Cisplatin and radiation induced hearing loss in head and neck cancer patients

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Cisplatin and Radiation Induced Hearing Loss in Head and Neck Cancer Patients

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
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Faculteit der Geneeskunde

"Living here day by day, you think it's the center of the world. You believe nothing will ever change. Then you leave: a year, two years. When you come back, everything's changed. The thread's broken. What you came to find isn't there. What was yours is gone. You have to go away for a long time... many years... before you can come back (...). But now, no. It's not possible. Right now you're blinder than I am."

Nuovo Cinema Paradiso (1988, Guiseppe Tornatore)

Aan mijn ouders

Aan Erik, Servaas en Philip

Contents

General introduction and outline of the thesis

General introduction

Head and neck cancer: treatment and quality of life

Head and neck squamous cell carcinoma accounts for almost 5% of new patients with cancer in the Netherlands.[1] The main risk factors for cancers of the upper aero-digestive tract are individual predisposition and a combination of excessive use of alcohol and tobacco and the trends therein over the last 30 years. Besides curing patients, the treatment of these carcinomas is focused on minimizing mutilation and preserving basic vital functions such as chewing, swallowing of food, and speech. In addition, an assessment of quality of life after therapy in terms of physical en functional well-being has become essential, especially as patients live longer. For this purpose, regional collaboration of specialists in multidisciplinary teams is needed and the vast majority of all new patients with head and neck cancer is treated in such centers nowadays.

Radiation therapy (RT), as single-modality treatment or adjuvant to surgery, is a common treatment modality for low staged head and neck cancer. However, the majority of patients with cancer of the oropharynx, oral cavity or supraglottic larynx suffer advanced stage III or IV disease.[1] The treatment of these locally advanced head and neck cancers is a challenge in view of the limited response to radiation therapy in case of inoperable disease, and the need to preserve vital functions in case of operable lesions. A combination of radiotherapy and concomitant chemotherapy - preferably cisplatin-based - showed improved response rates and allowed for organ preservation.[2,3] Although clinical outcome and tolerability of various low-dose and high-dose intravenously administered cisplatin CRT schedules have been evaluated extensively[4-10], a consensus about the optimal CRT schedule has not been reached yet.

In high-dose cisplatin CRT, adverse effects of CTCAE[11] grade $\geq$ 3 have been observed to an incidence of 89%[4,5]. Major toxicities induced by cisplatin are nephrotoxicity, nausea, vomiting, myelosuppression, and ototoxicity[12], and adverse effects of radiation therapy for head and neck cancer are fatigue, swallowing problems due to oral mucositis and/or dysfunction of the salivary glands, and painful epidermiolysis. When the ear is involved in the radiation protocol, adverse effects include (chronic) infection of the external and middle ear, sensorineural hearing loss, and, in the long-term, osteoradionecrosis of the temporal bone.[13] However, to increase drug doses in the tumor with minimal systemic toxicity, a superselective intra-arterial administration scheme of high-dose cisplatin with concurrent radiotherapy was designed (acronym Radplat).[14] In this CRT regimen, cisplatin was infused directly in the nutrient artery of the tumor, while sodium thiosulfate for systemic cisplatin neutralization was infused intravenously at the same time. However, in this treatment scheme up to 60% of clinically significant hearing loss was observed.[15]

Vulnerability of the auditory system

Clinically, cisplatin ototoxicity has been described as a bilateral, cumulative, dose-related and usually permanent sensorineural hearing loss (SNHL), that starts at ultra-high frequencies and, with increasing dose or prolonged treatment, progressively extends to frequencies involved in speech perception.[16,17] This ultra-high to low frequency gradient seems biologically explained by the finding that outer hair cells near the base of the cochlea are reported to be affected first by cisplatin, progressing to apical cells with increasing dose[18-20] or time-interval after cisplatin injection[21]. In addition, the drug interferes with the morphology and function of the stria vascularis with special affinity to the marginal cells in the basal turn of the cochlea.[22]

Adverse effects of radiotherapy involving the ear are (chronic) external otitis, stenosis of the external ear canal, atrophy or ulceration of the skin, otitis media due to dysfunction of the Eustachian tube, and, in the long-term, osteoradionecrosis of the temporal bone and mastoiditis.[13] Radiation-induced sensorineural hearing loss has been observed to an incidence of 49% directly post-treatment and to an incidence of 46% at 4-5 years after therapy of patients treated with RT fields exposing the inner ear.[23-25] Radiation-induced vascular insufficiency has been regarded as the etiology of SNHL, while in animal models, the exposure of inner ears to radiation resulted in destruction of outer hair cells and inner hair cells, atrophy of the stria vascularis, and a reduced number of afferent nerve endings.[26-28]

Monitoring the auditory system

Pure-tone audiometry

In head and neck disease, conventional pure-tone audiometry at frequencies 0.125 kHz to 8 kHz is regularly used for the monitoring of pre-treatment and post-treatment hearing capability. In clinical audiometry, hearing thresholds have to be assessed in a sound proof booth, both for air conduction (AC) and bone conduction (BC)**1** and are expressed in dB HL**2**.

1 Conduction of sound through the auditory system (external ear, middle ear, inner ear and acoustic nerve) is defined as air-conduction (AC) and is measured by offering pure-tones (from quiet to loud) through headphones, at which the patient has to respond immediately to the first sound he hears. By vibration, sound can also be conducted directly to the inner ear and acoustic nerve and this is defined as bone-conduction (BC) and is measured through a vibrator connected to the skull.

