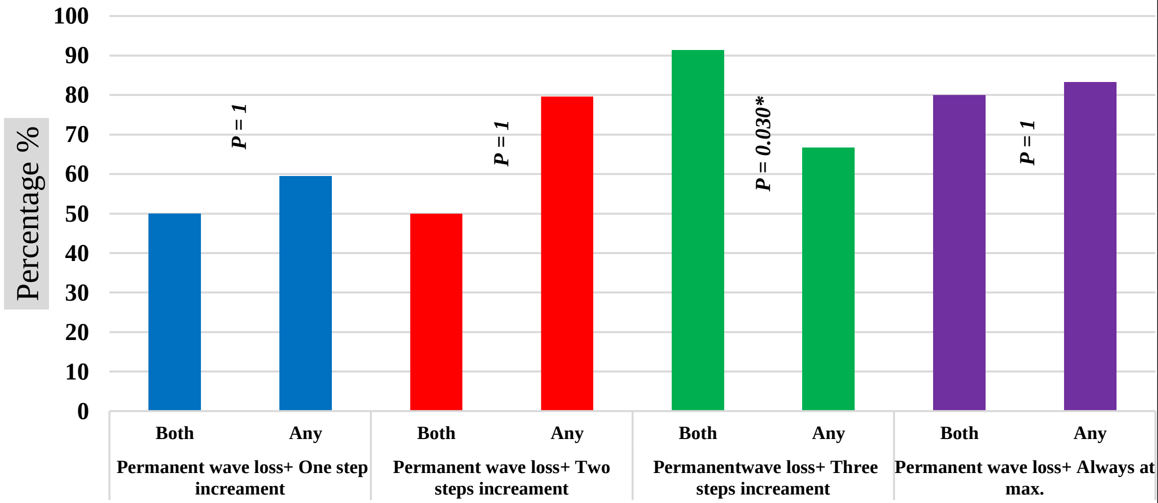


Figure 18: The percentage of postoperative hearing loss in patients with permanent wave loss in combination with other signs (one, two, three-steps increment of the stimulus intensity and always at maximum intensity).

The significant intraoperative BAEP signs for postoperative hearing loss were:

1. Permanent loss of wave V.
2. Three steps increment of the stimulus intensity to obtain a clearly visible response during the intraoperative recording.
3. Permanent loss of wave V in combination with three-steps increment of the stimulus intensity during the intraoperative recording.

3.8 Difference between patients with postoperative hearing loss and patients with postoperative hearing preservation regarding the thresholds obtained during intraoperative direct recording of cochlear nerve

As explained in chapter 2.2.3.2, the responses were directly recorded from cochlear nerve after removal of the tumor using the ball electrode. The mean of the response thresholds was calculated in patients who experienced postoperative hearing loss and in patients who had postoperative hearing preservation. The mean of the response thresholds in patients with postoperative hearing preservation was 59.78 dBnHL, while in patients with postoperative hearing loss the mean response thresholds was 65.63 dBnHL (Table 8). The difference in response thresholds between the groups was statistically significant (p= 0.021).

Table 8: The descriptive statistics (Range, Mean and Standard deviation (SD) of the response thresholds with ball electrode in patients with postoperative hearing loss and in patients with postoperative hearing preservation

		Postoperative hearing loss		P-value
		No	Yes	
Threshold with the ball electrode	Range	(35-95)	(35-100)	0.021*
	Mean± SD	59.78±14.986	65.63±13.613	

3.9 Determination of the diagnostic ability of intraoperative significant BAEP signs and intraoperative direct recording of cochlear nerve as markers for postoperative hearing loss

To find out how much did each of the significant BAEP signs increase the risk of the postoperative hearing loss, we performed logistic regression analysis (Table 9).

The most significant risk factor of postoperative hearing loss is permanent loss of wave V as it increased the probability of postoperative hearing loss by 18 times (p-value < 0.001). Permanent loss of wave V in combination with three-steps increment of the stimulus intensity increased the probability of postoperative hearing loss by

15.64 times (p-value < 0.001). Three-steps increment of the stimulus intensity during the intraoperative recording increased the probability of postoperative hearing loss by 5.75 times (p-value < 0.001). Finally Each unite increment of the response thresholds obtained during intraoperative direct recording of cochlear nerve increased the risk of postoperative hearing loss by 6.7% (p-value < 0.001).

