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Towards the prevention of cancer treatment-related hearing loss

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Citation
Duinkerken, C. W. (2025, September 12). *Towards the prevention of cancer treatment-related hearing loss*. Retrieved from https://hdl.handle.net/1887/4260415

Version:	Publisher's Version
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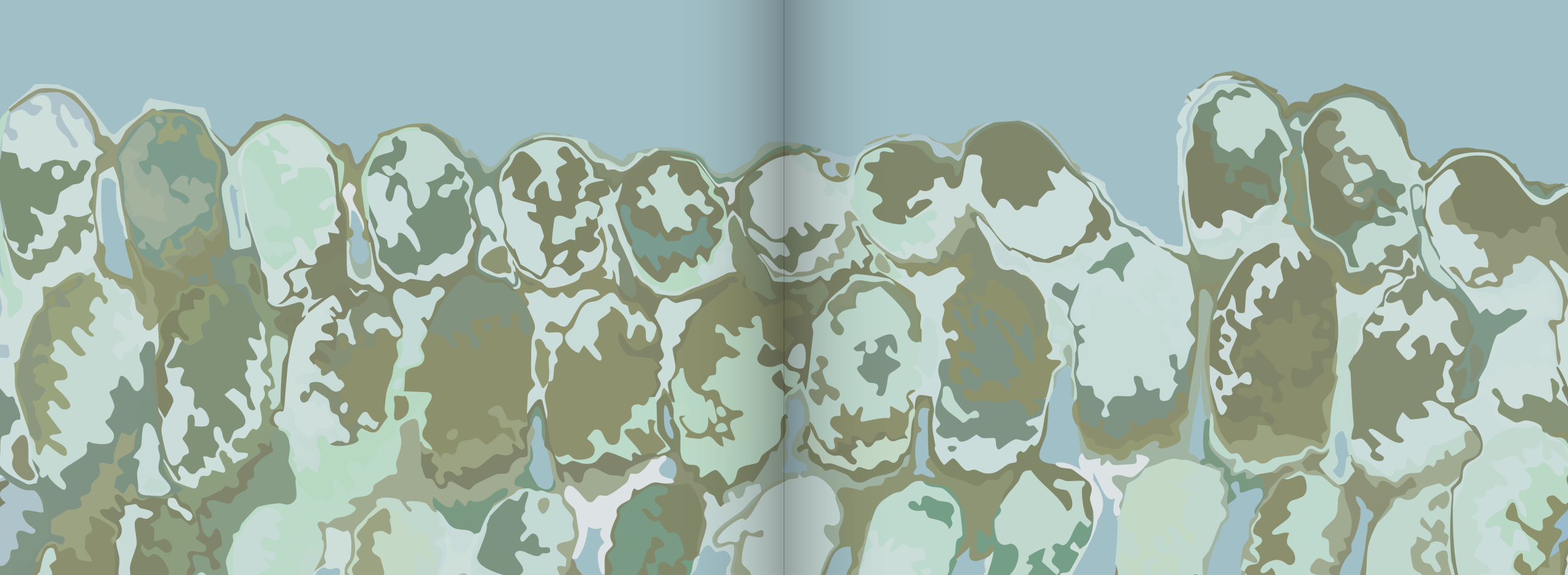
INTRODUCTION



Head and neck squamous cell carcinoma

Over 3000 patients were diagnosed with head and neck squamous cell carcinoma (HNSCC) in the Netherlands in 2022. (1) HNSCC includes tumors of mucosal epithelium origin, involving different anatomic subsites, i.e. the oral cavity, nasal cavity, paranasal sinuses, pharynx (oropharynx, nasopharynx, hypopharynx) and larynx, see Figure 1. Due to potential interference of tumor growth with vital functions like speech and swallowing, choices of treatment for patients with HNSCC need to be individualized. According to national guidelines, treatment decisions are made in a multidisciplinary team with expert professionals from different specialties, as amongst others head and neck (reconstructive) surgery, radiation oncology, medical oncology, radiology, nuclear medicine, speech therapy, physical therapy, and pathology. To this respect, several factors are taken into account, including tumor (sub-)site, TNM classification, Human Papilloma Virus status[1], and patient specific characteristics, such as age and comorbidities. (2) In broad terms, the main therapies for lower staged HNSCC are surgery or radiotherapy (RT). Locally advanced disease is generally treated with definite RT, which functions both as an organ preservation strategy and as a treatment modality for non-resectable disease. (2) In patients younger than 70 years old, RT is often combined with concomitant chemotherapy (CRT) using high-dose cisplatin (with a cumulative dose of ≥ 200 mg/m^2).

