Ototoxicité induite par le cisplatine

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" OTOTOXICITÉ INDUITE PAR LE CISPLATINE "

Thèse
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Résumé en français

Introduction

Le cancer est la deuxième cause la plus fréquente de décès dans le monde. Les chimiothérapies anti-cancéreuses sont donc largement utilisées mais sont également connues pour leurs effets secondaires, dont les séquelles à long-terme méritent de plus de plus d'attention. En effet, la population de survivants aux cancers augmente progressivement dans les pays développés. Parmi ces séquelles, l'atteinte de l'oreille interne est un effet collatéral reconnu des chimiothérapies à base de platine, dont la plus répandue est le *cisplatine*, utilisé depuis les années 70' contre les carcinomes pulmonaires, pharyngés, les cancers germinaux et d'autres. L'atteinte dommageable de l'oreille interne par le cisplatine est appelée *ototoxicité*, et se traduit classiquement par une perte auditive neurosensorielle bilatérale prédominant dans les fréquences aiguës, souvent associée à un acouphène. Les méthodologies et les critères d'évaluation étudiant cette ototoxicité dans la littérature médicale sont très hétéroclites et les études à disposition rapportent une incidence de perte auditive induite par le cisplatine variant entre 12,5%-100% chez les enfants et 26-100% chez les adultes. Pour cette raison, une surveillance de l'audition chez les patients devant bénéficier d'un traitement à base de cisplatine est réalisée dans de nombreuses institutions dans le monde, bien qu'il n'y ait pas de standardisation, et ce même en Suisse. Habituellement cependant, une évaluation de l'audition consiste en une consultation médicale par un médecin spécialiste en otorhinolaryngologie, avec un examen des tympans et un test auditif appelé *audiogramme tonal*. A ce jour, bien que certains mécanismes de la perte auditive induite par le cisplatine soient connus, aucune thérapie causale n'est disponible, et seuls l'appareillage auditif et l'implantation cochléaire peuvent partiellement soulager les symptômes.

Objectifs

Dans le département d'Oncologie des Hôpitaux Universitaires de Genève (HUG), environ 110 patients adultes sont traités avec du cisplatine chaque année pour différents types de cancers. Dans ce travail de thèse de médecine, nous avons souhaité obtenir des données épidémiologiques chez ces patients concernant l'ototoxicité induite par le cisplatine. Des informations précises quant à l'incidence et la sévérité de la perte auditive, ainsi que l'identification de candidats potentiels pour de futures thérapies otoprotectrices sont nécessaires à la planification d'études à venir. En effet, différentes pistes thérapeutiques sont actuellement explorées dans le monde, en particulier dans le *laboratoire de l'oreille interne et de l'olfaction* du Professeur SENN au Centre Médical Universitaire de Genève. Dans ce travail, seuls les troubles auditifs sont étudiés, les affections vestibulaires ne sont pas traitées.

Cette thèse rédigée en anglais expose dans un premier temps les rappels anatomiques et physiologiques de l'audition, ainsi que les méthodes permettant son évaluation clinique. La surdité, l'ototoxicité

médicamenteuse et le cisplatine seront ensuite détaillés séparément. Une revue de la littérature médicale relevante concernant l'ototoxicité induite par le cisplatine est présentée. Finalement, le cœur de ce travail est l'étude de l'incidence et de la sévérité de l'ototoxicité induite par le cisplatine chez nos patients aux HUG, ainsi que de leurs potentiels facteurs favorisants.

Méthodes

Une analyse rétrospective des dossiers médicaux des adultes traités avec une base de cisplatine aux HUG de janvier 2015 à janvier 2019 a été effectuée. Seuls les patients ayant bénéficié d'un audiogramme tonal prétraitement, sans radiothérapie concomitante au niveau de l'oreille interne ni médication ototoxique concomitante ont été retenus. Des statistiques descriptives et comparatives ont été réalisées. Une revue de la littérature a également été réalisée avec le moteur de recherche PubMed, en utilisant les mots-clefs *ototoxicity, cisplatin, platinum, hearing loss*.

Résultats

401 patients ont été retenus. L'incidence de perte auditive due au cisplatine était de 20%. Parmi ces patients, 60% ont présenté un acouphène concomitant. La perte auditive était neurosensorielle et atteignait les deux oreilles symétriquement avec une prédominance dans les fréquences aiguës. Aucune perte auditive totale n'a été observée. Aucune des variables analysées comme potentiel facteur favorisant était statistiquement significative. On note cependant une tendance à une incidence augmentée de perte auditive en cas de dose cumulée moyenne de cisplatine plus élevée et chez le sexe masculin.

Discussion

L'incidence de perte auditive lors d'un traitement par cisplatine est élevée, et ce indépendamment du genre, de l'âge et des comorbidités habituelle étudiées. La présence d'un acouphène est hautement suspecte d'ototoxicité chez ces patients et devrait entraîner la réalisation d'un contrôle auditif et une adaptation du traitement si possible, le cas échéant. Les informations de la littérature sont hétérogènes est peu précises. Malgré le caractère rétrospectif de cette étude sous-évaluant probablement la véritable incidence de l'ototoxicité induite par le cisplatine, ces données sur un collectif important permettent une bonne évaluation épidémiologique et peuvent fournir une référence pour des futures études thérapeutiques.

Summary

Introduction

Chemotherapies against cancer are widely used worldwide and are known for their side effects. The damage to the inner ear - called *ototoxicity* - remains a classical collateral effect of platinum derivatives, of which the most widely used compound is *cisplatin*. In this medical thesis, we wish to obtain epidemiological data in our adult patients concerning the ototoxicity induced by cisplatin, in order to plan more precisely possible future studies. Indeed, different therapeutics are currently being explored around the world, and in particular in Professor SENN's *Inner ear and Olfaction laboratory* at the Geneva University Medical Center. In this work, we first remind to the reader the anatomy and physiology of hearing, as well as the methods of its clinical evaluation. Hearing loss, drug-induced ototoxicity and cisplatin will then be detailed separately. A review of the relevant medical literature concerning ototoxicity induced by cisplatin is presented. Finally, the heart of this thesis is the evaluation of the incidence and severity of cisplatin-induced ototoxicity in our patients at Geneva University Hospitals (HUG), as well as their potential contributing factors.

Methods

A retrospective analysis of the medical records of adult patients treated with a base of cisplatin at the HUG from January 2015 to January 2019 was carried out. Only patients with pretreatment tonal audiogram, no concomitant radiotherapy of the inner ear and ototoxic medication were selected. Descriptive and comparative statistics were used. A review of literature was performed using PubMed, with the keywords *ototoxicity, cisplatin, platinum, hearing loss*.

Results

401 patients were collected. The incidence of hearing loss due to cisplatin was 20%. Among these patients, 60% experienced simultaneous tinnitus. Hearing loss was sensorineural, bilateral, and affected the high frequencies. None of the variables analyzed as potential contributing factors were statistically significant.

Discussion

The incidence of hearing loss during treatment with cisplatin is high, regardless of gender, age and comorbidities usually studied. The presence of tinnitus is highly suspect of ototoxicity in these patients and should lead to a new auditory assessment and, if possible, adjustment of chemotherapy. The data in the literature are heterogeneous and imprecise. Despite the retrospective nature of this study probably underestimating the true incidence of cisplatin-induced ototoxicity, these data on a large group allow a good epidemiological evaluation and can provide a reference for future therapeutic studies.

1 Introduction

1.1 Background

Cancer is the second most frequent cause of death world-wide[1], and therefore chemotherapies are also widely used. Apart from being essential to treat patients with cancer, they also have well-known side effects. Drug-induced damage of the inner ear, called *ototoxicity*, is one of the recognized side effects of platinum-derived chemotherapies, commonly used in the treatment of a variety of cancers, such as carcinomas (pulmonary, oropharyngeal), germinal cancers, among others. Symptoms of ototoxicity include temporary and irreversible bilateral hearing loss, tinnitus[2-5] and imbalance. Hearing loss occurs in 12,5-100% in children and 26-100% in adults depending of the studies, representing an important additional burden in this suffering population. For this reason, audiological monitoring at baseline before and during ototoxic chemotherapy is performed in many health care institutions world-wide. However, even in Switzerland audiological monitoring is not standardized and varies from one institution to another.[6] In addition, the results provided from these studies show an important variability with respect to incidence and severity across different institutions (see **Tables 6a** and **6b** at the end). To date, no causative therapy for cisplatin-induced hearing loss is available, and hearings aids as well as cochlear implants only partially alleviate the symptoms.

At the *Inner ear and Olfaction laboratory* at the Geneva's University Medical Center (CMU), headed by Prof. SENN, new otoprotective and preventive strategies are developed to counteract ototoxic insults and chemotherapy-induced hearing loss. Before effective preventive therapies can be tested in clinical settings, a systematic analysis of ototoxicity-induced hearing loss in our institution is an important base to which future preventive therapies can be compared to. In addition, clear numbers in-house will allow to plan potential clinical studies more accurately. In the Oncology Department at University Hospitals of Geneva (HUG), around 110 patients receive cisplatin treatment every year for different kinds of cancer, providing a meaningful base to investigate incidence and severity of ototoxic side-effects and to identify potential candidates for future otoprotective interventions.

In the first part of the present thesis, anatomy and physiology of hearing will be introduced as well as the clinical audiological examinations. In the second part, the existing literature on drug-induced ototoxicity with a special emphasis on cisplatin are reviewed. The core of the thesis will report the incidence and severity of cisplatin-induced ototoxicity (incidence and severity of hearing loss and incidence of tinnitus) in patients treated at HUG, who underwent routinely audiological screening before the onset of a cisplatin therapy, from January 2015 to January 2019. Finally, medical and demographic data will be analyzed to identify potential risk factors for developing hearing loss with cisplatin therapy.

1.2 Anatomy and physiology of hearing

The human ear transforms sound into electrical information, which is conveyed via the auditory nerve to the brain. The ear is classically divided into 3 different parts known as *external*, *middle* and *inner (internal)* ear (**Figure 1**). The inner ear again is composed of two parts, the *cochlea*, responsible for hearing and the *vestibule*, responsible for the sense of balance. In this thesis, the vestibular part of the inner ear is not considered and the remaining text will be exclusively focusing on hearing.

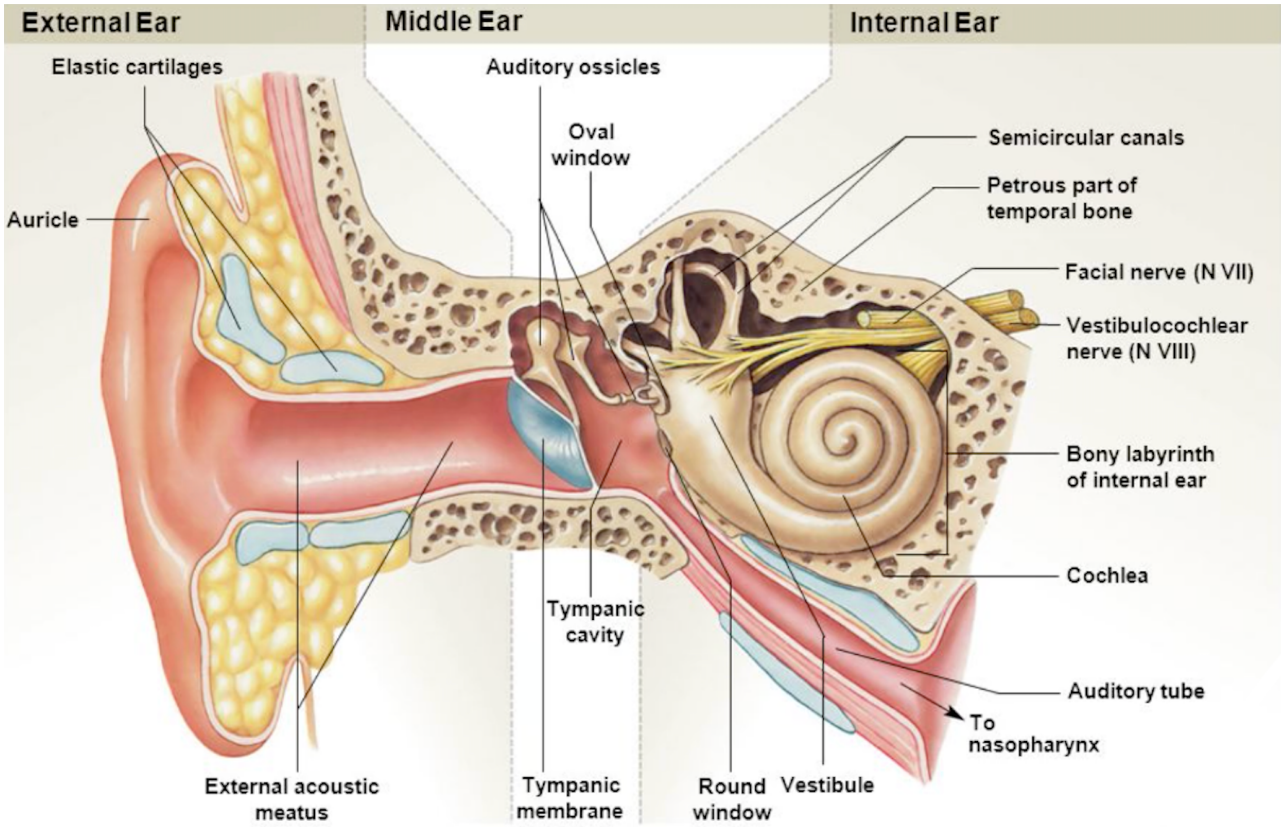

Figure 1: Frontal section of the right human ear, divided into *external*, *middle* and *internal (inner).*

The hearing process is complex and involves a variety of physical, anatomical, biological, physiological and neuropsychological processes, which are detailed below. The external ear captures and amplifies sound waves, mechanical movements of air particles generated by a sound source such as another person speaking, a dog barking or an object falling to the ground. Sound waves are defined by their wave length, amplitude and frequency (**Figure 2**). The human ear can perceive frequencies from around 20 to 20'000 Hz (with individual extremes ranging from 12 to 28'000 Hz under certain conditions).[7, 8]

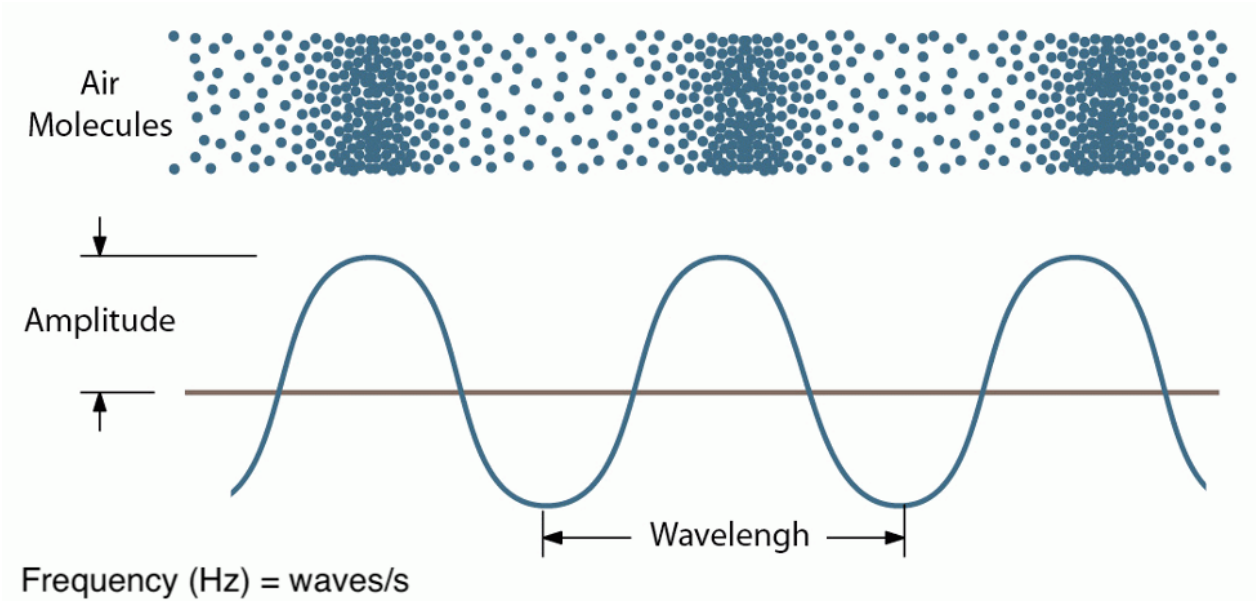

Figure 2: Physics of sound wave.[9]

Sound intensity is measured in decibel sound pressure level (dB SPL), a logarithmic scale that expresses the ratio of the amplitude comparing to a reference level of 20 µPa. For example, during a conversation between two persons in a quiet room, the intensity of the speaker's voice is measured typically around 60 dB SPL, whereas the intensity of a jet airplane's engine close by will be measured at around 130 dB SPL (**Figure 3**).