Table 9: Logistic regression analysis.

	Odds Ratio	95% Confidence Interval	P value
The pattern of loss of intraoperative recorded waves:			
Constant	Reference		
Permanent	18	5.85-55.45	<0.001*
Number of steps increment of the stimulus intensity:			
No	Reference		
Three	5.75	2.2-15.04	<0.001*
Permanent loss in combination with three-steps increment of the stimulus intensity:			
Any	Reference		
Both	15.64	4.52-54.2	<0.001*
The response thresholds obtained during intraoperative direct recording of cochlear nerve	1.067	1.03-1.11	<0.001*

Sensitivity, specificity, positive predictive value PPV and negative predicting value NPP were calculated for each significant intraoperative BAEP sign which had been statistically proven to increase the risk of postoperative hearing loss, as well as for response thresholds obtained during intraoperative direct recording of the cochlear nerve (Table 10). Three-steps increment of the stimulus intensity had the highest sensitivity in detecting postoperative hearing loss (70.18 %), while permanent loss of wave V had the highest specificity in detecting postoperative hearing loss (93.22 %).

Table 10: Diagnostic ability (percentage) of each significant intraoperative BAEP sign and intraoperative direct recording of the cochlear nerve in detecting the postoperative hearing loss (sensitivity, specificity, PPV, NPV and accuracy)

	Permanent loss	**Three steps increment of the stimulus intensity**	**Permanent loss in combination with three steps increment of the stimulus intensity**	**Response threshold with ball electrode**
Sensitivity	56.72	70.18	69.57	77.42
Specificity	93.22	70.97	70	55.56
PPV	90.48	81.63	91.43	66.7
NPV	65.48	56.41	33.33	68.2
Accuracy	73.81	70.45	69.64	67.2

Additionally, ROC curve and AUC were established (Figure 19) to determine the optimal cut off point (optimal obtained intraoperative threshold, at which intraoperative direct recording of cochlear nerve was able to diagnose or exclude postoperative hearing loss correctly). The optimal cut off point of response thresholds obtained during intraoperative direct recording of cochlear nerve was >57.5 dBnHL. The direct intraoperative recording of cochlear nerve had a sensitivity of 77.42 % and a specificity of 55.56% at cut-off point > 57.5 dBnHL.