An increased AC hearing level may represent pathology of the external ear, and/or middle ear and/or inner ear structures/acoustic nerve, and an increased BC level represents solely pathology of the inner ear and/or acoustic nerve. Hence, the difference between AC and BC level equals potential pathology of the external and/or middle ear, and is called an air-bone gap (ABG).

2 The ear can perceive sounds of very low and very high intensities and to comprehend this large range of volumes a logarithmical scale is used to express sound levels in decibel Sound Pressure Level (dB SPL). However, when the intensity of sound is calculated relative to the perception threshold of that sound for a group of people with normal hearing capability, the perceived intensity of sound is expressed in decibel Hearing Level (dB HL). The conversion from dB SPL to dB HL varies for every sound frequency (pure tone) and is defined in the ISO-norm.[29]

In addition, in the monitoring of ototoxicity, ultra-high frequency pure-tone audiometry at 8 kHz to 16 kHz is usually obtained for early detection of the onset of drug induced hearing loss.[30] In a population of 50 patients treated with cisplatin, the intra-individual standard deviation in audiograms with pre-treatment damage at frequencies to 0.25 kHz to 8 kHz was calculated 3.8 to 4.1 dB. At ultra-high frequencies 10 kHz to 16 kHz the intra-individual standard deviation was 3.4 to 4.0 dB.[31] The advantage of using pure-tone audiometry is the possibility to distinguish between BC for sensorineural hearing loss and AC for total hearing loss, and therefore the assessment of air-bone gaps (ABGs). ABGs are the difference between AC and BC and, hence, the reflection of potential middle ear pathology. In addition, based on audiograms, ototoxic grading criteria can be set to specifically defined steps of hearing deterioration. However, pure-tone audiometry is time consuming, especially when conventional and ultra-high frequency pure-tone audiometry are combined. Patients enduring physically intensive treatment schemes may then be too ill to perform the whole test.

OAEs

Otoacoustic emissions (OAEs) are sounds of cochlear origin, recorded by a probe with microphone fitted into the ear canal. OAEs are a fast and easy audiological diagnostic test, also suitable for patients who are too ill to perform pure tone audiometry at the audiology department. OAEs can be obtained in a quiet environment but do not necessarily require a sound-proof room. In addition, OAEs are normally stable over long time periods (analogous to fingerprints) which makes them potentially suitable for follow-up.

OAEs arise as follows[32]: Pure-tones or clicks enter the ear canal and are conducted through the middle ear ossicles to the oval window to induce cochlear fluid motion in the perilymph, resulting in displacement of the basilar membrane (BM). The traveling wave of the BM propagates to the apex of the cochlea, while the organ of Corti converts the BM motion to a fluid motion across the inner hair cells (IHCs), leading to neural stimulation through their synapses with acoustic nerve fibers. During this process, the traveling wave intensity decreases as its energy is absorbed by the organ of Corti in a substantial way. However, outer hair cells (OHCs) are thought to act as a cochlear amplifier, by generating motile forces opposing the forces of the viscous fluid (endolymph). OAEs are a by-product of this cochlear amplifier, as BM disturbances travel back to the base of the cochlea. Here, the motion of the BM exerts fluid pressure on the oval and round windows causing vibration of the middle ear ossicles and ear drum and hence OAEs.

The most frequently applied method to evoke OAEs is the use of clicks. Clicks stimuli are wide-band stimuli, exciting the whole of the cochlea, resulting in transient evoked otoacoustic emissions (TEOAEs). However, TEOAE responses can give a frequency specific indication of the cochlear status, by splitting the response into frequency bands after recording. TEOAEs are highly sensitive to cochlear pathology: OAEs at frequencies with hearing thresholds above 30/40 dB HL are typically absent. In adults, the response is strongest at frequencies 1-4 kHz. A second method of obtaining OAEs uses a stimulus composed of 2 tones with frequency f_1 and f_2 , resulting in distortion product otoacoustic emissions (DPOAE) with a

certain frequency f_{dp}. DPOAEs offer a wider frequency range of observation. In addition, DPOAEs can be recorded with moderate SNHL, when no TEOAE can be detected.

Otoacoustic emissions for the monitoring of ototoxicity were applied in a number of previous studies focusing on ototoxicity in children during treatment with aminoglycosides. However, there is little agreement on which type of emissions and which aspect of the emissions should be used as an outcome measure: emission strength, signal to noise ratio, or (band) reproducibility. In a number of studies, OAEs are reported to serve as an early identifier of ototoxicity, reveiling (subclinical) damage to the cochlea prior to the presentation of audiometric hearing loss.

Outline of the thesis

In **Chapter 1** we conducted a prospective assessment of the incidence and extent of hearing loss due to high-dose intra-arterial cisplatin chemo-irradiation with systemic sodium thiosulfate for cisplatin neutralization (CRT-IA or acronym Radplat). Patient and treatment variables were studied in a multivariate analysis to determine their explanatory role or predictive value in hearing loss after therapy. In **Chapter 2** the prediction analysis of chapter 1 was used to introduce a prediction formula, that was tested on its feasibility for a prediction of cisplatin chemoradiation-induced hearing loss at frequencies vital for speech perception prior to the applied treatment. In **Chapter 3** we aimed to deduce the audiometric patterns of hearing loss at individual frequencies (125 Hz to 16 kHz) in patients treated with Radplat. In **Chapter 4** a prospective analysis of hearing thresholds was performed at low and (ultra-) high frequencies obtained before, during, and after treatment in 158 patients, randomized for either Radplat or systemically administered high-dose cisplatin CRT without cisplatin rescue (CRT-IV). **Chapter 5** focuses on hearing loss due to low-dose cisplatin CRT and compares results with findings of our high-dose cisplatin CRT cohorts. **Chapter 6** comprehends a prospective assessment of the dose-effect relationship between radiation therapy (RT) and hearing loss in a group of patients treated with (postoperative) Intensity-Modulated RT for head and neck cancer. None of the patients received chemotherapy. A multivariate analysis was performed to reveal individual and treatment-related risk factors for radiation-induced hearing loss. The objective of **Chapter 7** was to study the feasibility of using OAEs in a hearing loss monitoring program for head-and-neck cancer patients treated with (high-dose or low-dose) cisplatin CRT or single-modality RT.