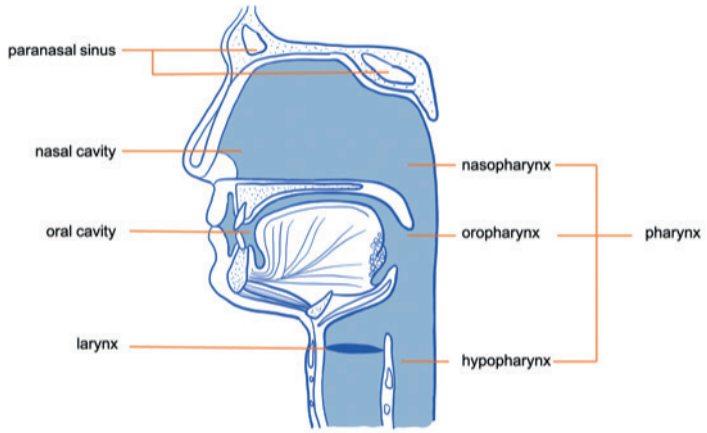


Figure 1. Anatomic sub-sites of the head and neck area.
Created by C.W. Duinkerken[2]

1 HPV tumors have a better prognosis. (2)

2 Maxillary and ethmoid sinuses are not depicted in this midsagittal view.

Cisplatin

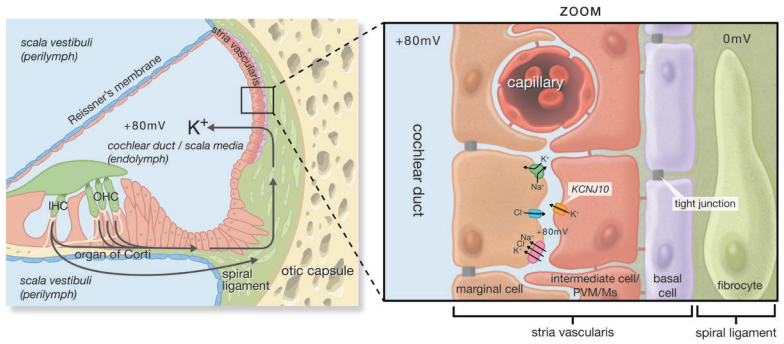
Platinum-derivates, like cisplatin and carboplatin, play an essential role in the treatment of several solid cancers since the 1970's. (3-5) Platinum causes cancer cell-death via intra- and inter-strand crosslinking with the tumour's DNA purine bases. (4) In locally advanced HNSCC, concurrent cisplatin CRT gives an absolute 6.5% overall survival benefit compared to RT alone (6), in which a cumulative cisplatin dose of ≥ 200 mg/m^2 is needed to achieve a significantly increased anticancer efficacy when compared to RT alone. (7, 8) However, both the number of cycles of intravenous cisplatin administration and the cumulative cisplatin (or carboplatin) dose are limited due to dose-limiting toxicities. These include nephrotoxicity, nausea, vomiting, myelosuppression, neuropathy, and ototoxicity. (3, 9, 10) Nephrotoxicity can be prevented by intravenous hyperhydration. However, for ototoxicity and neuropathy (peripheral nerve toxicity) no standardized preventive or curative options are available yet.

Cisplatin-induced hearing loss

The clinical presentation of cisplatin-induced hearing loss (CIHL) is comprised of irreversible, dose-dependent, and symmetrical hearing loss. (3, 4, 11) It typically starts in the (ultra)high frequencies, but as treatment continues, hearing loss may progress to lower frequencies vital for the perception of speech [1 to 4 kHz hearing level (HL)]. As there is heterogeneity amongst studies in the used cisplatin dose and criteria for the definition of CIHL, it is hard to report on the exact incidence of CIHL. A meta-analysis, assessing over a million patients treated with high-dose cisplatin for various solid cancer types, reported that 43.17% of patients develops CIHL. (12) Nevertheless, also higher incidences up to 80% have been reported. (3, 13-15)

At molecular level, multiple processes are involved in the development of CIHL. (16, 17) Cisplatin can enter the cochlea via the stria vascularis, which is a vascularized tissue that functions as a blood-labyrinth barrier, see Figure 2 (*left and right*). (17, 18) The most widely known mechanism of CIHL is the destruction of the outer hair cells within the organ of Corti, see Figure 2 (*left*). (16, 17) Typically, this begins in the hair cells located at the basal cochlear windings, resulting in hearing loss at ultrahigh frequencies. With ongoing platinum therapy (and higher cumulative dose), the lower frequencies will be affected too, due to involvement of the apical windings. (3, 19, 20) Next, other cochlear cells may be damaged, including the inner hair cells, spiral ganglion, and stria vascularis. (16) The stria vascularis is responsible for cochlear homeostasis, which is needed for normal hearing, by generating the endolymphatic potential (+ 80mV) via potassium (K^+) recycling, see Figure 2 (*left*). (17, 18) Furthermore, cisplatin induces hearing loss by the release of toxic reactive oxygen species (ROS). (16, 17) In addition, cisplatin can negatively impact the

cochlea's own defense mechanism against ROS, as cisplatin reduces the cochlear availability of normally otoprotective endogenous antioxidants. (3, 4, 17, 21-23)