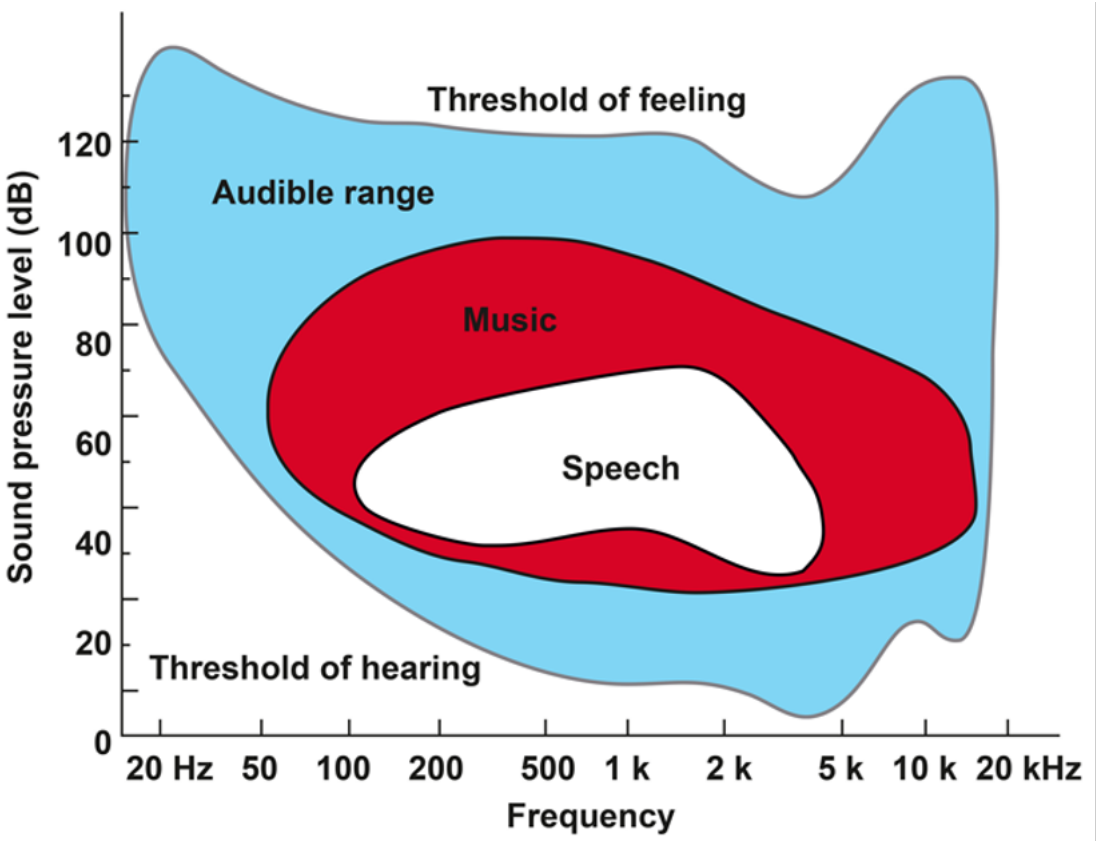

Figure 3: Human audible range of frequencies and intensity.[10]

Due to amplification, filtration and distortion of the sound intensity and spectrum by the structures of the ear, the perception of sound by human is displayed on a logarithmic scale for each tested frequency of the audible spectrum, based on the statistically minimal perceptible sound (mean threshold) in a healthy population, called decibel hearing level (dB HL).

Sound waves collected by the external ear are transmitted through the ear canal and set in motion the eardrum (tympanic membrane), which transfers the vibrations via the ossicular chain of the middle ear into the inner ear. The ossicular chain is composed of three ossicles, called *malleus*, *incus* and *stapes*, the smallest bone in the body, with a diameter of the footplate of around 3 mm and a height of 3 - 4 mm.[11, 12] Here the ossicular vibrations generate movements of the inner ear liquids. These so-called travelling waves propagate along the *basilar membrane* of the cochlea and generate mechanical displacements of the membrane according to the frequency maximums of the sound spectrum (**Figure 4**). The cochlea and its structures are built and organized in a tonotopic pattern, meaning that high frequencies are coded at the base of the cochlea and low frequencies at the apex. The *organ of Corti* is the mechano-sensory organ of the inner ear and is constituted by a well-organized mosaic of sensory hair cells and their surrounding supporting cells. Whereas the *outer hair cells* are mainly responsible for selectively amplifying the mechanical movements of the basilar membranes and thereby increasing the sensibility of the organ, the *inner hair cells* are responsible to transduce mechanical movements of their hair bundles into electrical signals, which are then sent through the auditory nerve towards the brain and there perceived as sound (**Figures 5a** and **5b**).

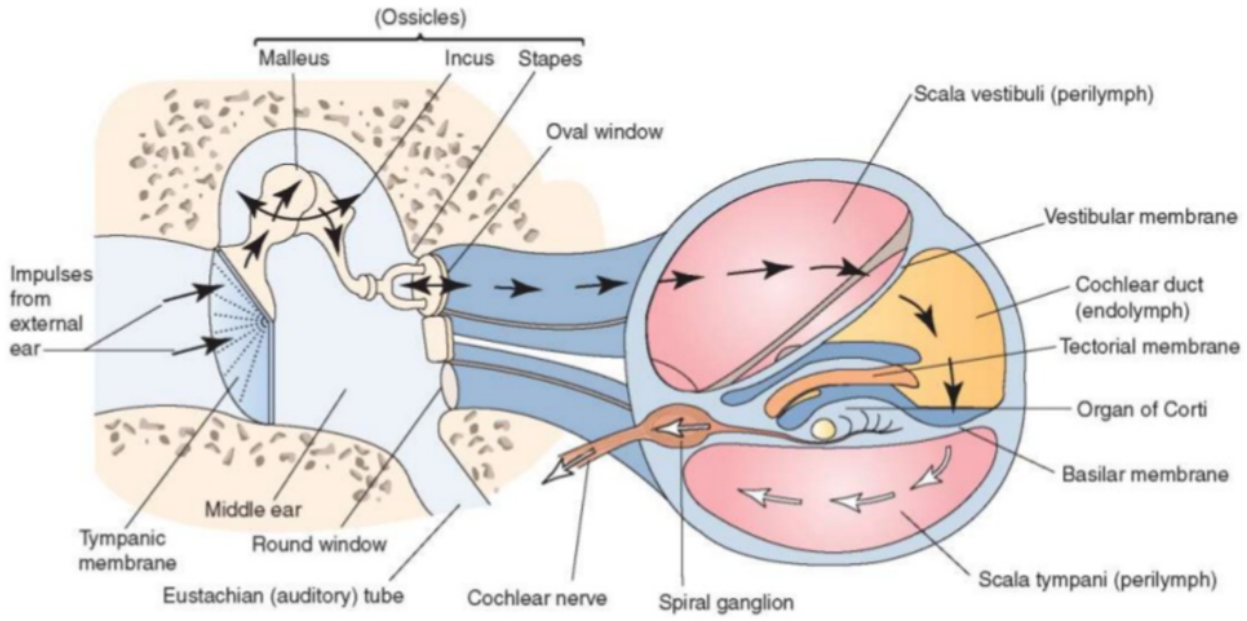

Figure 4: Transduction of sound in a frontal section of the right human ear: air waves are transmitted from the auditory canal to cochlear nerve, via the eardrum, the ossicles, the inner ear liquids and the hair cells of the organ of Corti.[13]

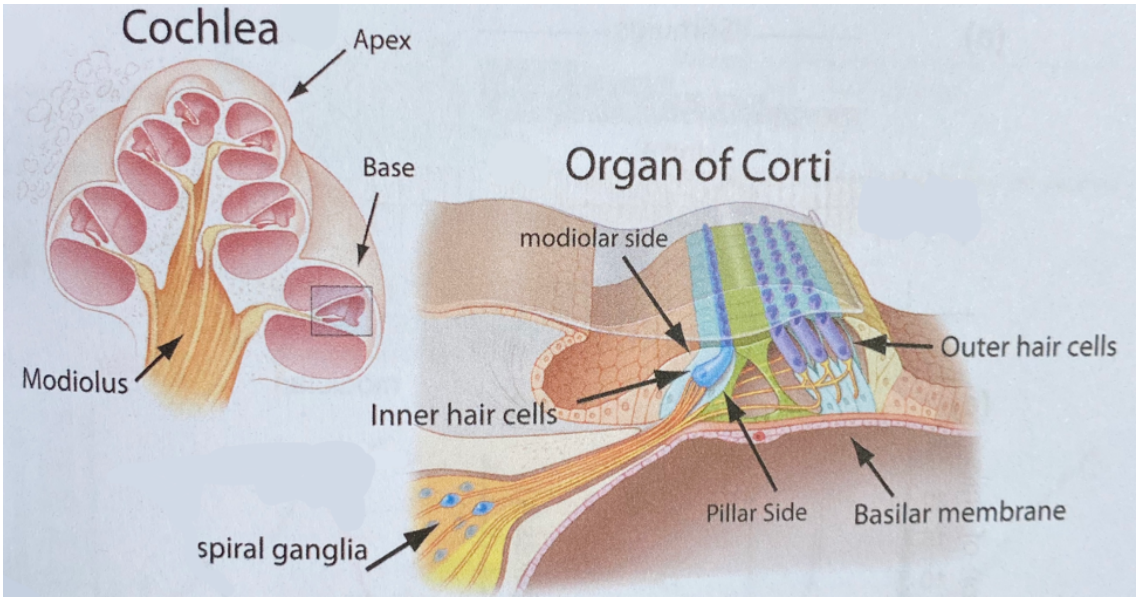

Figure 5a: Magnified view of the organ of Corti with the cochlea: the heart of hearing process.[14]

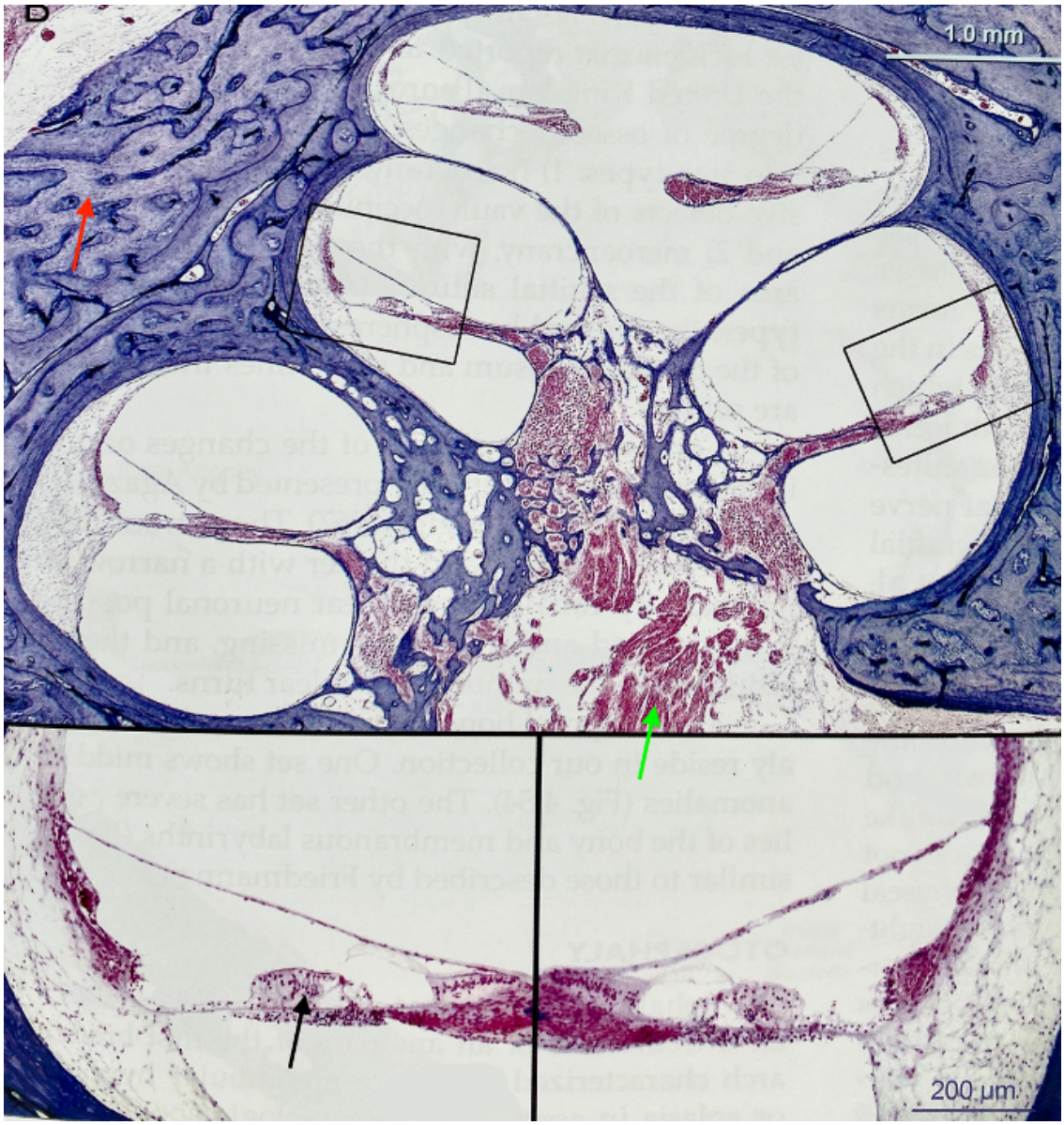

Figure 5b: Histological sections of the human cochlea with the organ of Corti (black arrow), the cochlear nerve (green arrow) and the surrounding bone (red arrow).[11]

1.3 Clinical assessment of hearing

The evaluation of the anatomical structures involved in hearing and the hearing acuity in a clinical or research setting at the public or private institution has to be done by a team of well-trained healthcare professionals. In our service for otorhinolaryngology (ORL) at HUG, the assessment typically involves a trained audiometry technician and a medical doctor specialized or specializing in ORL under supervision of a senior staff medical or an engineer. A full medical exam of the hearing system starts with the assessment of the detailed ORL and otological history followed by an ORL medical exam. Actual ORL problems, specific hearing problems (hearing loss) or the presence of tinnitus (phantom sound subjectively perceived in absence of an external sound source) will be addressed and also prior ORL and specific ear diseases or surgeries will be evaluated and noted into the patient's file. A careful examination of the ear is then performed with an otoscope or microscope (**Figure 6a**), assessing external ear canal integrity and tympanic membrane condition (**Figure 6b**).

