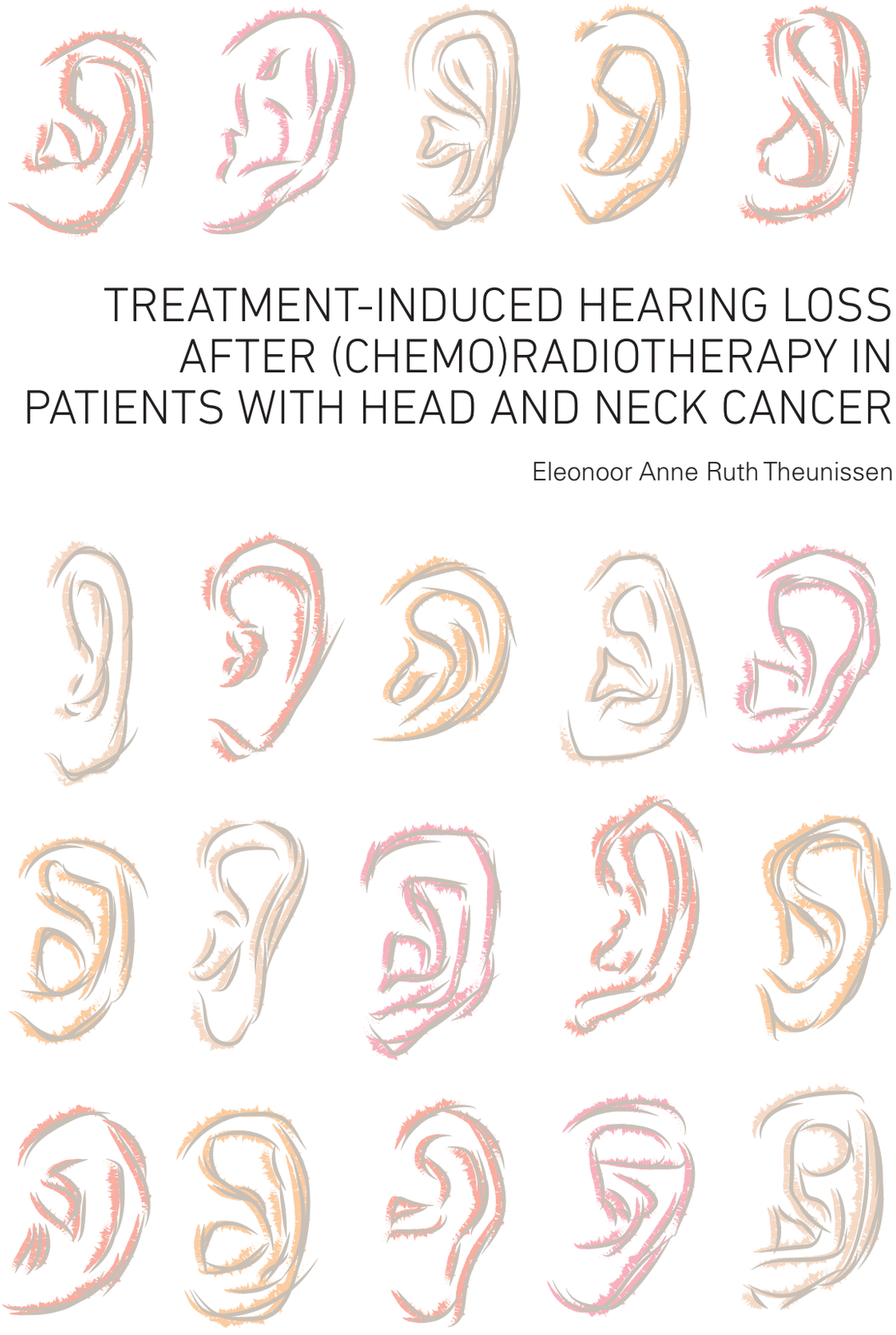
Treatment-induced hearing loss after (chemo)radiotherapy in patients with head and neck cancer

Theunissen, E.A.R.

Publication date
2015

Document Version
Final published version



TREATMENT-INDUCED HEARING LOSS AFTER (CHEMO)RADIOTHERAPY IN PATIENTS WITH HEAD AND NECK CANCER

Eleonoor Anne Ruth Theunissen

TREATMENT-INDUCED HEARING LOSS AFTER (CHEMO)RADIOTHERAPY IN PATIENTS WITH HEAD AND NECK CANCER

Noortje Theunissen

TREATMENT-INDUCED HEARING LOSS AFTER (CHEMO)RADIOTHERAPY IN PATIENTS WITH HEAD AND NECK CANCER

Eleonoor Anne Ruth Theunissen

The research described in this thesis was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands. The research was partly funded by the Riki Stichting.

The printing of this thesis was financially supported by:
ACTA, ATOS Medical BV, Beter Horen, Chipsoft, Daleco Pharma BV, Dos Medical, EmiD audiologische apparatuur, Joosten Hoorspecialisten, Nederlandse KNO-vereniging, NKI-AVL, Mediq Tefa, Olympus Nederland BV, Schoonenberg Hoorcomfort, Specsavers Hearcare.

Cover & Layout	myra nijman concept & design | info@myranijman.nl
Printed by	GVO Drukkers en Vormgevers BV | Ponsen & Looijen
ISBN	978-90-6464-865-6
Online	http://dare.uva.nl

Treatment-induced hearing loss after (chemo)radiotherapy in patients with head and neck cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

ten overstaan van een door het College voor Promoties ingestelde

commissie, in het openbaar te verdedigen in de Agnietenkapel

op woensdag 10 juni 2015, te 14.00 uur

door

Eleonoor Anne Ruth Theunissen

geboren te Bloemendaal

PROMOTIECOMMISSIE

Promotores:	Prof. dr. A.J.M. Balm
	Prof. dr. ir. W.A. Dreschler
Co-promotores:	Dr. C.L. Zuur
	Prof. dr. C.R.N. Rasch
Overige leden:	Prof. dr. M.W.M van den Brekel
	Prof. dr. ir. J.H.M Frijns
	Prof. dr. G. Laurell
	Prof. dr. J.H.M. Schellens
	Dr. Y.J.W. Simis
	Prof. dr. L.E. Smeele

Faculteit der Tandheelkunde

CONTENTS


01

CHAPTER 01

General introduction and outline of the thesis

Head and neck cancer

A head and neck squamous cell carcinoma is a malignant tumor that arises in the head and neck area (lip, oral cavity, nasal cavity, paranasal sinuses, pharynx, and larynx). Five percent of all newly diagnosed cancers worldwide are head and neck squamous cell carcinomas (HNSCC).[1] In the Netherlands in 2012, there were 2.999 new cases, which accounts for 3% of the total number of new patients with cancer during that year.[2] Among the most common cancers in the Netherlands, HNSCC currently ranks number nine for women and number seven for men.[2] The most common malignant diseases are prostate cancer in men and breast cancer in women, which in the Netherlands average 11.700 and 14.100 each year, respectively. While the incidence of HNSCC is much lower, the numbers have been increasing.

Worldwide there are differences observed regarding most common tumor locations for HNSCC. In Oceania, India and Europe, common locations are the oral cavity and pharynx; whereas in Southeast Asia, nasopharynx carcinoma is the most common. The highest incidence of laryngeal cancer is reported in Europe.[3]

Treatment of head and neck cancer

Because the head and neck region embodies complex anatomical structures essential for vital functions, the treatment of a tumor in this area is focused on minimizing mutilation and preserving functions such as breathing, chewing, swallowing of food, and speech. These multiple functions involved warrant a multidisciplinary approach by a treatment team including head and neck surgeons, medical oncologists, radiation oncologists, as well as dentists, dieticians, speech and swallow therapists, specialized nurses, and physical therapists.

The mainstays of treatment are surgery, concurrent chemoradiation (CCRT), and radiotherapy (RT).[4,5] The decision which treatment modality to use depends on tumor site, stage, radiological and histological characteristics, and co-morbidity of the patient. In general, low staged cancers (stage I and II) are often treated with surgery and/or radiation therapy, whereas locally advanced staged diseases (stage III and IV) are preferably treated with surgery and/or concomitant chemoradiation, depending on the expected post-treatment functional loss.[4]

In case of CCRT, cisplatin is currently the most commonly used drug in HNSCC. Studies have shown the benefit of cisplatin added to RT. Pignon et al. reported a larger effect on locoregional control and survival of chemotherapy in concomitant schemes than in neo-adjuvant and adjuvant chemotherapy, suggesting that cisplatin may have a synergistic effect on radiotherapy. An absolute survival benefit of 6.5% for the addition of concomitant chemotherapy to radiotherapy has been reported.[4,6,7] Presently, the concomitant chemoradiation regime in the Netherlands consists of 3 cisplatin infusions of 100 mg/m^2, on days 1, 22, and 43 during 7 weeks of radiotherapy (70 Gray in 35 fractions).

Radiotherapy and cisplatin induced toxicities

Radiotherapy in the head and neck region leads to fatigue, xerostomia, swallowing problems, oral mucositis, dysfunction of the salivary glands, painful epidermiolysis, and ototoxicity.[8] In addition, cerebral radiation necrosis, radiation-induced cranial nerve palsy, and osteoradionecrosis are described as late complications of radiotherapy. However, due to improvements radiotherapy techniques, these toxicities are nowadays less frequently occurring. For example, before application of IMRT for nasopharyngeal cancer, the reported incidences of osteoradionecrosis varied from 5.4 to 11.8%, whereas IMRT decreased the incidence of osteoradionecrosis and cranial nerve palsy significantly to 3% and 0-5%, respectively.[9] More side effects are seen when the radiation dose is higher.[10]

Cisplatin will cause systemic toxicities such as nephrotoxicity, nausea, vomiting, neurotoxicity, ototoxicity, and myelosuppression.[11] Nephrotoxicity can be managed with hydration, and the gastrointestinal side effects can be managed with anti-emetic agents. However, no effective medical treatment for the prevention of ototoxicity is developed yet.[11] The severity of the side effects is dose dependent; a higher cisplatin dose results in more severe side effects.

Adding cisplatin to radiotherapy does not only implement increased tumor responses, but also a synergistic effect on the side effects during **CCRT**.[6,12,13] The addition of high-dose cisplatin (100 mg/m^2, 3 infusions in 7 weeks) to radiotherapy induced an increase in acute adverse effects of CTCAE grade ≥3 from 52% to 89%[6] and from 34% to 77%.[13] Comparing radiotherapy as a single modality treatment to radiotherapy with

concomitant low-dose cisplatin (6 mg/m^2, daily infusions, 7 weeks), the 42% incidence of acute adverse effects remained unaltered.[7]

Treatment-induced ototoxicity

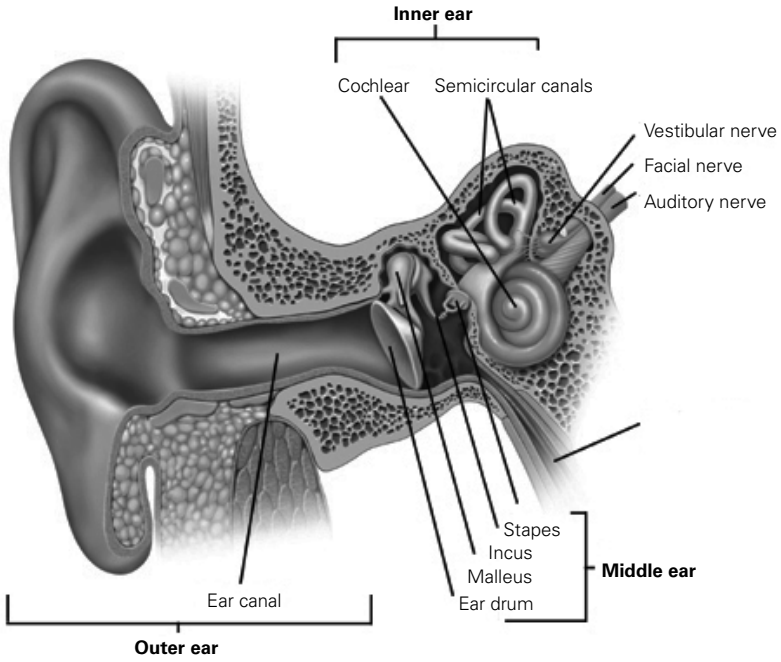
When describing the human ear, three parts can be distinguished: the external hearing canal, the middle ear, and the inner ear (figure 1). Different types of hearing loss can arise, depending on the localization of the damage: conductive hearing loss (CHL), which originates in the external canal and/or in the middle ear, versus sensorineural hearing loss (SNHL), which originates in the inner ear (damage to the cochlea) in retro-cochlear organs (e.g. damage to the eight nerve). Treatment-induced ototoxicity may consist of hearing loss (both conductive and sensorineural) and vestibular effects, such as vertigo. The focus of this thesis will be on the middle and inner ear pathology rather than on the vestibular effects.

In general, several different compounds can cause ototoxicity. Anti-malarial, antihypertensive, antibiotics, platinum-based chemotherapeutic agents, and radiotherapy applied on the head and neck area all may exert hearing loss.[15-17] In the cochlea, ototoxicity is characterized by starting at the basal (perception of ultra-high frequency tones) and then progressing to the apical end (perception of the low frequency tones). This sensorineural hearing loss is irreversible, whereas conductive hearing loss (as often found after RT) is mainly reversible.[18]

Radiotherapy in the acute phase will cause conductive hearing loss as a result of inflammation, edema, and/or fibrosis of the middle ear and/or Eustachian tube. Although this is an uncomfortable complication, it is often transient and reversible. Sensorineural hearing loss can be an acute or a late result of RT to the inner ear and may be an irreversible adverse effect. It is most likely caused by vascular insufficiency and radiation induced lesions to the inner ear or acoustic nerve.[19] Winther described in 1969 an extensive degeneration of outer hair cells (OHCs) of the organ of Corti in guinea pigs after radiation of the inner ear.[20] Also, in humans, destruction of the organ of Corti and atrophy of the audio-vestibular nerve after radiation to the temporal bone have been demonstrated.[21] Furthermore, loss of OHCs, loss of spiral ganglion cells in the basal turn of the cochlea, atrophy of the stria vascularis, changes in nerve vessels, and a damaged organ of Corti, macula of the utricle and the cristae of the semicircular canals, have been

showed in postmortem investigation of the human temporal bone in patients treated with RT.[22,23] In radiation-induced ototoxicity, cochlear cell apoptosis and reactive oxygen species (ROS) generation were observed after irradiation. In addition, p53 was thought to play a key role.[12] In response to DNA damage in cochlear cells, activation of the p53 pathway was observed, followed by cell cycle arrest and apoptosis.

Figure 1 | Anatomy of human ear.[14]



Cisplatin induced ototoxicity induces sensorineural hearing loss (SNHL). It may start in the acute phase of treatment and is characterized by bilateral, irreversible, and progressive high frequency loss.[24] Animal studies showed that cisplatin damages outer hair cells within the organ of Corti and the marginal cells within the stria vascularis. The dose of cisplatin is reported as an important factor of the extent of ototoxicity: studies in guinea pigs showed damage at the stereocilia tip-link connections, followed by disorganization and fusion of stereocilia after low-dose cisplatin infusions. Higher

doses resulted in total loss of stereocilia and of the hair cells itself, atrophy of the striavascularis, collapse of Reissner's membrane, and damage to the supporting cells.[11]

Platinum induced-cytotoxicity is caused by the binding of cisplatin to guanine bases in the DNA, which may lead to the formation of inter- and intrastrand crosslinks. Once formed, these lesions can trigger apoptotic cascades via the mitochondrial pathway, including p53. It is suggested that similar events are occurring in the inner ear.[25] Platinum toxicity is also attributed to oxidative stress, followed by the generation of free radicals, specifically reactive oxygen species (ROS). ROS can increase lipid peroxidation, triggering events that initiate apoptosis. In the inner ear this will lead to apoptosis of hair cells, supporting cells, stria vascularis, and the auditory nerve.[11,26] It is reported that the outer hair cells of the cochlear base are more susceptible to free radical damage than the outer hair cells of the cochlear apex.[11] Also, an in vivo animal study showed that 10 minutes after administration of an ototoxic dose of cisplatin, the concentration of cisplatin in the perilymph was 4-fold higher in the basal turn of the cochlea than in the apex. After 30 minutes no differences in concentrations were seen. They suggest that this initial high concentration of cisplatin in the basal turn gives a longer exposition time to high levels of ototoxic cisplatin. This might favor the loss of outer hair cells in the base of the cochlea.[27]

Another factor associated with inner ear damage is the cisplatin uptake from the stria vascularis into the cochlear fluids and hair cells. Because cisplatin is a small and highly reactive molecule, various transporters have been suggested to be involved in cisplatin uptake by cells. Transport proteins such as copper transporter CTR1, megalin LRP2, and organic cat-ion transporter OCT2 are suggested to play an important role in this process.[25,28] The CTR1 transporter has been found to be expressed in the outer hair cells, the inner hair cells, and the stria vascularis. Deletion of the CTR1 gene in yeast resulted in an increased cisplatin resistance and a reduction in intracellular cisplatin content.[28] Furthermore, there are studies suggesting that an important factor in the development of ototoxicity is a genetic variant in LRP2. Identification of other genes that contribute to susceptibility to platinum-related ototoxicity is a major topic in current research. Also thiopurine S-methyl transferase (TPMT) or cathechol O-methyl transferase (COMT) are suggested to play a role in the individual susceptibility to ototoxicity.[29]

An in vitro study of Low et al.[12] evaluated the effects of cisplatin alone, radiotherapy alone, and a **combined treatment** on the cellular and molecular mechanisms leading to ototoxicity. They found that the negative effect on the viability of the OC-k3 cells (a cell line derived from the organ of Corti) of a combined treatment (CRT), is greater than the negative effect of radiotherapy alone or cisplatin alone. Furthermore, combined cisplatin-radiation lead to a greater increase in the sub-G1 phase when compared to cisplatin alone and radiation alone (DNA-fragmentation resulting from apoptotic cell death manifests in the sub-G1 phase). Finally, combined cisplatin-radiation treatment triggered more apoptotic-related gene expressions than when cisplatin or radiotherapy was used alone. However, it is not shown that the total effect of the combined treatment is greater than the sum of the effects of the treatments as a single modality treatment.

Although a substantial number of studies concerning ototoxicity due to cisplatin-based CCRT in HNSCC patients have been carried out, the exact incidences remain unknown. Just like mentioned earlier, the synergistic effect of cisplatin in combination with radiotherapy may also be present in the inner ear. The reported incidence of SNHL as a result of RT or CCRT varies widely from 0-85% after RT to 46-89% after CCRT.[10,30] Those wide ranges may be explained by differences in the treatment modalities and the populations under investigation. Moreover, and probably the most important complication for combining the results of different studies, a lot of different definitions of ototoxicity are used in the current literature. There is still no agreement regarding the definition of hearing impairment. This results in various outcomes of reported incidences and also impedes comparisons between different studies.

Risk factors for ototoxicity

Several treatment and patient characteristics are associated with the development of treatment-induced hearing loss. Many studies showed that a higher radiation dose to the cochlea is significantly associated with more SNHL, starting from doses of 45 Gy and higher.[10,31-34] Furthermore, cisplatin-based CRT will exert more SNHL compared to RT alone,[32,34-36] with a higher dose of cisplatin increasing the incidence of ototoxicity.[32,33,37] Moreover, hearing loss seems to be progressive in case of a longer follow-up time. Many authors ascribe this to a long-term effect of the primary treatment rather than to ageing.[24,31-33,38] Concerning patients characteristics, age and baseline hearing level influence the risk of treatment-induced hearing loss. Patients with a good baseline

hearing level, i.e. younger patients, may endure relatively more severe hearing loss (in dB) but will finish with better thresholds (in dB HL) after treatment compared to older patients. In reverse, patients with unfavorable hearing levels at baseline, for example older patients, may not suffer large hearing deteriorations in terms of dB, but are characterized by higher thresholds in dB HL after treatment.[39,40] Gender was not associated as a risk factor of developing ototoxicity. Finally, as mentioned earlier, there are studies suggesting that gene mutations play an important factor in the development of ototoxicity. Once proven, these factors may also contribute to a more precise risk factor analysis.

Detecting ototoxicity

The most widely used test to assess hearing is pure tone audiometry in which an audiometer generates pure tone signals of frequency 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz at variable intensities ranging from –10 dB hearing level (HL) to +120 dB HL usually in steps of 5 dB. Although not widely used, ultra-high frequencies (i.e. 10, 11.2, 12.5, 14, and 16 kHz) can also be measured at variable intensities of dB Sound Pressure Level (SPL), and has proven to be effective in early detection of ototoxicity.

Tests are performed in a sound-proof room with adequate masking to avoid cross-hearing. Signals of decreasing intensity at each frequency are presented to the person tested, from a level the person can hear to the point at which he/she fails to hear. The hearing levels are usually plotted on a graph or audiogram with sound intensity relative to the thresholds of young normal hearing subjects (dB HL) on the vertical axis, and the frequency (kHz) along the horizontal axis (figure 2). The hearing level is defined as the quietest sound heard by the person being tested. The more severe the hearing loss, the higher the measured threshold in dB HL will be (and the corresponding curve shift downwards). Audiometry is accompanied with a normal variability in threshold determination due to subjective factors as fatigue and concentration. A recent meta-analysis showed an overall test-retest variability of 2.3 dB (±3.9 dB) in manual pure tone audiometry.[41]

Both conductive hearing loss and sensorineural hearing loss can be detected by pure tone audiometry. Air conduction thresholds assess the function of both the conductive and sensorineural components of the ear, whereas bone conduction thresholds

assess the function of the cochlea and auditory nerve (sensorineural). Using these two measures, the type of hearing loss can be classified into CHL, SNHL, or mixed type.
In standard audiometry frequencies 0.125 to 8 kHz are measured. However, to monitor ototoxicity, ultra-high frequencies up to 12.5 kHz should also be measured to detect early onset of drug-induced hearing loss.[18] However, audiometry is time consuming, especially when ultra-high frequencies are included. Patients enduring intensive treatment schemes may sometimes be too ill to perform the whole test. Hence, there is a need to fast and easy audiological diagnostics, suitable for patients who are too ill to perform pure tone audiometry. There is a tendency to apply tests on otoacoustic emissions (OAEs) more often to screen the auditory function. Otoacoustic emissions are an objective, noninvasive, and fast (seconds) method to screen the function of the inner ear. An OAE is a sound of cochlear origin, recorded by a probe with microphone fitted into the external ear canal. OAEs can be obtained in a quiet environment but do not necessarily require a sound-proof room. Nowadays, OAEs are used widely in newborn hearing screening programs and are validated by professional organizations as a reliable and objective tool for an overall hearing screening.[42,43]

Since the emissions are generated by the outer hair cells in the cochlea, which are assumed to be a vulnerable site of ototoxicity, OAEs yield a promising instrument of monitoring ototoxicity, with earlier detection of inner ear damage.[44] In a number of studies OAEs were applied for monitoring ototoxicity in children.[45-47] Also, a few studies are performed in an adult population.[44,48-50] For example, Yilmaz et al.[49] showed that cisplatin ototoxicity could be discovered out with transient evoked OAE test before it is seen with pure tone audiometry. More recently, Yu et al.[50] compared the effectiveness of monitoring cisplatin-induced ototoxicity with pure tone audiometry and distortion-product OAE. They conclude that the two hearing tests could be used to complement one another. Nevertheless, studies focusing on OAE monitoring ototoxicity in adults are sparse, often not longitudinal, and based on relatively small populations. Therefore, this topic needs more high quality research.

Quality of life after treatment for head and neck cancer

There is ample research concerning quality of life after treatment for head and neck cancer. These studies mainly described the impact of speech and swallowing problems after treatment. Eating problems seems to be the most important cause of a decreased

quality of life for survivors of head and neck cancer.[51] However, studies involving the impact of ototoxicity on quality of life are sparse. Although ototoxicity is not a life-threatening complication, it may have a large impact on quality of life. Hearing loss itself, regardless of the cause, is reported to result in a notable deterioration in quality of life in both adults and children.[52,53] Several authors described that hearing loss in adults is a health problem that has been linked to a reduced quality of life, as it can impair the exchange of information and can lead to isolation, dependence, and frustration.[53,54] Given the fact that hearing is an indispensable component for speech and language development, young children with hearing loss may be at risk for neurocognitive and psychosocial delays. Even when the hearing loss is mild, it is reported that children suffer from problems with reading, word analysis, spelling, and phonological discrimination ability.[55]

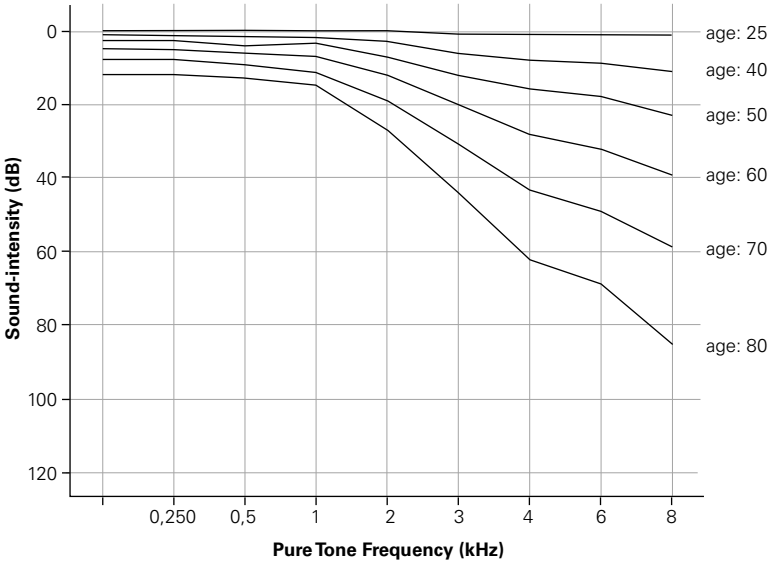
Presbycusis

A decrease in hearing ability with age is a normal physiological phenomenon called presbycusis. Presbycusis is characterized by progressive deterioration of auditory sensitivity, loss of the auditory sensory cells, and central processing functions associated with the cochlear degenerative process of aging.[56] It is a complex disease, with a controversial physiopathology, which is influenced by genetic, environmental, and medical factors. Presbycusis is bilateral, symmetrical, starts in (ultra)-high frequencies, and is slowly progressive.[54] It affects 40% of the population older than 75 years of age. According to the world health organization (WHO) it is the most commonly chronic disease in the elderly. In our aging society, it is becoming more prevalent. In 2010, there were 1.4 million hearing impaired in the Netherlands.[57] In general, males are affected at an earlier age then females.[58] The normal age-related deterioration in hearing is registered in an international standard, made by the International Organization for Standardization (ISO).[59] Median hearing thresholds according to the ISO at different ages are shown in figure 2.

It is suggested that both etiologies of treatment-induced hearing loss and presbycusis lead to similar patterns of audiometric changes and cochlear cellular degeneration.[12] The cellular and molecular mechanisms involved in sensorineural hearing loss from diverse causes appear to lead to a final common pathway, which results in apoptosis of cochlear hair cells. Therefore, it is difficult to distinguish between hearing loss as a result of

treatment or presbycusis.

Figure 2 | Pure-tone audiometry for different aged males according to International Organization for Standardization (ISO), standard number 7029:2000.[59]



OUTLINE OF THE THESIS

The main objective of the ototoxic research described in this thesis is to improve our knowledge of (chemo-)radiation induced ototoxicity in patients with head and neck cancer. By performing a systematic review of the international literature, risk factor analyses, long-term analyses, and the design of a prediction formula, this thesis contributes to a more evidence based counseling of the individual head and neck cancer patient.

In **Chapter 2** a systematic review of the literature about (chemo)radiation-induced hearing loss is conducted to obtain more insight into the side effects of the described treatment modalities. A comprehensive search of the Medline and Embase databases is obtained. Included articles are evaluated on incidences of sensorineural hearing loss (SNHL) and risk factors to develop SNHL. This review clearly demonstrates the need for an internationally accepted uniform ototoxicity grading scale. The development of such grading scale is described in **Chapter 3**. Within this chapter the limitations of the currently existing grading scales are described. To improve the current criteria a new grading system is presented. We intended to define grading scales translating the impact of treatment-induced hearing loss to relevant situations in a patient's daily life. This grading scale may also be useful to signal hearing loss in an early stage during treatment.

The main problem in the counseling process to the individual patient remains the prediction of hearing loss per individual, prior to treatment or after the first cisplatin infusion during CCRT. Conclusions on the expected hearing loss after therapy are still based on a subjective impression based on the physician's personal experience. In **Chapter 4** we develop a prediction formula predicting hearing loss after CCRT to be used in the outpatient clinic prior to treatment. This model is based on hearing thresholds and several treatment and patient characteristics, using a linear regression model and cross validation.

Knowledge about long-term ototoxicity after chemoradiation is scarce. In **Chapter 5** we analyze whether the chemoradiation-induced SNHL after treatment is progressive over time or not. Moreover, we compare the differences of two cisplatin treatment

schedules (intra-arterial versus intravenous infusions of cisplatin). Also, long-term results regarding ototoxicity after Intensity Modulated Radiation Therapy are lacking in current literature. In **Chapter 6**, a long-term analysis in patients treated with Intensity Modulated Radiation Therapy is performed. We compare the measured deteriorations in hearing with the expected age-related deteriorations according to the International Organization of Standardization (ISO).

Ototoxicity is not only an adverse effect occurring in the older aged group; treatment for head and neck cancer in children may also induce ototoxicity. **Chapter 7** describes a long-term analysis on hearing status in children treated with different types of radiotherapy for rhabdomyosarcoma in the head and neck region. The thesis ends with a summary, discussion and future perspectives in **Chapter 8**.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* Dec 15 2010;127(12):2893-2917.

2. Berglin CE, Pierre PV, Bramer T, et al. Prevention of cisplatin-induced hearing loss by administration of a thiosulfate-containing gel to the middle ear in a guinea pig model. *Cancer Chemother Pharmacol.* Dec 2011;68(6):1547-1556.

3. Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet.* Nov 24 2012;380(9856):1840-1850.

4. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* Jul 2009;92(1):4-14.

5. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* May 6 2004;350(19):1945-1952.

6. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* Jan 1 2003;21(1):92-98.

7. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. *J Clin Oncol.* Sep 1 2004;22(17):3540-3548.

8. Bhide SA, Harrington KJ, Nutting CM. Otological toxicity after postoperative radiotherapy for parotid tumours. *Clin Oncol (R Coll Radiol).* Feb 2007;19(1):77-82.

9. Wang X, Hu C, Eisbruch A. Organ-sparing radiation therapy for head and neck cancer. *Nature reviews. Clinical oncology.* Nov 2011;8(11):639-648.

10. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head Neck.* Nov 2013;35(11):1662-1668.

11. Goncalves MS, Silveira AF, Teixeira AR, Hyppolito MA. Mechanisms of cisplatin ototoxicity: theoretical review. *J Laryngol Otol.* Jun 2013;127(6):536-541.

12. Low WK, Kong SW, Tan MG. Ototoxicity from combined Cisplatin and radiation treatment: an in vitro study. *Int J Otolaryngol.* 2010;2010:523976.

13. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* May 6 2004;350(19):1937-1944.

14. Virtual Medical Centre. http://www.myvmc.com/anatomy/ear/

15. Obasikene G, Adobamen P, Okundia P, Ogusi FO. Prevalence of ototoxicity in University of Benin Teaching Hospital, Benin city: a 5-year review. *Niger J Clin Pract.* Oct-Dec 2012;15(4):453-457.

16. Schacht J, Talaska AE, Rybak LP. Cisplatin and aminoglycoside antibiotics: hearing loss and its prevention. *Anat Rec (Hoboken).* Nov 2012;295(11):1837-1850.

17. Vyskocil A, Truchon G, Leroux T, et al. A weight of evidence approach for the assessment of the ototoxic potential of industrial chemicals. *Toxicol Ind Health.* Oct 2012;28(9):796-819.

18. Zuur CL, Simis YJ, Lansdaal PE, et al. Audiometric patterns in ototoxicity of intra-arterial Cisplatin chemoradiation in patients with locally advanced head and neck cancer. *Audiol Neurootol.* 2006;11(5):318-330.

19. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys.* Mar 1 2010;76(3 Suppl):S50-57.

20. Winther FO. X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the cochlea. *Acta Otolaryngol.* Jul-Aug 1969;68(1):98-117.

21. Moretti JA. Sensori-neural hearing loss following radiotherapy to the nasopharynx. *The Laryngoscope.* Apr 1976;86(4):598-602.

22. Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. *J Laryngol Otol.* Jan 2010;124(1):32-36.

23. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. *Otol Neurotol.* Mar 2004;25(2):168-173.

24. Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. *Br J Cancer.* Jun 1990;61(6):927-931.

25. Langer T, Am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci.* Aug 2013;34(8):458-469.

26. Rybak LP. Mechanisms of cisplatin ototoxicity and progress in otoprotection. *Curr Opin Otolaryngol Head Neck Surg.* Oct 2007;15(5):364-369.

27. Hellberg V, Wallin I, Ehrsson H, Laurell G. Cochlear pharmacokinetics of cisplatin: an in vivo study in the guinea pig. *The Laryngoscope.* Dec 2013;123(12):3172-3177.

28. Waissbluth S, Daniel SJ. Cisplatin-induced ototoxicity: transporters playing a role in cisplatin toxicity. *Hear Res.* May 2013;299:37-45.

29. Pussegoda K, Ross CJ, Visscher H, et al. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clin Pharmacol Ther.* Aug 2013;94(2):243-251.

30. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol.* Aug 20 2007;25(24):3759-3765.

31. Petsuksiri J, Sermsree A, Thephamongkhol K, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. *Radiat Oncol.* 2011;6:19.

32. Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys.* Apr 1 2009;73(5):1335-1342.

33. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer.* Feb 15 2006;106(4):820-829.

34. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *Int J Radiat Oncol Biol Phys.* Feb 1 2007;67(2):469-479.

35. Low WK, Toh ST, Wee J, Fook-Chong SM, Wang DY. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol.* Apr 20 2006;24(12):1904-1909.

36. Kwong DL, Wei WI, Sham JS, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. *Int J Radiat Oncol Biol Phys.* Sep 1 1996;36(2):281-289.

37. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys.* Aug 1 2007;68(5):1320-1325.

38. Yilmaz YF, Aytas FI, Akdogan O, et al. Sensorineural hearing loss after radiotherapy for head and neck tumors: a prospective study of the effect of radiation. *Otol Neurotol.* Jun 2008;29(4):461-463.

39. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiother Oncol.* Oct 2002;65(1):9-16.

40. Zuur CL, Simis YJ, Lamers EA, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* Jun 1 2009;74(2):490-496.

41. Mahomed F, Swanepoel DW, Eikelboom RH, Soer M. Validity of Automated Threshold Audiometry: A Systematic Review and Meta-Analysis. *Ear Hear.* May 31 2013.

42. White KR, Vohr BR, Maxon AB, Behrens TR, McPherson MG, Mauk GW. Screening all newborns for hearing loss using transient evoked otoacoustic emissions. *Int J of pediatric otorhinolaryngology.* Jun 1994;29(3):203-217.

43. Eiserman WD, Hartel DM, Shisler L, Buhrmann J, White KR, Foust T. Using otoacoustic emissions to screen for hearing loss in early childhood care settings. *Int J of pediatric otorhinolaryngology.* Apr 2008;72(4):475-482.

44. Biro K, Noszek L, Prekopp P, et al. Characteristics and risk factors of cisplatin-induced ototoxicity in testicular cancer patients detected by distortion product otoacoustic emission. *Oncology.* 2006;70(3):177-184.

45. Toral-Martinon R, Shkurovich-Bialik P, Collado-Corona MA, Mora-Magana I, Goldgrub-Listopad S, Shkurovich-Zaslavsky M. Distortion product otoacoustic emissions test is useful in children undergoing cisplatin treatment. *Arch Med Res.* May-Jun 2003;34(3):205-208.

46. Foust T, Eiserman W, Shisler L, Geroso A. Using otoacoustic emissions to screen young children for hearing loss in primary care settings. *Pediatrics.* Jul 2013;132(1):118-123.

47. Dhooge I, Dhooge C, Geukens S, De Clerck B, De Vel E, Vinck BM. Distortion product otoacoustic emissions: an objective technique for the screening of hearing loss in children treated with platin derivatives. *Int J Audiol.* Jun 2006;45(6):337-343.

48. Ress BD, Sridhar KS, Balkany TJ, Waxman GM, Stagner BB, Lonsbury-Martin BL. Effects of cis-platinum chemotherapy on otoacoustic emissions: the development of an objective screening protocol. Third place-Resident Clinical Science Award 1998. *Otolaryngology--head and neck surgery.* Dec 1999;121(6):693-701.

49. Yilmaz S, Oktem F, Karaman E. Detection of cisplatin-induced ototoxicity with transient evoked otoacoustic emission test before pure tone audiometer. *Eur Arch Oto-rhino-laryngol.* Jul 2010;267(7):1041-1044.

50. Yu KK, Choi CH, An YH, et al. Comparison of the effectiveness of monitoring Cisplatin-induced ototoxicity with extended high-frequency pure-tone audiometry or distortion-product otoacoustic emission. *Korean journal of audiology.* Sep 2014;18(2):58-68.

51. Funk GF, Karnell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. *Arch Otolaryngol Head Neck Surg.* Feb 2012;138(2):123-133.

52. Hetu R. The stigma attached to hearing impairment. *Scand Audiol Suppl.* 1996;43:12-24.

53. Li CM, Zhang X, Hoffman HJ, Cotch MF, Themann CL, Wilson MR. Hearing Impairment Associated With Depression in US Adults, National Health and Nutrition Examination Survey 2005-2010. *JAMA Otolaryngol Head Neck Surg.* Mar 6 2014.

54. Ciorba A, Bianchini C, Pelucchi S, Pastore A. The impact of hearing loss on the quality of life of elderly adults. *Clin Interv Aging.* 2012;7:159-163.

55. Tharpe AM. Unilateral and mild bilateral hearing loss in children: past and current perspectives. *Trends Amplif.* Mar 2008;12(1):7-15.

56. Li-Korotky HS. Age-related hearing loss: quality of care for quality of life. *Gerontologist.* Apr 2012;52(2):265-271.

57. Snik AFM, Leijnendeckers JM, Marres HAM. Behandeling van ouderdomsslechthorendheid. *Nederlands tijdschrift voor geneeskunde* 2013;157(22):1046-1050.

58. Huizinga E.H SGB, de Vries N, Graamans K, van de Heyning P. . Keel-neus-oorheelkunde en hoofd-halschirurgie. Bohn Stafleu van Loghum; 2007:89-90.

59. Standardization IOf. 2nd edition, Reference number ISO 7029:2000 (E). International Standard. Acoustics - Statistical distribution of hearing thresholds as a function of age.


02

CHAPTER 02

Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: a systematic review of the literature

E.A.R. Theunissen | S.C.J. Bosma | C.L. Zuur | R. Spijker | S. van der Baan
W.A. Dreschler | J.P. de Boer | A.J.M. Balm | C.R.N. Rasch

Head & Neck. 2015 Feb; 37(2): 281-92

ABSTRACT

Objective

Both radiotherapy (RT) and cisplatin-based chemoradiotherapy (CRT) in head and neck cancer patients may cause sensorineural hearing loss (SNHL). The purpose of this review is to provide more insight into SNHL because of CRT compared to RT.

Methods

Comprehensive search of Medline and Embase with the terms 'radiotherapy' combined with 'ototoxicity', 'head and neck squamous cell carcinoma', and synonyms.