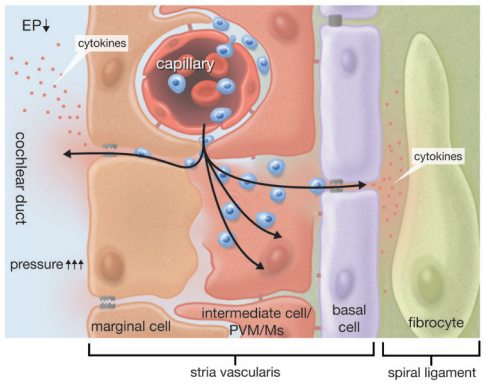


Figure 2. Anatomy of the inner ear.
Left: a schematic cross-section through the human cochlea, depicting the different inner ear structures and the route of potassium (K^+) recycling. *Right (zoom):* a schematic model of the cochlear capillaries, the three cell types of the stria vascularis, the spiral ligament, and the most important ion-transporters for K^+-recycling. (24) Abbreviations: IHC: inner hair cell; OHC: outer hair cell; PVM/Ms: perivascular-resident macrophage-like melanocytes.

Detection of (cancer-)therapy related hearing loss

In this thesis, pure tone audiometry was used for the detection of hearing loss. With this technique, pure tones at different sound intensities for the frequencies 0.125 to 8 kHz (HL) are presented to the subject. Because CIHL usually starts at the ultrahigh frequencies, ultrahigh frequency audiometry - measuring the frequencies from 8 up to 20 kHz (in sound pressure level (SPL)) - was also performed. Audiometry is performed in a soundproof room. At each individual frequency, signals are presented in different sound intensities (from -10 dB up

to +120 dB). The threshold (in dB) at which the person is able to hear the signal is plotted in an audiogram, see Figure 3. To detect therapy-related hearing loss, audiometry needs to be performed pre-treatment (baseline) and post-treatment (follow-up). In the studies included in this thesis, Pure Tone Averages (PTAs) were calculated. The average hearing threshold at 1, 2, and 4 kHz in dB HL was used for the PTA relevant for the perception of speech in noise (further referred to as PTA 1-2-4 kHz). For the perception of ultra-high frequencies (needed for e.g. high-pitched ring tones or high tones in music) we used the average hearing threshold at 8, 10, and 12.5 kHz in dB SPL (further referred to as PTA 8-10-12.5 kHz).

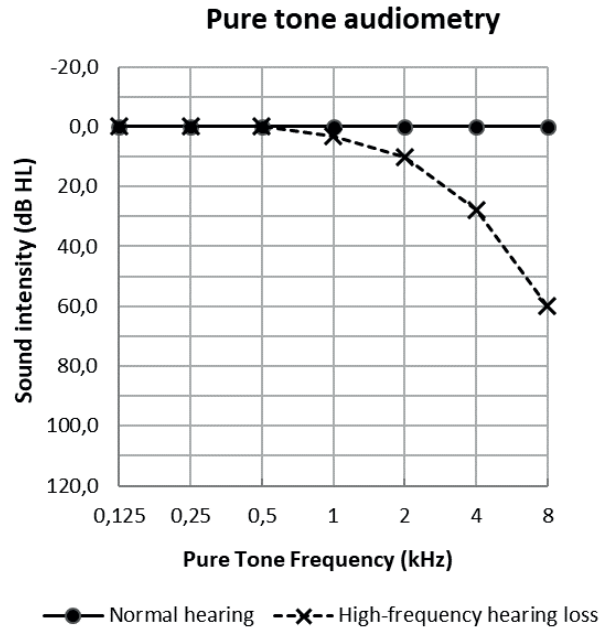


Figure 3. Pure tone audiometry showing normal hearing (uninterrupted line) and hearing loss at high frequencies as seen in presbycusis or cisplatin-related hearing loss (dotted line). In this audiogram, hearing thresholds (in dB HL) for frequencies 0.125 up to 8 kHz are plotted. Abbreviations: dB: decibel; HL: hearing level; kHz: kilohertz.