Figure 6a: Examination of a patient's right ear under the microscope. The subject consented to the use of this photograph.

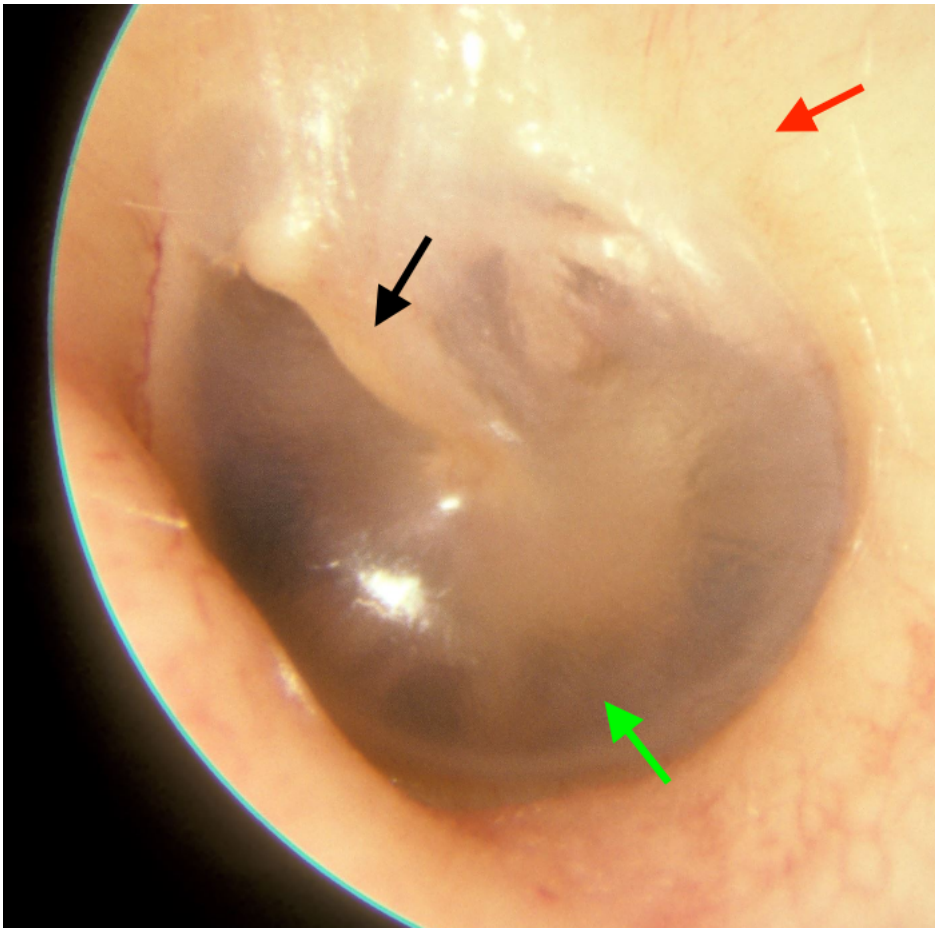

Figure 6b: Microscopic view of a normal left tympanic membrane (green arrow), with bony ear canal (red arrow) and malleus manubrium seen through (black arrow).[15]

Each ORL resident can himself perform a rough clinical judgement on a patient's ability to hear by using a tuning fork (440 Hz or 512 Hz) and his own voice by whispering, speaking or shouting numbers at a given distance from a patient's ear and requesting the patient to correctly repeat the numbers heard. Despite being far from accurate, a first judgement can be obtained quite rapidly and inexpensively. Proper tonal and vocal audiometry is performed to assess hearing in a validated sound-treated chamber using calibrated, professional equipment and trained personal (**Figure 7a**). *Tonal audiometry* measures pure tone hearing thresholds in dB HL at different frequencies ranging from 125 Hz to 8000 Hz in each ear. The hearing threshold is plotted against a background of the hearing thresholds of normalized, healthy controls (**Figure 7b**). To assess vocal discrimination, the patient hears lists of calibrated words and numbers at different intensities and is asked to repeat them. The scores are plotted against normative data of healthy controls in the background and are displayed as percentage of 100% (**Figure 7c**).

Figure 7a: Audiometric examination of a patient in the quiet chamber. The subject consented to the use of the photograph.

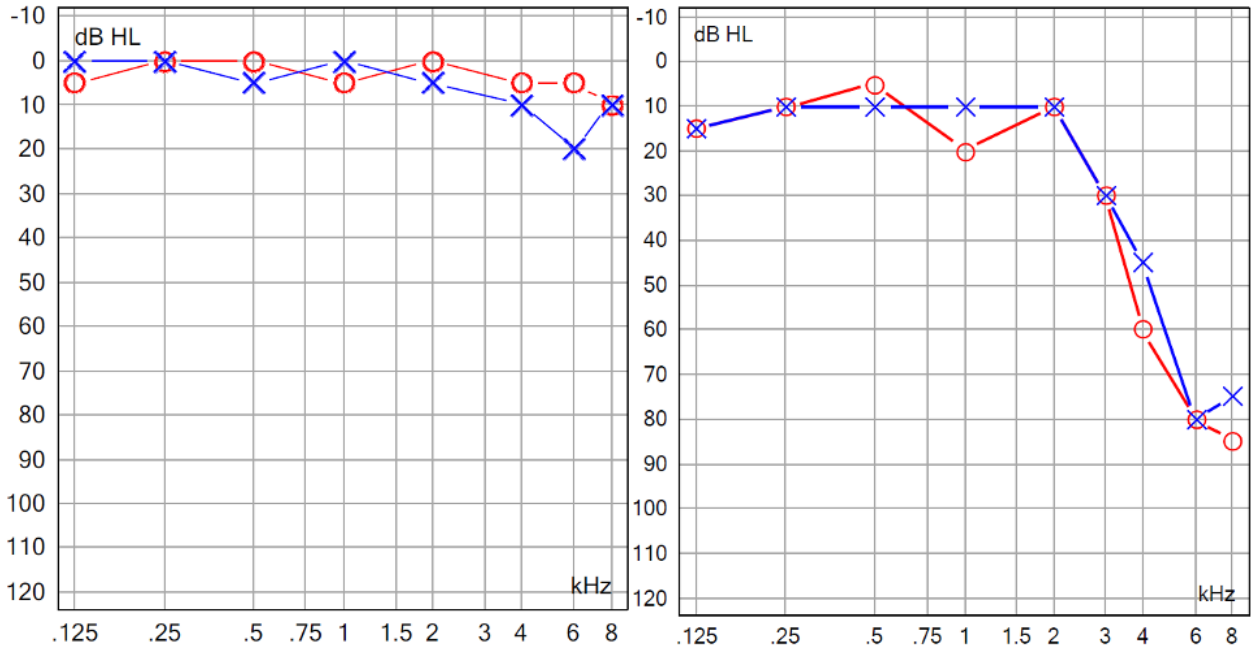

Figure 7b: On the left, tonal audiogram of a 32-year-old man with normal hearing (right ear in red, left ear in blue). On the right, symmetrical threshold elevation in the high frequencies of a 69 years-old man, corresponding to age-related hearing loss.

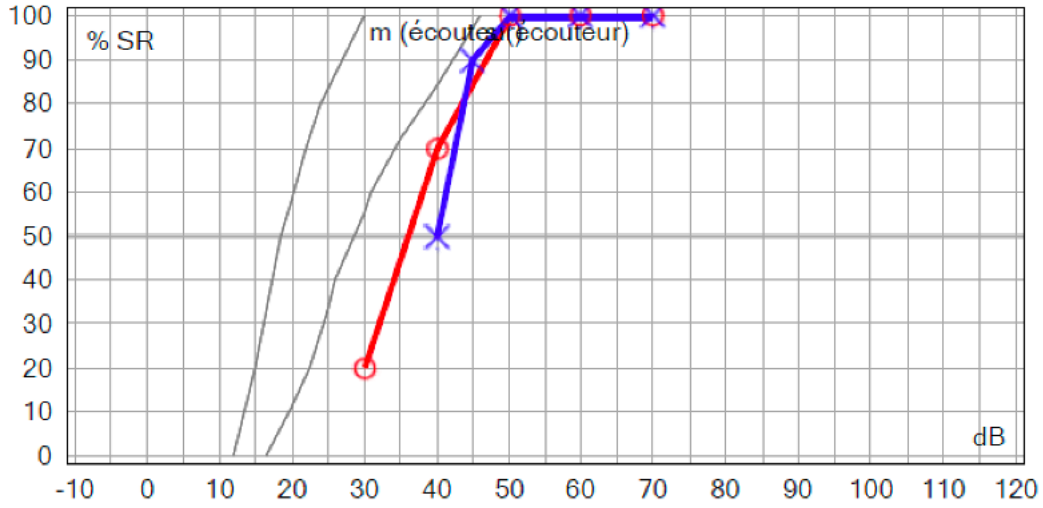

Figure 7c: Vocal audiogram of a 27-year-old woman with normal hearing (right ear in red, left ear in blue). 50% of words are understood at 35 dB HL and 40 dB HL on the right and left side respectively.

Additional routinely performed examinations include the testing of *otoacoustic emissions* (OAE), which objectively detect cochlear-produced sounds in response to an acoustic stimulation[16], reflecting the function of the cochlear amplifier. At the cellular level, the selective and active movements of the outer hair cells produce a sound that can be amplified and measured by a probe inserted into the ear canal (**Figures 8a** and **8b**). Because this test doesn't require active participation of the subject, it can be easily performed in patients who are not able to cooperate and is therefore particularly useful in newborns and children. In Switzerland nowadays, around 98% of newborns receive a screening of their hearing function in the first days after birth in order to detect and treat hearing loss as early as possible (**Figure 8c**).[17] Despite this advantage linked to the ease-of-use and the rapidity, OAE testing only mostly provides information, whether peripheral functional hearing in frequencies between 1000 and 4000 Hz is present or absent. Any hearing loss greater than 40 dB HL cannot be assessed using this method. To estimate a hearing threshold objectively beyond 40 dB HL, *auditory brainstem response* (ABR) measurements have to be performed. They are electroencephalographic recordings of electrical responses of the ascending auditory pathway and its different synaptic relay nuclei in the brainstem (**Figure 9**). Just like the OAE, ABR measurements are used to assess hearing in difficult-to-test populations such as young children.[18]

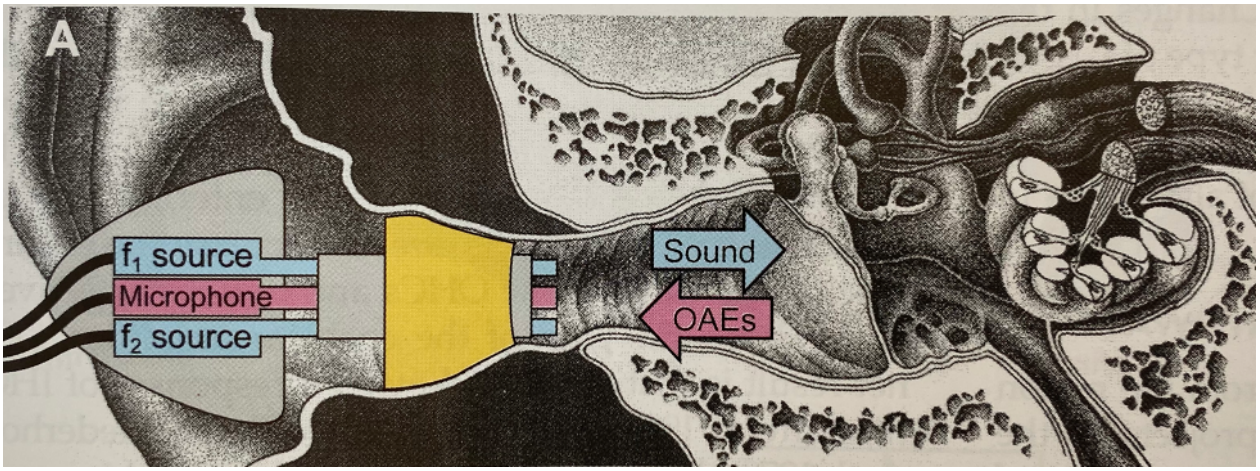

Figure 8a: Probe (yellow) air-sealed in the right acoustic canal for measurements of otoacoustic emissions (OAE).[19]

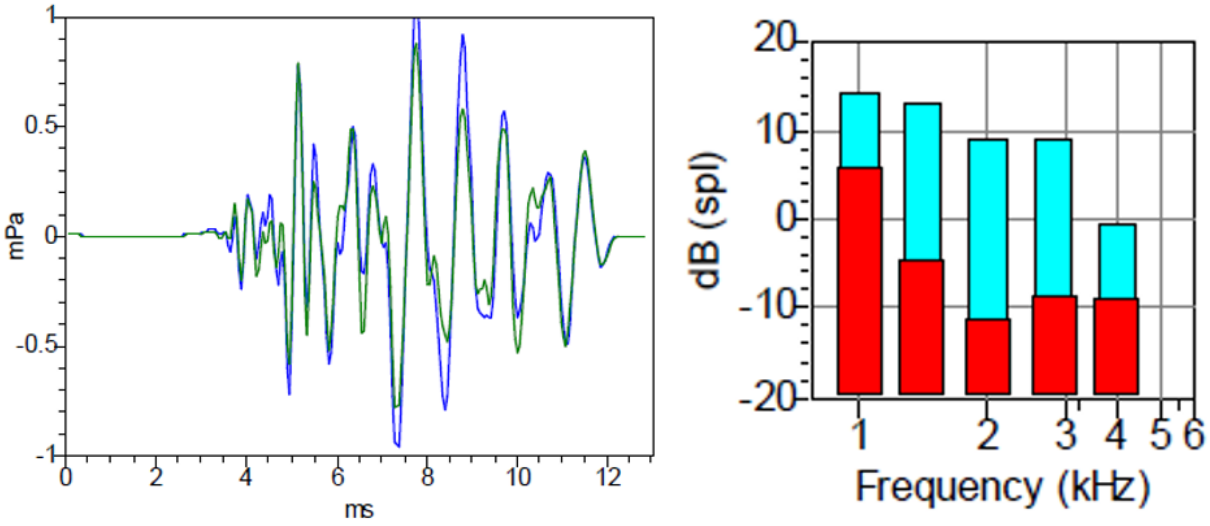

Figure 8b: Transient evoked otoacoustic emissions (OAE) with normal response by a 32-year-old man. On the left the sound pressure waveform in sealed ear canal after click stimulus. On the right the amplitude of recorded sound (blue) out of ambient noise (red) at different frequencies stimulus.