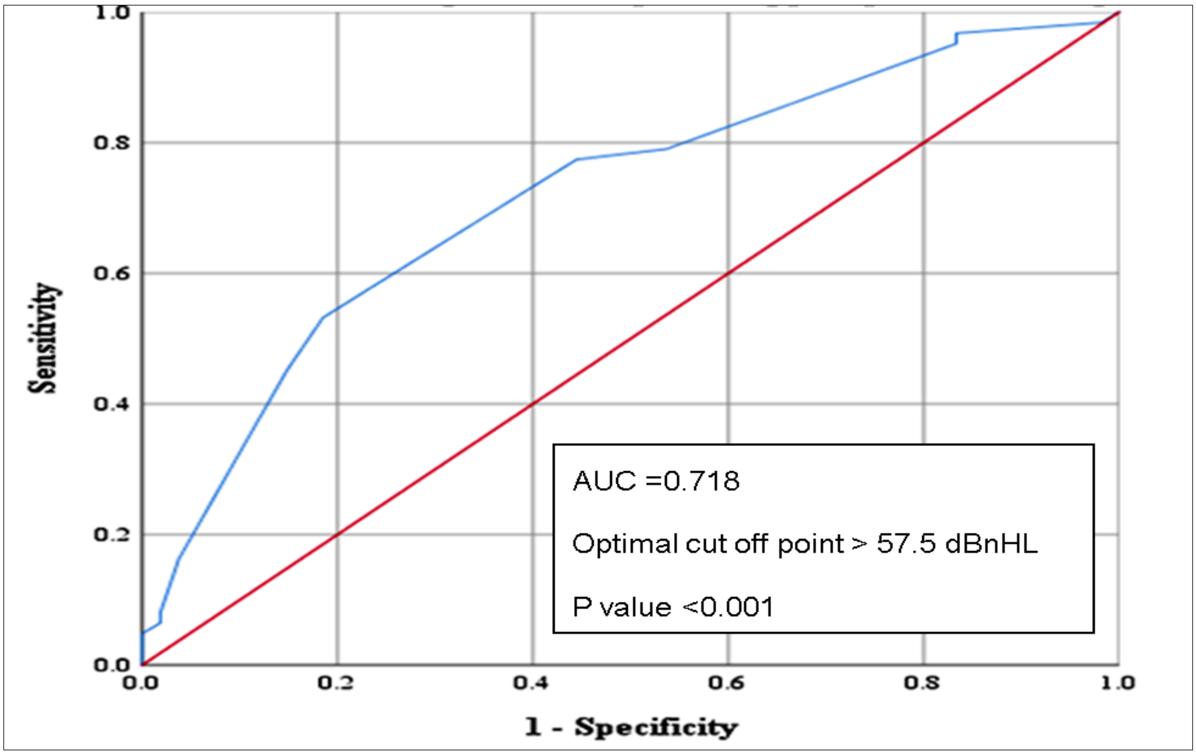


Figure 19: ROC curve and AUC of thresholds obtained during intraoperative direct recording of cochlear nerve.

Table 11: Summary of the analyzed BAEP parameters and different groups.

		Postoperative hearing		Total	P value
		Preservation	Loss		
Latency shift of wave V	≤1	39(46.4%)	45(53.6%)	84	0.815
	>1	30(48.4%)	32(51.6%)	62	
Transient loss of wave V	Constant	55(65.5%)	29(34.5%)	84	0.199
	Transient	10(50%)	10(50%)	20	
Permanent loss of wave V	Constant	55(65.5%)	29(34.5%)	84	<0.001*
	Permanent	4(9.5%)	38(90.5%)	42	

One-step Increment of the stimulus intensity	No	22(56.4%)	17(43.6%)	39	0.072
	Yes	26(76.5%)	8(23.5%)	34	
Transient loss of wave V in combination with one-step increment of the stimulus intensity	Any	32(64%)	18(36%)	50	0.294
	Both	2(100%)	0(0%)	2	
Permanent loss of wave V in combination with one –step increment of the stimulus intensity	Any	30(40.5%)	44(59.5%)	74	1
	Both	0(50%)	1(50%)	1	
Two-steps Increment of the stimulus intensity	No	22(56.4%)	17(43.6%)	39	0.679
	Yes	7(50%)	7(50%)	14	
Transient loss in combination with two-steps increment of the stimulus intensity	Any	15(53.6%)	13(46.4%)	28	0.600
	Both	1(33.3%)	2(66.7%)	3	

Permanent loss in combination with two-steps increment of the stimulus intensity	Any	11(20.4%)	43(79.6%)	54	1
	Both	0(50%)	1(50%)	1	
Three-steps increment of the stimulus intensity	No	22(56.4%)	17(43.6%)	39	<0.001*
	Yes	9(18.4%)	40(81.6%)	49	
Transient loss in combination with three-steps increment of the stimulus intensity	Any	7(16.3%)	36(83.7%)	43	0.055
	Both	6(46.2%)	7(53.8%)	13	
Permanent loss in combination with three-steps increment of the stimulus intensity	Any	7(33.3%)	14(66.7%)	21	0.030*
	Both	3(8.6%)	32(91.4%)	35	
Always at maximum intensity	No	22(56.4%)	17(43.6%)	39	0.737
	Yes	5(50%)	5(50%)	10	

Transient loss of wave V in combination with being always at maximum intensity	Any	13(46.4%)	15(53.6%)	28	0.483
	Both	1(100%)	0(0%)	1	
Permanent loss of wave V in combination with always at maximum intensity	Any	7(16.7%)	35(83.3%)	42	1
	Both	1(20%)	4(80%)	5	

3.10 Surgical steps that caused permanent loss of wave V and required three-steps increment of the stimulus intensity

The percentage of patients with permanent loss of wave V and patients who needed three-steps increment of the stimulus intensity to obtain intraoperative clearly visible waves were calculated at each surgical step to find out which surgical step was mostly responsible for postoperative hearing loss. 82.8% of the patients experienced permanent loss of wave V during the tumor removal and 71.4% patients needed three-steps increment of the stimulus intensity to obtain intraoperative clearly visible waves during the tumor removal (Figure 20).