Results

Of the 2507 studies found, 21 were included in this study. Pooled analysis could not be committed because of heterogeneity. Incidence rates of SNHL after RT and CRT varied considerably, with percentages ranging from 0 to 43% and 17 to 88%, respectively. Factors that influenced the risk of SNHL were radiation dose to the cochlea, follow-up time, age, baseline hearing level, and cisplatin dose.

Conclusion

The wide range of SNHL incidence rates makes it impossible to draw any conclusions on the severity of RT- and CRT-induced ototoxicity. To allow for future comparison of study outcomes, development of uniform criteria is of utmost importance.

INTRODUCTION

Radiotherapy (RT), as a single-modality treatment or adjuvant to surgery, is a treatment modality in low staged head and neck squamous cell carcinoma (HNSCC). Patients with locally advanced disease, inoperable, or high-risk HNSCC, are generally treated with cisplatin-based concomitant chemoradiotherapy.[1-6]

Sensorineural hearing loss (SNHL) can be an adverse event of RT to the head and neck region and is most likely caused by lesions in the cochlea or retro-cochlear component of the auditory system.[7-8] In 1969, Winther[9] described an extensive degeneration of outer hair cells in the organ of Corti in guinea pigs after radiation of the inner ear. Also, in humans, destruction of the organ of Corti and atrophy of the audio-vestibular nerve after radiation to the temporal bone have been demonstrated.[10] Furthermore, loss of outer hair cells, loss of spiral ganglion cells in the basal turn of the cochlea, atrophy of the stria vascularis, changes in nerve vessels, and absence of the organ of Corti, macula of the utricle, and the cristae of the semicircular canals have been shown in postmortem studies of the human temporal bone in patients treated with RT.[11-12]

Apart from RT, cisplatin may also cause ototoxicity. Animal studies showed that cisplatin also damages outer hair cells within the organ of Corti and the marginal cells within the stria vascularis.[13-15] The destructive pattern of outer hair cells loss progresses from lateral to medial, starting at the cochlear base (high frequencies) and progressing upward to the cochlear apex (low frequencies) with each cisplatin infusion.[15] Cisplatin induced SNHL may start in the acute phase of treatment and is characterized by bilateral, irreversible, progressive high frequency loss.[15-16]

A substantial amount of studies concerning ototoxicity because of RT or cisplatin-based chemotherapy (CRT) in HNSCC have been carried out. However, results of these studies vary in the incidence, time of onset, type, and severity of the hearing loss. The main problems with the clinical data are the lack of comparable pretreatment and posttreatment audiologic parameters, differences in follow-up time, and small or heterogeneous patient groups. Therefore, before treatment, the exact risk for clinically significant hearing loss after (C)RT in patients with HNSCC is still unknown.

A recent review by Mujica-Mota studied the characteristics of SNHL after RT alone[17], emphasizing that radiation-induced SNHL is permanent, dose-dependent, and progressive in time. Aiming at a further improvement of counseling of patients with HNSCC, we reviewed the literature to obtain more insight into cisplatin-based CRT compared to RT-induced SNHL.

MATERIALS AND METHODS

Search strategy

Studies for this review were identified by a comprehensive search of both MEDLINE (1948 to April 2013) and Embase (1980 to April 2013) using the OvidSP platform in cooperation with a medical information specialist. The search strategy included keywords 'radiotherapy' combined with 'ototoxicity', 'head and neck squamous cell carcinoma' and (combinations of) synonyms for these terms. The complete search strategy for MEDLINE in OvidSP is included in table 1; the search strategy was subsequently adapted for Embase. The last search was conducted on April 2, 2013.

Study selection

All retrieved articles were screened for title and abstract by 2 independent researchers (E.A.R.T., S.C.J.B.) In case of disagreement or doubt, a third researcher was consulted. Studies were included if they reported hearing loss because of RT or cisplatin-based CRT as a primary treatment in patients with HNSCC. The hearing results had to be obtained from a pure tone audiogram (air and bone conduction or bone conduction only) conducted both pretreatment and posttreatment. Exclusion criteria were postsurgery studies, case reports, reviews, conference letters or abstracts, language other than English, Dutch, French, or German, studies of intra-cranial tumors, studies comparing patients' hearings thresholds with the other ear, intra-arterial cisplatin infusions, children cohorts, and studies with cisplatin as single modality therapy.

Table 1 | Search strategy OvidSP (MEDLINE 1948 – April 2013

Patient: (expOtorhinolaryngologic Neoplasms/) OR (hnscc.ti,ab) OR (scchn.ti,ab) OR ((((upper adjaerodigestiveadj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neopla s* or malignan* or metasta*)).ti,ab.) OR ((ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.) OR (exp "Head and Neck Neoplasms"/) OR (((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or ear or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.)

Intervention: (exp Radiotherapy/) OR (radiotherapy.ti,ab.) OR ((radiation adj3 (therapy or therapies)).ti,ab.) OR ((radiation adj3 oncology).ti,ab.) OR (xrt.ti,ab.) OR (rtx.ti,ab.) OR (imrt.ti,ab.) OR ((intensity adj modulated).ti,ab.) OR (dahanca.ti,ab.) OR ((rapid adj arc).ti,ab.) OR (exp Radiation/) OR (radiation.ti,ab.) OR (ionizing.ti,ab.)

Outcome: (exp Hearing Disorders/ or ototoxicity.mp. or exp Hearing Loss/) OR ((auditory or cochlea* or ear).ti,ab.) OR (radionecrosis.ti,ab.) OR ((pure-tone adj (audiom* or average$)).ti,ab.) OR (PTA.ti,ab.) OR (exp Audiometry/) OR (audiometr*.ti,ab.) OR (((bone or air) adj conduction).ti,ab.) OR ("decibel hearing level".ti,ab.) OR (dBHL.ti,ab.) OR ("decibel sound pressure level".ti,ab.) OR (dBSPL.ti,ab.)

Search: P AND I AND O

Assessment of study quality

All articles included were critically assessed on methodological quality and the risk of bias. From each study data extraction was performed according to the STROBE checklists ('Strengthening the reporting of observational studies in epidemiology').[18] The assessment of risk of bias in studies was based on checklists according to evidence-based medicine criteria (table 2).[19-20] Articles were excluded when 'no' was scored ≥5 times.

RESULTS

Search results

The literature search resulted in a list of 2507 publications (after removal of the duplicates). After excluding 2467 articles by screening the titles and abstracts, 40 studies were retrieved for more detailed evaluation. Out of these 40 studies, 29 met all inclusion criteria after screening the full text. Of these, 2 studies were excluded because they analyzed the same patient cohort as in a later study by the same authors[21-22] and 6 studies were excluded after critical appraisal.[10, 12, 23-26] Hence, 21 articles were included for review (figure 1).

Table 2 | Risk of bias assessment criteria

Study group	**Selection bias** (representative: yes/no) • If the described study group consisted >90% of the patients treated with (C)RT included in the original cohort.	**Reporting bias** (well defined: yes/no): • If the mean/median range of the cumulative cisplatin dose was mentioned and/or the radiation dose to the cochlea *and* • When it was described what other treatment was given.
Follow-up	**Information bias** (adequate: yes/no): • If the outcome was measured in >80% of the study group.	**Reporting bias** (well defined: yes/no): • If the length of (audiological) follow-up was mentioned.
Outcome	**Detection bias** (blind: yes/no) • If the assessors of the audiometry were blinded to the given therapy.	**Reporting bias** (well defined: yes/no): • If the definition of SNHL and the detection of SNHL were clearly defined.
Risk assessment	**Confounding** (adjustment for other factors: yes/no) • If factors as age, gender, other ototoxic drugs, cisplatin dose, RT dose, baseline hearing level and follow-up time were taken into account.	**Analysis** (well defined: yes/no): • If repeated measures analysis, uni- or multivariate analysis was done.

Abbreviations: RT= radiotherapy; CRT = Chemoradiotherapy; SNHL = Sensorineural Hearing Loss;

The characteristics of the included studies are shown in table 3.[27-47] Most of the studies were prospective (16 of 21). There was 1 randomized controlled trial included, comparing the ototoxic effect of RT and CRT.[39] In 7 studies, patients were treated with RT, in 5 studies with CRT and in 9 studies with either CRT or RT. Twelve studies concerned nasopharyngeal cancer (NPC), in the remaining studies, other types of HNSCC were treated at various tumor sites (e.g. oropharynx, larynx, hypopharynx, parotid, sinus, skin, and other). The number of patients per study ranged from 11 to 325. The mean follow-up time differed from directly after accomplishing treatment to 78 months.

Figure 1 | Flow diagram of the search strategy

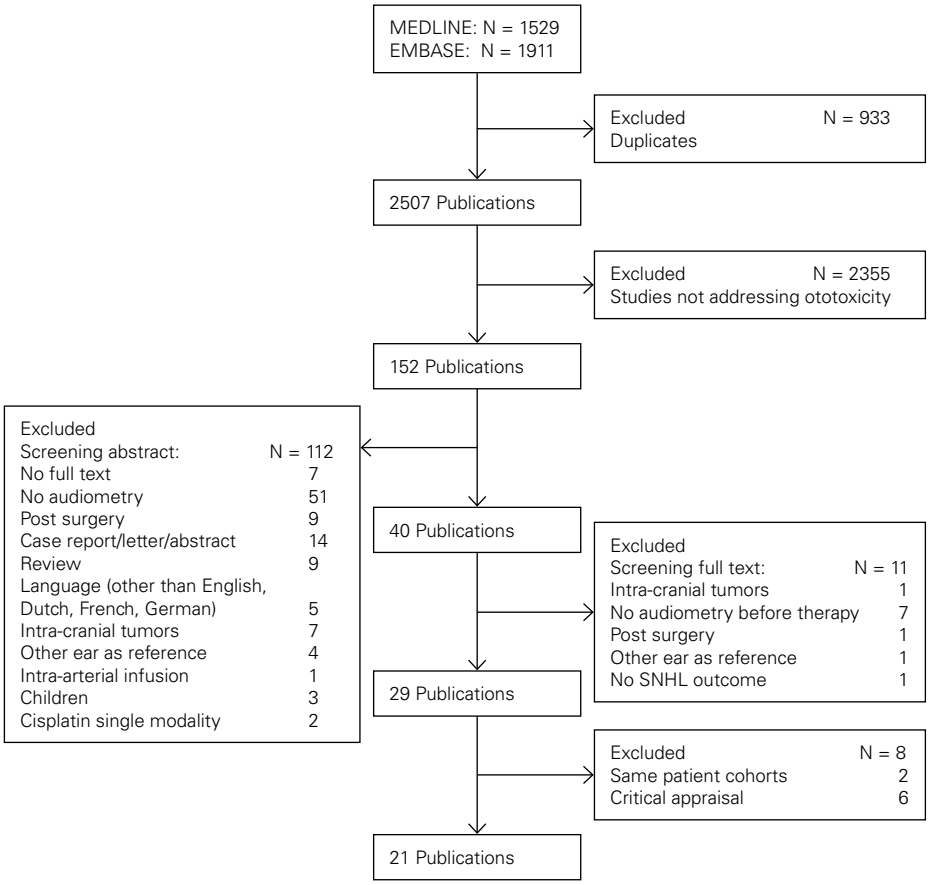


Table 3 | Study characteristics

Author	Study design	Treatment	Patient no.	No. patient / ears	Age y (range)	Tumor site	RT protocol	Mean cochlear RT dose in Gray ; range	Cisplatin protocol	Cisplatin dose No of infusions x mg/m2; cumulative/m2 ; range	Mean FU time in mo ; range
1.Tsang et al 2012[27]	Prospective cohort	RT		53 / 106	46 (27-75)	NPC	Conventional / IMRT	IMRT: 50 Conventional: 68	-	-	60 ; -
2. Dell'Aringa et al 2011[28]	Prospective cohort	RT		19 / 38	63 (37-87)	HNSCC	Conventional	Not described	-	-	0.5 ; -
3. Li et al 2010[29]	Prospective cohort	RT		42 / 84	46 (28-56)	NPC	Conventional	Not described	-	-	- ; 12-60
4. Zuur et al 2009[30]	Prospective cohort	RT		101 / 202	61.3 ± 12.2	HNSCC	IMRT	16.2 ; 0.2-69.7	-	-	2 ; 0.25-28
5. Yilmaz et al 2008[31]	Prospective cohort	RT		19 / 38	52.7 (42-74)	HNSCC	Conventional	90% of 60-70	-	-	12 ; -
6. Herrmann et al 2006[32]	Prospective cohort	RT		32 / 64	54 (32-77)	HNSCC	Conformal	- ; 1.7- 64.3*	-	-	6 ; -
7. Honoré et al 2002[33]	Retrospective cohort	RT		20 / 36	44.6 (20-74)	NPC	Conventional	- ; 0-68.1	-	-	29 ; 7-79
8. Zuur et al 2008[34]	Prospective cohort	CRT		60 / 120	62 ± 11	HNSCC	Conventional / IMRT	16.4 ; ± 12.9	Concurrent	20-25 x 6 ; 220 ; 78-300	1.3 ; ± 0.6
9. Zuur et al 2007[35]	Prospective cohort	CRT		158 / 298	56 (25-83)	HNSCC	Conventional / CT guided/ IMRT	Conventional: 14* CT: 19.2* IMRT: 12.7*	Concurrent	3x 100 ; 180 ; -	2 ; -
10. Liberman et al 2004[36]	Prospective cohort	CRT		11 / 22	48 (39-64)	HNSCC	Not defined	46.6 ; 3.5–51.1	Concurrent	6x 20 ; - ; -	6.9 ; 5-10
11. Oh et al 2004[37]	Prospective cohort	CRT		25 / 48	46 (20-74)	NPC	Conventional Conformal IMRT	Conv.: 66.6 ; ± 6.2 Conf.: 64.4 ; ± 7.1 Mix: 69.6 ; ± 11.8	Concurrent	2-3x 80 ; 229 ; 58	40 ; 24-57
12. Chen et al 2006[38]	Retrospective cohort	CRT		22 / 44	45 (14-71)	NPC	Conformal / IMRT	IMRT: 48* ; 29-70 Conf.: 51* ; 29-70	Concurrent	1-6x 100 ; >200 ; -	29 ; 12-76

13. Low et al 2006[39]	RCT	CRT + RT	57 CRT 58 RT	115 / 206	45 (15-74)	NPC	Conventional	46.7 ; ± 11.2	Concurrent	3x 100; 160 ; 112-213	1 – 24
14. Chan et al 2009[40]	Prospective cohort	CRT + RT	72 CRT 15 RT	87 / 170	50 (23-70)	NPC	Conformal / IMRT	48.9* ; 33-71.1	Concurrent Non-concurrent	2-3x 100 ; - ; -	24 ; 6-30
15. Hitchcock et al 2009[41]	Prospective cohort	CRT + RT	41 CRT 21 RT	62 / 124	62 (26-81)	HNSCC	Conformal / IMRT	10.56* ; 0.49–76.9	Concurrent	6x 40 or 1-3 x 100 ; - ; -	2 ; -
16. Wang et al 2004[42]	Prospective cohort	CRT + RT	213 CRT 7 RT	220 / 395	49.7 (12-77)	NPC	Conventional	Not described	Neoadjuvant	1-2x 8-120 ; - ; 160-240	36 ; 12-135
17. Ho et al 1999[43]	Prospective cohort	CRT + RT	73 CRT 221 RT	294 / 526	48 (15-80)	NPC	Conventional	- ; 70–91	Neoadjuvant	1-3x 60-100 ; 275 ; 130-512†	30 ; 3-102
18. Kwong et al 1996[44]	Prospective cohort	CRT + RT	52 CRT 80 RT	132 / 227	46 (15-74)	NPC	Conventional	Not described	Neoadjuvant	1-3x 60 ; - ; -	30 ; ? – 56
19. Petsuksiri et al 2011[45]	Retrospective cohort	CRT + RT	66 CRT 2 RT	68 / 134	47.5 (18-70)	NPC	Conventional / IMRT	IMRT: 51.02 ; 25.09-75.54	Concurrent	3x 100+1x 80; 689 ; 120-980†	27.5 ; 8-65
20. Wakisaka et al 2011[46]	Retrospective cohort	CRT + RT	15 RT 9 CRT	24 / 48	55.9 (25-83)	NPC	Not defined	48.6 ; 34-62	Concurrent	- ; - ; 75-480	78 ; 12-146
21. Bhandare et al 2007[47]	Retrospective cohort	CRT + RT	296 RT 29 CRT	325 / 650	Not described	HNSCC	3D Conformal	Not described	Neoadjuvant Concurrent	Not described	66 ; 6-360

Abbreviations: RCT = Randomized Controlled Trial; RT = Radiotherapy; CRT = Chemoradiotherapy; NPC = Nasopharyngeal Carcinoma; HNSCC = Head and Neck Squamous Cell Carcinoma; IMRT = Intensity Modulated Radiation Therapy; FU = Follow-up
* = median dose
† = cumulative dose in mg total

Treatment protocols

Various RT techniques were used in the studies included: 3D conformal, conventional and Intensity Modulated Radiation Therapy (IMRT). In some studies, different treatment schedules were used.[27, 34-35, 37-38, 40-41, 45] In 15 studies, the dose to the cochlea was measured, with mean cochlear dose varying from 10.6 to 69.6 Gray (Gy). Also, different cisplatin doses and schedules were used (e.g. neoadjuvant, concurrent, adjuvant, or combinations). The total cumulative cisplatin dose varied from 75 to 480 mg/m^2.

Audiometry

Audiometry was performed before and after therapy. All studies used air conduction (AC) and bone conduction (BC) measurements at frequencies of 0.5, 1, 2, and 4 kHz. Some studies also measured (ultra)-high frequencies.[29-30, 34-35] Pure Tone Averages (PTAs) were calculated at PTA 0.5-1-4 kHz and/or PTA 1-2-4 kHz. Eight studies obtained multiple audiometric tests during follow-up.[29, 31, 37, 39-40, 42-44] Thirteen studies reported ototoxicity incidences relative to the number of ears, whereas 8 studies reported incidences relative to the number of patients.

Results are shown in table 4. Various definitions of clinically relevant SNHL were used; the majority defined SNHL as an increase in BC threshold. Compared to baseline audiometry, the threshold should consist of an increment of >10, 15, or 30 decibel (dB) at frequencies PTA 0.5-1-2 kHz or 4 kHz alone. Some authors[28, 36, 38] used the American Speech Language Hearing Association (ASHA) criteria[48], which describes ototoxicity as a shift of ≥20 dB at any BC frequency or as a shift of ≥10 dB at two or more consecutive BC frequencies. In other cases[30, 34-35] the Common Terminology for Criteria for Adverse Events version 3 (CTCAEv3) were used.[49] The CTCAEv3 for hearing impairment consists of 4 scales, based on increasing threshold shifts at 2 to 3 contiguous frequencies. The various selected studies are briefly described below and are classified according to the aforementioned definitions of SNHL and type of treatments.

Sensorineural hearing loss after radiotherapy

Bone conduction threshold increment

Li et al[29] prospectively studied 42 patients with NPC treated with conventional RT (dose at cochlea not described). Audiograms were conducted before RT and at 1, 12, 24, and 60 months after therapy. After 1 month, there was a statistically significant increase

in BC hearing threshold at high frequency 8 kHz compared with pre-RT data (mean threshold deterioration of 8.6 dB, $p<0.001$). The incidence of SNHL at 4 kHz was 12.5%, 42%, and 50% after 1 month, 1 year and 2 years respectively.

Yilmaz et al[31] prospectively studied 19 patients with HNSCC treated with RT (mean cochlear dose 90% of 60-70 Gy). Compared with pretreatment audiological tests, none of the patients had SNHL 1 month after RT. However, 47% of the ears showed a median of 22.6 dB loss (range, 10-40 dB) at any BC frequency (2, 3, 4, or 6 kHz) 1 year after RT.

American Speech Language Hearing Association criteria

Dell' Aringa et al[28] described hearing status after RT for HNSCC in 19 patients (dose at cochlea not described). According to the ASHA criteria, 36.8% of the ears had reduction in their auditory thresholds immediately after the end of the radiotherapy.

Common Terminology for Criteria for Adverse Events version 3

Zuur et al[30] studied 101 patients treated with IMRT in HNSCC (mean cochlear dose of 16.2, range, 0.2-69.7 Gy). When including ultra-high frequencies up to 16 kHz in the CTCAEv3 an incidence of 43% was seen compared to 24% when only frequencies up to 8 kHz were included.

Sensorineural hearing loss after cisplatin chemoradiotherapy

Bone conduction threshold increment

Oh et al[37] evaluated BC thresholds after CRT for NPC in 48 ears compared with BC thresholds before treatment. The mean cochlear dose varied between 64.4 Gy within conformal RT and 69.6 Gy within mixed type of RT. At 3 to 6 months after treatment, a total of 13 ears (27%) showed SNHL and 8 among them were persistent (17% of the total group). At 1 year after treatment, 14 ears (29%) showed SNHL and 10 among them were persistent (21% of the total group). Forty months after treatment, 44% developed high-frequency SNHL (4 kHz) and 17% ears developed low-frequency SNHL (PTA 0.5-1-2 kHz).

American Speech Language Hearing Association criteria

Liberman et al[36] prospectively studied a smaller group of patients with HNSCC (n=11). Patients received a mean cochlear dose of 46.6 Gy (range 3.5-51.1 Gy). According to

Table 4 | Incidence of sensorineural hearing loss 1 to 2 months, 3 to 6 months, 12 months, 24 months, and 60 months after therapy

Author	Treatment	Definition SNHL	Analysis per (n)	High frequencies most sensitive	1-2 months	3-6 months	12 months	24 months	60 months
1.Tsang et al 2012[27]	RT	Threshold change	Ear (106)	Yes					PTA: 6.6 dB 4 kHz: 15.0 dB
2. Dell' Aringa et al 2011[28]	RT	ASHA	Ear (38)	Yes	36.8%				
3. Li et al 2010[29]	RT	>15 dB loss BC	Ear (84)	Yes	PTA: 8%, 4 kHz: 12.5% 8 kHz: 31%		PTA: 21%, 4 kHz: 42% 8 kHz: 44%	PTA: 31%, 4 kHz: 50% 8 kHz: 48%	PTA: 42%, 4 kHz: 58% 8 kHz: 54%
4. Zuur et al 2009[30]	RT	CTCAEv3	Patient (101)	Yes	≤8 kHz: 24% ≤16 kHz: 43%				
5. Yilmaz et al 2008[31]	RT	>10 dB loss BC	Ear (38)	Yes	0%		47%		
6. Herrmann et al 2006[32]	RT	>15 dB loss BC	Patient (32)	Yes	50% at dose of 20-25 Gray				
7. Honoré et al 2002[33]	RT	>15 dB loss BC	Patient (20)	Yes	4 kHz: 33%				
8. Zuur et al 2008[34]	CRT	CTCAEv3	Patient (60)	Yes	≤8 kHz: 31% ≤16 kHz: 47%				
9. Zuur et al 2007[35]	CRT	CTCAEv3	Patient (158)	Yes	≤8 kHz: 79% ≤16 kHz: 88%				
10. Liberman et al 2004[36]	CRT	ASHA	Patient (11)	Not described		36%			
11. Oh et al 2004[37]	CRT	>15 dB loss BC	Patient (25)	Yes		27.1%	29.2%		PTA: 17%, 4 kHz: 43.8%
12. Chen et al 2006[38]	CRT	ASHA	Ear (44)	Yes				57%	

13. Low et al 2006[39]	CRT + RT	Threshold change	Ear (206)	Yes	PTA: RT: 18.3 dB, CRT 19.2 dB 4 kHz: RT: 25 dB, CRT 45 dB	PTA : RT: 15 dB, CRT 18.3 dB 4 kHz: RT: 25 dB, CRT 55 dB	PTA : RT: 11.7 dB, CRT 22.5 dB 4 kHz: RT: 20 dB, CRT 57.7 dB	PTA: RT: 15 dB, CRT 23.3 dB 4 kHz: RT: 25 dB, CRT 55 dB	
14. Chan et al 2009[40]	CRT + RT	>15 dB loss BC	Ear (170)	Yes		PTA: 9%, 4 kHz: 49%	PTA: 14%, 4 kHz: 55%	PTA: RT: 7.9%, CRT 16.7% 4 kHz: RT: 33.3%, CRT: 55%	
15. Hitchcock et al 2009[41]	CRT + RT	≥10 dB loss BC	Ear (124)	Yes	41%				
16. Wang et al 2004[42]	CRT + RT	>10 dB loss BC	Ear (395)	Yes		PTA: 9.9%, 4 kHz: 18.5%	PTA: 12%, 4 kHz: 20%	PTA: 12.3%, 4 kHz: 23.8%	PTA: 9.9%, 4 kHz: 29.6%
17. Ho et al 1999[43]	CRT + RT	>10 dB loss BC	Ear (526)	Yes		PTA: 14%, 4 kHz: 31%			PTA: 18%, 4 kHz: 60%
18. Kwong et al 1996[44]	CRT + R	>15 dB loss BC	Ear (227)	Yes	PTA: 5.4% 4 kHz: 23.8%		PTA: 7.1%, 4 kHz: 28.9%	PTA: 8.5%, 4 kHz: 30.1%	PTA: 5.2%, 4 kHz: 34.5%
19. Petsuksiri et al 2011[45]	CRT + RT	>15 db loss BC	Ear (134)	Not described			4 kHz Conv.: 48.8%, IMRT: 37% PTA Conv.: 5%, IMRT: 7.4%		
20. Wakisaka et al 2011[46]	CRT + RT	>30 dB loss BC	Ear (48)	Not described					Ipsilateral 13%, contralateral 8%
21. Bhandare et al 2007[47]	CRT + RT	>15 dB loss BC	Patient (325)	Not described				15%	

Abbreviations: RT= radiotherapy; CRT = Chemoradiotherapy; SNHL = Sensorineural Hearing Loss; ASHA = American Speech Language Hearing Association; dB = Decibel; CTCAEv3 = Common Terminology for Criteria for Adverse Events version 3; PTA = Pure Tone Average 0.5-1-2 kHz; Conv. = Conventional; IMRT = Intensity Modulated Radiation Therapy

the ASHA, 36% of the patients had SNHL 6.9 months posttherapy. Chen et al[38], in a retrospective study, found that 57% of the ears met the ASHA criteria for SNHL after a median follow-up time of 29 months after CRT for NPC in 22 patients (mean cochlear dose 50 Gy within IMRT and 53 Gy within conformal RT).

Common Terminology for Criteria for Adverse Events version 3

In a prospective study of Zuur et al,[35] 73 high-dose CRT-IV (3 courses cisplatin of 100 mg/m^2 during RT with median cochlear dose of 16.3 Gy) patients were scored for ototoxicity using the CTCAEv3. The incidence of SNHL was 88% according to CTCAEv3 up to 16 kHz. Disregarding the ultra-high frequencies (>8 kHz), a lower incidence of ototoxicity was observed (79%). The same was seen in another study of Zuur et al,[34] where the incidence was 47% scored by CTCAEv3 up to 16 kHz and 31% when scored up to 8 kHz after low-dose CRT (cisplatin 6 mg/m^2 with concurrent RT with mean cochlear dose of 16.4 Gy).

Characteristics of hearing loss

When described, studies indicate that SNHL starts at high frequencies (17 of 21). Also, the incidences of SNHL observed at higher frequencies (≥4 kHz) are higher compared to lower frequencies (table 4). In studies with measurements at different posttreatment time points, an increase in incidence was reported at longer follow-up times.[29, 31, 37, 39-40, 42-44] Bhandare et al[47] and Wakisaka et al[46] reported a time of onset of 1.8 year (range, 0.5-5.9) and 7.1 year (range, 3-10) post-RT, respectively. In a prospective study, Ho et al[43] assessed 526 ears from patients with NPC treated by (C)RT. With a follow-up of 4.5 years, they observed that SNHL (defined as >10 dB loss at BC 4 kHz or PTA 0.5-1-2 kHz) started immediately after the end of the RT. After 2 years, 40% of the patients partially recovered from their SNHL, while other patients showed worsening as the years passed.

Risk factors for sensorineural hearing loss after (chemo)radiotherapy

Risk factors for developing SNHL are shown in table 5. Overall, there was agreement that a higher radiation dose to the cochlea was significantly associated with more SNHL.[30, 32-33, 35, 38, 40, 47] Bhandare et al[47] retrospectively studied 325 patients with HNSCC treated with RT. Univariate and multivariate analyses indicated that a higher dose to the cochlea significantly (p<0.0001) increased the incidence of SNHL. Five-year risk of

SNHL increased to 37% above doses of 60.5 Gy compared to 3% at doses <60.5 Gy (p<0.0001). Hermann et al[32] showed a dose-effect analysis that revealed an ED50 (dose at which a 50% incidence is expected) of 20 to 25 Gy for significant changes in hearing thresholds (≥15 dB). Other studies included in this review reported an increased risk for SNHL when the cochlea received a total dose of at least 47 to 55 Gy.[38, 40, 45, 47]

Table 5 | Results of risk factor analysis

Author	Treatment	Cochlear dose	Additional chemo	Cisplatin dose	Follow-up time	Age	Baseline HL	Sex
Li et al 2010[29]	RT	-	-	-	Sig	-	-	-
Zuur et al 2009[30]	RT	Sig	-	-	-	Sig	Sig	-
Herrmann et al 2006[32]	RT	Sig	-	-	Sig	Sig	-	NSD
Honoré et al 2002[33]	RT	Sig	-	-	NS	Sig	Sig	-
Zuur et al 2008[34]	CRT	NSD	-	NSD	-	Sig	NSD	NSD
Zuur et al 2007[35]	CRT	Sig	-	Sig	-	Sig	-	-
Chen et al 2006[38]	CRT	Sig	-	Sig	Sig	NS	NSD	-
Chan et al 2009[40]	CRT + RT	Sig	Sig	Sig	-	Sig	NSD	NSD
Wang et al 2004[42]	CRT + RT	-	NSD	-	Sig	Sig	NSD	-
Kwong et al 1996[44]	CRT + RT	-	NS	-	-	Sig	-	Sig
Bhandare et al 2007[47]	CRT + RT	Sig	Sig	-	-	Sig	-	NSD

Abbreviations: RT = Radiotherapy; CRT = Chemoradiotherapy; HL = Hearing Level; Sig = Significant; NS = Non Significant; NSD = No Significant Differences.
Note: Only studies with repeated measurements, univariate and multivariate analysis were included for risk factor analysis.

Also, cisplatin-based CRT resulted in more SNHL compared to RT alone[39-40, 44, 47], with a higher dose of cisplatin increasing the incidence of SNHL.[35, 38, 40] Low et al[39] prospectively conducted a single, blinded, and randomized study of 57 patients treated with CRT and 58 patients treated with RT. Directly after treatment, they reported a mean loss of 18 dB after RT compared to 19 dB after CRT at PTA 0.5-1-2 kHz (p>0.05). At high frequency (4 kHz) the loss after CRT was 45 dB vs. 25 dB after RT (p<0.05). During follow-up, the mean loss in the CRT group was systematically higher compared with the RT group. After 1 year, these differences were statistically significant at PTA 0.5-1-2 kHz and 4 kHz. Chan et al[40] also reported more SNHL after concurrent CRT compared with

RT (55% vs. 33%; $p<0.01$, multivariate) at high frequency 4 kHz. At low frequencies (PTA 0.5-1-2 kHz), no significant differences were seen (8% vs. 17%; $p=0.17$). With respect to the dosages of cisplatin, Zuur et al[35] studied patients treated with CRT. The mean cisplatin dose was 180 mg per infusion. In the multivariate analysis cumulative cisplatin dose was found to be associated with hearing loss during and after treatment ($p<0.0001$). Similar observations were reported by Chen et al[38] using univariate logistic regression analysis, cisplatin dose was a significant independent factor in determining the incidence of SNHL ($p=0.03$).

As described above in the section of the incidences of SNHL after (C)RT, and also in uni- and multivariate analysis, a longer follow-up time was associated with more SNHL.[29, 32-33, 38, 42] Furthermore, many authors reported that an increasing age was associated with an increasing incidence risk of developing SNHL.[30, 32-34, 38, 40, 42, 44, 47] Nevertheless, Zuur et al[35] found that younger patients had a larger amount of dB loss compared to older patients. Concerning baseline hearing level, Zuur et al[30] prospectively studied 101 patients treated with IMRT with a mean cochlear dose of 11.4 Gy (0.2–69.7). Multivariate analysis showed that, in patients with excellent pretreatment hearing capability, the relative hearing deterioration in dB was larger compared with patients with unfavorable baseline hearing ($p<0.0001$). Furthermore, patients with unfavorable baseline hearing levels had a higher risk of a lower hearing level posttreatment, although their hearing deterioration in terms of dB was less ($p<0.0001$). This is in agreement of analyses obtained by Honoré et al.[33]

Sex was not found to be a risk factor for SNHL development in several studies.[32, 34, 40, 47] One study found a significantly increased risk for men[44]; the authors reported an incidence of 30% in men vs. 16% in women ($p=0.0132$). In 1 study patients with green eyes experienced greater hearing loss at all frequencies compared with patients with blue or brown eyes ($p<0.0001$).[30]

Also, post irradiation otitis media with effusion was described as a risk factor, which significantly increased the risk of persistent SNHL by two different authors.[37, 44] In their discussion, Kwong et al described that it is unlikely that middle ear damage after RT can cause SNHL, but that the development of RT-induced serous otitis media might indicate individual sensitivity to radiation. Therefore, patients with RT-induced serous otitis media

might also be more vulnerable for SNHL as an adverse event of RT. Ho et al refers to a study of Jung et al who demonstrates that one of the inflammatory mediators of otitis media, nitric oxide, causes irreversible changes in isolated outer hair cells. They suggest that nitric oxide radicals as a result of chronic otitis media are possibly involved in the development of SNHL.[50]

DISCUSSION

We have searched all articles reporting SNHL after radiotherapy or cisplatin-based chemoradiotherapy for HNSCC. The studies included, however, seemed to be heterogenic in population, tumor site, follow-up time, definition of ototoxicity, RT protocol, and cisplatin dose. Pooled analysis was therefore impossible.

Studies included in this article showed an incidence of SNHL over all measured frequencies of 0 to 43% directly after RT and 17 to 88% directly after CRT. In general, incidences were higher when scored by criteria including (ultra-)high frequencies. Also, higher incidences after CRT compared with RT are reported.[39-40, 44, 47]

Jereczek-Fossa et al[8] reviewed data from several studies and observed that post-RT SNHL occurred in about 33% patients treated by RT with radiation fields not sparing and, thus, including the inner ear. In another review, Raaijmaker and Engelen[51] suggested that, when averaged over all measured frequencies, the incidence of SNHL was 18% ± 2%, and that at least one third of patients receiving a dose of 70 Gy to the inner ear are likely to develop hearing impairment of ≥10 dB in the 4 kHz region. Differences in reported incidences are the result of a large spread in patient, treatment, and study characteristics. Moreover, various definitions of SNHL are used. To assess the impact of this phenomenon, we applied all definitions on one high-dose CRT patient cohort from our institute[35], resulting in large variations in outcome (table 6). The incidence of SNHL according to the CTCAEv3 or ASHA is much higher when compared to a definition of a threshold increment of 15 dB, as a result of different frequencies used (79 to 89% vs. 56% respectively). Consequently, it is difficult to draw unambiguous conclusions about the exact incidence of (C)RT-induced SNHL. In the future it would be strongly desirable to develop a uniform grading scale for research on ototoxicity. In our opinion,

grading criteria should be able to translate the impact of treatment-induced hearing loss to relevant situations in patient's daily life. Specific pure tone frequency regions involved in speech intelligibility and sound quality, like PTA 1-2-4 kHz and PTA 8-10-12.5 kHz, should be incorporated. Furthermore, when using both the degree of threshold shifts (in dB) and the posttreatment hearing level instead of the degree of threshold shift only, a more precise grading scale can be developed.

Table 6 | Number of patients with SNHL when different definitions of SNHL were applied on one patient cohort[35]

CRT high-dose Number of patients: 73	**Up to 8 kHz**	**Up to 16 kHz**	**PTA 0.5-1-2 BC**	**4 kHz BC**
CTCAEv3	58 (79%)	64 (88%)	-	-
ASHA	59 (81%)	65 (89%)	-	-
>10 dB threshold increment	-	-	11 (15%)	47 (65%)
>15 dB threshold increment	-	-	7 (9%)	41 (56%)
>30 dB threshold increment	-	-	0	23 (31%)

Abbreviations: SNHL = Sensorineural Hearing Loss; CRT = Chemoradiotherapy; CTCAEv3 = Common Terminology for Criteria for Adverse Events version 3; ASHA = American Speech Language Hearing Association; PTA = Pure Tone Average

Detection of ototoxicity

Currently, besides audiometry, otoacoustic emissions are increasingly used to screen the auditory function. There is a need of fast and easy audiological diagnostics, also suitable for patients who are too ill to perform pure tone audiometry. Because the emissions are generated by the outer hair cells in the cochlea, which are assumed to be the most vulnerable site of ototoxicity[9], otoacoustic emissions yield a promising instrument of monitoring ototoxicity. Otoacoustic emissions are an objective, noninvasive method to screen the function of the inner ear. Another advantage of this method seems to be earlier detection of inner ear damage.[52]

Of the 21 studies included in this review, only one study mentioned the use of otoacoustic emissions. In the study of Yilmaz et al, both pure tone audiometry and distortion product-otoacoustic emissions were measured before, 1 month after, and 12 months after treatment. One month after treatment, none of the patients had a change >10 dB at

any frequency based on audiometry. However, the amplitudes of the distortion product-otoacoustic emissions measurements were significantly lower in 50% of the ears at 4 kHz, 60% at 6 kHz, and 63% at 8 kHz. Moreover, in all the patients who eventually developed SNHL on audiometry, the amplitudes of the otoacoustic emissions obtained in the first month were significantly lower when compared to baseline. This difference suggests that otoacoustic emissions measurement is a more sensitive and objective tool for detecting treatment-induced inner damage in an early stage.

In a number of studies focusing on ototoxicity in children, otoacoustic emissions were applied for monitoring ototoxicity.[53-55] Currently, otoacoustic emissions are used widely in newborn hearing screening programs and are validated by professional organizations as a reliable and objective tool.[53] Nevertheless, studies focusing on otoacoustic emissions monitoring ototoxicity in adults are sparse.[52] In the future, first, adequate comparisons of otoacoustic emissions and audiometry in adult populations should be obtained.

Risk factors

Many authors reported that a higher RT **dose to the cochlea** was significantly associated with more SNHL.[30, 32-33, 35, 38, 40, 47] However, in one study,[46] no significant association (p=0.086) was reported, although patients with SNHL after RT did receive a higher dose compared with patients without SNHL (50.0 Gy vs. 48.2 Gy). It should be admitted that the difference in radiation dose is relatively small. Also, in one study of Zuur et al, no association between dose to the cochlea and hearing loss was reported.[34] However, the median cochlear dose was low (16.4 ± 12.9 Gy). Based on the overall findings of the studies included, the risk of SNHL will increase if a larger radiation dose to the cochlea is given, starting from 47 Gy.[40] Limiting the radiation dose to the cochlea by IMRT technique is therefore important. By this technique, high doses to the tumor region can be delivered while sparing organs at risk from high doses of radiation. The risk of SNHL can thereby be reduced.[38]

Also, the incidence of SNHL seems to increase during **follow-up time**.[29, 31-32, 37-40, 42-43] Yilmaz et al[31] explained this with the hypothesis of increased progression of impaired circulation that occurs in the cochlea after (C)RT treatment. Of the 10 studies reporting progressive hearing loss over time, the mean cochlear dose was >47 Gy in 6 studies

(in 4 studies the cochlear dose was not described). Furthermore, studies reporting a demarcation of a radiation dose associated with more SNHL (ie, from 47 Gy), also showed (if evaluated) a progressive hearing loss when follow-up time was longer.[38, 40] This suggests that the extent of progressive SNHL may be radiation-dose dependent. However, when follow-up time increases, hearing also decreases because of natural causes (ie, presbycusis). Only the study by Ho et al[43] compared the incidence of SNHL to a normal population standard. According to a formula suggested by Robinson and Sutton for the calculation of the median thresholds at different ages, the expected age-related threshold shift within the 4.5 years of follow-up was found to be lower than the hearing deterioration seen in their patients. Therefore, the threshold shift after 4.5 years was ascribed to both age-related degeneration and former (C)RT.

