Long-term ototoxicity after cisplatin-based chemotherapy

A study of long-term hearing loss and tinnitus in patients after receiving cisplatin-based chemotherapy

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Abbreviations

ABR – Auditory Brainstem Response

ARHL – Age-Related Hearing Loss

ASHA – American Speech-language-Hearing Association

CBCT – Cisplatin-Based ChemoThearpy

CRN – Cancer Register of Norway

DPOAE – Distortion Product OtoAcustic Emissions

HUNT – HelseUndersøkelsen i NordTrøndelag

MOGCT – Malignant Ovarian Germ Cell Tumor

OAE – OtoAcustic Emissions

PROM – Patient-Reported Outcome Measures

PTA – Pure Tone Average

ROS – Reactive Oxygen Species

SCIN – Scale for Chemotherapy-Induced long-term Neurotoxicity

SNR – Signal to Noise Ratio

SPC – Serum Platinum Concentration

SRT – Speech Reception Threshold

TCS – Testicular Cancer Survivors

THI – Tinnitus Handicap Inventory

VRA – Visual Reinforcement Audiometry

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Gynecol Oncol. 2017 Apr;145(1):148-153. doi: 10.1016/j.ygyno.2017.02.006. Epub 2017 Feb 12. PMID: 28202195

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Laryngoscope. 2020 Sep;130(9):E515-E521. doi: 10.1002/lary.28543. Epub 2020 Feb 17. PMID: 32065408

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Jakob Skalleberg, Marte Myhrum, Milada Cvancarova Småstuen, Terje Osnes, Sophie D. Fosså*, Marie Bunne*

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Introduction

Speech is the main communication mode among humans. Our ability to understand and recognize speech depends largely on our ability to hear. Thus, hearing is a very important sense for most people throughout life, starting already before birth [1]. Most of us are hugely dependent on hearing in our daily life to be able to communicate with others and to warn us about possible dangers. Many also take great pleasure in listening to music. However, hearing is not constant throughout life, and most people will experience some degree of hearing loss either due to disease, or as a normal part of the aging process [2].

Cisplatin-based chemotherapy (CBCT) has become a cornerstone in the treatment of several types of malignancies over the last decades. Ototoxicity is one of several well-documented side effects [3-7]. With increasing survival rates, it is important to know how CBCT will affect hearing in these survivors over a very long time. It is well documented that cisplatin can cause high-frequency hearing loss in connection with the treatment. Elevated Serum Platinum Concentrations (SPC) have been demonstrated several years after CBCT and this might theoretically cause a continuous progression of hearing loss [8-12]. Some studies have shown possible progression of hearing loss over the first years after treatment, but to the best of the author's knowledge, none of them have more than 10 years follow-up [6, 7, 11, 13, 14]. Further, sufficient adjustment for the expected Age-Related Hearing Loss (ARHL) in an ageing population is rarely included.

Since most patients treated for testicular and ovarian cancer are relatively young, and treatment has a very high success rate, the vast majority of survivors are expected to live for many decades after treatment. We know that the high-frequency hearing in the general population declines with age, but little is known about how this will affect CBCT-treated patients [2]. Hence it is important to investigate their hearing abilities in the very long-term perspective.

The aim of the present thesis was to explore hearing function and tinnitus in cancer survivors in a very long-term perspective, and to compare our findings with those of the general population. We aimed to assess hearing both quantitatively with hearing tests and subjectively by a self-reported questionnaire. We also wished to evaluate the clinical relevance of our findings, in order to provide important pre-treatment information to patients as to what they can expect regarding hearing abilities in the long-term after CBCT.

Anatomy and physiology of the ear

Sound is a mechanical vibration that sets up small oscillations of air molecules. This creates a pressure wave when air molecules come closer together and the pressure increases (compression), and as they move further apart and the pressure decreases (rarefication).

The frequency describes the pitch of a sound and is determined by the number of compressions and rarefactions per second, measured in Hertz (Hz). Human hearing is limited to sounds between 20 – 20 000 Hz. Although the human ear can detect sounds up to 20 kHz (in childhood), the highest frequencies are of less importance in daily life, which is why standard hearing tests only include frequencies between 125 – 8000 Hz. Figure 1 is often used to show where the Norwegian pronunciation of the different letters are placed in the frequency scale. The intensity describes the loudness of a sound and is determined by how tightly the air molecules are packed during the compression phase of the sound wave. It is measured in decibel (dB). The decibel scale is logarithmic, reflecting that the human ear functions in a nonlinear fashion and responds much more efficiently to sounds of small amplitude than to sounds of larger amplitudes.

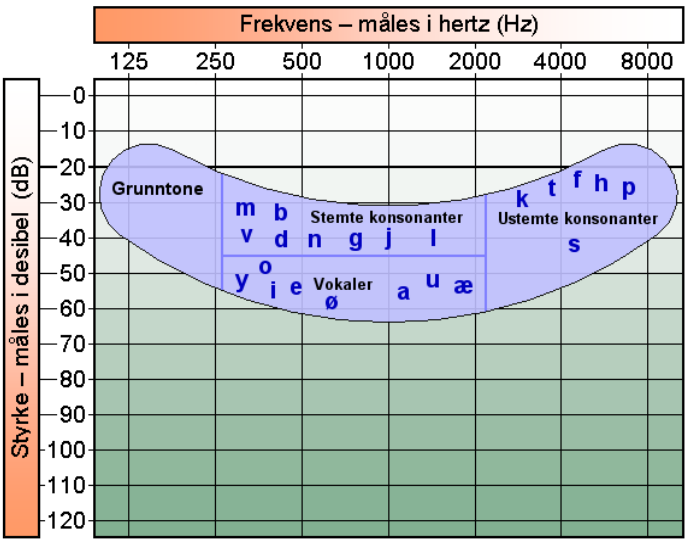


Figure 1. Audiogram showing letters in Norwegian arranged by frequency. © Statped. www.sansetap.no. Reprinted with permission.

The human ear can be divided into three parts: the external or outer, the middle and the inner ear (Figure 2). The external ear consists of the pinna and the external auditory canal. The pinna funnels sound waves from the environment into the external auditory canal. The tympanic membrane at the inner end of the external auditory canal represents the border between the external ear and the middle ear. It consists of three

layers with squamous epithelium laterally, a middle fibrous layer and a medial mucosal epithelium. This construction allows the membrane to vibrate when exposed to sound waves.

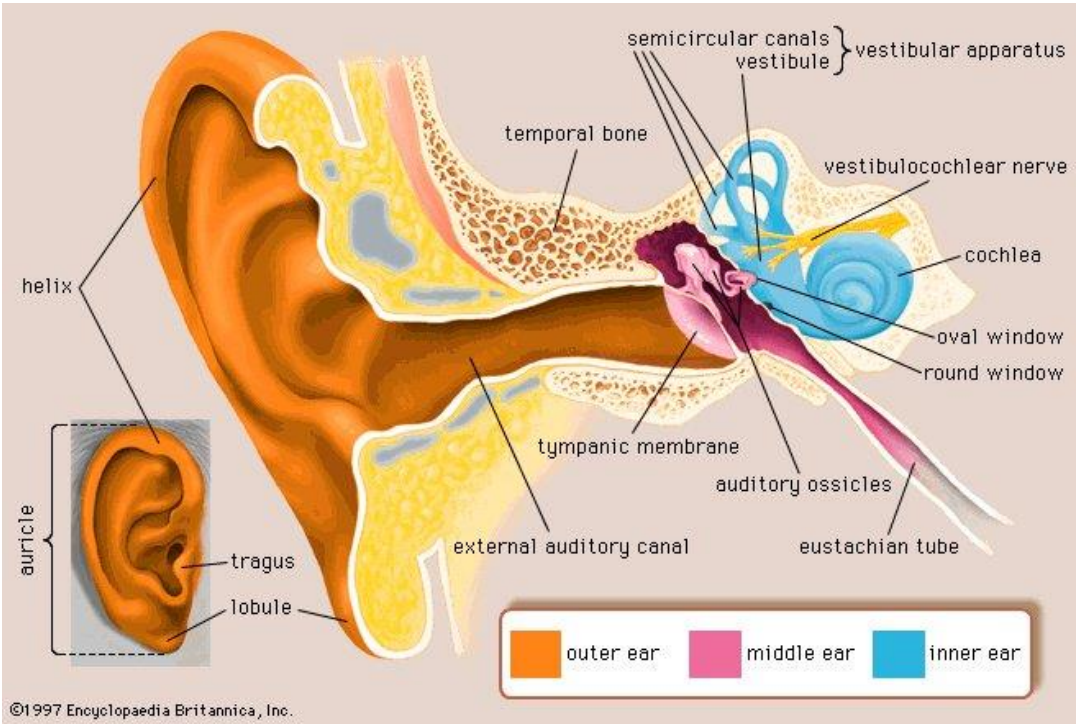


Figure 2. Anatomy of the ear. © Britanica, inc. Reprinted with permission.

Inside the tympanic membrane is the middle ear. It contains the ossicular chain, composed of three ossicles; malleus, incus and stapes. The malleus is attached to the tympanic membrane and articulates with the incus, which articulates with the stapes. As the sound pressure wave reaches the tympanic membrane it causes vibration of the membrane, which in turn makes the ossicular chain vibrate and amplify the sound. The stapes transmits the vibrations into the inner ear through the footplate, situated in the oval window.

The inner ear is composed of two functional parts: The cochlea which is dedicated to hearing, and the vestibular system, dedicated to balance. From the inner ear, the vestibular and cochlear nerves transmit information to the central nervous system.

The cochlea is a spiral structure with three fluid filled chambers: scala vestibuli, scala media (cochlear duct) and scala tympani, separated by the Reissners' membrane and the basilar membrane [15] (Figure 3).

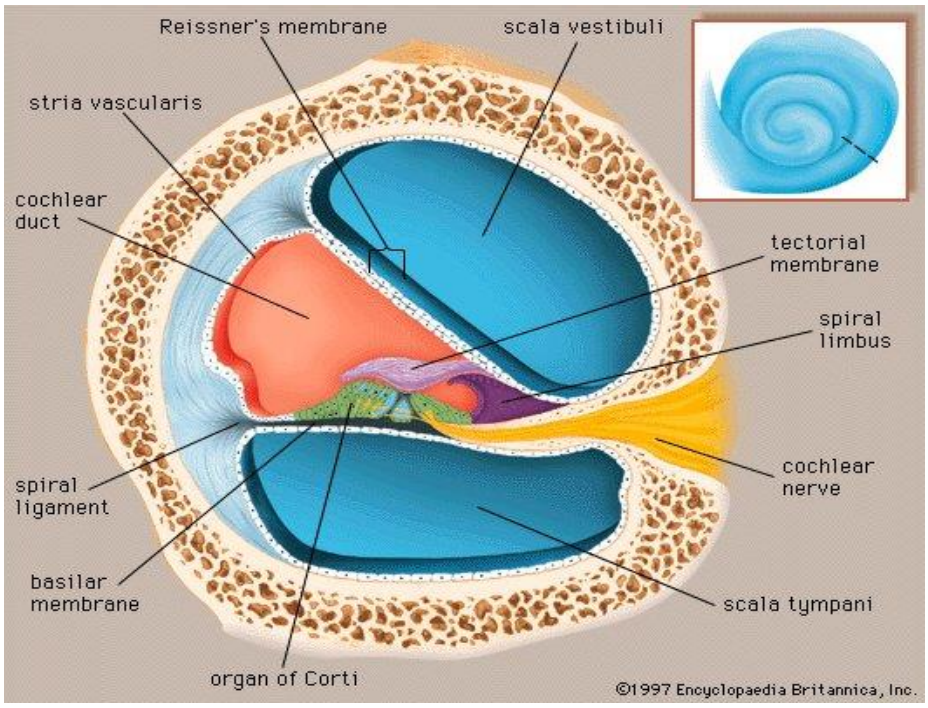


Figure 3. Cross-section of the cochlea. © Britanica, inc. Reprinted with permission.

The stria vascularis is a highly vascular and metabolically active structure, situated in the lateral wall of the cochlea. It helps maintain a high concentration of potassium ions within the scala media, contrasting the lower concentration in the other scalae. The organ of Corti is located in the scala media, situated between the scala vestibuli and scala tympani. Here, the mechanical energy (pressure wave) is transformed into an electric signal (nerve potential). The organ of Corti contains three rows of outer hair cells and one row of inner hair cells. At the apical part of the hair cells there are stereocilia which are in contact with the overlaying tectorial membrane. The vibrations of the footplate in the oval window cause a movement of the fluid, called perilymph, in the scala vestibuli from the base toward the apex of the cochlea, which in turn makes the basilar membrane vibrate, causing a travelling wave of the basilar membrane. This wave peaks close to the base for high-frequency sounds and closer to the apex for low frequency signals. When movements of the basilar membrane cause the stereocilia to brush against the tectorial membrane, mechanically gated ion channels will open and allow influx of positively charged ions causing depolarization of the cell and the generation of a receptor potential. The receptor potential opens voltage gated calcium channels that cause influx of calcium. This leads to the release of neurotransmitters at the base of the hair cell. When the neurotransmitters bind to a nerve receptor of a cochlear nerve fiber, an action potential is generated in the cochlear nerve. The transformation of mechanical vibration into an electrochemical signal is referred to as *forward transduction [15]*.

The nerve fibers situated in middle of the cochlea (modiolus) comprise the peripheral end of the cochlear nerve, which transfers the signal to the brainstem. From there,

central auditory pathways transmit sound information to the auditory cortex on both sides (Figure 4).

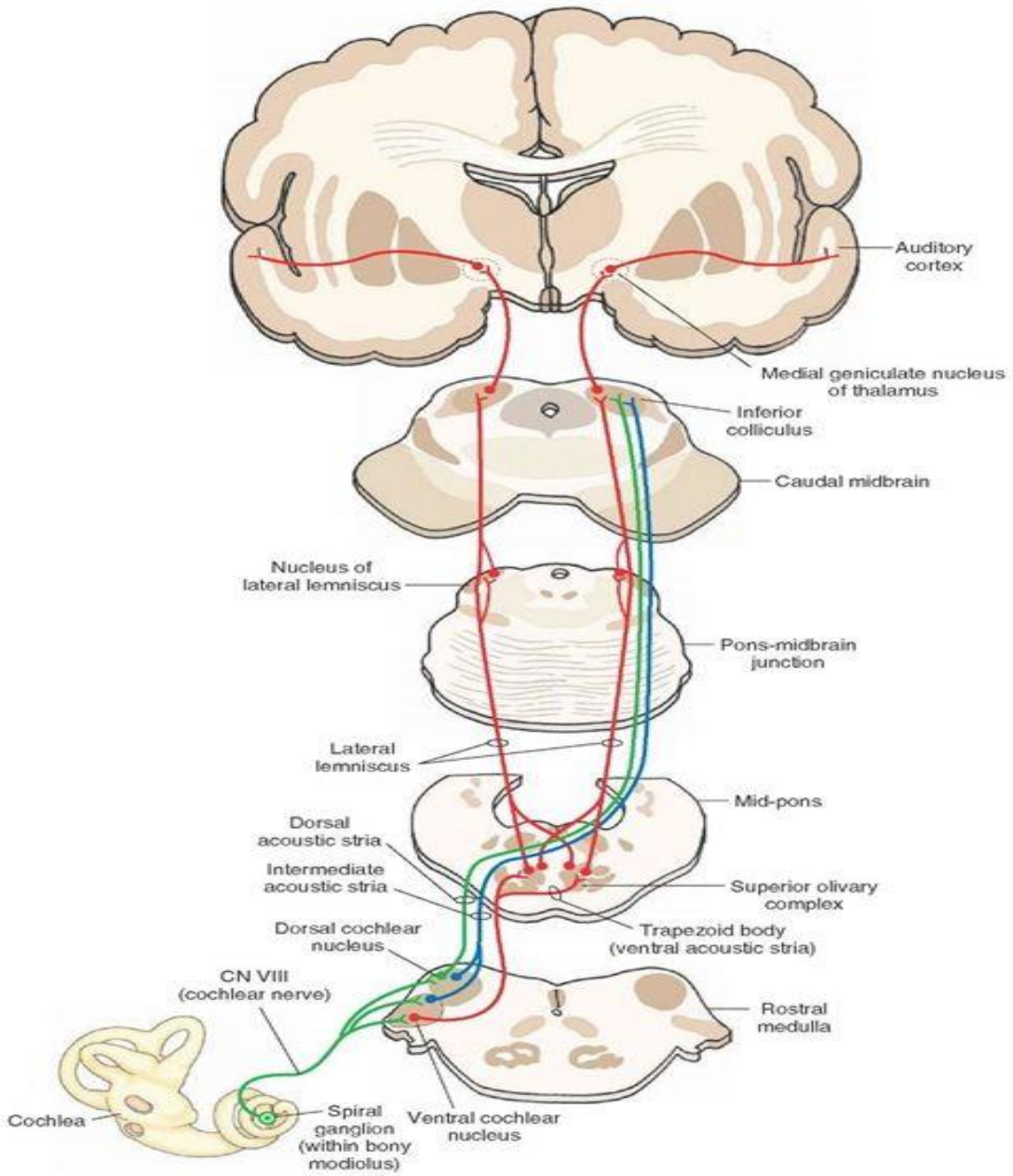


Figure 4. Central auditory pathway. http://what-when-how.com/neuroscience/auditory-and-vestibular-systems-sensory-system-part-2/ . Reprinted with permission

Hearing tests

There are numerous tests available for investigating different aspects of hearing. Among the most frequently used are different versions of *audiometry*, which tests a patient's ability to hear pure tones. The standard pure tone audiometry is usually performed in the frequency range 125 – 8000 Hz. Extended *high frequency audiometry*

tests frequencies > 8000 Hz but requires more resources. Other tests in this category include *play audiometry* and *Visual Reinforcement Audiometry (VRA)*, usually performed in children. Pure tone audiometry is a basic test that can be performed in most outpatient clinics. These tests provide a good impression of a patient's ability to hear pure tones in the tested frequency range, but it requires cooperation from the test subject. It is important to recognize that these tests provide no information about speech perception, although there is usually some correlation between results from pure tone audiograms and speech perception tests.

OtoAcoustic Emissions (OAE) is an objective test which registers a response from the outer hair cells of the cochlea to an external sound stimulus, and thereby provides information about the cochlear function. Distortion Products OAE (DPOAE) is a subtype of OAE which is more sensitive for high frequency hearing loss. *Auditory Brainstem Responses (ABR)* is another objective test using a stimulus presented through the ear canal or by an implant, of which a response can be followed from the level of the cochlea and the cochlear nerve to the midbrain. Objective tests do not require any active participation from the patient, but they are very sensitive to movements and ambient noise.

All the above-mentioned tests provide valuable information about a patient's ability to hear a stimulus, but they do not reflect the full picture. Additional tests are required to evaluate other aspects like speech perception, difficulties with hearing in noise, and sound localization. *Speech audiometry* is a widely available test often performed together with pure tone audiometry. This test evaluates the patient's ability to perceive words at given dB (loudness) levels. It is performed in a soundproof room and will therefore not reveal difficulties with speech perception in noise.

Hearing In Noise Test (HINT) is a speech perception test using sentences which was developed by Nilsson et al., with a validated Norwegian version by Myhrum et al. [16, 17]. The mean presentation level (in quiet or in noise) at which the patient can repeat 50% of the sentences correctly is defined as Speech Reception Threshold (SRT). When testing in noise, the masking noise is set at 65 dB. The difference between SRT and the noise level is usually expressed as a Signal-to-Noise Ratio (dB SNR), which tells us how much louder speech must be presented to be perceivable in background noise. For HINT in quiet conditions (HINT Q), results are presented as dBA (SRT). Some centers abroad use a set speech presentation level and adapts the noise level instead. The test can be performed either with headphones simulating free-field conditions, or with speakers in a sound field. While speech is presented form the front, the background noise, a standardized speech-spectrum noise, is added from one of three directions: Noise Front (NF, at 0° azimuth), Noise Right (NR, at 90° azimuth) and Noise Left (NL, at 270° azimuth). Results from normal-hearing young adults are presented in Table 1. Separate HINT scores from the pediatric population exist, but no age-matched HINT scores from the ageing general population are available [18]. HINT scores decline with ageing, possibly due to both expected ARHL and decline in

cognitive function, so this is important to consider when testing an ageing population [19-21].

Table 1. Headphone norms for the Norwegian HINT. The threshold and intelligibility change, defined as the expected difference in intelligibility between the mean (50th percentile) and the percentile at the head of each column. Individuals scoring below the 50th percentile are expected to have lower intelligibility, and those scoring above the 50th percentile are expected to have higher scores. H-scores, as described in the introduction paper, are also provided for each percentile.

Percentile	**2.5**	**5**	**10**	**20**	**25**	**30**	**40**	**50**	**60**	**70**	**75**	**80**	**90**	**95**	**97.5**
H-score	**51**	**59**	**68**	**79**	**83**	**87**	**94**	**100**	**106**	**113**	**117**	**121**	**132**	**141**	**149**
Quiet, Mn = 17.5, SD = 2.9															
Threshold (dBA)	23.2	**22.3**	21.2	19.9	**19.5**	19.0	18.2	**17.5**	16.8	16.0	**15.5**	15.1	13.8	**12.7**	11.8
Intelligibility change (%)	−52%	**−44%**	−34%	−22%	**−18%**	−14%	−7%	**0%**	7%	14%	**18%**	22%	34%	**44%**	52%
Noise front, Mn = −3.2, SD = 1.0															
Threshold (dB S/N)	−1.2	**− 1.6**	−1.9	−2.4	**−2.5**	−2.7	−2.9	**−3.2**	−3.5	−3.7	**−3.9**	−4.0	−4.5	**−4.8**	−5.2
Intelligibility change (%)	−18%	**−15%**	−12%	−8%	**−6%**	−5%	−2%	**0%**	2%	5%	**6%**	8%	12%	**15%**	18%
Noise right, Mn = −10.3, SD = 1.1															
Threshold (dB S/N)	−8.1	**−8.5**	−8.9	−9.4	**−9.6**	−9.7	−10.0	**−10.3**	−10.6	−10.9	**−11.0**	−11.2	−11.7	**−12.1**	−12.5
Intelligibility change (%)	−20%	**−17%**	−13%	−9%	**−7%**	−5%	−3%	**0%**	3%	5%	**7%**	9%	13%	**17%**	20%
Noise left, Mn = −10.4, SD = 1.1															
Threshold (dB S/N)	−8.2	**−8.6**	−9.0	−9.5	**−9.7**	−9.8	−10.1	**−10.4**	−10.7	−11.0	**−11.1**	−11.3	−11.8	**−12.2**	−12.6
Intelligibility change (%)	−20%	**−17%**	−13%	−9%	**−7%**	−5%	−3%	**0%**	3%	5%	**7%**	9%	13%	**17%**	20%
Noise Composite, Mn = −6.7, SD = 0.8															
Threshold (dB S/N)	−5.1	**− 5.4**	−5.7	−6.0	**−6.2**	−6.3	−6.5	**−6.7**	−6.9	−7.1	**−7.2**	−7.4	−7.7	**−8.0**	−8.3
Intelligibility change (%)	−14%	**−12%**	−9%	−6%	**−5%**	−4%	−2%	**0%**	2%	4%	**5%**	6%	9%	**12%**	14%

Table 1. HINT scores from young, normal hearing, general population with percentiles. Myhrum et al [17]. Reprinted with permission.

As mentioned above, these hearing tests all have strengths and weaknesses. A full audiological workup should include several of the described tests. However, many of them are quite time consuming, and they require special equipment and professional skills which are not available in every clinic. The most commonly performed hearing test for detection and grading of ototoxicity in the literature is pure tone audiometry. Studies have shown that extended high-frequency audiometry and DPOAE have higher sensitivity for early detection of ototoxic hearing loss, which can be important during treatment, especially in children [7, 22-25]. These tests are however unavailable in many clinics. If extended high-frequency testing is to be used it is very important to perform baseline tests since hearing loss at frequencies > 8 kHz is present in many patients pre-treatment [14]. In the author´s opinion, DPOAE and extended high-frequency tests are of less value for long-term follow up of adult patients because of low specificity and limited clinical relevance. Pure tone audiometry up to 8 kHz, including speech audiometry, is a readily available test that gives a good impression of a patient's hearing. Speech audiometry, although performed in silence and not including background noise, enhances the utility. When available, the HINT test is preferable since it adds valuable information about hearing in a setting which is closer to everyday life. A draw-back is that it is time consuming and, at least in Norway, currently only available in specialized centers.

Questionnaires

Over the last decades Patient-Reported Outcome Measures (PROMs) have gained increased attention and the patients' feedback as to how they evaluate their disease,

treatment, surgery etc. is important. Hearing loss is readily measured and quantified, but to evaluate the clinical impact of a hearing loss it is also important to include PROMs. When using self-reports in long-term follow-up, one should keep in mind that needs and expectations regarding hearing are likely to change with age. Hearing is expected to decrease with increasing age, but elderly may not be as exposed to background noise and difficult listening situations in daily life as younger people. A young person who is exposed to substantial environmental noise is therefore likely to be more bothered by a high frequency hearing loss than an older person with the same hearing loss with less background noise exposure, and who is perhaps also surrounded by people with similar hearing. Questionnaires including the patients' subjective opinion about their own hearing are therefore important to put the results from the hearing tests into a clinical setting.

Hearing loss

Hearing loss can be classified based on the site of damage in the ear or in the peripheral or central auditory pathways. A conductive hearing loss is caused by dysfunction in the parts conducting sound vibrations mechanically. A sensorineural hearing loss reflects a damage of neural elements. While most conductive hearing losses predominantly cause a low-frequency loss, most sensorineural hearing losses first affect the higher frequencies. Other causes of hearing loss such as central and psychogenic hearing loss do not primarily represent a dysfunction of the ear or the peripheral auditory pathways and will not be discussed in further detail here.