References

1. Head and Neck tumours in the Netherlands 1989-1995, Netherlands Cancer Registry.
2. Pignon JP, Bourhis J, Domenge C, et al: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355:949-55, 2000
3. Bernier J. Alteration of radiotherapy frectionation and concurrent chemotherapy: a new frontier in head and neck oncology? Nat Clin Pract Oncol 2005;2(6):305-314.
4. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-98.
5. 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 Eng J Med 2004;350:1937-44.
6. Vega de la FA, Vera Garcia R, Dominguez D, et al. Hyperfractionated radiotherapy and concomitant cisplatin for locally advanced laryngeal and hypopharyngeal carcinomas. Am J Clin Oncol 2003;26(6):550-557.
7. Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. Head and Neck 2006;28:189-196.
8. Beckmann GK, Hoppe F, Pfeundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. Head and Neck 2005;27:36-43.
9. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily cisplatin chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-3548.
10. Bartelink H, Bogaert van den W, Horiot JC, Jager J, Glabbeke van M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial. Eur J Cancer 2002;38:667-673.
11. Cancer Therapy Evaluation Programm, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (http://ctep.cancer.gov). publ date: December 12, 2003.
12. Evans WE, Yee GC, Crom WR, Pratt CB, Green AA: Clinical pharmacology of bleomycine and cisplatin. Head Neck Surg 1981;4(2):98-110.
13. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R, Radiotherapy-induced ear toxicity. Cancer Treatm Rev 2003;29:417-430.
14. Robbins KT, Vicario D, Seagren S, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. Am J Surg. 1994;168(5):419-422.
15. Madasu R, Ruckenstein MJ, Leake F, et al: Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 123(9):978-981, 1997
16. Aguilar-Markulis NL, Beckly S, Priore R, Mettlin C: Auditory effects of long-term cis-dichlorodiammineplatinum II therapy in genitourinary cancer patients. J Surg Oncol 1981;16(2):111-123.
17. Schweitzer VG: Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 1993;103(4 Pt 2):1-52.
18. Cardinaal RM, De Groot JC, Huizing EH, Veldman JE, Smoorenburg GF: Dose-dependent effect of 8-day cisplatin administration upon the morphology of the guinea pig cochlea. Hear Res 2000;144(1-2):135-146.
19. Tange RA: Differences in the cochlear degeneration pattern in the guinea pig as a result of gentamicin and cis-platinum intoxication. Clin Otorhinolaryngol Allied Sci. 1984;9(6):323-327.

20. Van Ruijven MW, De Groot JC, Smoorenburg GF: Time sequence of degeneration pattern in the guinea pig cochlea during cisplatin administration. A quantitative histological study. Hear Res 2004;197(1-2):44-54.

21. Laurell G, Bagger-Sjöbäck D: Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol 1991;20(3):158-167.

22. Tange RA, Vuzevski VD: Changes in the stria vascularis of the guinea pig due to cis-platinum. Arch Otorhinolaryngol 1984;239(1):41-47.

23. Kwong DLW, Wei WI, Sham JST, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Rad Oncol Biol Physiol 1996;36:281-289.

24. Wang L, Kuo W, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.

25. Ho WK, Wei WI, Kwong DL, Sham JST, Tai PTH, Yuen APW, Au DKK. Long-term sensorineural deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head Neck 1999;21(6):547-553.

26. Hultcrantz M. Correlation between auditory brainstem recordings and morphology as seen through the scanning electron microscope. Scanning Microscopy 1988;2(3):1125-1131.

27. Hultcrantz M, Anniko M, Borg E. The influence of prenatal gamma irradiation on the ageing of the cochlea. Acta Otolaryngol (Stockh) 1989;108:414-423.

28. Kim CS, Shin S. Ultrastructural changes in the cochlea of the guinea pig after fast neutron irradiation. Otolaryngol Head Neck Surg 1994;110:419-27.

29. ISO/TR 389-1 and 5, 1998

30. Tange RA, Dreschler WA, Van der Hulst RJAM. The importance of high-tone audiometry in monitoring for ototoxicity. Arch Otorhinolaryngol 1985;242:77-81.

31. Dreschler WA, vd Hulst RJAM, Tange RA, Urbanus NAM. The role of high-frequency audiometry in early detection of ototoxicity. Audiology 1985;24:387-395.

32. Kemp, D.T. (2002) Otoacoustic emissions, their origin in cochlear function, and use. Br Med Bull, 63, 223-241

Chapter 1

Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer; a multivariate analysis

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ABSTRACT

Purpose: Cisplatin chemo-irradiation is increasingly used in locally advanced squamous cell carcinoma of the head and neck. The objective of this study is to determine risk factors of ototoxicity due to intra-arterial high-dose cisplatin chemoradiation (acronym RADPLAT).

Methods and Materials: A prospective analysis of hearing thresholds at low and (ultra) high frequencies obtained before, during and after treatment in 146 patients. Treatment consisted of intra-arterial infusion of high-dose cisplatin (150 mg/m^2, four courses) with sodium thiosulfate rescue and concurrent radiation therapy (70 Gy). Patient and chemoradiation variables were studied in a multivariate analysis.