Prevention of platinum-induced hearing loss

While cure remains unquestionably the cornerstone of treating patients with HNSCC, there is growing focus on the improvement of post-treatment quality of life. As CIHL is characterized by irreversible hearing loss for which no treatment options are yet available, several research groups are still trying to find a preventive strategy to protect against CIHL. Different approaches, including both systemic and topical (transtympanic) administration, have been explored in attempts to prevent from CIHL with varying successes. (12, 25-27) Among these, antioxidants have

arose as particularly promising, with the ability to counteract the damaging release of ROS by cisplatin. The antioxidant sodium thiosulfate (STS) also has the capacity to inactivate cisplatin by binding to its active form. (4, 18, 28) Encouraging effects of intravenous STS against CIHL were demonstrated in two phase III trials in children. (29, 30) Nevertheless, the clinical application of intravenous STS is limited due to its potential interference with cisplatin's antitumor efficacy and potential side effects. (4, 29) The development of a topical approach is therefore needed.

Identification of patients that may suffer from CIHL

In order to select patients that may benefit from prophylaxis against CIHL, the identification of patient groups at risk for the development of CIHL is most important. Apart from cisplatin dose, several co-occurring risk factors for the development of CIHL have been reported. For patients with HNSCC, one of the most important risk factors is RT: a radiation dose to the cochlea of ≥ 30 Gray is known to cause clinically relevant hearing loss, which can be both sensorineural and conductive of origin. (13, 31)

Another risk factor for the development of CIHL is a favorable pre-treatment hearing level). (12, 14, 19, 20, 26, 32) Obviously, excellent hearing is mainly observed in younger patients who do not suffer from age-related hearing loss.

In addition, patients may have a genetic vulnerability for CIHL, as several single-nucleotide polymorphisms (SNPs) have been associated with increased CIHL. (33-37) At a molecular level, cochlear melanoma antigen expression seems also to be involved in cancer therapy related hearing loss in patients treated with T cell receptor gene therapy against metastatic cutaneous melanoma. (38)

From a systemic point of view, vulnerability for cisplatin toxicity may vary pending on interindividual variabilities in the distribution of cisplatin into the tissues. As cisplatin mainly distributes to the fat-free mass, patients with a low skeletal muscle mass (sarcopenia) might experience higher peak dosages of cisplatin. Therefore, they are potentially at risk for platinum-related toxicities, including CIHL. (39)

At last, CIHL depends on the dose intensity of cisplatin. In the Netherlands, the standard of care CRT for HNSCC uses 3-weekly 100 mg/m^2 cisplatin (on days 1, 22, and 43). Approximately 30% of cisplatin-treated patients suffer from dose-limiting toxicities. (40-42) In order to reduce toxicity and increase compliance to cisplatin therapy, recently, some Dutch centers have adapted their schedule and now employ weekly cisplatin infusions of 40 mg/m^2 (during seven consecutive CRT weeks).

Remaining issues in cancer therapy related hearing loss

Based on preclinical models, topical application of STS as an otoprotector against CIHL seems promising. However, this approach needs to be investigated to learn whether transtympanic application of STS is safe and feasible in humans too. In addition, the pharmacokinetics of systemically available cisplatin after topical STS application needs to be assessed, to ensure that the anticancer effect of cisplatin is not compromised by transtympanic STS. Next, it would be desirable to identify which patients are most at risk for the development of clinically relevant CIHL, as these patients may require prophylaxis against CIHL in the future. Also, given the substantial developments in the field of cancer treatments, one should be aware of the option that hearing loss may also arise after new forms of cancer therapy, especially when inner ear structures are being targeted.

AIM AND OUTLINE OF THIS THESIS

The general aim of this thesis is to move forward in the development of preventive strategies against CIHL.

To this respect, our first aim was to assess whether it is safe and feasible to use transtympanic STS injections to avoid systemic anti-cisplatin effects in a phase I randomized clinical trial (**Chapter 2**). The efficacy of this intervention will be studied in an upcoming multicenter phase III randomized clinical trial (protocol in **Appendix II**).

Our second aim was to identify patient-groups that may benefit from preventive strategies in the future: which patients are particularly at risk for the development of CIHL? To gain more insight into CIHL risk profiling the following studies were performed:

- Assessment of the extent of CIHL in young men with testicular cancer treated with high dose cis- or carboplatin for primary or recurrent disease (**Chapter 3**);
- Research into SNPs which might be related to the development of CIHL in patients treated for HNSCC (**Chapter 4**);
- HNSCC patient cohort data analysis to study whether pre-treatment sarcopenia is correlated to increased CIHL after treatment with cisplatin-based CRT (**Chapter 5**);
- Investigation of the difference in CIHL between two different cisplatin dose-intensity CRT schedules for HNSCC (**Chapter 6**).

In the last part of this thesis, we present a novel form of cancer-therapy related hearing loss. We provided a rationale for severe sensorineural hearing loss with unilateral deafness that may occur during T-cell receptor gene therapy applied for metastatic melanoma (**Chapter 7**).

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