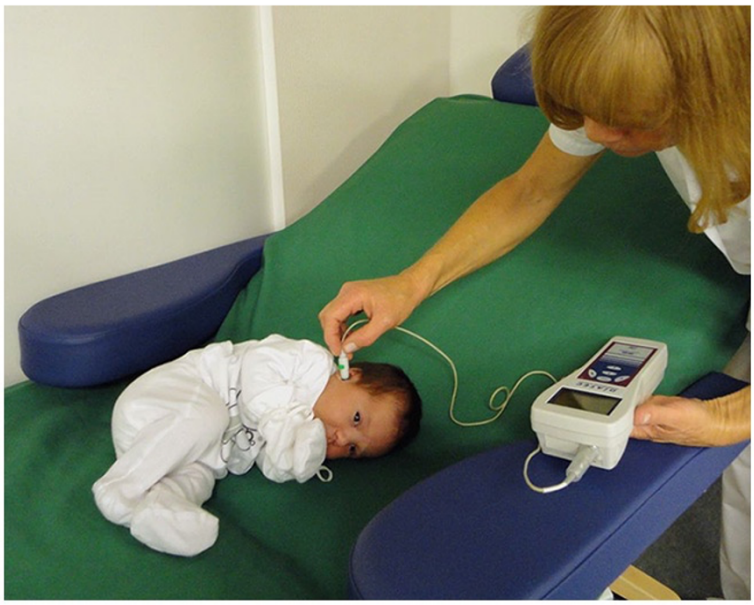

Figure 8c: Hearing screening of the right ear with otoacoustic emissions in a newborn.[17]

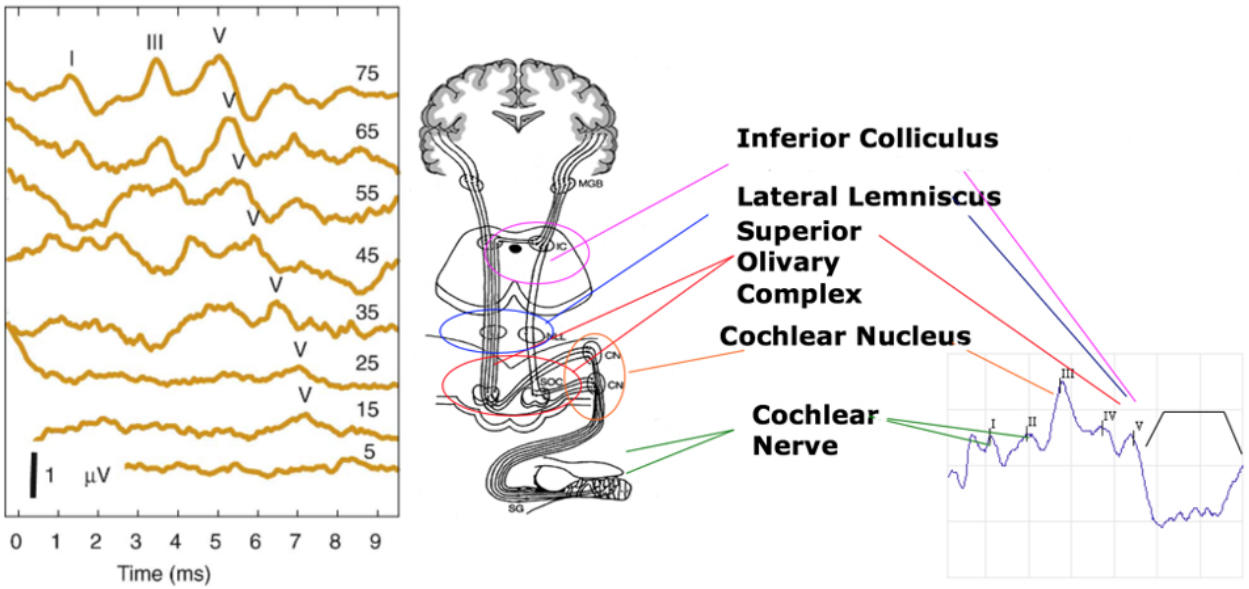

Figure 9: On the left, auditory brainstem response (ABR) from a normal-hearing patient. Wave V is the last to be reckonable at low intensity of sound.[18] On the right, correspondence between ABR waves and neural activity from synaptic relays in nuclei along the ascending auditory pathway.[20]

Finally, *impedancemetry* measurements explore middle-ear function with help of a sealed probe in the ear canal. It comprises *tympanometry* and *stapedial reflexes* measures. Tympanometry provides information about maximal compliance of tympanic membrane, by measuring the acoustic energy reflected during air pressure variations. Stapedial reflex measurements explore the changes in the compliance of eardrum when reflex contraction of stapedial muscle is elicitated by a pure tone noise between 70 – 100 dB SPL. It measures threshold and latency of the acoustic reflex (**Figure 10**).[18]

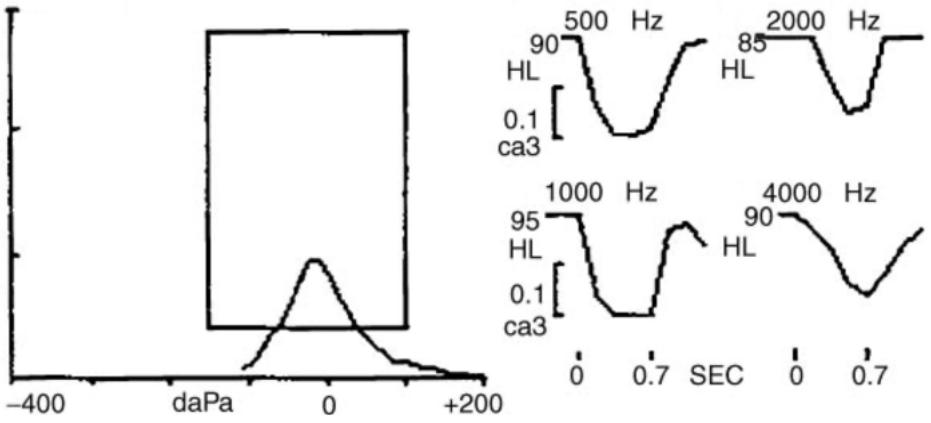

Figure 10: On the left, normal tympanogram with symmetrical air pressure from either side of eardrum. On the right, normal stapedial reflexes elicitated at different frequencies.[21]

1.4 Hearing loss

As indicated above, by measuring the hearing thresholds, automatically a comparison to the averaged thresholds of normal-hearing young controls is displayed. The World Health Organization (WHO) defines hearing impairment or hearing loss if the average hearing threshold of the tested individual goes beyond

an intensity of 25 dB HL at the frequencies of 0.5, 1, 2 and 4 kHz in the better ear. Hearing loss is classified into the categories *mild*, *moderate*, *severe* or *profound* (deafness) (**Figure 11**).[22]

Impairment	Hearing thresholds in better ear (averages of values at 500, 1000, 2000, 4000 Hz)	Performance
None	≤ 25 dB HL	Whispering voice understood
Mild	26-40 dB HL	Whispering voice well understood at 1 m
Moderate	31-60 dB HL (child) 41-60 dB HL (adult)	Normal voice well understood at 1 m
Severe	61-80 dB HL	Shouting voice partially understood
Profound	> 80 dB HL	Shouting voice not understood

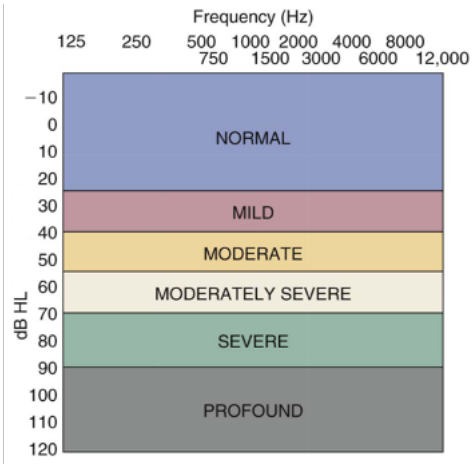

Figure 11: On the left, hearing impairment categories according to World Health Organization (WHO)[22], with ranges represented on an audiogram on the right.[18]

Hearing loss can affect one ear or both, be transient or permanent, congenital or acquired. Depending on the anatomical location of the causal problem, hearing loss is categorized as *conductive*, *sensorineural* or *mixed*. Conductive hearing loss is defined by the impossibility for the soundwaves to reach the inner ear liquids, thus concerning the outer and middle ear. Different etiologies can destroy or seal the anatomical passage from the external ear canal to stapedial footplate, such as ear wax, exostoses, traumatic scaring, acute, chronic or serous otitis media, cholesteatoma, otosclerosis, among others. Sensorineural hearing loss is due to a malfunction in the inner ear, auditory nerve or central auditory pathways. Etiologies causing sensorineural hearing loss include age-related hearing loss, congenital malformations, genetic diseases, noise traumatism, infections (viral, bacterial, fungal, prion-related), vascular lesion (ischemia, hemorrhage), tumors, drug-induced toxicity which will be extensively addressed in this thesis, chemical-induced toxicity, Menière's disease and auto-immune diseases. Mixed hearing loss is a combination of conductive and sensorineural hearing loss, for example the combination of conductive hearing loss due to a perforated ear drum in chronic otitis media and sensorineural hearing loss due to the inner ear damage caused through the same chronic ear infection.

Congenital hearing loss is observed in around 1-2 children per 1000 born in developed countries.[23] In developing countries, the prevalence is estimated to be around 19-24/1000.[24] Etiologic causes comprise genetics (syndromic or not), infection (cytomegalovirus, rubella, syphilis, zika virus)[24], birth asphyxia, drugs, severe jaundice[25] and malformation. Acquired hearing loss is the life-time most frequent etiology and the leading cause is age-related hearing loss – or *presbycusis*. A study on world burden of disease in 2017 ranked age-related hearing loss at 5th world leading cause of disability, and it is increasing.[26]. Presbycusis is a multifactorial degenerative disease with a prevalence of 59-73% in population over 70 years old, affecting less females and black race.[27] The hearing impairment in presbycusis is progressive, exponential,

symmetrical and typically affects high frequencies. The risk of developing presbycusis is cumulative with other causes, such as noise exposure, comorbidities and medication.[28]

In 2019, the WHO stated that over 5% of the world's population (466 million people) suffers from *disabling* hearing loss, among them 7% of children. The majority of affected individuals is living in low- and middle-income countries.[25] This number underestimates hearing impairment in the general population, considering that the WHO defines *disabling* as hearing levels as high as 35 dB HL or more in the better ear for children and 40 dB HL for adults. Hearing impairment is mostly mild, increases exponentially with age and is higher among males than females.[29] Hearing loss is a world-wide public issue with substantial costs, affecting learning of language and being associated with lower academic achievement and fewer job opportunities.[30] Individually, in adults, effects of hearing loss with time can impair social interactions, accelerate physical decline, affect emotional well-being, correlate with cognitive decline and thus, impact independence.[31] Even mild and moderate hearing loss can affect communication skills and learning abilities. In children, the risk is to miss critical developmental periods with direct consequences on educational performances.[32] Therefore, hearing loss during childhood has more serious consequences, even if it is far less common compared to adulthood prevalence.

1.5 Drug-induced ototoxicity

The inner ear and more generally the hearing function are known to be sensitive to surgery[33], tumors[34], ionizing radiations[35] and certain drugs.[36] When side-effects of drugs impair hearing (cochlear effect) and/or balance (vestibular effect), the phenomenon is called *ototoxicity*. The first medical mention of drug-induced damage of hearing, or ototoxicity, dates from 11th century and concerned mercury vapors. Other reports on ototoxic side-effects followed: in 1843 quinine was described, then Salicin in 1877 and more drugs were linked to hearing loss, particularly after 1960.[37] Mechanisms of ototoxicity differ depending on the molecules, including biochemical and metabolic changes, reduction of blood flow, but sometimes the exact mechanism is unknown.[36]

Commonly used systemic drugs with ototoxicity are described according to their ototoxic potency in **Table 1**. One should mention that even topical drops can be ototoxic in case of permeability of the eardrum, because of passive and active passage through the round window (chlorhexidine, aminoglycosides, chloramphenicol)[38, 39], as well as through the oval window and bony otic capsule.[40] This mechanism is for instance used to purposely suppress the vestibular function with transtympanic aminoglycosides injection in selected patients with *Menière's disease*, a chronic inner ear condition associating episodes of vertigo, tinnitus and hearing loss.[41]

Table 1: Ototoxic drugs are classified according to their ototoxic potency, with a summary of the main ototoxic characteristics of each compound. Legend: +++ often, ++ sometimes, + rare, (+) very rare.