Results: After treatment, 23 percent of the ears were under consideration for hearing aids due to therapy. Twenty-two percent of the patients developed an increase in air-bone gap > 10 dB during or after therapy. In the multivariate explanatory analysis, cumulative dose of cisplatin and radiation therapy, and young age displayed a causal relationship with increased sensorineural hearing loss during and after therapy ($p<0.001$). In the multivariate prediction analysis, pre-treatment hearing level of the concerning ear was identified as an independent predictive factor for hearing capability after therapy ($P<0.0001$).

Conclusions: Both cisplatin and RT were proven to induce sensorineural hearing loss, in this study with short-term follow-up. Of all patient and treatment variables studied, the patients pre-treatment hearing level appeared to be the main predictive factor for hearing capability after high-dose intra-arterial cisplatin chemoradiation.

INTRODUCTION

Head and neck cancer has a worldwide incidence of approximately 780,000 new cases per year and over 70% of these patients present with stage III and IV disease.[1] The treatment of these locally advanced head and neck cancers is a challenge in view of the limited response to radiation monotherapy in case of inoperable disease and the need to preserve vital functions in case of operable lesions. A combination of radiotherapy and concomitant chemotherapy - preferably cisplatin-based - shows improved response rates and allows for organ preservation. Taken this into consideration and aiming to increase drug doses in the tumor with minimal systemic toxicity, a superselective intra-arterial administration scheme of high-dose cisplatin with sodium thiosulfate for cisplatin neutralization combined with radiotherapy was designed.[2,3] Recent evaluations show favourable results.[4,5] However, this treatment scheme induces an incidence of 60% sensorineural hearing loss (SNHL) at speech frequencies.[6] Also in other studies including high-dose cisplatin administration or cranial irradiation, up to 41% of patients experience a notable hearing loss at speech frequencies.[7-12] Nevertheless, retrieving the degree of ototoxicity was biased due to heterogeneity of data collection methods. Some authors excluded ears with pre-existent SNHL[7,8] or patients with conductive hearing losses.[8,13] Others selected small patient numbers or assembled incomparable treatment schedules for different types of tumors.[7,9,10,13] Moreover, comparison across studies was difficult as ototoxicity was not defined according to uniform criteria. In addition, as limited patient and treatment variables were studied, previously identified risk factors of ototoxicity were not proven to be of explanatory or predictive value.

The objective of this study is a prospective assessment of hearing loss due to high-dose intra-arterial cisplatin chemo-irradiation. Patient and chemoradiation variables are studied in a multivariate analysis to determine their explanatory role or predictive value in ototoxicity.

METHODS AND MATERIALS

Population and chemoradiation characteristics

From 1997 to 2003, 146 patients with a locally advanced stage III/IV squamous cell carcinoma of the head and neck were treated with intra-arterial infusion of high-dose cisplatin (150 mg/m^2, four courses on days 1, 8, 15 and 22) and concurrent radiation therapy (70 Gy) (acronym RADPLAT).[5] Simultaneously, sodium thiosulfate (9g / m^2 / 30min, followed by 12g / m^2 / 2h) was administered intravenously for cisplatin neutralization. Neck dissection for residual disease was considered part of the primary treatment. All patients signed an informed consent.

Radiation therapy protocols and the calculation of applied dose on the inner ear

Patients received 70 Gray (Gy) fractionated radiation therapy (RT) in 35 daily fractions of 2 Gy. The applied dose to the inner ear was 13 Gy median (range 0-82 Gy). Hundred-twenty-eight patients were treated with 2 lateral radiation portals on the head and neck, plotted on x-rays or CT scans. By revision of these images, we were able to measure distances from the inner ears to the boundary of the radiation field and to convert these distances to the applied dose to the auditory system according to simulated patient models. By repeating these measurements on X-rays and CT-scans we found an uncertainty of 3.2 mm and 1.0 mm (median), respectively. In recent years, 18 patients were given intensity-modulated radiation therapy (IMRT), in which multiple portals at different angles were applied to the head and neck sparing the organs (ear) contralateral to the tumor.

Audiometry and analysis of audiometric data

Audiometry was performed before therapy, after each cisplatin infusion and median 7.5 weeks after therapy (range 1 to 59 weeks, 89% of patients within 4 months). Air-conduction (AC) thresholds were measured at frequencies 0.125, 0.250, 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11.2, 12.5, 14 and 16 kHz and bone-conduction (BC) thresholds were measured at 0.5, 1, 2 and 4 kHz. Pure Tone Averages (PTAs) were computed to obtain the mean AC threshold at three frequency areas: the low frequency area related to speech perception in quiet (PTA 0.5-1-2 kHz), the high frequency area related to speech perception in noise (PTA 1-2-4 kHz) and the ultra-high frequency area related to the perception of high tones in music and/or in nature (PTA 8-10-12.5 kHz). Air-bone gaps (ABGs) were determined by the difference between AC and BC at 0.5-1-2 kHz.

In the audiograms up to 8 kHz 97-100% of the air-conduction thresholds were measured. However, at ultra-high frequencies 9-16 kHz, many thresholds were not measured, as some patients were not fit enough to complete the audiometry session. We hypothesized that these patients suffered severely from therapy and therefore might have endured relatively severe chemoradiation toxicity. In addition, some patients displayed hearing thresholds beyond the maximum output of the audiometer. Excluding these patients may lead to an underestimation of hearing thresholds during chemoradiation. Therefore, we reconstructed missing hearing thresholds by extrapolation, using a straight line with the same slope that was found *on average* in the patients of our study that were indeed measured at all frequencies.