Many authors reported an increased risk of developing SNHL with increasing **age**.[30, 32-34, 40, 42, 44, 47] Nevertheless, Zuur et al[35] measured that younger patients had a larger amount of dB loss than older patients. Obviously, **baseline hearing level** itself is related to age. Therefore, patients with a good baseline hearing level (i.e., younger patients) may endure relatively more hearing loss (in dB) but will finish with lower threshold (in dB HL) after treatment compared to older patients. In reverse, patients with unfavorable baseline hearing levels (i.e., older patients) may not have large hearing deteriorations in terms of dB, but are characterized by a higher chance of higher threshold in dB HL after treatment.[30, 33] In agreement, Ho et al[43] showed that ears with more preirradiation hearing loss (BC level of >60 dB at 4 kHz) were less likely to develop deterioration of the hearing threshold (in dB) at 4 kHz after RT. However, they indicated that patients older than 50 years were more likely to have >10 dB hearing loss at 4 kHz when assessed within 3 months after completion of RT compared with patients <50 years old (p=0.0051). They suggested that ears in these patients might have pre-existing degenerative changes that make them more vulnerable to irradiation toxicity. In 4 other studies, the baseline hearing level was not associated with increased risk of SNHL development.[34, 38, 40, 42] However, 1 study showed that age correlated with baseline hearing level at both PTA 0.5-1-2 kHz and 4 kHz and in multivariate analysis, higher age was significantly associated with higher risk of SNHL in dB hearing level.[40]

As both **radiation to the head and neck region and cisplatin** induce SNHL, combined cisplatin and radiation may cause more SNHL than radiotherapy alone. Studies by Low

et al[39] and Chan et al[40] reported significantly more hearing loss after CRT compared to RT. In disagreement is Wang et al.[42] They compared a group of patients treated with CRT (cumulative cisplatin dose 160-240 mg/m^2) with a group treated with RT only. No significant differences were noted. However, the distribution of patients between the groups was unequal (7 in RT group versus 213 in CRT group). Moreover, patients were treated with neoadjuvant cisplatin and it was not reported whether the baseline audiogram was conducted before the start of cisplatin infusions or before the start of RT. In the latter case, the ototoxic effect of cisplatin may have occurred unnoticed. This possible bias was also found in the studies of Ho et al[43] and Kwong et al.[44]

In current practice, cisplatin CRT with either high-dose cisplatin (100 mg/m^2, every 3 weeks) or low-dose (30-40 mg/m^2, weekly) has been used widely. A mean ototoxicity incidence of 33% has been reported when patients received a single dose of ≥50 mg/m^2 cisplatin or a total dose of ≥400 mg.[23, 56] Cumulative **cisplatin dose** was also reported to correlate with hearing loss after therapy.[35, 38, 40] Hitchcock et al[41] showed that RT might potentiate the effect of cisplatin as they described its effect at 40 Gy as approximately twice as great as that at 10 Gy. Because the cisplatin schedules, doses, and the number of infusions were various or sometimes not clearly described, it remains difficult to compare the influence of different schedules. Interestingly, in a study of Rademaker et al[56] less hearing impairment occurred after once a week (6 weeks) cisplatin administrations compared to once every 2 weeks for a total of 4 courses cisplatin administration (p=0.011). Dose-intensity of cisplatin was equal in both schedules. They suggest that lower doses over a more frequent time interval are less ototoxic than higher doses over a broader time interval.

Clinical impact

Weeks, months, or years after finishing treatment, the impact of SNHL on quality of life cannot be neglected and should not be underestimated. For some individuals, like musicians, teachers or the vision-impaired, SNHL can have a major impact on social life and working ability. Therefore, radiotherapists and oncologists should inform patients about this adverse event.

Protection of sensorineural hearing loss

To protect the inner ear from ototoxicity while continuing the optimal platinum

chemotherapy, several agents were studied to indentify otoprotective agents. A variety of agents with chemoprotective action against cisplatin ototoxicity are successfully tested in animals.[57-58] Currently, researchers are focusing on the otoprotective effect of several agents in humans. A few studies in humans have been recently completed.[59-61] Meanwhile, sodium thiosulfate and N-acetylcysteine have received a Food and Drug Administration orphan status for the indication of otoprotection.[58] We have documented an otoprotective effect of sodium thiosulfate in patients receiving 4 courses of high-dose cisplatin (150 mg/m^2) by intra-arterial infusion[35, 62], but reconfirmation by others is needed.

CONCLUSION

SNHL is a common adverse event after (C)RT, with higher incidences among patients undergoing CRT. However, results are difficult to compare mainly because of the various definitions of ototoxicity criteria used. Factors that influence the risk of SNHL are cochlear radiation dose, follow-up time, age, baseline hearing level, and (cumulative) cisplatin dose. A minimum cochlear radiation dose of 47 Gy was reported to be a risk factor. Therefore, when possible, limiting the radiation dose to the cochlea by IMRT technique is crucial.

It is recommended to perform a pretreatment and posttreatment audiological evaluation with special emphasis on high frequencies. Moreover, in future research, it would be desirable to use uniform grading scales to report treatment-related SNHL.

AKNOWLEGMENTS

This work was supported by an unrestricted grant from the Riki Stichting.

REFERENCES

1. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. Apr 1998;16(4):1310-1317.

2. Al-Sarraf M, Pajak TF, Marcial VA, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG Study. *Cancer*. Jan 15 1987;59(2):259-265.

3. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. Mar 18 2000;355(9208):949-955.

4. Wee J, Tan EH, Tai BC, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol*. Sep 20 2005;23(27):6730-6738.

5. Huncharek M, Kupelnick B. Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. *Am J Clin Oncol*. Jun 2002;25(3):219-223.

6. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. Jul 2009;92(1):4-14.

7. Bhide SA, Harrington KJ, Nutting CM. Otological toxicity after postoperative radiotherapy for parotid tumours. *Clin Oncol (R Coll Radiol)*. Feb 2007;19(1):77-82.

8. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. *Cancer Treat Rev*. Oct 2003;29(5):417-430.

9. Winther FO. X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the cochlea. *Acta Otolaryngol*. Jul-Aug 1969;68(1):98-117.

10. Moretti JA. Sensori-neural hearing loss following radiotherapy to the nasopharynx. *Laryngoscope*. Apr 1976;86(4):598-602.

11. Bhandare N, Mendenhall WM, Antonelli PJ. Radiation effects on the auditory and vestibular systems. *Otolaryngol Clin North Am*. Aug 2009;42(4):623-634.

12. Leach W. Irradiation of the ear. *J Laryngol Otol*. Oct 1965;79(10):870-880.

13. Laurell G, Viberg A, Teixeira M, Sterkers O, Ferrary E. Blood-perilymph barrier and ototoxicity: an in vivo study in the rat. *Acta Otolaryngol*. Oct 2000;120(7):796-803.

14. Riedemann L, Lanvers C, Deuster D, et al. Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. *Pharmacogenomics J*. Feb 2008;8(1):23-28.

15. Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. *Br J Cancer*. Jun 1990;61(6):927-931.

16. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys*. Mar 1 2010;76(3 Suppl):S50-57.

17. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head Neck*. Nov 2013;35(11):1662-1668.

18. STROBE. Strengtening the reporting of observational studies in epidemiology. 2007; Version 4: http://www.strobe-statement.org/index.php?id=available-checklists.

19. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet*. Jan 26 2002;359(9303):341-345.

20. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. Jun 1998;52(6):377-384.

21. Grau C, Moller K, Overgaard M, Overgaard J, Elbrond O. Sensori-neural hearing loss in patients treated with irradiation for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. Aug 1991;21(3):723-728.

22. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys*. Aug 1 2007;68(5):1320-1325.

23. Pearson SE, Meyer AC, Adams GL, Ondrey FG. Decreased hearing after combined modality therapy for head and neck cancer. *Am J Otolaryngol*. Mar-Apr 2006;27(2):76-80.

24. Low WK, Fong KW. Hearing disability before and after radiotherapy for nasopharyngeal carcinoma. *J Laryngol Otol*. Feb 1996;110(2):121-123.

25. Leighton SE, Kay R, Leung SF, Woo JK, Van Hasselt CA. Auditory brainstem responses after radiotherapy for nasopharyngeal carcinoma. *Clin Otolaryngol Allied Sci*. Aug 1997;22(4):350-354.

26. Dias A. Effects on the hearing of patients treated by irradiation in the head and neck area. *J Laryngol Otol*. Mar 1966;80(3):276-287.

27. Tsang RK, Kwong DL, Ho AC, To VS, Ho WK, Wei WI. Long-term hearing results and otological complications of nasopharyngeal carcinoma patients: comparison between treatment with conventional two-dimensional radiotherapy and intensity-modulated radiotherapy. *ORL J Otorhinolaryngol Relat Spec*. 2012;74(4):228-233.

28. Dell'Aringa AH, Isaac Mde L, Arruda GV, Dell'Aringa AR, Esteves MC. Audiological findings in patients treated with radiotherapy for head and neck tumors. *Braz J Otorhinolaryngol*. Jul-Aug 2010;76(4):527-532.

29. Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. *J Laryngol Otol*. Jan 2010;124(1):32-36.

30. Zuur CL, Simis YJ, Lamers EA, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys*. Jun 1 2009;74(2):490-496.

31. Yilmaz YF, Aytas FI, Akdogan O, et al. Sensorineural hearing loss after radiotherapy for head and neck tumors: a prospective study of the effect of radiation. *Otol Neurotol*. Jun 2008;29(4):461-463.

32. Herrmann F, Dorr W, Muller R, Herrmann T. A prospective study on radiation-induced changes in hearing function. *Int J Radiat Oncol Biol Phys*. Aug 1 2006;65(5):1338-1344.

33. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiother Oncol*. Oct 2002;65(1):9-16.

34. Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol*. Oct 2008;89(1):38-43.

35. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol*. Aug 20 2007;25(24):3759-3765.

36. Liberman PH, Schultz C, Gomez MV, et al. Auditory effects after organ preservation protocol for laryngeal/hypopharyngeal carcinomas. *Arch Otolaryngol Head Neck Surg*. Nov 2004;130(11):1265-1268.

37. Oh YT, Kim CH, Choi JH, Kang SH, Chun M. Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. *Radiother Oncol*. Jul 2004;72(1):79-82.

38. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer*. Feb 15 2006;106(4):820-829.

39. Low WK, Toh ST, Wee J, Fook-Chong SM, Wang DY. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol*. Apr 20 2006;24(12):1904-1909.

40. Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys*. Apr 1 2009;73(5):1335-1342.

41. Hitchcock YJ, Tward JD, Szabo A, Bentz BG, Shrieve DC. Relative contributions of radiation and cisplatin-based chemotherapy to sensorineural hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys*. Mar 1 2009;73(3):779-788.

42. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. *Otol Neurotol*. Mar 2004;25(2):168-173.

43. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: A prospective study. *Head Neck*. Sep 1999;21(6):547-553.

44. Kwong DL, Wei WI, Sham JS, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. *Int J Radiat Oncol Biol Phys*. Sep 1 1996;36(2):281-289.

45. Petsuksiri J, Sermsree A, Thephamongkhol K, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. *Radiat Oncol*. 2011;6:19.

46. Wakisaka H, Yamada H, Motoyoshi K, Ugumori T, Takahashi H, Hyodo M. Incidence of long-term ipsilateral and contralateral ototoxicity following radiotherapy for nasopharyngeal carcinoma. Auris Nasus Larynx. Feb 2011;38(1):95-100.

47. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *Int J Radiat Oncol Biol Phys*. Feb 1 2007;67(2):469-479.

48. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy. ASHA 36:11-19, 1994.

49. Common Terminology for Criteria for Adverse Events, Version 3.0; 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

50. Jung TT, Llaurado RJ, Nam BH, Park SK, Kim PD, John EO. Effects of nitric oxide on morphology of isolated cochlear outer hair cells: possible involvement in sensorineural hearing loss. *Otol Neurotol*. Jul 2003;24(4):682-685.

51. Raaijmakers E, Engelen AM. Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. *Radiother Oncol*. Oct 2002;65(1):1-7.

52. Biro K, Noszek L, Prekopp P, et al. Characteristics and risk factors of cisplatin-induced ototoxicity in testicular cancer patients detected by distortion product otoacoustic emission. *Oncology*. 2006;70(3):177-184.

53. Foust T, Eiserman W, Shisler L, Geroso A. Using otoacoustic emissions to screen young children for hearing loss in primary care settings. *Pediatrics*. Jul 2013;132(1):118-123.

54. Toral-Martinon R, Shkurovich-Bialik P, Collado-Corona MA, Mora-Magana I, Goldgrub-Listopad S, Shkurovich-Zaslavsky M. Distortion product otoacoustic emissions test is useful in children undergoing cisplatin treatment. *Arch Med Res*. May-Jun 2003;34(3):205-208.

55. Dhooge I, Dhooge C, Geukens S, De Clerck B, De Vel E, Vinck BM. Distortion product otoacoustic emissions: an objective technique for the screening of hearing loss in children treated with platin derivatives. *Int J Audiol*. Jun 2006;45(6):337-343.

56. Rademaker-Lakhai JM, Crul M, Zuur L, et al. Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol*. Feb 20 2006;24(6):918-924.

57. van den Berg JH, Beijnen JH, Balm AJ, Schellens JH. Future opportunities in preventing cisplatin induced ototoxicity. *Cancer Treat Rev*. Aug 2006;32(5):390-397.

58. Langer T, Am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci*. Aug 2013;34(8):458-469.

59. Doolittle ND, Muldoon LL, Brummett RE, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Re*s. Mar 2001;7(3):493-500.

60. Neuwelt EA, Gilmer-Knight K, Lacy C, et al. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. *Pediatr Blood Cancer*. Aug 2006;47(2):174-182.

61. Riga MG, Chelis L, Kakolyris S, et al. Transtympanic injections of N-acetylcysteine for the prevention of cisplatin-induced ototoxicity: a feasible method with promising efficacy. *Am J Clin Oncol*. Feb 2013;36(1):1-6.

62. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer*. May 1 2010;116(9):2159-2165.


03

CHAPTER 03

A new grading system for ototoxicity in adults

E.A.R. Theunissen | W.A. Dreschler | M.N. Latenstein | C.R.N. Rasch
S. van der Baan | J.P. de Boer | A.J.M. Balm | C.L. Zuur

Annals of Otology, Rhinology, Laryngology, 2014; 123(10): 711-8

ABSTRACT

Objective

This study aimed to propose an ototoxicity grading system sensitive to the impact of ototoxicity on specific daily life situations like speech intelligibility and the perception of ultra-high sounds, and to test its feasibility compared to current criteria.

Methods

Pure Tone Averages (PTAs) for speech perception (1-2-4 kHz) and ultra-high frequencies (8-10-12.5 kHz) were incorporated. Threshold shift and hearing level posttreatment were taken into account. Criteria were tested on head and neck cancer patients treated with (chemo-)radiotherapy ((C)RT), and compared with the Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) and the American Speech Language Hearing Association criteria (ASHA).

Results

Grades 1 and 2 were based on threshold shifts from baseline (in dB) and subjective complaints. Grade 3 and 4 were defined as treatment-induced hearing loss of ≥35 at PTA 1-2-4 kHz and ≥70 dB at PTA 1-2-4 kHz, respectively. In high-dose cisplatin CRT incidences by the new criteria, CTCAEv4 and ASHA were comparable (78%-88%). In RT and low-dose cisplatin CRT, incidences were 36-39% in the new criteria, versus 22-53% in CTCAEv4 and ASHA.

Conclusion

The new criteria show an increased sensitivity to ototoxicity compared to CTCAEv4 and ASHA and provide insight into the impact of hearing loss on certain daily life situations. The new grading system seems feasible for clinic and research purposes.

INTRODUCTION

Ototoxicity is an often-reported adverse event that can be caused by different compounds such as anti-malarial, antihypertensive, antibiotic drugs, chemotherapy, and radiotherapy (RT) to the auditory apparatus.[1-4] Ototoxicity may consist of vestibular toxicity, cochleotoxicity (sometimes accompanied by tinnitus), and conductive hearing loss. Cochleotoxicity is characterized by starting at the basal end of the cochlea (high frequencies, ≥4 kHz) and then progressing to the apical end (low frequencies, <4 kHz).[5] Therefore, hearing deterioration at (ultra)-high frequencies usually precedes hearing loss at lower frequencies.[6]

In head and neck oncology, treatment-induced hearing loss has been reported in up to 79% in patients treated with high-dose cisplatin chemoradiotherapy (CRT) (100 mg/m^2 cisplatin, 3 courses in 7 weeks of RT).[7] In addition, single-modality RT (70 Gray) and low-dose cisplatin CRT (6 mg/m^2 cisplatin, 20-25 daily doses with concurrent RT in 6 weeks) are followed by incidence rates of ototoxicity of 24% and 31%, respectively.[8-9] Hence, cisplatin and RT both exert ototoxicity, depending on the cisplatin dose and RT intensity.[5, 8, 10-12]

Although ototoxicity may seem a small price to pay for curing malignancies, patients may perceive a major impact in daily functioning and quality of life.[13] For example, hearing loss at speech frequencies up to 4 kHz may result in a deterioration of speech intelligibility in a noisy environment. Hearing loss at higher frequencies (>4 kHz) might have an adverse impact on the recognition and appreciation of sounds perceived in nature and music (birds, instruments, melodies). Hence, decreased hearing sensitivity at (ultra-)high frequencies has consequences for a patient's well-being that are different from decreased hearing sensitivity at lower frequencies. In addition, limited hearing loss (expressed in dBs) in patients with favorable hearing prior to therapy may be 'inconvenient', whereas the same hearing loss in patients with pre-existent presbycusis may leave the patient quite dysfunctional in group conversations, meetings or even in quite environment. In our opinion, a patient's informed consent prior to treatment should preferably include both the predicted extent of hearing loss (in dB) AND hearing levels (in dB HL) resulting from treatment, as well as the specific nature of expected treatment-related ototoxicity.

In addition, hearing loss at the (ultra-)high frequencies can be regarded as a warning signal for ototoxicity soon affecting the lower frequencies. As a consequence, appreciating high-frequency hearing loss during therapy may lead to deliberate continuation of chemotherapy for specific patients in whom hearing capability is crucial to functioning in daily life (i.e. school teachers, musicians). Registration of ultra-high frequency loss is required for both systematic validation of this phenomenon and potential future opportunities in a clinical setting.

However, currently used ototoxicity grading systems such as Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) and the American Speech Language Hearing Association (ASHA) system (table 1)[14-15] do not strongly relate to specific daily life situations, or appreciate the impact of ultra-high frequency hearing loss. They also have certain limitations: The ASHA criteria do not define which frequencies to use to score the hearing loss. Moreover, its criteria do not assess a step-by-step increase of hearing impairment. The CTCAEv4 for adults indicates use of frequencies 1-8 kHz, disregarding ultra-high frequencies. Since each of these frequencies weighs equally, CTCAEv4 does not consider the clinical importance of specific frequency regions for speech intelligibility or appreciation of sounds as in music. In addition, CTCAEv4 grades 2 and 3 are coarsely defined (width of 25-80 dB loss), which may further hamper the translation of the impact of a certain grade on a patient's functioning in daily life. Finally, in CTCAEv4 ultra-high frequencies are disregarded, although hearing impairment generally starts at these frequencies. In summary, currently used criteria are coarsely defined with regard to frequency importance and a gradually increase in the extent of hearing loss (in dB and dB HL). As a consequence, the clinical impact per grade remains unclear and grading systems are not used systematically. Hence, results of evaluated patient cohorts using ASHA and CTCAEv4 are not easily translated to a patient's informed consent.

To stimulate the use of one uniform grading system, the current criteria should be improved. Over the years, several new criteria have been developed over the years for children.[16-21] Criteria for adults were improved in 2010 by replacing the CTCAEv3 by the CTCAEv4. The main improvement in the CTCAEv4 was the description using frequencies 1 to 8 kHz when applying the system, which was unclear in the CTCAEv3. In 2012, Gurgel and coworkers created a new hearing outcomes scale for clinical trials

in adults, by introducing a scattergram relating the air conduction thresholds shifts due to treatment to the posttreatment word recognition score (WRS).[22] The new standard of Gurgel et al enables a more nuanced representation of hearing outcome. Nevertheless, a WRS is still not always included in standard audiometry practice.

Table 1 | CTCAEv4 and ASHA criteria

CTCAEv4 Adults	*Adults enrolled in Monitoring Program (a 1, 2, 3, 4, 6 and 8 kHz audiogram):* Grade 0: No hearing loss Grade 1: Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in absence of a Grade 1 threshold shift Grade 2: Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear Grade 3: Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear Grade 4: Profound bilateral hearing loss (>80 dB at 2 kHz and above)
ASHA	NO: No hearing loss YES: Threshold shift ≥20 dB shift at any frequency OR threshold shift ≥10 dB shift at two consecutive frequencies

Abbreviations: CTCAEv4 = Common Terminology Criteria for Adverse Events version 4; ASHA =American Speech Language Hearing Association

In this article, we aimed to develop an alternative grading system in case of missing WRS, with suggestions to improve the potential shortcomings of the current criteria as described above, using solely pure tone audiometric data. We intended to translate the impact of treatment-induced hearing loss to relevant situations in the patient's daily life, by using specific pure tone frequency regions involved in speech intelligibility and sound quality. To this end, the new system was tested for its feasibility and compared to the current criteria.

MATERIALS AND METHODS

In the present article, the term ototoxicity includes all types of hearing loss and excludes vestibular toxicity. Pure tone audiometry is used to measure the hearing thresholds and prior to each audiogram patients were asked whether they experienced new symptoms of hearing loss and/or tinnitus.

Building the new grading system

The potential impact of hearing loss at frequencies involved in speech intelligibility

Several models have been studied to determine speech frequency importance. The Articulation Index (AI) expresses the proportion of the average information in a speech signal that is audible to a patient with a specific hearing loss. The speech signal is divided into frequency bands, each weighted according to the theoretical contribution to speech intelligibility.[23] Mueller and Killion designed a more accessible version of the AI involving 100 dots on an audiogram, each representing 1% of the essential speech information.[24] The highest density of the dots was concentrated in the frequency regions between 750, 1500 and 3000 Hz. However, in standard audiometry 750, 1500 and 3000 Hz are not routinely measured, whereas 1, 2 and 4 kHz are. Following the count-the-dots method, frequency bands for 1-2-4 kHz are equivalent to frequency bands at 750, 1500 and 3000 Hz, covering the regular conversation levels that are located between 20 and 50 dB hearing level. Therefore, we considered an absolute hearing level of ≥35 dB at Pure Tone Average (PTA) 1-2-4 kHz to represent a 50% loss of the speech intelligibility at conversation levels. Finally, a loss of ≥70 dB HL at PTA 1-2-4 kHz is assumed to be equivalent to profound hearing loss, if not compensated with hearing aids.

The potential impact of hearing loss at frequencies involved in (ultra-)high sounds

Areas of high frequency sounds (4-8 kHz) and ultra-high frequency sounds (up to 16 kHz) are frequently perceived in nature. In addition, in music performances, keynotes and overtones (up to 16 kHz) are crucial for the timbre, the identification of the instruments, and the articulation of sound. Moreover, as ototoxicity starts in ultra-high frequencies and extends to lower frequencies, this ultra-high frequency region may allow for detection of ototoxicity in an early stage.[25-26]

Relevant threshold shifts and subjective complaints

Previous analyses showed that patients may have subjective complaints of tinnitus and/or hearing loss due to treatment although the audiogram remained unaltered.[8] In this high-dose CRT patient cohort, 24 patients (8%) complained of hearing loss or tinnitus after the first cisplatin administration. Thirty-three percent of them did not show any change at PTA 1-2-4 kHz or PTA 8-10-12.5 kHz. We assumed a loss of ≥10 dB as clinically relevant and well perceptible for individual patients. In general, 5 dB is the standard error of audiometry, and we regarded a 5 to 10 dB shift as not noticeable for humans.

Definition of the "TUNE" Grading System

We called the proposed grading system the TUNE system as we are fine-TUNing the currently used ototoxicity criteria (table 2).

Table 2 | The TUNE grading system

Grade 0: No hearing loss
Grade 1a: Threshold shift ≥10 dB at [8-10-12.5] OR subjective complaints in the absence of a threshold shift *Grade 1b:* Threshold shift ≥10 dB at [1-2-4]
Grade 2a: Threshold shift ≥20 dB at [8-10-12.5] *Grade 2b:* Threshold shift ≥20 dB at [1-2-4]
Grade 3: Hearing level ≥35 dB HL at [1-2-4] de novo *Grade 4:* Hearing level of ≥70 HL dB at [1-2-4] de novo

Abbreviations: [8-10-12.5] = PTA 8-10-12.5 kHz; [1-2-4] = PTA 1-2-4 kHz; HL = Hearing Level
Note 1: dB Hearing levels are expressed in air conduction levels.
Note 2: Grading system is to be applied per ear.

Following the Articulation-Index for speech intelligibility and the importance of high frequencies, TUNE grade 1 and 2 are based on threshold shifts at PTA 1-2-4 and 8-10-12.5 kHz (in dB, relative to the pretreatment audiogram). In the first grade, TUNE also includes subjective treatment-related symptoms. Furthermore, TUNE grade 3 comprehends a treatment-induced transition to ≥35 dB HL at PTA 1-2-4 kHz AC, as a demarcation for significant and clinically overt loss of speech intelligibility (50%) at conversation levels. Finally, grade 4 comprises patients with treatment-induced profound hearing loss (≥70 dB HL at PTA 1-2-4 kHz).

The proposed TUNE grading criteria are expressed in AC thresholds. AC thresholds represent the functionality of the whole auditory system, whereas BC comprises solely the inner ear. In general, sensorineural hearing loss induced by cisplatin or RT is depicted by BC thresholds and is considered irreversible.[5, 10, 28] However, we decided to use AC measurements, as we feel that the grading criteria should comprehend the overall hearing loss due to treatment.

Testing the feasibility of the proposed grading system

We aimed to test the feasibility of the proposed grading system by reviewing 3 large and prospectively designed patient cohort studies previously performed in our institute.[7-9] Three-hundred nineteen patients underwent high-dose (158 patients), low-dose (60 patients) cisplatin based concurrent CRT, or Intensity Modulated Radiation Therapy (IMRT) (101 patients) for head and neck cancer between 1999 and 2006.[7-9] The majority were male (71%) and the median age was 61 years (27-95). Patients of the high-dose CRT cohort received 4 courses of intra-arterial cisplatin infusions (150 mg/m^2, on days 1, 8, 15, and 22 during 7 weeks RT), or 3 courses of intravenously administered cisplatin (100 mg/m^2, on days 1, 22, 43 during 7 weeks RT). Patients of the low-dose CRT cohort received daily courses intravenously administered cisplatin (6 mg/m^2, 20-25 days during 7 weeks RT). Patients of the IMRT cohort did not receive any chemotherapy. All patients received 70 Gray (Gy) fractionated RT in 35 fractions.[7-9] Median radiation doses to the cochlea were 14.3 (0.2-67.4), 11.4 (3.0-67.2), and 11.2 (0.2-69.7) Gy in high-dose CRT, low-dose CRT, and IMRT, respectively.

Audiometry of these cohorts was conducted in a prospective setting one week before, during and after therapy (median 8 weeks after high-dose CRT, 11 weeks after low-dose CRT and 17 weeks after IMRT). The hearing tests were performed in a soundproof testing room using the Decos system (Audiology Workstation). Air conduction (AC) thresholds were measured at frequencies 0.125, 1, 2, 3, 4, 6, and 8 kHz in dB HL and the PTA 1-2-4 kHz values we used were also expressed in dB HL. In addition, AC thresholds were measured at frequencies 8, 10, and 12.5 kHz, using different headphones. These thresholds were expressed in dB sound pressure levels (SPLs) and this also applied to the average PTA 8-10-12.5 kHz. Bone Conduction (BC) thresholds were measured at frequencies 0.5, 1, 2, 4 kHz (dB HL). If measurements at 3 and 6 kHz were missing (32% and 29%, respectively), interpolation of the data was performed.[27] In case of missing measurements at 10 and 12.5 kHz and when there was no response at the maximum output of the audiometer, thresholds were calculated by extrapolating the data (28% at 10 kHz and 50% at 12.5 kHz).[7-9] An Air Bone Gap (ABG) was defined as a difference of ≥10 dB between AC and BC.

The outcome of the proposed system was compared to the current CTCAEv4 and ASHA criteria. ASHA criteria were scored twice: once using frequencies up to 8 kHz (as

in CTCAEv4) and once using frequencies up to 12.5 kHz (as in TUNE).

False positive rate

According to the confirmation method described by Dobie et al[29], threshold shifts (based on the difference between baseline and post-treatment test) that do not persist on a third test (i.e. a second post-treatment test, time interval not specified) are considered as false positives (FPs).[29] To calculate the false positive rates of the new and existing criteria, we used the high-dose CRT patient group, in which more than 2 audiograms were conducted. We graded the patients after their last cisplatin infusion and evaluated whether this threshold shift persisted at the control audiogram a few weeks after finishing treatment. A FP was scored when a higher grade was assigned after the last cisplatin infusion, compared to the control audiometry.

RESULTS

Incidence of ototoxicity defined by CTCAEv4, ASHA and TUNE

The databases of 319 patients were included to test the grading systems.[7-9] Forty-one ears (29 patients; 12 bilateral, 17 unilateral) were excluded from analyses: in 14 ears posttreatment audiometry was not performed; in 11 ears there was no pretreatment audiogram available; and in 16 ears high frequencies were missing. Hence, 307 patients and 597 ears (290 bilateral, 17 unilateral) were included.

The incidences of hearing loss scored by CTCAEv4, ASHA, and TUNE criteria are shown in table 3. The scores of the grading systems are shown per patient cohort. The last column shows the overall incidence of ototoxicity after high-dose CRT, according to the different grading systems: CTCAEv4 78%, ASHA up to 8 kHz 78%, ASHA up to 12.5 kHz 88% and TUNE 80%. After low-dose CRT, the overall incidence varies between 24% and 53% and for IMRT between 22% and 36%. In high-dose CRT, CTCAEv4 categorized a larger number of patients in grade 3 (39%) compared to grade 2 (19%), which was the opposite in TUNE (grade 3: 21% versus grade 2: 37%).

Table 3 | Incidence of hearing impairment scored by CTCEAv4 for adults, ASHA,TUNE

Grade	0	1a*	1b	2a	2b	3	4	Total
High-dose CRT, n = 149 patients / 296 ears								
CTCAEv4	33 (22%)	30 (20%)		28 (19%)		58 (39%)		116 (78%)
ASHA 1-8 kHz	65 (22%)	231 (78%)						231 (78%)
ASHA 1-12.5 kHz	35 (12%)	261 (88%)						261 (88%)
TUNE	58 (20%)	37 (13%)	17 (6%)	102 (34%)	10 (3%)	62 (21%)	10 (3%)	238 (80%)
Low-dose CRT, n = 58 patients / 109 ears								
CTCAEv4	44 (76%)	7 (12%)		3 (5%)		4 (7%)		14 (24%)
ASHA 1-8 kHz	77 (71%)	32 (29%)						32 (29%)
ASHA 1-12.5 kHz	53 (47%)	56 (53%)						56 (53%)
TUNE	67 (61%)	25 (22%)	1 (1%)	6 (6%)	0	7 (7%)	3 (3%)	42 (39%)
IMRT, n = 100 patients / 192 ears								
CTCAEv4	78 (78%)	12 (12%)		3 (3%)		7 (7%)		22 (22%)
ASHA 1-8 kHz	147 (77%)	45 (23%)						45 (23%)
ASHA 1-12.5 kHz	141 (73%)	51 (27%)						51 (27%)
TUNE	124 (64%)	40 (20%)	7 (4%)	3 (2%)	0	15 (8%)	3 (2%)	68 (36%)

Abbreviations: CRT= Chemoradiotherapy; IMRT = Intensity Modulated Radiation Therapy; CTCAEv4 = Common Terminology Criteria for Adverse Events version 4; ASHA =American Speech Language Hearing Association.
Note: CTCAEv4 were applied per patient. TUNE and ASHA criteria were applied per ear.
* = 'yes' in case of ASHA since ASHA does not assess a step-by-step increase of hearing impairment.

The ABG incidence in patients was relatively low after high-dose CRT (13%), after low-dose CRT (12%), and after IMRT (12%).[7-9] When all ears with an ABG were excluded for analysis, incidences of ototoxicity slightly decreased according to CTCAEv4, ASHA and TUNE. Decreased incidences compared to the score with ABG-ears included, were smallest in ASHA up to 12.5 kHz and TUNE (table 4).

False positive rate

According to TUNE, in the high-dose CRT group, 35 of the 296 ears were graded higher after their last infusion compared to the control audiometry. So, in TUNE, 35 of 296 ears (12%) were false positives. In CTCAEv4, 16 of the 149 patients were graded higher after their last infusion compared to the control audiometry. So, according to the CTCAEv4, 16 of 149 patients (11%) were false positives. When applied on CTCAEv4 per ear instead of per patient, percentages did not change. ASHA up to 8 kHz showed no false positives at all, and when scored up to 12.5 kHz, 3% of the ears were a false positive.

Table 4 | Incidence of hearing impairment scored by CTCEAv4 for adults, ASHA, TUNE; ears with an air bone gap excluded

Grade	0	1a*	1b	2a	2b	3	4	Total
High-dose CRT, n = 138 patients / 258 ears								
CTCAEv4	36 (26%)	30 (22%)		27 (19%)		45 (33%)	0	102 (74%)
ASHA 1-8 kHz	55 (22%)	203 (78%)						203 (78%)
ASHA 1-12.5 kHz	29 (11%)	229 (89%)						229 (89%)
TUNE	52 (20%)	34 (13%)	16 (6%)	97 (38%)	7 (3%)	51 (19%)	1 (1%)	206 (80%)
Low-dose CRT, n = 53 patients / 96 ears								
CTCAEv4	44 (83%)	6 (11%)		3 (6%)		0	0	9 (17%)
ASHA 1-8 kHz	70 (73%)	26 (27%)						26 (27%)
ASHA 1-12.5 kHz	48 (50%)	48 (50%)						48 (50%)
TUNE	62 (65%)	23 (24%)	1 (1%)	5 (5%)	0	5 (5%)	0	34 (35%)
IMRT, n = 93 patients / 169 ears								
CTCAEv4	83 (89%)	7 (8%)		3 (3%)		0	0	10 (11%)
ASHA 1-8 kHz	140 (83%)	29 (17%)						29 (17%)
ASHA 1-12.5 kHz	124 (73%)	45 (27%)						45 (27%)
TUNE	114 (67%)	40 (23%)	5 (3%)	3 (2%)	0	6 (4%)	1 (1%)	55 (33%)

Abbreviations: CRT= Chemoradiotherapy; IMRT = Intensity Modulated Radiation Therapy; CTCAEv4 = Common Terminology Criteria for Adverse Events version 4; ASHA =American Speech Language Hearing Association.
Note: CTCAEv4 were applied per patient. TUNE and ASHA criteria were applied per ear.
* = 'yes' in case of ASHA since ASHA does not assess a step-by-step increase of hearing impairment.

Loss of speech intelligibility at conversation levels

At PTA 1-2-4 kHz AC, 71 of all 307 patients (89/597 ears) had a loss of ≥ 35 dB HL de novo, representing a 50% loss of speech intelligibility at conversation levels due to treatment. After high-dose CRT treatment, patients had a higher chance of suffering such a loss; 50 patients (16%) compared to 14 patients (5%) after IMRT and 7 patients (2%) after low-dose CRT.

Using the CTCAEv4, 38/71 (54%) of the patients with a loss of ≥35 dB HL at PTA 1-2-4 kHz AC were scored as grade 0, 1, or 2 (table 5). In the TUNE criteria all those ears were scored as grade 3 (n=85) or grade 4 (n=4).

Table 5 | Number of patients with 50% loss of speech intelligibility at conversation levels

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CTCAEv4 (n=71 patients)	16 (23%)	13 (18%)	9 (13%)	33 (46%)	0
TUNE (n=89 ears)	0	0	0	85 (96%)	4 (4%)

Abbreviation: CTCAEv4 = Common Terminology Criteria for Adverse Events version 4

DISCUSSION

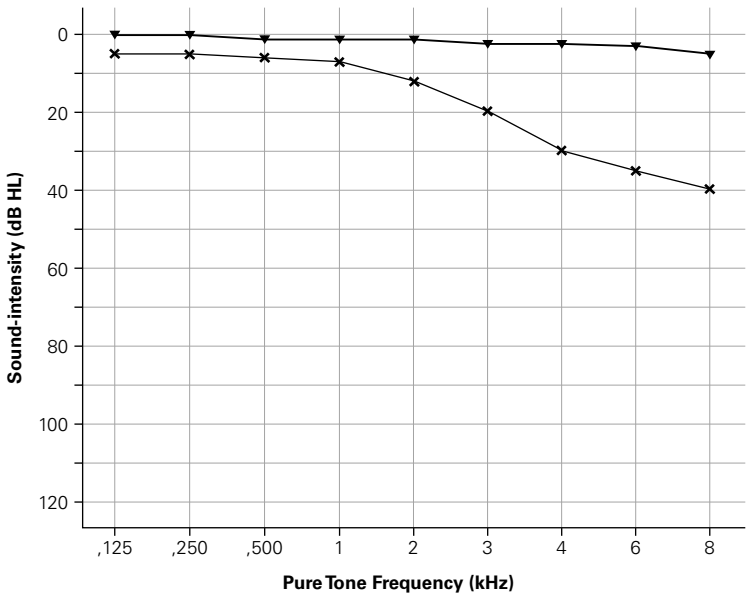
With this manuscript we aim to define a new grading system (TUNE) for ototoxicity in adults. This system focuses on the impact of treatment-related hearing loss in specific situations in a patient's daily life. We aimed for the TUNE system to preferably allow for an appraisal of a patient's speech intelligibility after treatment. In addition, the criteria are able to sense early toxicity as subjective symptoms and ultra-high hearing loss are incorporated. The newly designed criteria, when fully integrated and systematically used in future research, might eventually enable an improved patient's informed consent prior to or during therapy.

Overall, incidences of ototoxicity scored by TUNE were higher compared with CTCAEv4 and AHSA up to 8 kHz. Due to the role of subjective symptoms and the ultra-high frequencies, TUNE grade 1a and 2a were responsible for an important increase in sensitivity, mainly demonstrated in the relatively less intensive treatment schemes. The overall incidences of TUNE and ASHA up to 12.5 kHz were comparable. However, ASHA lacks a step-by-step grading to score the severity of the hearing loss.