A conductive hearing loss can be caused by any mechanical disruption or blockage preventing the optimal transmission of sound waves to the inner ear, including obliteration of the external ear canal (e.g. cerumen), tympanic membrane disorders (e.g. perforation), or middle ear disorders (e.g. otitis media, ossicular chain disruption or fixation, cholesteatoma, tumors, malformations, etc.). In most cases, the cause of a conductive hearing loss can be identified. Many are potentially reversible, either with surgery or by spontaneous improvement.

A sensorineural hearing loss on the other hand, is usually caused by damage to the inner ear structures, particularly the organ of Corti with the inner ear hair cells, and the stria vasculare. Since the cochlear structures have little or no regeneration potential, these changes are generally permanent [26, 27]. There are many causes of sensorineural hearing loss including genetics, noise, ischemia, toxicity, inflammation, malformations, trauma, etc. Since most of these tend to affect the higher frequencies, and patients may have a combination several factors, it can be difficult to identify and separate one cause from the other, especially when based solely on results from hearing tests.

The Global Burden of Disease Study found that hearing loss is the fourth leading cause of disability globally when measuring years lived with disability [28]. The prevalence varies slightly, but it is estimated that about one third of the population above 60 years of age have some degree of hearing loss and 80% aged > 85 years have hearing loss that affects daily communication [29-31]. With an ageing population in most developed countries this problem is likely to increase over the upcoming decades. Untreated hearing loss in adults is also known to have psychosocial and economic effects as well since they often lead to social isolation and reduced quality of life [32-34]. Older persons with hearing impairment have higher rates of hospitalization and death compared to age-matched persons with normal hearing [35, 36]. Several studies have also suggested that hearing loss is an important risk factor for developing dementia, and it is possibly the most important potentially modifiable factor for developing dementia [37-40]. Therefore, recognition and hearing rehabilitation of hearing loss is important, since it is likely that early identification and intervention with hearing aids will decrease the risk of cognitive decline and dementia, although evidence is limited so far.

Age-Related Hearing Loss

Age-Related Hearing Loss (ARHL) is a term used to describe the progressive hearing loss that normally occurs with increasing age [2]. It is characterized by a symmetric, bilateral, sensorineural hearing loss [41]. The pathogenesis is thought to be multifactorial and includes ageing, noise exposure, genetic susceptibility, otological disorders, and exposure to ototoxic agents [2, 41]. These combined effects lead to a loss of outer and inner hair cells, loss of central and peripheral neurons, atrophy of the stria vasculare, and loss of cochlear nerve synapses [41, 42].

Since ARHL is multifactorial and dependent on both external and genetic factors, there is a considerable variability between individuals, and it is not possible to predict ARHL on an individual basis. It can also be very difficult to single out the relative contribution of each factor to the total loss, especially with long term follow-up. A large study in Norway, Helseundersøkelsen i Nord-Trøndelag (HUNT), examined hearing thresholds of more than 50 000 people in order to determine sex- and age-specific hearing thresholds that can serve as an estimated expected rate of ARHL in the Norwegian population (Figure 5).

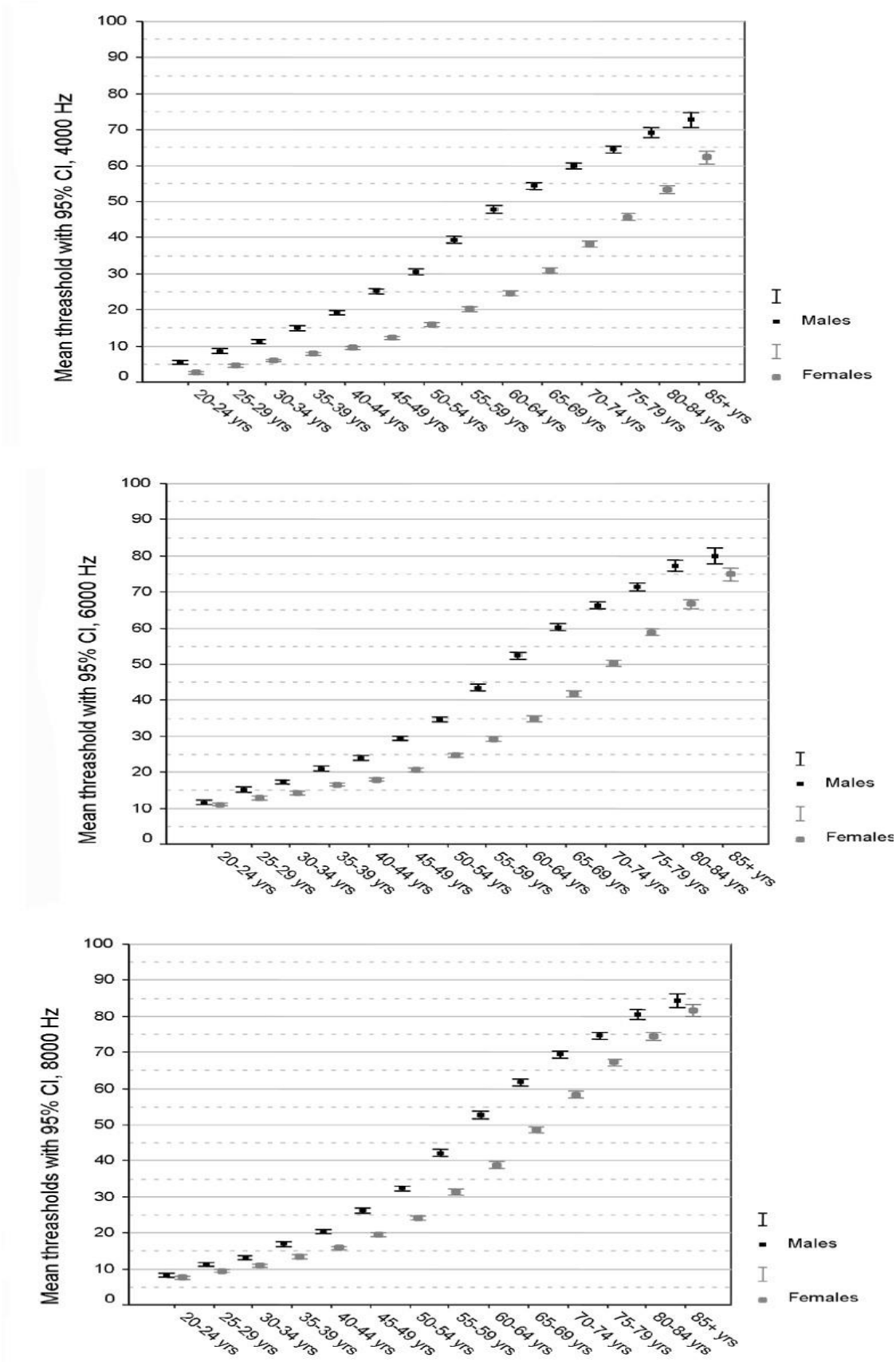


Figure 5. Mean unscreened hearing thresholds (mean of both ears) for 4, 6 and 8 kHz with 95% confidence intervals specified for age and gender from the HUNT II study [43]. Reprinted with permission.

HUNT

Helseundersøkelsen i Nord-Trøndelag (HUNT) is a general health care screening performed in the Norwegian county of Nord-Trøndelag. This is a rural county with relatively stationary population and five small towns, some heavy industry and some farms. The first survey (HUNT I) was conducted between 1984 – 1986 and all persons ≥ 20 years and living in this county (according to public address registry provided by the governmental Statistics Norway) were invited to participate. This survey focused mainly on hypertension and diabetes. Between 1995 – 1997 a second survey (HUNT-II) was performed. In this survey, the participants were also invited for audiometry with the purpose of determining age- and sex-specific hearing thresholds in the Norwegian "general population" [43, 44]. A total of 51 975 subjects out of 82 141 invited (63%) gave their written consent to participate. Audiometry was performed in the same session as the general health examination for all participants except for 5 110 patients living in the town of Levanger, since the general health exam was already performed in this town when the audiometric testing started. It was important to include the hearing test in the same session as the general health examination since it decreases the risk of selection bias towards participants with poorer hearing as might have been the case if patients were invited for hearing test separately.

The audiometry was performed by two ambulant teams, each including at minimum one authorized operator and one assistant. Each team conducted audiograms in 5 parallel, self-administered, automatic audiometers linked to a computer. The audiometers were calibrated before start, and every 6 months during the survey. The operators also checked the audiometers every day prior to testing. In-booth background noise was measured for random samples of rural examination room and for all 5 towns. Results were within the ISO 8253-1:1989 standard at 250 – 8000 Hz, but at the criterion at 200 Hz.

Cisplatin

Michele Peyrone first described the compound *cis*-$[Pt(NH_3)_2Cl_2]$ in 1844 known as Peyrone's salt [45]. More than 100 years later Barnett Rosenberg discovered that platinum-containing compounds inhibited cell division. He was investigating the effects of an electric field on bacterial growth when he accidentally discovered that E. coli ceased to divide when placed in the electric field. He eventually discovered that

this was due to the platinum electrodes he was using to deliver the current [46]. This led to his article published in 1969 showing that cisplatin treatment caused marked tumor regression in rats with sarcoma (Figure 6) [47]. In the following years, extensive research into cisplatin effect on other tumor cell lines led to FDA approval in the US for the use of cisplatin treatment for testicular and ovarian cancer in December 1978.

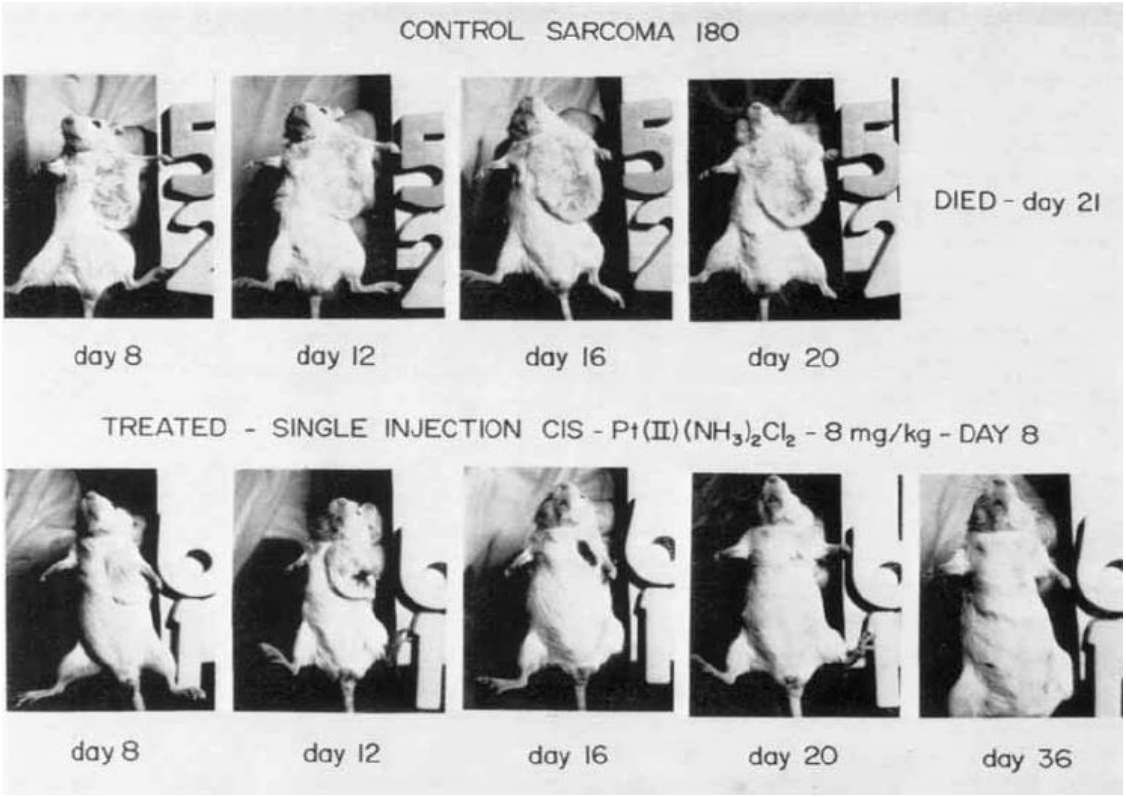


Figure 6. Marked tumor regression in rat with sarcoma treated with cisplatin compared to control. Rosenberg et al [47]. Reprinted with permission

Since then, cisplatin has proved to be an effective and widely used chemotherapeutic agent for the treatment of solid tumors including ovarian, testicular, cervical, lung, head and neck, and bladder cancers in adult patients. It is also standard therapy for many types of cancer in children, including neuroblastoma, osteosarcoma and hepatoblastoma [3, 4, 6, 13, 48, 49]. However, CBCT has considerable acute and long-term toxic side effects including nausea/vomiting, neurotoxicity, ototoxicity, and nephrotoxicity [3, 50, 51].

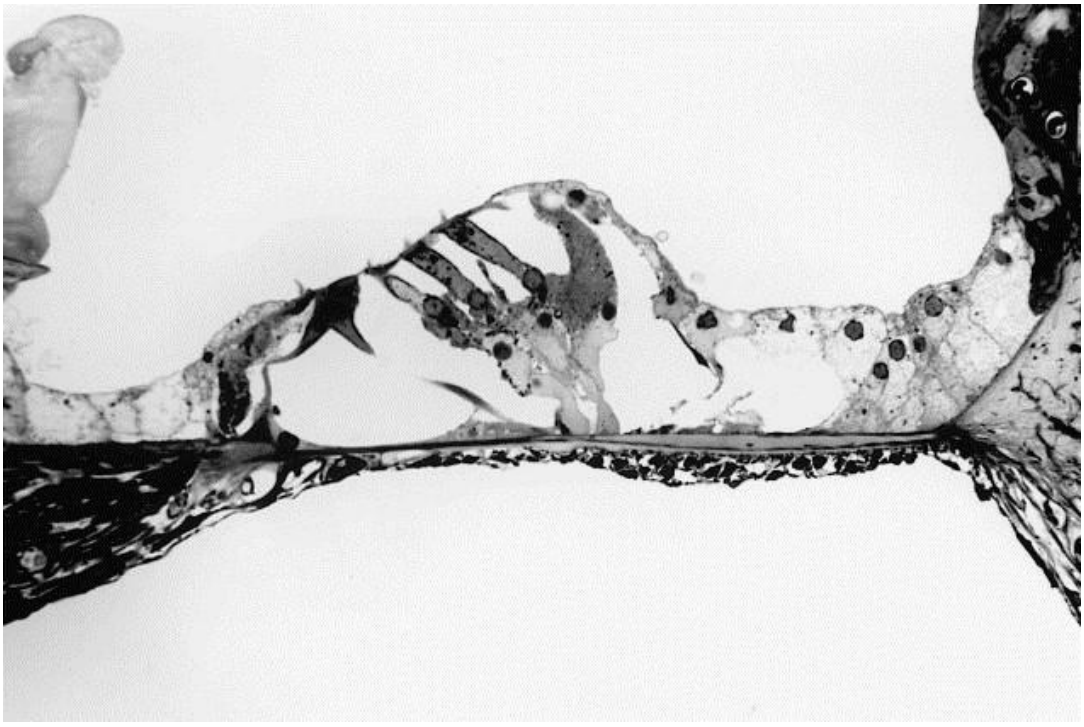
Ototoxicity

Ototoxicity (toxicity to the ear) is a side effect of treatment with several different drugs including chemotherapeutic agents, aminoglycosides, loop diuretics, and

salicylates [52]. Some of these effects are considered reversible, but particularly aminoglycosides, commonly used for severe infections, and platinum-based chemotherapy are known to cause irreversible hearing loss which initially affects the higher frequencies [3, 24, 50, 52].

Ototoxicity is a well-documented side effect of CBCT [3-7, 13, 50, 53]. Cisplatin targets the DNA of proliferating cancer cells by the inhibition of DNA synthesis, suppression of RNA transcription, cell cycle arrest, and apoptosis [54]. Since the cells of the inner ear proliferate and regenerate slowly or not at all, the ototoxic damage within these cells is thought to be caused by the release of proapoptotic factors and the generation of toxic levels of reactive oxygen species (ROS), both of which can initiate cell death through caspase activation [55].

Cisplatin-related ototoxicity mainly affects three sites of the inner ear: the organ of Corti (especially the outer hair cells), the lateral wall of the scala media including the stria vascularis and the spiral ligament, and the spiral ganglion cells (Figure 7) [49, 50, 53]. This damage is regarded as permanent because inner ear cells generally have a poor regenerative potential, or indeed none at all [56-58]. CBCT initially affects the basal turn of the cochlea, resulting in a high-frequency hearing loss [3, 6, 7, 13, 50, 53]. These changes are dose-dependent, but with great individual differences in susceptibility, probably due to genetic variations [5, 50, 53, 59-61]. Several different genes have been suggested to be involved, but the genetic susceptibility seems to be dependent on several rather than one single gene [5, 59-62].



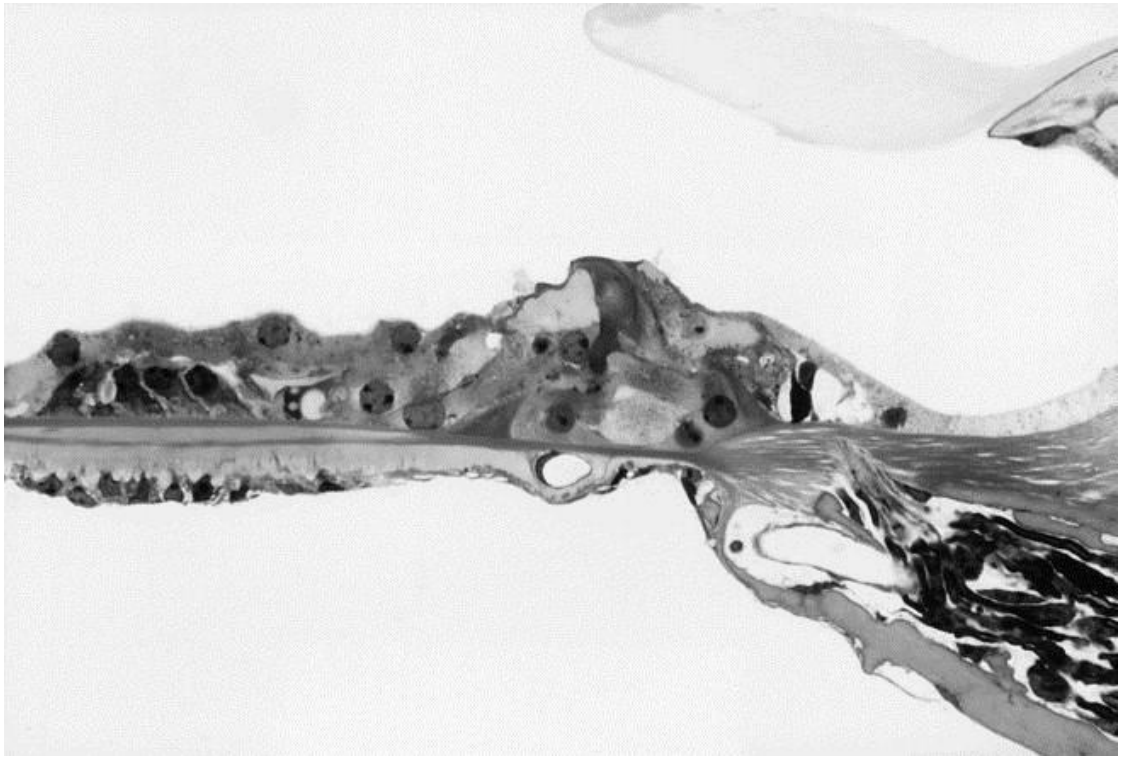


Figure 7. Light micrograph of the organ of Corti from the basal cochlear turn from a non-treated guinea pig (upper) and from a guinea pig treated with cisplatin at a daily dose of 1.5 mg/kg for 8 consecutive days (lower). Cardinal et. al [63]. Reprinted with permission.

It has also been suggested that CBCT can lead to adverse health conditions that usually occur during ageing "premature aging" [64]. Recent findings that cisplatin can be retained in both serum and cochlea for several decades after treatment raised the question if the ototoxic damage could continue to progress over many years post-treatment [9, 13, 49, 64-68]. Therefore, long term follow-up with audiometry is often recommended. It is however not known how long this progression continues. Of particular interest is how the expected ARHL affects these patients, since both ARHL and CBCT-related hearing loss initially affect the higher frequencies and similar sites of the cochlea.

Prevention of Ototoxicity

Despite the ototoxic side effect, cisplatin is still the cornerstone treatment for several types of cancer because of the extraordinary anti-tumor effect. Hence, prevention of ototoxicity has been an important goal, and several studies have tried to find ways to minimize the ototoxic effects of cisplatin [22, 52, 69-72]. Since Reactive Oxygen Species (ROS) is thought to play an important role in cisplatin-related ototoxicity, free radical scavengers are suggested as possible otoprotectants. Antioxidants and substances that increase endogenous antioxidant production like amifostine, N-acetylcysteine, vitamin E, and sodium thiosulfate have shown promising results in

preclinical trials [22, 52]. Since formation of free radicals is an important part of the anti-tumor effect of cisplatin, there are concerns that systemic treatment with free radical scavengers will decrease the anti-tumor effect. A possible way to bypass this problem is to inject the protective substance into the middle ear to let it diffuse across the round window into the cochlear fluid [73].

Another currently explored approach is to selectively inhibit transporters which mediate the uptake of cisplatin to the inner ear. The transport proteins OCT2 and CTR1 were found to facilitate the transportation of cisplatin into the hair cells [74, 75]. If the tumor cells do not exhibit these transporters, then selective protection of nonmalignant tissue might be possible. However, so far no otoprotectants are recommended as a part of routine cisplatin treatment [76].

Ototoxic grading systems

Numerous ototoxic grading systems have been developed to detect and grade ototoxicity [77-83]. Most of these classifications are based on pure tone audiometry, either as absolute values or as threshold shifts compared to a baseline audiogram.

The Brock scale was originally developed to detect cisplatin-induced hearing loss in pediatric patients [78]. The scale is based on threshold cut-off at ≥ 40 dB with grade 1 defined as thresholds ≥ 40 dB at 8 kHz and increasing grade as lower frequencies are involved.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) is a classification widely used in the oncologic community to describe unwanted effects associated with oncologic treatment, including ototoxicity [77]. This classification is primarily based on threshold shifts compared with baseline audiograms. Grade 1 includes threshold shifts of 15 - 25 dB at two contiguous frequencies. NCI-CTCAE also contains a grading system for patients without baseline audiograms, and a separate grading for pediatric patients.

Several other ototoxic grading systems have been developed over the past decades, but they will not be described in further detail since they are less commonly used, and hence beyond the scope of this thesis.

There are also several classifications of general hearing loss, though not specifically developed for ototoxicity. In two of the most common ones, American Speech-language-Hearing Association (ASHA) classification and World Health Organization (WHO), hearing loss is described based on measured hearing thresholds relative to defined normal hearing thresholds (Figure 8) [84, 85].

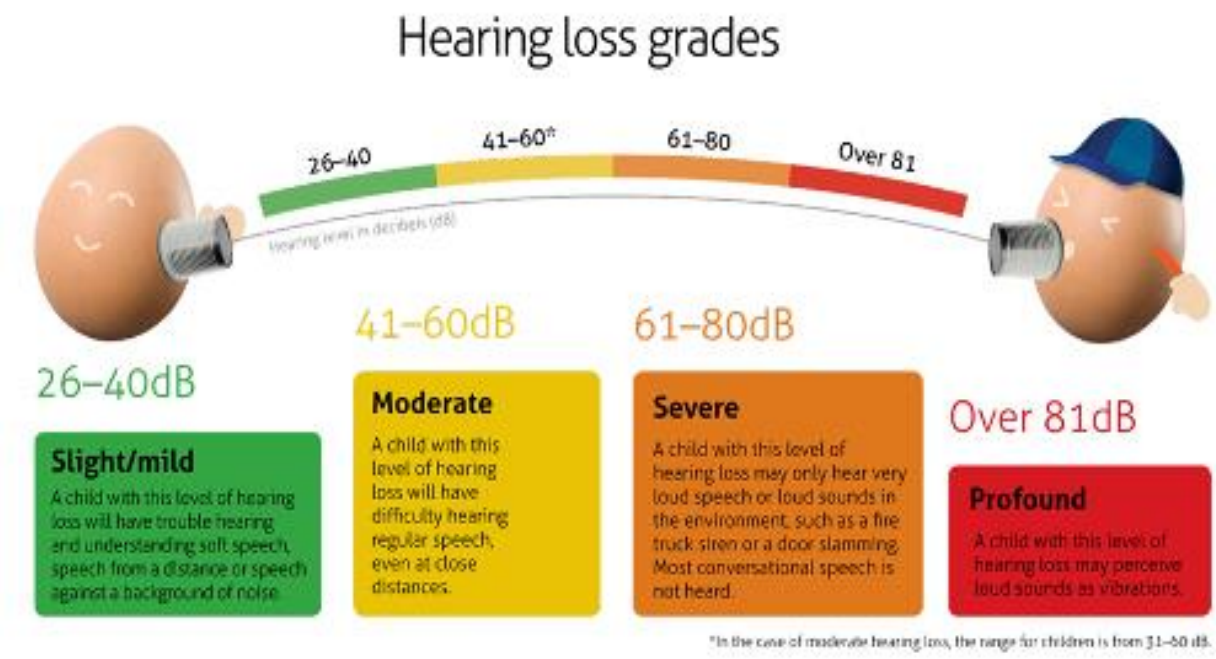


Figure 8. WHO classification of hearing loss grades. Reprinted with permission

Most of the ototoxic grading systems are designed for detecting ototoxic damage during and immediately after treatment. The ASHA and WHO classifications, on the other hand, are useful when describing a patient's hearing at a given point compared to a defined "normal hearing" based on healthy young adults. However, none of these classifications are suitable for detecting ototoxic damage in a very long-term perspective, because they do not consider the expected high-frequency hearing loss in the general population. Hence, none of them will be able to distinguish between ARHL and ototoxicity in an ageing group of cancer survivors. We therefore chose to describe our results as thresholds compared to a control group or to a general age-matched population instead of using these classifications.