Statistics

Repeated measurement analysis using all thresholds was performed to study the relationship between patient or treatment variables and hearing loss. Audiometric thresholds were logarithmically transformed after adding 10 dB. P-values < 0.001 were considered statistically significant. Thirty-four patients with insufficiently detailed radiotherapy data were excluded. SD's and correlations were modelled using a general covariance matrix for 10 measurements (PTA AC and BC 0.5-1-2 kHz, PTA AC and BC 1-2-4 kHz, PTA 8-10-12.5 kHz, both ears) per occasion (audiogram) with a first-order autoregressive model linking the same type of threshold (PTA) over occasions. Additionally, the slopes of the thresholds versus cisplatin dose

were assumed to vary normally with arbitrary covariance matrix. The effect of cumulative cisplatin dose was assumed to be linear and to have interaction with type of threshold with third order interactions (including implied main effects and second order interactions) with cisplatin infusion side, age and gender. Main effects and interactions with threshold type were included for infusion-specific cisplatin dose (including third order interaction with infusion side), cumulative and cycle-specific radiotherapy dose, occasion and side of ear. Hierarchical backward elimination (P>0.10) was applied to facilitate interpretation. P-values were calculated from approximate type III F-tests, confidence intervals from approximate t-distributions. The number of patients defined the denominator degrees of freedom for between-patient factors and the number of measurements for the within-patient factors. PROC MIXED of SAS® (8.2 for Windows) was used.

To predict PTA AC 1-2-4 kHz after the 4th cisplatin infusion, a repeated measurement analysis was used with arbitrary covariance matrix for the two thresholds. Multiple imputation[14] (5 imputations) based on the conditional Gaussian model with data augmentation[15] was used to deal with lacking explanatory variables. The results were combined using the methods of Barnard[16] and Rubin and Hesterberg[17]. These methods are used as implemented in the "missing" library of the statistical package S+ (version 6.2): ninety-one patients with known thresholds were used. Finally, the performance of the predictor was evaluated using leave-one-out cross-validation (LOOCV).[18]

RESULTS

Patients and treatment

Chemo-irradiation was applied to 112 men and 34 women, aged 54 years (median). Patient and treatment characteristics are summarized in table 1. Four patients did not complete the treatment protocol, due to impaired physical condition.

Overall hearing loss

The percentages of patients completing the audiometry schedule were: 96% before therapy, 91%, 91%, 84% and 59% after cisplatin infusion I, II, III, and IV and 62% after therapy.

The largest threshold shifts at (ultra) high frequencies 3 to 16 kHz, were seen after the 2nd and 3rd cisplatin infusions (figure 1). The largest threshold shifts at low frequencies (0.125 to 1 kHz) were observed after therapy, due to an increase in ABG: Sixteen of seventy-three patients (22%) (measured at both AC and BC 0.5, 1 ànd 2 kHz) developed an increase in ABG > 10 dB mainly after therapy, probably due to radiation-induced mucosal swelling or middle ear pathology. This hypothesis is supported by the finding that ears ipsilateral to the tumor experienced a higher ABG than ears contralateral to the tumor, mainly in patients with tumors of the pharynx.

Table 1. Patient and treatment characteristics (n = 146)

Characteristics		Value
Median age		54 years
Gender		
	male	112 (77%)
	female	34 (23%)
T classification		
	2	2 (1%)
	3	32 (22%)
	4	111 (76%)
	unknown	1 (1%)
N classification		
	0	33 (23%)
	1	18 (12%)
	2	73 (50%)
	3	21 (14%)
	unknown	1 (1%)
Tumor site		
	oral cavity	27 (19%)
	oropharynx	91 (62%)
	supraglottic larynx	5 (3%)
	hypopharynx	23 (16%)
Cisplatin dose, median, mg/infusion		263 mg
Cisplatin infusion side	ipsilateral / contralateral	72 (49%)
	double sided	74 (51%)
Radiation therapy dose to inner ear, median		13 Gray
Radiation therapy dose to inner ear, range		0-82 Gray

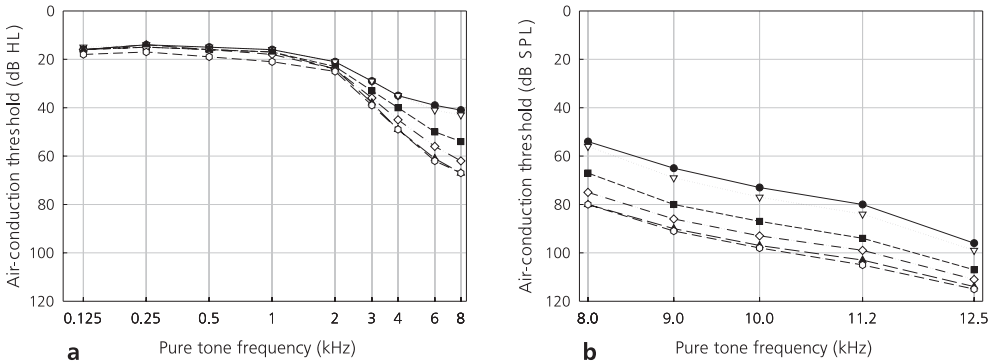

Fig. 1. Mean hearing thresholds of all patients (146) before targeted high-dose cisplatin chemoradiation (●), after the 1st, 2nd, 3rd and 4th cisplatin infusions (▽, ■, ◇ and ▲, respectively) and after therapy (o). Figure 1a: Air-conduction at low and high frequencies in dB HL. Figure 1b: Air-conduction at ultra-high frequencies in dB SPL.