In addition, the incidence of TUNE grade 3 was relatively small compared to CTCAEv4 grade 3. This can be explained by the strict requirements of TUNE grade 3: hearing sensitivity ≥35 dB HL at 1-2-4 kHz *de novo*, a demarcation of treatment-induced significant loss of speech intelligibility. As ototoxicity starts at ultra-high frequencies, it takes, in general, substantial treatment intensity before speech frequencies are affected. The exact moment of crossing the 35 dB HL at 1-2-4 kHz is not dependent only on treatment intensity, but also on baseline hearing capability. Younger patients with more favorable pre-treatment hearing may endure relatively large hearing loss in dB, but finish

with better hearing level after treatment compared to older patients with pretreatment presbycusis. Older patients who may not suffer large hearing deteriorations in terms of dB are characterized by a higher chance of a higher post-treatment hearing threshold.[6, 30] The 30 year old man in figure 1 may suffer a deterioration of 20 dB at 1-2-4 kHz, and still enjoy an adequate speech intelligibility, but the 60 year old man would experience 50% loss of his speech intelligibility at conversation levels 1-2-4 kHz. More than half (54%) of the patients with a treatment-induced hearing threshold of ≥35 dB at PTA 1-2-4 kHz, scored grade 0, 1 or 2 according to CTCAEv4. These scores are, in our opinion, an underestimation of the severity of this treatment-induced hearing loss. This means that although the CTCAEv4 clearly denotes scales of increasing ototoxicity, the clinical implications of the individual grading criteria remain hard to interpret.

Figure 1 | Pure-tone audiometry of a 30-year old man (▼) and a 60-year old man (×) according to International Organization for Standardization (ISO), standard number 7029:2000[32].



As described earlier, ultra-high frequency loss might be a signal for upcoming speech frequencies loss and therefore may allow for detection of ototoxicity in an early stage. Since in our high-dose CRT population, audiometry was obtained after each cisplatin infusion, we were able to analyze the progression of any hearing loss. After the first cisplatin infusion, 54 ears graded 1a according to TUNE, of which 79% progressed to grade 1b or worse after therapy. Second, after the first cisplatin infusion, 25 ears graded 2a, of which 64% scored worse by the end of therapy. So, patients graded 1a or 2a (i.e., ultra-high frequencies loss) after the first cisplatin infusion tend to show a progressive loss at the end of therapy (i.e., speech frequencies loss). Therefore, in patients for whom hearing is crucial in daily practice (e.g., school teachers, musicians, the partially sighted) applying the TUNE criteria during therapy may indeed be useful to detect early changes in hearing.[26]

Limitations of the criteria

There are also limitations to the TUNE criteria. First, the new criteria are more time-consuming since the system comprises both subjective and objective hearing loss including ultra-high frequencies. Second, our criteria do not take into account the WRS, whereas criteria designed by Gurgel and coworkers did.[22] Although the grading system of Gurgel and colleagues seems more accurate, the large variability in how WRS data is acquired and the fact that for many countries WRS is not even included in standard audiometry practice, hamper the uniform implementation of the system. In addition, performing both pure tone audiometry and WRS may be a big effort for a (sometimes very ill) patient. So, in case of a missing WRS, our grading system is a reliable alternative to the system of Gurgel. Moreover it is an easier method to obtain in clinical practice with ill patients when compared to the Gurgel criteria. Third, due to the retrospective design of present study, we were not able to estimate the false positive rates (FP) of the measured threshold shifts in all of our patients. Only in the high-dose CRT group were more than 2 audiograms obtained. In this subgroup, the FP rates in TUNE and CTCAEv4 are comparable. As FPs may also be the result of audiometric test-retest variability, the use of PTAs instead of singly frequencies will reduce the effect of test-retest variability in our grading system.

Future directions

We assume this new ototoxicity grading system is still in a premature phase and needs

validation in an independent group of patients. Before routine use in a clinical setting, external validation in a prospective study is necessary. A prospective trial including patients with head and neck cancer treated with CRT, in which audiometry is obtained before, during, and after the treatment, should be established. Audiometric data should then be scored according to TUNE, ASHA and CTCAE. To test whether the grading by TUNE is clinically relevant, questionnaires should be filled in by the patients, preferably with use of the Hearing Handicap Inventory (HHI) questionnaire.[31] The correlation between the questionnaire and the TUNE grading should be examined.

CONCLUSION

The new proposed grading system facilitates a nuanced grading system, based on pure tone audiometry only. TUNE distinguishes between hearing loss at speech intelligibility and hearing loss at higher frequencies. So, in the future TUNE may potentially be used to assess the impact of hearing loss in specific situations in daily life and for the quality of sound. Furthermore, its criteria discriminate well between mild, moderate, and severe degrees of ototoxicity, resulting in an increased sensitivity for ototoxicity compared to the existing grading systems. In our opinion, the TUNE grading system is feasible for both clinical and research purposes.

AKNOWLEGMENTS

This work was supported by an unrestricted grant from the Riki Stichting.

REFERENCES

1. Obasikene G, Adobamen P, Okundia P, Ogusi FO. Prevalence of ototoxicity in University of Benin Teaching Hospital, Benin city: a 5-year review. *Niger J Clin Pract.* Oct-Dec 2012;15(4):453-457.

2. Schacht J, Talaska AE, Rybak LP. Cisplatin and aminoglycoside antibiotics: hearing loss and its prevention. *Anat Rec (Hoboken).* Nov 2012;295(11):1837-1850.

3. Ding D, Allman BL, Salvi R. Review: ototoxic characteristics of platinum antitumor drugs. *Anat Rec (Hoboken).* Nov 2012;295(11):1851-1867.

4. Vyskocil A, Truchon G, Leroux T, et al. A weight of evidence approach for the assessment of the ototoxic potential of industrial chemicals. *Toxicol Ind Health.* Oct 2012;28(9):796-819.

5. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys.* Mar 1 2010;76(3 Suppl):S50-57.

6. Zuur CL, Simis YJ, Lansdaal PE, et al. Audiometric patterns in ototoxicity of intra-arterial Cisplatin chemoradiation in patients with locally advanced head and neck cancer. *Audiol Neurootol.* 2006;11(5):318-330.

7. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol.* Aug 20 2007;25(24):3759-3765.

8. Zuur CL, Simis YJ, Lamers EA, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* Jun 1 2009;74(2):490-496.

9. Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol.* Oct 2008;89(1):38-43.

10. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. *Cancer Treat Rev.* Oct 2003;29(5):417-430.

11. Low WK, Toh ST, Wee J, Fook-Chong SM, Wang DY. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. *J Clin Oncol.* Apr 20 2006;24(12):1904-1909.

12. Petsuksiri J, Sermsree A, Thephamongkhol K, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. *Radiat Oncol.* 2011;6:19.

13. Prestes R, Daniela G. Impact of tinnitus on quality of life, loudness and pitch match, and high-frequency audiometry. *Int Tinnitus J.* 2009;15(2):134-138.

14. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

15. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy. *ASHA* 36:11-19, 1994.

16. Brock PR, Knight KR, Freyer DR, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new international society of pediatric oncology Boston ototoxicity scale. *J Clin Oncol.* Jul 1 2012;30(19):2408-2417.

17. Chang KW, Chinosornvatana N. Practical grading system for evaluating cisplatin ototoxicity in children. *J Clin Oncol.* Apr 1 2010;28(10):1788-1795.

18. Gurney JG, Bass JK. New international society of pediatric oncology Boston ototoxicity grading scale for pediatric oncology: still room for improvement. *J Clin Oncol.* Jul 1 2012;30(19):2303-2306.

19. Neuwelt EA, Brock P. Critical need for international consensus on ototoxicity assessment criteria. *J Clin Oncol.* Apr 1 2010;28(10):1630-1632.

20. Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: a practical grading system. *Med Pediatr Oncol.* 1991;19(4):295-300.

21. Chang KW. Clinically accurate assessment and grading of ototoxicity. *Laryngoscope.* Dec 2011;121(12):2649-2657.

22. Gurgel RK, Jackler RK, Dobie RA, Popelka GR. A new standardized format for reporting hearing outcome in clinical trials. *Otolaryngol Head Neck Surg*. Nov 2012;147(5):803-807.

23. Pavlovic CV. Use of the articulation index for assessing residual auditory function in listeners with sensorineural hearing impairment. *J Acoust Soc Am*. Apr 1984;75(4):1253-1258.

24. Mueller HG, Killion MC. An Easy Method For Calculating the Articulation Index. *Hearing Journal*. 1990;43(9):1-4.

25. Fausti SA, Frey RH, Erickson DA, Rappaport BZ, Cleary EJ, Brummett RE. A system for evaluating auditory function from 8000–20 000 Hz. *J Acoust Soc Am*. Dec 1979;66(6):1713-1718.

26. Fausti SA, Schechter MA, Rappaport BZ, Frey RH, Mass RE. Early detection of cisplatin ototoxicity. Selected case reports. *Cancer*. Jan 15 1984;53(2):224-231.

27. Gurgel RK, Popelka GR, Oghalai JS, Blevins NH, Chang KW, Jackler RK. Is it valid to calculate the 3-kilohertz threshold by averaging 2 and 4 kilohertz? *Otolaryngol Head Neck Surg*. Jul 2012;147(1):102-104.

28. Dell'Aringa AH, Isaac ML, Arruda GV, et al. Audiological findings in patients treated with radio- and concomitant chemotherapy for head and neck tumors. *Radiat Oncol*. 2009;4:53.

29. Dobie RA. Audiometric threshold shift definitions: simulations and suggestions. *Ear Hear*. Feb 2005;26(1):62-77.

30. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys*. Aug 1 2007;68(5):1320-1325.

31. Newman CW, Weinstein BE, Jacobson GP, Hug GA. The Hearing Handicap Inventory for adults: psychometric adequacy and audiometric correlates. *Ear Hear* 1990;11:430-433

32. International Organization for Standardization 2000, Reference number ISO 7029:2000 (E). International Standard. Acoustics - Statistical distribution of hearing thresholds as a function of age.


04

CHAPTER 04

Prediction of hearing loss due to cisplatin chemoradiotherapy

E.A.R. Theunissen | C.L. Zuur | K. Jóźwiak | M. Lopez-Yurda | M. Hauptmann
C.R.N. Rasch | S. van der Baan | J.P. de Boer | W.A. Dreschler | A.J.M. Balm

Revisions submitted

ABSTRACT

Objective

To predict treatment-induced hearing loss, and therefore to improve counseling of patients with head and neck cancer suffering chemoradiotherapy-induced hearing loss. We hypothesized that several patient and treatment characteristics can be used to predict the absolute post-treatment hearing level.

Methods

Patients with head and neck cancer treated with concomitant chemoradiotherapy as primary treatment modality during 1997 and 2011 were included. Outcome of the model was the post-treatment bone conduction hearing threshold at Pure Tone Average 1-2-4 kHz. Predictors were baseline hearing levels, radiation dose to the cochlea, and cisplatin dose. A multilevel mixed-effects linear regression model for predicting whether or not post-treatment hearing was ≥35 dB was established and cross-validated sensitivity and specificity were obtained.

Results

Based on data from 81 patients, i.e., 162 ears, the area under the receiver operating characteristic curve was 0.68, with a sensitivity of 29% (95% CI: 13%-51%) at a specificity of 97% (95% CI: 88%-100%), resulting in a positive predictive value of 0.78.

Conclusion

This study demonstrates that patient- and treatment characteristics can be used to predict post-treatment hearing level. This is the first step in evidence based individual counseling for treatment-induced hearing loss.

INTRODUCTION

Concomitant chemoradiotherapy (CCRT), using cisplatin as chemotherapeutic agent, is currently the preferred organ-sparing therapy for patients with advanced head and neck carcinoma.[1,2] However, both radiotherapy (RT) in the head and neck region and cisplatin exert ototoxic effects. These effects consist of hearing loss and/or tinnitus and may have a major influence on quality of life.[3,4] In the acute phase, RT will exert conductive hearing loss as a result of inflammation or edema of the external or middle ear. These effects are mainly temporary. The permanent effect of RT on hearing is sensorineural hearing loss (SNHL) due to radiation damage at the inner ear.[5] However, nowadays, Intensity Modulated Radiation Therapy (IMRT) may spare the cochlea from high radiation dose, thereby reducing the incidence of RT-induced sensorineural hearing loss.[6] Apart from RT, cisplatin is also known to cause permanent SNHL starting immediately after the first cisplatin infusion. This SNHL is characterized by bilateral, irreversible, and progressive high frequency loss.[7] In daily clinical practice, adding cisplatin to RT or continuing CCRT treatment is often discussed on account of the ototoxic effects, particularly in patients for whom preservation of hearing is important.[1,8]

Several factors are known to influence the severity of ototoxicity. There is agreement that SNHL risk increases with increasing radiation dose to the cochlea and an increasing cumulative cisplatin dose.[5,8] Other determinants are age and baseline hearing level.[8,9] Former research on risk factors for ototoxicity also demonstrated that patients with unfavorable baseline hearing were less likely to develop SNHL compared to patients with a favorable baseline hearing.[8,10] However, up to now, weighing all involved variables remains difficult and leads to no more than a subjective impression of expected post-treatment hearing loss. Hence, recommendations are still based on personal experience and an effective counseling is hampered. If we could use a statistical prediction of post-treatment hearing level, this would allow evidence based counseling to the patient. Therefore, in this study, we developed a statistical model to predict treatment-induced hearing loss after cisplatin infusions based on the aforementioned factors.

MATERIALS AND METHODS

Patient selection

In a retrospective cohort study, we selected patients who were treated with high-dose CCRT (100 mg/m^2, 3 courses on days 1, 22 and 43 during 7 weeks of RT to 70 Gray in 35 fractions on tumor bearing areas) for advanced staged head and neck squamous cell carcinoma between 1997 and 2011. Only patients treated with high-dose CCRT as a primary treatment were selected. Medical charts and radiotherapy treatment plans were reviewed for cumulative cisplatin dose and the radiation dose to the cochlea.

Audiometry

Pure tone audiometry was conducted 1-7 days before, 15-20 days after the first cisplatin infusion and median 14 weeks (3-31) after treatment. Air conduction (AC) thresholds were measured at 0.125, 0.250, 0.5, 1, 2, 3, 4, 6, 8, 10, 12.5 kHz and bone conduction (BC) thresholds were measured at 0.5, 1, 2, 4 kHz. When necessary, BC thresholds were masked to avoid cross-hearing. We presented audiological data in decibel (dB) Hearing Level (HL) at frequencies 0.125 to 8 kHz and in dB Sound Pressure Level (SPL) at frequencies 8 to 12.5 kHz.

Since BC thresholds are less vulnerable to temporary changes in hearing (e.g. temporary middle ear pressure changes or local infections) compared to AC thresholds, we incorporated BC thresholds when available, i.e. for the frequencies up to 4 kHz. Therefore, Pure Tone Averages (PTAs) were calculated at 0.5-1-2 kHz (BC), 1-2-4 kHz (BC), and 8-10-12.5 kHz (AC) as these PTAs are essential for speech perception in quiet, speech perception in noise, and the perception of (ultra)-high frequencies as in nature, respectively.

Statistical analyses

We modeled BC hearing level at PTA 1-2-4 kHz, based on multilevel mixed-effects linear regression. Since CCRT-induced hearing loss may not be the same in both ears because the ear ipsilateral to the tumor receives a higher dose of radiation compared to the contralateral ear, and hearing may change during the treatment, the outcome is expressed per ear on two occasions. Therefore, each patient contributed 4 outcome measurements, i.e., left and right ear after the first cisplatin infusion plus left and right

ear after the end of treatment. The model can be used to predict hearing level after the first dose of chemotherapy but we focused on the prediction of post-treatment hearing level since it is more clinically relevant. Candidate explanatory variables were gender, age, ear (left or right), tumor side (ipsilateral or contralateral), cisplatin dose, radiation dose to the cochlea, subjective hearing loss and/or tinnitus prior to treatment, as well as thresholds at PTAs for low, high, and ultra-high frequencies prior to treatment. These variables were considered as fixed effects in the model and only those being significant determinants of the outcome were retained in the model.

Missing audiometry data at baseline (2.5% of the ears for PTA 0.5-1-2 kHz BC, 3.5% for PTA 1-2-4 kHz BC, and 2% for PTA 8-10-12.5 kHz AC), but particularly after the first infusion (37% of the ears for PTA 0.5-1-2 kHz BC, 43% for PTA 1-2-4 kHz BC, and 22.5% for PTA 8-10-12.5 kHz AC) were imputed. Multivariate imputation was based on chained equations (MICE)[11,12] with 100 imputations, assuming missing at random, and results were combined using the methods of Barnard and Rubin.[13,14] Imputations were functions of the outcome, explanatory variables and auxiliary variables (i.e., low and high frequency AC hearing measures) as well as an indicator variable for grouped measurements. Including this indicator as a fixed effect we allowed the functions of the imputed variables to vary by patient. Variables were transformed for normality when necessary, and back-transformed for use in the model. Patients with missing frequencies at audiometry post-treatment were excluded, so no imputations of the outcome were performed.

The evaluation of the performance of the prediction model was on the patient level, i.e., a prediction was considered wrong if the observed outcome for at least one ear of the two ears of each patient was different from the predicted outcome. We constructed the receiver operating characteristics (ROC) curve by plotting 10-fold cross-validated sensitivity versus one minus specificity when using all possible thresholds of predicted hearing level in order to predict observed BC hearing level ≥35 dB HL at PTA 1-2-4 kHz which is the Dutch threshold for a hearing aid (HA) qualification.[15] The area under the ROC curve (AUC) was calculated, which represents the probability that among two patients with good and poor observed hearing, the one with the higher predicted probability of poor post-treatment hearing is actually the one with observed post-treatment hearing level ≥35 dB. Furthermore, we calculated the intraclass correlation coefficient (ICC), which describes how strongly measurements for the same subjects resemble

each other. Patients with pre-treatment hearing level of ≥35 dB were excluded from performance evaluation since they were not at risk of treatment-induced deterioration of hearing from <35 dB to ≥35 dB. All analyses were performed using STATA version 13.

RESULTS

Patient selection

From 1997 to 2011, 156 patients received high-dose CCRT as a primary treatment of head and neck cancer. We excluded 15 patients because the exact radiation dose to the cochlea was missing, as well as 41 patients because they had either no data on PTA 1-2-4 kHz BC post-treatment (n=32) or had only undergone a long-term audiometry (n=9). Hence, 100 patients (64%) and 200 ears were included. The total cumulative cisplatin dose among patients ranged from 315-600 mg (median 546 mg). The median radiation dose to the cochlea was 13.6 Gy (range 1.1-70.9) as the patients were, in general, treated with IMRT. Nineteen patients had a hearing level of ≥35 dB on at least one ear before the treatment and were not included in the model validation.

Statistical model

The model predicting hearing capability at PTA 1-2-4 kHz post-treatment, is shown in figure 1. Gender, age, ear, tumor side and subjective complaints were weak determinants of hearing level and were excluded from the model.

Predicted versus observed post-treatment hearing levels for each participating ear (each dot represents one ear) are shown in figure 2. Demarcation lines at 35 dB hearing level are reflecting the qualification criteria for a HA in the Netherlands.[15] When observed hearing level is modeled using predicted hearing level as the explanatory variable in the multilevel mixed-effects linear regression, the ICC is 0.71.

Figure 1 | Prediction model: Formula for the prediction of post-treatment hearing level per ear at Pure Tone Average 1-2-4 kHz BC.

Post-treatment PTA 1-2-4 kHzBC =

-5.56 + 0.02*C + 0.21*RT + 0.05*PTAL + 0.68*PTAH + 0.10*PTAU

Legend:

C = Cisplatin dose (mg)

RT = Radiation dose to the cochlea (Gray)

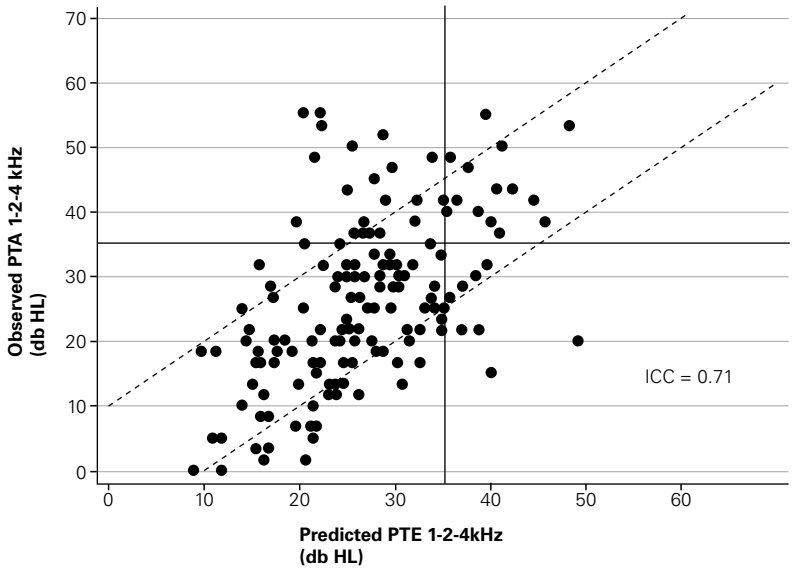
PTAL = PTA low prior to treatment, 0.5-1-2 kHz BC in dB HL

PTAH = PTA high prior to treatment, 1-2-4 kHz BC in dB HL

PTAU = PTA ultra-high prior to treatment, 8-10-12.5 kHz AC in dB SPL

Abbreviations: PTA = Pure Tone Average; BC = Bone Conduction; AC = Air Conduction; dB = deciBel; HL = Hearing Level; SPL = Sound Pressure Level

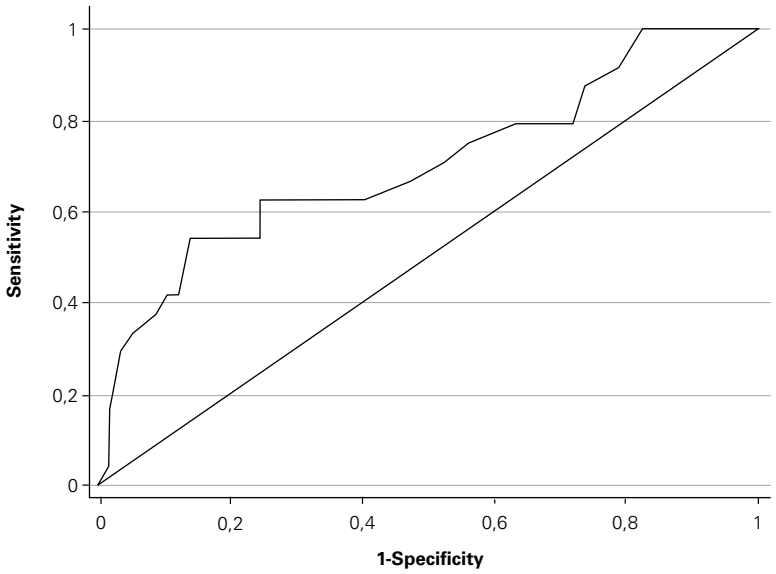
Figure 2 | Scatterplot: The observed (y-axis) against 10-fold cross-validated predicted (x-axis) pure tone average 1-2-4 kHz BC per ear in dB hearing level based on 162 ears. Lines at 35 dB are reflecting the criteria for a hearing device. Area between the dotted lines resembles a 10 dB margin.



Abbreviation: ICC = Intraclass correlation coefficient

Figure 3 shows the ROC curve with an area under the curve of 0.68. The sensitivity and specificity to predict observed hearing level ≥35 dB were 29% (95% CI: 13%-51%) and 97% (95% CI: 88%-100%), respectively, if a cutoff point of 40 dB was used as a threshold of predicted hearing level. As a result, the model achieved a false negative rate (1-sensitivity) of 71% and a false positive rate (1-specificity) of 3%. The positive predictive value was 78% and the negative predictive value was 76%, leading to a false positive prediction (1-PPV) of 22% and to a false negative prediction (1-NPV) of 24%. Results changed when alternative cutoff points were chosen. This is illustrated in the ROC curve (figure 3) and in table 1.

Figure 3 | ROC curve: 10-fold cross-validated receiver operating characteristic (ROC) curve for PTA 1-2-4 kHz BC.



In practical terms, sensitivity is the probability that a patient who will eventually need a HA is predicted as such, i.e., a correct prediction for a HA. In reverse, specificity indicates a true negative prediction, i.e., correctly predicted to not qualify for a HA. The PPV is the probability that a person with a positive prediction will need a hearing aid,

whereas the NPV is the probability that a person with a negative prediction will not need a hearing aid.

We considered a high specificity (and therefore a low false positive rate, or equivalently high PPV) as most relevant, since a false positive prediction is the most undesirable clinical error. In case of a false positive prediction (i.e., a false prediction of ≥35 dB HL at speech frequencies due to treatment), treatment might be unnecessarily adjusted.

Table 1 | 10-fold cross validated performance of prediction model. Different cutoff used to classify patients as ≥35 dB for at least one ear, based on 81 patients of which 24 became eligible for a hearing aid after treatment while 57 patients did not.

Cut off point	True positive N (% = sensitivity)	True negative N (% = specificity)	False negative N (% = 1-sensitivity)	False positive N (% = 1-specificity)	PPV	NPV	False positive prediction = 1-PPV	False negative prediction = 1-NPV
35dB	13 (54%)	49 (86%)	11 (46%)	8 (14%)	62%	82%	38%	18%
36dB	10 (42%)	50 (88%)	14 (58%)	7 (12%)	59%	78%	41%	22%
37dB	10 (42%)	51 (90%)	14 (58%)	6 (10%)	63%	78%	37%	22%
38dB	9 (38%)	52 (91%)	15 (62%)	5 (9%)	64%	78%	36%	22%
39dB	8 (33%)	54 (95%)	16 (67%)	3 (5%)	73%	77%	27%	23%
40dB	7 (29%)	55 (97%)	17 (71%)	2 (3%)	78%	76%	22%	24%

Abbreviations: PPV = Positive Predictive Value; NPV = Negative Predictive Value

DISCUSSION

To improve a patient's counseling we established a prediction model for hearing capacity after cisplatin CCRT in patients with head and neck cancer. The model requires baseline hearing thresholds, cisplatin dose, and radiotherapy dose to the cochlea. It predicts hearing level above and below 35 dB at 97% specificity and 29% sensitivity. In the past, patients with severe hearing loss at baseline were often withdrawn from a cisplatin-based treatment as it was assumed that in those

patients ototoxicity would have too much negative impact on their hearing. However, the study of Zuur et al[8] caused a paradigm shift, demonstrating that patients with a severe baseline hearing level will lose less in terms of dB compared to patients with excellent baseline hearing level. Still, the exact hearing loss per patient remains unknown, making the development of a prediction model desirable.

Our results of using hearing thresholds as a predictive tool are in agreement with other recent publications.[16,17] Johnson et al. for example, developed a model based on 31 patients receiving chemotherapy for cancer at several sites (head and neck, and urologic tumor sites).[16] In their study, the coefficients from a quadratic fit of the baseline audiogram AC were fed into a logistic regression of hearing loss as defined by the American Speech-Language-Hearing Association (ASHA) criteria. No further patient or treatment characteristics were incorporated. Of the 31 patients, 15 (48%) developed hearing loss according to the ASHA, while 16 patients (52%) did not. This resulted in a sensitivity and specificity of both 80% and an area under the ROC curve of 0.84. The validity of this model improved when only subjects who received concurrent CRT for head and neck cancer were included (AUC 0.91). However, when we applied their approach to our data, i.e. re-estimating the quadratic model for each patient and using the coefficients in a logistic regression model, results were found to be poorer. Of our 156 patients, 140 had sufficient data to determine ASHA hearing loss. Of these, 127 patients (91%) developed hearing loss according to ASHA, while 13 patients (9%) did not. The leave-one-out cross-validated AUC was 0.75, with a specificity of 69% and the sensitivity ranging between 42% and 86%. In contrast to the model of Johnson et al., including patients with different tumor sites from all over the body, we only included patients with head and neck cancer. This difference in patient cohorts might also explain why in our cohort many more patients suffered from ASHA-defined hearing loss compared to patients in the Johnson study (91% versus 48%): CCRT-induced hearing loss in head and neck cancer results in more hearing loss than cisplatin-induced hearing loss alone due to the combined effect of cisplatin and radiotherapy in the head and neck area.[1,18,19]

Hypothetical clinical implication

We considered a high specificity as clinically important because it results in a high positive predictive value. Our model showed an AUC of 0.68 with a specificity of 97% at a sensitivity of 29%. Hence, in 97% of the patients who turned out to be not eligible

for a hearing aid after treatment, the prediction was correct (i.e. true negative). Thus, out of 24 patients who needed a HA after treatment the model classified 7 patients (29%) as such and out of 57 patients who did not need a HA the model classified 55 patients (97%) as such. For clinical use, the positive and negative predictive value illustrates the accuracy of the prediction: in case of a positive prediction (i.e. qualifying for a hearing aid due to treatment), this prediction was correct in 78%. Hence, in 22% of the patients with a positive prediction, this prediction was wrong: the patient did not qualify for a hearing aid. In reverse, in case of a negative prediction (i.e. not qualifying for a hearing aid due to treatment), this prediction was correct in 76%. Hence, in 24% of the patients with a negative prediction, this prediction was wrong: the patient did qualify for a hearing aid. Both errors have clinical consequences. 1) In case of a false positive prediction a treatment adjustment to a less ototoxic treatment might have been considered when in fact this was not necessary. Currently, no large randomized trials comparing efficiency and toxicity of other chemotherapeutic agents (such as carboplatin or cetuximab) versus cisplatin are published. Hence, a treatment adjustment might be considered without exact knowledge of treatment adjustment on tumor control. 2) In case of a false negative prediction a wrong reassurance not needing a hearing aid is given to the patient. For patients highly dependent on preservation of hearing (e.g. the vision impaired, musicians) a false negative prediction would have more consequences compared to a patient in whom hearing loss has less impact in daily life. Moreover, the risk of ototoxicity may outweigh the risk of adjusting treatment without the exact knowledge of the effect on tumor control. Hence, for those patients a model with a high sensitivity would be more appropriate than a model with a high specificity. Table 1 shows sensitivity and specificity for different cutoff points. In this report results are based on a cutoff point of 40 dB. However, one could use different cutoffs for more specific or more sensitive predictions, as needed.

The low sensitivity (29%) might indicate that there are unknown variables currently missing in the model, e.g., individual sensitivity to ototoxicity. There are studies suggesting that variants in thiopurine S-methyl transferase (TPMT), cathechol O-methyl transferase (COMT) or Low density lipoprotein (LRP2, Megalin) are important risk factors in the development of ototoxicity.[23,24] Individual sensitivity due to these genetic variants might be incorporated by adding the hearing thresholds after the first infusion as explanatory variables. In this approach, the sensitivity of our model would increase to 46% at the specificity of 95%. However, such a model could not be used for counseling

prior to therapy but only after the first cisplatin dose. Pussegode et al.[24] showed that a model including clinical variables (age, treatment, germ-cell tumor, and cranial irradiation) and genetic variables (variants in TPMT, ABCC3, and COMT) significantly improved the prediction of treatment-induced hearing loss development in children when compared with a prediction model using clinical variables only (AUC 0.786 vs. 0.708, p=0.00048). However, studies in adults on these genetic variables are currently lacking, but future integration might improve the sensitivity.

Limitations of the model

Due to the retrospective design of this study, high percentages of missing values were seen. This might be explained by the fact that audiometric testing is time consuming, especially when ultra-high frequencies and bone conduction thresholds are included. Patients enduring intensive treatment schemes may sometimes be too tired or too ill to perform the whole audiometric procedure. Assuming that data were randomly missing, we imputed these using a MICE imputation mechanism.[25] Furthermore, the prediction model requires 5 inputs (figure 1) including a baseline pure tone audiogram, cisplatin dose and the radiation dose to the inner ear. Fortunately, PTAs 0.5-1-2 and 1-2-4 kHz are automatically calculated by the audiology system. However, 8-10-12.5 kHz calculations are not yet automated and radiation dose to the cochlea may not be available by default. However, we do feel that in patients suffering hearing loss due to treatment, it is still worth to record these variables.

Future directions

Before implementation in a clinical setting, external validation of the present model is required. As a first step we used the '10-fold cross-validation', reducing the effect of over-optimistic assessment of a model built and validated on the same data. In the future, an internal patient cohort should be used to further test our statistical model. Thereafter, external validation should be attempted. Furthermore, the current model is based on patients treated with chemoradiation as their primary treatment for head and neck cancer. In clinical practice, the problem of hearing loss as an adverse event is also seen in patients treated with cisplatin for lung, bladder, gynecological cancer, or applied in a postoperative setting. So, to use the prediction model in other patient cohorts, further external validation in other patient cohorts is needed.

CONCLUSION

Overall, our prediction model is a step towards improving individual counseling of patients with head and neck cancer at risk for CCRT-related hearing loss. However, future research concerning more variables as risk factors for hearing loss is needed. Furthermore, before implementation in a clinical setting, external validation of the present model is required.

AKNOWLEGMENTS

This work was supported by an unrestricted grant from the Riki Stichting.

REFERENCES

1. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. Jul 2009;92(1):4-14.

2. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. Mar 18 2000;355(9208):949-955.

3. Hetu R. The stigma attached to hearing impairment. *Scand Audiol Suppl*. 1996;43:12-24.

4. Prestes R, Daniela G. Impact of tinnitus on quality of life, loudness and pitch match, and high-frequency audiometry. *Int Tinnitus J*. 2009;15(2):134-138.

5. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head Neck*. Nov 2013;35(11):1662-1668.

6. Zuur CL, Simis YJ, Lamers EA, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys*. Jun 1 2009;74(2):490-496.

7. Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. *Br J Cancer*. Jun 1990;61(6):927-931.

8. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys*. Aug 1 2007;68(5):1320-1325.

9. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiother Oncol*. Oct 2002;65(1):9-16.

10. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol*. Aug 20 2007;25(24):3759-3765.

11. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. Mar 30 1999;18(6):681-694.

12. Raghunathan TE, Lepkowski JM, Hoenwijk v. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Survey Methodology*. 2001;27(1):85-95.

13. Barnard J, Rubin DB. Small-sample degrees of freedom with multiple imputations. *Biometrika* 1999;86:948-955.

14. Rubin DB: Multiple imputation for nonresponse in survey. Inc., Hoboken, NJ, USA, John Wiley& Sons, 1987, pp 75-79

15. Dutch Health Insurance; article 2.10.a: Hulpmiddelen ter compensatie van beperkingen in het luisteren of bedienen van communicatieappartuur.

16. Johnson A, Tarima S, Wong S, Friedland DR, Runge CL. Statistical model for prediction of hearing loss in patients receiving cisplatin chemotherapy. *JAMA Otolaryngol Head Neck Surg*. Mar 2013;139(3):256-264.

17. Dille MF, Wilmington D, McMillan GP, Helt W, Fausti SA, Konrad-Martin D. Development and validation of a cisplatin dose-ototoxicity model. *J Am Acad Audiol*. Jul-Aug 2012;23(7):510-521.

18. Low WK, Kong SW, Tan MG. Ototoxicity from combined Cisplatin and radiation treatment: an in vitro study. *Int J Otolaryngol*. 2010;2010:523976.

19. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. Jan 1 2003;21(1):92-98.

20. Waissbluth S, Daniel SJ. Cisplatin-induced ototoxicity: transporters playing a role in cisplatin toxicity. *Hear Res*. May 2013;299:37-45.

21. Pussegoda K, Ross CJ, Visscher H, et al. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clin Pharmacol Ther*. Apr 10 2013.

22. Steyerberg EW: Clinical Prediction Models, University Medical Center Rotterdam, The Netherlands, *Springer*, 2009, pp. 135


05

CHAPTER 05

Long-term hearing loss after chemoradiation in patients with head and neck cancer

E.A.R. Theunissen | C.L. Zuur | S.C.J. Bosma | M. Lopez-Yurda | M. Hauptmann
S. van der Baan | J.P. de Boer | L. van der Molen | C.R.N. Rasch | W.A. Dreschler
A.J.M. Balm

The Laryngoscope, 2014; 124(12): 2720-5

ABSTRACT

Objective

The purpose of this study was to determine whether concomitant chemoradiation (CCRT)-induced hearing loss is progressive over time or not.

Methods

Between 1999 and 2004, 158 patients with head and neck cancer were treated with intravenous (IV) CCRT (n=80) or intra-arterial (IA) CCRT (n=78). Audiometry was performed before, short-term, and long-term post-treatment. Differences in hearing were assessed with a multivariable linear regression analysis, incorporating the effect of ageing.

Results

Long-term audiometry (median 4.5 years) was available in 64 patients (41%). At short-term follow-up, a deterioration of 21.6 decibel was seen compared to baseline at pure-tone-average (PTA) 8-10-12.5 kHz. At long-term follow-up, this deterioration further increased with 5 dB (p=0.005). Only in CCRT-IV patients, a significant progressive treatment-induced hearing loss was seen, at PTA 8-10-12.5 kHz (p=0.005), PTA 1-2-4 kHz air conduction (p=0.014) and PTA 0.5-1-2 kHz bone conduction (p=0.045).

Conclusion

CCRT-induced hearing impairment was progressive over time, especially in higher frequencies and only in CCRT-IV patients, with a modest deterioration of 5 decibel 4.5 years post-treatment, at PTA 8-10-12.5 kHz.

INTRODUCTION

In locally advanced head and neck cancer, concomitant chemoradiation (CCRT) using cisplatin as chemotherapeutic agent, is often used as a primary treatment. A meta-analysis reported an absolute survival benefit of 6.5% after the addition of concomitant chemotherapy to radiotherapy (RT) in patients with head and neck cancer.[1-2] However, both RT and cisplatin are known for their ototoxic effects, leading to hearing loss and/or tinnitus.[3-4]

There is an overall agreement that a higher radiation dose to the cochlea and a higher total cisplatin dose are associated with increased hearing loss after therapy.[5-9] Moreover, hearing loss seems progressive during follow-up, mainly ascribed to treatment.[6, 10-13] However, it is difficult to disentangle age-related hearing loss (presbycusis) from treatment-related hearing loss, and current evidence in the literature is very limited. Both conditions may also share a common apoptotic pathway.[14] In this study we aimed to define the influence of ageing and treatment in the development of progressive hearing loss during long-term follow-up after chemoradiation.

MATERIALS AND METHODS

Patient selection

Between 1999 and 2004, 158 patients with locally advanced head and neck squamous cell carcinoma were treated with concomitant CRT. Patients were included in a randomized controlled trial and were treated either with intravenously administered cisplatin (CCRT-IV) (n=80) or with intra-arterially administered cisplatin (CCRT-IA) (n=78).[15-16] The study was approved by the local ethics committee and an informed consent was signed by all patients before treatment. The patients treated with CCRT-IV received 100 mg/m^2 cisplatin at days 1, 22, and 43 during seven weeks of RT. The patients treated with CCRT-IA received 150 mg/m^2 cisplatin at days 1, 8, 15, and 22 during seven weeks of RT with simultaneously intravenously administered sodium thiosulfate (STS) (9 g/m^2/30 minutes, followed by 12 g/m^2/2 hours) for cisplatin neutralization. All patients received RT schedules of 70 Gray (Gy) in daily fractions of 2 Gy.

Audiometry

Pure tone audiometry was performed in a soundproof testing room using the Decos system (Audiology Workstation) at the Netherlands Cancer Institute, Amsterdam, The Netherlands. Both ears were tested. Audiometry was conducted in a prospective setting one week before treatment and at a median of 3.2 months (range 0.8-9.5 months) short-term (ST) post-treatment. Long-term (LT) post-treatment audiometry was performed at a median of 4.5 years (range 1.0-12.0 years) after treatment. When more than two LT treatment audiograms were available in one patient, the last was used as LT. Speech perception test, tympanometry, or otoscopic examination was not performed at LT follow-up.