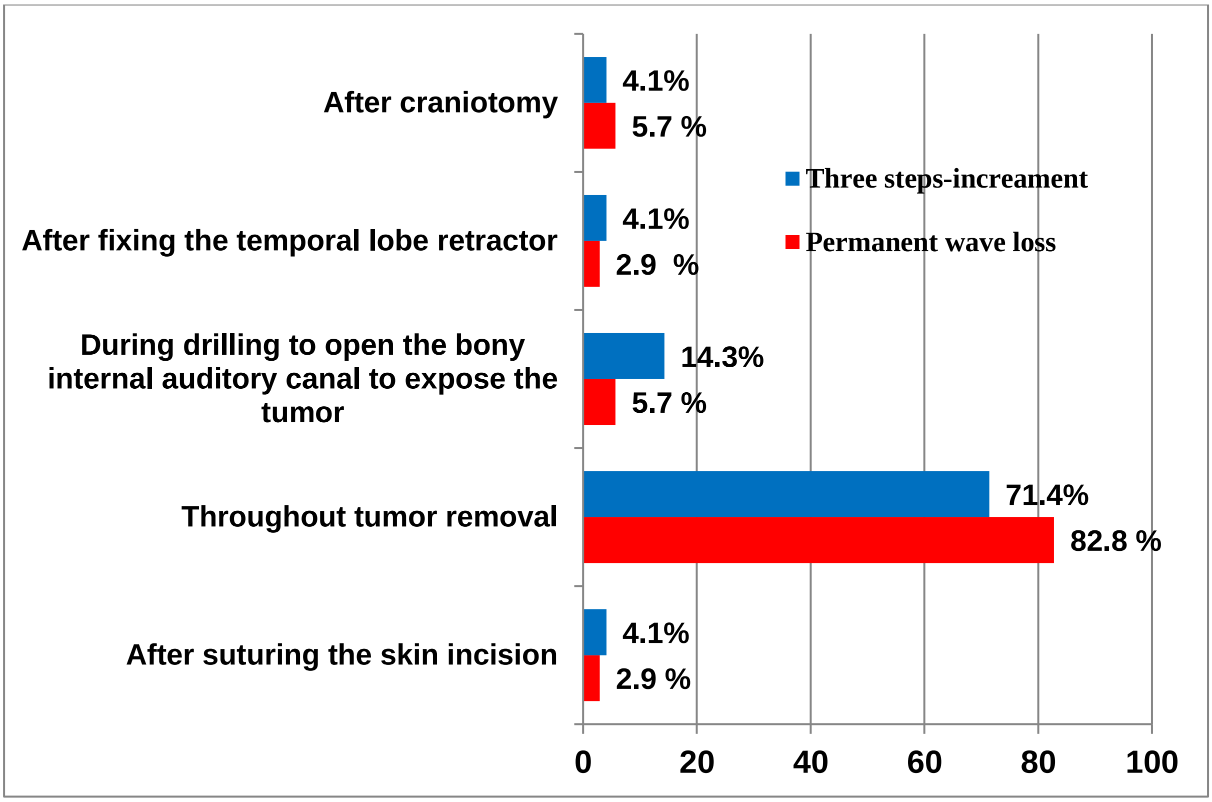


Figure 20: The percentage of patients with permanent loss of wave V and patients who needed three-steps increment of the stimulus intensity at each surgical step.

4. Discussion

In this study, the presence of preoperative residual hearing before transtemporal acoustic neuroma surgery was considered to be one of the selection criteria. The total number of patients was 162, however, a complete set of data was available for 146 patients. 16 patients were excluded because of the failure of intraoperative recording of BAEP waves either due to intraoperative artifacts that interfered with proper identification of BAEP waves or insufficient sensation level to perform the recording because of the presence of severe hearing loss at the frequency range 2-4 kHz preoperatively.