Drug	Ototoxicity	Characteristics
Aminoglycosides[42, 43]	+++	Up to 41%, permanent
- *Amikacin*		
- *Gentamicin*		
- *Kenamycin*		
- *Neomycin*		
- *Netilmicin*		
- *Paromomycin*		
- *Spectinomycin*		
- *Streptomycin*		
- *Tobramycin*		
Platinum derivatives	+++	At least 20%, permanent
- *Cisplatin*		
- *Carboplatin*		
Deferoxamine[44]	+++	Around 20%, partial reversibility
Salicylates[45, 46]	++	Dose-related and reversible, but rare nowadays[47]
Non-steroidal anti-inflammatory drugs[48, 49]	+	
Macrolides[50]	+	Dose-related, mostly reversible
- *Erythromycin*		
- *Azithromycin*		
- *Clarithromycin*		
Loop diuretics[51]	+	Reversible or permanent. Potentiate aminoglycosides' ototoxicity
- *Furosemide*		
- *Ethacrynic acid*		
- *Bumetanide*		
Antimalarials[36, 52, 53]	+	Mostly reversible
- *Quinine*		
- *(Hydroxy)chloroquine*		
Cyclophosphamide[54]	+	
Nitrogen mustard[55]	+	
Bleomycin[55]	+	
Estrogens[56]	(+)	
Interferon-α[57]	(+)	
Cocaine[58]	(+)	
Phosphodiesterase-5 inhibitors[59]	(+)	
Polymyxin[60]	(+)	
Chloramphenicol[39]	(+)	
Vancomycin[61, 62]	(+)	
Vinca alkaloids[63]	(+)	
- *Vincristine*		
- *Vinblastine*		
- *Vinorelbine*		

1.6 Cisplatin

According to WHO, cancer is the second most frequent cause of death worldwide (9,6 million human deaths in 2018), 70% of which occur in low- and middle-income countries. Tobacco use is the most important single risk factor, responsible for 22% of cancer deaths.[1] In Switzerland, cancer is the first most frequent cause of death in males and the second most frequent cause in women[64], as well as the most frequent cause of years of potential life lost.[65] In developed countries, the population of cancer survivors grows with time (e.g. in Switzerland[66] or in USA), because of both aging of the population and advances in early detection and treatment.[67] Therefore, management of long-term sequelae of cancer disease as well as side-effects related to their treatment (such as nausea, anorexia, diarrhea and hair loss[68]) become more frequent and important. Chemotherapies involve anti-cancer drugs and are used alone, or in combination with radiotherapy and/or surgery, depending of the cancer type and staging. They are well-known for their toxic side effects, inherent to their cytotoxic nature. These side-effects may be significantly underreported, considering they are reported in literature by clinicians rather than by patients themselves.[68] This is especially true for hearing loss, considered as an "invisible condition". Indeed, hearing loss in the high frequencies are not always easily recognizable by patients, and are often subjectively less symptomatic compared to other, more prominent side effects such as loss of hairs, sickness of mucosa, neuropathy and others.

Platinum (Pt) is a chemical element belonging to the precious metals. *Cis-diamminedichloroplatinum(II)* $[Pt(NH_3)_2Cl_2]$, or *cisplatinum,* or *cisplatin*, originally known as *Peyrone's Chlorid*, is an active complex of platinum that was first synthesized by Michele PEYRONE in 1844.[69] Inhibition of cell division in Escherichia Coli by the electrolysis products of platinum was accidentally observed in 1965.[70] Its anti-tumor properties were acknowledged in animals in 1968, the first human patient was treated in 1971 and the authorization for clinical human use in the USA was granted in 1978.[71] It is one of the most effective anticancer agents used against solid tumors[72] and has been incorporated to the WHO's list of "essential medicines".[73] Thousands of chemical analogues have been synthesized and tested, with different toxicity and efficacy, but only 13 of these have been evaluated in clinical trials. Among them, only *carboplatin* has achieved evidence of an advantage over cisplatin in terms of limiting certain side effects (especially hearing loss).[71, 72] To a lesser extent, *oxaliplatin* has proved to have a superior efficacy in digestive cancers[74] and shows no ototoxicity.[75] Both are also considered by WHO as essential medicines.[73]

Cisplatin is applied intravenously (alone or in combination with other agents) against lung cancer (especially small cell variant), ovarian cancer, head and neck squamous cell carcinoma, breast cancer, testicular cancer, uterus cancer, ovarian cancer, bladder cancer, refractory non-Hodgkin's lymphomas, recurrent childhood brain tumors, osteosarcoma, hepatoblastoma, gastric cancer, anal cancer and leukemia.[72, 76] A synergistic

effect with different molecules has been described[72]. Platinum-derivates have also a radiosensitization effect, thus potentializing radiotherapy.[77]

The mechanism of cytotoxicity of cisplatin is explained by DNA damaging, as well as DNA synthesis and mitosis inhibition. Molecular mechanisms include reactive oxygen species production, lipid peroxidation, induction of p53 signaling and cell cycle arrest, down regulation of protooncogenes and anti-apoptotic proteins, and activation of intrinsic and extrinsic pathways of apoptosis (**Figure 12**).[72]

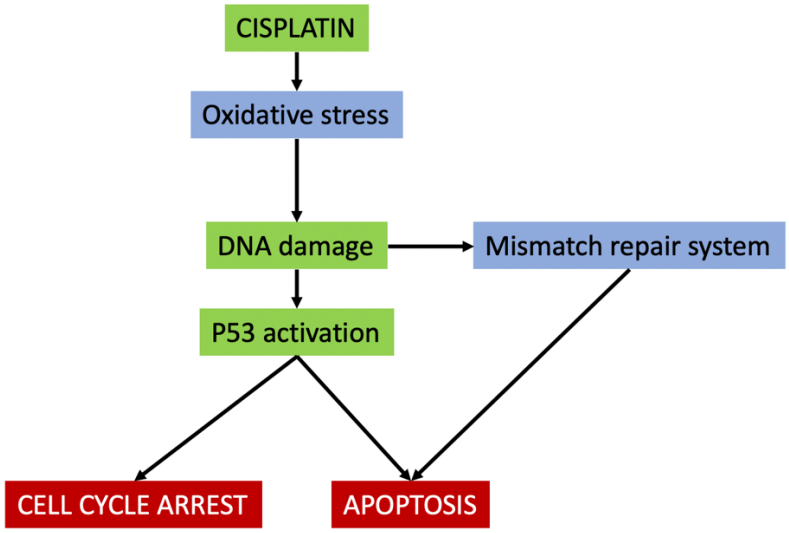

Figure 12: Molecular mechanisms of cisplatin cytotoxicity (simplified from [72]).

Because of the intrinsic cytotoxic properties of cisplatin, it is widely associated with toxic side-effects in different organs and tissues. Although cisplatin is mostly excreted in urine[78], probable storage organs exist, because plasmatic detection can be positive up to 20 years after treatment[79]. Post-mortem studies have shown long-term platinum accumulation in liver, uterus, testes, ovary, thyroid[80] and of particular interest for this thesis, in the cochlea.[81] The long-term pharmacokinetic is largely unknown but circulating cisplatin after therapy correlates with cumulative dose and renal function before and after treatment. Late adverse effects exist[82], especially the severity of neurotoxicity (including ototoxicity) is correlated with the long-term serum platinum level.[83] Over 40 years of experience in medical use with cisplatin have brought extensive knowledge of its adverse effects, such as nausea, nephrotoxicity, neurotoxicity, cardiotoxicity, hepatotoxicity, gastrotoxicity, myelosuppression, allergic reaction and finally ototoxicity.[72] As an example, nephrotoxicity is managed by hydration during administration of cisplatin-based therapy[78] but to date, no preventive drug or measure is validated against ototoxicity.

Cisplatin-induced ototoxicity typically induces mostly bilateral, symmetrical, irreversible sensorineural hearing loss, affecting primarily the high frequencies (**Figures 13a** and **13b**), often occurring in combination with tinnitus.[35] The latter can occur transiently or permanently, also without the presence of hearing loss.

Cumulative dose, number of cycles administered, method of administration (bolus, continuous) and impaired renal function influence the incidence and severity of cisplatin-ototoxicity.[84, 85] Genetic susceptibility may be an important factor, data are however controversially discussed.[76] Noise exposure, concomitant other chemicals and ototoxic drugs can potentiate cisplatin-induced hearing loss.[84] In the oncological context, it is important to note that radiotherapy – another free-radical inducing therapy – in fields including the inner ear can induce sensorineural hearing loss in up to one-third of patients.[86] Interestingly, literature suggests a predisposing role of melanin in the context of cisplatin ototoxicity.[87] At the cellular level, cisplatin-related ototoxic mechanisms include excessive generation of reactive oxygen species (ROS) with consecutive cochlear inflammation, causing apoptosis of outer hair cells, inner hair cells, stria vascularis, and spiral ganglion neurons.[88]

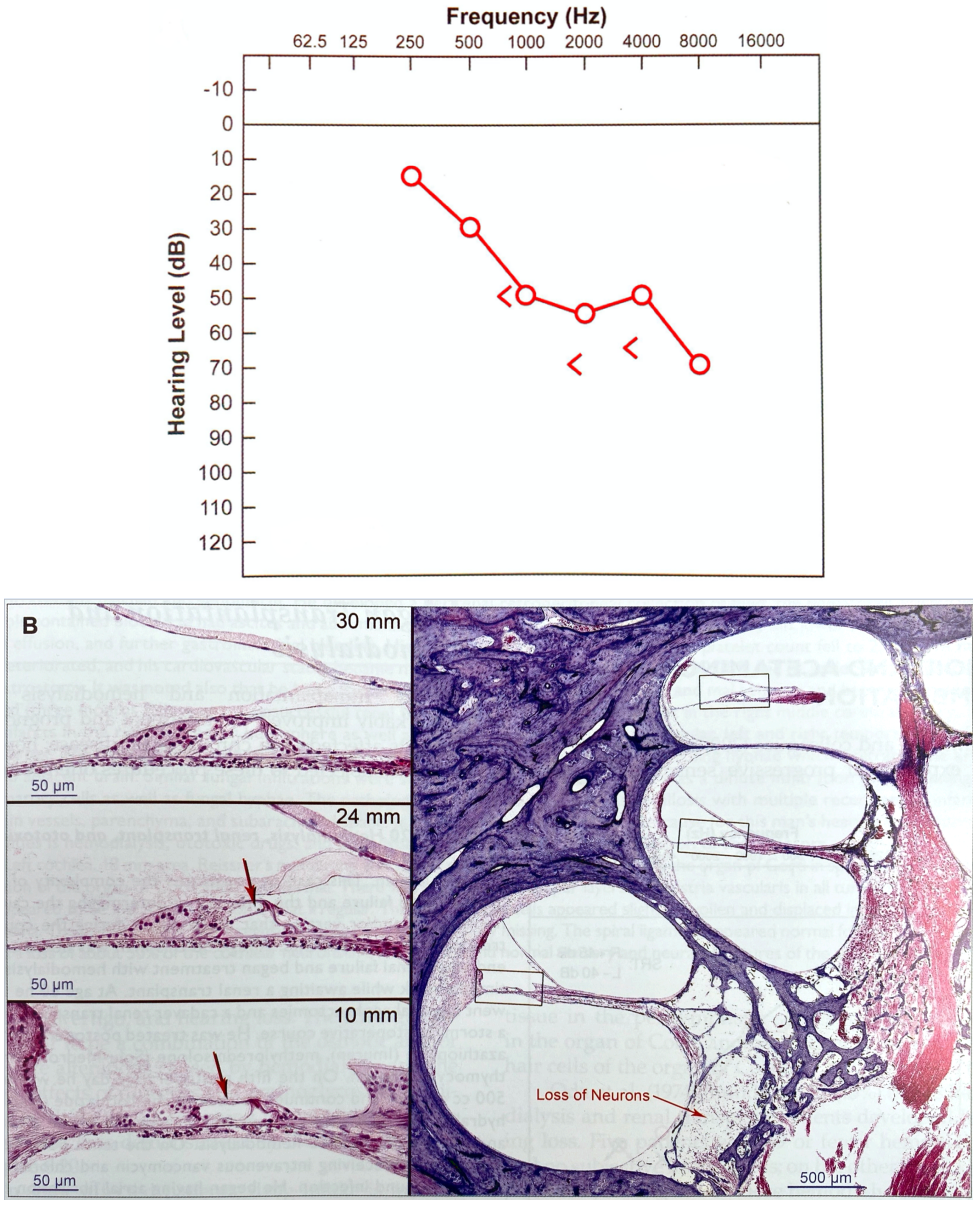

Figure 13a: Upper figure: the tonal audiogram of a 14-year-old boy with cisplatin-induced hearing loss in the high frequencies. Bottom figure: the corresponding histological sections of the cochlea shows a progressive loss of outer hair cells in the organ of Corti (red arrows) towards the basal parts of the cochlea (10 mm distance from the round window) along with loss of auditory neurons.[11]

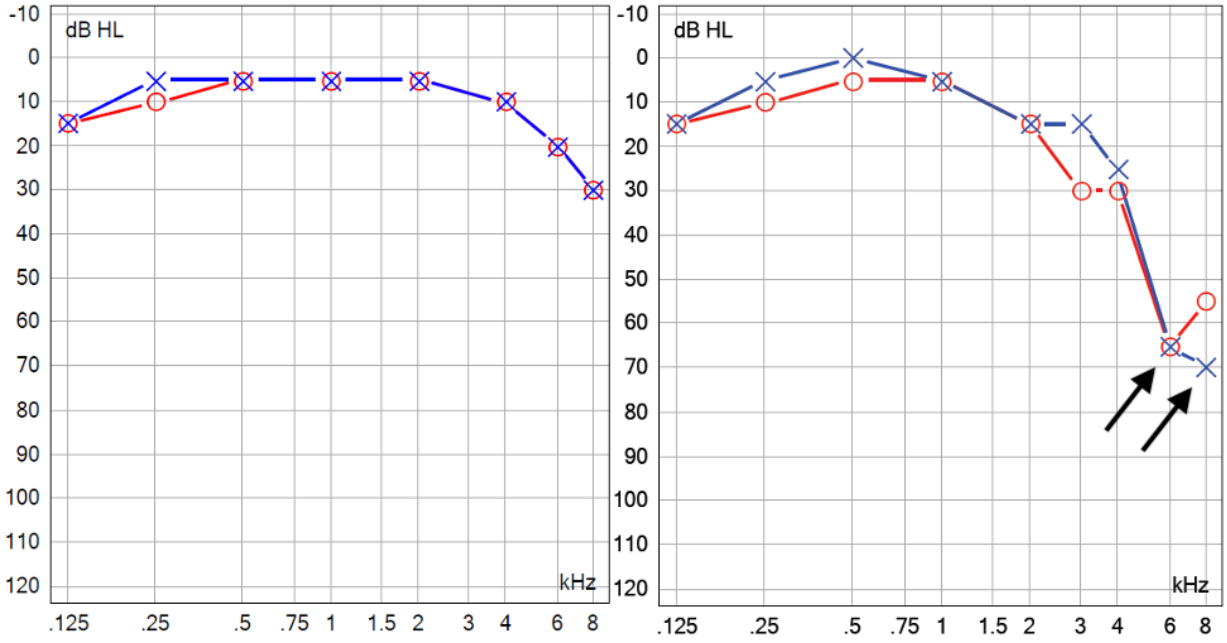

Figure 13b: Typical tonal audiogram of a 53-year-old-man showing cisplatin-induced ototoxicity: On the left, hearing thresholds before treatment. On the right, elevation of thresholds in the high frequencies (6 and 8 kHz) after treatment (arrows).