Table 2. Mean hearing thresholds of the whole population before and after therapy

	PTA AC* 1-2-4 kHz† mean (median)	PTA AC 8-10-12.5 kHz†† mean (median)
Before therapy	24 (22)	74 (72)
After therapy	32 (27)	98 (94)

* AC = Air-Conduction
† PTA AC 1-2-4 kHz = Mean threshold at 1, 2 ànd 4 kHz (in dB Hearing Level)
†† PTA AC 8-10-12.5 kHz = Mean threshold at 8, 10 ànd 12.5 kHz (in dB Sound Pressure Level)

At high frequencies and ultra-high frequencies total threshold shifts were on average 8 and 24 dB respectively (table 2).

Eligibility for Hearing Aids

Of 256 measured ears without an indication for a hearing aid before therapy, 59 ears (23%) were under consideration for a hearing aid after therapy, as they developed an AC > 35 dB HL at frequency PTA 1-2-4 kHz, considered the criterium for reimbursement of hearing aids in the Netherlands.

Subjective complaints

Before therapy, 14% of the patients experienced subjective hearing loss and 7% of the patients experienced tinnitus. After the 1st, 2nd, 3rd and 4th infusion of cisplatin, increased subjective hearing loss is noted in 5%, 11%, 9% and 11% of the ears, respectively. For tinnitus these numbers were 15%, 24%, 32% and 19%.

The multivariate explanatory analysis

Effect of treatment variables

Hearing loss during and after treatment, expressed in (a percentage change in) dB of pre-treatment hearing level, was found to be associated with cumulative cisplatin dose ($p<0.0001$). However, the strength of this association depended on the frequency area ($p<0.0001$), age ($p=0.0029$) and gender ($p=0.0043$). A mean cumulative cisplatin dose of 1050 mg led to hearing deterioration after therapy at *ultra-high* frequencies of 34% (95% CI: 28-41%) and at *high* frequencies (BC) of 21% (95% CI: 12-31%), for the mean population, whereas *no* effect was found on low frequencies (neither AC nor BC).

Interestingly, an increase in radiation dose of 15 Gray was related to an increase in hearing loss at *low* frequencies AC and BC ($p<0.0001$) of 18% (95% CI: 11-25%) and 13% (95% CI: 6-20%), respectively, whereas the hearing loss at high (BC) and ultra high frequencies was 9% (3%-15%) and 3% (-1%-7%), respectively.

There was no evidence that the *relative* increase in hearing loss per mg cisplatin of the measured ear related to an ipsilateral infusion ($p>0.2$) or to whether we assessed the right ear or the left ear ($P=0.0047$). Nevertheless, if the measured ear is at the side of the infusion

hearing loss is 4.1 dB higher at PTA AC 1-2-4 kHz (p=0.0007), and mean hearing deterioration was 22.6 dB and 24.1 dB in the right and left ear, respectively (P<0.05).

Effect of patient variables

The effect of age on hearing loss appeared highly significant (p<0.0001). The younger the patient, the more hearing loss due to cisplatin chemoradiation. A difference in age of 20 years implied a 55% (36%-77%) difference in both baseline audiometry ànd hearing loss at PTA AC 1-2-4, whereas this age effect was 13% (5%-22%) at PTA AC 8-10-12.5 kHz.

Gender is not associated with in- or decreased hearing loss in the mean population (p=0.3). Nevertheless, cisplatin (1050 mg) resulted in an increase of hearing loss of 26% (14%-39%) in women of 53 years old against 11% (4%-18%) in men of the same age (multivariate analysis), possibly due to dissimilarity in pre-treatment hearing capability in favour of women as compared to men (p<0.01, univariate analysis).

In this explanatory analysis, hearing capability was an outcome measure and could therefore not be considered a variable. However, to illustrate the effect of baseline audiometry, we