The patients consisted of 82 men (50.6%) and 80 women (49.4%). In our study the incidence of acoustic neuroma was equally distributed in males and females. Studies that included large numbers of patients reported no statistically significant difference in the incidence of acoustic neuroma regarding sex distribution (Gal et al. 2010 and Kleijwegt et al. 2016). However, Samii and Matthies (1997) reported a higher incidence of acoustic neuroma in females.

The age at the time of surgery ranged from 16 to 79 years with a mean age of 52.3 years with a peak incidence in the age group between 51-60 (Figure 1). This agrees with Gal et al. (2010) who examined a total of 1621 patients with a mean age of 53.1 years and Kleijwegt and his colleagues who reported a peak incidence of acoustic neuroma at the age of 55 to 59 years (Kleijwegt et al. 2016).

Regarding the tumor size, this study included small tumor sizes T1 (47.5%) and T2 (52.5%).The tumors of larger extension (T3 and T4) are mainly operated on by the department of neurosurgery using the suboccipital approach. The tumor was located on the right side in 82 (50.6%) of the patients and on the left side in 80 (49.4%) of the patients. No statistically significant difference was observed in the laterality of the tumor which agrees with Inskip et al. (2003).

4.1 Preoperative audiological findings

To determine the hearing function, the patients were examined both preoperatively and postoperatively with a tone threshold audiometry as well as with a speech discrimination test. For proper categorization of the hearing ability of the patients, the collected data were divided based on 2 classification systems (AAO-HNS and

Gardner-Robertson Classification). The majority of the patients had a PTA ≤ 30 dB and a SDS ≥ 70%. This can be attributed to the introduction of MRT which has a high sensitivity and specificity in the early diagnosis of acoustic neuromas (Bonneville et al. 2007).

4.2 The relationship between preoperative and postoperative hearing

Postoperative hearing did not improve in most of the patient as compared to preoperative situation, however, based on the AAO-HNS classification, one patient in class B shifted postoperatively to class A, one patient in class D shifted to class A, two patients in class D shifted to class B and four patients in class D shifted to class C postoperatively. This improvement of hearing can be postulated by the relief of the conduction block caused by the tumor and can be related also to the better vascularization of the cochlea and auditory nerve after surgical removal of the tumor (Kveton 1990 a). Ischemia of the cochlea and auditory nerve, manipulations of the tumor and mechanical injury of the nerve are possible mechanisms that explain hearing loss (Colletti et al. 1997 and Mom et al. 2000).

4.3 Hearing preservation rate

The definition of preservation of hearing in the literature is not consistent. Most of the authors define hearing preservation as pure tone thresholds less than 50 dB HL and speech discrimination scores greater than 50% (Kanzaki et al. 1989). Some authors consider any useful speech discrimination or pure tone thresholds less than 70 dB between 0.5 and 2.0 kHz as preservation (Nadol et al. 1987). Others suggest a classification scheme in which postoperative hearing remains in one of three categories compared with preoperative assessment into: good when the speech reception threshold (SRT) < 30 dB and speech discrimination score (SDS) >70%, serviceable when the: SRT <50 dB and SDS > 50% and measurable when any measurable hearing is present (Shelton et al. 1989).

In the present study, we have a total number of 83 patients out of 162 patients with preserved hearing based on AAO-HNS classification (Figure 12) and 116 patients out of 162 patients based on Gardner-Robertson classification (Figure 13). The hearing preservation rate was higher using Gartner-Robertson classification because