Aims of the project

The overall aim of the project was to describe CBCT-related ototoxicity in an extended long-term perspective over three decades. The different aspects explored were hearing thresholds (audiometry), speech perception in noise and quiet, self-reported hearing as estimated by questionnaires, and tinnitus. For available variables we studied changes between two different surveys within a period of three decades post CBCT. Finally, an important part of the project was to compare the development of CBCT-related hearing loss with the hearing loss in the general population over time.

Paper I

Paper I is a cross-sectional case-control study aiming to describe hearing loss and tinnitus in women who received CBCT for Malignant Ovarian Germ Cell Tumor (MOGCT) up to 30 years post treatment. In a sub-analysis we measured SPC-levels in serum and analyzed if they correlated with the degree of ototoxic damage.

Paper II

In this longitudinal study we wanted to investigate how hearing loss in Testicular Cancer Survivors (TCS) treated with CBCT evolved between the first and the third decade post treatment. We also compared it with the expected course of age-related hearing loss in the general population.

Paper III

Paper III is a cross-sectional case-control study in which we aimed to evaluate the clinical relevance of CBCT-related hearing loss for TCS 30 years post treatment by testing speech perception in silent and noisy conditions, using the Hearing In Noise Test (HINT). Further, these results were compared with self-reported hearing loss.

Materials and methods

Paper I presents the audiological findings from a cross-sectional, multidisciplinary, long-term survey of MOGCT survivors treated between 1980 – 2009. Papers II and III are based on longitudinal multidisciplinary follow-up surveys of TCS treated with CBCT between 1980 – 1994. Common for all patients, and the reasons for studying survivors of MOGCT and TC, is the combination of their young age at the time of diagnosis/treatment, and an exceptionally good long-term survival prognosis which is making them very well suited for long-term studies of CBCT-related adverse effects.

Paper I

Paper I is based on data collected from a national survey in 2013/2014 on MOGCT survivors identified through the Cancer Register of Norway (CRN). Inclusion criteria for the survey were:

- Diagnosed with MOGCT as their first lifetime malignancy between 1st of January 1980 and 31st of December 2009.
- Alive and living in Norway as of June 2012
- Minimum 18 years of age at the time of survey
- Cancer-free during the preceding 3 years

One hundred and sixty-three patients had been diagnosed with MOGCT during this period, of which 153 were still alive and living in Norway. These 153 MOGCT survivors were invited to participate in a 2-day multi-disciplinary survey on long-term health effects, which included several out-patient consultations at Oslo University Hospital (OUS) and the completion of a mailed questionnaire. The out-patient consultations included general clinical examination (including BMI and blood pressure), gynecological examination (including ultrasound), otologic examination including tympanometry and audiometry, cardiac function (including ultrasound), neurological examination including objective tests for peripheral neuropathy, and blood tests. Blood samples were collected from fasting patients at 8 am on day 2 for analysis. A serum sample was frozen at -70° C for later analysis.

Ninety-four patients responded, 74 of whom accepted both questionnaire completion and out-patient visit (Figure 9). These patients were then grouped into Cases (patients who had received CBCT), and Controls (patients with other treatment than CBCT).

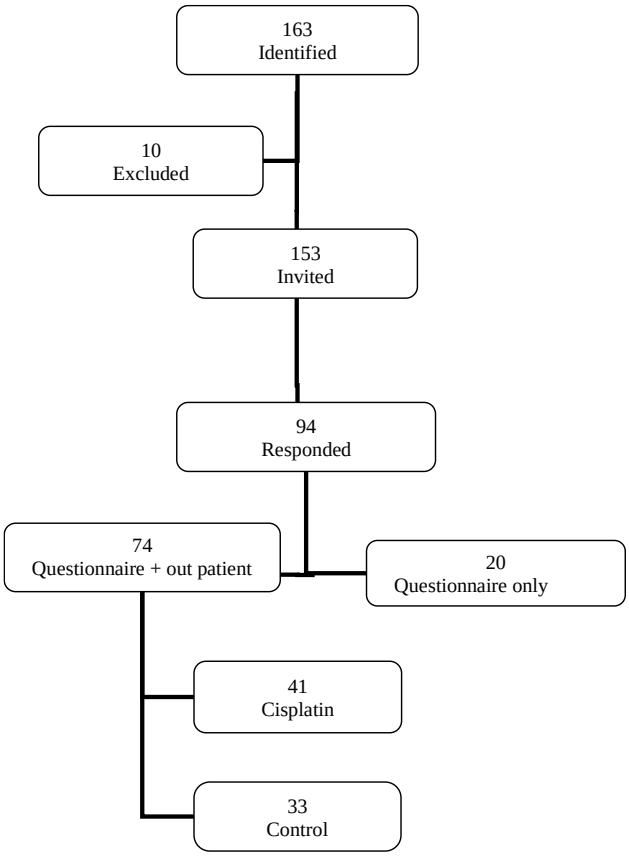


Figure 9. Flow chart of patient selection Paper I

Paper II and III

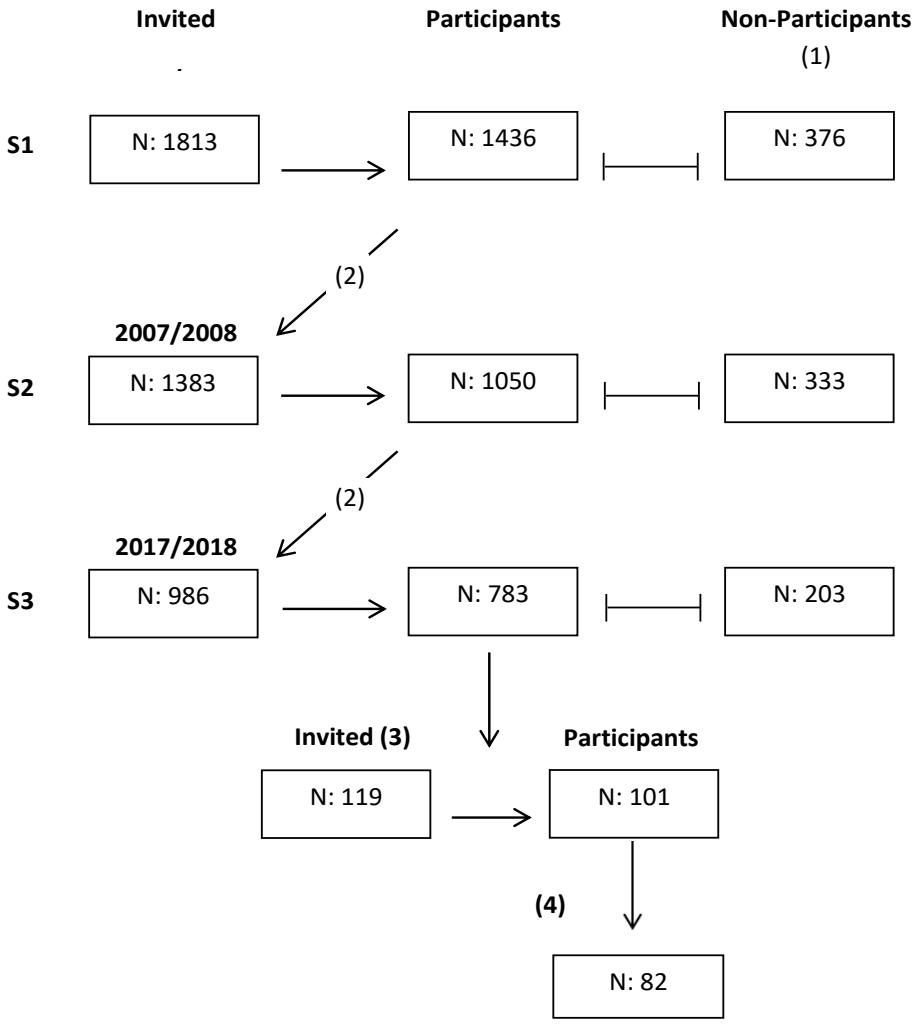
Papers II and III are based on longitudinal, multicenter follow-up studies of TCS treated at the four university hospitals in Norway between 1980 and 1994. Inclusion criteria for the survey were:

- Diagnosed and treated for TC as their first malignancy between 1st of January 1980 and 31st of December 1994.
- Alive and living in the health care region of Oslo University Hospital (OUS) as of January 2016
- Minimum 18 years of age at the time of the first survey

- Participation in all three surveys

The first survey (S1) was conducted between 1998 – 2001, S2 between 2007 – 2008, and S3 between 2017 – 2018. One thousand eight hundred and fourteen patients were identified and invited to participate in S1. Only patients included in the previous survey were invited to the subsequent (Figure 10). The time between surveys was defined as *survey interval*.

(S1; S2; S3) and otologic examination at S3



(1) Alive, with known address

(2) Difference explained by death/Unknown address/Withdrawal/Logistic error

(3) Only patients in the health care region of Oslo University Hospital were invited.

(4) Chemotherapy; Audiogram from S1; Living in South-East Norway.

Figure 10. Flow chart of study population Paper II and III.

Only patients living in the south-east health care region of Norway (Helse Sør-Øst) were included due to financial restrictions in the project. Paper II is restricted to patients with an available audiogram from S1. As there were no audiograms in S2, the survey interval in this paper refers to the time between S1 and S3.

Paper III includes the same patients as Paper II, but the sample is supplemented with patients without a previous audiogram from S1.

Since, to the best of our knowledge, no age-adjusted data for HINT scores exists, we also included a control group in Paper III consisting of age-matched randomly selected males from the LiRe public health care survey who were already serving as a control group for a cardiologic survey at our hospital [86]. LiRe is a public health survey inviting all persons > 18 years in the Norwegian county Lier (just outside Oslo) to participate. Nineteen controls from LiRe were supplemented by 11 age-matched male healthcare workers in the hospital because in view of the SARS-Cov-2 pandemic, it was deemed unjustifiable to bring in healthy persons to the hospital just to serve as controls.

Treatment

Malignant ovarian germ cell tumor

Prior to the cisplatin era, MOGCT patients without metastases were treated primarily with surgery, occasionally supplemented by radiotherapy. Metastatic disease treatment included adriamycin and alkylating agents in combination with surgery and radiotherapy. After the FDA approval of cisplatin in 1978, cisplatin was gradually introduced into the treatment regimen for metastatic MOGCT from the early 1980s. The treatment usually consisted of surgery combined with three-week cycles of cisplatin given in combination with bleomycin and vinblastine (CVB) or combined with etoposide and bleomycin (BEP). Generally, 100 mg/m² cisplatin was given at each cycle. Initially (1980s and early 1990s) some patients were given more than three cycles of CBCT, but the standard treatment was later restricted to three cycles [87].

Testicular cancer

Treatment followed protocols of either the Swedish-Norwegian Testicular Cancer Project or the European Organization for Research and Treatment of Cancer Genito-Urinary Group [88-90]. All patients were operated with orchiectomy and metastatic patients received three or four cycles of CBCT, most often in combination with vinblastine and bleomycin (CVB) or bleomycin and etoposide (BEP) with a standard cisplatin dose of 100 mg/m² per cycle [91]. In the beginning of the cisplatin era in the early 1980s, some patients received higher cisplatin doses per cycle [92]. A few patients with recurrent disease also received > 4 cycles [93].

Questionnaires

Both TCS and MOGCT survivors who accepted the invitation to participate in the surveys, were asked to fill out comprehensive questionnaires sent to them by mail. For TCS, similar questionnaires were used in all three surveys (S1, S2 and S3). The Scale for chemotherapy-induced long-term neurotoxicity/ototoxicity (SCIN) (Appendix) was included in all questionnaires. The validated SCIN instrument contains questions regarding peripheral neuropathy and subjective hearing/tinnitus, and was validated in connection with the S1 study of TCS [48]. In S3, a question about hearing in noise was added since this is a very common problem for patients with high-frequency hearing loss.

Patients were also asked about tinnitus by the otologist. Those who reported tinnitus were then asked to complete the Tinnitus Handicap Inventory (THI) and the tinnitus VAS score along with the tinnitus question included in SCIN [94]. THI contains 25 questions and grades tinnitus according to McCombe's grading system as no interference with sleep or daily activities (score 1 - 16), mild (17 - 36), moderate (37 - 56), severe (57 - 76) and catastrophic (77 - 100) [95]. The questionnaire is validated and translated to Norwegian. Patients with a high THI score or severe subjective complaints were counselled regarding tinnitus, and if motivated they were referred to rehabilitation.

Questionnaires from patients with unilateral deafness or severe asymmetric hearing loss that were considered unlikely to be a result of CBCT were excluded.

Hearing tests and otological examination

TCS participating in S1 underwent otoscopy by an oncologist prior to testing. In TCS at S3 and in MOGCT survivors, otological examination including otomicroscopy was performed by an ENT specialist or senior resident prior to testing.

At S1, audiometry was performed for the frequencies 0,125 – 8 kHz in a soundproof room using the Micromate 304® Screening Audiometer (MadsenElectronics, Taastrup, Denmark). MOGCT survivors and TCSs in S3 were tested for the same frequencies in a soundproof testing room using the Aurical® audiometer. Bone conduction was performed in case of thresholds worse than 20 dB to exclude conductive hearing loss. Ears with a conductive hearing loss, deemed unlikely to be a result of CBCT, were excluded from further analyses. The average thresholds from both ears were used for all surveys. For patients with severe asymmetry/single-sided

hearing loss, only the better ear was included. Measured results of audiograms were termed *absolute hearing thresholds.*

All audiograms were then age-adjusted for each patient, one tested frequency at the time, by subtracting the age-, sex- and frequency-matched threshold from the general population in the HUNT study from the measured thresholds in the study population. The resulting value was called *age-adjusted threshold* and shows how much the patient's hearing differs from 0, which represents the expected threshold in the general population.

We defined *absolute hearing loss* as absolute hearing threshold of > 20 dB at any frequency, and *age-adjusted hearing loss* as age-adjusted hearing threshold of > 20 dB at any frequency.

Patients with subjective complaints of hearing loss and an audiogram indicating benefit from hearing aids were referred for fitting of such at their local audiology center.

Speech in noise perception was assessed with the Norwegian version of HINT performed in an anechoic chamber under headphones using the HINT Pro SW Bio-logic® [17]. Three noise conditions (in addition to testing in quiet) were used: Noise Front (NF, 0°), Noise Right (NR, 90°) and Noise Left (NL, 270°) with sentences always presented from the front (0°). The noise level was fixed at 65 dBA. The resulting score represents the ratio between the speech level and noise level (signal-to-noise ratio, SNR) expressed in decibels. The test estimates the SNR at which the listener can repeat 50% of the sentences correctly. Increasing SNR values reflect worse speech perception and negative values mean that speech is understood although noise is louder. For the noise conditions (HINT NF, HINT NR and HINT NL), scores are expressed as dB SNR. Additionally, speech perception in quiet was assessed (HINT Q). The HINT Q score is not a ratio, but represents the speech reception threshold (SRT, expressed in dBA) at which 50% of the sentences are repeated correctly.

Serum Platinum Concentration (SPC)

At the time of the survey, serum was collected and stored at -80 °C for approximately two years. Samples were then sent to St. Olavs hospital in Trondheim for determination of cisplatin SPC. Details on the methodology are described elsewhere and is beyond the scope of this thesis [9].

Statistical analyses

All data analyses were performed with the assistance of a statistician, using SPSS software for PC version 21 and 25 (IBM Corp Chicago, IL). The level of significance was set at to 5% for all the studies, and all tests were two-sided. Continuous variables were described with median and range, while categorical variables with counts and proportions.

Paper I and III

The observation time was defined as the number of years between the date of diagnosis and the date of survey. Crude differences between Cases and Controls were assessed using the Mann-Whitney Wilcoxon test, while associations between pairs of continuous numerical variables or pairs of ordinal variables were assessed using the Spearman correlation. Multiple linear regression was used to determine factors that were associated with HINT scores. All assumptions for linear regression were fulfilled and residuals followed standard normal distribution.

Paper II

Follow-up time was defined as time in years between treatment and S1 or S3, respectively. The term *survey interval* refers to the number of years between S1 and S3. Wilcoxon signed ranks test was used to evaluate differences between groups and hearing thresholds at S1 and S3. A linear mixed model for repeated measures was used to estimate the effect of the survey interval, of the cisplatin dose (standard vs higher) and of age at S1 on age-adjusted threshold shifts from S1 to S3, with separate models fitted for frequencies 4, 6 and 8 kHz.

Main findings

Patients

The first paper includes 74 women treated for MOGCT between 1980 – 2009. All participants underwent clinical examination and answered the questionnaire. Patients were dichotomized into 41 Cases and 33 Controls based on CBCT or other treatment. The follow-up time since treatment was similar in both groups (15 and 16 years respectively), but the Controls were significantly older (35 vs 50 years at survey).

The second paper includes 82 TCSs treated with CBCT between 1980 – 1994 who had audiograms from both S1 and S3. Median age was 61 years with a median follow-up time of 31 years.

The third paper includes 101 TCS (Cases) also treated with CBCT between 1980 and 1994 and 30 Controls with a median age of 60 years and 61 years, respectively. Median follow up time was 30 years for Cases.

Audiometry

In Paper I we found that the absolute hearing thresholds did not differ between Cases and the significantly older Controls, but after age-adjustment, Cases had significantly worse hearing than Controls at 4, 6 and 8 kHz. The results from Paper III support this finding, with significantly worse age-adjusted thresholds at 6 and 8 kHz for Cases compared with Controls. There were no statistically significant differences in the lower frequencies or in PTA.

Most Cases (both MOGCT and TCS) had absolute hearing thresholds worse than 20 dB for at least one frequency, but after age-adjustment the proportion of Cases with age-adjusted hearing loss was more than halved among MOGCT (51% to 22%) and 3-foldly reduced among the TCS (96% to 33%).

Cases with long observation time (> 15 years) in Paper I exhibited worse age-adjusted thresholds at 6 and 8 kHz than matched Controls (Figure 11). This difference was not seen with shorter follow-up time. However, it is important to notice that Cases with longer follow-up also received higher CBCT doses as the standard cisplatin dose generally decreased during the time period from which we included patients.

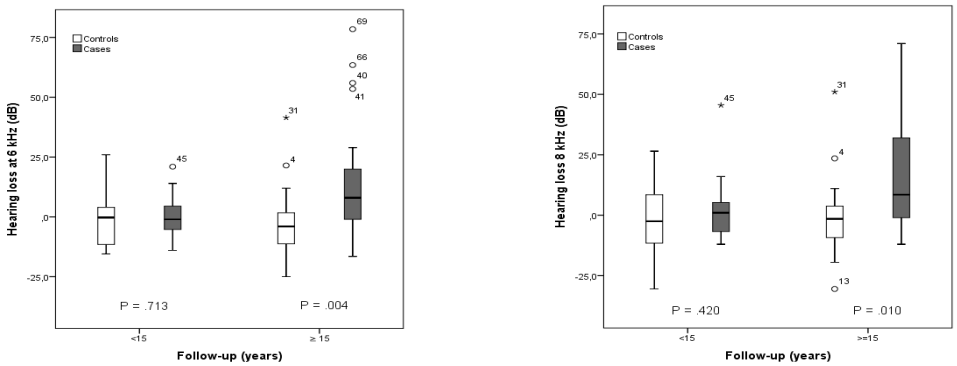


Figure 11. Age-adjusted hearing thresholds at 6 and 8 kHz among patients with observation times < 15 and ≥ 15 years.

In Paper II we found that absolute hearing thresholds at 4, 6 and 8 kHz increased significantly during the 20 years between S1 and S3. However, after adjusting for expected age-related hearing loss during this time period, hearing thresholds approached those of the control group (HUNT) during the survey interval (Figure 12). Similarly, the proportion of patients with absolute hearing loss increased from 73% to 94% between the two surveys, while after age-adjustment the corresponding numbers where 45% and 30%. We found that during the survey interval the high-frequency hearing thresholds of patients > 40 years old at S1 approached those of the general population significantly more than for patients ≤ 40 years at S1 (Figure 13a). Survivors having received higher doses of CBCT had significantly worse high-frequency thresholds than those who received lower doses during the whole survey interval (Figure 13b).

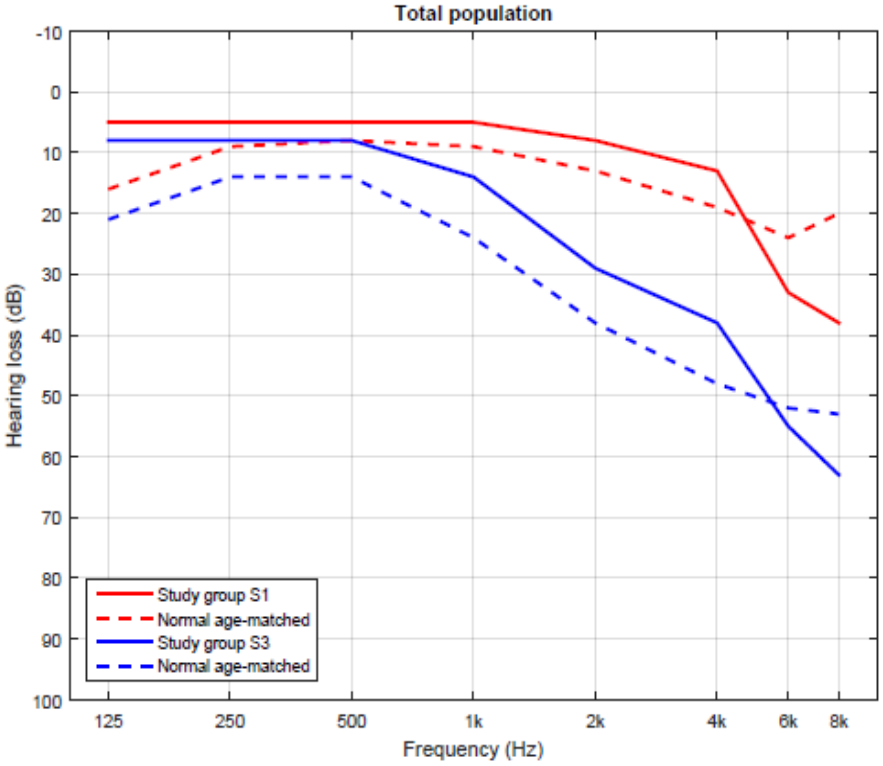
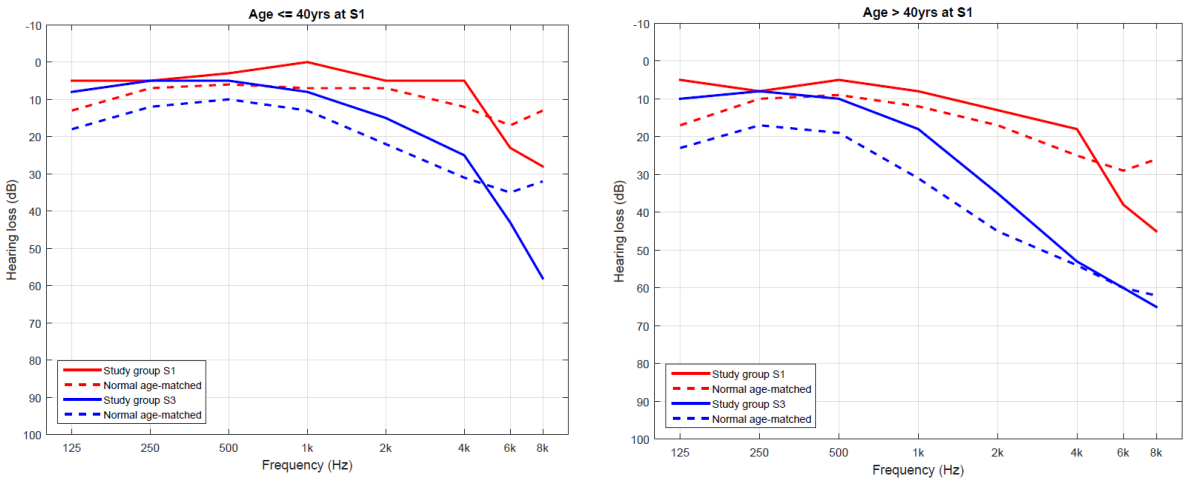


Figure 12. Absolute hearing thresholds at S1 and S3 compared with the general, age-matched male population. The dotted lines represent sex- and age-matched normal data from the HUNT-II survey.