Air conduction (AC) thresholds were measured at frequencies 0.125, 0.250, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12.5 kHz and bone conduction (BC) thresholds were measured at 0.5, 1, 2, and 4 kHz. Hearing thresholds were reported in decibel (dB) hearing level (HL) at frequencies 0.125 to 8 kHz and in dB sound pressure level (SPL) at frequencies 8 to 12.5 kHz. We used dB SPL values for calculating the pure-tone average (PTA) 8-10-12.5, and dB HL values for the PTA values in the conventional frequency range.

If measurements at 3 and 6 kHz were missing (56% at 3 kHz, 61% at 6 kHz), the missing data were computed by interpolation of the existing data.[17] In case of missing measurements at high frequencies (23% at 10 kHz and 30% at 12.5 kHz) or if the threshold was higher than the maximum level of the Audiology Workstation (16% at 10 kHz and 24% at 12.5 kHz), thresholds were calculated by linear extrapolation based on patients with complete data. Exclusion of these patients could lead to bias due to an underestimation of deterioration of hearing thresholds.

Mean AC thresholds were calculated at three PTAs: 0.5-1-2 kHz and 1-2-4 kHz in dB HL, and 8-10-12.5 kHz in dB SPL. Those PTAs are assumed to be relevant for speech perception in quiet areas, speech perception in noise, and for the perception of high sounds (e.g. music, nature), respectively. Mean BC thresholds were calculated at PTAs 0.5-1-2 kHz and 1-2-4 kHz in dB HL. An air bone gap (ABG) was defined as a difference of ≥10 dB between AC and BC at PTA 0.5-1-2 kHz. Audiometric data were compared to a normal population standard, namely the International Organisation for Standardization (ISO) standard 7029:2000.[18]

Grading hearing impairment

The incidence and severity of the hearing impairment was scored using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4).[19] The CTCAEv4 for hearing impairment acknowledges four grades, based on threshold shifts at contiguous test frequencies between 1 and 8 kHz.

Statistical analysis

Patient characteristics were compared with Pearson's Chi-square test in the case of categorical variables, Mann-Whitney U test for continuous variables, and Cochran-Armitage trend test for ordinal variables. Differences in hearing thresholds at baseline, ST, and LT post-treatment were assessed using Wilcoxon signed-rank test and a multivariable linear regression analysis with repeated measures. In the multivariable regression analysis we adjusted for ear, protocol, gender, age, T classification, hearing level at the earliest measurement, and the time-interval between both measurements. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 20 (IBM Corp., Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NY).

RESULTS

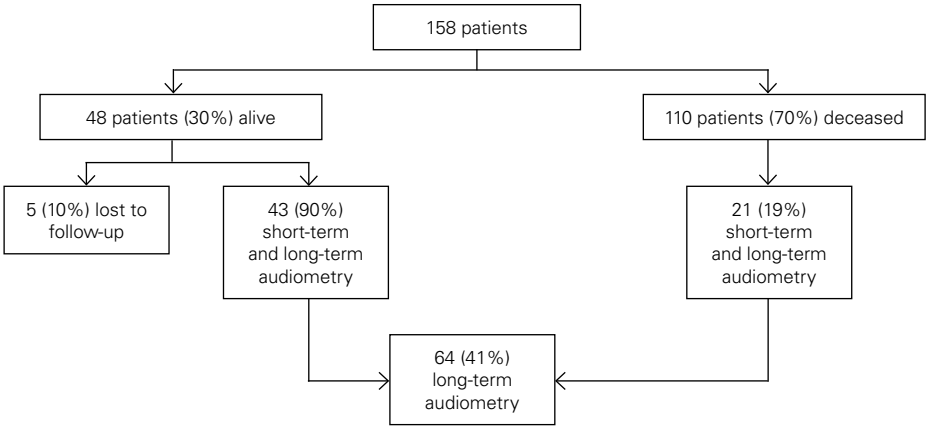
Patient characteristics

At the start of this research project, 48 of the initial 158 patients (30%) were still alive. Of those, 43 patients (90%) underwent LT audiometry (median 4.5 years; range 1-12). Five patients (10%) were lost to follow-up or declined to participate. In 21 of the 110 deceased patients, both a ST and a LT audiogram were available. Hence, 64 patients (41%) and 128 ears were included for analysis (figure 1).

Patient characteristics are shown in table 1. Patients had a median age of 54 years (range 26-70) at the start of treatment, a median age of 55 years (range 26-70) at ST analysis, and a median age of 60 years (range 33-75) at LT analysis. There were no differences in age, gender, follow-up time, or primary tumor site between the CCRT-IA and CCRT-IV group. The T and N classification significantly differed by CCRT-IA and CCRT-IV group with the latter including more T4 and N+ classifications. As expected,

the total cisplatin dose was significantly higher in the CCRT-IA patient group (p<0.001) compared to the CCRT-IV group. Baseline hearing level at all PTAs was similar in both patient groups and none of the patients had middle ear pathology at baseline otoscopy (results not shown).

Figure 1 | Flowchart of patient selection



Mean overall hearing loss

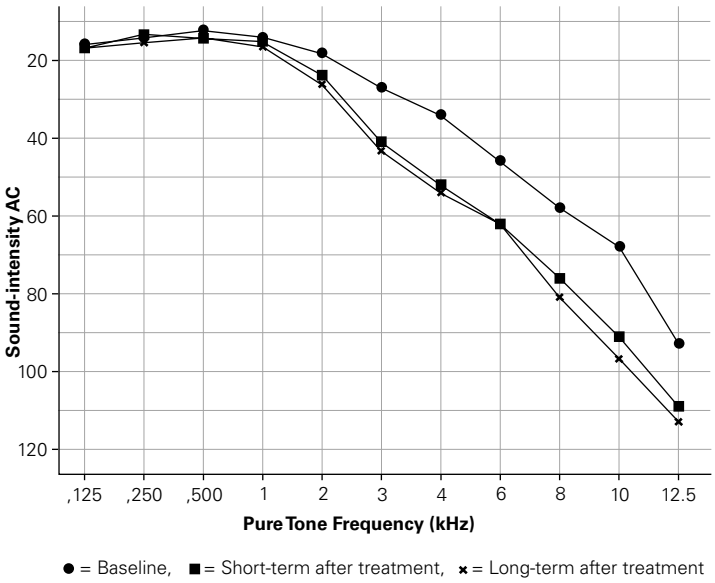
Figure 2 shows the mean AC hearing thresholds at all frequencies, before, ST after, and LT after treatment, of the 64 patients (128 ears) included in this follow-up study. There was an explicit deterioration in ST hearing for audiometric frequencies of 2 kHz and higher. At long-term, hearing levels were slightly worse when compared to the ST hearing levels.

Table 1 | Patient and treatment characteristics

	Total	**CCRT-IA**	**CCRT-IV**	**p-value**
Number of patients	64	28 (44%)	36 (56%)	
Age (years), median (range)				
Before	54 (26-70)	53	55	0.346*
Short-term	55 (26-70)	54	55	0.293*
Long-term	60 (33-75)	59	60	0.225*
Gender				
Male	48 (75%)	20 (72%)	28 (78%)	0.561†
Female	16 (25%)	8 (28%)	8 (22%)	
Audiological follow-up, median				
Short-term (months)	3.2 (0.8-9.5)	3.3 (0.8-8.9)	3.2 (1.2-9.5)	0.486*
Long-term (years)	4.5 (1.0-12.1)	4.7 (1.0-12.1)	4.3 (1.2-11.6)	0.818*
Dose to cochlea in Gray				
Mean	15.3	14.3	16.6	0.055*
Median	13.0	10.3	17.6	
Range	2.6-50.9	2.6-50.9	5.4-30.3	
Total cisplatin dose in milligram				
Mean	776	1078	542	<0.001*
Median	600	1113	551	
Range	423-1340	675-1340	423-640	
Primary tumor site				
Oropharynx	42 (66%)	16 (57%)	26 (72%)	0.215†
Hypopharynx	14 (22%)	9 (32%)	5 (14%)	
Oral cavity	8 (12%)	3 (11%)	5 (14%)	
T classification				
2	2 (3%)	2 (7%)	0	0.017‡
3	32 (50%)	17 (61%)	15 (42%)	
4	30 (47%)	9 (32%)	21 (58%)	
N classification				
0	25 (39%)	15 (53%)	10 (28%)	0.001‡
1	13 (20%)	10 (36%)	3 (8%)	
2	21 (33%)	2 (7%)	19 (53%)	
3	5 (8%)	1 (4%)	4 (11%)	

CCRT= Concomitant Chemoradiation; IA = Intra-Arterial; IV = Intravenous
* = Mann-Whitney U test, † = Pearson's Chi-Square test, ‡ = Cochran-Armitage test

Figure 2 | Mean hearing thresholds of total group (n=128 ears) at baseline, short-term and long-term follow-up



Results of the regression analysis are shown in table 2. Hearing levels significantly deteriorated at all PTAs between LT after treatment and before treatment. After adjusting for ear, gender, protocol, T classification, time-interval between measurements, age, and hearing sensitivity at pre-treatment audiometry, these deteriorations were statistically significant, implying a treatment-induced hearing loss (p<0.001). The deteriorations in hearing between long- and ST hearing were only significant for PTA 8-10-12.5 kHz (p=0.005). When we dropped 40 ears with missing ultra-high frequency measurements (i.e., 10 and 12.5 kHz), instead of extrapolating them, the deterioration for PTA 8-10-12.5 kHz was still significant (p=0.007).

Table 2 | Hearing level at Pure Tone Averages

Hearing levels of the whole patient cohort and both CCRT-IV and CCRT-IA group at baseline, short-term and long-term follow-up

PTA	0.5-1-2 kHz AC Mean (SD)	1-2-4 kHz AC Mean (SD)	8-10-12.5 kHz AC Mean (SD)	0.5-1-2 kHz BC Mean (SD)	1-2-4 kHz BC Mean (SD)
			Whole patient group		
Number of ears	128	128	127	115	118
Before treatment	14.6 (9.5)	22.0 (12.6)	70.4 (23.8)	12.0 (8.3)	18.9 (11.0)
Difference ST - BT	3.1 (7.6)	8.4 (10.3)	21.6 (18.7)	1.8 (5.7)	7.0 (8.3)
Difference LT - BT	3.6 (7.6)	10.1 (10.0)	26.2 (21.4)	3.1 (7.9)	7.0 (8.3)
p-value LT vs. BT*	<0.0001	<0.0001	<0.0001	0.0007	<0.0001
p-value LT vs. ST*	0.545	0.172	0.005	0.076	0.323
			Intra-arterial cisplatin CCRT group		
Number of ears	56	56	56	52	52
Before treatment	13.5 (7.6)	20.2 (10.5)	65.2 (21.8)	11.0 (6.8)	16.9 (8.5)
Difference ST - BT	1.0 (3.5)	4.8 (5.9)	21.4 (20.2)	0.3 (4.7)	3.2 (7.1)
Difference LT - BT	0.9 (5.7)	4.8 (9.4)	25.8 (19.8)	0.3 (6.1)	3.3 (8.8)
p-value LT vs. BT*	0.209	0.001	<0.0001	0.876	0.075
p-value LT vs. ST*	0.386	0.240	0.170	0.559	0.205
			Intravenous cisplatin CCRT group		
Number of ears	72	72	71	63	66
Before treatment	15.5 (10.8)	23.5 (13.9)	74.5 (25.6)	12.8 (9.2)	20.3 (12.5)
Difference ST - BT	4.6 (8.0)	11.1 (10.4)	21.6 (18.2)	3.2 (6.4)	10.3 (8.6)
Difference LT - BT	5.7 (8.2)	14.0 (10.8)	26.6 (22.7)	5.7 (8.5)	11.9 (9.2)
p-value LT vs. BT*	0.0001	<0.0001	<0.0001	0.0002	<0.0001
p-value LT vs. ST*	0.180	0.014	0.005	0.045	0.104

PTA = Pure Tone Average; ST = Short-term; LT = Long-term; BT = Before Treatment; SD = Standard Deviation; AC = Air Conduction; BC = Bone Conduction

* Multivariable linear regression analysis adjusted for ear, protocol, gender, age, T classification, hearing level at the earliest measurement, and the time-interval between both measurements

Cisplatin schedule

The absolute hearing deteriorations at LT versus ST were significantly higher in the CCRT-IV group compared with the CCRT-IA group at all PTAs, except for PTA 0.5-1-2 (p=0.068) and PTA 8-10-12.5 (p=0.218) (table 3).

Table 3 | Hearing deterioration in decibels per Pure Tone Average
Comparison of hearing deteriorations from before/short-term to long-term after treatment between CCRT-IV and CCRT-IA

Deterioration (dB) at long-term follow-up compared to baseline

	Intra-arterial cisplatin CCRT Mean (SD)	*Intravenous cisplatin CCRT Mean (SD)*	*p-value**
PTA 0.5-1-2 kHz AC	0.9 (5.7)	5.7 (8.2)	0.004
PTA 1-2-4 kHz AC	4.8 (9.4)	14.0 (10.8)	0.001
PTA 8-10-12.5 kHz AC	25.8 (19.8)	26.6 (22.7)	0.081
PTA 0.5-1-2 kHz BC	0.3 (6.1)	5.7 (8.5)	0.005
PTA 1-2-4 kHz BC	3.3 (8.8)	11.9 (9.2)	0.001

Deterioration (dB) at long-term follow-up compared to short-term follow-up

	Intra-arterial cisplatin CCRT Mean (SD)	*Intravenous cisplatin CCRT Mean (SD)*	*p-value**
PTA 0.5-1-2 kHz AC	0.1 (6.9)	1.1 (10.7)	0.068
PTA 1-2-4 kHz AC	0.0 (9.1)	2.9 (10.9)	0.007
PTA 8-10-12.5 kHz AC	4.4 (17.7)	5.0 (15.1)	0.218
PTA 0.5-1-2 kHz BC	0.0 (6.1)	2.5 (7.2)	0.031
PTA 1-2-4 kHz BC	0.1 (7.6)	1.6 (7.3)	0.040

dB = Decibel; CCRT= Concomitant Chemoradiation; SD = Standard Deviation; AC = Air Conduction; BC = Bone Conduction

* Test of difference between hearing loss by treatment based on repeated measurement analysis

As seen in table 2, LT versus ST after treatment, a significant progressive treatment-induced hearing loss was found in patients receiving CCRT-IV at PTA 8-10-12.5 kHz (p=0.005), PTA 1-2-4 kHz AC (p=0.014), and PTA 0.5-1-2 kHz BC (p=0.045), adjusted for ear, protocol, gender, age, T classification, hearing level at the earliest measurement, and the time-interval between both measurements. Audiometric changes in patients treated with CCRT-IA did not show any significant hearing deterioration at LT follow-up versus ST follow-up (p>0.1). Results were similar in analyses only adjusted for ear.

Common Terminology Criteria for Adverse Events

When hearing loss was scored according to the Common Terminology Criteria for Adverse Events, 48 of the 64 patients (72%) experienced hearing loss short-term after treatment. At LT follow-up this percentage slightly increased to 75% (p=0.79, Wilcoxon

Signed Rank test). At LT follow-up, a higher incidence of hearing loss was scored in the IV group compared to the IA group: 81% versus 68%, respectively. This difference was not significant.

Table 4 | Number of patients with hearing impairment expressed in CTCAEv4
Comparison of scorings between the CCRT-IA and CCRT-IV group

Grade	**Total cohort n=64**	**CCRT-IA n=28**	**CCRT-IV n=36**	**p-value***
Short-term versus before				
0	18 (28%)	10 (36%)	8 (22%)	
1	13 (20%)	4 (14%)	9 (25%)	
2	30 (47%)	14 (50%)	16 (44%)	
3	3 (5%)	0	3 (8%)	
4	0	0	0	
Total 1-4	48 (72%)	18 (64%)	28 (78%)	0.29
Long-term versus before				
0	16 (25%)	9 (32%)	7 (19%)	
1	14 (22%)	4 (14%)	10 (28%)	
2	32 (50%)	15 (54%)	17 (47%)	
3	2 (3%)	0	2 (6%)	
4	0	0	0	
Total 1-4	50 (75%)	19 (68%)	29 (81%)	0.43

CCRT= Concomitant Chemoradiation; IA = intra-arterial; IV = intravenous
* Cochran-Armitage trend test

Air bone gap

In 119/128 (93%) ears, both AC and BC thresholds were measured either before, ST, and LT after treatment. Before treatment, four ears (3%) had an air bone gap. Short-term after treatment this percentage increased to 7%. At LT follow-up an ABG was present in three ears (3%). These were three other ears than the ears with an ABG before treatment or at ST post-treatment. One patient had a bilateral ABG at ST follow-up, all other ABGs were unilateral. Because tympanometry and otoscopy were not performed at LT follow-up, explanations for the ABGs could not be given and the presence of a middle ear effusion cannot be excluded.

DISCUSSION

Among patients treated with high-dose CCRT for head and neck cancer, we observed a relatively common treatment-induced hearing loss. At LT follow-up (median 4.5 years), there was a discrete increase (up to 5 dB) in hearing loss compared to ST follow-up values (median 3 months), which was statistically significant at ultra-high frequencies.

Our long-term results are in agreement with others.[10-13] Ho et al. also reported a progressive loss after (chemo)radiation which could not be attributed to ageing only.[13] In their study, the expected age-related threshold shift over years was calculated according to a formula developed by Robinson and Sutton.[20] Within 4.5 years of follow-up, the expected age-related threshold shift according to the formula of Robinson and Sutton was lower than the hearing deterioration measured by audiometry. Therefore, Ho et al.[13] concluded that the hearing deterioration in their patient population was a result of both ageing and treatment. In our patient cohort, baseline hearing levels turned out to be significantly worse than expected according to the ISO norm[18], which is based on the formula of Robison and Sutton (p<0.001 at each PTA, results not shown). Therefore we decided to use a multivariate regression analysis instead, incorporating the effect of presbycusis. In agreement with Ho et al., we also found that hearing loss at LT was a result of both ageing and an LT adverse event of treatment (table 2).

The treatment-related progressive hearing loss found at LT follow-up might be the result of late onset effects of radiotherapy on the inner ear, just as a late onset of radiotherapy-induced neuropathy of the cochlear nerve.[7] A prospective study of Pan et al. examined the relationship between the radiation dose to the inner ear and LT hearing loss in head and neck patients treated with CCRT.[21] The results showed that an increase in the mean dose to the inner ear was associated with increased hearing loss at high frequencies (≥2 kHz), and that clinically apparent hearing loss started at a threshold dose of 45 Gy. Based on these findings, a dose limit of ≤45 Gy to the inner ear was suggested. Unfortunately, the effect on ultra-high frequencies was not described. The median radiation dose in our patients was significantly low, i.e. 13.0 Gy, making a single effect of radiotherapy unlikely. Nevertheless, in animal studies it has been demonstrated that radiation as well as cisplatin effectuate their ototoxic effect at similar targets in the cochlea: the outer and inner hair cells, the stria vascularis, and the

nerve endings.[22-23] Therefore, the earlier described synergistic effect between cisplatin and RT[1] may also play a role in the inner ear. If so, non-toxic cochlear radiation doses of ≤45 Gy may then even become toxic by the addition of cisplatin. So, with a median dose of 13 Gy radiation dose to the cochlea in our patient group, a potentiating effect of cisplatin cannot be ruled out completely. In current literature, studies reporting an adequate dose-effect relationship between radiation doses and hearing loss including ultra-high frequencies in head and neck cancer patients treated with CCRT are absent. However, an adequate analysis of the potential synergistic effect of RT and cisplatin can only be obtained in a comparison of different patient groups treated with RT as a single modality treatment and cisplatin as a single modality treatment, compared to cisplatin based CCRT. However, in head and neck cancer patients, it is impossible to obtain such a trial, as cisplatin as a single modality curative treatment has no place in head and neck oncology.

Long-term progressive effects are also observed after a single modality treatment with cisplatin in patients where this kind of treatment does have a place.[24-25] After an interval of 8 to 75 months post-treatment, platinum is still detectable in the serum, up to >30 times higher than the mean level of unexposed controls.[26] Even 20 years after completion of cisplatin based chemotherapy, cisplatin is still detectable in plasma.[27] These observations might also explain a longstanding deteriorating effect of cisplatin.

Brouwers et al[26] showed that LT plasma platinum levels in humans were reduced by 71% by IV co-administration of sodium thiosulfate (STS). This is a strong indication for the neutralizing effect of STS in CCRT-IA patients, who showed significantly less hearing loss at both ST and LT post-treatment measurements compared to CCRT-IV patients. Moreover, CCRT-IA patients showed no LT treatment-induced hearing loss compared with short-term measurements, whereas CCRT-IV patients did. Thus, although the CCRT-IA patients received a significantly higher total dose of cisplatin (1078 mg vs. 542 mg, p=<0.001), the hearing deterioration was less severe in this patient group at both ST and LT follow-up. In a phase 3 trial comparing CCRT-IA with CCRT-IV, loco-regional control, survival, and (short-term) toxicities were evaluated. No differences were seen regarding loco-regional control and survival. Renal toxicity was more outspoken in the IV arm and statistically different from IA (p=<0.0001), whereas neurological toxicity was more outspoken in the IA arm (p=0.005). Ototoxicity (>5 dB) during treatment did

not differ statistically between the two groups.[15] Although a neutralizing effect of STS seems likely to explain the long-term preservation of hearing, reduction of cisplatin levels by STS cannot be ruled out completely.

The observed hearing loss of less than median 5 dB at LT follow-up compared to ST follow-up is modest. Although this hearing deterioration is statistically significant (p=0.005), it does not seem to be clinically relevant. A hearing deterioration of 5 dB in an individual patient at a single frequency might also be the result of a false positive measurement, which may be caused by 'test-retest variability' during audiometry.[28] We tried to reduce the effect of test-retest variability by calculating averages of PTAs. Moreover, because the 5 dB deterioration was the result of the total group analysis, the risk of test-retest variability is low.

CONCLUSION

Within this high-dose cisplatin CCRT patient population, treatment-related long-term hearing loss was found particularly at frequencies 8-10-12.5 kHz and in the CCRT-IV group, although clinically to a limited extent (5 dB) when compared to short-term hearing loss. This is one of the first studies demonstrating a long-term treatment-related effect; future studies are needed to confirm our results.

AKNOWLEGMENTS

This work was supported by an unrestricted grant from the Riki Stichting.

REFERENCES

1. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. Mar 18 2000;355(9208):949-955.

2. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. Jul 2009;92(1):4-14.

3. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head Neck*. Nov 2013;35(11):1662-1668.

4. Rademaker-Lakhai JM, Crul M, Zuur L, et al. Relationship between cisplatin administration and the development of ototoxicity. *J Clin Oncol*. Feb 20 2006;24(6):918-924.

5. Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys*. Apr 1 2009;73(5):1335-1342.

6. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer*. Feb 15 2006;106(4):820-829.

7. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys*. Mar 1 2010;76(3 Suppl):S50-57.

8. Theunissen EA, Bosma SC, Zuur CL, et al. Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: A systematic review of the literature. *Head Neck* (2013). doi: 10.1002/hed.23551. Epub 2013.

9. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys*. Aug 1 2007;68(5):1320-1325.

10. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. *Otol Neurotol*. Mar 2004;25(2):168-173.

11. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiother Oncol*. Oct 2002;65(1):9-16.

12. Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. *J Laryngol Otol*. Jan 2010;124(1):32-36.

13. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: A prospective study. *Head Neck*. Sep 1999;21(6):547-553.

14. Low WK, Kong SW, Tan MG. Ototoxicity from combined Cisplatin and radiation treatment: an in vitro study. *Int J Otolaryngol*. 2010;2010:523976.

15. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer*. May 1 2010;116(9):2159-2165.

16. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *J Clin Oncol*. Aug 20 2007;25(24):3759-3765.

17. Gurgel RK, Popelka GR, Oghalai JS, Blevins NH, Chang KW, Jackler RK. Is it valid to calculate the 3-kilohertz threshold by averaging 2 and 4 kilohertz? *Otolaryngol Head Neck Surg*. Jul 2012;147(1):102-104.

18. International Organization for Standardization 2000, Reference number ISO 7029:2000 (E). International Standard. Acoustics - Statistical distribution of hearing thresholds as a function of age.

19. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. Available at: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

20. Robinson DW, Sutton GJ. Age effect in hearing - a comparative analysis of published threshold data. *Audiology*. 1979;18(4):320-334.

21. Pan CC, Eisbruch A, Lee JS, Snorrason RM, Ten Haken RK, Kileny PR. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys*. Apr 1 2005;61(5):1393-1402.

22. Gamble JE, Peterson EA, Chandler JR. Radiation effects on the inner ear. *Arch Otolaryngol*. Aug 1968;88(2):156-161.

23. Winther FO. X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the cochlea. *Acta Otolaryngol*. Jul-Aug 1969;68(1):98-117.

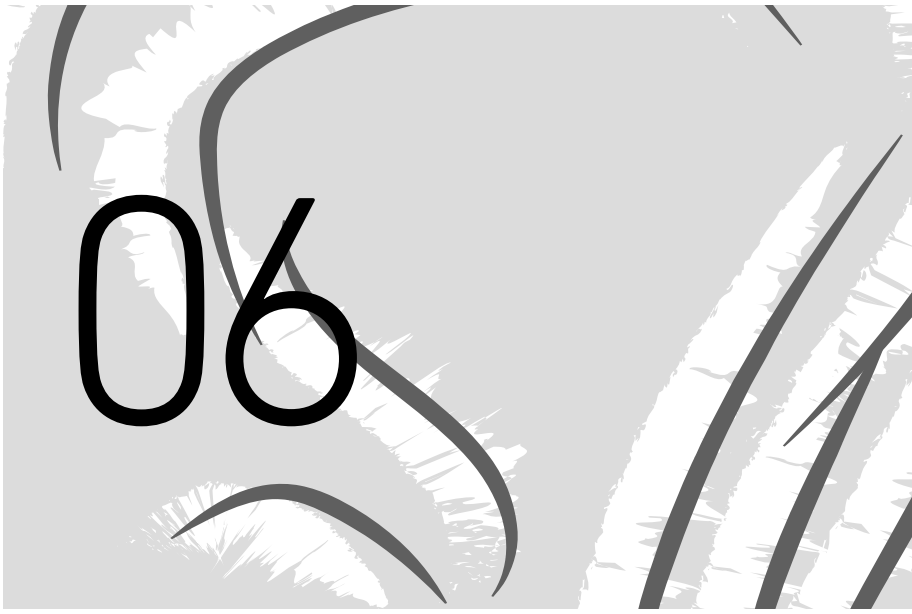
24. Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. *J Pediatr Hematol Oncol*. Oct 2004;26(10):649-655.

25. Sprauten M, Darrah TH, Peterson DR, et al. Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. *J Clin Oncol*. Jan 20 2012;30(3):300-307.

26. Brouwers EE, Huitema AD, Beijnen JH, Schellens JH. Long-term platinum retention after treatment with cisplatin and oxaliplatin. *BMC Clin Pharmacol*. 2008;8:7.

27. Gietema JA, Meinardi MT, Messerschmidt J, et al. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet*. Mar 25 2000;355(9209):1075-1076.

28. Dobie RA. Audiometric threshold shift definitions: simulations and suggestions. *Ear Hear*. Feb 2005;26(1):62-77.


06

CHAPTER 06

Cochlea sparing effects of Intensity Modulated Radiation Therapy in head and neck cancer patients: a long-term follow-up study

E.A.R. Theunissen | C.L. Zuur | M. Lopez-Yurda | S. van der Baan | A.F. Kornman
J.P. de Boer | A.J.M. Balm | C.R.N. Rasch | W.A. Dreschler

Journal of Otolaryngology - Head and Neck Surgery. 2014; 43:30

ABSTRACT

Objective

Radiation to the inner ear may lead to (irreversible) sensorineural hearing loss. The purpose of this study was to demonstrate the long-term effect of radiotherapy on hearing in patients treated with Intensity Modulated Radiation Therapy (IMRT), sparing the inner ear from high radiation dose as much as possible.

Methods

Between 2003 and 2006, 101 patients with head and neck cancer were treated with IMRT. Audiometry was performed before, short-term, and long-term after treatment. Data were compared to normal hearing levels according to the International Organisation for Standardization (ISO). Statistical analysis was done using repeated measurements. None of the patients received chemotherapy.

Results

In 36 patients an audiogram at long-term follow-up (median 7.6 years) was available. The mean dose to the cochlea was 17.8 Gy (1.0 - 66.6 Gy). Compared to measurements at short-term, a hearing deterioration of 1.8 dB at Pure Tone Average (PTA) 0.5-1-2 kHz (p=0.11), 2.3 dB at PTA 1-2-4 kHz (p=0.02) and 4.4 dB at PTA 8-10-12.5 kHz (p=0.01) was found. According to the ISO, the expected age-related hearing loss was 2.7, 4.8, and 8.8 dB at PTA 0.5-1-2 kHz, 1-2-4 kHz and 8-10-12.5 kHz, respectively.

Conclusion

After IMRT with radiation dose constraint to the cochlea, potential long-term adverse effects of IMRT remained subclinical. The progressive hearing loss over time was mild and could be attributed to the natural effects of ageing. Therefore, we recommend that a dose constraint to the cochlea should be incorporated in the head and neck radiotherapy protocols.

INTRODUCTION

Radiotherapy (RT), as single-modality treatment or adjuvant to surgery, is a common treatment modality for head and neck (H&N) cancer.[1] Hearing loss is one of the adverse events of RT used in the management of H&N malignancies as the auditory system is often included in the treatment area. As a result, conductive hearing loss (CHL) may be the (reversible) effect of RT to the middle and external ear.[2,3] In addition, radiation to the inner ear may lead to (irreversible) sensorineural hearing loss (SNHL). Recent systematic reviews reported incidences of SNHL of 42 ± 3% after RT.[4,5] It is well known that a higher dose to the cochlea is associated with a higher risk of SNHL [3,4,6-10], with a minimum cochlear dose reported to be a risk factor of 45 Gray (Gy).[4]

Currently, the use of Intensity Modulated Radiation Technique (IMRT) spares the organs at risk from high radiation doses, which can improve quality of life. Such improvements have been demonstrated in the aspect of preservation of salivary function, trismus, and neck fibrosis.[11-13] Equally so, IMRT will reduce the dose to the cochlea, if possible, and therefore the risk of SNHL. The advantage of IMRT on hearing status short-term after treatment is reported by different authors who compared the use of IMRT with conventional or conformal techniques in patients with H&N cancer.[4,8,13,14] In a prospective study of Zuur et al., 101 patients with head and neck cancer were treated with IMRT, while sparing the inner ear from radiation dose as much as possible.[6] The radiation-induced hearing deterioration was found to be rather modest, namely 1.5 decibel (dB) at speech frequencies and 2.7 dB at ultra-high frequencies, indicating that IMRT is a safe treatment modality concerning the hearing status.

Vascular insufficiency has been proposed as the etiology of SNHL after radiotherapy. Animal studies showed that this may cause lesions in the stria vascularis, in afferent nerve endings, and in the hair cells of the cochlea.[15,16] In long-term follow-up studies showing a progressive SNHL after conventional or conformal RT techniques, it is hypothesized that this toxicity is either caused by an increased progression of impaired circulation, or that a late onset of cochlear pathology is playing a role.[2,6,17-19] To elucidate a long-term beneficial effect of IMRT, we evaluated in the present study the same patients of our earlier published IMRT patient cohort[6], at median 7.6 years post-treatment.

METHODS

Between 2003 and 2006, 101 patients received IMRT for head and neck cancer at different tumor sites, i.e. parotid gland, oropharynx, larynx, oral cavity, maxillary sinus, submandibular gland, nasal cavity, and external ear. Audiometry was conducted in a prospective setting one week before treatment (BT), and at a median of 3.5 months (range 1.0-14.1 months) short-term (ST) post-treatment. Audiometry at long-term follow-up was defined as an audiogram at more than three years after completion of the treatment. When more than one long-term audiometry was available in one patient, the latest audiogram was used for analysis. The study was approved by the local ethics committee and an informed consent was signed by all patients before treatment.

Intensity Modulated Radiation Technique protocol

Computed tomography-generated treatment plans were made for all patients. The computed tomography data sets were transferred to the treatment planning systems (UM plan, version 3.38, University of Michigan, Ann Arbor, MI; and Pinnacle, version 7.3, Philips, Best, The Netherlands). The clinical target volumes (primary tumor and neck lymph nodes on both sides) and the organs at risk (parotid glands, oral cavity, brain stem, spinal cord, and the cochleae), were delineated on each relevant computed tomography slice. Thereafter, RT doses to the cochleae were calculated. For more details we refer to the previous study.[6] None of the patients received neoadjuvant or adjuvant chemotherapy.

Audiometry

Long-term testing was performed in a soundproof testing room with Decos system (Audiology Workstation). Both ears were tested. Air conduction (AC) thresholds were measured at frequencies 0.125, 0.250, 0.5, 1, 2, 3, 4, 6, 8, 10, 12.5 kHz and bone conduction (BC) thresholds were measured at 0.5, 1, 2, 4 kHz. Audiometric data were presented in dB Hearing Levels (HL) at frequencies 0.125 to 8 kHz and in dB Sound Pressure Levels (SPL) at frequencies 8 to 12.5 kHz. If measurements at 3 and 6 kHz were missing (72% at 3 kHz, 85% at 6 kHz) interpolation of the data was performed.[20] In case of missing measurements at high frequencies (8% at 10 kHz and 8% at 12.5 kHz) or when there was no response to the maximum output of the audiometer (4% at 8 kHz, 19% at 10 kHz, and 50% at 12.5 kHz), we calculated the thresholds by extrapolating the

data, using a straight line with the same slope that was found on average in the patients who responded at all frequencies. Speech perception was not routinely measured.

Mean AC thresholds were calculated at three Pure Tone Averages (PTAs): 0.5-1-2 kHz, 1-2-4 kHz, and 8-10-12.5 kHz, chosen to estimate the expected degree of disability for speech perception in quiet, speech perception in noise, and the perception of high sounds (e.g. music, nature), respectively. We calculated mean BC thresholds at PTAs 0.5-1-2 kHz and 1-2-4 kHz. We used dB SPL values for calculating the average PTA 8-10-12.5, while we used dB HL values for the PTA of speech frequencies. An air bone gap (ABG) was calculated by the difference between AC and BC at PTA 0.5-1-2 kHz.
Audiological data were compared to normal hearing levels according to the International Organization for Standardization (ISO) standard 7029:2000 for frequencies 0.125 to 8 kHz and to a model of hearing threshold levels based on otologically unscreened, non-occupationally noise-exposed population in Sweden for frequencies 8, 10 and 12.5 kHz.[21,22] The ISO hearing levels were calculated per patient and per frequency at baseline, short-term follow-up, and long-term follow-up.

Otological examination

At long-term follow-up, both ears of a patient were examined with otoscopy by a head and neck surgeon. The presence or absence of the following items were scored: tympanic membrane perforation, otitis media with effusion (OME), acute otitis media (AOM), external otitis, chronic otitis media (COM), atelectasis, tympanosclerosis, stenosis of external auditory canal, and skin lesions like erythema, desquamation, eczema, and ulcerations.

Grading of hearing impairment

Hearing impairment was expressed using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4).[23] The CTCAEv4 for hearing impairment consist of four grades, based on threshold shifts at frequencies between 1 and 8 kHz: Grade 1 = threshold shift of 15–25 dB averaged at two contiguous frequencies in at least in one ear or a subjective change in hearing; Grade 2 = threshold shift of >25 dB averaged at two contiguous frequencies in at least in one ear; Grade 3 = threshold shift of >25 dB averaged at three contiguous frequencies in at least in one ear; Grade 4 = profound bilateral hearing loss (>80 dB at 2 kHz and above).

Statistical analysis

The differences between hearing thresholds at baseline, short-term follow-up, and long-term follow-up were assessed using repeated measurement analysis. In the repeated measures analysis we adjusted for ear, gender, age and hearing level at the earliest of the measurements, and time between both measurements. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 20 and SAS version 9.2.

RESULTS

Patient selection

In 36 of the 101 patients (36%), audiometry at long-term follow-up was obtained. Sixty-five patients (65%) were deceased, lost to follow-up, or did not want to participate anymore. Patient and treatment characteristics are shown in table 1. Pure tone audiometry was conducted one week before treatment (BT), at a median of 3.5 months (1.0-14.1) as short-term (ST) follow-up, and at a median of 7.6 years (3.7-9.3) as long-term (LT) follow-up after treatment. Age at short-term follow-up ranged from 32-78 years, with a median age of 59 years. Patients were median 66 years old (39-85) at long-term follow-up. The mean dose to the cochlea was 17.8 Gy (1.0-66.6 Gy). Three patients received a radiation dose to the cochlea of more than 45 Gy because of the location and stage of the tumor: one patient had a tumor in the external hearing canal, one patient received post-operative IMRT for a muco-epidermoid carcinoma of the parotid gland, and the third patient received post-operative IMRT for pleomorphic adenoma of the parotid gland.

Table 1| Patient and treatment characteristics; n=36 patients

Age (years), median (range)	
Short-term	59 (32-78)
Long-term	66 (39-85)
Gender	
Male	25 (70%)
Female	11 (30%)
Audiological follow-up, median	
Short-term (months)	3.5 (1.0-14.1)
Long-term (years)	7.6 (3.7-9.3)
Dose to cochlea in Gray	
Mean	17.8
Median	13.1
Range	1.0-66.6
Primary tumor site	
Parotid gland	11 (30%)
Oropharynx	9 (25%)
Larynx	8 (22%)
Oral cavity	3 (8%)
Maxillary sinus	1 (3%)
Submandibular gland	1 (3%)
Nasal cavity	1 (3%)
External ear	1 (3%)
Unknown primary	1 (3%)
T classification	
1	7 (19%)
2	18 (50%)
3	2 (5.5%)
4	2 (5.5%)
Unknown primary	1 (3%)
Not applicable*	6 (17%)
N classification	
0	22 (61%)
1	4 (11%)
2	4 (11%)
Not applicable*	6 (17%)

* = 6 patients with recurrent or incompletely excised pleomorphic adenoma

Mean overall hearing loss

Hearing thresholds before, at short-term follow-up, and at long-term follow-up are summarized in table 2. Overall, there were no significant changes at BC thresholds up to 4 kHz. At AC thresholds, hearing deteriorated with 1.8 dB, 2.9 dB, and 7.3 dB at low,

high, and ultra-high frequencies, respectively, when audiometry at long-term follow-up was compared with audiometry at baseline. These differences were significant for PTA 1-2-4 (p=0.03) and 8-10-12.5 kHz (p<0.001). When AC thresholds at long-term follow-up were compared to AC thresholds at short-term follow-up, the following deteriorations were seen: 1.8 dB at PTA 0.5-1-2 kHz (p=0.11), 2.3 dB at PTA 1-2-4 kHz (p=0.02), and 4.4 dB at PTA 8-10-12.5 kHz (p=0.01). According to the ISO, the age-related deterioration in hearing between audiometry at long-term and at short-term follow-up was expected up to 2.7 dB at PTA 0.5-1-2 kHz, 4.8 dB at PTA 1-2-4 kHz, and 8.8 dB at PTA 8-10-12.5 kHz.