Gartner-Robertson classification depends on the pure tone average of 500Hz, 1 and 2 kHz while AAO-HNS classification depends on the pure tone average of 500Hz, 1 and 3 kHz. The higher frequencies are more susceptible to a hearing loss in acoustic neuroma than the lower ones (Johnson 1977). Reviewing the literature regarding hearing preservation rates, diverging results have been reported: 65 % (Hilton et al., 2011), 63.2% (Kutz et al. 2012), 47.7% (Rabelo de Freitas et al. 2012), 84% (Wang et al. 2013), 44% (Chovanec et al. 2015), and 65% (Scheich et al. 2017). This variation in hearing preservation rates in literature can be due to several factors, one of which is the preoperative hearing level. It is reported that better hearing outcomes are associated with a good preoperative pure tone average at or better than 30 dB with speech discrimination scores better than 70 % (Khrais/Sanna 2006 and Sanna et al. 2004 a). Another predictive factor for hearing preservation after the surgery is the tumor size; the smaller the size of the tumor, the higher the chance to preserve hearing postoperatively (Abramson et al. 1985; Brackmann et al. 2000 and Khrais/Sanna 2006). Moreover, hearing preservation rates differ from one surgical approach to the other, although it is reported that transtemporal approach yielded better hearing preservation rates (Gjuric et al. 2001 and Meyer et al. 2006), some authors reported equal hearing preservation rates in retrosigmoid and transtemporal approaches (Yamakami et al. 2009).

4.4 Effect of the tumor extension on the hearing preservation rate

In the present study, a tendency to higher hearing preservation in patients with T1 is present. This agrees with the report of Scheich et al. (2017) who investigated hearing preservation in 208 patients and reported higher hearing preservation in patients with intrameatal tumors. It is generally accepted that the less the tumor extension, the better the hearing outcome (Jacob et al. 2007; Phillips et al. 2010 and Post et al. 1995). Larger tumors have had more time to compromise the cochlear nerve function either by direct mechanical compression or by impairing its vascular supply. Additionally, the risk of hearing loss in large tumors is associated with the need of longer time to drill the IAC and extensive manipulations to remove the tumor (Phillips et al. 2010).

4.5 Critical warning signs of BAEP during intraoperative monitoring

The results of this study showed that the following intraoperative BAEP signs increased the risk of postoperative hearing loss (arranged in terms from the most critical to the least critical):

1. Permanent loss of wave V as it increased the risk of postoperative hearing loss by 17 times (p-value < 0.001).
2. Permanent loss of wave V in combination with three-steps increment of the stimulus intensity as it increased the risk of postoperative hearing by 14.64 times (p-value < 0.001).
3. Three steps-increment increment of the stimulus intensity as it increased the risk of postoperative hearing by 4.75 times (p-value < 0.001).

In this study, the percentage of postoperative hearing loss in patients with permanent wave V loss was 90.5 %. A similar risk of postoperative hearing loss was reported by Matthies/Samii (1997 b) who reported a 90% risk of postoperative hearing loss in patients experienced intraoperative permanent loss of wave V during surgical resection of acoustic neuroma via subocciptal approach. Park and his colleagues reported the largest percentage of postoperative hearing loss in patients with permanent loss of wave V during intraoperative monitoring of cochlear nerve during microvascular decompression for hemifacial spasm (Park et al. 2018). The high frequency of postoperative hearing loss in patients with permanent loss of wave V could be clarified on the basis of severe damage to cochlear nerve during the operative removal of the tumor.

On the other side, four patients (9.5%) with permanent loss of wave V intraoperatively did not experience postoperative hearing loss. Postoperative hearing preservation in spite of the intraoperative permanent loss of wave V can be explained by the fact that the presence BAEP waves attributed to the proper synchronization of impulses within the auditory pathway rather than the presence of normal hearing (Chiappa et al. 1980). Therefore, normal pure tone audiometry in the presence of BAEP abnormalities occurred in some pathological conditions that lead to dispersion of the click-induced waves as they ascend the affected auditory pathway. During the operation, mechanical manipulations can lead to vascular impairment of the cochlea and auditory nerve, which has been reported to have a negative effect of synchronization of the action potentials that results in an intraoperative permanent wave V loss without postoperative hearing loss (Sohmer et al. 1974). As a result, we conclude that an intraoperative permanent loss of wave V considered as a critical intraoperative BAEP sign that alerts to postoperative hearing loss, however, it is not always a reliable sign in all cases as the BAEP can disappear during the operation due to a synchronization defect and not due to true hearing loss. This can explain also the high specificity (93%) and high PPV (90%) of intraoperative permanent wave V loss as a predictive sign for postoperative hearing loss.