A



B

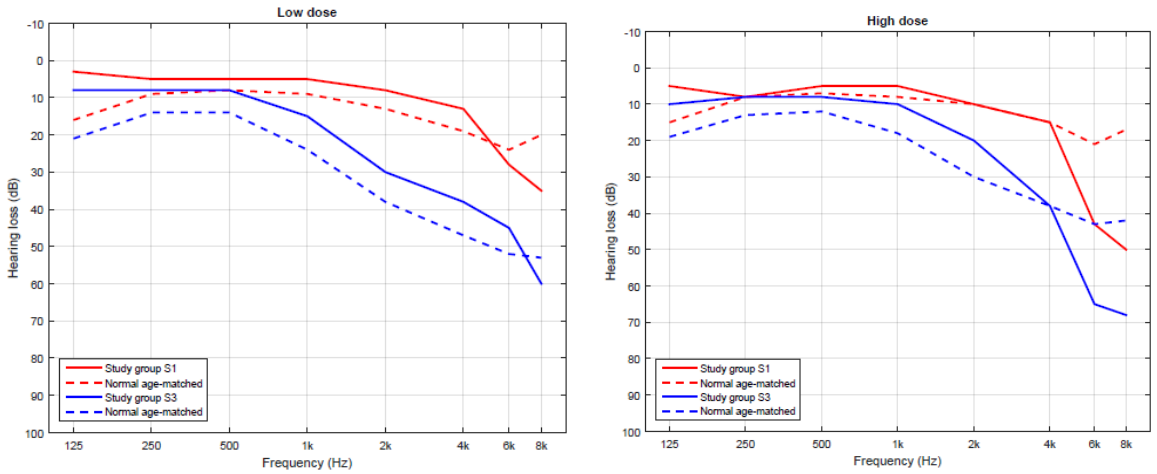


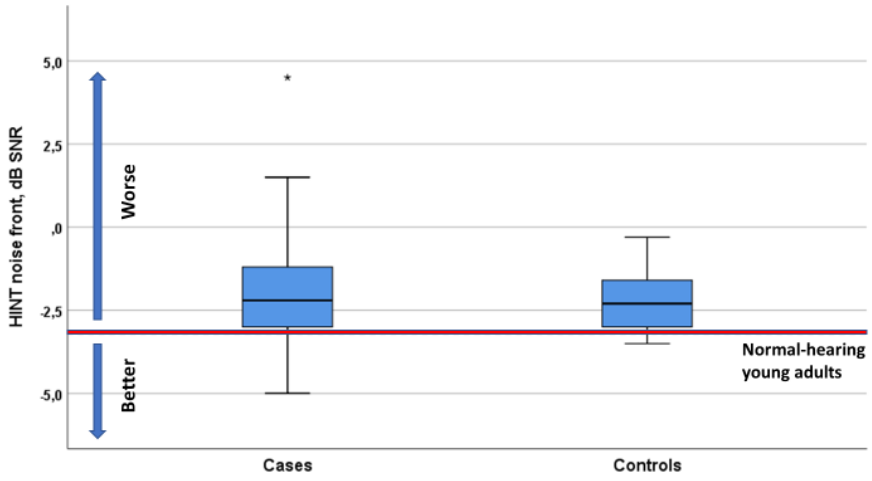
Figure 13. Absolute hearing thresholds at S1 and S3 for subgroups. A) Age ≤ 40 years vs age > 40 years at S1; B) Standard dose vs higher dose cisplatin.

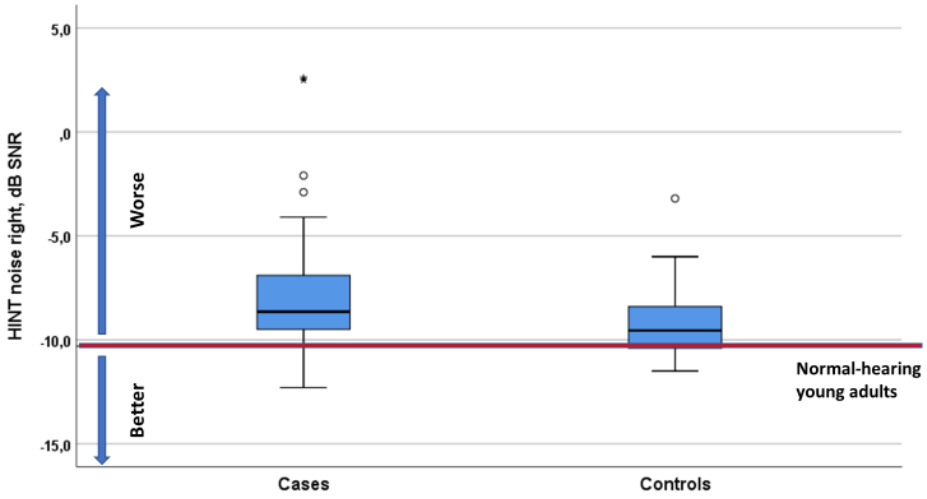
With a linear mixed model for repeated measures, we found that the survey interval was significantly associated with a reduction of age-adjusted thresholds at 6 and 8 kHz. This means that the absolute hearing thresholds of TCS approached those of the general population with long observation.

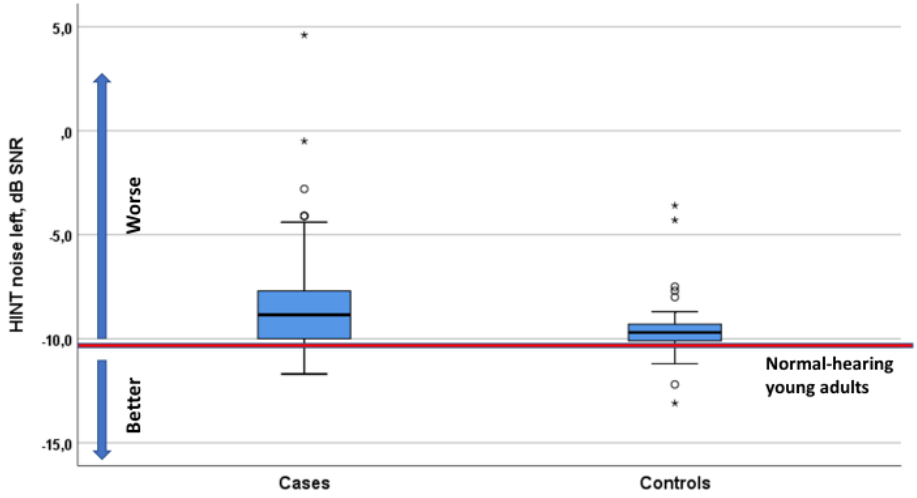
Speech audiometry showed that > 95% of TCS reached 100% speech perception in quiet conditions.

HINT

For the third paper we also included the HINT test to better assess the clinical relevance of our findings since there seemed to be a ceiling effect with almost all Cases reaching 100 % speech perception score with basic speech audiometry in quiet environment. We found no statistically significant difference between Cases and age-matched Controls in quiet conditions (Q), or with noise from front (NF) (25.4 dBA vs 24.5 dBA and -2.2 dB SNR vs -2.3 dB SNR, respectively) (Figure 14). Controls scored significantly better than Cases with signal from front and noise from either side (NR: -9.6 dB SNR vs -8.6 dB SNR, p = 0.034 and NL: -9.7 dB SNR and -8.8 dB SNR p = 0.015 respectively)


HINT noise front, dB SNR
5,0
2,5
,0
-2,5
-5,0
Worse
Better
Normal-hearing
young adults
Cases
Controls


HINT noise right, dB SNR
5,0
,0
-5,0
-10,0
-15,0
Worse
Better
Normal-hearing
young adults
Cases
Controls


HINT noise left, dB SNR
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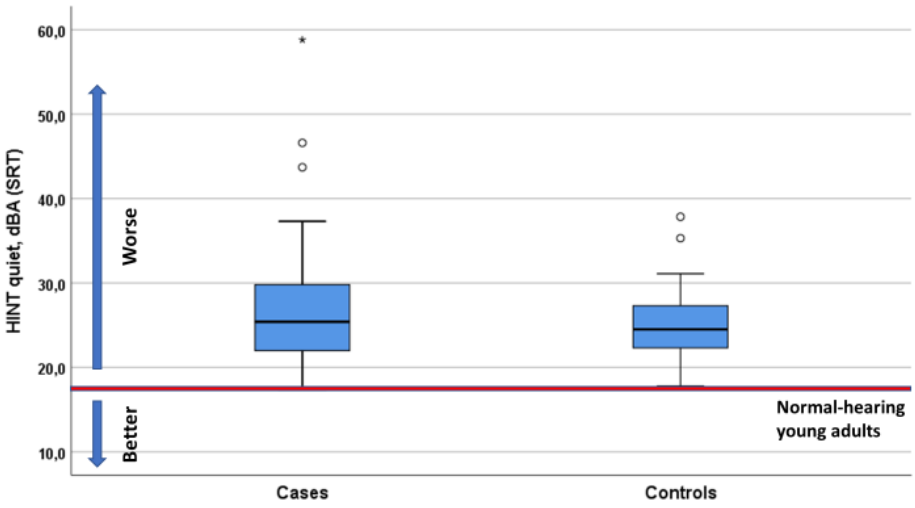

Figure 14. HINT scores for Cases and Controls. HINT NF, NR and NL presented as dB SNR, HINT Q presented as dBA (speech reception threshold). Red lines indicate the mean threshold from normal-hearing young adults (median age 28 years).

A multiple linear regression to determine which factors were associated with HINT scores showed that increasing PTA was significantly associated with poorer HINT score for all outcomes (NF, NR, NL, Q). Increasing age was significantly associated with worse HINT NF and Q. Hearing loss at 4, 6 and 8 kHz was not significantly associated with HINT scores in this regression model, but high-frequency thresholds were highly correlated with PTA and might therefore have confounded the results. Cisplatin treatment 30 years previously was not associated with worse HINT score.

Self-reported hearing

Hearing loss was reported by 27% of the cisplatin-treated MOGCT survivors and 21% of the Controls. The corresponding numbers among the TCS at S3 were 23% of Cases and only 7% of Controls.

Paper II presents self-reported hearing loss among TCS both 10- and 30-years post-treatment. We found that, while all Cases reporting hearing loss 10 years after treatment also had an age-adjusted hearing loss, only 65% of Cases reporting hearing loss 30 years post-treatment had an age-adjusted hearing loss. Among the cisplatin-treated MOGCT patients reporting hearing loss median 15 years after treatment, only 36% had age-adjusted hearing loss.

TCS reported difficulties with hearing in noise more commonly than problems with hearing in general (46% vs 23%).

Tinnitus

Tinnitus did not differ significantly between Cases and Controls in Paper I (27% and 21% for Cases and Controls, respectively), although the prevalence in both groups where higher than expected in the general population based on previous studies [96, 97]. Among the considerably older TCS in Paper III, the corresponding proportion was 38%. Only 10% of Controls reported tinnitus in Paper III.

Tinnitus correlated with significantly worse hearing thresholds at 4, 6 and 8 kHz for TCS, and at 8 kHz among MOGCT survivors. TCS with higher total cisplatin dose reported more tinnitus, while we did not find this correlation among MOGCT survivors. Neither age nor observation time was not significantly associated with tinnitus in any of the surveys.

Serum Platinum Concentration

In the first paper we demonstrated that serum platinum concentrations were significantly higher in Cases compared with Controls (125 and 69 ng/l, respectively $p < 0.001$). SPC decreased with longer observation time but was still significantly higher in Cases up to 20 years after CBCT ($p = 0.016$) (Figure 15). However, SPC did not correlate significantly with hearing thresholds or number of treatment cycles after correcting for observation time.

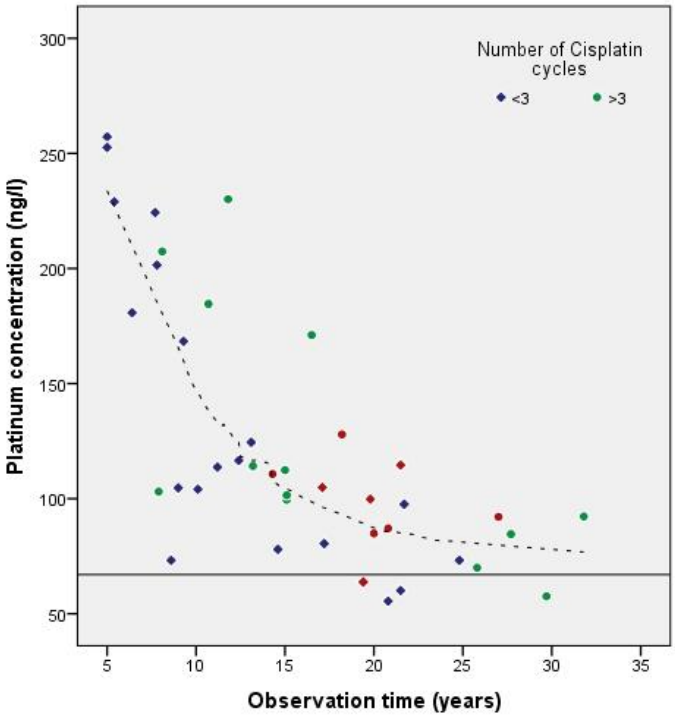

Figure 15. Serum platinum concentrations and observation time. Cases with age-adjusted hearing loss are marked in red. Solid line shows median platinum concentration for Controls.

Discussion

Results

Measured hearing loss and speech perception

It is well documented that CBCT is ototoxic and can cause hearing loss particularly in the high frequencies [3, 5-7, 13, 50, 78, 98]. There are also several studies documenting long-term hearing after CBCT, but to the best of our knowledge there is none with audiometry and follow-up beyond a decade [3, 6, 7, 13]. Further, none of the studies corrected sufficiently for the expected age-related hearing loss. In our first paper, we investigated ototoxic hearing loss in a very long-term perspective, and how it correlated with SPC. When comparing the Cases with the significantly older Controls, we found no difference in absolute hearing thresholds. However, after age-adjusting the hearing thresholds we found significantly worse thresholds at 4, 6 and 8 kHz in Cases compared with Controls. There were no significant differences in the lower frequencies. These results are in line with previous studies showing that cisplatin generally affects the higher frequencies, but the difference was not apparent until the results were age-adjustment [3, 5-8, 13, 50]. It is also highlighted that although statistically significant, the numerical differences in terms of hearing thresholds were quite small, however with great variability. The larger inter-individual variability among Cases was also present in Paper II and III and is consistent with other reports [5, 59-61, 99]. It is believed that genetic factors are important in determining individual susceptibility to ototoxic damage, as some patients seem more sensitive than others [5, 53, 59-62, 72]. Several possible genes have been identified, but probably the increased susceptibility is multifactorial and not controlled by one single gene.

After dichotomizing the MOGCT survivors in paper I based on follow-up years, we found significantly higher age-adjusted hearing thresholds in Cases compared with Controls at 6 and 8 kHz after ≥15 years of follow-up, but not with observation times <15 years. We hypothesized that this difference might be due to an accelerated ageing of the inner ear but made it clear that the result might not be representative due to the above-mentioned factors and that further studies were necessary. The higher age-adjusted thresholds in those with longer follow-up was not corrected for number of cycles, due to small numbers, but we know that patients treated in the early 1980s have the longest observation time and that they generally received higher doses than patients treated towards the end of the study period. Based on our results in Paper II, it seems more likely that this difference was explained by higher cisplatin doses given early in the study period rather than an accelerated ageing process.

For the second paper we wanted to follow up the results from the first paper and study the development of CBCT-related hearing loss in an extended long-term perspective.

Since testicular cancer predominantly appears in younger men and long-term survival rates are high, TCS were chosen for this study. It was already well documented that that cisplatin could cause high-frequency hearing loss, and some had suggested it might progress for several years after treatment, but little was known about what to expect beyond the first decade [6, 7, 13]. Further, the finding of increased SPC in patients up to 20 years after treatment in the first study, together with the suggestion by Breglio et.al that cisplatin may be retained in the cochlea indefinitely, raised the question whether the ototoxic damage could continue beyond the first decade [11, 66]. Paper II presents a long-term follow-up of 30 years with repeated audiograms almost 20 years apart. We found that the absolute hearing thresholds at 4,6 and 8 kHz increased during the survey interval as expected, since high-frequency hearing declines with age [2]. However, after adjusting the hearing thresholds for expected age-related hearing loss, high-frequency thresholds of TCS actually approached those of the general population during the survey interval.

A possible explanation for this finding is that cisplatin mainly affects the basal turn of the cochlea which is where high frequencies are processed. This is the very same part of the cochlea which is exposed to and affected by factors contributing to age-related hearing loss [41, 42, 50, 100]. If the high-frequency region of the cochlea is already damaged by cisplatin at a younger age, the relative effect of other factors contributing to age-related hearing loss may hypothetically be less prominent since the hair cells in this area are already damaged. This theory is supported by animal studies showing a similar "less-than-additive" effect of cisplatin in mice with preexisting noise-induced hearing loss [100]. It is further supported by our finding that those who were older at treatment (>40 years at S1), generally had more severe ARHL, showed hearing thresholds closer to the general population at S3 than the younger ones.

Using a linear mixed model for repeated measures we also found that age-adjusted thresholds at 6 and 8 kHz significantly decreased during the survey interval. This was not the case for the lower frequencies. We found similar changes irrespective of dose, although the patients receiving higher doses (>400 mg/m^2) displayed worse thresholds at both S1 and S3. This is in line with other articles showing that ototoxicity is dose-dependent [7, 13, 49, 50, 98].

It is important to recognize that previous studies have shown progression of cisplatin-induced ototoxicity during the first decade after therapy and given that our first audiogram was performed around 10 years after treatment, our results do not contradict these findings [13, 68].

Pure tone audiograms do not necessarily reflect a patient's speech perception, especially not in background noise. Since the clinical impact of an isolated high-frequency hearing loss is variable, we wanted to test speech perception in a setting closer to daily life. Hence, for the studies on TCS, speech perception tests and HINT was performed to explore the clinical relevance of CBCT-related hearing loss in a long-term perspective. We found a ceiling effect for the standard speech perception

test in quiet conditions; it was not difficult enough to discriminate between the two groups since >95 % of TCS scored 100% word recognition in quiet conditions. For Paper III we therefore included HINT, which is closer to listening situations in daily life with a various degree of background noise. The results of HINT revealed no significant difference between Cases and Controls 30 years after treatment in quiet conditions or with both signal and noise from the front. However, Cases scored slightly worse than Controls with noise from either side. This might be explained by poorer Spatial Release of Masking (SRM), i.e. the ability to utilize that noise and signal comes from different directions. SRM depends on the *head shadow effect*, which makes the sound reach the ears at slightly different times and volumes. Since the head shadow filters out high frequencies more, SRM in Cases is expected to be worse due to their high-frequency loss [101]. In line with results from pure tone audiometry and our previous studies, the variability in HINT scores were greater among Cases. A few scored quite poor, but on the group level TCS had similar scores to Controls in background noise. This further supports the conclusion that although a few patients develop severe hearing loss in relation to CBCT, most have a limited hearing loss. Our results also showed that although Cases had poorer high-frequency thresholds compared to Controls (as shown for both MOGCT and TCS), the clinical impact of this hearing loss is limited for most patients. Nevertheless, clinicians need to be aware that a few patients definitely suffer from a quite severe hearing loss after CBCT. It is important to identify these patients and refer them to hearing rehabilitation and follow-up. In most cases pure tone audiometry will be sufficient to identify these patients, but for patients with severe subjective problems with hearing in noise and limited hearing loss on pure tone audiometry, HINT provides valuable extra information.

Self-reported hearing loss

Subjective hearing loss was reported by 11 (27%) Cases and 7 (21%) Controls in Paper I. After age-adjustment only 4 Cases and 2 Controls had hearing loss that exceeded the expected age-related hearing loss. The difference in subjective hearing loss between the two groups was not significant.

In Paper II we found that subjective hearing loss corresponded well with age-adjusted hearing loss at S1. All (12) patients who reported subjective hearing loss also showed age-adjusted hearing loss. At S3, all of the 23 patients reporting hearing loss had an absolute hearing loss, but only 2/3 also had an age-adjusted loss. This suggests that the specificity of self-reported hearing loss for detecting ototoxicity is higher for younger patients, because with increasing age other factors such as ARHL will also affect subjective hearing.

Paper III revealed that self-reported hearing loss (both in general and in background noise) was considerably more common among Cases compared with Controls, although the difference in speech perception tests and HINT was minimal.

Self-reported hearing loss is likely to be affected by a subject's expectations to hearing, awareness of possible hearing loss, and the hearing environment in daily life, in addition to the hearing loss itself. A possible explanation for our findings in Paper III is that Cases were informed of the possibility of hearing loss in connection with their treatment and thus more aware of changes in hearing. Another possibility is that Cases might have acquired their hearing loss at a younger age and more suddenly, resulting in a greater awareness than Controls in which the hearing loss is likely to have progressed slowly over several years. The differences in self-reported hearing seen in the study on TCS were considerably smaller and not significant, in the MOGCT study. However, in contrast to the studies on TCS, Controls in the MOGCT study were also patients with ovarian germ cell tumors who had been through a treatment (although not ototoxic) which might increase awareness of their own health. Further, Controls in Paper I were older than the Cases and absolute hearing thresholds were poorer. This is in line with the results from the study on TCS showing that questionnaires long time after treatment were not able to differentiate between age-related hearing loss and ototoxicity.

Tinnitus

There were high rates of tinnitus among both Cases and Controls in Paper I, and no significant difference between the two groups among the MOGCT survivors. However, we found tinnitus to be much more common among TCS than among the Controls in Paper III. These results are similar to what we found with self-reported hearing loss and, as with hearing, they might reflect that Controls in Paper I also represent patients who are treated for a serious disease, while Controls in Paper III did not. It is not unlikely that getting a cancer diagnosis at a young age will increase the awareness of health-related symptoms. This may explain the high rates of tinnitus among Controls in Paper I (21%), while among Controls in Paper III (10%) it was closer to reported prevalence in the general population (10-15%) [97].

Tinnitus is not an objectively measurable entity. As a subjective perception it is difficult to grade, and thus depends on the patient´s reporting of the symptom. The high rates in Cases might indeed reflect the high frequency hearing loss associated with cisplatin treatment. However, since tinnitus is such a subjective symptom, the overall awareness of disease-related symptoms is likely to influence how a person reports tinnitus. Further, anxiety and depression are known risk factors for tinnitus [97]. It is possible that high rates in all groups representing cancer patients could partly be explained by the fact that these persons have been diagnosed with a very serious disease at a young age that might influence the score.

Finally, the vast majority of patients reporting tinnitus scored themselves as having mild/moderate tinnitus, reflecting that this is not a major symptom. Several patients who reported tinnitus at the consultation also remarked that even if the tinnitus was constant, they did not pay attention to it in daily life and it did not bother them. However, as with hearing loss there were a few patients with severe tinnitus that interfered with daily activities and substantially decreased the quality of life. It is indeed important to identify these patients in order to provide tinnitus rehabilitation. In the author's opinion the SCIN question about tinnitus or a tinnitus VAS score is sufficient for screening patients who need further evaluation and possibly rehabilitation. THI is an extensive questionnaire which is time-consuming and does not necessarily reflect the severity of tinnitus in a correct way, as the response to several questions are affected by personality, general mental status and thus the coping abilities of the person filling out the form.

SPC

Cases in Paper I had elevated SPC up to 20 years after treatment. Previous studies have shown a correlation between elevated long-term SPC and increasing toxicities, including subjectively assessed hearing impairment/tinnitus [8, 10, 65]. However, we found no correlation between SPC and measured hearing impairment or tinnitus. It is known that cisplatin is retained in serum and human tissues including the cochlea for a very long time after treatment [66], so a continuous worsening of the inner ear damage seemed possible. However, our results from Paper II imply that the damage occurs mainly during the first decade, and that hearing thresholds actually approach the general population with very long follow-up. Further, although SPCs are elevated up to 20 years post-treatment, the concentration is highest during the first years after treatment, so it is likely that a worsening of hearing will occur mainly during this period.

General considerations

Paper I and II highlight the importance of age-adjusting hearing thresholds when evaluating ototoxicity in a long-term perspective. Age-related hearing loss is multifactorial and usually described as high-frequency hearing loss caused by the combination of ageing itself, noise exposure, genetic susceptibility and exposure to ototoxic agents, generally all of whom initially affect the higher frequencies. In our view it is therefore not possible to assess long-term ototoxicity without taking expected age-related hearing loss into consideration, since this will overestimate the long-term effects of the ototoxic drug. Glendenning et al. reported hearing loss >25 dB at 8 kHz in 70% of cisplatin-treated patients. However, 43% of the control group also

displayed hearing loss [6]. Frisina et al. found hearing loss in 80% of TCS treated with cisplatin, 18% were defined as having severe/profound hearing loss based on a threshold in any one single frequency up to 12 kHz [7]. These numbers probably overestimate the CBCT-related part of the hearing loss greatly, since they do not adjust properly for age-related hearing loss.

Further, the clinical relevance of these isolated high-frequency hearing losses can be questioned. Glendenning et al. conclude that "Detectable effects on high frequency hearing remained but caused little symptomatic problems", and despite the reports by Frisina et al. of 18% having severe/profound hearing loss and an additional 21% with moderately severe hearing loss, only 2.4% used hearing aids. Although financial reasons, restricted access to rehabilitation, and late referral might account for lower counts of hearing aid users than those being in need, these numbers indicate that the majority of cisplatin-related hearing losses do not have a major clinical impact. The corresponding number of patients using hearing aids was 5% in Paper I and 1% in Paper II, with an additional 7% being referred based on our tests. In Norway, hearing aids are fully reimbursed, so financial reasons are excluded. However, any clinically relevant hearing loss is important to detect in order to secure proper hearing rehabilitation, given that hearing loss is a known risk factor for social isolation, reduced quality of life, declining cognitive capacity, and possibly dementia [29, 32-34, 37-40].

Which tests are then appropriate for detecting hearing loss in the short-and long-term follow-up after CBCT? Extended high-frequency testing beyond 8 kHz can be appropriate in the early detection of ototoxicity in children, in which even a limited high-frequency hearing loss can affect language development [4, 24, 80]. For long-term follow-up of ototoxicity in adult patients, this method is less relevant. Haugnes et al showed that the median extended high-frequency thresholds (9-14 kHz) exceeded the ASHA defined thresholds of hearing loss already prior to cisplatin treatment [14]. This indicates that when used, extended high-frequency audiometry will have little clinical value without baseline tests pre-treatment.