Hearing loss can develop years after completion of therapy[89], remembering that plasmatic detection of the molecule can be positive up to 20 years after treatment[79]. The inner ear itself has a very small capacity to eliminate platinum, as it could be found in the post-mortem cochlea 18 months after a patient's last cycle, suggesting that cisplatin could be retained in the cochlea indefinitely and that hyper-accumulation of cisplatin could drive its ototoxicity rather than hypersensitivity.[81] A broad variety of cochleoprotective therapeutic targets have been proposed and a few have been studied on animal models. None have been validated for human clinical trial yet.[88]

The incidence and severity of cisplatin-induced ototoxicity vary widely in the literature. Dozens of studies exist, with a broad range of methodologies, outcome measurements (especially hearing loss criteria) and populations. A significantly higher incidence and severity of hearing loss has been observed in very young children.[76] The reasons for this age-dependent vulnerability could be the physiological differences compared to adults, as well as treatment regimen variations. A 2019 Cochrane systematic review on cisplatin ototoxicity included 2837 children in 13 cohort studies using very heterogeneous methodologies, hearing loss definitions, treatment regimens, diagnostic tests, patient characteristics, other concomitant potential ototoxic drugs and follow-up durations. Prevalence of hearing loss ranged between 1,7% and 90% and the review concluded that prevalence and risk factors remain both unclear, with no clear data for tinnitus.[85] For this thesis - in addition to the analysis of our own data - a literature review about the cisplatin-induced ototoxicity in children and adults was performed. Using PubMed, with the keywords *ototoxicity, cisplatin, platinum, hearing loss*, it included only studies with a baseline audiometry exam before treatment. According to this more focused review, the incidence of cisplatin-induced ototoxicity ranges

from 12,5-100% in children and 26-100% in adults. The detailed results are presented in **Tables 6a** and **6b** at the end.

Different ototoxicity grading scales have been proposed[90-95], with various limitations such as their complexity of use and certain choices of auditory frequencies and thresholds.[76, 96] Additionally, we would like to underline that baseline audiometry testing before treatment is essential for proper objective interpretation of any post-treatment hearing test, assuming that preexisting hearing impairments are frequent, especially in the older population.[97] This fundamental prerequisite is often missing in studies. Some studies include patients with concomitant cranial radiotherapy, which is known for its ototoxicity[86], confounding the true incidence and severity of cisplatin-related damages.

The American Speech-Language-Hearing Association (ASHA) has published guidelines in 1994, suggesting close audiological monitoring with baseline audiometry when using potential cochleotoxic drug therapy.[98] These guidelines have been recommended for children by a Swiss expert group.[6] Our protocol at HUG is in line with these recommendations, comprising a systematical ORL consultation with audiological measurements prior to any ototoxic chemotherapy.

2 Materials and methods

2.1 Design

This is a single-center (tertiary care) retrospective study. Authorization from the Ethical Committee of Geneva was obtained (protocol n°2018-02065).

2.2 Participants

Eligible patients were adults treated with cisplatin-based chemotherapy at HUG from January 2015 to January 2019. Every cisplatin-based chemotherapy included intravenous dexamethasone for its anti-emetic effect. Cisplatin was either administrated alone or in combination with etoposide phosphate, gemcitabine, bleomycin, pemetrexed, docetaxel,, fluorouracil, vinorelbine, ifosfamide, paclitaxel, cytarabine, mitomycin, rituximab, bevacizumab, cetuximab, methotrexate, vinblastine, doxorubicin, dacarbazine and interferon alpha, depending on the medical context. Inclusion criteria were age over 18 years old, chemotherapy which protocol included at least one dose of cisplatin and audiological screening prior to the beginning of treatment.

Exclusion criteria were bilateral pre-existing cophosis, bilateral ear pathology not compatible with accurate hearing measurement (middle and inner ear malformations, acute and chronic otitis media and malignant disease involving the external, middle or inner ear), disease of the central hearing pathway (vestibular schwannoma, meningioma, auto-immune, hemorrhagic or ischemic condition, malignant tumor), concomitant ototoxic drugs therapy, concomitant radiotherapy involving inner ear and chronic renal insufficiency.

A listing of all patients treated with cisplatin-based chemotherapy during this period was obtained from the Oncology Department and the medical file of each patient was analyzed to assess inclusion and exclusion criteria, as well as the different outcomes described hereafter.

2.3 Hearing assessment

Every patient underwent hearing assessment in the ORL Department prior to the beginning of cisplatin-based therapy. They were all seen first by an ORL physician who obtained the medical history - focusing on hearing - and then performed otoscopy, adding the cleaning of the external ear canal, if needed. Audiometric measurements were then performed by different trained audiometrists, comprising tonal audiometry for frequencies between 125 and 8000 Hz (*Equinox 2.0*, *Interacoustics*) and in some cases additional tympanometry and otoacoustic emissions (*Titan*, *Interacoustics*).

Patients were asked by their oncologist during their follow-up if any audiological side-effects appeared, especially hearing loss and tinnitus, or they spontaneously reported audiological symptoms. In these cases, a new ORL assessment with audiometry was performed.

Hearing loss was defined as a loss of ≥ 15 dB HL in any of the frequencies tested (125 Hz to 8000 Hz), because an experimental error of ±5 dB HL across audiograms has to be considered.[99] As a consequence, a 10 dB HL threshold shift in any tested frequencies would still be considered non-significant.

2.4 Statistical analysis

Primary outcomes: Incidence and severity of hearing loss in comparison to the baseline and tinnitus in patients treated with cisplatin were expressed in absolute percentage and means with standard deviations of hearing thresholds.

Secondary outcomes: The association of ototoxicity incidence with different qualitative variables (gender, smoking, diabetes, hypertension, vascular, dyslipidemia) was assessed with *Chi-squared test*. The association of ototoxicity incidence with the quantitative variables age and mean cumulative cisplatin dose and the association between severity of hearing loss and gender were assessed with *Student's t-test*. The associations of severity of hearing loss with age and mean cumulative cisplatine dose were assessed with *linear regression*.

The statistical tests were two-sided and a p value <0.05 was considered statistically significant.

3 Results

From January 2015 to January 2019, the medical files of n=401 adult patients who met inclusion criteria were analyzed (age ranged from 18 to 80 years). Mean age was 56 years (ranging from 18 to 80 years). **Table 2** summarizes the pertinent patient related data including the number of patients with risk factors. Cisplatin-chemotherapy was administered for 30 types of cancers in the patient collective (**Table 3**).

Table 2: Overview of pertinent patient-related data.

Patient characteristics	**N (%)**
Total number of patients included	401 (100)
Males	236 (59)
Females	165 (41)
Smokers	141 (35)
Patients with hypertension	88 (22)
Patients with diabetes	37 (9)
Patients with dyslipidemia	49 (12)
Patients with vasculopathies	31 (8)
Patients with 2 risk factors	80 (20)
Patients with ≥3 risk factors	45 (11)

Table 3: Cancer types in the cohort (number of patients).

Pulmonary (121)	Nasopharynx (11)	Osteosarcoma (2)
Oropharynx (43)	Lymphoma (9)	Prostate (2)
Uterus (33)	Neuroendocrine (8)	Renal (2)
Esophagus (24)	Anal (8)	Intestinal (2)
Oral (20)	Unknown primary (7)	Mammary (2)
Germinal (19)	Ovary (7)	Leukemia (1)
Urothelial (18)	Genital (5)	Adrenal gland (1)
Gastric (18)	Nasal (5)	Thymus (1)
Larynx (12)	Melanoma (4)	Yolk sac (1)
Hypopharynx (10)	Mesothelioma (4)	Multiple myeloma (1)

3.1 Hearing loss

Hearing loss occurred in n=81 patients (20%). Among them, preexisting hearing loss was present in n=48 (60%) and tinnitus was reported by n=49 (60%). In patients when the information was available (n=37), hearing loss occurred after the first cycle of chemotherapy in 54% of the cases, after the second in 29%.

In patients with hearing loss, the mean threshold shift over the entire frequency spectrum between 125 and 8000 Hz was 9.5 dB HL (± 6.5). As mentioned earlier, the representation of threshold shifts over the

entire frequency spectrum is of limited value, as mainly high frequencies are affected by the ototoxic side effects of cisplatin. In our cohort, mainly the frequencies starting from 4000 Hz were affected (so 4000, 6000 and 8000 Hz) (**Figure 14**). When averaging these three frequencies, the mean threshold shift was 18 dB HL (± 12), 45% of the patients had <15 dB HL and 55% ≥ 15 dB HL. There was no statistical difference between right and left ear (overlapping of 95% confidence interval).

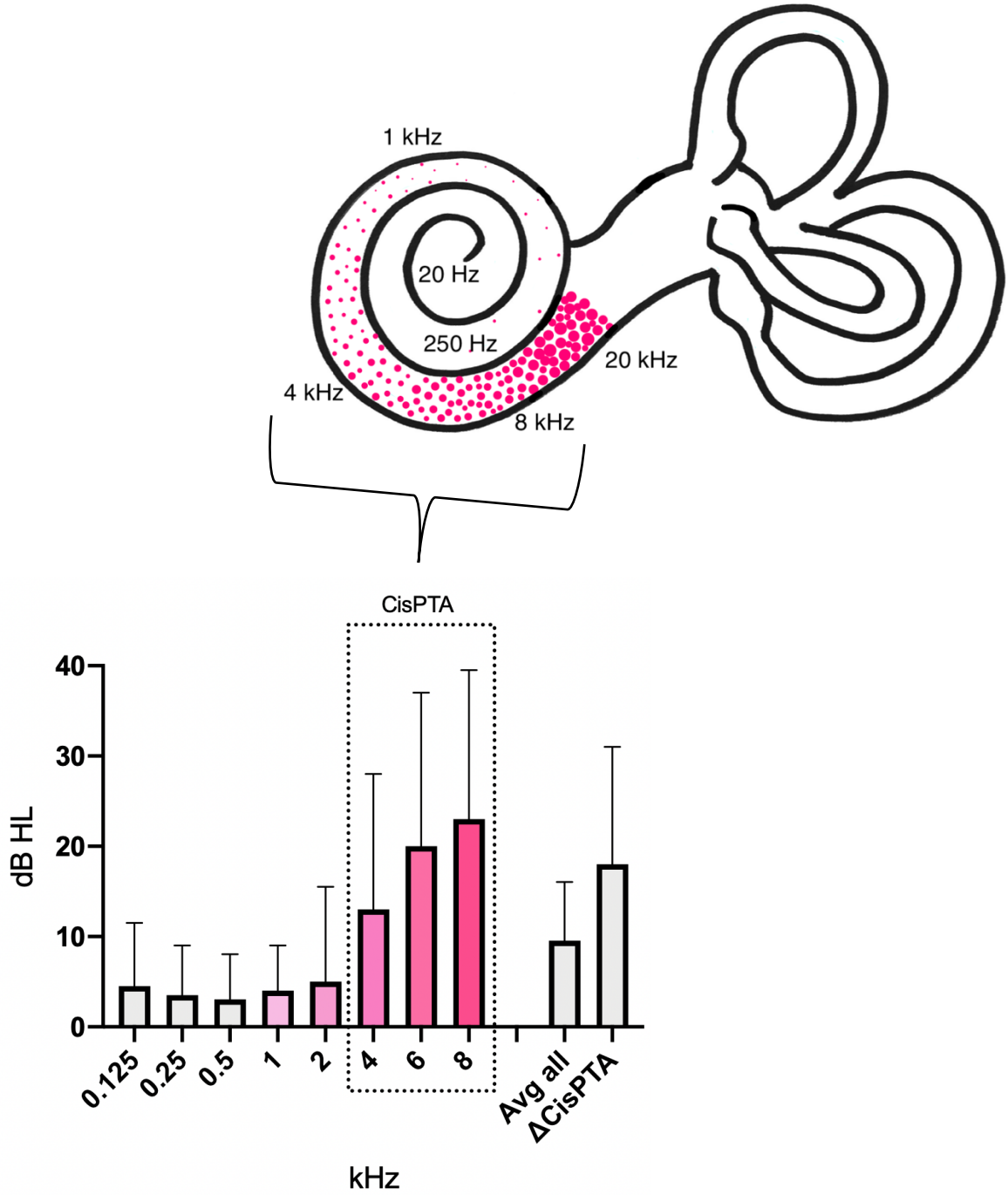

Figure 14: Mean threshold shifts (± 1 SD) across frequencies in n=81 patients with ototoxic hearing loss and their tonotopical location in the cochlea. The color intensity represents the severity of ototoxicity depending of the frequency affected.

The mean hearing thresholds in patients with hearing loss before vs. after the onset of chemotherapy is shown in **Figure 15** for left and right ears combined.

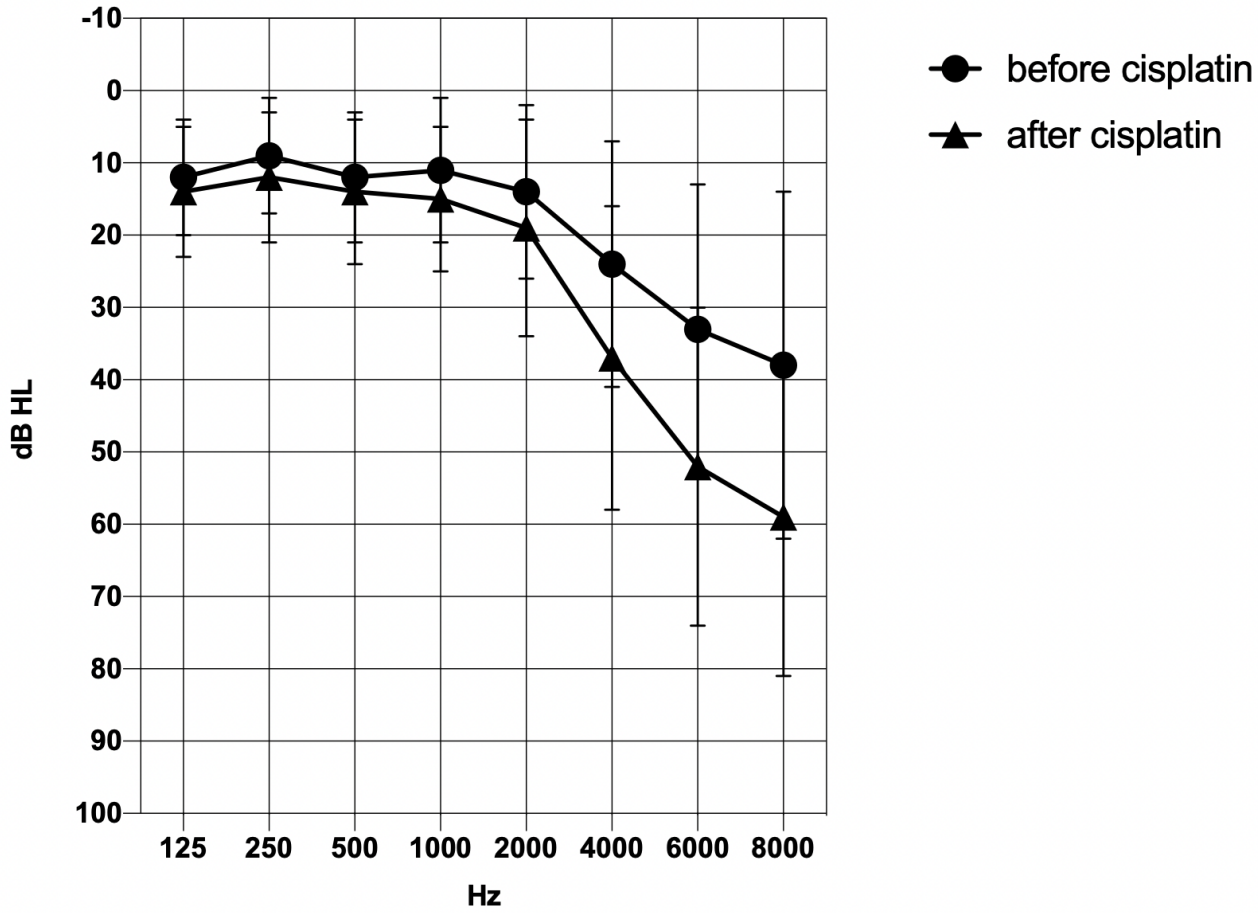

Figure 15: Averaged sensorineural hearing thresholds ± 1 SD before and after cisplatin treatment in n=81 patients with ototoxic hearing loss.