For a detailed analysis of patients’ data who had permanent wave loss, we calculated the frequency of postoperative hearing loss in patients with permanent loss of wave V in combination with one-step, two-steps, three-steps increment of the stimulus intensity or being always at maximum intensity to obtain a clearly visible response during intraoperative recording. A higher rate of postoperative hearing loss (91.4%) in patients with permanent loss of wave V in combination with three-steps increment of the stimulus intensity was found when compared to patients who had permanent loss of wave V alone or who had one of the previous parameters alone. This significance has considerable importance because the combined sign (three-steps increment of the stimulus intensity) can be used to alarm the surgeon before the occurrence of permanent hearing loss.

Regarding transient wave V loss, our date included only 20 patients with transient wave loss; ten of them showed postoperative hearing loss (50%). The absence of significance of the ability of transient wave V loss to predict postoperative hearing may be due to the small number of patients. This may be also due to the fact that during operative removal of the acoustic neuroma the monitoring team alerts the surgeon when they note transient wave loss; the surgeon stops the manipulation while waiting for wave recovery, thus decreasing the risk of postoperative hearing loss in this group of patients. Analysis of patients with transient wave V loss in combination with the number of steps-increment of stimulus intensity was also limited due to the small number of patients with transient wave V loss.

The third factor analyzed in this study was the latency shift of the intraoperative recorded waves; we did not find a statistically significant difference between patients with latency shift >1ms and those with latency shift of 0-1ms regarding the frequency of postoperative hearing loss. The same observation was reported by Phillips et al. (2010). However, James and Husain (2005) considered latency shift of 1 ms to be a significant indicator to postoperative hearing loss. Normal latency of BAEP depends on the presence of auditory fibers that have a normal latency and can generate potentials while the normal BAEP amplitude is achieved by the availability of intact functional ability of whole auditory fibers. If some cochlear nerve fibers were injured, the remaining intact auditory fibers that have normal latency can generate potentials with low amplitude and normal latency. There is strong evidence that the BAEP latency is not the best measure to reflect injury or pathology of cochlear nerve fiber (Hatayama/Moller 1998). Moreover, latency shift during the intraoperative monitoring could occur as a result of fluid collection in the middle ear and mastoid which disappears in most of patients within the first postoperative week (Yamakami et al. 2003).

Finally, the number of steps increment of the stimulus intensity needed to obtain a clear BAEP response was used as an indirect measurement for the amplitude. The percentage of postoperative hearing loss in patients who needed three-steps increment of the stimulus intensity was 81.6% while hearing preservation was possible only in 18.4%. As explained above the amplitude is considered a good indicator for the integrity of cochlear nerve fibers (Hatayama/Moller 1998). Therefore, reduction of amplitude that requires three-steps increment of the stimulus intensity to obtain clear response is expected to be a sensitive sign for postoperative hearing loss.

4.6 Difference between patients with postoperative hearing loss and patients with postoperative hearing preservation regarding the thresholds obtained during intraoperative direct recording of cochlear nerve

The rate of postoperative hearing loss was significantly higher in patients with higher thresholds with ball electrode, which means that thresholds obtained with direct recording of the cochlear nerve are considered to have a predictive role in the determination of postoperative hearing loss. This agrees with several reports that confirmed high sensitivity and specificity of intraoperative direct recording of cochlear nerve in detecting postoperative hearing loss (Danner et al. 2004 and Yamakami et al. 2009). The use of intraoperative direct recording of cochlear nerve has the advantage of high amplitudes (Colletti et al.1998), less amount of artifacts (Yamakami et al. 2002) and shorter duration of recording (Matthies and Samii 1997 a).

4.7 Determination of the diagnostic ability of intraoperative significant BAEP signs and intraoperative direct recording of cochlear nerve as markers for postoperative hearing loss

With respect to the diagnostic ability of intraoperative significant BAEP signs, the need of three-steps increment of the stimulus intensity (as an indirect measurement of the amplitude reduction) was the most sensitive sign to predict postoperative hearing loss, while permanent wave loss was the most specific one. This finding agrees with Park et al. (2018) who reported a specificity of 99% of permanent wave loss in predicting the postoperative hearing loss in the patients with hemifacial spasm, however, he reported higher sensitivity (90%) of combined latency shift of >1 ms with amplitude decrement >50%. This study reported a sensitivity of 70% and a specificity of 55% of intraoperative direct recording of cochlear nerve at a cut-off point > 57.5 dBnHL. Ehrmann-Müller and her colleagues proved a sensitivity of 100% and a specificity of 70% of the direct recording (Ehrmann-Müller et al. 2012). However, Ehrmann-Müller and her colleagues studied a smaller group of patients and divided them based on the detectability of cochlear nerve action potential.