In the author's opinion, pure tone audiometry up to 8 kHz is sufficient for monitoring ototoxic treatment and detecting clinically relevant hearing loss in adult patients. SCIN or other PROMs of hearing may reveal hearing loss, but they will not differentiate between ototoxicity and ARHL in elderly. For selected patients with severe subjective problems with hearing in noise and limited hearing loss on pure tone audiometry, HINT provides additional information, but the test is too time-consuming for general screening. Extended high-frequency audiometry can indeed reveal ototoxic changes earlier than standard pure tone audiometry, but it is difficult to see a clinical relevance for routine testing above 8 kHz and especially in long-term follow up studies. Finally, and importantly, the stronger the indication for CBCT, the less relevant an isolated hearing loss in the frequencies > 8 kHz will be. The decision to change treatment based on detection of ototoxicity will always have to be weighed against the indication for CBCT. Baseline testing and testing between each cycle is preferrable. However,

our results indicate that long-term follow-up with audiometry after the first decade adds very little and is not considered necessary.

Methodological considerations

The first paper is an observational, case-control study. One of the major methodological challenges with this type of studies is the selection of patients. Since we only examined a subgroup of the whole population there will always be a risk of selection bias, and one of the most important aspects of this type of studies is to evaluate if the studied selected sample represents the target population. For this study we invited all women treated for MOGCT in the period between 1980 - 2009 who were still alive and living in Norway. One hundred and sixty-three women were treated during this time period and 153 were invited. Only 10 patients were excluded due to emigration or death. Ninety-four agreed to fill in the questionnaire and 74 agreed to both questionnaire and clinical exam. Since fewer than 2/3 of the invited women accepted to participate it is important to consider the non-participants. We found no significant differences between the participants and the non-participants except for post-surgical therapy. Among the participants, 84% had received adjuvant therapy, compared with 45% of the non-participants. We believe that the lower participation among patients who did not receive adjuvant therapy is explained by the fact that patients treated with surgery only had limited disease to begin with, and therefore represent the subgroup with least side effects from treatment, hence they may be less interested in participation in a follow-up study. However, the opposite might also be true; that the non-participants are the ones with most side-effects and that they feel too weak to participate, but given their less aggressive initial disease and treatment, this is less likely. The optimal situation would of course be if all the invited patients were included, but considering the very long follow-up time, and the fact that these patients live across Norway and participation would require many of them to travel several hundred kilometers for clinical exams in Oslo, we consider the participation satisfactory. In addition, as we were able to compare the participants with the non-participants, we consider our results to be valid and possible to be generalized to a sub-population of women with MOGCT who received adjuvant therapy.

Paper II is a longitudinal, observational study. All TCS treated in Norway between 1980 - 1994 were invited to participate in S1. The general participation in the follow-up studies has been satisfactory, although the number has decreased slightly for each of the three surveys (Figure 10). Although we consider the participation good considering the very long observation time, it is recognized that some patients inevitably drop out between each of the three surveys. A study performed by our group showed that the TCS drop-outs between each survey had worse general health than the ones remaining in the study [102]. This means that there is a degree of positive selection over the years, and that the patients remaining at S3 represent a subgroup

with slightly better general health than the whole population. This kind of positive selection is almost inevitable with follow-up studies of > 30 years since some of the sickest patients will die or not be able to participate in the study. It should nevertheless be kept in mind when interpreting the results [103]. Although the positive selection is mainly due to general health/mortality and not directly related to hearing, we cannot make conclusions about the potential bias on hearing results. All TCS living in our health care region (Helse Sør-Øst) were invited for comprehensive audiological examinations. Since we invited *all* patients in a given geographical area it is unlikely with selection bias based on invitation. We also consider it unlikely that patients living in Helse Sør-Øst would differ significantly from other regions of the country. One hundred and nineteen TCS were invited and 101 accepted, which we consider quite satisfactory for a follow-up study 30 years after treatment. Paper II only presents results from 82 patients since some patients lacked audiograms from S1. While audiograms were routinely achieved at S1 from all patients treated at Oslo University Hospital, some of the 101 TCS were treated elsewhere, and for some we could not find audiograms in their journal.

Paper III is a cross-sectional case-control study. This study included all the 101 patients described in Paper II. This study focused mainly on the clinical relevance of cisplatin-related hearing loss after very long observation time, so we also included the 19 patients without an audiogram from S1. The reference group used to develop the Norwegian HINT test comprised normal hearing, considerably younger adults (median age 28 years). To the best of the authors´ knowledge there were no age-matched HINT scores from the general population in Norway or elsewhere. Therefore it was important to include an age-matched control group to evaluate our results. The Controls were randomly selected persons from the LiRe public health survey and from the hospital. Optimally all controls would have been random participants from the LiRe project, but as described under Methods, this was not possible given the situation. Hence, 11 age-matched male health workers at the hospital were invited, of which all agreed to participate. Their results did not differ significantly from the rest of the control group, so it is unlikely that this caused bias.

Considering the collection of audiological data, all audiograms for Paper I and Paper III, plus the S3 part of Paper II, were performed by a trained audiologist at the audiology unit of Rikshospitalet, after otomicroscopy by a senior resident or consultant ENT physician. The equipment is tested and calibrated regularly, and the tests were performed in soundproof booths to minimize the possibility of information bias from testing. For S1, audiograms were performed by a trained nurse at Radiumhospitalet. Since Radiumhospitalet does not have an audiology unit, a soundproof room was constructed, tested and approved by an audiologist from Rikshospitalet. We therefore consider the risk of information bias from these tests small.

The lack of pre-treatment audiograms was also subject to consideration. Optimally we would have audiograms before, during and after treatment. However, since our project

was exploring the very long-term effects of cisplatin, we invited patients from the beginning of the cisplatin era when audiometry was not routinely performed pre-treatment. Our survivors were generally young and otherwise healthy before treatment, and since there is no known association between these cancer forms and reduced hearing, we assume that their pre-treatment hearing did not differ from the general population. A few patients with known hearing loss pre-treatment, were either totally excluded, or if unilateral, the ear with hearing loss was excluded from analysis.

We decided to use the hearing thresholds from the HUNT study as our reference representing the general population for both Paper I, II and III. The test conditions at HUNT were slightly different since the test booths were transportable and included self-testing. The background noise was tested and found to be within the ISO 8253-1:1989 standard, and the tests were validated [43, 44]. However, these slight differences in test conditions between HUNT and our studies probably explain why our test results were generally slightly better than the general population in Paper II. This is further supported by the finding of slightly better hearing thresholds in the control group in Paper I and III, compared with age-matched peers in the HUNT. However, in our view this does not affect the relative change in thresholds between S1 and S3 found in Paper II.

We also consider it a major strength to have age- and sex-matched hearing thresholds from such a large survey representative of the Norwegian general population. The use of a second control group in Paper I and III adds to the strength by serving as an extra control regarding hearing thresholds, measured in exactly the same way as Cases. According to the author´s opinion many of the long-term studies conducted on cancer survivors have not taken sufficiently into consideration the fact that hearing also deteriorates in the general population with aging. Since both ARHL and ototoxicity initially affects the higher frequencies it is very important to have a control group or adjust for expected hearing loss in the general population. Lack of age-adjustment is likely to contribute to overestimation of the long-term effects of CBCT as we have shown in our studies.

Ethical considerations

All studies were approved by the regional ethics committee for our health care region (REK Sør-Øst).

Paper I: No 2011/1368

Paper II and III: No 2015/1264

There were few ethical dilemmas regarding our studies since they generally did not include experiments or interventions with potential harm for the participants. The first study included a blood sample from each participant to determine SPC, but except for that, our studies included only data collection from journals and non-invasive hearing tests. Blood sampling comes with minimal discomfort and practically no risk. However, for the first study we invited patients from all over Norway to come to Oslo for a 2-day multi-disciplinary health check including among others gynecological, neurological and cardiac exam. This meant traveling quite far for several patients and also some exams with considerably more discomfort than the hearing test. So, although there were few ethical considerations regarding the audiological aspects of the survey, the patients had to accept to spend considerable time in the hospital and also more invasive exams than the hearing test. They did, however, have the possibility to accept only parts of the survey. Further, those who accepted got a free, thorough health examination, and those of our participants who might benefit from a hearing aid got a referral to a local audiology unit.

For the second and third paper we only included patients from our health-care region to come to the hospital for hearing tests. The testing lasted for 1-2 hours and there was no risk involved. Patients received free hearing tests and referral if they needed hearing aids. However, when it came to the Controls for Paper III, we had to stop inclusion from the LiRe project as described under methods. We did not find it ethical to invite otherwise healthy persons to the hospital for hearing test only to serve as controls during the SARS-Cov-2 situation with increased risk of infection in the hospital.

All participants gave their written informed consent and had the possibility to withdraw consent at any time during the survey. Participants also finished their treatment and routine follow-ups several years prior to the survey so there was no reason to fear worse treatment or follow-up if they declined.

Conclusion/Future aspects

Hearing is crucial for communication for most people. Many of the patients who experience hearing loss after cisplatin treatment at a young age are worried about what will happen with their hearing in the long term. Our findings are therefore important when it comes to counseling these patients. The physician should inform patients about the possibility of hearing loss related to cisplatin prior to treatment. Our results

show that some patients will experience severe hearing loss, but for most patients it seems limited to some degree of high-frequency hearing loss with limited clinical impact. Our results further indicate that cisplatin-related hearing loss is unlikely to progress beyond the first decade after CBCT. On the contrary, it seems possible that due to a less-than additive effect with age-related hearing loss, the high-frequency thresholds will approach those of the general population with ageing.

It is emphasized that some patients develop a substantial hearing loss following CBCT. It is important to identify these patients and to provide hearing rehabilitation in order to reduce the negative consequences of hearing loss, including social isolation, reduced quality of life and possibly dementia. Based on our results it does not seem necessary to monitor these patients with regular hearing tests beyond the first decade, but more studies are needed to verify our findings. It is also important to acknowledge that our findings are limited to adult-onset cancer.

In the future it would be very interesting to perform a larger case-control study which includes audiograms both pre- and post-treatment with very long follow-up to confirm our findings. Norway has good national registers to identify all patients with a given oncologic diagnose and audiograms are now routinely performed pre-CBCT. Further, given that the median age of the TCS was 60 years, it would also be interesting to perform an S4 study in another 10 – 15 years to observe what will happen to the hearing thresholds at an age where ARHL is expected to be even more pronounced.

We plan to extend our HINT control group to determine normative age-specific speech reception thresholds for the general Norwegian population for future studies.

Further, the author is currently counselling an ongoing multicenter study aiming to evaluate the late effects of patients treated for head and neck cancer in Norway in the 1990s and early 2000. He also participates in a pediatric project which evaluates hearing of children treated with carboplatin for retinoblastoma in Norway.

Finally, it is highlighted that several ongoing studies aim to find otoprotective agents that can be given in connection with CBCT to limit the ototoxic side effects. If successful, CBCT-related ototoxicity may become considerably less common in the future.

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Long-term ototoxicity in women after cisplatin treatment for ovarian germ cell cancer

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HIGHLIGHTS

- This is the first study to explore long-term ototoxicity of cisplatin in women.
- Cisplatin related hearing loss was found subjectively in 27% and objectively in 22%.
- Hearing loss was unevenly distributed and generally mild.
- Long-term ototoxicity must always be controlled for age-related hearing loss.
- Elevated serum cisplatin levels were detected up to 20 years after treatment.

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ABSTRACT

Objective. Evaluate long-term cisplatin-induced ototoxicity in women treated for malignant ovarian germ cell tumors (MOGCT).

Methods. Seventy-four women treated for MOGCT in Norway (1980–2009) were analyzed: 41 had received cisplatin-based chemotherapy (CBCT) ("Cases") and 33 had no CBCT ("Controls"). Median follow-up was 15 years. Hearing was assessed by pure tone audiometry and by the SCIN questionnaire. Air conduction thresholds were reported as absolute hearing thresholds and age-adjusted thresholds. Absolute and age-adjusted hearing loss were defined as thresholds of >20 dB at any frequency. Tinnitus was evaluated using the Tinnitus Handicap Inventory. Serum Platinum Concentration (SPC) was determined.

Results. Absolute hearing loss was identified in 21 Cases (51%) and 24 Controls (73%). After adjusting for age, only 9 Cases (22%) and 5 Controls (15%) remained. Age-adjusted hearing thresholds at 4, 6 and 8 kHz were slightly but significantly higher in Cases compared to Controls. Subjective hearing loss was reported by 27% of Cases and 21% of Controls, who were significantly older. Elevated SPC values were detected up to 20 years after CBCT, but SPC did not correlate significantly with age-adjusted hearing loss. The rate of tinnitus was similar in Cases and Controls.

Conclusion. Long-term MOGCT survivors treated with CBCT have small but significant reductions in age-adjusted hearing thresholds at 4, 6 and 8 kHz versus Controls. Approximately one in four women experienced subjective hearing loss. To avoid overestimation of clinically relevant cisplatin-induced ototoxicity, absolute hearing thresholds should be age-adjusted and compared to an age-matched control group.

1. Introduction

Cisplatin is widely used to treat various types of cancer, and achieves particularly high response rates in germ cell cancer [1]. Although cisplatin is a highly effective anti-cancer drug, it is associated with considerable and frequently irreversible long-term adverse effects including tinnitus and bilateral sensorineural hearing loss [1–3].

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Cisplatin-related ototoxicity is due to damage at three inner ear sites: the organ of Corti (especially the outer hair cells), the lateral wall including the stria vascularis and spiral ligament, and the spiral ganglion cells. Because inner ear cells generally have a poor regenerative potential, or indeed none at all, this damage is permanent [4,5] and appears to progress during post-treatment follow-up [6,7]. The pathogenesis of tinnitus is complex and not fully understood, but it involves dysfunction of peripheral neurons in the inner ear and of a network of central auditory and non-auditory neural pathways [8].

In testicular cancer survivors (TCSs) long-term ototoxicity, has been observed in 15–40% of cases [1,9,10]. Ototoxicity has been reported in up to 80% of TCSs, based on audiometry performed at frequencies up to 12 kHz [11,12]. Serum cisplatin levels appear to correlate with ototoxicity [13].

To our knowledge, no studies have assessed long-term ototoxicity after cisplatin-based chemotherapy (CBCT) in women with germ cell cancer. One animal study showed an increased prevalence of hearing loss, with more severe damage to spiral ganglions and brainstem tissues, in female rats versus male rats following administration of cisplatin [14]. In contrast, a clinical pediatric study described more severe cisplatin-associated ototoxicity in boys than in girls [15]. Further studies of ototoxicity are required, particularly regarding the long-term effects in women.

This descriptive study aimed to explore the long-term ototoxic effects of CBCT in women, based on questionnaires, otological examination and audiograms. Serum platinum concentrations (SPC) were analyzed for correlations with late ototoxicity.

2. Materials and methods

2.1. Patients

The current study is part of a multidisciplinary follow-up survey in ovarian germ cell cancer survivors [16]. Patients were identified by means of the Cancer Registry of Norway. Between 1980 and 2009, 163 women were treated for malignant ovarian germ cell tumor (MOGCT) in Norway, of whom 153 were still alive and living in Norway in 2012. These 153 individuals were invited to participate in a follow-up survey. All patients gave written informed consent, and the study was approved by the regional committee for medical research ethics.

2.2. Treatment

Until the mid-1980s, non-metastatic patients with MOGCT underwent surgery occasionally supplemented by abdomino-iliac radiotherapy. Metastatic patients received chemotherapy with adramycin and alkylating agents combined with surgery and radiotherapy. From 1980 onwards, CBCT was gradually introduced for the treatment for metastatic MOGCT. The regimen consisted of three-week cycles of 1) bleomycin, etoposide and cisplatin; 2) cisplatin, vinblastine, bleomycin; or 3) etoposide, cisplatin with 100 mg/m^2 cisplatin applied at each cycle, typically combined with surgery [16]. The cytostatic drugs were given during Days 1 to 5 with a booster dose of bleomycin on Day 15 of each 21-day cycle. During the 1980s and early 1990s, more than three cycles were usually used, after which standard chemotherapy was restricted to three cycles of CBCT. One patient with recurrent disease received eight cycles. Another patient received carboplatin instead of cisplatin, and her per-cycle exposure to platinum was calculated by dividing each cycle's carboplatin dose by 4 [17]. For the purposes of the current study, patients were grouped into those who had received CBCT (Cases), and those without CBCT (Controls) (Fig. 1).

2.3. Questionnaires

The questionnaire comprised the validated Scale for Chemotherapy-Induced Neurotoxicity (SCIN), and one additional question about hearing in noise [18]. The first assesses subjective hearing by asking "Do you suffer from reduced hearing?". The second question concerns difficulties in hearing in noisy surroundings. The possible responses for both questions are 0: “Not at all”; 1: “A little”; 2: “Quite a bit”; and 3: “Very much”. Subjective hearing loss was defined as a score ≥ 2 for one or both questions. Tinnitus was assessed during the consultation with the otologist. If tinnitus was reported, the patient completed the validated Tinnitus Handicap Inventory (THI) [19]. THI scores were subcategorized into slight tinnitus, with no interference with sleep or daily activities [1 to 16], mild (17 to 36), moderate (37 to 56), severe (57 to 76) and catastrophic (77 to 100) according to McCombe's grading system [20].

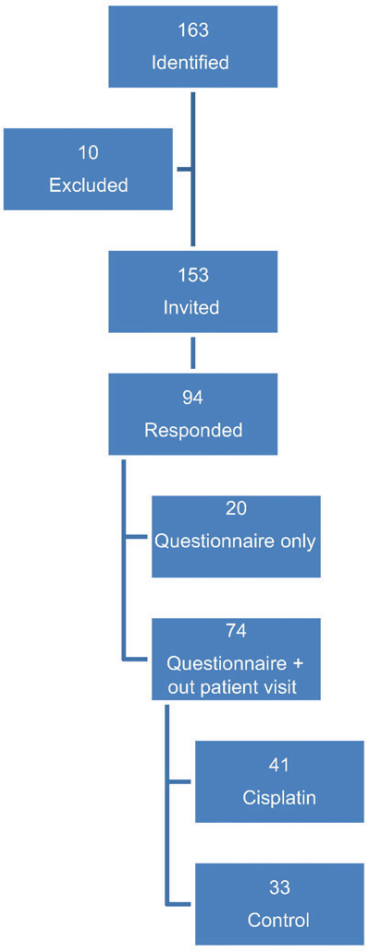

Fig. 1. Flow chart of patient disposition.

2.4. Otological examination

All patients were examined by otomicroscopy prior to audiometry. Objective hearing was evaluated by audiometry, performed in a soundproof testing room using the Aurical® audiometer. Both ears were tested. Air conduction thresholds were measured by decibel hearing level (dB HL) at the following frequencies: 0.125, 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz which are defined as absolute hearing thresholds. The mean dB HL threshold from both ears was used for statistical calculations except for in two patients, one of whom had single-sided conductive hearing loss and one who reported single-sided deafness since childhood. These two ears were excluded from all analyses. Absolute hearing loss was defined as presence of absolute hearing thresholds >20 dB at any frequency, consistent with the study by Frisina et al. [11]. No patient

had an absolute hearing threshold of >20 dB at frequencies below 4 kHz without also displaying hearing impairment at frequencies of 4 kHz or above. The prevalence of hearing loss was thus evaluated based on findings from frequencies of ≥4 kHz. In order to rule out conductive hearing loss, bone conduction thresholds were measured if air conduction thresholds exceeded 20 dB HL at any frequency. The pure tone average (PTA) of air conduction thresholds was calculated for 0.5, 1, 2 and 3 kHz.

To eliminate age as a confounding factor for hearing loss, the absolute thresholds for 4, 6 and 8 kHz were adjusted for age using age-matched data from the general female population in Norway, obtained from the HUNT-II study [21,22]. Age-adjusted hearing thresholds were calculated by subtracting the expected age-related hearing loss from the absolute threshold. As a consequence, negative values were obtained for patients whose hearing was above the norm. Age-adjusted hearing loss was defined as the presence of age-adjusted threshold

> 20 dB at any frequency, and thus represents hearing loss from causes other than normal aging.

2.5. Serum platinum concentration (SPC)

At the time of the survey, serum was collected and stored at −80 °C for approximately two years. After thawing, SPC was determined for Cases and Controls using methods described previously [13].

2.6. Statistical analyses

Continuous variables are presented as median and range values, and categorical variables as counts and proportions. Crude differences between Cases and Controls were assessed using the Mann-Whitney Wilcoxon test. Associations between pairs of continuous variables were assessed using Spearman correlation. The observation time was defined as the number of years between the date of diagnosis and the date of survey, dichotomized by its median (15 years). The age-adjusted hearing thresholds were compared between Cases and Controls within observation times of <15 and ≥15 years. All tests were two-sided. *P*-values <0.05 were considered statistically significant. Since the study was an exploratory analysis, no correction for multiple testing was performed.

All statistical analyses were performed using SPSS version 21 (IBM Corp Chicago, IL).

3. Results

3.1. Patients

In total, 153 patients were invited to participate, of whom 74 patients completed the questionnaire and were examined by the otologist (Fig. 1). The median observation time was 15 years (range 5 to 34 years) (Table 1). Forty-one patients had received CBCT (Cases) and 33 had no CBCT (Controls). The Controls were significantly older than the Cases (median age 50 versus 35 years, respectively; $P = 0.005$). The Cases received between 3 and 8 treatment cycles (median = 3).

3.2. Hearing

3.2.1. Objective hearing

Hearing thresholds from 146 ears were analyzed (Table 2). Conductive hearing loss was diagnosed in only one Control patient, who had a previous diagnosis of unilateral mechanical hearing loss. PTA was 6 dB and 7 dB for Cases and Controls, respectively.

There was no difference in the absolute hearing thresholds between Cases and Controls. After adjustment for age, however, the Cases" hearing thresholds at 4, 6 and 8 kHz significantly exceeded those of Controls, though the numerical differences between the median values were small (≤5 dB) (Table 2). Age-adjusted hearing thresholds did not correlate significantly with age at diagnosis or number of treatment cycles.

Table 1
Patient characteristics.

	Cases ($n = 41$)	Controls ($n = 33$)	All subjects ($n = 74$)
Age category, n (%)			
<40 years	24 (59)	3 (9)	27 (36)
40–50 years	12 (29)	14 (42)	26 (35)
>50 years	5 (12)	16 (48)	21 (28)
Age at diagnosis, years			
Median (range)	20 (10–47)	30 (14–76)	23 (10–76)
Age at survey, years			
Median (range)	35 (18–64)	50 (29–83)	45 (18–83)
Observation time, years			
Median (range)	15 (5–32)	16 (6–34)	15 (5–34)
Total cisplatin dose, mg			
Median (range)	540 (450–1050)		
Number of cycles			
Median (range)	3 (3–8)		

Absolute hearing loss at one or more frequencies was present in 21 Cases (51%) and 24 Controls (73%). After adjustment for age, the proportion of patients with hearing loss was reduced almost five-fold in Controls (from 73% to 15%) compared with approximately two-fold in Cases (from 51% to 22%) in Cases, indicating a far higher proportion of presbycusis in Controls versus Cases. Notably, five out of the six Cases who received ≥6 cycles did not exhibit age-adjusted hearing loss.

After a minimum observation time of 15 years, age-adjusted hearing thresholds at 6 and 8 kHz, but not at 4 kHz, were significantly higher among Cases than among Controls ($P = 0.004$ and $P = 0.010$, respectively) (Fig. 2a and b). This difference was not seen with a shorter observation time (<15 years). However, patients with observation time ≥ 15 years received a median of 4 CBCT cycles (range 3 to 8) compared with a median of 3 cycles (range 3 to 6) in patients with shorter observation times.

3.2.2. Self-reported hearing loss (subjective hearing loss or difficulties hearing in noise)

This was reported by 11 Cases and 7 Controls (Table 2). Two Cases (47 years old/5 cycles; 50 years old/6 cycles) and three Controls (46, 73 and 82 years old) used hearing aids. Among patients who reported

Table 2
Hearing and tinnitus.

	Cases (n=41)		Controls (n=33)		*P*-value
Objective hearing					
Hearing thresholds, dBHL, median (range)					
PTA	6	(-4–27)	7	(-1–35)	0.227
4 kHz					
Absolute	10	(-10–80)	15	(-5–65)	0.205
Age-adjusted	2	(-16–62)	-2	(-15–31)	0.026
6 kHz					
Absolute	20	(-5–105)	20	(0–70)	0.429
Age-adjusted	2	(-17–79)	-3	(-25–42)	0.017
8 kHz					
Absolute	15	(0–100)	25	(0–75)	0.212
Age-adjusted	2	(-12–71)	-2	(-31–51)	0.020
Hearing loss, n (%)					
Absolute	21 (51%)		24 (73%)		0.061
Age-adjusted	9 (22%)		5 (15%)		0.461
Subjective hearing[a]					
Self-reported hearing loss, prevalence, n (%)	11 (27%)		7 (21%)		
Not at all	14 (34%)		18 (55%)		
A little	16 (39%)		8 (24%)		
Quite a bit	7 (17%)		5 (15%)		
Very much	4 (10%)		2 (6%)		
Tinnitus[a]					
Number of patients, n (%)	11 (27%)		7 (21%)		
THI category					
Slight	7 (17%)		3 (9%)		
Mild	2 (5%)		3 (9%)		
Moderate	2 (5%)		1 (3%)		
Severe	0		0		
Catastrophic	0		0		

[1]Abbreviations: dBHL, decibel hearing level; PTA, Pure Tone Average of 0.5, 1, 2 and 3 kHz; THI, Tinnitus Handicap Inventory
[a]No significant *P*-values for Cases versus Controls.
The dashed line indicates the separation of patients with or without subjective hearing loss.