3.2 Risk factors

There was a positive difference of 51 mg/m^2 in mean cumulative cisplatin dose in patients developing hearing loss compared to the patients without occurrence of hearing loss (n=355, [95%CI: -5 ; 107], p=0.08). In logistic regression, the odds ratio to develop ototoxicity depending on the total dose of cisplatin is 1.0 (n=355, [95%CI: 0.99 ; 1.0], p=0.08), represented on **Figure 16**. The average of hearing threshold shift in patients with hearing loss was not correlated with the cumulative dose of cisplatin (n=355, r^2=0.02, p=0.17).

There was a difference of 0.8 years in mean age in patients affected by hearing loss compared to those without hearing loss after chemotherapy (95%CI: -2.1 ; 3.7), p=0.6. There was no statistical association between age and average of hearing threshold shift (r^2=0, p=0.5). There was a difference of 0.3 dB HL in the average of hearing threshold shift in males compared to females (95%CI: -2.5 ; 3.2), p=0.8.

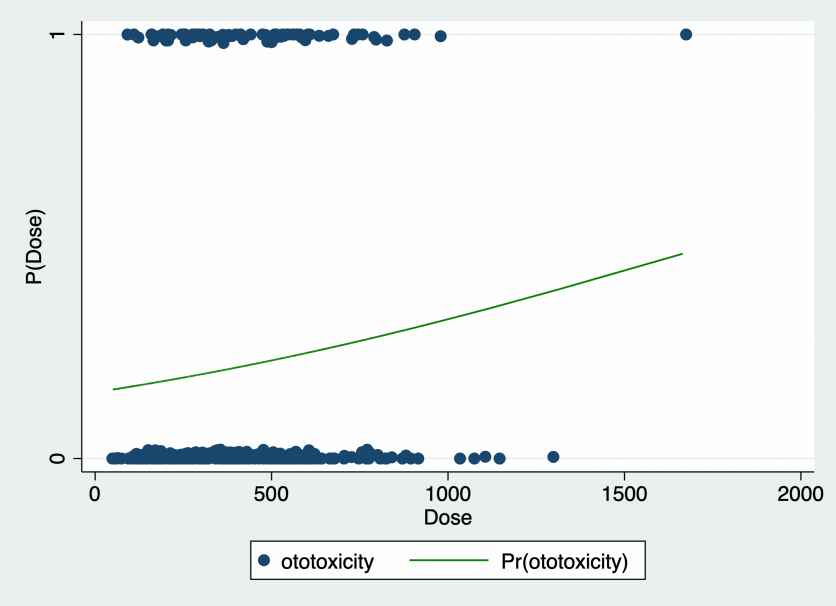

Figure 16: Probability to develop ototoxicity depending on cumulative dose of cisplatin (n=355), in logistic regression.

There was no significant difference of ototoxicity incidence in the different most prevalent chemotherapeutic regimen compared to cisplatin only regimen (all p-value > 0.3). The most prevalent cisplatin-based regimens are detailed in **Table 4**. The hearing loss incidence with qualitative cofactors is shown in **Table 5**.

Table 4: Different cisplatin-based regimens.

Cisplatin only	n=127 (31%)
Cisplatin + docetaxel	n=75 (19%)
Cisplatin + etoposide phosphate	n=65 (16%)
Cisplatin + pemetrexed	n=38 (10%)
Cisplatin + gemcitabine	n=32 (8%)
Cisplatin + bleomycine + etoposide phosphate	n=20 (5%)
Others	n=44 (11%)

Table 5: Association of hearing loss incidence with different cofactors.

Risk factor (number of patients) - hearing loss incidence in %	**Risk ratio (95% CI)**	**Difference (95% CI)**	**p-value**
Male gender (236) - 23	1.5 (0.1 ; 2.3)	0.08 (0 ; 0.2)	0.06
Smoking (141) - 22.5	1.2 (0.8 ; 1.8)	0.04 (-0.05 ; 0.1)	0.35
Diabetes (37) - 16	0.8 (0.3 ; 1.7)	-0.04 (-1.7 ; 0.08)	0.5
Hypertension (88) - 14.5	0.7 (0.4 ; 1.1)	-0.07 (-0.2 ; 0.02)	0.15
Vascular (31) - 9.5	0.5 (0.2 ; 1.3)	-0.1 (-0.2 ; 0)	0.1
Dyslipidemia (49) - 26.5	1.3 (0.8 ; 2.3)	0.07 (-0.06 ; 0.2)	0.2
2 risk factors (80) – 22.5	0.7 (0.3 ; 1.5)	-0.05 (-0.16 ; 0.06)	0.4
≥ 3 risk factors (45) – 15.5	1.1 (0.7 ; 1.8)	0.03 (-0.7 ; 0.1)	0.5

4 Discussion

In this collective of 401 patients treated with cisplatin chemotherapy, a total of 80 patients (20%) developed a significant hearing loss with a threshold shift equaling or greater than 15 dB HL in at least one frequency, mainly in the high frequencies from 4 to 8 kHz. On average, the loss in these three highest frequencies tested was 18 dB HL (± 12). Because no statistically significant hearing loss (≥ 15 dB HL) was found in the lower frequencies, we propose a new *pure tone average* (PTA) named *CisPTA*, which can serve as a practical summary of the relevant hearing loss in relation to cisplatin chemotherapy with one single quantitative and comparable number. Typically, the term PTA has been introduced to rapidly judge on surgical outcome and for an easy comparison across hearing results before and after surgery and is classically calculated for the frequencies 0,5-4 kHz in most of the studies.[100] For cisplatin ototoxicity, this makes absolutely no sense, and we chose to use the frequencies 4-6-8 kHz to calculate our pure tone average (see **Figure 14**), separated in *low* (<15 dB HL) and *high* (≥15 dB HL). A *CisPTA* could really make a difference for us to judge and compare the severity of hearing loss at a glance. In our collective, 45% had a *lowCisPTA* and 55% a *highCisPTA*.

Hearing loss occurred typically after the first cycle of cisplatin-based treatment, and to a lesser extent after the second. Hearing loss was sensorineural and affected both ears symmetrically with predominance in the high frequencies between 4 and 8 kHz. No complete hearing loss (cophosis) was observed.

The incidence of hearing loss was higher in patients receiving higher cumulative doses of cisplatin, however the association did not reach statistical significance. This suggests that individual susceptibility of inner ear toxicity from cisplatin is not just a question of dose. It is therefore difficult for us to make recommendations or at least to establish a risk threshold of dose, as clearly seeable in **Figure 16**. Nevertheless, the overall weak trend of correlation of hearing loss severity with cumulative cisplatin dose is in line with the literature on the topic, where several studies have shown a clear and statistically significant correlation.[3, 101, 102]

We did not find any tested medical factors influencing the occurrence of ototoxicity or to be associated with the severity of hearing loss. Especially vascular comorbidities didn't seem to precipitate cochlear damage, as it could have been anticipated. The literature on the topic is unclear, and some associations described are not always to be trusted, depending on the methodology of the study. There is however a tendency of increased incidence of hearing loss in men, without statistical significance.

One interesting finding is the 60% prevalence of tinnitus reported in patients with proved cochleotoxicity induced by cisplatin in our cohort. During the course of a cisplatin-based chemotherapy, the presence of this indicative symptom by any patient should therefore elicit a high suspicion of drug-induced ototoxicity, leading to a full audiometric evaluation. If significant hearing loss is found with a *CisPTA* less than 15 dB HL, the attitude needs to be thoroughly discussed between the patient, otolaryngologist and oncologist. Either

the therapy is continued with a lower dose of cisplatin or the less ototoxic compound carboplatin can be chosen, if the overall oncological context allows a modification of the treatment regimen. If a severe hearing loss is found with a *CisPTA* beyond 15 dB HL, this discussion needs to be held similarly, but with even more weight given to an eventual modification or even cessation of the chemotherapy, if the overall medical context does allow it. If the acute oncological phase is terminated and the patient suffers from significant hearing loss, treatment options need to be investigated and eventually proposed to the patient. The first line therapy available today is the administration of hearing aids, when the patient has lost at least 20% or more of his hearing capacity based on audiometric evaluation. In case hearing aids would not be sufficiently performing to compensate the hearing loss, cochlear implants can be evaluated. In our series, none of the patients developed severe or profound hearing loss and therefore, no cochlear implant provision was necessary. It is noteworthy that ototoxic inner ear damage may be occurring simultaneously or sequentially with other progressive etiologies such as presbycusis or genetic preconditions[28], as 60% of our collective patients with ototoxicity had preexisting hearing loss (see **Figure 17**).

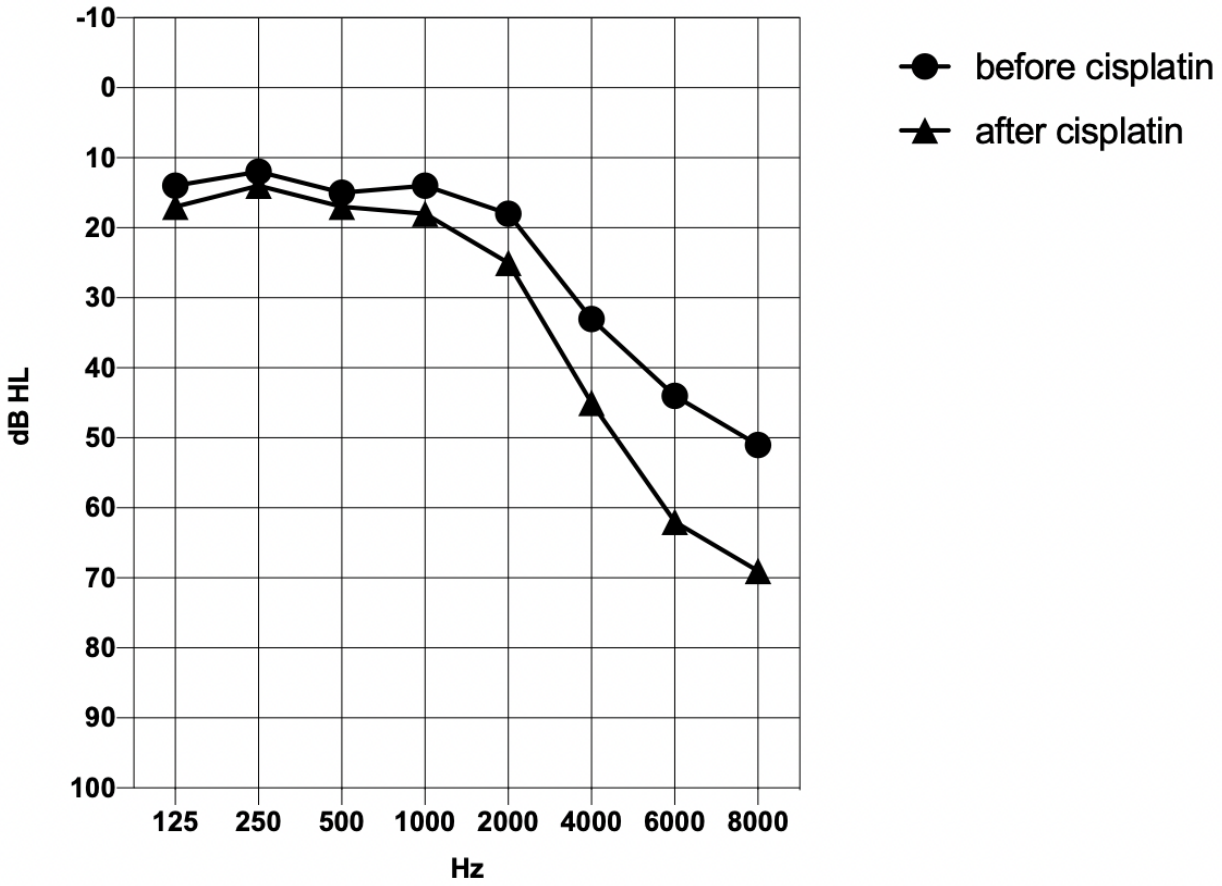

Figure 17: Averaged sensorineural hearing thresholds before and after cisplatin treatment in n=48 ototoxic hearing loss patients with preexisting hearing loss.

Audiological baseline examination is a prerequisite to identify patients with ototoxic side effects of cisplatin chemotherapy. However, its application is not routine in many centers.[6] Despite the fact that baseline examination is performed in our institution, our audiological work up in cancer patients is likely to

underestimate the true incidence and prevalence of ototoxic hearing loss caused by cisplatin chemotherapy. Until 2019, follow-up examinations were done only in patients who reported tinnitus or hearing loss spontaneously or after being specifically asked by their oncologist. For this reason, patients who did not themselves report hearing-related symptoms - which is often not a priority in case of significant other cancer-related morbidity - may not have been included in the analysis and their hearing loss undetected. This hypothesis is corroborated by the fact that in other studies with prospective enrollment of cancer patients into strict audiological work-up protocols including baseline examination and fixed follow-up evaluation, the incidence of cisplatin ototoxicity is much higher, reaching up to 64% depending of the hearing loss criteria used.[96, 103-105] Centers performing in addition high-frequency audiometries up to 20 kHz report higher incidence of ototoxic side effects than centers with the standard audiometric measurements including frequencies only up to 8 kHz, as done in our center.[102, 106] Taken together, we believe that our current practice is underestimating the true scope of ototoxic side-effects and that to address this shortcoming, prospective studies with a strict audiological protocol including baseline examination and late follow-up are mandatory to have an accurate judgement. In addition, our center is evaluating the acquisition of high-frequency audiometers to address the reported shortcoming.