4.8 Surgical steps that caused permanent loss of wave V and required three-steps increment of the stimulus intensity

Manipulation during tumor removal was the most critical surgical step that led to permanent wave loss in 82.8% of patients with permanent loss of wave V and resulted in amplitude reduction of the recorded waves in 71.4% of patients who needed three-steps increment of the stimulus intensity to obtain clearly visible responses. This finding agrees with Hummel et al. (2016) who found that drilling of the internal auditory canal and manipulation of the cochlear nerve caused BAEP impairment in about 37% of the patients. The same observation was done by Gouveris and Mann (2009) who studied the association between intraoperative BAEP obtained during surgical resection of acoustic neuroma and postoperative hearing outcome. They concluded that the amplitude reduction of the BAEP and compound action potentials were reported mainly during tumor dissection and drilling of the internal auditory canal (Gouveris and Mann 2009). Ischemic compromisation and mechanical stretch of cochlear nerve are known causes of hearing loss (Wazen 1994).

5. Summary

In this study, I analyzed the BAEP during intraoperative monitoring as well as the response thresholds obtained during intraoperative direct recording of cochlear nerve aimed at identifying the critical warning signs for a postoperative hearing loss. We performed logistic regression analysis in order to find out how much these signs contribute in the postoperative hearing loss. The significant warning signs for postoperative hearing loss can be arranged from the most critical one to the least critical as follows: 1. Permanent loss of wave V, 2. Permanent loss of wave V in combination with three steps increment of the stimulus intensity and 3. Three steps increment of the stimulus intensity to obtain clear response.

The sensitivity and specificity of each significant intraoperative BAEP sign was calculated. Permanent loss of wave V was the most specific sign while the need of three-steps increment of the stimulus intensity to obtain clear response (an indirect measure of the amplitude reduction) was the most sensitive sign in detecting postoperative hearing loss. However, I conclude that deterioration of wave V in the form of three-steps increment of the stimulus intensity to obtain clear responses can be used efficiently to alarm the surgeon to stop the manipulation for a few seconds before the occurrence of permanent wave loss which was observed to carry the highest risk of postoperative hearing loss.

Regarding the direct recording of the cochlear nerve function, we found that the higher thresholds obtained with ball electrode were associated with higher frequency of postoperative hearing loss. The intraoperative direct recording of cochlear nerve has a sensitivity of 77.42% and a specificity of 55.56% at optimal cut-off point >57.5 dBnHL.

One of the limiting factors in this study was the small number of patients with transient wave loss. I recommend studying transient wave loss as a predicting sign of postoperative hearing loss using a bigger sample.

In conclusion, the critical signs in intraoperative BAEP and direct recording of cochlear nerve during IOM detected in this study may be used as helpful tools to predict postoperative hearing loss in the patients with acoustic neuroma.

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6.2 List of figures

6.3 List of tables

6.4 List of abbreviations

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery classification
AUC	Area Under the Curve
AN	Acoustic Neuroma
BAEP	Brainstem Auditory Evoked Potentials
CNAP	Cranial Nerve Action Potential
CO2	Carbon Dioxide
dB	decibel
dB HL	decibel Hearing Level
dB nHL	decibel Normal Hearing Level
EEG	Electroencephalography
EMG	Electromyography
Hz	Hertz
IAC	Internal Auditory Canal
IOM	Intra Operative Monitoring
kHz	Kilohertz
kOhm	Kiloohm

M1 and M2	Mastoid 1 and Mastoid 2
MRI	*Magnetic Resonance Imaging*
NF2	Neurofibromatosis type II
PTT	Pure Tone Threshold
ROC	Receiver Operating Characteristic
SD	Standard deviation
SDS	Speech Discrimination Scores
SRT	Speech Reception Threshold
SRS	Stereotactic Radiation Therapy

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