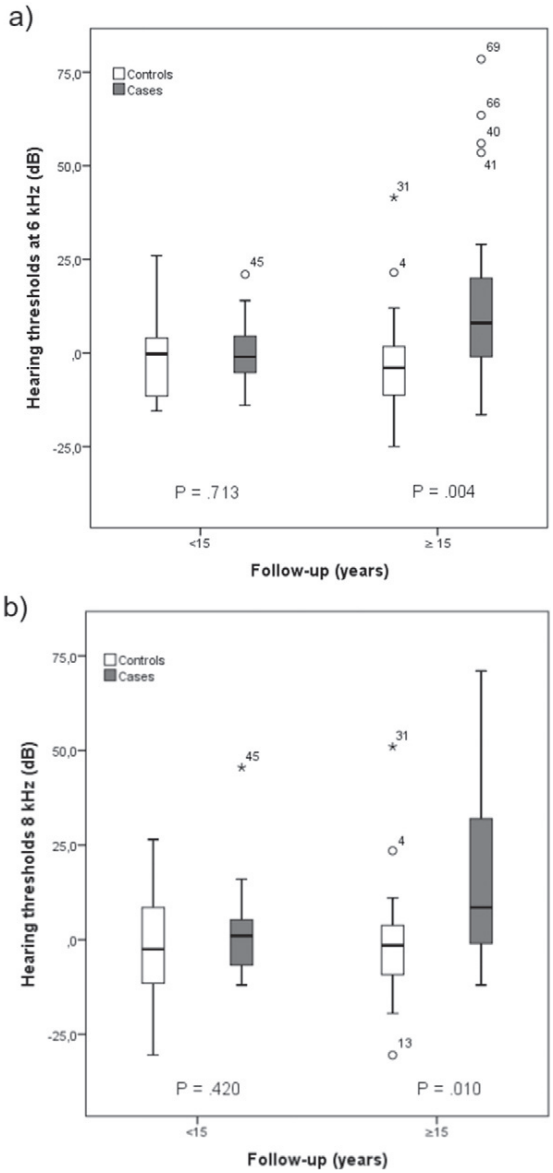

Fig. 2. Age-adjusted hearing thresholds at a) 6 and b) 8 kHz among patients with observation times <15 or ≥15 years.

hearing loss, only four Cases and two Controls had objective age-adjusted hearing loss, i.e., exceeding the expected age-related hearing loss.

3.3. Tinnitus

The proportion of patients with tinnitus did not differ significantly between Cases ($n = 11$, 27%) and Controls ($n = 7$, 21%) (Table 2). When Cases and Controls were combined, patients with tinnitus had significantly higher age-adjusted hearing thresholds at 8 kHz ($P = 0.043$) than those without tinnitus, but no significant difference was detected at lower frequencies. The THI score did not correlate with number of cycles, age at treatment, or observation time.

3.4. Serum platinum concentrations

The median SPC values in Cases and Controls were 125 and 69 ng/l, respectively ($P < 0.001$). SPC decreased with longer observation times (Fig. 3). Significantly higher SPC serum levels were found in Cases

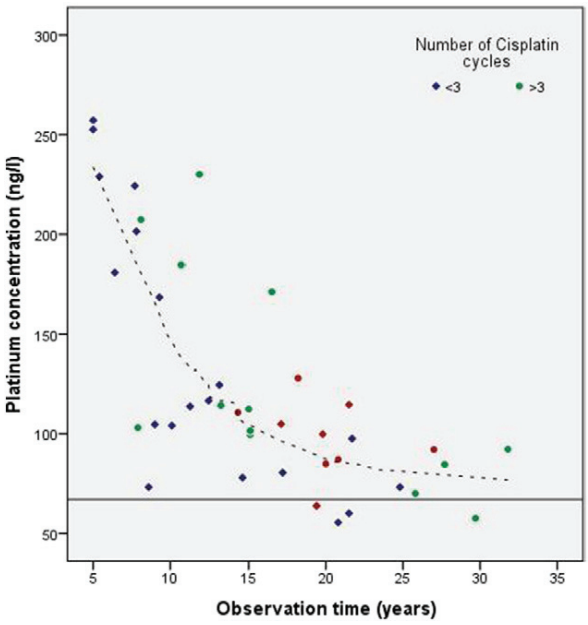

Fig. 3. Serum platinum concentrations and observation time. Cases with age-adjusted hearing loss are marked in red. Solid line indicates the median platinum concentration for Controls.

versus Controls after 15 and 20 years ($P < 0.001$ and $P = 0.016$, respectively). After 25 years, the difference was no longer statistically significant, but after 25 to 32 years, five out of six Cases still had serum SPC higher than the median value for Controls. SPC did not show a significant correlation with hearing thresholds or number of treatment cycles when adjusted for observation time.

4. Discussion

To our knowledge, this is first study to examine long-term ototoxicity in women with germ cell cancer treated with CBCT. No significant differences in absolute hearing thresholds were detected between 41 Cases and 33 Controls, but after adjustment for age the between-group differences in thresholds at 4, 6 and 8 kHz became significant. These differences did not, however, translate to a significant difference in the number of patients with age-adjusted hearing loss. PTA, averaging the mid-frequencies 0.5 to 3 kHz, did not differ between Cases and Controls. Subjective hearing loss was reported by 27% of Cases and 21% of Controls, who were significantly older.

Elevated serum levels of cisplatin were detected up to 20 years after CBCT, but did not correlate with age-adjusted hearing loss or the number of treatment cycles. The incidence of patient-reported tinnitus was similar between Cases and Controls. At 8 kHz patients with tinnitus had significantly higher age-adjusted hearing thresholds than those without tinnitus.

The ototoxic effect of cisplatin in adult cancer patients is well-established, not least from studies in TCSs [1,9–12]. In a long-term follow-up study of TCSs, Glendenning et al. found that 138 of 199 (70%) patients who had received CBCT had an absolute hearing threshold >25 dB at 8 kHz, and 8% of patients reported hearing difficulties. These percentages were almost double those of TCSs without chemotherapy [12]. Using combined audiometric and self-reported observations, Bokemeyer et al. documented clinically relevant hearing difficulties in 21% of TCSs [1]. Oldenburg et al. reported that 24% of individuals in a series of 238 patients answered “Quite a bit” or “Very much” to the SCIN

questionnaire about hearing loss, significantly more than patients who had received only surgical treatment [18]. All these studies had a cross-sectional design and there was no adjustment for age. However, comparison with TCSs contemporaneously treated without CBCT partly overcame this methodological weakness. The rate of reduced hearing among Cases in our study (27%) is comparable with most of the figures cited above. On the other hand, subjective hearing loss showed a similar prevalence in Cases and in the significantly older Controls, indicating that hearing loss after CBCT may be experienced as a feature of accelerated aging.

The current findings must be viewed against the background of a recent study in which Frisina et al. described hearing loss >20 dB at any one frequency between 0.250 and 12 kHz in 80% of 488 TCSs after CBCT [11]. Almost 20% of patients were described as having severe or profound hearing loss according to American Speech-Language-Hearing Association (ASHA) criteria. Importantly, the figure of 80% was not age-adjusted and a relevant control group was not included [11]. The comparable figures of 70%, shown by Glendinning et al. [12] and our estimate of 51% (before age adjustment) are not very different, taking into account the fact that only frequencies up to 8 kHz were measured.

From a scientific point of view it is interesting that the adverse effect of CBCT on hearing is most pronounced at the highest frequencies, as described in pediatric cancer patients [3]. In adult cancer survivors, however, the question remains as to the relative contributions of cisplatin and increasing age to high-frequency hearing loss, since age-related hearing loss also starts in the highest frequencies [23]. This is reflected by Glendenning et al. who reported hearing loss at 8 kHz in 43% of TCSs without CBCT [12]. Our study thus emphasizes the necessity of age adjustment, or comparison with an age-matched control group, when hearing impairment after CBCT is assessed by audiometric methods. This is particularly relevant for high-frequency hearing thresholds since this is the first area to be affected in most etiologies of sensorineural hearing loss, including presbycusis. We therefore strongly support the Editorial comments accompanying the original paper by Frisina et al. [24] suggesting that age-related hearing decline probably represented much of the observed hearing loss which might not be optimal for cross-sectional studies without preceding measurements.

The clinical relevance of CBCT-related high-frequency hearing loss also merits consideration. It should be borne in mind that severe hearing loss in only one frequency, especially if in the highest frequency range, will have little relevance for daily interpersonal communication if the PTA is normal. This is reflected by the low proportion of patients using hearing aids in our study and that of Frisina et al. [11] (2 Cases [5%], 3 Controls [9%] and 6 Cases [1.2%] respectively), although further patients would likely benefit from a hearing aid. Furthermore, audiometric descriptors alone should not be used to measure communication problems in situations with background noise, the primary complaint of individuals with hearing loss.

Thus, our study demonstrates important methodological problems when assessing CBCT-related ototoxicity and strongly suggests that future research should include age-matched controls, preferably in longitudinal studies that include pre-treatment data.

Age-adjusted hearing thresholds at 6 and 8 kHz were significantly higher among Cases than among Controls after ≥15 years' follow-up but not with observation times <15 years. Although results were not adjusted for the number of cycles due to small numbers, our results are in line with pediatric data indicating that ototoxic effects progress with longer follow-up [6]. These observations could reflect CBCT–related accelerated aging of the inner ear, but require confirmation in larger, longitudinal studies that include pre-treatment assessments. As reported by other authors, we observed considerable inter-individual variability in hearing impairment, possibly related to genetic factors [9].

Much work is currently being put into finding ways to protect the inner ear from ototoxic effects. Although some results are promising, no agent is currently recommended for routine use [25].

Contrary to the findings of Oldenburg et al. [9] and Glendenning et al. [12] tinnitus was not more common in Cases (27%) than Controls (21%), but was related to age-adjusted hearing thresholds at 8 kHz in all patients. The proportions of Cases and Controls with tinnitus were higher than expected in the general population (10 to 15%) [8,26]. Due to the high subjectivity of tinnitus, methodological shortcomings may have contributed to the similarity of incidence in Cases and Controls, but these preliminary results do not support the hypothesis that CBCT represents a major risk factor for the development of tinnitus in adults.

Other investigators have reported elevated SPC up to 30 years after CBCT treatment, and one study correlated SPC levels with hearing impairment and tinnitus [13,27,28]. We found no correlation between SPC and hearing thresholds, age-adjusted hearing loss or tinnitus in this small series. Nevertheless, the long-term post-CBCT elevation of serum cisplatin merits further research, particularly in view of the recently reported increased risk of a second cancer in the urinary tract [29].

MOGCT is a rare disease, and the limited number of cases available for analysis represents a major limitation of the study. Furthermore, only 45% of the invited patients participated in the survey, which could potentially mean that the sample is not representative. However, considering the long observation time (median 15 years), we find this acceptable especially since most non-participants were treated with surgery alone. The strengths of the study are its population-based design, the availability of treatment details, and the long observation time. Finally, the study protocol enabled comparison between subjective and objective findings, and application of age adjustment.

In conclusion, after a median observation time of 15 years, 11 out of 41 women (27%) treated with CBCT for MOGCT reported reduced hearing, similar to figures reported previously for TCSs. Based on audiometric results, age-adjusted hearing loss was identified in 9 of 41 (22%) Cases. Compared with Controls, women treated with cisplatin-based chemotherapy had significantly higher age-adjusted hearing thresholds at frequencies 4, 6 and 8 kHz, although the numerical differences were small. In order to avoid over-estimation of CBCT-related long-term ototoxicity, future studies on CBCT-related hearing impairment should control for age. A longitudinal study including an age-matched control group and pre-treatment audiograms would be the optimal design. Tinnitus was overrepresented in this study but did not differ between Cases and Controls.

Acknowledgement of research support (if any)

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Conflicts of interest

The authors have no conflicts of interest to declare.

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II

The Laryngoscope

The Relationship Between Cisplatin-related and Age-related Hearing Loss During an Extended Follow-up

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Objectives: Cisplatin-related hearing loss (HL) is claimed to progress after treatment. This controlled longitudinal study with extended follow-up investigates HL in testicular cancer survivors (TCSs) after cisplatin-based chemotherapy (CBCT).

Study Design: Controlled longitudinal study.

Methods: Eighty-two TCSs treated with CBCT between 1980 and 1994 in Norway participated in two surveys (S1/S3), including pure-tone audiograms (0.125–8 kHz) and self-reported HL, 12 and 31 years after treatment, respectively. Hearing thresholds were age-adjusted based on age-matched hearing thresholds from the general population (controls). Hearing loss was defined as thresholds >20 dB at any frequency.

Results: Between the two surveys, the prevalence of high-frequency HL (4, 6, and 8 kHz) increased from 73% to 94% but approached those of the aging general population after age adjustment. In TCSs aged >40 years at first survey, HL at the subsequent survey equaled that of controls. Self-reported HL increased from seven (9%) at S1 to 20 (26%) at S3. At S1, age-adjusted HL was identified in all (seven) TCSs reporting decreased hearing whereas at S3, hearing thresholds did not differ from controls in seven out of 20 patients reporting HL.

Conclusion: CBCT-related ototoxicity causes high-frequency HL, but in contrast to reports from follow-up studies from the first post-treatment decade, no major progression was found beyond the first post-treatment decade for frequencies 0.125–8 kHz. Importantly, with extended follow-up, hearing thresholds of patients approach those of the general population, possibly due to a less-than-additive effect with age-related hearing loss (ARHL) in CBCT-treated patients. Age-and sex-matching is strongly advised in long-term follow-up of CBCT-related ototoxicity. Specificity for detecting ototoxicity with self-reported questionnaires decreases with extended follow-up.

Key Words: Ototoxicity, cisplatin, hearing-loss, aging.

Level of Evidence: 3

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INTRODUCTION

Cisplatin-based chemotherapy (CBCT) is widely used for treatment of several malignancies, including head and neck cancers. It is a cornerstone in the treatment of patients with testicular cancer (TC) in Norway, resulting in 15-year relative survival rates exceeding 98%.[1–3] CBCT has considerable toxic side effects including ototoxicity with high-frequency HL.[4–6] This is described in multiple cross-sectional studies after pediatric- and adult-onset cancer and most often documented in testicular cancer survivors (TCSs).[4,6–10] However, longitudinal studies which also consider age-related HL (ARHL) are lacking.

The reported incidence of ototoxicity in TCSs varies greatly depending on diagnostic criteria and the cumulative dose of cisplatin.[6–8,11–13] Analyzing audiograms, Glendenning et al. reported HL >25 dB at 8 kHz in 70% of 199 patients 11 years after CBCT.[6] Frisina et al. documented HL in 80% of 488 patients 4 years after CBCT when applying American Speech-Language-Hearing Association (ASHA) definitions of HL.[7] Bokemeyer et al. found significant HL in 21% of 90 patients 58 months after CBCT.[4] Eleven years after CBCT, Oldenburg et al. described self-reported HL in 24% of 238 TCSs.[9] Thus, the literature suggests that self-reported and clinically significant CBCT-related HL is considerably less common (21%–24%) than isolated high-frequency loss on audiometry (70%–80%), which is the criteria used in the articles with the highest frequencies of ototoxicity.

CBCT-related ototoxic damage affects the cochlea at three main sites: the organ of Corti (primarily the outer hair cells), the lateral wall including the stria vascularis and spiral ligament, and the spiral ganglion cells.[14–16]

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TABLE I.
Patient Characteristics (N = 82).

Age at diagnosis, yr*	30 (16–51)	
Survey interval S1 – S3, yr*	18 (16–19)	
Histology, n		
Seminoma	14 (17%)	
Non-seminoma	68 (83%)	
Initial stage, n		
1	24 (29%)	
2	39 (48%)	
3/4	19 (23%)	
Cumulative cisplatin dose, mg/m^2*	400 (84–708)	
High dose (>400 mg/m^2)	n = 21	
Standard/low dose	n = 61	
Survey	**S1 (n = 82)**	**S3 (n = 82)**
Age at survey, yr*	42 (27–64)	61 (46–83)
Age category, n		
<40 yr	31 (38%)	0
40–49 yr	34 (41%)	8 (10%)
50–59 yr	15 (18%)	27 (33%)
60–69 yr	2 (2%)	34 (41%)
≥70 yr	0	13 (16%)
Follow-up time, yr*	12 (3–18)	31 (22–37)
Follow-up time category, n		
4–9 yr	29 (35%)	0
10–14 yr	38 (46%)	0
15–19 yr	15 (18%)	0
20–24 yr	0	10 (12%)
25–29 yr	0	21 (26%)
≥30 yr	0	51 (62%)

*Median (range).

TABLE II.
Objective and Subjective Hearing at S1 and S3.

	S1 (n = 82)	S3 (n = 82)	Median Difference
Objective hearing			
Hearing thresholds, dBHL,* Standard PTA†			
Absolute	6 (–1–55)	14 (1–62)	9 (–1–35)
Age-adjusted	–4 (–10–43)	–7 (–22–34)	–7 (–21–21)
4 kHz			
Absolute	13 (–10–73)	38 (3–90)	23 (–5–50)
Age-adjusted	–4 (–25–46)	–5 (–35–36)	–7 (–34–22)
6 kHz			
Absolute	33 (–5–90)	53 (10–100)	15 (–7–53)
Age-adjusted	5 (–26–61)	1 (–45–45)	–15 (–38–22)
8 kHz			
Absolute	38 (–10–90)	63 (13–95)	18 (–23–43)
Age-adjusted	17 (–27–64)	6 (–47–46)	–18 (–58–10)
High-frequency PTA‡			
Absolute	24 (–8–83)	52 (13–93)	17 (–1–47)
Age-adjusted	5 (–26–56)	2 (–38–40)	–13 (–33–17)
Hearing loss, n			
Absolute	60 (73%)	77 (94%)	
Age-adjusted	37 (45%)	25 (30%)	
Subjective hearing	**S1 (n = 75)**	**S3 (n = 77)**	
Not at all	48 (64%)	23 (30%)	
A little	20 (27%)	34 (44%)	
Quite a bit	7 (9%)	15 (19%)	
Very much	0 (0%)	5 (6%)	

*Median (range).
†PTA: pure tone average of 0.5, 1, 2, and 3 kHz.
‡High frequency PTA: pure tone average of 4, 6 and 8 kHz.
dBHL = decibel hearing level.

Due to poor or no regenerative potential of the inner ear structures, these changes are considered irreversible. Based mainly on studies in children, these changes are also believed to progress for years after treatment.[12,17–19] In a previous study, our group showed that high-frequency HL progressed in 29 TCSs between completion of CBCT and 10 years' follow-up.[18] The course of CBCT-related ototoxicity beyond the first decade has, however, not yet been studied. This is of particular interest in young cancer survivors.

The present exploratory study provides a longitudinal analysis of CBCT-related HL in TCSs 3 decades after their CBCT, based on audiograms, speech audiometry, and patient-reported hearing. We hypothesized that objectively measured HL after CBCT in aging TCSs would increasingly exceed that of the general population due to continuous progression of CBCT-related ototoxicity in addition to ARHL.

MATERIALS AND METHODS

Patients

The current study is based on data from the first and third round of a national multicenter, long-term follow-up survey of TCSs treated at four Norwegian university hospitals from 1980 to 1994.[9,11,20–22] Each of the three post-treatment surveys (S1 [1998–2001], S2 [2007/2008], S3 [2016/2017]) comprised extensive questionnaires on quality of life, morbidity, and socioeconomic factors, clinical examination, and blood sampling. Surviving patients who had participated in the preceding round were eligible to participate in the subsequent round.

At S1, audiometry was performed for all TCSs surveyed at Oslo University Hospital. At S3, all 119 TCSs treated with CBCT and living in the southeast region of Norway were offered a comprehensive hearing examination by an otologist and 100 patients accepted. Eighty-two of them had a previous audiogram from S1 and represent the cohort of the present study. Their median age was 30 years at treatment, 42 years at S1, and 61 years at S3 (Table I).

All patients gave their written informed consent, and the study was approved by the regional committee for medical research ethics (No 2015/1264).

Treatment

After orchiectomy (surgical removal of the testicle) patients were staged according to the Royal Marsden Hospital staging system.[23] Further treatment followed protocols of either the Swedish-Norwegian Testicular Cancer Project or the European Organization for Research and Treatment of Cancer Genito-

Urinary Group.[24–26] Metastatic patients received three or four cisplatin-based cycles, most often CVB (cisplatin, vinblastine, bleomycin) or BEP (bleomycin, etoposide, cisplatin), which represented the most frequently used chemotherapy with a standard cisplatin dose of 100 mg/m^2 per cycle.[27] During the early 1980s a few patients received higher per-cycle cisplatin doses.[28] Recurrent patients usually had >4 cycles. Two cycles of CBCT were given as adjuvant therapy after primary removal of retroperitoneal lymph node metastases.[29] Patients with a total cumulative dose CBCT (≤400 mg/m^2) were separated from those with high-dose CBCT (>400 mg/m^2).

Questionnaire

The validated Scale for Chemotherapy-Induced Neurotoxicity (SCIN) was a part of the comprehensive general questionnaire. SCIN includes one question about self-assessed HL: "Do you suffer from reduced hearing?"[9] Response alternatives were: 0 = "Not at all"; 1 = "A little"; 2 = "Quite a bit"; and 3 = "Very much". Subjective HL was defined as a score ≥2. Answers from five patients were excluded due to a preexisting unilateral HL.

Otologic Examination

All patients underwent pure tone audiometry, at S1 in a soundproof room using the Micromate 304 Screening Audiometer (MadsenElectronics, Taastrup, Denmark) and at S3 in a soundproof room using the Aurical audiometer. Air conduction thresholds, here defined as *absolute hearing thresholds*, were measured by decibel hearing level (dB HL) at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. At S3, speech audiometry, tympanometry, and stapedius reflexes were also performed by an audiologist and otomicroscopy by a trained otologist. To exclude conductive HL, bone conduction thresholds were measured if air conduction thresholds exceeded 20 dB HL at any frequency.

Data from both ears were analyzed except for five patients with preexisting severe unilateral HL at S3, in whom only the better ear was included in the analysis. Three of them reported unilateral sudden HL occurring after CBCT completion.

Pure tone average (PTA) of 0.5, 1, 2, and 3 kHz and of 4, 6, and 8 kHz (*high-frequency PTA*) of air conduction thresholds were calculated. *Absolute HL* was defined as thresholds >20 dB at *any* frequency, in line with previous studies.[7,12] In each patient, thresholds for every frequency, standard PTA and high-frequency PTA were then age-adjusted for S1 and S3 separately. Age-matched thresholds were obtained by subtracting published thresholds of age-matched males from the general population in the HUNT-II survey (controls) from the threshold obtained for each single TCS.[30,31] Ototoxic HL is thus reflected as *age-adjusted HL* and was defined as *age-adjusted hearing thresholds* > 20 dB at any frequency.

Statistical Analyses

Follow-up time reflects the years between treatment and S1 or S3, respectively. S*urvey interval* refers to the time between S1 and S3. Continuous variables are presented as medians and ranges, and categorical variables as counts and proportions (percentages). Wilcoxon signed ranks test was used to evaluate differences between hearing thresholds at S1 and S3. A linear mixed model for repeated measures was used to estimate the effect of the survey interval, of the cisplatin dose (standard vs. higher) and of age at S1 on age-adjusted threshold shifts from S1 to S3. Separate models were fitted for frequencies 4, 6, and 8 kHz. All tests were two-sided. *P*-values <.05 were considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corp, Chicago, IL).

Absolute hearing thresholds in TCSs and comparable Controls are graphically depicted as medians for *all* TCSs, and for two subgroups reflecting age at S1 (≤40 vs. >40 years) and the

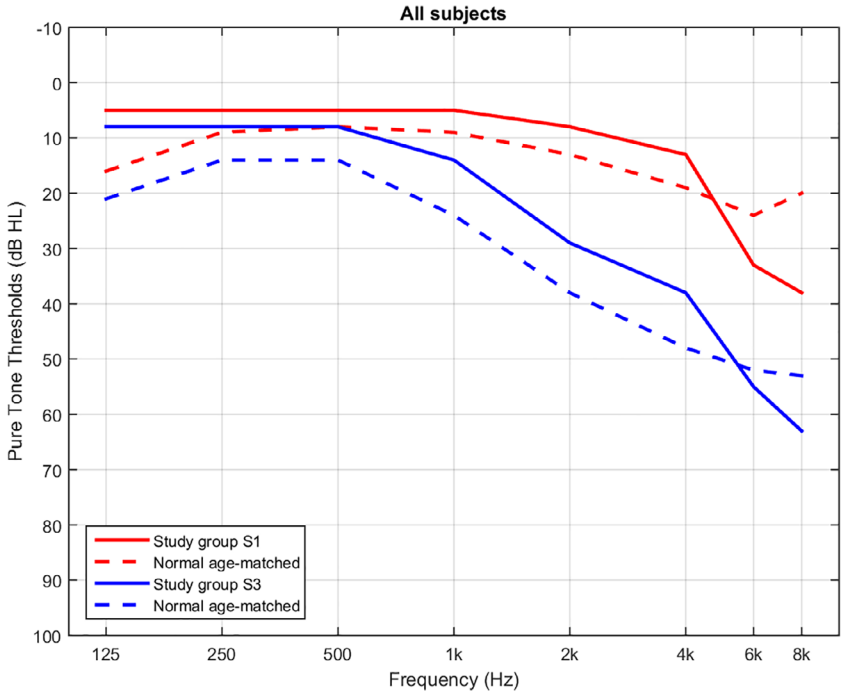

Fig. 1. Absolute hearing thresholds at S1 and S3 compared with the general, age-matched male population. The dotted lines represent sex- and age-matched normal data from the HUNT-II survey. High-frequency thresholds in testicular cancer survivors (TCSs) are worse than those expected in the general population.

cumulative cisplatin dose/m^2 (standard ≤400 mg/m^2 vs. higher >400 mg/m^2).