Table 2 | Measured hearing levels in decibel at pure tone averages

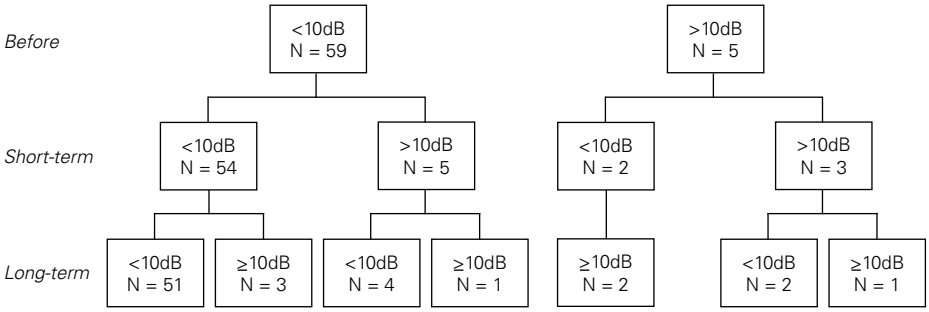
	0.5-1-2 kHz AC Mean (SD) median	1-2-4 kHz AC Mean (SD) median	8-10-12.5 kHz Mean (SD) median	0.5-1-2 kHz BC Mean (SD) median	1-2-4 kHz BC Mean (SD) median
Number of ears	72	72	67	66	66
Before treatment	20.3 (13.3) 16.7	28.6 (16.8) 25.0	75.4 (23.6) 74.8	17.4 (12.2) 14.1	24.3 (35.1) 20.8
ST after treatment	20.3 (15.4) 15.8	29.2 (18.9) 25.0	78.3 (22.3) 79.0	16.6 (12.7) 13.3	22.9 (15.1) 20.9
LT after treatment	22.1 (15.7) 18.3	31.5 (19.0) 29.2	82.7 (23.3) 82.9	17.3 (12.9) 13.3	23.2 (15.1) 20.0
Difference ST and BT	0 dB	0.6 dB	2.9 dB *	-0.8 dB	-1.4 dB
Difference LT and ST	1.8 dB	2.3 dB *	4.4 dB *	0.7 dB	0.3 dB

Abbreviations: ST = Short-term; LT = Long-term; BT = Before Treatment; AC = Air Conduction; BC = Bone Conduction; SD = Standard deviation; dB = Decibel
* = Statistically significant (p<0.05)

Air bone gap

In 64/72 ears (89%) both AC and BC thresholds were measured before, at short-term follow-up, and at long-term follow-up. Before treatment, 59 ears had no ABG of which five ears developed an ABG at short-term follow-up and three ears at long-term follow-up (figure 1). In patients with an existing ABG before therapy (n=5), the ABG was still present (n=3) or disappeared (n=2) at long-term follow-up.

Figure 1 | Number of ears with an air bone gap at pure tone average 0.5-1-2 kHz



Common Terminology Criteria for Adverse Events

In table 3 hearing loss is expressed according to the CTCAEv4 for hearing impairment. Considering the audiogram LT after treatment compared to the audiogram ST after treatment, only a minor change in total incidence was seen: 39% (grade 1-3) at short-term follow-up versus 36% (grade 1-3) at long-term follow-up. See for further details table 3.

Table 3 | Number of patients with hearing impairment according to the Common Terminology Criteria for Adverse Events version 4

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total Grade 1-4
Short-term	22 (61%)	6 (17%)	4 (11%)	4 (11%)	0	14 (39%)
Long-term	23 (64%)	6 (17%)	4 (11%)	3 (8%)	0	13 (36%)

Patients with progressive treatment-induced hearing loss

Two ears (3%, 2 patients) deteriorated more than expected according to the ISO at both PTAs BC, implying a treatment-induced hearing loss. At AC thresholds, three ears (5%), four ears (6%) and seven ears (10%) deteriorated more than expected according to the ISO at PTAs 0.5-1-2 kHz, 1-2-4 kHz, and 8-10-12.5 kHz, respectively (table 4).

From the total cohort, three patients received a radiation dose of more than 45 Gy to the cochlea in one ear (i.e. 51.6, 52.2 and 66.6 Gy). The hearing loss of two patients was explicitly higher than the expected age-related deterioration according to the ISO: at PTA 0.5-1-2 kHz BC 11.1 dB versus 3.6 dB, at PTA 1-2-4 kHz BC 12.2 versus 6.5 dB, and at PTA 8-10-12.5 kHz 13.1 versus 6.8 dB (table 3). The third patient lost approximately the same as expected by ISO at PTA 0.5-1-2 and 1-2-4 kHz BC. At PTA 8-10-12.5 kHz the measured hearing deterioration was 2.6 dB worse than expected according to the ISO.

Table 4 | Number of ears with treatment-related hearing loss

	Number (ears)	Number (ears) with more hearing loss than expected according to ISO	Explanation
PTA 0.5-1-2 kHz BC	66	2 (3%)	2x: SNHL, RT dose to cochlea >45 Gy
PTA 1-2-4 kHz BC	66	2 (3%)	2x: SNHL, RT dose to cochlea >45 Gy
PTA 0.5-1-2 kHz AC	72	3 (4%)	2x: SNHL, RT dose to cochlea >45 Gy 1x: ABG
PTA 1-2-4 kHz AC	72	4 (6%)	2x: SNHL, RT dose to cochlea >45 Gy 2x: ABG
PTA 8-10-12.5 kHz	67	7 (10%)	2x: SNHL, RT dose to cochlea >45 Gy 2x: ABG at PTA 1-2-4 kHz 3x: Unexplained

Abbreviations: PTA = Pure Tone Average; AC = Air Conduction; ISO = International Organization for Standardization; SNHL = Sensorineural Hearing Loss; RT = Radiotherapy; ABG = Air Bone Gap

Otological adverse events

Tympanosclerosis was the most frequently observed event during otological examination (24%). An OME was seen in two patients (7%), external otitis in two patients (7%), atelectasis in three patients (10%), and skin lesions in two patients (7%). None of patients had a perforated tympanic membrane, COM, AOM, or stenosis of the external auditory canal.

DISCUSSION

This manuscript describes the long-term follow-up results on hearing status in a cohort of patients with head and neck cancer, treated with IMRT wherein the inner ear was defined as an organ of risk.[6] To our knowledge, this is one of the first reports describing the long-term effects after IMRT in head and neck cancer. Our results indicate that when the inner ear is regarded as an organ at risk, the treatment-induced hearing loss is modest and not progressive over time in most patients. The average change in hearing thresholds after a median interval of 7.6 years post-treatment was 1.8 - 2.3 dB at speech frequencies (PTA 0.5-1-2 kHz AC and PTA 1-2-4 kHz AC) and 4.4 dB at ultra-high frequencies (PTA 8-10-12.5 kHz) when compared to the thresholds at short-term follow-up. There were no significant changes at BC thresholds up to 4 kHz. Correction for presbycusis during follow-up time according to the ISO-standard indicated that these hearing deteriorations are part of the natural effects of ageing, as the averaged calculated hearing loss using ISO was 2.7 dB at PTA 0.5-1-2 kHz, 4.8 dB at PTA 1-2-4 kHz, and 8.8 dB at PTA 8-10-12.5 kHz. This is even higher than the measured deteriorations.[21,22]

A recent long-term follow-up study of Tsang et al. studied patients with nasopharyngeal cancer (NPC) treated with IMRT or conventional therapy on their long-term hearing status (56 ears).[24] They concluded that there was a BC threshold shift of 16.1 dB at 4 kHz 5 years after IMRT treatment and that this deterioration, in general, could not be attributed to ageing alone. In our data, no changes were seen at BC thresholds. However, patients treated with IMRT in the Tsang study received a dose of 50 Gy to the cochlea, whereas in our study the dose to the cochlea was 17.8 Gy. This difference in radiation dose is probably related to the inclusion of only patients with NPC, whereas we included various head and neck tumor locations without any NPC patients. Nevertheless, in our IMRT population, sparing of the cochlea was not always possible depending on tumor location and stage. This happened in three patients with a tumor of the external ear or in the parotid gland. Two of them developed a progressive treatment-induced hearing loss at both AC and BC thresholds at long-term follow-up (table 4).

In our patient cohort the cochlea was regarded as an organ at risk. However, in current practice, it is not standard to constrain the radiation dose to the cochleae. Even so, the Radiotherapy Oncology Group (RTOG) has not formulated any guidelines yet regarding

dose constrains to the cochlea in H&N treatment protocols. However, a limitation of IMRT is that the dose given to tissues not considered as organs at risk can be higher compared to conventional or conformal treatment plans. A study of Hitchcock revealed this effect: patients with head and neck cancer were treated with IMRT (n=21) or conformal RT (n=41).[25] As no attempt was made to limit the dose to the cochlea, patients treated with IMRT had a significantly higher dose delivered to the cochlea than those treated with a conformal treatment plan. Therefore, to better preserve hearing in most patients while using IMRT, the cochlea should be recognized and treated as an organ at risk. If possible, the radiation dose to the cochlea should be limited as much as possible, preferably lower than 45 Gy[4], although an exact safe radiation threshold is still missing in the literature. Pacholke et al. described a guideline for contouring the middle and inner ear.[26] These guidelines can be of practical help to radiation oncologists.

Limitations of the study

This study has certain limitations. In the beginning the patient group was large (101 patients), but audiometry at long-term follow-up was only available in 36 patients (36%), since 64% was deceased, lost to follow-up, or not willing to participate any longer. However, given the fact that the hearing deteriorations were rather modest, the risk of selection bias, meaning that only patients with subjective hearing complaints continued the follow-up, is very low. Furthermore, time between short-term follow-up and long-term follow-up measurements differed between patients. However, this bias was taken into account by adjusting for time between both audiograms in the statistical analysis.

Also, a more precise conclusion may be drawn when a control group and/or a patient group treated with IMRT with high radiation doses to the cochlea, was available. Currently, due to the small sample size and the relatively large number of small radiation doses to the cochlea, a comparison between clinically relevant high and small radiation doses could only be analyzed in a descriptive manner. In our former study, reporting on the total patient cohort (n=101), we demonstrated a dose-effect relationship between increasing radiation dose and hearing loss. Nevertheless, due to a limited number of patients receiving relatively high radiation doses (median cochlear dose was 11.4 Gy), a maximum safe cochlear dose for hearing preservation could not be calculated.[6] However, we feel that current results are sufficient enough to conclude that IMRT-induced hearing loss is rather modest at both short-term and long-term follow-up, provided that the radiation dose to the cochlea is low.

Finally, in our patient cohort, only small incidences of ABGs were found. With this limited number of ABGs no reliable conclusion can be made about the occurrence of middle ear pathology long-term after IMRT. In addition, the results of otological examination showed no abnormalities. The incidence of 24% of tympanosclerosis is, in our opinion, a normal percentage as it is correlated to ear infections in the past.[27] Of the seven patients with tympanosclerosis, five (71%) reported a medical history of recurrent ear infections before the start of IMRT. Future studies are needed to review the effect of IMRT to the middle ear and Eustachian tube function.

CONCLUSION

The current follow-up study of our earlier analyzed patients with head and neck cancer treated with IMRT, resulted in a smaller sample size of the patient population and a greater diversity. Nevertheless, the importance of regarding the cochlea as an organ at risk during IMRT is well established. Based on our former ànd current results, patients suffer from modest and clinical irrelevant IMRT-induced hearing loss at both short-term ànd long-term follow-up, provided that the radiation dose to the cochlea is limited. Therefore, we recommend that a dose constraint to the cochlea should be incorporated in the head and neck radiotherapy protocols.

AKNOWLEGMENTS

This work was supported by an unrestricted grant from the Riki Stichting.

REFERENCES

1. Schwartz DL, Garden AS. Radiotherapy for head and neck cancer. *Hematol Oncol Clin North Am.* Apr 2006;20(2):259-285.

2. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. *Int J Radiat Oncol Biol Phys.* Feb 1 2007;67(2):469-479.

3. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. *Cancer Treat Rev.* Oct 2003;29(5):417-430.

4. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head & neck.* Nov 2013;35(11):1662-1668.

5. Theunissen EA, Bosma SC, Zuur CL, et al. Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: A systematic review of the literature. *Head & neck.* Nov 7 2013.

6. Zuur CL, Simis YJ, Lamers EA, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* Jun 1 2009;74(2):490-496.

7. Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys.* Apr 1 2009;73(5):1335-1342.

8. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer.* Feb 15 2006;106(4):820-829.

9. Oh YT, Kim CH, Choi JH, Kang SH, Chun M. Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. *Radiother Oncol.* Jul 2004;72(1):79-82.

10. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys.* Mar 1 2010;76(3 Suppl):S50-57.

11. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys.* Nov 15 2006;66(4):981-991.

12. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys.* Jan 1 2006;64(1):57-62.

13. Peng G, Wang T, Yang KY, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. *Radiother Oncol.* Sep 2012;104(3):286-293.

14. Petsuksiri J, Sermsree A, Thephamongkhol K, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. *Radiat Oncol.* 2011;6:19.

15. Winther FO. X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the vestibular sensory epithelia. *Acta Otolaryngol.* Dec 1969;68(6):514-525.

16. Gamble JE, Peterson EA, Chandler JR. Radiation effects on the inner ear. *Arch Otolaryngol.* Aug 1968;88(2):156-161.

17. Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. *J Laryngol Otol.* Jan 2010;124(1):32-36.

18. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. *Radiother Oncol.* Oct 2002;65(1):9-16.

19. Herrmann F, Dorr W, Muller R, Herrmann T. A prospective study on radiation-induced changes in hearing function. *Int J Radiat Oncol Biol Phys.* Aug 1 2006;65(5):1338-1344.

20. Gurgel RK, Popelka GR, Oghalai JS, Blevins NH, Chang KW, Jackler RK. Is it valid to calculate the 3-kilohertz threshold by averaging 2 and 4 kilohertz? *Otolaryngol Head Neck Surg*. Jul 2012;147(1):102-104.

21. International Organization for Standardization 2000, Reference number ISO 7029:2000 (E). International Standard. Acoustics - Statistical distribution of hearing thresholds as a function of age.

22. Johansson MS, Arlinger SD. Hearing threshold levels for an otologically unscreened, non-occupationally noise-exposed population in Sweden. *Int J Audiol*. Apr 2002;41(3):180-194.

23. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. Available at: http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

24. Tsang RK, Kwong DL, Ho AC, To VS, Ho WK, Wei WI. Long-term hearing results and otological complications of nasopharyngeal carcinoma patients: comparison between treatment with conventional two-dimensional radiotherapy and intensity-modulated radiotherapy. *ORL J Otorhinolaryngol Relat Spec*. 2012;74(4):228-233.

25. Hitchcock YJ, Tward JD, Szabo A, Bentz BG, Shrieve DC. Relative contributions of radiation and cisplatin-based chemotherapy to sensorineural hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys*. Mar 1 2009;73(3):779-788.

26. Pacholke HD, Amdur RJ, Schmalfuss IM, Louis D, Mendenhall WM. Contouring the middle and inner ear on radiotherapy planning scans. *Am J Clin Oncol*. Apr 2005;28(2):143-147.

27. Asiri S, Hasham A, al Anazy F, Zakzouk S, Banjar A. Tympanosclerosis: review of literature and incidence among patients with middle-ear infection. *J Laryngol Otol*. Dec 1999;113(12):1076-1080.


07

CHAPTER 07

Radiation-induced hearing loss in survivors of childhood head and neck rhabdomyosarcoma: a long-term follow-up study

E.A.R. Theunissen* | R.A. Schoot* | O. Slater | M. Lopez-Yurda | C.L. Zuur
M.N. Gaze | Y. Chang | H.C. Mandeville | J.E. Gains | K. Rajput | B.R. Pieters
R. Davila Fajardo | R. Talwar | H.N. Caron | A.J.M. Balm | W.A. Dreschler
J.H.M. Merks | * Contributed equally

Submitted

ABSTRACT

Objective

To determine the hearing status of survivors treated for head and neck rhabdomyosarcoma (HNRMS) at long-term follow-up. We compared hearing loss between survivors treated with the international standard: external beam radiotherapy (EBRT-based local therapy: London) and survivors treated with AMORE (Ablative surgery, MOld technique afterloading brachytherapy and surgical REconstruction) if feasible, otherwise EBRT (AMORE-based local therapy: Amsterdam).

Methods

A prospective analysis was conducted of hearing thresholds obtained by audiometry. Differences between hearing were assessed using linear regression analyses.

Results

Seventy-three survivors were included (median follow-up 11 years). We found clinically relevant hearing loss at speech frequencies in 19% of survivors. Multivariable analysis showed that survivors treated with EBRT-based treatment and those with parameningeal tumors had significantly more hearing impairment, compared to survivors treated with AMORE-based treatment and non-parameningeal tumors.

Conclusion

One in five survivors of HNRMS developed clinically relevant hearing loss. The AMORE-based treatment resulted in less hearing loss compared to the EBRT-based treatment. As hearing loss was highly prevalent and also occurred in survivors with orbital primaries, we recommend systematic audiological follow-up in all HNRMS survivors.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children.[1] Forty percent of RMS are located in the head and neck region (HNRMS). Patients with HNRMS are treated with a combination of multidrug chemotherapy, surgery and radiotherapy.[2,3] Due to the position and infiltrative nature of the tumor into vital structures in the head and neck area, a complete surgical resection is often impossible without severe morbidity. Therefore, radiotherapy is needed in the majority of patients to obtain local control. Radiotherapy is known to result in long-term adverse events (AE) such as impaired growth of bone and soft tissue leading to facial asymmetry and deformity, trismus, decreased vision, xerostomia, and hearing loss.[4-7]

In order to minimize radiation-induced AEs in these young children (median age 5 years[8]), an innovative multidisciplinary local treatment strategy was developed in Amsterdam in 1990.[9] This strategy consists of consecutive Ablative surgery, MOld technique afterloading brachytherapy, and surgical REconstruction (AMORE). Earlier reports showed that the AMORE strategy is an effective local treatment modality in HNRMS patients, with survival figures comparable to other international study groups.[9-14]

The purpose of this study is to evaluate long-term hearing loss in survivors of pediatric HNRMS. We performed audiological examinations in survivors treated at four large pediatric oncology centers: Great Ormond Street Hospital (GOSH), London, the Royal Marsden Hospital (RMH), Sutton, University College London Hospitals (UCLH), London, and the Emma Children's Hospital-Academic Medical Center (EKZ-AMC), Amsterdam. All four centers have used the same treatment protocols in the past 20 years being part of the International Society of Pediatric Oncology-Malignant Mesenchymal Tumor group (SIOP-MMT) and since 2005 the European *pediatric* Soft Tissue Sarcoma Study Group (E*p*SSG). There was only one difference between local treatment strategies in London and Amsterdam; patients in London were treated with external beam radiotherapy (EBRT) (EBRT-based treatment) whereas patients in Amsterdam were treated with AMORE or with EBRT in case AMORE was considered not feasible (AMORE-based treatment). Audiological evaluation was part of a multi-disciplinary outpatient clinic, investigating AEs of local HNRMS treatment. Results on the complete overview of adverse events of local treatment in this cohort, including survival figures, are presented

elsewhere.[15] Aim of this study is to assess hearing loss in HNRMS survivors. Second aim is to compare hearing loss between survivors treated with EBRT-based and AMORE-based local treatment.

MATERIALS AND METHODS

Patients

Children, treated for HNRMS between 1990 and 2010 in London or Amsterdam and two years after completion of treatment, were eligible for this study. Written informed consent was obtained from survivors treated in London. In Amsterdam, the institutional review board decided that the Act on Medical Research Involving Human Subjects did not apply, because data were collected during regular follow-up clinics. Tumor sites were classified as parameningeal, orbital, and non-parameningeal, as described in the E*p*SSG RMS 2005 protocol (table 1).

Table 1 | Tumor sites

Parameningeal	**Non-parameningeal**	**Orbit**
Nasal cavity	Oral cavity	Orbit
Nasopharynx	Oropharynx	Eyelid
Paranasal sinuses	Hypopharynx	
Middle ear / mastoid	Larynx	
Pterygoid fossa	Parotid region	
Infratemporal fossa	Buccal region	
Orbit with intracranial extension	Thyroid and parathyroid	
	Soft tissues of the neck	
	Cheek	
	Scalp	

Rhabdomyosarcoma treatment

Both cities treated patients according to the same guidelines of the successive SIOP-MMT[16,17] and E*p*SSG[18] protocols. Treatment started with initial surgery (biopsy) and induction chemotherapy. The chemotherapy regimens did not include cisplatinum. The maximum carboplatin dose administered was 3600 mg/m^2,[8,16] mean doses administered

per patient were not available. After induction chemotherapy (two or three courses), patients qualified for delayed local treatment. Within the SIOP-MMT philosophy it is allowed to withhold radiotherapy in favourable patient groups that achieve complete remission after initial surgery and induction chemotherapy. Local treatment consisted of EBRT (London: EBRT-based treatment) or AMORE if feasible, otherwise EBRT (Amsterdam: AMORE-based treatment). AMORE was considered feasible if a macroscopic radical resection seemed possible without severe mutilation, to be followed by adequate brachytherapy mold placement.[9]

Audiometry

This prospective study was a cross sectional assessment of hearing loss in HNRMS survivors: baseline audiometry was not available. We measured both ears at follow-up. Air conduction (AC) thresholds were measured at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz and bone conduction (BC) thresholds at 0.5, 1, 2, 4 kHz. We calculated the average threshold at Pure Tone Average (PTA) 0.5-1-2 kHz AC and BC and the average thresholds at 4 kHz. Middle ear (dys)function was assessed by calculating air bone gaps (ABGs) as the difference between AC and BC at PTA 0.5-1-2 kHz. If measurements at 3 and 6 kHz were missing we calculated those frequencies by interpolation of the data.[19] Tympanometry and audiology took place within the same visit. Otoscopy was part of the examination performed by the head and neck surgeon attending the multi-disciplinary clinic. Speech audiometry was not available.

Outcome measures and analyses

We assessed the following primary outcomes: hearing thresholds, the number of patients with clinically relevant hearing loss, and hearing impairment graded according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0) and Boston criteria (table 2).[20,21] Firstly, we compared measured hearing thresholds for all HNRMS survivors to age-corrected normal hearing levels as determined by the International Organization for Standardization (ISO).[22] We assumed hearing levels to be zero in survivors <18 years. Secondly, we compared the primary outcomes between the EBRT-based and AMORE-based treatment group. Clinically relevant hearing loss was defined as a deterioration of ≥20 decibel (dB) at PTA 0.5-1-2 kHz or at 4 kHz. We compared hearing thresholds using univariable regression analysis, adjusted for ear, for the following variables: treatment group, tumor localization, age at audiometry, and follow-up time. Furthermore

we conducted a multivariate analysis, adjusted for treatment group and tumor localization.

To prevent potential selection bias by selecting patients with more favorable prognosis for the AMORE procedure, we compared the complete cohort of HNRMS treated with EBRT-based treatment, with the complete cohort of patients treated with the AMORE-based treatment (including patients not eligible for AMORE).

Statistics

Patient characteristics were compared using the Pearson's Chi-square test for categorical variables, the T-test for continuous variables, and the Linear-by-Linear test for ordinal variables. Since audiometry was performed for both ears, the difference between hearing thresholds for both treatment groups was assessed using repeated measurements linear regression analyses. Audiometric thresholds were logarithmically normalized after adding 1 dB to improve normality. Statistical analyses were performed using IBM SPSS version 20 and SAS version 9.2.

Table 2 | Grading scales

	CTCAEv4 (Pediatrics) *	**CTCAEv4 (Adults) ***	**Boston**
Grade 1	>20 dB at any frequency tested and does not meet criteria >grade 2	Threshold shift of 15-25 dB averaged at 2 contiguous test frequencies in at least one ear	>20 dB HL SNHL above 4 kHz (i.e. 6 or 8 kHz)
Grade 2	>20 dB at >4 kHz	Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear	>20 dB HL SNHL at 4 kHz and above
Grade 3	>20 dB at 3 kHz and above in one ear, indication for therapeutic intervention	Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear	>20 dB HL SNHL at 2 or 3 kHz and above
Grade 4	Indication for cochlear implant	Profound bilateral hearing loss (>80 dB at 2 kHz and above); non-serviceable hearing	>40 dB HL SNHL at 2 kHz and above

*Measured frequencies: 1, 2, 3, 4, 6, 8 kHz
Abbreviations: CTCAEv4; Common Terminology Criteria for Adverse Events version 4, HL; Hearing Level, SNHL; Sensorineural hearing loss, dB; decibel

RESULTS

Patient and treatment characteristics

We evaluated 80 HNRMS survivors for local adverse events; 31 were treated with EBRT-based treatment and 49 with AMORE-based treatment. Audiological assessment was not performed in seven survivors (too young, n=1, logistical reasons, n=6). Hence, 73 survivors (91%) were included in this study: EBRT-based, n=27, AMORE-based, n=46 (table 3). We found no statistically significant differences between patient characteristics of both groups. Median follow-up was 11 years (range 2.6 – 21.7).

Patients were treated according to guidelines of the SIOP-MMT 89 (n=20), SIOP-MMT 95 (n=40) and E*p*SSG RMS 2005 (n=11) or other (n=2). In the EBRT-based treatment group, radiotherapy was initially withheld in 2/27 (7%) patients, as is allowed by the SIOP-MMT and E*p*SSG protocols.[15] 25/27 patients (93%) were treated with EBRT. In the AMORE-based treatment group, radiotherapy was initially withheld in 11/46 patients (24%), 23/46 patients (50%) were treated with AMORE, 10/46 patients (22%) with EBRT, and 2/46 patients (4%) with proton therapy. When including relapse treatment: 26/27 patients (96%) in the EBRT-based treatment group received EBRT. In the AMORE-based treatment group 4/46 patients (9%) never received local treatment, 24/46 patients (52%) were treated with AMORE, 7/46 patients (15%) with EBRT, 2/46 patients (4%) with proton beam treatment and 9/46 patients (20%) received a combination of AMORE and EBRT (five primarily AMORE salvaged by EBRT at relapse, four EBRT salvaged by AMORE at recurrence). Survival was similar for the EBRT-based and the AMORE-based treatment group.[15]

Audiometry

For logistical reasons, measurements were not conducted at 0.125 kHz in survivors with EBRT-based treatment. Measurements at 3 and 6 kHz AC were missing in 40/146 ears (27%) and 58/146 (40%) ears respectively, and were interpolated. Bone conduction thresholds were missing in 42/54 ears (80%) in survivors with EBRT-based treatment and in 6/92 ears (7%) in survivors with AMORE-based treatment. We were able to calculate ABGs in 98/146 (67%) ears with BC measurements available at PTA 0.5-1-2 kHz.

Table 3 | Patient and treatment characteristics

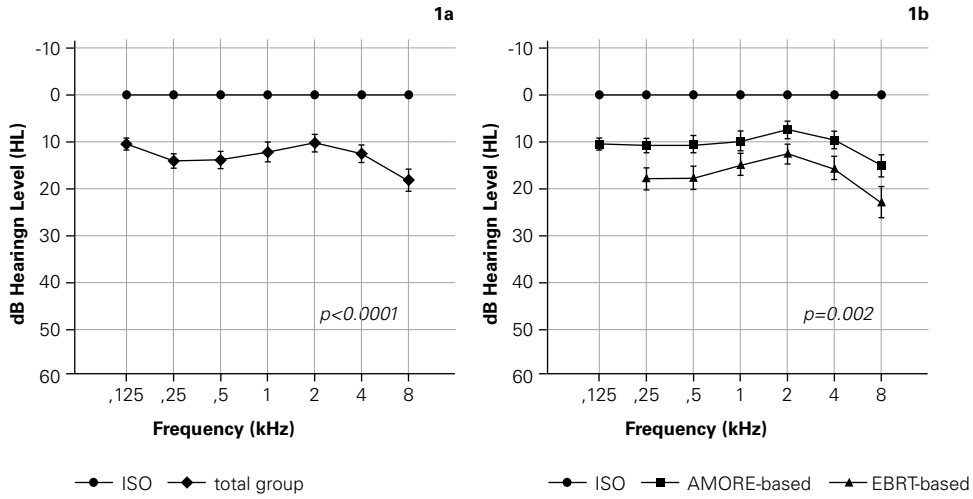
		Total n=73	EBRT-based n=27	AMORE-based n=46	p-value
Age at diagnosis	Mean (range)	5.9 (0.03-13.7)	5.3 (1.0-12.7)	6.3 (0.03-13.7)	0.367[a]
	Median	5.2	5.2	5.7	
Age at follow-up	Mean	17.4 (5.9-33.6)	16.8 (8.5-27.9)	17.8 (5.9-33.6)	0.552[a]
	Median	16.8	16.7	17.6	
Age ≥18	No	42 (58%)	18 (67%)	24 (52%)	0.227[b]
	Yes	31 (42%)	9 (33%)	22 (48%)	
Follow-up (year)	Mean (range)	11.5 (2.6-21.7)	11.5 (2.8-21.7)	11.5 (2.6-21.0)	0.914[a]
	Median	11.0	11.0	11.0	
Gender	Male	48 (66%)	21 (78%)	27 (59%)	0.097[b]
	Female	25 (34%)	6 (22%)	19 (41%)	
Tumor histology	Embryonal	61 (84%)	20 (74%)	41 (89%)	0.055[b]
	Alveolar	9 (12%)	4 (15%)	5 (11%)	
	Other	3 (4%)	3 (11%)	0	
Tumor localization	Parameningeal	40 (55%)	17 (63%)	23 (50%)	0.472[b]
	Orbit	24 (33%)	8 (30%)	16 (35%)	
	Non-parameningeal	9 (12%)	2 (7%)	7 (15%)	
Radiotherapy	No RT	6 (8%)	2 (7%)	4 (9%)	<0.001[b]
	Brachytherapy	22 (30%)	0	24 (50%)	
	EBRT	32 (44%)	25 (93%)	7 (15%)	
	Multiple RT	11 (11%)	0	9 (20%)	
	Proton	2 (3%)	0	2 (4%)	

Abbreviations: Abbreviations: EBRT; external beam radiotherapy, AMORE; Ablative surgery, MOld brachytherapy and REconstruction, RT; Radiotherapy
[a] T-test
[b] Pearson Chi-Square test

Overall hearing thresholds

Hearing loss is presented in mean values and plotted against age-corrected normal hearing status (ISO) in figure 1. Hearing thresholds were significantly higher in HNRMS survivors compared to the ISO standard (p<0.0001, figure 1a), implying treatment-induced hearing loss. Hearing thresholds were higher in survivors with EBRT-based treatment compared to survivors with AMORE-based treatment (p=0.002, figure 1b).

Figure 1 | Mean air conduction hearing thresholds with standard errors in decibel hearing level at long-term follow-up



Abbreviations: EBRT; external beam radiotherapy, AMORE; Ablative surgery, MOld brachytherapy and REconstruction, ISO; International Organization for Standardization

In this cohort of HNRMS survivors, the median hearing threshold at PTA 0.5-1-2 kHz AC was 6.7 dB HL (table 4). This median hearing threshold was higher in the EBRT-based treatment group compared to the AMORE-based treatment group (10.0 dB HL and 5.0 dB HL respectively; p=0.0002). At 4 kHz the median hearing threshold was 5.0 dB in the complete cohort of HNRMS survivors; 10.0 dB HL for survivors with EBRT-based treatment and 5.0 dB HL for those with AMORE-based treatment (p=0.0007).

Table 4 | Hearing level in decibel at pure tone averages

	Total	EBRT-based	AMORE-based	p-value[a]
PTA 0.5-1-2 kHz AC				
Number of ears	146	54	92	
Mean	11.7	15.4	9.6	0.0002
Median	6.7	10.0	5.0	
Std. dev	17.0	15.7	17.4	
Range	0-118.3	0-75	0-118.3	
4 kHz AC				
Number of ears	146	54	92	
Mean	12.1	15.9	9.9	0.0007
Median	5.0	10.0	5.0	
Std. dev	18.8	18.3	18.8	
Range	0-115	0-85	0-115	

Abbreviations: EBRT; external beam radiotherapy, AMORE; Ablative surgery, MOld brachytherapy and REconstruction. PTA = Pure Tone Average; AC = Air Conduction; Std. dev = standard deviation
[a] repeated measurements analysis of log (PTA kHz HL + 1 dB) for each PTA

Clinically relevant hearing loss

At PTA 0.5-1-2 kHz AC, 14/73 survivors (19%) had clinically relevant hearing loss. 7/27 (26%) survivors in the EBRT-based treatment group developed clinically relevant hearing loss versus 7/46 (15%) survivors in the AMORE-based treatment group (p=0.26). At 4 kHz AC, we found clinically relevant hearing loss in 18/73 survivors (25%): 9/27 survivors (33%) in the EBRT-based treatment group versus 9/46 survivors (20%) in the AMORE-based treatment group (p=0.19).

To distinguish between types of hearing loss we evaluated ABGs in ears with clinically relevant hearing loss (i.e. ≥20 dB loss), combined with results from the tympanometry and/or otoscopy. Of the 15 ears with clinically relevant hearing loss at PTA 0.5-1-2 kHz, 14 ears (93%) had an ABG, an abnormal tympanogram, or an abnormal otoscopy, implying a conductive or mixed type of hearing loss. In one ear, hearing loss was assumed to be sensorineural since the tympanogram and otoscopy were normal.

Grading scales

Hearing impairment graded according to CTCAEv4.0 and Boston criteria is presented in table 5. We used AC thresholds for toxicity assessment as BC thresholds were missing

in 48/146 ears. We detected hearing loss in 42% according to the CTCAEv4.0 and in 55% according to the Boston scale. We found no statistically significant differences between treatment groups.

Table 5 | Number of patients with ototoxicity scored by grading scales

Scale	Grade	Total cohort n=73	EBRT-based n=27	AMORE-based n=46	p-value
CTCAEv4	0	42 (58%)	15 (56%)	27 (59%)	0.551[a]
	1	9 (12%)	3 (11%)	6 (13%)	
	2	5 (7%)	1 (3%)	4 (8%)	
	3	17 (23%)	8 (30%)	9 (20%)	
	4	0 (0%)	0 (0%)	0 (0%)	
	Total 1-4	31 (42%)	12 (44%)	19 (41%)	
Boston	0	33 (46%)	11 (41%)	22 (48%)	0.669[a]
	1	17 (23%)	7 (26%)	10 (22%)	
	2	1 (1%)	0 (0%)	1 (2%)	
	3	14 (19%)	6 (22%)	8 (17%)	
	4	8 (11%)	3 (11%)	5 (11%)	
	Total 1-4	40 (55%)	16 (59%)	24 (52%)	

Abbreviation: EBRT; external beam radiotherapy, AMORE; Ablative surgery, MOld brachytherapy and REconstruction. CTCAEv4; Common Terminology Criteria for Adverse Events version 4
[a] = Linear-by-Linear Association Test

Regression analysis

In the univariate analysis the hearing threshold was approximately 6.6 dB higher for survivors in the EBRT-based treatment group compared to survivors in the AMORE-based treatment group (p=0.002; table 5). Hearing threshold in survivors with parameningeal tumors was 7.3 dB higher compared to survivors with non-parameningeal tumors (p=0.006). Age at diagnosis, age at audiometry, and follow-up time did not correlate with post-treatment hearing loss.

Table 6 | Expected hearing threshold based on a repeated measurements analysis (146 ears)

Characteristic	Expected hearing threshold, in dB HL (95% CI)	Difference in Expected hearing threshold, in dB	p-value
Treatment group			
AMORE-based	5.9 (4.0-8.4)	Ref.	
EBRT-based	12.5 (8.6-18.0)	6.6	0.002
Tumor localization			
Parameningeal	10.5 (7.6-14.4)	Ref.	
Orbit	6.9 (4.2-11.0)	-3.6	0.13
Non-parameningeal	3.2 (1.2-7.2)	-7.3	0.006
Age at diagnosis (years)			
<=7	9.6 (6.8-13.4)	Ref.	
8-17	6.4 (3.9-9.9)	3.2	0.12
Age at audiometry (years)			
<=7	7.5 (1.5-27.9)	-0.4	0.94
8-17	8.7 (5.9-12.6)	0.8	0.73
>=18	7.9 (5.2-11.9)	Ref.	
Follow-up time (years)			
<=4	14.3 (6.6-30.0)	7.3	0.11
5-9	7.0 (4.3-11.0)	Ref.	
10-14	8.1 (4.7-13.5)	1.1	0.67
15-19	7.5 (4.2-12.7)	0.5	0.85
>=20	11.9 (5.0-26.8)	4.9	0.27

Abbreviations: EBRT; external beam radiotherapy, AMORE; Ablative surgery, MOld brachytherapy and REconstruction, dB; decibel
Results are based on a repeated measurements linear regression of log(PTA 0.5-1-2 kHz HL + 1 dB) together with each variable in the table separately. Regression *p*-values and expected hearing thresholdfor the left ear are reported. Results for right ear are similar. Difference in expected hearing thresholdis calculated within each characteristic as expected hearing thresholdin the corresponding category minus the expected hearing thresholdin the reference category in the regression analysis.

In the multivariate analysis, the difference in hearing threshold between treatments groups remained significant after adjustment for localization (5.4 dB, p=0.001). Also, the parameningeal tumor localization still predisposed to a higher threshold, after adjustment for treatment group (6.6 dB, p=0.008).

DISCUSSION

Clinically relevant hearing loss (i.e. ≥20 dB deterioration) occurred in 19% of HNRMS survivors at speech frequencies (PTA 0.5-1-2 kHz) and in 25% of survivors at 4 kHz. When graded according to the CTCAEv4.0 and Boston scale criteria we detected hearing loss in 42% and 55% of HNRMS survivors, respectively. Hearing thresholds were 5.4 dB higher in survivors with EBRT-based treatment compared to survivors with AMORE-based local treatment (p=0.001), after adjustment for tumor site. Parameningeal site predisposed for higher hearing thresholds in both treatment groups.

Remarkably, the hearing loss reported in this study was mainly conductive. Radiation-induced growth inhibition of the skull bones, may lead to deformities in the area of middle ear and Eustachian tube, causing obstruction of discharge of middle ear effusions. This could finally lead to fibrosis of the Eustachian tube, sclerosis of the tympanic membrane, and ankylosis of the ossicles. Literature regarding hearing loss in HNRMS survivors is sparse. Incidence rates of hearing loss varied between 10% and 50%.[5,6,23,24] However, none of these studies systematically assessed hearing loss in a prospective setting. In addition, neither a clear definition of hearing loss, nor a validated grading scale was used. This study suggests an advantage of the AMORE approach for long-term hearing status in survivors of HNRMS compared to the international standard: EBRT. Nevertheless, the difference in hearing loss we detected in this study was small.

Limitations of the study

Ototoxic chemotherapeutics or antibiotics may have contributed to the sensorineural component of the hearing loss. No information regarding ototoxic medication was available for either cohort. However, the maximum dose of carboplatin was 3600 mg/m^2. The exact carboplatin dose causing ototoxicity is yet unknown: some studies reported no hearing loss after median carboplatin doses up to 8400 mg/m^2, while others reported ototoxicity after carboplatin doses between 1020 to 4710 mg/m^2.[25] Hence, carboplatin-induced ototoxicity cannot be ruled out completely. However, the type of hearing loss in our survivors was mainly conductive while carboplatin induced ototoxicity would cause sensorineural hearing loss instead. An important limitation of this study is that the EBRT techniques used are now historical by current standards. The earliest patients in this study received conventional

radiotherapy with fields defined by simulation and two dimensional radiotherapy planning. Three dimensional conformal radiotherapy only became available in the mid 1990s. Intensity modulated radiotherapy (IMRT) for instance, allows a higher degree of conformity and homogeneity than was possible with previous techniques, and so will possibly carry a significantly lower risk of hearing loss. However, this inaccuracy is inherent to studying late AEs, where AEs will occur when newer treatments already have been developed. Therefore, ongoing studies are required to study radiotherapy induced hearing loss in survivors treated with newer techniques, such as IMRT and proton beam, and compare these results with survivors treated with AMORE.