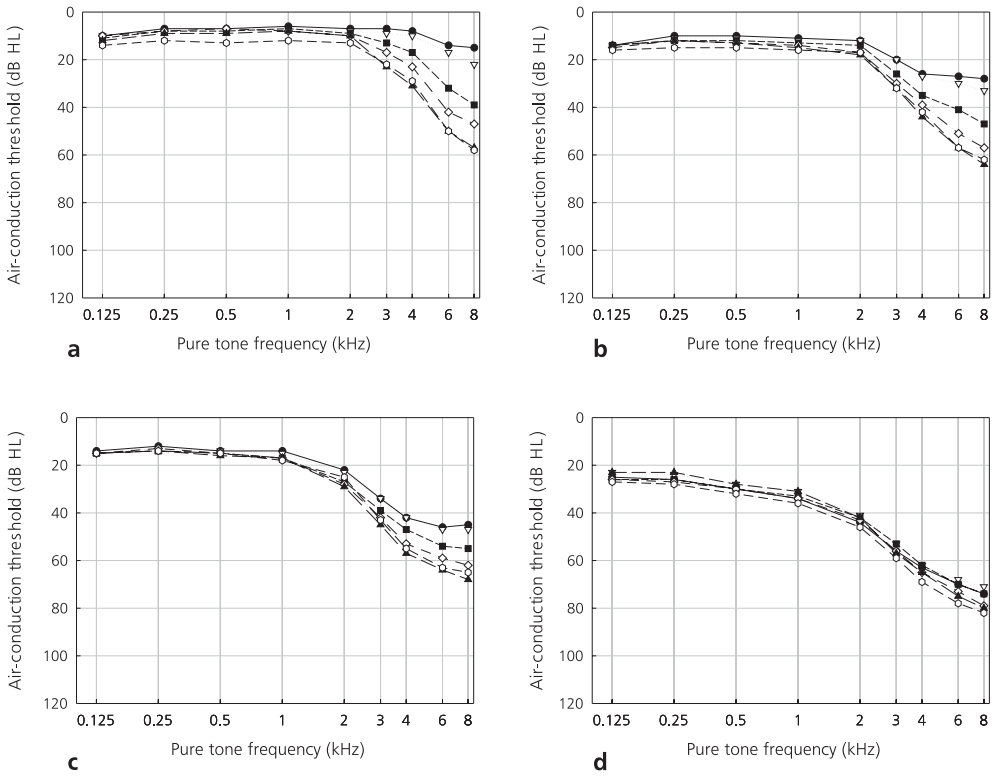

Fig. 2. Averaged audiograms of all ears classified into quartiles of pretreatment hearing level at PTA AC 1-2-4 kHz (in dB HL). Quartiles 1, 2, 3 and 4 are figures 2a, 2b, 2c and 2d, respectively. Mean hearing thresholds before targeted high-dose cisplatin chemoradiation (●), after the 1st, 2nd, 3rd and 4th cisplatin infusions (▽, ■, ◇ and ▲, respectively) and after therapy (o).

compared hearing thresholds in ears of the 1st quartile (pre-treatment PTA AC 1-2-4 kHz is 0.0 – 11.7 dB HL, aged 48 years) with hearing thresholds in ears of the 2nd quartile (pre-treatment PTA AC 1-2-4 kHz is 13.3 – 20 dB HL, aged 53 years), 3rd quartile (pre-treatment PTA AC 1-2-4 kHz is 21.7 – 28.3 dB HL, aged 56 years) and the 4th quartile (pre-treatment PTA AC 1-2-4 is 31.7 – 116.1 dB HL, aged 61 years) (Figure 2). Ears with good hearing before therapy experienced significant SNHL, whereas ears with poor hearing before treatment displayed a non-significant shift. Tumor site, TNM classification or side of the tumor did not influence the degree of SNHL.

The multivariate prediction analysis

To reveal factors predicting hearing capability after treatment at PTA AC 1-2-4 kHz, we performed a prediction model. The pre-treatment hearing level of the concerning ear at PTA AC 1-2-4 kHz proved to be an independent predictive factor for the hearing capability after therapy ($P<0.0001$); The more unfavourable the hearing level prior to therapy, the more unfavourable the hearing capability after cisplatin chemoradiation, as illustrated in figure 2. Other patient and treatment variables (gender, age, subjective hearing loss, subjective tinnitus, right or left ear, cumulative cisplatin dose, cisplatin infusion side and cumulative radiation dose) were potentially predictive, but not statistically proven to be of independent predictive value ($p > 0.001$).

DISCUSSION

This is the first multivariable analysis of ototoxicity in a consecutive series of patients treated with high-dose cisplatin chemo-irradiation for advanced squamous cell carcinoma of the head and neck.

In our study, the cumulative cisplatin dose and the cumulative dose of cranial irradiation displayed different causal relationships with SNHL due to treatment: High-dose cisplatin demonstrated increasing hearing loss with increasing frequencies (and no effect on PTA 0.5-1-2 kHz), whereas the cumulative radiation therapy dose displayed increasing hearing loss with descending frequencies, mainly at low frequency air-conduction ànd bone-conduction 0.5-1-2 kHz. In previous studies, however, cranial irradiation as single treatment modality has been found to induce a higher incidence of SNHL at frequencies 4 kHz and 8 kHz compared to PTA 0.5-1-2 kHz.[19-21] In our analysis, it could well be that a larger radiotherapy effect at increasing frequencies was masked by the adverse effects of cisplatin.

In our explanatory analysis, young age was identified as a risk factor of ototoxicity too. In addition, it was illustrated that patients with good hearing capability prior to therapy endured, on average, the highest degree of hearing deterioration during treatment (in dB). Patients with limited hearing deterioration were those with pre-existent extensive SNHL due

to presbyacusis (age) or other types of pre-treatment SNHL. However, the phenomenon that good pre-treatment hearing capability means, on average, a greater vulnerability for hearing loss (in dB) could not be proven, as hearing capability was an outcome measure and, therefore, could not be considered a variable in this analysis. Moreover, we have to approach this subject with care: in case of relatively good hearing thresholds before treatment, we may expect a larger decrease after therapy than in patients with poorer hearing thresholds before treatment purely by chance (regression to the mean).

In a second analysis, we weighed patient and treatment variables in view of their potential predictive value for hearing loss due to therapy. In contrast to the explanatory analysis, hearing capability could now be considered a variable too. The main outcome was that, if patients endure Radplat, the patients pre-treatment hearing level of the concerning ear at PTA AC 1-2-4 kHz became the strongest predictive variable for hearing capability after therapy. In the past, the role of age and pre-treatment hearing capability was studied, indicating either no relationship with ototoxicity[10], or actually a correlation between pre-existent hearing loss and an increased incidence of hearing deterioration.[8,22] In children and adolescents, the role of age was proven to be a predictive factor in cisplatin ototoxicity, although they did not consider pre-treatment hearing capability as a predictive factor.[23]

The chemoradiation-induced hearing loss found in our patients is in accordance with other studies concerning intra-arterially or intravenously administered high-dose cisplatin chemoradiation, that show an incidence up to 60% of clinically relevant hearing loss.[5-10] However, several reports on RADPLAT in advanced head and neck cancer do not explicitly comment on hearing loss due to treatment.[24-26] In addition, radiation-induced SNHL has been found short- and long-term after cranial irradiation without cisplatin.[11-12,27] In several prospective studies the latency time of SNHL was found to be between 1-3 months after termination of radiation therapy.[19-21,28] In addition, the probability for hearing loss at 4 kHz was reported to increase with follow up time to 4.5 years and 10 years after treatment[19-21]. In our study, follow up time (range of 1 - 59 weeks after treatment, 89% of patients within 4 months) may have influenced the incidence and extent of hearing loss either positively or negatively, when we consider the studies of Ho[19] describing both patients with recovery (41%) and patients with further deterioration (25%) of SNHL at 4 kHz up to 2 years after therapy, and Kwong[28] reporting an increase of hearing loss at PTA BC 0.5-1-2 kHz up to 2 years and then a decrease up to 4-5 years after therapy.