RESULTS

Patients

The median follow-up times from treatment were 12 years at S1 and 31 years at S3, reflecting a median survey interval of 18 years (16–19 years) (Table I). At S1, 31 patients (38%) were aged ≤40 years. The median cumulative cisplatin dose was 400 mg/m^2 (range 84–708), with higher doses given in 21 patients and 61 patients receiving standard dose.

Audiometry

Between S1 and S3, absolute hearing thresholds at 4, 6, and 8 kHz increased significantly by a median of 23, 15, and 18 dB, respectively ($P < .001$), reflecting worsening of hearing during the survey interval (Table II). However, after age-adjustment, the corresponding median threshold changes between S1 and S3 were negative, reflecting that absolute hearing thresholds in TCSs deteriorated less than the thresholds in the general population. PTA and high-frequency PTA showed similar changes. During the survey interval the proportion of TCSs with absolute HL increased from 73% to 94% whereas the corresponding proportions of age-adjusted HL decreased from 45% to 30%.

Figure 1 depicts the median absolute hearing thresholds at S1 and S3 as compared with those of controls from the HUNT-II survey. On the group level, thresholds of the TCSs followed those of the general male population through the lower and middle frequencies but diverged at 6 and 8 kHz with worse thresholds for the TCSs than for the controls. However, these differences decreased significantly from S1 to S3 for 6 kHz (from 18 to 10 dB) and 8 kHz (from 9 to 3 dB), respectively (both $P < .001$), reflecting that thresholds of the TCSs approach those of the controls with longer follow-up. The closure of the high-frequency gap

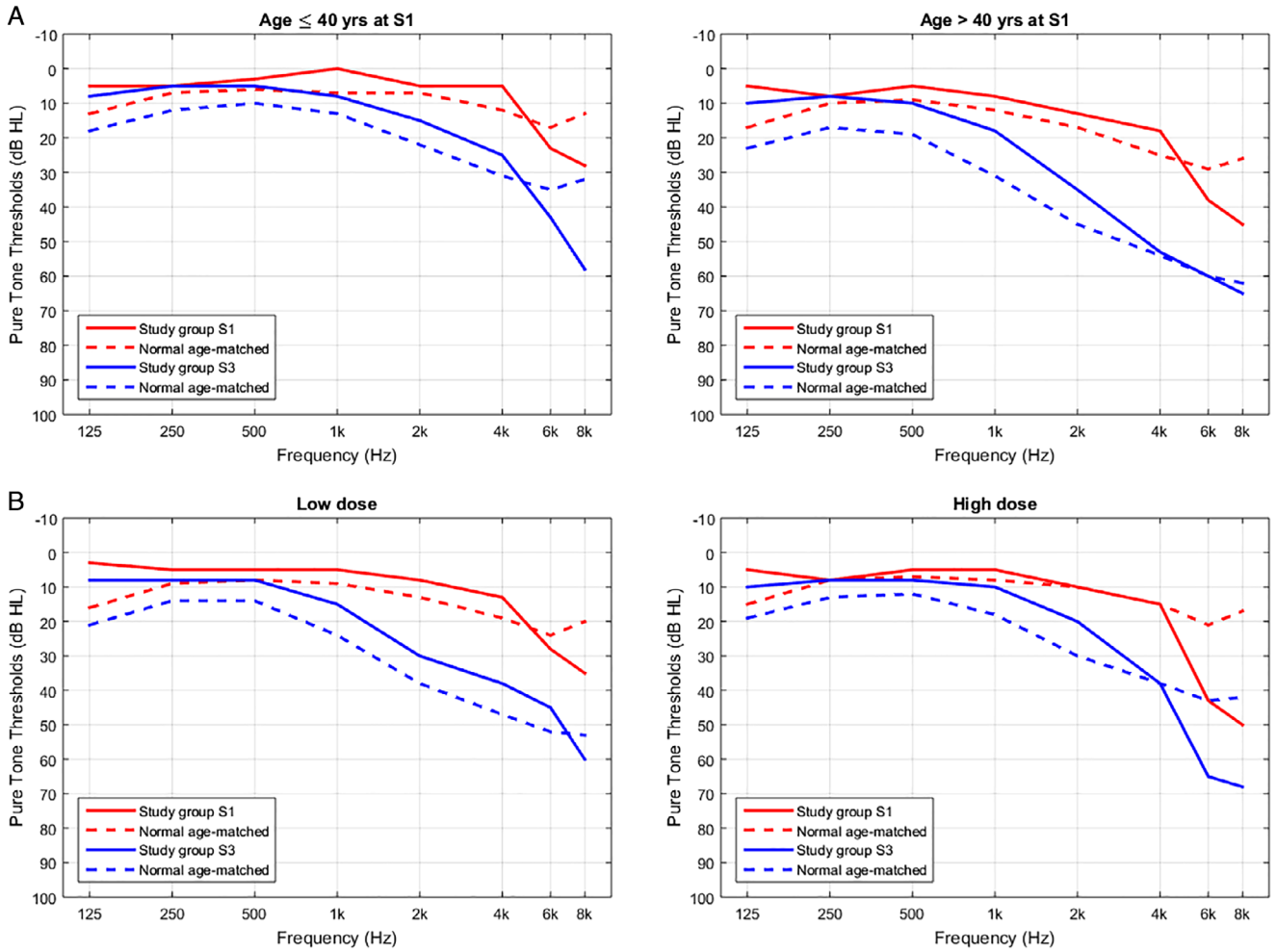

Fig. 2. Absolute hearing thresholds at S1 and S3 for subgroups. (A) Age ≤40 years versus age >40 years at S1; (B) Standard dose versus higher dose cisplatin. (A) illustrates that testicular cancer survivors (TCSs) ≤40 years (left) had worse high-frequency hearing than controls at both S1 and S3, whereas thresholds of older TCSs (right) equal the expected age-related HL at S3. (B) shows more pronounced differences in high-frequency thresholds between TCSs and controls for higher dose of cisplatin (right) compared with standard/lower dose (left). Thresholds deteriorated in a similar way between S1 and S3.

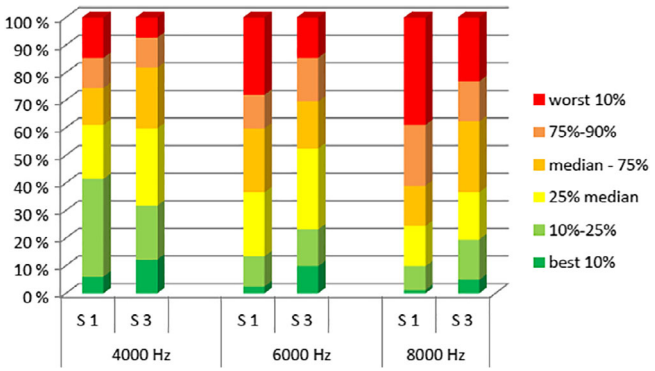

Fig. 3. Absolute high-frequency hearing thresholds at S1 and S3 as percentiles. From S1 to S3 there is an increasing proportion of testicular cancer survivors (TCSs) in the best hearing quartile and a decreasing proportion in the worst quartile of hearing.

between TCSs and controls was more pronounced in TCSs aged >40 years at S1, from 20 dB at S1 to 1 dB at S3. In the younger group, ≤40 years at S1, the gap increased from 12 to 21 dB between S1 and S3 ($P < .001$) (Fig. 2A). The high-frequency gap (TCSs vs. controls) decreased between S1 and S3 in both the standard and higher dose CBCT groups, but with a persisting difference of 21 dB at 8 kHz after high-dose CBCT as compared with 4 dB after standard dose (Fig. 2B). Figure 3 shows TCSs percentiles based on absolute thresholds and compared with percentiles of the general population at 4, 6, and 8 kHz. For 6 and 8 kHz there is a marked reduction of number of TCSs in the worst quartile, especially in the worst 10% between S1 and S3. At the same time there is an increase in number of patients in the better percentiles through the same time period.

The linear mixed model for repeated measures revealed that the survey interval was significantly and positively associated with reduction of age-adjusted hearing thresholds at 6 and at 8 kHz by 9, 8 and 11, 4 dB ($P = .002$ and .001, respectively), but not at 4 kHz. Higher cisplatin dose, as compared with standard dose, was significantly associated with higher age-adjusted thresholds at 4, 6, and 8 kHz at both S1 and S3. Finally, age at S1 was not associated with age-adjusted threshold shifts in any of the models for 4, 6, and 8 kHz.

At speech audiometry, all but five ears tested reached 100% at a median speech presentation level of 35 dB (20–85 dB). One patient reached 90% on one ear, and two patients reached 80% and 50%, respectively, on their best ear.

Otomicroscopy, tympanometry, and presence of air-bone conduction gaps did not indicate middle ear or Eustachian tube pathology of clinical significance.

Self-Reported Hearing

Subjective HL was reported by seven patients (9%) in S1 and by 20 patients (26%) in S3. At S1, all seven patients who reported HL had age-adjusted HL, with median thresholds of 42 dB at 6 kHz and 55 dB at 8 kHz, reflecting a substantial high-frequency HL. At S3 however, the 20 TCSs who reported HL did have an absolute HL, but 7 of them (35%) did not have age-adjusted HL (median thresholds of 21 dB at both 6 and 8 kHz). This implies that, although absolute hearing thresholds generally declined over time, 35% of TCSs reporting reduced hearing at S3 actually did not have different thresholds from those of age-matched men in the general population.

Only one patient (1%) was using a hearing aid at S3. An additional six patients were referred for fitting of hearing aids, based on audiograms and subjective HL.

DISCUSSION

To the best of our knowledge, this is the first study which provides longitudinal data on extended long-term development of cisplatin-related HL in survivors after adult-onset cancer. The longitudinal follow-up of TCSs over 3 decades includes audiograms and self-reported HL from two surveys, S1 and S3, on average 12 and 31 years post-CBCT, respectively. By comparing absolute hearing thresholds with those from age-matched men from the general population we show, as a new finding, that high-frequency thresholds up to 8 kHz in aging TCSs approach those in the general population, in particular for patients aged >40 years at S1. This is reflected by reduced age-adjusted hearing thresholds in the TCS group. The same development was seen irrespective of higher or standard dose CBCT given, although high-dose recipients retained worse hearing thresholds during the survey interval. In about one third of cancer survivors reporting reduced hearing 30 years after CBCT, hearing was similar to age-matched controls from the male general population. Although 94% of TCSs had hearing thresholds >20 dB, predominantly at 4, 6, and 8 kHz, all but three patients reached 100% speech audiometry score on both ears.

Cisplatin is well known to cause ototoxic damage to the inner ear, reflected by increasing hearing thresholds particularly in the higher frequencies.[4,6,7,10,12,21,22,32–34] Depending on the cumulative cisplatin dose and diagnostic criteria for HL, the reported prevalence of cisplatin-related ototoxicity in TCSs varies from 21–80%.[6–8,11–13] Absolute hearing thresholds in our study correspond well with these results. The highest percentages are reported in studies which define HL by any single frequency, including frequencies beyond 8 kHz.[7] Importantly, audiograms in these studies were not sufficiently adjusted for ARHL, and the clinical relevance of an HL in a single frequency is debatable. Further, the clinical relevance of HL >8 kHz in long-term follow-up studies on CBCT in adults can be questioned, given that many patients already have elevated hearing thresholds >8 kHz pre-treatment.[18,35] To our knowledge, no larger age-matched control group exists for these audiometric frequencies. Early markers of ototoxic damage such as extended high-frequency testing and distortion-products otoacoustic emissions (DPOAE) are, in our view, more suitable for early detection of ototoxic damage during treatment, when findings might evoke a change in treatment.

During CBCT, cisplatin is retained in the cochlea where it may remain, possibly indefinitely.[36,37] Elevated

cisplatin serum concentrations have been detected for up to 20 years.[12,38] Due to such persistence of cisplatin in the human body and based on few longitudinal studies, particularly in children, progression of once established CBCT-related ototoxicity has been claimed.[17–19] These studies, however, do not cover more than the first decade post-CBCT. Our findings support the observation that the ototoxic damage to the inner ear occurs mainly during the first decade. Thereafter, the relative impact of CBCT-related ototoxicity on frequencies up to 8 kHz seems to decrease, particularly in older patients. This is clinically relevant when counseling patients prior to treatment.

We found that the proportion of patients with HL and the degree of cisplatin-related HL at S1 were significantly reduced after age adjustment, and decreased further during the survey interval, reflecting physiological aging. The high-frequency HL after CBCT is audiometrically similar to findings related to expected ARHL. Although the exact pathophysiologic mechanisms are complex and may not be identical, there are several similarities between the two. Schuknecht et al. described four types of ARHL depending on pathomechanism involved, two of which are relevant to our study: sensory and metabolic.[39] In the sensory type of ARHL there is a progressive degeneration of the organ of Corti including outer hair cells starting at the basal portion of the cochlea and gradually progressing toward the apex. Metabolic ARHL is characterized by atrophy and degeneration of the stria vascularis and the spiral ligament, causing a decrease in endocochlear potential. Both the sensory and metabolic subtypes of ARHL have similarities with cisplatin-related damage on the organ of Corti. Hair cells in the high-frequency area of the basal turn of the cochlea and stria vascularis/spiral ligament are the first sites to be affected by both CBCT and ARHL.[4,6,7,12,14,16,39–42]

The increased thresholds after CBCT are thus similar to those seen with ARHL but occur in young and middle-aged individuals before the typical age of ARHL. According to NIH, ARHL affect about one third of people >65 years in the United States.[43] Since CBCT-related ototoxicity involves several of the same areas as subsequent ARHL, the latter might be less pronounced in CBCT patients, and may theoretically represent an expression of premature aging, a phenomenon which is increasingly recognized in the oncological literature.[44,45]

A similar less-than-additive model has been suggested for the effect of ARHL in individuals with noise-induced HL, both of which predominantly affect the high frequencies. According to these studies, the effect of aging on the cochlea becomes less evident since the high frequency area of the cochlea is already damaged to some extent by noise.[46–48] Also, a less-than-additive model has been shown in relation to noise-exposed guinea pigs exposed to cisplatin.[49] This has to the best of our knowledge never been shown in relation to CBCT-related ototoxicity in humans.

Self-reported HL was more prevalent at S3 as compared with S1 and corresponds to the increase in absolute hearing thresholds between S1 and S3. Interestingly and admittedly based on small numbers, all of the seven patients with self-reported HL at S1 also had age-adjusted HL, while only two thirds of the 20 TCSs with self-reported HL at S3 had age-adjusted HL. Thus, self-reported HL after CBCT in younger individuals is most likely due to cisplatin-related ototoxic damage, while in older patients, the more hybrid nature of the hearing loss (ie, including both cisplatin and aging effects) makes self-reported HL assessed by a simple question less specific for CBCT-related ototoxicity.

Three patients experienced sudden, idiopathic HL in one ear after treatment. The reported incidence of this condition typically ranges from 2–20/10^5 per year.[50,51] A vascular incidence in the inner ear is one possible etiological factor.[52] Patients receiving CBCT have an increased risk of cardiovascular late effects which hypothetically could explain the observed high number (three of 82 TCSs).[53–55]

Audiograms in S1 and S3 generally showed slightly better thresholds in the lower and middle frequencies compared with the general population. This could be explained by slightly different test conditions at the HUNT-II survey where transportable, less sound-proof boxes were used, yielding somewhat higher thresholds. Nevertheless, background noise was tested and within the ISO 8253-1 standard and the audiometric results from HUNT-II were found to be valid.[31,56] In our view, these differences have negligible relevance for the principal finding of relative threshold shifts between the TCSs and controls.

A limitation of this study is the relatively small number of patients and lack of pre-treatment audiograms, since the ototoxic effect was not yet recognized when the first patients were treated. Since patients were relatively young males at diagnosis, their hearing should not differ significantly from the general population of the same age before treatment, although pre-treatment audiograms would have been optimal. Extended high frequency audiometry was not performed. Since no such data were available from S1, the longitudinal design would not have allowed for a comparison between S1 and S3. Thus, our findings and conclusions are limited to frequencies through 8 kHz. Strengths of this study are the very long observation time, its longitudinal design with audiograms performed at both S1 and S3, and the availability of age-matched audiograms based on data form a large sample of the general Norwegian population. A further strength is the extended otologic examination at S3, which also includes speech audiometry, which may reflect experienced hearing disability better than pure-tone audiograms.

CONCLUSION

By longitudinal audiograms and age-adjustment of absolute hearing thresholds, we demonstrate that cisplatin-related hearing loss beyond the first post-CBCT decade approaches that of the age-matched general population, thereby excluding major progression of ototoxicity up to 8 kHz. Subsequent ARHL is less pronounced after CBCT. Since CBCT-related HL audiologically mimics ARHL, a less-than-additive effect of CBCT-related HL and ARHL is theoretically possible.

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III

Original article:

Speech perception 30 years after Cisplatin based chemotherapy in adults: Limited clinical relevance of long-term ototoxicity?

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Abstract

Background: Cisplatin-based chemotherapy (CBCT) can cause high-frequency hearing loss, but little is known about the development and clinical relevance of this hearing loss in survivors of adult-onset cancer with very long-term follow-up. This case-control study investigates hearing and speech perception both in quiet and with background noise 30-years after CBCT.

Patients and methods: One-hundred-and-one patients (Cases) who received CBCT for testicular cancer between 1980 – 1994 were assessed with pure-tone audiometry (.125 – 8 kHz) and speech perception tests including hearing in noise test (HINT). Self-reported hearing and tinnitus was scored by participants. Results were compared with 30 age-matched controls.

Results: The median age of Cases and Controls was 60 (46 – 83) and 61 years (51 – 74), respectively. The median observation time for Cases was 30 years (22 -37). Compared with Controls, Cases had 8 and 19 dB worse age-adjusted high-frequency hearing at 6 and 8 kHz, respectively ($p < .05$), while thresholds at lower frequencies did not differ. All but 4 Cases reached 100% speech perception with basic speech audiometry. There was no difference between Cases and Controls in speech perception neither in quiet nor with both speech and background noise from the front, although the within-group variance was greater among Cases. Cases scored slightly worse with speech from front and noise from either side. Self-reported hearing loss (both hearing loss in general and specifically with background noise), and tinnitus were about 3 times more common among Cases compared with Controls.

Conclusion: Cisplatin causes high-frequency hearing loss, but speech perception tests performed both in quiet and in background noise 30 years post-treatment indicate that the clinical relevance is limited for most patients. Few patients develop severe hearing loss that requires rehabilitation but it is important to identify these patients. Self-reported hearing loss and tinnitus were more common among Cases compared with Controls.

Keywords: Cisplatin, ototoxicity, hearing loss, tinnitus, HINT

Introduction

The ototoxic side effect of Cisplatin Based ChemoTherapy (CBCT) is well known and has been documented in numerous studies, mainly based on pure-tone audiometry or self-reports in questionnaires [1-9]. CBCT affects hearing primarily in the high frequencies and there are studies, particularly from pediatric patients, suggesting that ototoxic damage can progress over several years after treatment [9-14]. However, there are few long-term studies on ototoxicity in survivors after adult-onset cancer who have undergone CBCT, and to the best of our knowledge, only one with 2-3 decades follow-up [15].

The reported incidence of CBCT related ototoxicity varies greatly depending on the diagnostic criteria used. The highest incidence (up to 80%) is reported in studies which, based on pure tone audiometry, define ototoxicity as hearing loss at one single frequency, most often within the high frequency range [3, 7-9, 16]. The clinical relevance of such solitary high-frequency loss (HFL) can be questioned on the background of the much lower prevalence of self-reported hearing loss (20-30%) [9, 17, 18].

Pure tone audiometry is a useful tool for detecting ototoxic damage both during and after CBCT, but the test does not assess the clinically important outcome of speech perception. Speech perception is different in quiet and in noisy conditions. Speech audiometry is a test of word recognition, often performed together with pure tone audiometry. Both are performed in quiet conditions and thus do not match real life conditions. Difficulties with speech perception in noise is a common problem among patients with high-frequency hearing loss, experienced both after CBCT and with Age-Related Hearing Loss (ARHL). Comparative studies are therefore needed to evaluate the true impact of CBCT on long-term hearing and speech perception. However, studies reporting long-term speech perception after adult-onset cancer are lacking.

In the present case-control study we evaluate speech perception both in quiet and with background noise, and assess the results in relation audiometrically and self-assessed hearing loss in long-term Testicular Cancer Survivors (TCS) who received CBCT two to three decades previously. We also compare the findings with those from age-matched Controls.

Materials and methods

Patients

This study is based on the third round of a longitudinal, national multicenter, long-term follow-up survey of TCS treated in Norway between 1980 and 1994 (Norwegian Testicular Cancer Project 1998: NorTeCaP-1998) [11, 13, 16, 17, 19-25]. The three surveys (S1 [1998-2001]; S2 [2007/2008]; S3 [2016/2017]) included questionnaires, clinical examination, and blood sampling. Surviving patients who had participated in the preceding round were invited to participate in the subsequent round. At S3, these patients participated in a comprehensive

hearing test panel including pure tone audiometry, basic speech audiometry, and tests of hearing in background noise and quiet conditions.

All patients gave their written informed consent, and the study was approved by the regional committee for medical research ethics (No 2015/1264).

Treatment

Patients were staged according to the Royal Marsden Hospital staging system, and treatment followed protocols of either the Swedish-Norwegian Testicular Cancer Project or the European Organization for Research and Treatment of Cancer Genito-Urinary Group [26-29]. Patients with metastatic disease received three or four cisplatin-based cycles, most often CVB (cisplatin, vinblastine, bleomycin) or BEP (bleomycin, etoposide, cisplatin) with a standard cisplatin dose of 100 mg/m² per cycle [30]. A few patients, those treated during the early eighties, received higher per-cycle cisplatin doses [31]. Patients with recurring disease typically had >4 cycles. Two cycles of CBCT were given as adjuvant therapy after primary removal of retroperitoneal lymph node metastases [32]. No patients had supradiaphragmatic radiotherapy.

Audiometry

All patients underwent otomicroscopy prior to audiometry. Testing was performed in a soundproof testing room at Oslo University Hospital using the Aurical® audiometer. Both ears were tested, and the mean threshold in decibel hearing level (dB HL) was used for statistical calculations except for six patients with asymmetric hearing loss, one of whom had single-sided conductive hearing loss and five with single-sided sensorineural moderate or profound hearing loss. These six ears were excluded from all analyses and only the better ear was included for audiometry. These patients were also excluded from hearing tests in noise and questionnaire evaluation. Air conduction thresholds were measured in dB HL at the frequencies; 0.125, 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz and were defined as absolute hearing thresholds. Absolute hearing loss was defined as absolute hearing thresholds >20 dB at any frequency, in line with previous studies [8, 9, 15]. Except for the one patient with conductive hearing loss, no patient had absolute hearing thresholds exceeding 20 dB at frequencies below 4 kHz without also displaying hearing impairment at frequencies of 4 kHz or above. The prevalence of hearing loss was therefore evaluated based on findings from frequencies ≥4 kHz.

To rule out conductive hearing loss (which is not likely to be related to ototoxicity), bone conduction thresholds, which reflect the inner ear function, were measured if air conduction thresholds exceeded 20 dB HL at any frequency. The pure tone average (PTA) of air conduction thresholds at; 0.5, 1, 2 and 3 kHz was calculated. PTA, and absolute thresholds for 4, 6 and 8 kHz were adjusted for age-related hearing loss (ARHL) by using age-matched data from the general male population in Norway, obtained from the HUNT-II study [33, 34]. Age-

adjusted hearing thresholds were calculated by subtracting the expected ARHL from the absolute threshold. Hence, negative values were obtained for patients with hearing thresholds better than the age-matched general population. Age-adjusted hearing loss was defined as an age-adjusted threshold >20 dB at any frequency. Basic speech audiometry according to validated Norwegian standards (ISO 8253-3) was performed routinely for each ear following pure-tone audiometry. This test evaluates the perception of standardized monosyllabic words in quiet conditions.

Hearing in Noise Test (HINT)

A widely used test of speech perception in noise in clinical practice is the Hearing in Noise Test (HINT) [35, 36]. Normative data from young adults with normal hearing are reported for several languages including Norwegian [37, 38]. To the best of our knowledge, no normative data for elderly people has been published in any language to date.

Speech in noise perception was assessed with the Norwegian version of HINT [38]. Testing was performed in an anechoic chamber under headphones using the HINT Pro SW Bio-logic® in which the source locations were simulated for speech and noise. Three noise conditions were used: Noise Front (NF, 0°), Noise Right (NR, 90°) and Noise Left (NL, 270°) with sentences always presented from the front (0°) (Figure 1). The noise level was fixed at 65 dBA, whereas the speech level varied according to the listener's response on the previous sentence [35]. The resulting score represents the ratio between the speech level and noise level, the signal-to-noise ratio (SNR) expressed dB SNR. The test estimates the SNR at which the listener can repeat 50% of the sentences correctly. Increasing SNR values reflect worse speech perception, negative values mean that speech can still be understood although noise is louder. For the noise conditions, the HINT score is expressed as dB SNR. Additionally, speech perception in quiet was assessed, using the same procedure but without noise (HINT Q) and hence the score represents the speech reception threshold (SRT) in quiet, expressed in decibels (dBA) at which 50% of the sentences are repeated correctly.