In this cohort of HNRMS survivors, hearing loss was predominantly conductive. BC measurements were missing in 33% of survivors, making adequate comparisons between treatment groups concerning sensorineural hearing loss impossible. Furthermore, we could not determine exact threshold shifts, as baseline audiograms were not available. Therefore, we assumed that the children had normal hearing levels at the start of therapy and that the decreased hearing level after therapy was the result of treatment. It would have been more accurate if a threshold shift could have been measured.

The results of this study would be of more value when radiation doses to the specific organs at risk were reconstructed and a more homogeneous group was tested. We realize that this is an important limitation of the study. Nevertheless, we are the first in presenting a prospective audiometric assessment in a consecutive cohort of HNRMS survivors in an international setting. Our results indicate that not only survivors with HNRMS sites surrounding the hearing apparatus are at risk for radiation damage, but also the other non-parameningeal head and neck sites. This study may serve as a baseline study for future international collaborative efforts, investigating hearing loss in HNRMS survivors.

CONCLUSION

Nineteen percent of HNRMS survivors developed clinically relevant hearing loss at speech frequencies. AMORE-based treatment resulted in a reduction of 6.6 dB compared to EBRT-based treatment. This study emphasizes that HNRMS survivors are at risk to develop hearing loss. Therefore, we recommend systematic audiological follow-up in this specific patient population.

REFERENCES

1. Miller RW, Young JL, Jr., Novakovic B. Childhood cancer. *Cancer.* Jan 1 1995;75(1 Suppl):395-405.

2. McDowell HP. Update on childhood rhabdomyosarcoma. *Arch Dis Child.* Apr 2003;88(4):354-357.

3. Paulino AC, Okcu MF. Rhabdomyosarcoma. *Curr Probl Cancer.* Jan-Feb 2008;32(1):7-34.

4. Fiorillo A, Migliorati R, Vassallo P, et al. Radiation late effects in children treated for orbital rhabdomyosarcoma. *Radiother Oncol.* Nov 1999;53(2):143-148.

5. Raney RB, Asmar L, Vassilopoulou-Sellin R, et al. Late complications of therapy in 213 children with localized, nonorbital soft-tissue sarcoma of the head and neck: A descriptive report from the Intergroup Rhabdomyosarcoma Studies (IRS)-II and - III. IRS Group of the Children's Cancer Group and the Pediatric Oncology Group. *Med Pediatr Oncol.* Oct 1999;33(4):362-371.

6. Fromm M, Littman P, Raney RB, et al. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. *Cancer.* May 15 1986;57(10):2070-2076.

7. Raney RB, Anderson JR, Kollath J, et al. Late effects of therapy in 94 patients with localized rhabdomyosarcoma of the orbit: Report from the Intergroup Rhabdomyosarcoma Study (IRS)-III, 1984-1991. *Med Pediatr Oncol.* Jun 2000;34(6):413-420.

8. Stevens MC. Treatment for childhood rhabdomyosarcoma: the cost of cure. *Lancet Oncol.* Feb 2005;6(2):77-84.

9. Buwalda J, Schouwenburg PF, Blank LE, et al. A novel local treatment strategy for advanced stage head and neck rhabdomyosarcomas in children: results of the AMORE protocol. *Eur J Cancer.* Jul 2003;39(11):1594-1602.

10. Schouwenburg PF, Kupperman D, Bakker FP, Blank LE, de Boer HB, Voute TA. New combined treatment of surgery, radiotherapy, and reconstruction in head and neck rhabdomyosarcoma in children: the AMORE protocol. *Head Neck.* Jul 1998;20(4):283-292.

11. Buwalda J, Blank LE, Schouwenburg PF, et al. The AMORE protocol as salvage treatment for non-orbital head and neck rhabdomyosarcoma in children. *Eur J Surg Oncol.* Oct 2004;30(8):884-892.

12. Buwalda J, Freling NJ, Blank LE, et al. AMORE protocol in pediatric head and neck rhabdomyosarcoma: descriptive analysis of failure patterns. *Head Neck.* May 2005;27(5):390-396.

13. Blank LE, Koedooder K, Pieters BR, et al. The AMORE protocol for advanced-stage and recurrent nonorbital rhabdomyosarcoma in the head-and-neck region of children: a radiation oncology view. *Int J Radiat Oncol Biol Phys.* Aug 1 2009;74(5):1555-1562.

14. Blank LE, Koedooder K, van der Grient HN, et al. Brachytherapy as part of the multidisciplinary treatment of childhood rhabdomyosarcomas of the orbit. *Int J Radiat Oncol Biol Phys.* Aug 1 2010;77(5):1463-1469.

15. Schoot RA, Slater O, Ronkers C, et al. Adverse events of local treatment in long-term head and neck rhabdomyosarcoma survivors after external beam radiotherapy or AMORE treatment. *European Journal of Cancer.* 2015; accepted for publication

16. Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. *J Clin Oncol.* Jul 10 2012;30(20):2457-2465.

17. Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology–SIOP Malignant Mesenchymal Tumor 89. *J Clin Oncol.* Apr 20 2005;23(12):2618-2628.

18. Bisogno G, Bergeron C, Jenney M. European paediatric soft tissue sarcoma study group RMS 2005 - a protocol for non metastatic rhabdomyosarcoma. 2005; Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2005-000217-35 Assessed on February 25, 2015.

19. Gurgel RK, Popelka GR, Oghalai JS, Blevins NH, Chang KW, Jackler RK. Is it valid to calculate the 3-kilohertz threshold by averaging 2 and 4 kilohertz? *Otolaryngol Head Neck Surg*. Jul 2012;147(1):102-104.

20. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009; Available at: *http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*. Assessed on February 25, 2015.

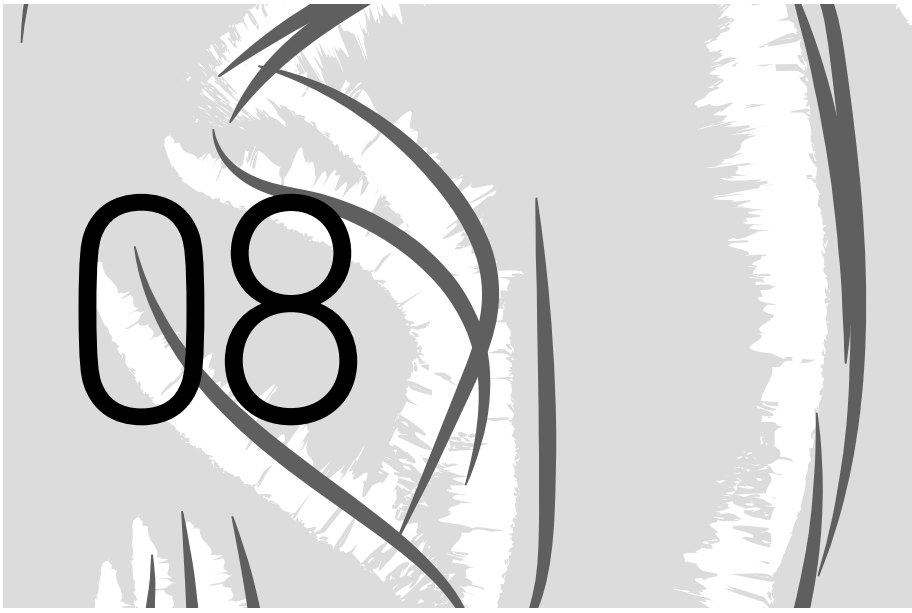
21. Brock PR, Knight KR, Freyer DR, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. *J Clin Oncol.* Jul 1 2012;30(19):2408-2417.

22. International Organisation for Standardization. Acoustics - Statistical distribution of hearing thresholds as a function of age. 2000, 2nd edition, Reference number ISO 7029:2000 (E).

23. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. *Int J Radiat Oncol Biol Phys*. Feb 1 2012;82(2):635-642.

24. Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. Dec 1 2000;48(5):1489-1495.

25. Jehanne M, Lumbroso-Le Rouic L, Savignoni A, et al. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. *Pediatr Blood Cancer*. May 2009;52(5):637-643.


08

CHAPTER 08

Summary
General discussion and future perspectives

SUMMARY

This thesis describes cisplatin and radiotherapy-induced ototoxicity in patients with head and neck cancer. Ototoxicity is a common adverse event after cisplatin treatment and radiotherapy to the head and neck area, with incidences reported up to 88% after chemoradiotherapy (CRT) and 54% after radiotherapy (RT).[1,2] Ototoxicity is not a life threatening disease, but it can have a major impact on a patient's quality of life. Counseling patients about this adverse event is important, especially for patients who rely heavily on auditory input (e.g. teachers, musicians, the vision impaired). The thesis main objective is to improve our knowledge of (chemo-) radiation induced ototoxicity in patients with advanced head and neck cancer. This knowledge will contribute to more evidence based counseling for the effected patients.

Treatment-induced ototoxicity is characterized by hearing loss, tinnitus, conductive and/or sensorineural, and vestibular effects, such as vertigo. This thesis focuses on the effects of hearing, rather than the vestibular effects.

The first study describes a systematic review of (chemo)radiotherapy induced sensorineural hearing loss (SNHL) in head and neck cancer patients (**chapter 2**). A comprehensive search of the Medline and Embase databases was obtained. All retrieved articles (2507) were screened for title and abstract by two independent researchers who also critically assessed the methodological quality and the risk of bias. Included articles were evaluated on incidences of SNHL and risk factors to develop SNHL. Twenty-one studies were included. Incidence rates of SNHL after RT and CRT varied considerably, with percentages ranging from 0 to 43% after RT and from 17 to 88% after CRT. Overall, a higher radiation dose to the cochlea was associated with a higher risk to develop sensorineural hearing loss after treatment, with a minimum ototoxic cochlear dose of 47 Gray. Also, the cumulative cisplatin dose is reported to be a significant independent factor in determining the incidence of SNHL. Furthermore, the literature showed that younger patients may endure relatively more hearing loss in terms of dB deterioration, but they will end up with better thresholds in terms of dB HL after treatment than older patients do.

Due to heterogeneity of the studies pooled analysis of the results was not possible. This heterogeneity was mainly caused by the various definitions used for ototoxicity. To assess the impact of this phenomenon, we applied all definitions to one high-dose CRT patient cohort from our institute. This resulted in a wide-spread variation in ototoxicity outcome values, ranging from 0-89% (table 6, chapter 2). Consequently, it is difficult to draw unambiguous conclusions about the exact incidence of (C)RT induced SNHL. We therefore recommend using one uniform grading scale in future research concerning treatment-related SNHL. To stimulate the use of one uniform grading system, this problem is further addressed in **chapter 3** of this thesis.

In this chapter we describe the currently existing standards and limitations. Existing standards to score hearing impairment are the Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) or the American Speech Language Hearing Association (ASHA) criteria. Although these criteria are available, they are not consistently used for research purposes. The inconsistent use of these criteria might be caused by the following: The ASHA criteria do not define which frequencies should be selected to be used for the scoring of hearing loss. Moreover, its criteria do not assess a step-by-step increase of hearing impairment. The CTCAEv4 for adults prescribes the use of frequencies between 1 and 8 kHz, but the CTCAEv4 weigh each of these frequencies equally and it does not consider the clinical importance of specific frequency regions for speech intelligibility or sound quality, e.g. in music. In addition, CTCAEv4 grades 2 and 3 are coarsely defined (width of 25-80 dB loss), which may further dissociate the grading of a hearing loss and its effect on the daily functioning of a patient. Finally, in CTCAEv4 ultra-high frequencies are disregarded, although hearing impairment generally starts at these frequencies.

To improve the current criteria, we translated the impact of treatment-induced hearing loss to relevant situations in the daily life of a patient by using the pure-tone thresholds in specific frequency regions as representative characteristics for different aspect of hearing: speech intelligibility and sound quality. We incorporated the degree of threshold shifts in dB, the post-treatment hearing level (dB hearing level), and the impact of hearing loss on speech intelligibility in new criteria. We designed four new ototoxicity grades (TUNE). Both Pure Tone Averages (PTAs) for speech perception (1-2-4 kHz) and perception of ultra-high frequencies (8-10-12.5 kHz) were incorporated.

The new criteria were tested on prospective cohorts of patients with head and neck cancer and compared to current ototoxicity criteria. Patients were treated with high-dose CRT, low-dose CRT, or Intensity Modulated Radiotherapy (IMRT). In total, 307 patients and 597 ears were scored. Incidences of hearing impairment due to high-dose CRT were comparable in the new and current criteria. In the IMRT and low-dose CRT patients, incidences were scored higher by the new criteria compared to the current criteria, implying a higher sensitivity of the new system. In the new criteria all patients with a treatment-induced 50% loss of speech intelligibility were scored as grade 3 or 4, whereas in the CTCAE criteria 54% of the patients with a treatment-induced 50% loss of speech intelligibility were scored as grade 0, 1 or 2.

Due to the ultra-high frequencies incorporated, our new grading system may also detect hearing loss in an early stage. This in turn can be considered a warning signal of upcoming loss at speech frequencies. However, the exact risk of hearing loss at speech frequencies per patient remains unknown. In daily clinical practice, continuation of cisplatin infusions is often discussed for reasons of expected ototoxic effects, not only at the start of treatment but also before embarking on a new cisplatin course. Unfortunately, precise answers cannot be given yet and recommendations are still based on personal experience. To overcome the clinical uncertainty regarding the prediction of chemoradiation-induced hearing loss in individual patients, we performed a statistical analysis using audiograms of 81 patients and we were able to construct a prediction model (**chapter 4**).

The main goal was to predict the hearing level at PTA 1-2-4 kHz bone conduction after treatment. A multilevel mixed-effect linear regression model was used, and a cross-validated sensitivity and specificity were obtained. Hearing levels, radiation dose to the cochlea, and cisplatin dose were included as variables for model construction. Eighty-one patients treated with chemoradiation as a primary treatment for head and neck cancer were included. Both ears (162 ears) were evaluated. Results of the 10-fold cross validation showed an area under the ROC of 0.68, with a sensitivity of 29% (95% CI:13%-51%) at a specificity of 97% (95% CI: 88%-100%), resulting in a positive predictive value of 0.78.

A long-term evaluation of cisplatin CRT-induced ototoxicity is presented in **chapter 5**, to study potential reversibility or worsening of treatment-induced hearing loss in time.

For this purpose, a large and homogeneously treated group of patients was selected. Differences between high-dose intravenous (IV, n=80) CRT and high-dose intra-arterial (IA, n=78) CRT-induced ototoxicity were evaluated. Of the initially 158 patients involved, long-term audiometry (median 4.5 years) was available in 64 patients (41%). A multivariable regression model was used to adjust for ear, treatment protocol, gender, age, hearing level, and interval between measurements. The audiometric data showed a significant deterioration (up to 21.6 dB at PTA 8-10-12.5 kHz) in hearing shortly (median 3 months) after treatment. At long-term follow-up (median 4.5 years) there was a discrete increase (up to 5 dB at PTA 8-10-12.5 kHz) in hearing loss compared to these short-term follow-up values. The absolute hearing deteriorations at long-term versus short-term were higher in the CRT-IV group compared to the CRT-IA group at all PTAs. This difference was significant at PTA 0.5-1-2 and 1-2-4 kHz BC (p=0.03 and p=0.04), and at PTA 1-2-4 kHz AC (p=0.007). In conclusion, we found a significant treatment-induced long-term hearing loss, particularly at frequencies 8-10-12.5 kHz and in the CCRT-IV group. However, the degree of hearing loss was relatively small (5 dB) and the clinical relevance may be regarded as modest.

Another long-term follow-up study is described in **chapter 6**. In this study only patients treated with Intensity Modulated Radiation Therapy (IMRT) were evaluated. Audiometry was performed before, short-term (median 3.5 months), and long-term (median 7.6 years) after treatment. Of the initially 101 patients, long-term audiometry was available in 36 patients (36%). To correct for presbycusis during the years of follow-up, age and gender differences were corrected by medians of the International Organization for Standardization (ISO) standard 7029:2000.[3] The average change in hearing thresholds after a median interval of 7.6 years post-treatment was 1.8 - 2.3 dB at speech frequencies (PTA 0.5-1-2 kHz AC and PTA 1-2-4 kHz AC) and 4.4 dB at ultra-high frequencies (PTA 8-10-12.5 kHz) when compared to the short-term follow-up after treatment. Those measured hearing deteriorations turned out to be lower than the expected age-related deterioration, as the averaged calculated hearing loss using ISO was 2.7 - 4.8 dB at speech frequencies and 8.8 dB at ultra-high frequencies. Therefore, it is likely that the modest progressive hearing loss over time can be attributed completely to the natural effects of ageing. Only in patients treated with a high cochlear dose (>45 Gray), a treatment-induced progression of the hearing loss was seen (n=2). Based on our former and current results, patients treated with IMRT in the head and neck area suffer from

modest and clinical irrelevant IMRT-induced hearing loss at both short-term and long-term follow-up, provided that the radiation dose to the cochlea is limited. In current radiotherapy planning the cochlea is still not regarded as an organ at risk. However, we recommend that a dose constraint to the cochlea should be incorporated in the head and neck radiotherapy protocols.

In **chapter 7** we evaluate the hearing status of children treated for a rhabdomyosarcoma in the head and neck region (HNRMS). We studied hearing levels of 73 children at a median of 11 years after treatment for HNRMS. Furthermore, we compared the hearing thresholds between patients treated in a center with the availability of an innovative multidisciplinary local treatment strategy with patients treated with external beam radiotherapy (EBRT). This innovative strategy consists of consecutive Ablative surgery, MOld technique afterloading brachytherapy and surgical REconstruction (acronym AMORE). At all frequencies, we found significantly higher hearing thresholds in the cohort of HNRMS survivors when compared to the ISO standard ($p<0.0001$). At PTA 0.5-1-2 kHz we found a median threshold of 6.7 dB (5.0 dB in survivors treated with AMORE-based treatment versus 10.0 dB in survivors treated with EBRT-based treatment, $p=0.0002$). Clinically relevant hearing loss (defined as a deterioration of ≥20 dB) was seen in 19% of the survivors at PTA 0.5-1-2 kHz. Less clinically relevant hearing loss was seen in the AMORE-based treatment group compared to EBRT-based treatment group: 15% versus 26% ($p=0.26$). Multivariable regression analysis showed that survivors treated with EBRT-based treatment and those with a parameningeal tumor were significantly associated with hearing impairment post-treatment. Unfortunately, a dose effect relationship between radiation dose to the ear and hearing loss could not be established as not all radiation doses to the cochlea were available due to the long time span of the study. However, this study indicates that the AMORE is a meaningful and clinically relevant treatment approach from an ototoxic point of view.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Grading

Over time, extensive research concerning treatment-induced ototoxicity has been conducted. However, in previous literature, various definitions of ototoxicity are applied, which undermine an adequate comparison of clinical data. A recent study comparing the CTCAE, Brock, and Chang grading scales in head and neck cancer patients showed that the Brock and Chang scales may be superior to the CTCAE, and indicated the limitations of the CTCAE. Nevertheless, the CTCAEv4 are to date the most widely accepted grading scales.[4]

In our grading scale study we translated the impact of treatment-induced hearing loss to relevant situations in the daily life of a patient. The new criteria showed a higher sensitivity of the new system compared to the other systems. However, to test the reproducibility of our grading scales, external validation with adequate estimation of the false positive rate and accuracy is required. As a first step, the grading system needs to be applied to another large patient cohort of head and neck cancer patients treated with (chemo)radiotherapy, using the same dosage schemes and preferably in a prospective setting. Patients will need audiometry prior to therapy, after each cisplatin infusion, and 6 weeks after accomplishing treatment. To allow for adequate false positive rates, a second post-treatment audiogram should be obtained within the same time interval (i.e. 6 weeks post-treatment). Both the currently best accepted grading system (the CTCAE) and the new TUNE grading system should be applied on the audiometric values of the same patients, making a comparison between results of incidence and the false positive rate possible. To test whether the grading by TUNE is clinically relevant, questionnaires should be filled out by the patients as well, preferably with use of the Hearing Handicap Inventory (HHI) questionnaire.[5]

Prediction

We demonstrated that patient- and treatment variables are valuable tools for the construction of a prediction formula for hearing level after treatment. By using the formula before the start of treatment an adjustment in treatment schedule can be considered if severe hearing loss is predicted. However, our results indicated that the accuracy of the formula was higher when hearing levels after the first infusion were

added. This difference in predictive power indicates that there might be unknown variables influencing the individual sensitivity to develop hearing loss. One of these unknown variables may be individual vulnerability induced by genetics variants. Some studies suggest that the presence of at least one of the single nucleotide polymorphisms (SNPs) in thiopurine S-methyl transferase (TPMT), cathechol O-methyl transferase (COMT), ATP-binding cassette transporter C3 (ABCC3), and Low density lipoprotein (LRP2, Megalin) are important risk factors in the development of ototoxicity.[6-10] A Kaplan Meier graph showed that the occurrence of one SNP is already associated with an increased risk of development of hearing loss, and that an increasing number of SNP's increases the risk of development of ototoxicity.[7] In the study of Pussegode et al.[9] a predictive model including clinical variables (age, treatment, germ-cell tumor, and cranial irradiation) and genetic variables (variants in TPMT, ABCC3, and COMT) had a significantly higher predictive power when compared with a prediction model using clinical variables only (area under the curve (AUC) 0.786 vs. 0.708, p=0.00048). In the future, integrating genetic variants as variables in our prediction model might therefore improve the predictive power. However, as current literature on genetic variants is mainly performed in pediatric cohorts, studies in adults regarding those SNPs are required. Furthermore some genetic associations shown in an original study have not yet been replicated.[9] Hence, further research is required to confirm the current results found by researchers described above.[11]

Since research regarding the genetic variants is still going on, it will take some time to finally implement these genetic variants as variables in the prediction model. Moreover, at the present time, it is not standard to investigate the DNA of every patient looking for genetic variants. Therefore, at this moment it is wise to further validate the prediction model based on clinical data. As a first step we already used the 10-fold cross-validation to exclude any overfitting. In the future an external validation needs to be performed. This way a validated model can be used in clinical practice. When consensus about genetic variants is found the added value of genetic information can be considered, as genetic information has the potential to improve the predictive power of the model.

Long-term effects

While a progression in treatment-induced hearing loss was found in patients treated with CRT, patients treated with IMRT as a single modality treatment did not show any

progressive hearing loss. This difference seems obvious, since CRT includes cisplatin whereas patients treated with IMRT did not receive any chemotherapy at all. The median radiation doses did not differ: both patients cohorts treated with CRT and IMRT received on average 13.0 Gray to the cochlea. However, due to a synergistic effect between cisplatin and RT, a median dose of 13 Gy may become toxic when combined with cisplatin. However, an adequate conclusion about the potentially synergistic effects of RT and cisplatin can only be arrived at after a comparison of different patient groups treated with RT as a single modality treatment and cisplatin as a single modality treatment, compared to cisplatin based CCRT. Unfortunately, this approach is not an option in head and neck cancer patients since cisplatin as a single modality curative treatment is not used in head and neck oncology.

In current clinical practice a limitation of the radiation dose to the cochleae is not standardly taken into consideration. Even stronger, the Radiotherapy Oncology Group (RTOG) has not formulated any guidelines yet regarding dose constrains to the cochlea in H&N treatment protocols. Even in IMRT with limited doses to the tumor surrounding tissues, doses given to tissues not considered as 'organs at risk' can be larger than the dose given in conventional or conformal treatment plans. Therefore the cochlea should be officially recognized and treated as an organ at risk, unless sparing of the cochlea is not possible for reasons of treatment margins. Although an exact safe radiation threshold is still missing in the literature, we suggest limiting the radiation dose to a maximum dose of 45 Gy, based on the results shown in the systematic review regarding radiotherapy-induced hearing loss.[12] Our data did not allow determining a dose-effect relationship for the radiation dose to the cochlea, so an exact threshold cannot be given. In our opinion, more research investigating the exact threshold dose is very difficult and will not lead to any other clinical consequences. It is common sense to assume that a lower dose to an organ at risk will exert fewer side effects. Therefore, it is important to emphasize that the cochlea should be addressed as an organ at risk. As a first step, Pacholke et al.[13] described a guideline for contouring the middle and inner ear. These guidelines can be of practical help to radiation oncologists as they described the landmarks, reference values for the volume, and reference values for the maximum axial dimensions of the middle ear, the cochlea, and the vestibular apparatus.

Ototoxicity in children

Hearing status in young children is very important for speech and language development. Even if the hearing loss is unilateral or mildly bilateral, young children are at risk for psycho-educational and psychosocial deficits.[14] Children treated for a rhabdomyosarcoma in the head and neck region (HNRMS) are at risk developing hearing loss. So far, hearing loss in those patients has been reported sparsely and has never been assessed systematically. We are the first reporting an extensive analysis of hearing loss in HNRMS patients. Future studies need to confirm our results. Since 19% of HNRMS survivors experience hearing loss after treatment it is strongly recommended to perform audiometry as a standard procedure during the follow-up in patients treated for HNRMS. Moreover, when the AMORE (Ablative surgery, MOld technique afterloading brachytherapy and surgical REconstruction) procedure is feasible as a local treatment modality, this approach should be preferred.

In order to study a large number of patients with HNRMS an international cooperation is needed. International trials concerning treatment options are performed by The International Society of Pediatric Oncology-Malignant Mesenchymal Tumor group (SIOP-MMT) and/or the European *pediatric* Soft Tissue Sarcoma Study Group (E*p*SSG). Ideally, all these patients should also be screened for hearing loss. That way the hearing status can be monitored in a large population. Moreover, the effect of different radiotherapy modalities such as brachytherapy, Intensity Modulated Radiation Therapy, and proton treatment can be compared, provided that standardized criteria and evaluation procedures will be used. In addition, collecting data regarding the radiation dose delivered to the cochlea, may allow establishing an adequate dose-effect relationship.

Cisplatin and its side effects

This thesis focusses on the combined ototoxic effects of cisplatin and radiotherapy to the head and neck area. However, besides ototoxicity, cisplatin is also known to cause systemic toxicities such as nephrotoxicity, nausea, vomiting, and myelosuppression. Nephrotoxicity can be managed with hydration and the gastrointestinal side effects can be managed with anti-emetic agents.[15] However, no effective medical treatment for the prevention of ototoxicity has been developed yet.

To increase the cisplatin dose into the tumor, while simultaneously minimizing the systemic toxicity, an intra-arterial (IA) administration scheme of high-dose cisplatin with concurrent RT was developed. In this scheme cisplatin was infused directly in the nutrient artery of the tumor while sodium thiosulfate for cisplatin neutralization was infused intravenously (IV) at the same time. A phase 3 trial (acronym RADPLAT) comparing conventional radiation with either IV or IA cisplatin administration for anatomically and functionally irresectable locally advanced head and neck cancer was started in 2000. Eventually, CRT-IA was found to be neither superior nor inferior to CRT-IV regarding loco-regional control and survival.[16] However, less ototoxicity was reported in the CRT-IA group compared to the CRT-IV group at speech frequencies.[17] In our study concerning the long-term effects of cisplatin based CCRT on hearing, a progression in treatment-induced hearing loss was seen in the CRT-IV group, whereas this was not found in patients in the CRT-IA group. This phenomenon might be explained by the simultaneous infusions of sodium thiosulfate (STS) in the CRT-IA group, suggesting an otoprotective effect of STS. However, a reduction of cisplatin levels by STS cannot be ruled out completely. So, studies concerning local or systemic otoprotective agents are needed.

Otoprotective agents

To protect the inner ear from ototoxicity, while continuing the optimal platinum chemotherapy, several agents were studied to identify otoprotective agents.[18-27] A variety of agents with chemoprotective action against cisplatin ototoxicity have been successfully tested in animals[18-21,24-27] and in auditory cell lines.[22,23] Meanwhile, STS and *N*-acetylcysteine have received a Food and Drug Administration (FDA) orphan status for the indication of otoprotection in humans.[19] To avoid systematic reduction of anti-tumor activity, local administration to the middle ear cavity is an opportunity to achieve the beneficial effect on hearing, without reducing the cytotoxic effect to the tumor cells. A few studies in humans have been recently completed and reported promising results using STS, *N*-acetylcysteine, or dexamethason as a local protective agent.[28-31] A recent Cochrane Review performed by van As et al.[32] searched for randomized controlled trials or controlled clinical trials evaluating platinum-based therapy together with any otoprotective medical intervention versus platinum-based therapy with placebo or no additional treatment. They concluded that presently there is no evidence for a protective effect for any of the otoprotective medical interventions studied.

In our institute a pharmaceutical formulation has been developed to apply STS to the middle ear. The developed gel formulation consists of a high viscosity sodium hyaluronan gel with the addition of 0.1M STS, which has been used in a previous preclinical study without the occurrence of side effects.[33] At the moment, we are including patients in a phase I/II trial to test the otoprotective effect of STS in humans. Patients who will receive cisplatin treatment with a cisplatin dose of at least ≥75 mg/m2 are included. A volume of 1.0 ml of the STS containing or placebo gel will be injected into the middle ear, 3 hours before each cisplatin infusion. Audiometric tests will be performed 21 days prior to start of treatment, within 7 days prior to start of each cisplatin infusion, and 4 weeks after the end of treatment. Hopefully, the otoprotective effect seen in animals will also be present in humans.

Alternatives for cisplatin

If cisplatin is contraindicated (nephrotoxicity, neuropathy, ischemic heart disease, or impaired hearing) an alternative drug must be obtained. Carboplatin is considered as an alternative chemotherapeutic agent since carboplatin has the similar mode of action. Carboplatin has a lot of advantages compared to cisplatin: it exerts lower rates of nephrotoxicity, neurotoxicity and emesis,[34] and it has an out-patient administration schedule, resulting in reduced costs. In a number of studies none, or only a low level of ototoxicity was reported after carboplatin treatment.[35] Regarding survival rates, four trials have directly compared cisplatin and carboplatin treatments in head and neck cancer patients. Two of them showed better overall survival after treatment with cisplatin.[36,37] The other two studies showed similar survival rates.[38,39] Wilkins et al in 2013 obtained a matched pair analysis comparing patients treated with concomitant radiotherapy with either carboplatin or cisplatin.[40] They showed no difference in loco-regional control, distant metastases, and overall survival. A meta-analysis in patients with advanced non-small-cell lung cancer showed that cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy.[41] In all studies described above, toxicity rates were more common in patients treated with cisplatin. However, given the fact that research concerning the effect on tumor control is more extensive in cisplatin than in carboplatin, cisplatin has become the standard when treatment with a platinum is indicated.[42]

Cisplatin in a low-dose regime (i.e. 6 mg/m^2, daily infusions for 5 weeks) is also given to patients contraindicated to cisplatin high-dose regime. It has been shown that cisplatin low-dose exerts less toxicities compared to cisplatin high-dose.[43] However, studies comparing the effects on loco-regional control and survival are absent from the literature.

A lot of research is done evaluating the effect of cetuximab in head and neck cancer patients. Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR).[44] It is involved in several mechanisms, including induction of apoptosis and enhancement of the response to chemotherapy and radiation.[45] A phase III study in locally advanced head and neck cancer demonstrated that cetuximab increases overall survival when combined with radiotherapy alone, while not enhancing the local toxicities.[46,47] In addition, the EXTREME (Erbitux (= cetuximab) in First-Line Treatment of Recurrent or Metastatic Head & Neck Cancer) study showed that addition of cetuximab to platinum-based chemotherapy with fluorouracil improved the overall survival, progression-free survival, and response rates.[48] Meanwhile, cetuximab has been approved by the US Food and Drug Administration in combination with radiation in locally advanced HNSCC, and as first-line treatment in combination with platinum/fluorouracil in the recurrent/metastatic setting. The TREMPLIN study compared radiotherapy with cisplatin versus radiotherapy with cetuximab.[49] After 3 cycles of induction chemotherapy with docetaxel, cisplatin, and fluorouracil, patients were randomized to either an arm treated with cisplatin during conventional radiotherapy or the arm treated with cetuximab during conventional radiotherapy. Overall survival did not differ between the two arms (median follow-up of 36 months). However, both arms had substantial overall toxicity (hearing loss not specified). Currently, an RTOG 1016 study is comparing accelerated IMRT + cisplatin versus accelerated IMRT+ cetuximab in HPV positive oropharyngeal cancers.[50] In the future, it might be possible that cisplatin is not the only chemotherapeutic option anymore regarding the treatment of head and neck cancer.

Personalized medicine

Ideally, all cancer patients should receive a treatment that has proven to be effective for their specific tumor, with acceptable side effects. Not only does a wide variety in tumor response exist, but the impact of side effects may also differ significantly from person to person. For example, patients with impaired vision will experience hearing loss as a

larger disabling side effect, than a person for whom hearing loss has less of an impact on daily life. Individualizing treatment schedules poses an enormous challenge for the head and neck oncologists. Researchers are focusing on the uniqueness of tumors by analyzing their characteristics. It is possible that tumors from the same origin have different characteristics, making their responsiveness to a specific treatment highly variable. For example, oropharyngeal cancers can be subdivided in human papilloma virus (HPV) positive and HPV negative cancers. HPV+/- oropharyngeal cancers are recognized as two different diseases, with different etiologies, demographics, and prognoses.[51] This can result in different treatment options for HNSCC and based on the tumor characteristics an optimal treatment can be chosen. In case of low-risk patients, less intensive treatment options can be considered. For example, de-intensification options for radiation therapy are reduction of the RT volume by unilateral radiation, or reduction of the beam path spread by using protons. In conclusion, in the future, an optimal treatment should incorporate both an effective tumor treatment and a consideration of the impact of the side effects that are likely to appear.

Overall, this thesis contributes to a better insight in cisplatin and/or radiotherapy induced hearing loss. It will make researchers and clinicians more aware of the complexity of the ototoxic effects and the problems we currently face. In addition, two clinical tools have been developed: a grading system and a prediction model. By using these tools, both research and the daily clinical practice regarding of this subject may be well improved.

REFERENCES

1. Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 20 2007;25(24):3759-3765.

2. Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. *The Journal of laryngology and otology.* Jan 2010;124(1):32-36.

3. International Organization for Standardization 2000, Reference number ISO 7029:2000 (E). International Standard. Acoustics - Statistical distribution of hearing thresholds as a function of age.

4. Colevas AD, Lira RR, Colevas EA, et al. Hearing evaluation of patients with head and neck cancer: Comparison of Common Terminology Criteria for Adverse Events, Brock and Chang adverse event criteria in patients receiving cisplatin. *Head & neck.* Apr 15 2014.

5. Newman CW, Weinstein BE, Jacobson GP, Hug GA. The Hearing Handicap Inventory for Adults: psychometric adequacy and audiometric correlates. *Ear and hearing.* Dec 1990;11(6):430-433.

6. Riedemann L, Lanvers C, Deuster D, et al. Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. *Pharmacogenomics J.* Feb 2008;8(1):23-28.

7. Ross CJ, Katzov-Eckert H, Dube MP, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. *Nat Genet.* Dec 2009;41(12):1345-1349.

8. Pussegoda KA. Genetic variants associated with cisplatin-induced hearing loss. *Clin Genet.* Jul 2010;78(1):33-35.

9. Pussegoda K, Ross CJ, Visscher H, et al. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clinical pharmacology and therapeutics.* Aug 2013;94(2):243-251.

10. Yang JJ, Lim JY, Huang J, et al. The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. *Clinical pharmacology and therapeutics.* Aug 2013;94(2):252-259.

11. Ratain MJ, Cox NJ, Henderson TO. Challenges in interpreting the evidence for genetic predictors of ototoxicity. *Clinical pharmacology and therapeutics.* Dec 2013;94(6):631-635.

12. Mujica-Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head & neck.* Nov 2013;35(11):1662-1668.

13. Pacholke HD, Amdur RJ, Schmalfuss IM, Louis D, Mendenhall WM. Contouring the middle and inner ear on radiotherapy planning scans. *American journal of clinical oncology.* Apr 2005;28(2):143-147.

14. Tharpe AM. Unilateral and mild bilateral hearing loss in children: past and current perspectives. *Trends Amplif.* Mar 2008;12(1):7-15.

15. Goncalves MS, Silveira AF, Teixeira AR, Hyppolito MA. Mechanisms of cisplatin ototoxicity: theoretical review. *The Journal of laryngology and otology.* Jun 2013;127(6):536-541.

16. Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer.* May 1 2010;116(9):2159-2165.

17. Zuur CL, Simis YJ, Lansdaal PE, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. *Int J Radiat Oncol Biol Phys.* Aug 1 2007;68(5):1320-1325.

18. van den Berg JH, Beijnen JH, Balm AJ, Schellens JH. Future opportunities in preventing cisplatin induced ototoxicity. *Cancer treatment reviews.* Aug 2006;32(5):390-397.

19. Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. *Trends in pharmacological sciences.* Aug 2013;34(8):458-469.

20. Fetoni AR, Eramo SL, Paciello F, et al. Curcuma longa (curcumin) decreases in vivo cisplatin-induced ototoxicity through heme oxygenase-1 induction. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* Jun 2014;35(5):e169-177.

21. Sagit M, Korkmaz F, Gurgen SG, Kaya M, Akcadag A, Ozcan I. The protective role of thymoquinone in the prevention of gentamicin ototoxicity. *American journal of otolaryngology.* Jul 10 2014.

22. Cho SI, Lee JH, Park JH, Do NY. Protective effect of (-)-epigallocatechin-3-gallate against cisplatin-induced ototoxicity. *The Journal of laryngology and otology.* Apr 15 2014:1-6.

23. Chang J, Jung HH, Yang JY, et al. Protective effect of metformin against cisplatin-induced ototoxicity in an auditory cell line. *Journal of the Association for Research in Otolaryngology : JARO.* Apr 2014;15(2):149-158.

24. Thomas Dickey D, Muldoon LL, Kraemer DF, Neuwelt EA. Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. *Hearing research.* Jul 2004;193(1-2):25-30.

25. Choe WT, Chinosornvatana N, Chang KW. Prevention of cisplatin ototoxicity using transtympanic N-acetylcysteine and lactate. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* Nov 2004;25(6):910-915.

26. Wimmer C, Mees K, Stumpf P, Welsch U, Reichel O, Suckfull M. Round window application of D-methionine, sodium thiosulfate, brain-derived neurotrophic factor, and fibroblast growth factor-2 in cisplatin-induced ototoxicity. *Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology.* Jan 2004;25(1):33-40.

27. Wang J, Lloyd Faulconbridge RV, Fetoni A, Guitton MJ, Pujol R, Puel JL. Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. *Neuropharmacology.* Sep 2003;45(3):380-393.

28. Doolittle ND, Muldoon LL, Brummett RE, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clinical cancer research: an official journal of the American Association for Cancer Research.* Mar 2001;7(3):493-500.

29. Neuwelt EA, Gilmer-Knight K, Lacy C, et al. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. *Pediatric blood & cancer.* Aug 2006;47(2):174-182.

30. Riga MG, Chelis L, Kakolyris S, et al. Transtympanic injections of N-acetylcysteine for the prevention of cisplatin-induced ototoxicity: a feasible method with promising efficacy. *American journal of clinical oncology.* Feb 2013;36(1):1-6.

31. Marshak T, Steiner M, Kaminer M, Levy L, Shupak A. Prevention of Cisplatin-Induced Hearing Loss by Intratympanic Dexamethasone: A Randomized Controlled Study. *Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Mar 11 2014;150(6):983-990.