The detection of as many patients as possible with ototoxic side effects of cisplatin is important already for the optimization of current treatment protocols. Only through detection of affected patients are the clinicians able to adapt the treatment regimens and thereby to prevent further damage, if the medical situation permits. In addition, several promising, translational research projects with the aim to prevent cisplatin ototoxicity are currently underway in different institutions, including the University hospital in Geneva. *The Inner Ear & Olfaction Laboratory*, headed by Prof. SENN, is for instance working on molecules that inhibit the production of free radical oxygens by a specific NADPH oxidase in the inner ear, *NOX3*. Other laboratories have different approaches, and also promising results. If basic scientists and clinicians work in close collaboration, the chances of developing a robust preventive therapy against cisplatin ototoxicity are higher and really tailored to the unmet clinical needs of the patients.

5 Conclusion

In this retrospective analysis of a large collective of adults without concomitant inner ear radiotherapy, cisplatin chemotherapy induced significant hearing loss in 20% of the cases, further decreasing the quality of life permanently. In order to prevent unnecessary ototoxicity, the systematic application of a thorough audiological examination before, during and after completion of cisplatin chemotherapy is mandatory. It will be interesting to see, if and how incidence and severity of this side effect may change, if a similar study is done prospectively in our institution. Only by identifying affected patients, the treatment protocols can be individually discussed and modified, if the clinical situation allows it. In addition, detection of affected patients lays the base for including meaningful numbers of patients into translational clinical studies aiming at reduction of cisplatin ototoxicity in the near future. Taken together, audiological monitoring is a useful tool offering benefits for patients today and opening doors for future preventive therapies against cisplatin ototoxicity.

Table 6a: Literature reporting cisplatin-induced cochleotoxicity in children with recorded baseline audiometry are listed.

Study	Methodology	Population	Chemotherapy	Outcome
Gupta 2006[107] Canada	Retrospective	39 children (median 9 years, 41% male) with germ cell tumor. Majority with baseline audiometry (frequencies not specified). Median follow-up 1.4 year.	Median cumulative dose 400 mg/m^2 of cisplatin by continuous infusion + etoposide and bleomycin	12,5% hearing loss (> 40 dB HL at 1, 2, 4 or 8 kHz), of which 2,6% were permanent
McHanney 1981[108] USA	Prospective	24 children (3.5-17.5 years) with neuroblastoma or other solid tumors. Baseline audiometry (0,5-8 kHz). Follow-up 1-25 months (median 5).	1-15 (median 6) courses of cisplatin 90 mg/m^2	88% hearing loss (>10 dB HL at 0,5, 1 and 2 kHz or >15 dB HL at 4, 6 and 8 kHz)
Ruiz 1989[109] USA	Prospective	54 children (5-18 years) with osteosarcoma. Baseline audiometry (0,25-8 kHz) in majority (91%) . Follow up to 6 months.	1-23 (mean 10) courses of cisplatin 150 mg/m^2 + methotrexate + adramycin	100% hearing loss (≥20 dB HL at any frequency)
Knight 2005[89] USA	Retrospective	67 mostly children (0.6-23 years, 67% male) with medulloblastoma, osteosarcoma, neuroblastoma, neuroectodermal tumor, germ cell tumor, non-CNS tumor or glioma. Baseline audiometry (9-16 kHz). Follow-up 6-44 months, mean 20.7.	59% cisplatin only (mean 493 mg/m2), 12% with carboplatin only (4701 mg/m^2) and 28% in combination. 34% with prior cranial radiation.	55% hearing loss with cisplatin 38% with carboplatin 84% with both agents (either Brock or CTCAE classification)
Knight 2007[110] USA	Retrospective	32 children (0,6-20 years) with medulloblastoma, neuroblastoma, osteosarcoma, germ cell tumor, hepatoblastoma, primitive neuroectodermal tumor of the central nervous system, astrocytoma of the spinal cord, adrenocortical carcinoma and Wilm's tumor. Baseline audiometry (0,5-8 kHz, 53% with extension to 9-16 kHz) for 88% of children.	65% received cisplatin, 31% received cisplatin and carboplatin, 3% received carboplatin only.	63% ototoxicity (≥20 dB HL in one frequency or 10 dB HL in two adjacent frequencies)
Landier 2014[111] USA	Retrospective	333 mostly children (0.3-29 years, 56% male) with neuroblastoma. Baseline audiometry (frequencies not specified).	Cisplatin up to 400 mg/m^2 or cisplatin 400 mg/m^2 + carboplatin 1700 mg/m2	64%-90% hearing loss depending on criteria (Brock, ASHA, Chang, CTCAE). Combination with Carboplatin enhanced ototoxicity rate.
Knight 2017[112] USA	Prospective	284 mostly children (0.1-21.3 years, 59% male) with germ cell tumor, hepatoblastoma, medulloblastoma, neuroectodermal tumor, neuroblastoma, osteosarcoma and others. Baseline audiometry (0,5-8 kHz).	Median cumulative dose cisplatin 395 mg/m^2, 15% with prior cranial radiation, 18% with prior single or multiagent chemotherapy	40-56% ototoxicity depending on the criteria (SIOP, CTCAE, ASHA, Brock)
Lewis 2009[113] USA	Retrospective	36 children (3-18 years, 39% male) with osteosarcoma. Baseline audiometry (0,25-8 kHz) Median follow-up 76 days.	Cisplatin cumulative dose 201-480 mg/m^2, mostly with methotrexate and doxorubicin, occasionally ifosfamide	Hearing loss 41% (>20 dB HL at ≥4 kHz)
Stavroulaki 2001[114] Greece	Prospective	12 children (4.6-14.5 years, 50% male) with neuroblastoma, osteosarcoma,	Cisplatin 50 mg/m^2, some also received	50% hearing loss (>15 dB HL in one frequency or >10 dB HL in

		medulloblastoma, rhabdomyosarcoma and neuroectodermal tumor. Baseline audiometry (0,25-8 kHz).	cyclophosphamide, adriamycin, doxorubicin, vancomycin and vincristine, 16% received prior cranial irradiation	two consecutive frequencies from 4-8 kHz)
Sivaprakasam 2011[115] India	Retrospective	38 children (0-11 years) with hepatoblastoma. Baseline audiometry (frequencies not specified).	Cisplatin (median cumulative dose 400 mg/m^2) ± Doxorubicin,	45% hearing loss (> 40 dB HL at 8 or/and 4 or/and 2 or/and 1 kHz)
Nitz 2013[116] Germany	Prospective	129 mostly children (median age 13,5 years, 51% male) with osteosarcoma and soft-tissue sarcoma. Baseline audiometry (0,125-8 kHz).	83% received cisplatin (median cumulative dosed 360 mg/m^2), 10% received carboplatin (median cumulative dose 1500 mg/m^2), 0,06% received both (median dose 240 mg/m^2 cisplatin and 1200 mg/m^2 carboplatin)	47% hearing impairment (≥20 dB HL at any frequency)
Stöhr 2005[117] Germany	Prospective	74 children and adults (3-38 years) with osteosarcoma. 57% with baseline audiometry (0,25-8 kHz).	Cisplatin (median cumulative dose 360 mg/m^2), 0,8% received additional carboplatin	51% hearing loss (>20 dB HL in the frequency range of 4-8 kHz)

Table 6b: Literature reporting cisplatin-induced cochleotoxicity in adults with recorded baseline audiometry are listed.

Study	Methodology	Population	Chemotherapy	Outcome
Low 2006[118] Singapore	Prospective	58 mostly adults (15-74 years, 88% male) with nasopharyngeal carcinoma. Baseline audiometry (0,5-4 kHz). Control group of 57 adult (30-70 years, median 43, 77% male) with same disease. Follow up 2 years.	Radiotherapy followed by cisplatin (median dose 160 mg) and fluorouracil, control group treated with radiotherapy only	Hearing threshold worse at all frequencies comparing to the control group
Niemensivu 2016[119] Finland	Prospective	22 adults (40-74 years, 77% male. Baseline audiometry (0,125-8 kHz).	Cisplatin (mean dose 205 mg/m^2) + radiotherapy in pharyngo-laryngeal region	50 % hearing loss (≥10 dB at 4 or 8 kHz). Tinnitus 40%.
Piel 1974[2] USA	Retrospective	30 adults (11-62 years, 60% male) with cancers types not specified. Baseline audiometry (0,25-8 kHz).	Cisplatin (dose not specified)	60 % hearing loss (≥15 dB HL at 8 kHz in one ear or ≥10 dB HL in both ears). 6% tinnitus.
Helson 1978[103] USA	Prospective	104 children and adults (8-78 years) with cancer types not specified. Baseline audiometry (0,5-8 kHz).	Cisplatin median dose 430 $mg/m^{2\ for}$ age 8-20, 255 mg for age 21-45, 220 mg for age >46	91% hearing loss (>20 dB HL at 2 any frequency)
Dutta 2005[101] India	Prospective	60 adults (83% male) with cancer types not specified. Baseline audiometry (frequencies not specified).	Cisplatin low dose in 51 patients (100 mg/m^2 in three doses) and high dose in 9 patients (120 mg/m^2 in two doses)	33% hearing loss in high dose group
Malgonde 2015[120] India	Prospective	34 patients (age not specified) with head and neck malignancies. Baseline audiometry (frequencies not specified).	Cisplatin (cumulative dose not specified) + radiotherapy	100% hearing loss at 1 year
Whitehorn 2014[121] South Africa	Retrospective	107 mostly adults (14-75 years, 74% male) with head and neck cancers, lymphoma, osteosarcoma and others. Baseline audiometry (0,5-8 kHz).	Cisplatin (cumulative dose median 180 mg/m^2 in group without ototoxicity and 236 mg/m^2 in group with ototoxicity)	55% ototoxicity (≥20 dB HL at any frequency or 10 dB HL at any two adjacent frequencies)
Arora 2009[102] India	Prospective	57 adults (19-76 years, 64% male) with cancer types not specified. Baseline audiometry (0,5-16 kHz). Follow-up 3 months.	Cisplatin groups low-dose ≤60 mg/m^2, middle-dose 61-80 mg/m^2, high dose ≥81 mg/m^2	100% hearing loss in middle- and high-dose groups (>10 dB HL of mean value of hearing thresholds at 0.5, 1 and 2 kHz or >20 dB HL at individual frequency)
Dell'aringa 2009[122] Brazil	Prospective	17 adults (40-75 years, 88% male) with head and neck cancers. Baseline audiometry (0,25-8 kHz).	Cisplatin (mean dose 299 mg/m^2) + concomitant radiotherapy including skull base	70% of hearing loss (≥20 dB HL in an isolated frequency or of ≥10 dB HL in two or more successive frequencies)
Shultz 2009[96] Brazil	Prospective	31 mostly adults (7-66 years, 51% male) with cancer types not specified. Baseline audiometry (frequencies not specified).	Cisplatin (mean dose 299 mg/m^2)	29%-61% of hearing loss depending of criteria (CTCAE, Brock, ASHA, David and Silverman)
Zuur 2008[106] Netherlands	Prospective	60 adults (mean age 62 years, 68% male) with sinus, oral, oropharynx,	Cisplatin (median cumulative dose 220	31% in low-dose group (CTCAE criteria up to 8 kHz)

		hypopharynx, larynx, neck, lung and esophagus cancers. Baseline audiometry (0,125-16 kHz).	mg/m^2) + radiotherapy reaching the inner ear field in 96% of patients	47% hearing loss (CTCAE criteria up to 16 kHz)
Reddel 1982[104] Australia	Prospective	32 adults (16-64 years) with germ cells tumors, ovary carcinoma and others. Baseline audiometry (0,25-8 kHz).	Cisplatin (mean cumulative dose 203 mg/m^2)	47% hearing loss (≥15 dB HL in one or more frequencies)
Esfahani 2017[3] Iran	Prospective	124 adults (18-78 years, 65% male). Baseline audiometry (1-8 kHz).	Cisplatin (mean dose 454 mg/m^2) + cyclophosphamide and adramycin in 6% + methylprednisolone in 6%	26% hearing impairment (>10 dB HL in at least one frequency). 3% tinnitus.
Greene 2015[123] USA	Retrospective	30 adults (17-81 years, 47% male) with head and neck, brain, lung, bladder, uterus, pelvic, ovarian cancers, unknown primary cancers. Baseline audiometry (0,25-10 kHz).	Cisplatin (mean dose 148 mg/m^2), 20% received cranial radiation	63% hearing loss (≥40 dB HL at ≥1 kHz or >20 and <40 dB HL at <4 kHz or >20 and >40 dB at 4 kHz)
Aguilar-Markulis 1981[105] USA	Prospective	50 adults (100% male) with genitourinary cancers. Baseline audiometry (0,5-8 kHz).	Cisplatin 1 mg/kg 1/week 6x and every 3 weeks thereafter for at least 12 months	64% ototoxicity (≥15 dB HL at any frequency)
Nagy 1999[97] USA	Retrospective	53 adults (40-75 years, 77% male) with esophagus, lung, or head and neck cancers. baseline audiometry (0,25-8 kHz).	Cisplatin at doses either 160 (87%) or 240 mg/m^2 (13%). Possibly until 38% received concurrent radiation therapy to the head and neck	36% hearing loss (>10 dB HL for any pure tone average or >20 dB HL for any frequency)
Waters 1991[124] Canada	Retrospective	60 adults (18-71 years) with ovarian carcinoma. Baseline audiometry (0,25-8 kHz).	Cisplatin at different doses (50 -100 mg/m^2) + adramycin	92% hearing loss in high dose treatment (>15 dB HL at any frequency)

CTCAE criteria[93]: Minimum ≥15 dB HL averaged at 2 contiguous frequencies at least in one ear relative to baseline audiogram, or subjective change in hearing. Ordinal 4-scale depending of the severity.

ASHA criteria[98]: Minimum ≥20 dB HL in one frequency or ≥10 dB HL in two adjacent frequencies.

Brock criteria[90]: Minimum ≥40 dB HL at 8 kHz. Ordinal 4-scale depending of the lower frequencies.

SIOP criteria[95]: Minimum >20 dB HL at any frequency. Ordinal 4-scale depending of the severity.

Davis and Silverman criteria[125]: Minimum >20 dB HL of mean value at 5,1 and 2 kHz. Ordinal 4-scale from mild to profound.

Pure Tone Average (PTA)[100]: Mean threshold elevation at 0,5-4 kHz.

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