Questionnaire

All Cases completed a comprehensive questionnaire which included the validated Scale for Chemotherapy-Induced Neurotoxicity (SCIN) [17]. All participants scored their hearing ability based on two questions: "Do you suffer from reduced hearing?" and "Do you suffer from reduced hearing in noisy environments?" Alternative responses were: 0= "Not at all"; 1= "A little"; 2= "Quite a bit"; and 3= "Very much". Self-reported hearing loss was defined as a score ≥2.

Tinnitus was scored based on the question: "Do you suffer from tinnitus/ringing in the ear?" with the same response alternatives and cut-off as for hearing.

Controls

We constructed a study-specific age-matched control group consisting of 30 males. They were initially randomly identified from the LiRe project, where individuals >18 years living in the Norwegian county Lier were invited to participate in a public health survey [39]. However, after having tested 19 Controls, we could no longer justify inviting healthy persons to the hospital due to the SARS-Cov-2 situation. We therefore supplemented with 11 age-matched male healthcare workers including nurses, doctors and radiographers since these were already working in the hospital.

Statistical analyses

Data was analyzed using SPSS® software for PC version 25 (IBM Corp Chicago, IL). All tests were two sided. P-values <0.05 were considered statistically significant and no correction for multiple testing was performed as the study was considered exploratory. Continuous variables were described with median and range and categorical variables with counts and proportions.

The observation time was defined as the number of years between diagnosis and the date of survey. Crude differences between Cases and Controls were assessed using the Mann-Whitney U test. Associations between pairs of continuous variables and pairs of ordinal data were quantified using Spearman correlation. Possible associations between the outcomes and selected covariates were assessed using linear regression analyses. All assumptions for multiple linear regression were fulfilled and residuals followed standard normal distribution. Dependent outcome variables were HINT NF, NR, NL and Q, with independent variables age, cisplatin treatment (yes [Cases] vs no [Controls]), PTA, and absolute thresholds at 6 and 8 kHz.

Results

Cases

One-hundred-and-one TCS participated in this study, with a median age of 60 years (range 48 – 83), whereas the median age of the 30 Controls was 61 years (range 51 - 74) (Table 1). Cases received a median of 3 cycles (range 3 - 8) with median observation time of 30 years (range 22 – 37).

Hearing

Pure tone audiometry and self-reported hearing/tinnitus

Hearing thresholds from 196 ears of Cases and 60 ears of Controls were analyzed. No significant differences in absolute PTA were found between Cases and Controls (14 dB and 12 dB, respectively). Age-adjusted PTA was -7 dB for both groups (Table 2). For the frequencies > 4 kHz, Cases had higher absolute thresholds compared to the Controls only at 8 kHz, and after age-adjustment both at 6 kHz and 8 kHz. All but 6 tested ears in 4 Cases reached 100% speech perception in quiet conditions.

Hearing loss was reported by 22 Cases (23%) compared to 2 Controls (7%) ($p = .007$). Hearing difficulties in background noise were reported by 44 Cases (46%) and 5 Controls (17%) ($p = .001$). Tinnitus was reported by 36 Cases (38%) and 3 Controls (10%) ($p < .001$), and it correlated significantly with worse hearing thresholds at 4, 6 and 8 kHz ($p < .05$) both before and after age-adjustment. Reported tinnitus was also correlated to self-reported hearing difficulties ($p < .001$; data not shown).

Hearing in Noise Test (HINT)

HINT scores were significantly higher (worse) for Cases and Controls with self-reported hearing loss in noise compared to those without (Supplementary Table 1). HINT *NF* with both speech and noise from front revealed no statistically significant difference in speech perception between Cases and Controls, with median scores -2.2 dB SNR and -2.3 dB SNR respectively (Figure 2). However, the within-group variance was greater among Cases including five Cases with HINT scores > 0 dB SNR. Cases scored significantly worse than Controls with speech from front and noise from either right or left side (-8.6 dB SNR vs -9.6 dB SNR, $p = .034$ and -8.8 dB SNR and -9.7 dB SNR $p = .015$ respectively). In quiet conditions (HINT Q), median scores in Cases and Controls were 25.4 dBA and 24.5 dBA, respectively.

Increased (worse) HINT scores were associated with poorer absolute hearing thresholds at PTA, 4, 6 and 8 kHz ($p < .001$; data not shown). Multiple linear regressions were performed with HINT NF, NR, NL and HINT Q as the dependent variable. All outcomes were significantly associated with PTA (but not with higher frequencies), and HINT NF and HINT Q were also associated with age (Table 3). Cisplatin treatment was not associated with worse HINT scores, neither was cisplatin dose or number of cycles which were analyzed in separate regression models.

Discussion

To the best of our knowledge, this is the first evaluation of CBCT-related long-term ototoxicity assessed by speech perception tests in survivors after adult-onset cancer. We found no significant differences in HINT scores between the 95 TCSs and the 30 age-matched male Controls with speech and noise from the front (HINT NF). Cases scored slightly, yet significantly, worse than Controls with speech from front and noise from either side. In quiet conditions (HINT Q) we found no significant difference between Cases and Controls. In

multiple linear regression analyses, increasing age and increasing PTA (mid-frequencies) were associated with worse speech perception both in quiet and with noise from the front. In this model, cisplatin treatment provided three decades previously was not significantly associated with HINT scores, although it was associated with high-frequency hearing loss.

Reduced speech perception, especially in noisy surroundings, is one of the most common challenges in daily life for people with hearing loss. Studies have shown that speech perception can also worsen with increasing age irrespective of hearing thresholds, probably due to decreased cognitive ability [40-42]. However, long-term studies which evaluate speech perception related to CBCT-induced high-frequency hearing loss, which is an important and clinically relevant end point, have been lacking.

The ototoxic effect of CBCT is well documented by pure-tone audiometry displaying treatment-induced hearing loss in the high frequencies [3, 7-9, 13, 15, 43]. This was confirmed by a previous long-term follow-up of TCS by our group, where we also documented that hearing thresholds of TCS approached those of the age-matched males from the general population 30 years after CBCT [15]. We now document that HINT scores in TCS 30 years after treatment are rather similar to those of the Controls, in spite of worse high-frequency hearing thresholds among the TCS. Our linear regression model revealed that PTA significantly affected speech perception both in noise and quiet. Although hearing loss at 4, 6 and 8 kHz was not significantly associated with HINT scores in our regression model, high-frequency thresholds are highly correlated with PTA thresholds and might therefore have confounded the results.

Importantly, the range of HINT scores both in noise and quiet was greater among Cases compared with Controls, indicating that individual patients may experience severe problems with speech perception. Cases had slightly, but statistically significant worse HINT scores with speech from front and noise from either side. This slight difference is likely due to the worse high-frequency thresholds among Cases, leading to a poorer sound localization and Spatial Release from Masking (SRM). SRM refers to the ability to utilize that speech and noise come from different directions. An important part of SRM is the head-shadow effect: with HINT NR/NL the sound reaches each ear at slightly different times and volumes. The brain uses these differences to localize the sound and to hear in background noise. The effect of a difference in volume is most pronounced in the higher frequencies because the shorter wavelengths of high-frequency sounds are more blocked by the human head than those of lower frequencies [44]. Hence, directional hearing and hearing in noise may be slightly poorer among TCS, for example identifying what is said from whom and where in a noisy environment.

Both Cases and Controls (median age 60 and 61 years, respectively) had worse HINT NF scores (higher values) than the Norwegian reference population consisting of normal-hearing young adults (median age 28 years) (-2.2 dB SNR and -2.3 dB SNR vs -3.2 dB SNR respectively). This is consistent with studies showing that speech perception in noise declines with age [40, 41, 45]. One dB worse HINT NF score equals approximately 10 % poorer

speech perception. The association between age and HINT scores (NF/Q) was also seen in our linear regression model.

CBCT 30 years previously was not associated with poorer HINT scores in our regression model. This is consistent with the finding in our previous study that hearing thresholds of TCS approach those of the general population with very long follow-up [15].

Self-reported hearing loss and tinnitus were more common among Cases than Controls. In addition to worse high-frequency thresholds, one possible explanation is that Cases have been aware of the possibility of ototoxicity in relation to their treatment and might therefore have been more aware of hearing problems than the general population. Another explanation is that CBCT-treated TCS are likely to have acquired their hearing loss/tinnitus more suddenly and at a young age in relation to the cisplatin treatment. In contrast, the high-frequency hearing loss of the Controls represents the expected age-related hearing loss which progresses slowly over many years, and appears at an older age.

Overall, our results indicate that reduced speech perception is a limited problem for the vast majority of TCS 30 years after CBCT. It is however important to identify the few patients who struggle with hearing problems after CBCT. The detection and the following aural rehabilitation of these patients are utterly important since hearing impairment is a known risk factor for social isolation, decreased quality of life, and possibly dementia [46-51]. The finding that only 4 TCS (4%) used hearing aids (another 3 were referred based on the results), further strengthens the view that most patients having received CBCT experience limited problems with hearing in daily life. A previous long-term study by our group showed that only 5% of patients treated with Cisplatin for malignant ovarian germ cell tumor used hearing aids, while a large study from the US found that 1.2% of TCS were using hearing aids [8, 9]. While cost might explain the low percent the latter study, economical limitations are not valid for Norwegian patients as hearing aids are fully reimbursed by the government. We conclude that for most patients, standard pure-tone audiometry seems to be a sufficient examination, but selected patients will benefit from speech perception tests.

Limitations of our study should be recognized. The relatively small sample size is related to financial restrictions and associated with limited power. Further, it is important to recognize that during the 30 years follow-up there is inevitably some degree of positive selection among patients as discussed in previous studies, although this bias is unlikely to be directly related to hearing loss [52, 53]. A strength of this study is the follow-up of 30 years. The comprehensive audiological work-up including pure-tone audiometry, speech perception, objective HINT testing and self-reported hearing is unique. We consider the participation rate (101 of 119 eligible) as very satisfactory, considering the long follow-up and the extent of testing required from participants. Although the Controls were recruited from two different populations, the limited variation of HINT scores indicates that the populations were similar.

Conclusion

Thirty years after CBCT, speech perception both in quiet environment and in background noise was similar between Cases and Controls, although Cases scored slightly worse with noise from either side. Increasing age and worse mid-frequency hearing were associated with poorer speech perception, but CBCT 30 years previously was neither associated with poorer speech perception in background noise nor in quiet surroundings. This indicates a limited prevalence of clinically relevant ototoxicity in most long-term TCS after CBCT. It is however important to identify survivors with more severe hearing loss so that aural rehabilitation can be initiated.

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The authors have declared no conflicts of interest.

Figure captions:

Table 1. Patient characteristics.

Table 2. Hearing and tinnitus

Figure 1. Setup of Hearing In Noise Test (HINT)

Figure 2. Boxplot of HINT scores for Cases and Controls (red line indicates mean score for normal-hearing young adults, median age 28 years). Results are presented as dB SNR for HINT noise front, noise right and noise left, and as dBA for HINT quiet.

Table 3. Multiple linear regression for HINT scores.

Supplementary table 1. Self-reported hearing vs objective hearing tests

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Table 1.

	Cases (n=101)	**Controls (n=30)**
Age category, frequency, n (%)		
40 -50 years	10 (10)	
50 -60 years	38 (38)	10 (33)
60 – 70 years	40 (40)	17 (56)
> 70 years	13 (13)	3 (10)
Age at diagnosis, years		
Median (range)	30 (16 - 51)	
Age at survey, years		
Median (range)	60 (46 - 83)	61 (51 - 74)
Post-treatment observation time, years		
Median (range)	30 (22 - 37)	
Total Cisplatin dose, mg		
Median (range)	780 (185 - 1655)	
Number of cycles		
frequency, n (%)		
• ≤ 3	88 (87)	
• > 3	13 (13)	

Table 2.

		Cases (n=101)		Controls (n=30)	P
Measured hearing					
Hearing thresholds, dBHL[1], median (range)					
PTA[2]					
• Absolute	14	(1 – 62)	12	(5 – 43)	.395
• Age-adjusted	-7	(-22 – 34)	-7	(-23 – 20)	.816
4 kHz					
• Absolute	35	(3 – 90)	28	(5 – 27)	.130
• Age-adjusted	-7	(-35 – 59)	-10	(-48 – 14)	.069
6 kHz					
• Absolute	46	(10 – 100)	38	(15 – 85)	.073
• Age-adjusted	0	(-45 – 55)	-8	(-40 – 22)	.017
8 kHz					
• Absolute	63	(13 – 95)	38	(10 – 95)	.012
• Age-adjusted	6	(-47 – 58)	-13	(-40 – 37)	.002
Hearing in Noise Test (HINT), median (range)		**(n=95)**		**(n=30)**	
• Noise front (*dB SNR[3]*)	-2.2	(-5 – 4.5)	-2.3	(-2.5 – -0.3)	.753
• Noise right (*dB SNR*)	-8.7	(-12.3 – 2.6)	-9.6	(-11.5 – -3.2)	.034
• Noise left (*dB SNR*)	-8.9	(-11.7 – 4.6)	-9.7	(-13.1 – -3.6)	.015
• Quiet (dBA)	25.4	(17.3 – 58.8)	24.5	(17.8 – 37.8)	.582
Hearing loss, frequency, n					
• Absolute		97 (96%)		27 (90%)	.619
• Age-adjusted		34 (33%)		4 (13%)	.009
Self-reported hearing		**(n=95)**		**(n=30)**	
Self-reported hearing loss, frequency, n					
• No		73 (77%)		28 (93%)	.007
• Yes		22 (23%)		2 (7%)	
Self-reported hearing loss in noise, frequency, n					
• No		51 (54%)		25 (83%)	.001
• Yes		44 (46%)		5 (17%)	
Tinnitus					
Frequency, n					
• No		59 (62%)		27 (90%)	.000
• Yes		36 (38%)		3 (10%)	

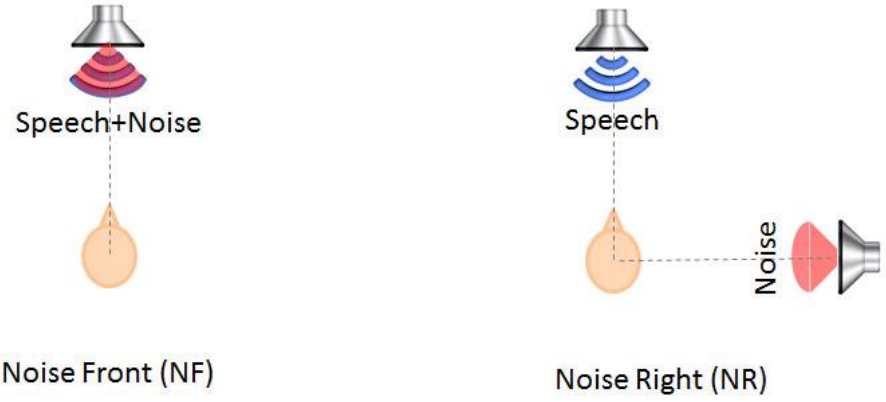
[1]dBHL, decibel Hearing Level; [2]PTA, Pure Tone Average of 0.5, 1, 2 and 3 kHz; [3]SNR, the mean signal-to-noise ratio at which the listener can repeat 50% of the sentences correctly.

Table 3.

	B	95% CI	Standardized Beta	P
HINT NF[1]				
• Age	.044	.013 – .075	.262	.006
• CBCT[2] (yes/no)	-.123	-.625 – .379	-.041	.628
• PTA[3] (absolute)	.031	.003 – .059	.243	.031
• 6000 Hz (absolute)	.006	-.014 – .025	.102	.568
• 8000 Hz (absolute)	-.001	-.019 – .017	-.018	.915
HINT NR[1]				
• Age	.033	-.013 – .078	.102	.156
• CBCT	-.493	-1.215 – .229	-.088	.179
• PTA (absolute)	.128	.087 – .168	.529	.000
• 6000 Hz (absolute)	.022	-.006 – .051	.210	.125
• 8000 Hz (absolute)	.000	-.026 – .026	-.002	.990
HINT NL[1]				
• Age	.043	-.004 – .090	.137	.076
• CBCT	-.728	-1.482 – .026	-.134	.058
• PTA (absolute)	.122	.079 – .164	.516	.000
• 6000 Hz (absolute)	.011	-.018 – .041	.111	.450
• 8000 Hz (absolute)	.002	-.025 – .029	-.019	.887
HINT Q[1]				
• Age	.188	.095 – .281	.233	.000
• CBCT	-.729	-2.220 – .762	-.051	.335
• PTA (absolute)	.413	.330 – .497	.674	.000
• 6000 Hz (absolute)	.055	-.003 – .114	.207	.064
• 8000 Hz (absolute)	-.047	-.099 – .006	-.180	.084

[1] HINT, Hearing In Noise Test: NF - Noise Front, NL – Noise Left, NR – Noise Right, Q – Quiet; [2] CBCT, Cisplatin Based ChemoTherapy; [3] PTA, Pure Tone Average of 0.5, 1, 2 and 3 kHz.

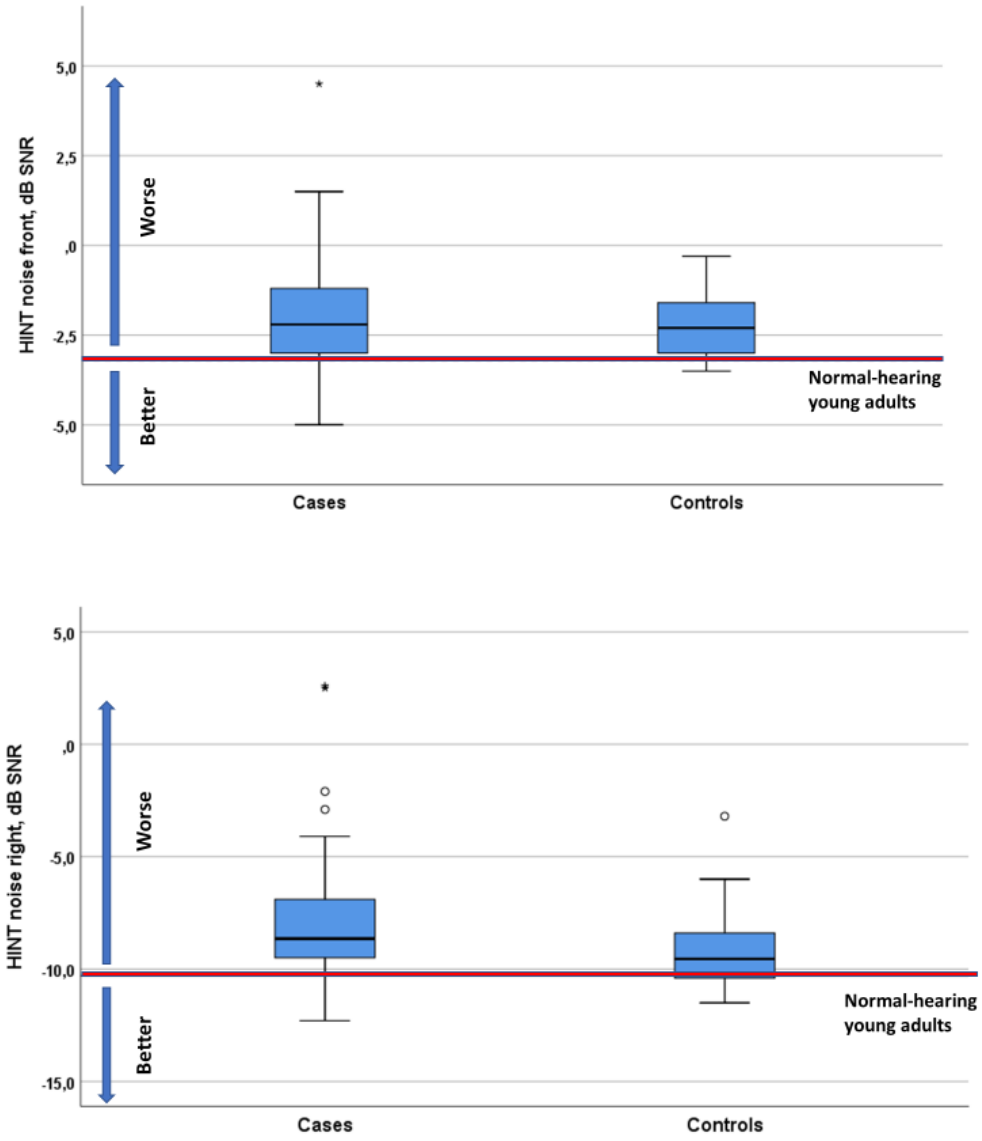
Figure 1.

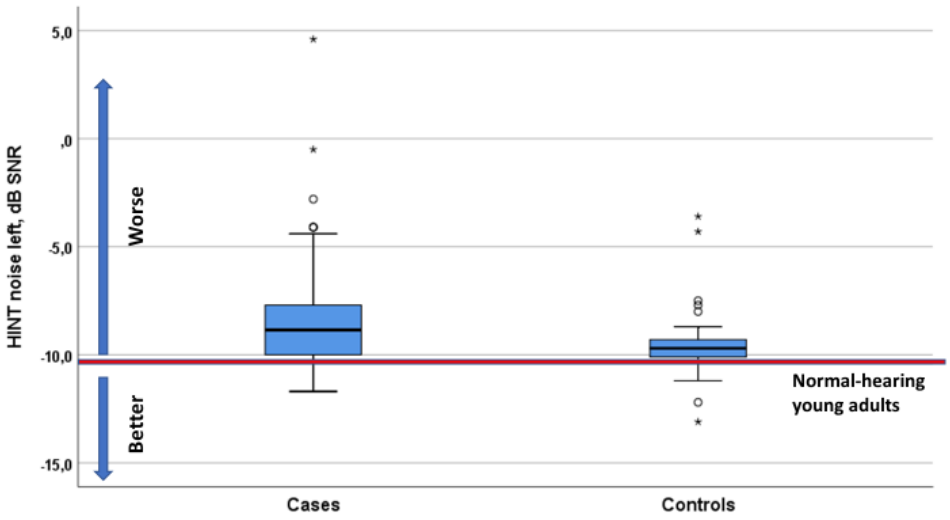


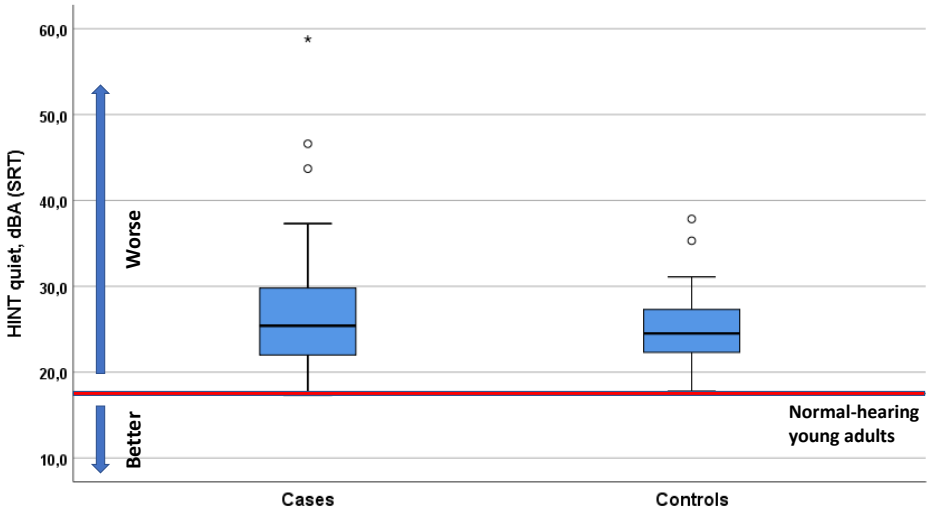
Noise Front (NF)

Noise Right (NR)

Figure 2.


HINT noise front, dB SNR
5,0
2,5
,0
-2,5
-5,0
Worse
Better
Normal-hearing young adults
Cases
Controls
HINT noise right, dB SNR
5,0
,0
-5,0
-10,0
-15,0
Worse
Better
Normal-hearing young adults
Cases
Controls


HINT noise left, dB SNR
5,0
,0
-5,0
-10,0
-15,0
Worse
Better
Normal-hearing
young adults
Cases
Controls


HINT quiet, dBA (SRT)
60,0
50,0
40,0
30,0
20,0
10,0
Worse
Better
Normal-hearing
young adults
Cases
Controls

Supplementary table 1.

	General self-reported hearing loss		P
	Yes (n=24)	**No (n=101)**	
Hearing thresholds, dBHL[1], median (range)			
PTA[2]			
• Absolute	22 (7 – 62)	11 (1 – 49)	.000
• Age-adjusted	-1 (-13 – 54)	-7 (-23 – 26)	.005
4 kHz			
• Absolute	63 (20 – 90)	28 (3 – 90)	.000
• Age-adjusted	10 (-18 – 59)	-11 (-48 – 36)	.000
6 kHz			
• Absolute	73 (25 – 100)	38 (10 – 95)	.000
• Age-adjusted	21 (-18 – 55)	-7 (-45 – 45)	.000
8 kHz			
• Absolute	75 (35 – 95)	48 (10 – 90)	.000
• Age-adjusted	21 (-13 – 58)	-2 (-47 – 45)	.000
Self-reported hearing loss in noise			
	Yes (n=49)	**No (n=76)**	
HINT[3] score, dB SNR[4] median (range)			
• NF	-1.9 (-4.5 – 4.5)	-2.4 (-5 – 0)	.045
• NR	-8.3 (-11.3 – 2.5)	-9.1 (-12.3 – 2.6)	.004
• NL	-8.7 (-11.4 – 4.6)	-9.6 (-13.1 – .5)	.013

[1]dBHL, decibel Hearing Level; [2]PTA, Pure Tone Average of 0.5, 1, 2 and 3 kHz; [3]HINT, Hearing in noise test; [4]SNR, the mean signal-to-noise ratio (SNR) at which the listener can repeat 50% of the sentences correctly.