32. van As JW, van den Berg H, van Dalen EC. Medical interventions for the prevention of platinum-induced hearing loss in children with cancer. *The Cochrane database of systematic reviews.* 2014;7:CD009219.

33. Berglin CE, Pierre PV, Bramer T, et al. Prevention of cisplatin-induced hearing loss by administration of a thiosulfate-containing gel to the middle ear in a guinea pig model. *Cancer Chemother Pharmacol.* Dec 2011;68(6):1547-1556.

34. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. *Ann Oncol.* Jan 1998;9(1):13-21.

35. Nitz A, Kontopantelis E, Bielack S, et al. Prospective evaluation of cisplatin- and carboplatin-mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients. *Oncol Lett.* Jan 2013;5(1):311-315.

36. De Andres L, Brunet J, Lopez-Pousa A, et al. Randomized trial of neoadjuvant cisplatin and fluorouracil versus carboplatin and fluorouracil in patients with stage IV-M0 head and neck cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jun 1995;13(6):1493-1500.

37. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 1992;10(8):1245-1251.

38. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* Apr 1997;43(1):29-37.

39. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *European journal of cancer.* Jun 2007;43(9):1399-1406.

40. Wilkins AC, Rosenfelder N, Schick U, et al. Equivalence of cisplatin and carboplatin-based chemoradiation for locally advanced squamous cell carcinoma of the head and neck: A matched-pair analysis. *Oral Oncol.* Jun 2013;49(6):615-619.

41. Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *Journal of the National Cancer Institute.* Jun 6 2007;99(11):847-857.

42. Nwizu T, Adelstein DJ. In squamous cell head and neck cancer: which platinum, how much and how often? *Expert review of anticancer therapy.* Sep 2014;14(9):1033-1039.

43. Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol.* Oct 2008;89(1):38-

44. Denaro N, Russi EG, Adamo V, Merlano MC. State-of-the-art and emerging treatment options in the management of head and neck cancer: news from 2013. *Oncology.* 2014;86(4):212-229.

45. Psyrri A, Dafni U. Combining Cetuximab With Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: Is More Better? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jul 7 2014.

46. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *The New England journal of medicine.* Feb 9 2006;354(6):567-578.

47. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *The lancet oncology.* Jan 2010;11(1):21-28.

48. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *The New England journal of medicine.* Sep 11 2008;359(11):1116-1127.

49. Lefebvre JL, Pointreau Y, Rolland F, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Mar 1 2013;31(7):853-859.

50. http://clinicaltrials.gov/show/NCT01302834.

51. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *The New England journal of medicine.* Jul 1 2010;363(1):24-35.


09

CHAPTER 09

Summary in Dutch | Nederlandse samenvatting
Authors and affiliations
Portfolio
Curriculum vitae
Dankwoord

09

Summary in Dutch | Nederlandse samenvatting

SUMMARY IN DUTCH | NEDERLANDSE SAMENVATTING

Bij de behandeling van patiënten met hoofd-hals kanker zijn radiotherapie en chemoradiotherapie onmisbaar. Met deze behandelmodaliteiten worden goede resultaten bereikt, echter niet zonder ernstige bijwerkingen. Gehoorverlies is een van die bijwerkingen en wordt veroorzaakt zowel door de radiotherapie (RT) als door de chemoradiotherapie (CRT) met cisplatin. Dit proefschrift beschrijft de door cisplatin en/of radiotherapie veroorzaakte gehoorschade, ook wel ototoxiciteit genoemd. De gerapporteerde incidentie van ototoxiciteit loopt op tot 88% na chemoradiotherapie met cisplatin en tot 54% na radiotherapie alleen. Deze ototoxiciteit kan een belangrijke negatieve invloed hebben op het dagelijks leven van een patiënt. Het is daarom van belang om patiënten voorafgaand aan de behandelingen goed te informeren over de risico's van het optreden van ototoxiciteit. Met name patiënten die beroepsmatig een goed gehoor nodig hebben, zoals musici en leerkrachten, maar ook mensen met een beperkte visus kunnen ernstig gehandicapt raken door de ototoxiciteit. Over de kans op het ontstaan van de door radiotherapie en chemoradiotherapie geïnduceerde ototoxiciteit en de ernst hiervan bestaat nog onduidelijkheid. Het doel van dit onderzoek is het verbeteren van de kennis van de ototoxiciteit bij patiënten met hoofd-hals kanker en te bekijken in hoeverre het optreden ervan voorspelbaar is. Het uiteindelijke doel is de patiënt voorafgaand aan de behandelingen beter te kunnen informeren over de ototoxische risico's van de therapie en zo in samenspraak met de patiënt tot een beter afgewogen therapiekeuze te komen.

Onder het begrip ototoxiciteit verstaan we niet alleen conductief of perceptief gehoorverlies maar ook tinnitus en evenwichtsproblemen (duizeligheid). Dit proefschrift richt zich alleen op de pathologie in het oor en niet op de effecten op het evenwichtsorgaan. De eerste studie van dit proefschrift betreft een literatuuronderzoek over door (chemo) radiotherapie geïnduceerd perceptief gehoorverlies (**hoofdstuk 2**). Daarvoor is een uitgebreide zoekactie in de databases Medline en Embase verricht. Onafhankelijk van elkaar hebben twee onderzoekers van in totaal 2507 artikelen de titel en samenvatting gescreend en de methodologische kwaliteit en het risico op bias beoordeeld. Eenentwintig studies werden uiteindelijk geïncludeerd en deze werden geëvalueerd op incidentie en risicofactoren op het ontwikkelen van perceptief gehoorverlies. De in deze studies gerapporteerde incidenties lopen enorm uiteen met percentages van 17% tot 88% na chemoradiotherapie en van 0% tot 43% na radiotherapie. Over het

algemeen is er overeenstemming dat een hogere bestralingsdosis op het oor een hoger risico op gehoorverlies geeft. Een dosis van 47 Gray of hoger wordt als risicofactor benoemd. Ook een hogere dosis cisplatin blijkt tot een verhoogd risico te leiden. De literatuur beschrijft tevens dat jongere patiënten vergeleken met oudere patiënten een groter verslechtering in het aantal decibel (dB) hebben. Oudere patiënten daarentegen eindigen na de therapie in het algemeen met een slechter gehoor.

Een gecombineerde analyse van alle resultaten van de geïncludeerde studies was niet mogelijk omdat de studies te heterogeen waren om samen te voegen. Deze heterogeniteit werd vooral veroorzaakt door de grote verschillen in de definitie van ototoxiciteit. Om het belang van een uniforme definitie aan te tonen hebben wij alle gebruikte definities van de geïncludeerde studies op één patiëntencohort toegepast. Dit resulteerde in een enorme variatie in de incidentie van ototoxiciteit: percentages liepen van 0% tot 89% (tabel 6, **hoofdstuk 2**). Het is daarom niet mogelijk om wetenschappelijke verantwoorde conclusies te trekken over de exacte incidentie van door (chemo)radiotherapie geïnduceerd gehoorverlies. Dit onderstreept het belang om te komen tot een eenduidige definitie van het begrip ototoxiciteit.

In **hoofdstuk 3** wordt bovengenoemd probleem van de verschillende definities van gehoorverlies verder uitgewerkt. Momenteel zijn er twee wereldwijde geaccepteerde normen die gehoorverlies kunnen vastleggen. Dit zijn de 'Common Terminology Criteria for Adverse Events versie 4' (CTCAEv4) en de 'American Speech Language Hearing Association' (ASHA) criteria. Hoewel deze criteria beschikbaar zijn, worden ze toch niet consequent gebruikt. Dit is waarschijnlijk het gevolg van een aantal tekortkomingen die deze criteria hebben: de ASHA definieert niet welke frequenties men moet gebruiken om het gehoorverlies vast te stellen. Bovendien geeft dit systeem geen gradering van de ernst van het gehoorverlies. De CTCAEv4 geeft aan gebruik te moeten maken van frequenties 1 kHz tot en met 8 kHz. Elke frequentie weegt echter even zwaar en daarom is de klinische betekenis van een specifieke frequentie regio (zoals die voor spraakverstaan) niet goed zichtbaar. Bovendien zijn graad 2 en 3 breed gedefinieerd (beide lopen van 25 dB tot 80 dB verlies), waardoor de klinische betekenis ervan niet goed zichtbaar is. Tot slot zijn de frequenties voor de ultrahoge tonen niet meegenomen in de CTCAEv4, terwijl ototoxiciteit juist het eerste zichtbaar wordt in deze frequenties.

Het doel van hoofdstuk 3 is het verbeteren van de bestaande criteria door zelf een nieuw graderingssysteem te ontwikkelen. Het ideaal is een systeem waarbij de klinische betekenis van het gehoorverlies zichtbaar is in de gradering van het verlies. Wij gebruikten hiervoor specifieke frequenties die het spraakverstaan en de kwaliteit van horen goed weergeven. Ook werden zowel de drempelverschuiving in het aantal decibel als de uiteindelijke gehoordrempel meegenomen in de nieuwe criteria. De Pure Tone Average (PTA, gemiddelde drempel over 3 frequenties) van het spraakverstaan (1-2-4 kHz) en van de perceptie van ultrahoge tonen (8-10-12.5 kHz) werden meegenomen. Vier graderingen werden ontwikkeld (TUNE 1 t/m 4).

De nieuwe criteria zijn toegepast op drie verschillende groepen patiënten met hoofd-hals kanker die met (chemo)radiotherapie zijn behandeld. De eerste groep was behandeld met een hoge dosis cisplatin chemoradiotherapie, de tweede met een lage dosis cisplatin chemoradiotherapie en de derde groep met Intensity Modulated Radiotherapy (IMRT). De uitkomsten werden vergeleken met de uitkomsten van de CTCAEv4 en ASHA. We scoorden 307 patiënten en 597 oren. De incidentie van gehoorverlies veroorzaakt door hoge dosis cisplatin chemoradiotherapie was vergelijkbaar in de nieuwe en de oude criteria. In de groepen patiënten die met IMRT of lage dosis cisplatin chemoradiotherapie waren behandeld was de incidentie hoger volgens de nieuwe criteria in vergelijking met de oude criteria. Dit impliceert een hogere gevoeligheid van het nieuwe systeem. In het nieuwe systeem zijn alle patiënten die door de therapie in aanmerking komen voor een hoortoestel gescoord als graad 3 of 4 gehoorverlies, terwijl 54% van deze patiënten volgens de oude criteria als graad 0, 1 of 2 werden gescoord.

Doordat in de nieuwe criteria ook de ultrahoge frequenties zijn meegenomen, zijn deze criteria geschikter om ototoxiciteit in een vroeg stadium te signaleren, hetgeen geïnterpreteerd kan worden als waarschuwing voor toekomstig uitgebreider gehoorverlies in de spraakfrequenties. Op individueel niveau is het risico op gehoorverlies als gevolg van de therapie moeilijk in te schatten. In de klinische praktijk is het toedienen van cisplatin vaak onderwerp van discussie vanwege de ototoxische effecten, zowel voorafgaand als tijdens de therapie, voorafgaand aan een nieuwe toediening van cisplatin. Helaas kunnen we op dit moment nog geen precieze uitspraken doen over de te verwachten ototoxische effecten, waardoor aanbevelingen momenteel enkel op de persoonlijke ervaringen van de behandelaars zijn gebaseerd. Om te bereiken dat we in de praktijk een betere uitspraak

hierover kunnen doen hebben we een model ontwikkeld waarmee de gehoordrempel na de therapie voorspeld kan worden. Dit model wordt beschreven in hoofdstuk 4.

Het doel van **hoofdstuk 4** is het voorspellen van de beengeleiding gehoordrempel op $PTA_{1\text{-}2\text{-}4}$ kHz na de behandeling. Een lineair regressie model werd gebruikt om het model te ontwerpen en een cross validatie werd gebruikt om de sensitiviteit en specificiteit te berekenen. Gehoordrempels, de radiotherapie dosis op het oor en de cisplatin dosis zijn de variabelen waarop het model gebouwd werd. Een-en-tachtig patiënten die behandeld waren met chemoradiotherapie als primaire behandeling voor hun hoofd-hals kanker werden geïncludeerd. Beide oren (162 oren) werden geëvalueerd. Resultaten van de 10-fold cross validatie liet een oppervlakte onder de ROC curve van 0.68 zien, met een sensitiviteit van 29% (95% CI: 13%-51%) en een specificiteit van 97% (95% CI: 88%-100%). Hieruit blijkt dat dit predictiemodel gebaseerd op gehoordrempels, de radiotherapie dosis op het oor en de cisplatin dosis een voorspellende waarde heeft op de kans van het optreden van ototoxiciteit.

In **hoofdstuk 5** zijn de lange termijn effecten van CRT beschreven. Het doel was om een eventuele reversibiliteit of progressie van het gehoorverlies vast te leggen. Hiervoor werd een grote homogene patiëntengroep geselecteerd. Verschillen tussen CRT intraveneus (IV, n=80) en CRT intra-arterieel (IA, n=78) werden bekeken. Van de oorspronkelijke 158 patiënten was er een lange termijn audiogram (na mediaan 4.5 jaar) beschikbaar in 64 patiënten (41%). Er werd gebruikt gemaakt van een multivariabele regressie analyse waarbij voor leeftijd, geslacht, de tijd tussen de verschillende meetmomenten, behandeling protocol (IV versus IA), en gehoordrempel gecorrigeerd is. De audiogrammen lieten een significante achteruitgang in gehoor (tot 21.6 dB op $PTA_{8\text{-}10\text{-}12.5}$ kHz) op korte termijn na therapie (mediaan 3 maanden) zien. Op lange termijn (4.5 jaar na therapie) werd een discrete progressie gezien van dit gehoorverlies ten opzichte van de getallen op korte termijn (tot 5 dB op $PTA_{8\text{-}10\text{-}12.5}$ kHz). De absolute achteruitgang in gehoor was zowel op korte termijn als op lange termijn ernstiger in de CRT-IV groep dan in de CRT-IV groep (op alle PTA's). Dit verschil was significant op FI 0.5-1-2 en 1-2-4 kHz been geleiding (p=0.03 en p=0.04) en op $PTA_{1\text{-}2\text{-}4}$ kHz lucht geleiding (p=0.007). Concluderend vonden wij op lange termijn een progressie van de door therapie geïnduceerd gehoorverlies, voornamelijk op de frequenties 8-10-12.5 kHz en in de CRT-IV groep. De klinische betekenis van dit verlies is echter marginaal (5 dB).

Een tweede lange termijn studie is beschreven in **hoofdstuk 6**. In dit hoofdstuk werden de patiënten met Intensity Modulated Radiation Therapy (IMRT) behandeld. Geen enkele patiënt kreeg cisplatin. Audiometrie werd verricht vooraf, op korte termijn na en mediaan 7.6 jaar na het beëindigen van de therapie. Van de oorspronkelijke 101 patiënten werd een lange termijn audiogram afgenomen bij 36 patiënten (36%). Om te corrigeren voor presbyacusis gedurende de follow-up jaren werden de gehoordrempels vergeleken met de normale gehoordrempels passend bij leeftijd en geslacht volgens de ISO standaard voor het gehoor (ISO 7029:2000). Na 7.6 jaar waren de gehoordrempels op de spraakfrequenties ($PTA_{0.5\text{-}1\text{-}2}$ kHz en $PTA_{1\text{-}2\text{-}4}$ kHz) met 1.8 - 2.3 dB verslechterd in vergelijking met de gehoordrempels op korte termijn. De ultrahoge tonen gingen met 4.4 dB achteruit ten opzichte van de korte termijn drempels. De verwachte normale gehoorverslechtering volgende de ISO bleek hoger te liggen: 2.7 - 4.8 dB voor de spraakfrequenties en 8.8 dB voor de ultrahoge frequenties. Daarom kan de verdere achteruitgang in gehoorverlies worden toegeschreven aan presbyacusis en niet aan therapie. Alleen bij patiënten die een hoge radiotherapie dosering op het oor kregen (>45 Gray) werd een hoger verlies dan voorspeld door de ISO gezien (n=2). Gebaseerd op deze en eerdere resultaten kunnen we concluderen dat patiënten die behandeld worden met IMRT weinig risico hebben op gehoorverlies, mits het oor beschouwd wordt als een risico orgaan. In de huidige radiotherapie protocollen is dat niet het geval. Onze aanbeveling is het oor altijd als een risico orgaan te beschouwen en daarom de protocollen aan te passen.

In **hoofdstuk 7** evalueren we het gehoor van kinderen die behandeld zijn voor een rhabdomyosarcoom in het hoofd-hals gebied (HNRMS). We bestudeerden de gehoordrempels van 73 kinderen mediaan 11 jaar na hun behandeling. Ook werd bekeken of er verschillen waren tussen patiënten die behandeld werden in een centrum waar een nieuwe therapie beschikbaar was en patiënten die behandeld werden in een centrum waar behandeling plaats vond met external beam radiotherapy (EBRT). De nieuwe therapie bestaat uit Ablative surgery, MOld technique afterloading brachytherapy and surgical REconstruction (acronym AMORE).

Bij de behandelde kinderen bleek de gehoordrempel op alle frequenties significant hoger te liggen in vergelijking met de ISO standard (p<0.0001). Op $PTA_{0.5\text{-}1\text{-}2}$ kHz was de mediane gehoordrempel 6.7 dB (5.0 dB in de groep behandeld met AMORE versus 10.0 dB in de groep behandeld met EBRT, p=0.0002). Klinisch relevant gehoorverlies

op $PTA_{0.5\text{-}1\text{-}2}$ kHz (gedefinieerd als >20 dB verlies) werd gezien bij 19% van de kinderen. Minder klinisch relevant gehoorverlies werd gezien na behandeling volgens het AMORE protocol in vergelijking met de behandeling met het EBRT protocol: 15% versus 26% (p=0.26). De multivariabele regressie analyse toonde aan dat de patiënten behandeld volgens het EBRT protocol en degene met een parameningeale tumor significant meer gehoorverlies hadden. Helaas kon een dosis-effect relatie tussen de radiotherapie dosis op het oor en gehoorverlies niet worden vastgesteld omdat de radiotherapie doseringen op het oor niet altijd bekend waren (veroorzaakt door de lange tijdspanne van het onderzoek). Deze studie toont aan dat AMORE in vergelijking met een EBRT behandeling een behandeling met minder ototoxische effecten is.

CONCLUSIE

Dit proefschrift draagt bij aan een beter inzicht in door radiotherapie of chemoradiotherapie geïnduceerd gehoorverlies. Het maakt onderzoekers en behandelaars bewuster van de complexiteit van de ototoxiciteit en de nog onopgeloste problemen en vragen waar we nu tegen aan lopen. Er zijn twee klinische modellen ontwikkeld: het TUNE graderingssysteem en het predictie model. Hoewel het verbeterde graderingssysteem en predictiemodel nog verder ontwikkeld dienen te worden zijn het goed bruikbare instrumenten in de dagelijkse klinische praktijk. Door het toe te passen kan zowel wetenschappelijk onderzoek naar ototoxiciteit als de patiëntenvoorlichting in de dagelijkse klinische praktijk worden verbeterd.

09

Authors and affiliations

Portfolio

AUTHORS AND AFFILIATIONS

S. van der Baan, MD, PhD. Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

A.J.M. Balm, MD, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands & Department of Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

J.P. de Boer, MD, PhD. Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

S.C.J. Bosma, MD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

H.N. Caron, MD PhD. Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

Yen-Ch'ing Chang, MRCP FRCR. Department of Pediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom & Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom

W.A. Dreschler, MSc, PhD. Department of Audiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

R. Davila Fajardo, MD. Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands

J.E. Gains, MRCP FRCR. Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom

M.N. Gaze, MD, FRCR. Department of Pediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom & Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom

M. Hauptmann, MSc, PhD. Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands

K. Józwiak, MSc, PhD. Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands

A.F. Kornman, SLP. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

M.N. Latenstein, SLP. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

M. Lopez-Yurda, MSc, PhD. Department of Epidemiology and Biostatistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands

H.C. Mandeville, MD, FRCR. Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom & Department of Radiotherapy, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

J.H.M. Merks, MD, PhD. Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

L. van der Molen, SLP, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

B.R. Pieters, MD, PhD. Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

K. Rajput, FRCS FRCP. Department of Audiology, Great Ormond Street Hospital, London, United Kingdom

C.R.N. Rasch, MD, PhD. Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

R.A. Schoot, MD. Department of Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

O. Slater, MD. Department of Pediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

R. Spijker, MSc. Dutch Cochrane Centre, Medical library, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

R. Talwar, FRSC. Department of Otorhinolaryngology, Great Ormond Street Hospital, London, United Kingdom

C.L. Zuur, MD, PhD. Department of Head and Neck Oncology and Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands & Department of Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

PORTFOLIO

PhD student:	E.A.R. Theunissen
Name PhD supervisors:	Prof. dr. A.J.M. Balm, Prof. dr. ir. W.A. Dreschler, Dr. C.L. Zuur, Prof. dr. C.R.N. Rasch

Courses

2013	Scientific Writing in English for Publication (ECTS 0.7)
2013	Basic Course in Legislation and Organization for Clinical Researchers (BROK) (ECTS 0.9)
2012	Basic Medical Statistics (ECTS 1.5)
2012	Pubmed Biomedical Sciences (ECTS 0.1)

Seminars, workshops and master classes

2011-2013	Monthly Werkgroep Hoofd-Hals Tumoren (WHHT) seminars (ECTS 4)
2011-2013	Monthly Heelkundige Oncologische Disciplines (HOD) department seminars (Sectie XI) (ECTS 4)

Presentations

2014	Radiotherapie geïnduceerd gehoorverlies in kinderen behandeld voor een hoofd-hals rhabdomyosarcoom. *Posterpresentatie Jonge onderzoekersdag Nederlands Werkgroep voor Hoofd-Hals Tumoren.* Januari 2014, Amsterdam (ECTS 0.5).
2013	Ototoxiciteit na (chemo)radiotherapie. *Wetenschapsdag KNO-heelkunde Academisch Medisch Centrum*. November 2013, Amsterdam (ECTS 0.5)
2013	Ototoxicity in head and neck cancer patients and middle ear thiosulfate-gel protection against cisplatin-induced hearing loss. *Sectie XI meeting, Antoni van Leeuwenhoek*. April 2013, Amsterdam (ECTS 0.5)
2013	Ototoxiciteit in hoofd-hals oncologie. *Werkgroep hoofd-hals tumoren,*

	Antoni van Leeuwenhoek. April 2013, Amsterdam (ECTS 0.5)
2013	Ototoxiciteit in hoofd-hals oncologie: lange termijn effecten en predictiemodel. *Audiologie werkgroep, Academisch Medisch Centrum.* April 2013, Amsterdam (ECTS 0.5)
2012	Nieuw scoringssysteem voor ototoxiciteit in volwassenen. *221e KNO vergadering.* November 2012, Nieuwegein (ECTS 0.5)
2012	Ototoxiciteit als gevolg van Intensity Modulated Radiation Therapy (IMRT). *Werkgroep hoofd-hals tumoren, Antoni van Leeuwenhoek.* Maart 2012, Amsterdam (ECTS 0.5)
2011	Gehoorverlies na cisplatin chemoradiotherapie bij patiënten met hoofd-hals kanker; een prospectieve lange termijn studie. *219e KNO vergadering.* November 2011, Groningen (ECTS 0.5)

Supervising

2011	S.C.J. Bosma, 3 months scientific internship (ECTS 1)

List of publications

Radiation-induced hearing loss in survivors of childhood head and neck rhabdomyosarcoma; a long-term follow-up study. ***E.A.R. Theunissen****, R.A. Schoot, O. Slater, M. Lopez-Yurda, C.L. Zuur, M.N. Gaze, Y. Chang, H.C. Mandeville, J.E. Gains, K. Rajput, B.R. Pieters, R. Davila Fajardo, R. Talwar, H.N. Caron, A.J.M. Balm, W.A. Dreschler, J.H.M. Merks.* Submitted

Prediction of hearing loss due to cisplatin chemoradiotherapy. ***E.A.R. Theunissen****, C.L. Zuur, K. Józwiak, M. Lopez-Yurda, M. Hauptmann, C.R.N. Rasch, S. van der Baan, J.P. de Boer, W.A. Dreschler. A.J.M. Balm.* Revisions submitted

Cochlea sparing effects of Intensity Modulated Radiation Therapy in head and neck cancer patients: a long-term follow-up study. ***E.A.R. Theunissen****, C.L. Zuur, M. Lopez-Yurda, S. van der Baan, A.F. Kornman, J.P. de Boer, A.J.M. Balm, C.R.N. Rasch, W.A. Dreschler.* Journal of Otolaryngology - Head and Neck Surgery. 2014; 43:30

Long-term hearing loss after chemoradiation in patients with head and neck cancer. ***E.A.R. Theunissen****, C.L. Zuur, S.C.J. Bosma, M. Lopez-Yurda, M. Hauptmann, S. van der Baan, J.P. de Boer, L. van der Molen, C.R.N. Rasch, W.A. Dreschler, A.J.M. Balm.* The Laryngoscope, 2014; 124(12): 2720-5

A new grading system for ototoxicity in adults. ***E.A.R. Theunissen****, W.A. Dreschler, M.N. Latenstein, C.R.N. Rasch, S. van der Baan, J.P. de Boer, A.J.M. Balm, C.L. Zuur.* Annals of Otology, Rhinology & Laryngology, 2014; 123(10): 711-8

Prognostic factors for pharyngocutaneous fistulization after total laryngectomy. *A.J. Timmermans, L. Lansaat,* ***E.A.R. Theunissen****, O. Hamming-Vrieze, F.J.M. Hilgers, M.W.M. van den Brekel.* Annals of Otology, Rhinology & Laryngology. 2014;123(3):153-161

Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: A systematic review of the literature. ***E.A.R. Theunissen****, S.C.J. Bosma, C.L. Zuur, R. Spijker, S. van der Baan, W.A. Dreschler, J.P. de Boer, A.J.M. Balm, C.R.N. Rasch.* Head Neck. 2015 Feb;37(2):281-92

Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy. ***E.A.R. Theunissen****, A.J. Timmermans, C.L. Zuur, O. Hamming-Vrieze, J.P. de Boer, F.J.M. Hilgers, M.W.M. van den Brekel.* JAMA Otolaryngology - Head & Neck Surgery. 2012;138(6):548-555

09

Curriculum vitae

CURRICULUM VITAE

Noortje Theunissen werd geboren op 4 maart 1985 te Overveen. Zij behaalde in 2003 het Gymnasiumdiploma met profiel Natuur & Gezondheid aan het Nieuwe Lyceum te Bilthoven. Vanaf september 2003 studeerde zij geneeskunde aan de Universiteit Utrecht. In 2007/2008 onderbrak zij haar studie voor een fulltime bestuursfunctie als quaestrix van de studentenvereniging UVSV/NVVSU. Vanaf augustus 2010 liep zij haar wetenschappelijke stage op de afdeling hoofd-hals chirurgie in het Antoni van Leeuwenhoek ziekenhuis. Gedurende deze stage onderzocht zij de functionele uitkomsten bij patiënten die een totale laryngectomie hebben ondergaan wegens een dysfunctionele larynx als gevolg van (chemo)radiotherapie (prof. dr. F.J.M. Hilgers, dr. C.L. Zuur). Aansluitend aan deze wetenschappelijke stage liep zij haar oudste coschap op de afdeling hoofd-hals chirurgie in ditzelfde ziekenhuis. In april 2011 behaalde zij haar artsendiploma en startte zij als arts-assistent Heelkundig Oncologische Disciplines (voornamelijk op de hoofd-hals chirurgie afdeling) in het Antoni van Leeuwenhoek ziekenhuis. Tegelijkertijd begon zij met het onderzoek naar de ototoxische effecten van (chemo)radiotherapie bij hoofd-hals kanker patiënten (prof. dr. A.J.M. Balm, prof. dr. ir. W.A. Dreschler, dr. C.L. Zuur en prof. dr. C.R.N. Rasch). Vanaf november 2012 tot en met september 2013 werkte zij als arts-onderzoeker verder aan dit onderzoek dat geresulteerd heeft in dit proefschrift. Sinds oktober 2013 is zij in opleiding tot Keel-, Neus- en Oorarts in het Academisch Medisch Centrum te Amsterdam (prof. dr. S. van der Baan, prof. dr. W.J. Fokkens en dr. A.M. König).

CURRICULUM VITAE

Noortje Theunissen was born in Overveen, the Netherlands on March 4th, 1985. In 2003 she graduated from the Nieuwe Lyceum in Bilthoven. In the same year she started to study medicine at the University of Utrecht. During the final year of her study she participated in a research project at the department of Head and Neck Oncology and Surgery of the Antoni van Leeuwenhoek Hospital, Amsterdam. Within this research project she evaluated the functional outcomes of patients who underwent a total laryngectomy for a dysfunctional larynx due to (chemo)radiotherapy (prof. dr. F.J.M. Hilgers, dr. C.L. Zuur). Afterwards she worked as an intern at the department of Head and Neck Oncology and Surgery of the same hospital. In April 2011 she graduated from medical school and started working as a resident at the department of Head and Neck Oncology and Surgery of the Antoni van Leeuwenhoek Hospital. At the same time started a research project on the ototoxic effects of (chemo)radiotherapy in head and neck cancer patients (prof. dr. A.J.M. Balm, prof. dr. ir. W.A. Dreschler, dr. C.L. Zuur and prof. dr. C.R.N. Rasch). From November 2012 until September 2013 she worked as a full-time researcher. The results have been described in this thesis. In October 2013 she started her residency at the department of Otorhinolaryngology at the Academic Medical Center in Amsterdam (prof. dr. S. van der Baan, prof. dr. W.J. Fokkens and dr. A.M. König).

09

Dankwoord

DANKWOORD

Een proefschrift schrijf je niet alleen. Gedurende de jaren waarin ik aan dit onderzoek heb gewerkt, heb ik van vele verschillende personen begeleiding en ondersteuning gehad. Uiteraard wil ik daar iedereen daarvoor heel hartelijk voor bedanken, waarvan een aantal mensen in het bijzonder:

Promotor **prof. dr. A.J.M. Balm**, beste Fons, mijn allereerste gesprek in het Antoni van Leeuwenhoek was met u. Ik was direct enthousiast en eigenlijk was ik dat altijd na een gesprek met u. U wist mij te stimuleren en te motiveren, ook in periodes waarin het even niet mee zat. Bedankt voor alle mogelijkheden die u mij geboden heeft, zowel in de wetenschap als in de kliniek.

Promotor **prof. dr. ir. W.A. Dreschler**, beste Wout, aan het begin van mijn onderzoeksperiode gaf jij mij een proefschrift met daarin de door jou geschreven woorden: 'voor Noortje, ter inspiratie bij je eigen zoektocht in de doolhof van de ototoxiciteit'. Mede dankzij jouw prettige begeleiding zijn de bordjes richting de uitgang van de doolhof in de goede richting gezet; veel dank daarvoor.

Co-promotor **dr. C.L. Zuur**, lieve Lot, bedankt voor het vertrouwen dat jij in mij stelde. Ik vond het een eer om jouw projecten voort te mogen voortzetten. Samenwerken met jou was voor mij altijd heel plezierig. Naast het onderzoek was je ook altijd geïnteresseerd in mij als persoon, en dat maakt samenwerken erg prettig. Ik heb bewondering voor je ambities en hoe jij je drukke privéleven met je werk tussen al die mannelijke hoofdhals chirurgen combineert. Dank je wel dat ik in het ototoxiciteit project jouw opvolgster mocht zijn.

Co-promotor **prof. dr. C.R.N. Rasch**, beste Coen, jouw kritische blik is altijd zeer nuttig geweest om een manuscript beter en duidelijker te maken. Vooral het predictiemodel manuscript is dankzij jouw bijdrage een veel beter artikel geworden. Hartelijk bedankt daarvoor.

Prof. dr. S. van der Baan, veel dank voor alle tips, uitleg en hulp vanuit de otologie-hoek. En natuurlijk heel veel dank voor de mogelijkheid die u mij geboden heeft om de opleiding tot KNO-arts te starten.

Dr. J.P. de Boer, beste Jan Paul, bedankt voor al je uitleg, hulp en de altijd snelle reacties. Jouw tips werkten altijd motiverend om iets tot een mooie einde te brengen.

Leden van de promotiecommissie: **prof. dr. M.W.M. van den Brekel**, **prof. dr. ir. J.H.M. Frijns**, **prof. dr. J.H.M. Schellens**, **dr. Y.J.W. Simis**, **prof. dr. L.E. Smeele**, bedankt dat u plaats wilde nemen in de commissie en voor de tijd die u allen heeft vrij gemaakt om mijn manuscript te beoordelen. **Prof. G. Laurell**: thank you for your time and enthusiasm in reading this manuscript.

De statistici: **Marta Lopez-Yurda** en **Michael Hauptman**, zijn twee oren van één persoon nou afhankelijk of onafhankelijk van elkaar? Door jullie realiseer ik me hoe vaak gepubliceerde data niet altijd even goed zijn. Dank voor jullie geduld en de enorme klus rondom het predictiemodel project. Het was een prettige samenwerking. Marta, dank ook voor de hulp rondom de andere manuscripten die we samen geschreven hebben. Het was heel prettig dat je zelfs vanuit thuis nog steeds voor mij klaar stond. **Katarzyna Jóźwiak**, thank you very much helping me finishing the predictionmodel manuscript.

Anne Kornman, **Merel Latenstein**, en **Lisette van der Molen**, jullie werk loopt als rode draad door dit proefschrift. Zonder alle audiogrammen en tympanogrammen was het onderzoek nergens geweest. Heel veel dank voor de uren die jullie in het maken van al deze audio's hebben gestoken en natuurlijk voor de gezellige samenwerking.

Sophie Bosma, dank je voor je hulp bij hoofdstuk 2 en 5. Veel succes met je eigen onderzoek en opleiding tot radiotherapeut.

Reineke Schoot, de samenwerking rondom hoofdstuk 7 vond ik altijd erg prettig, dank daarvoor. Veel succes met het afronden van je eigen promotieonderzoek en veel succes en plezier met de opleiding kindergeneeskunde! **Hans Merks**, bedankt voor de begeleiding van Reineke en mij rondom hoofdstuk 7.

Riki Stichting, zonder jullie donatie was mijn periode als fulltime onderzoeker niet mogelijk geweest. Deze maanden heb ik zeer efficiënt kunnen werken en alle data kunnen verwerken en analyseren. Heel erg veel dank daarvoor.

Hoofdhals chirurgen AVL: **Bing Tan**, **Martin Klop**, **Ludi Smeele**, **Peter Lohuis**, **Michiel van den Brekel en Baris Karakullukcu**, Ik heb genoten van de tijd dat ik werkzaam was in de kliniek. Ik ben blij dat een tijd deel mocht uitmaken van het hoofdhals team. Het samenwerken met jullie was altijd zeer prettig en ik heb daardoor enorm veel geleerd tijdens mijn eerste baan in de kliniek. **Prof. dr. F.J.M. Hilgers**, tijdens het schrijven van mijn allereerste artikel heb ik door uw begeleiding heel veel geleerd. Mede daardoor is het niet bij dat ene artikel gebleven, bedankt daarvoor.

Marion van Zuilen en **Henny Buis**, lieve dames, veel dank voor het regelen van van alles. Nooit was iets teveel gevraagd en jullie waren altijd bereid te helpen, ook vanaf een afstandje toen ik niet meer dagelijks in het AVL werkzaam was.

Secretaressen van de 5e etage AVL, bedankt voor al jullie hulp op moment dat ik ANIOS was en stapels dossiers aanvroeg, brieven verstuurde en antwoordenveloppen ontving. Door jullie werd de chaos wat minder groot. Ook dank aan alle **medewerkers van de hoofdhals poli van het AVL** voor het inplannen van alle afspraken voor de patiënten die meededen aan de lange termijn onderzoeken.

Arts assistenten HOD AVL, mooi om te zien hoe ieder zijn eigen weg is ingeslagen na een eerste baan in het AVL. Ik wens jullie veel succes in jullie verdere carrières en ik hoop jullie nog vaak te zien! **Arts assistenten hoofdhals AVL**, bedankt voor de momenten dat ik voor mijn onderzoek de zaal weer even moest verlaten en jullie 'alleen nog maar een labje' (oeps) voor mij moesten controleren… Ik ben jullie dankbaar voor jullie geduld.

Arts onderzoekers AVL, dank voor de gezelligheid rondom het werk, congressen, bijeenkomsten en de gezelligheid in het O-gebouw. Lieve **Jacqueline Timmermans**, ik was blij dat jij 'mijn' laryngectomie database overnam, het was altijd prettig samenwerken.

Mijn kamergenoten in het O-gebouw, **Rosa Djajadiningrat** en **Laura Mertens**, ik was heel blij met mijn gezellige plekje in het O-gebouw! Ook al was ik met mijn KNO-onderzoek wel een beetje vreemde eend tussen jullie piemel en blaas onderzoek, het was er niet minder gezellig om!

AIOS KNO AMC, dank jullie wel voor de enorme gezelligheid en samenwerking in het AMC. Ik ben heel blij met de fijne groep waarin ik in terecht ben gekomen. Ik kijk er naar uit om nog vele jaren met jullie samen te werken en natuurlijk naar alle gezellige festiviteiten er omheen! **Staf KNO AMC**, bedankt voor het creëren van researchtijd gedurende mijn klinische werkzaamheden.

Mrs A. Hathaway-Theunissen, tante Anneke, heel veel dank voor de controle op de Engelse taal. I am looking forward seeing you again in June!

Natuurlijk alle vrienden vanuit Utrecht en nu in Amsterdam, **de WB**, **jaarclub en de Bes**, bedankt voor de gezelligheid en afleiding buiten het werk om. Ik ben blij dat we nog steeds een hechte band hebben!

Myra Nijman, dank je wel voor het ontwerpen van de mooie cover en de lay-out van dit boek! En natuurlijk voor het zijn van een vriendin die altijd voor me klaar staat!

Mijn paranimfen, **Emily Postma en Pleuntje van Egmond**, fijn dat jullie naast mij willen staan op 10 juni. Emily; onze missie om ooit elkaars paranimf te zijn hebben we volbracht! Onze vriendschap vanaf het begin van onze studietijd is mij heel dierbaar, dank je wel daarvoor. Pleuntje; als er 1 valt vallen we allemaal toch? Het is fijn om tijdens de verdediging iemand naast me te hebben staan die bekend is met dat motto :). Het was een jaar om nooit te vergeten en ik kijk uit naar alle mooie momenten die we samen nog zullen beleven.

Pieter en Marieke, lief broertje en zusje, dank voor jullie eeuwige interesse in mijn werk en onderzoek. Nu kunnen jullie eindelijk echt zien waarmee ik al die tijd bezig ben geweest. Als oudste van ons drie is het mooi om te zien hoe ieder zijn eigen weg inslaat en successen boekt; ga zo door want ik ben trots op jullie!

Lieve **pap en mam**, dank jullie wel voor jullie onvoorwaardelijke steun en vertrouwen. Het is fijn om te weten dat jullie altijd voor mij klaar staan en altijd betrokken zijn in mijn dagelijkse leven. Jullie motiveren mij om hard te werken, maar ook om soms even te ontspannen. Het is dan ook altijd heerlijk om even thuis of in Loosdrecht te zijn.

Bas, lieve lieve schat, de dank voor jou is eigenlijk niet in woorden uit te drukken... Dank je wel voor je hulp, steun en liefde, wat zou ik zonder jou moeten. Ik verheug me op onze toekomst samen.