However, it is imperative to perform future studies concerning ototoxicity in high- or low-dose intravenously administered cisplatin chemo-irradiation *without* sodium thiosulfate rescue to determine whether the degree of hearing loss due to therapy and/or the potential predictive power of patient and treatment variables are similar to the outcome of the current study. Moreover, it will be of interest to assemble patient and treatment variables in a prediction formula to assess the hearing loss beforehand, and to reduce the number of audiograms needed during follow-up of these patients.

In addition, previous literature recommended either diverging ototoxicity criteria as guideline[29-30] or showed diverging ototoxic criteria used by different authors to analyse their results. Some grading systems combined subjective and objective findings and some grading systems defined criteria as "hearing loss interfering with function", "deafness not correctable" that allow for multiple interpretations. In the future it would be desirable to develop ototoxicity criteria that can be translated unambiguously to other patient studies and that allow for simple interpretation in patient counselling.

REFERENCES

1. Sankaranarayanan R, Masuyer E, Swaminathan R, et al. Head and neck cancer: a global perspective on epi-demiology and prognosis. Anticancer Res 1998;18(6B):4779-4786.
2. Robbins KT, Storniolo AM, Kerber C, et al. Phase I study of highly selective supradose cisplatin infusions for advanced head and neck cancer. J Clin Oncol 1994;12(10):2113-2120.
3. Robbins KT, Vicario D, Seagren S, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. Am J Surg 1994;168(5):419-422.
4. Robbins KT, Kumar P, Wong FS, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. Head Neck 2000;22(7):687-693.
5. Balm AJ, Rasch CR, Schornagel JH, et al. High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 2004;26(6):485-493.
6. Madasu R, Ruckenstein MJ, Leake F, et al. Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1997;123(9):978-981.
7. Kopelman J, Budnick AS, Sessions RB, et al. Ototoxicity of high-dose cisplatin by bolus administration in patients with advanced cancers and normal hearing. Laryngoscope 1988;98(8 Pt 1):858-864.
8. Fleming S, Ratanatharathorn V, Weaver A, et al. Ototoxicity from cis-platinum in patients with stages III and IV previously untreated squamous cell cancer of the head and neck. Am J Clin Oncol 1985; 8(4):302-306.
9. Myers SF, Blakley BW, Schwan S, et al. The "plateau effect" of cis-platinum-induced hearing loss. Otolaryngol Head Neck Surg 1991;104(1):122-127.
10. Laurell G, Jungnelius U. High-dose cisplatin treatment: Hearing loss and plasma concentrations. Laryngoscope 1990;100:724-734.
11. 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 2002;65(1):1-7.
12. Johannesen TB, Rasmussen K, Winther FO, et al. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 2002;53(1):86-90.
13. Van Der Hulst RJ, Dreschler WA, Urbanus NA. High frequency audiometry in prospective clinical research of ototoxicity due to platinum derivates. Ann Otol Rhinol Laryngol 1988;97(2 Pt 1):133-137.
14. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons Inc.; 1987.
15. Schafer JL. Analysis of incomplete multivariate data. London: Chapman and Hall; 1997.
16. Barnard J, Rubin DB. Small-sample degrees of freedom with multiple imputations. Biometrika 86:948-955, 1999.
7. Hesterberg TC. Combining multiple imputation t, chi-square, and f inferences. Seattle: MathSoft Inc.; 1998.
8. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. Statistics in Medicine 1990;9:1303-1325.
19. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head Neck 1999;21(6):547-553.
20. Wang L, Kuo W, Lee K, et al. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.
21. Pan C, Eisbruch A, Lee J, et al. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2005;61(5):1393-1402.

22. Vermorken JB, Kapteijn TS, Hart AA, et al. Ototoxicity of cis-diamminedichloroplatinum (II): Influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol 1983;19(1):53-58.

23. Schell MJ, McHaney VA, Green AA, et al. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 1989;7(6):754-760.

24. Michael II LM, Sorenson JM, Samant S, et al. The treatment of advanced sinonasal malignancies with pre-operative intra-arterial cisplatin and concurrent radiation. J Neuro-oncol 2005;72:67-75.

25. Regine WF, Valentino J, John W, et al. High-dose intra-arterial cisplatin and concurrent hyperfractionated radiation therapy in patients with locally advanced primary squamous cell carcinoma of the head and neck: report of a phase II study. Head Neck 2000;22:543-549.

26. Kovács AF, Schiemann M, Turowski B. Combined modality treatment of oral and oropharyngeal cancer including neoadjuvant intraarterial cisplatin and radical surgery followed by concurrent radiation and chemotherapy with weekly docebaxel – three year results of a pilot study. J Cranio-Maxillofacial Surg 2002;30:112-120.

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

28. Kwong D, Wei W, Sham J, 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 1996;36(2):281-289.

29. National Cancer Institute Common Toxicity Criteria (Adverse Events), Bethesda, Maryland, USA, version 2.0, 1999.

30. Brock PR, Bellman SC, Yeomans EC, et al. Cisplatin ototoxicity in children: a practical grading system. Med Pediatr Oncol 1991;19(4):295-300.

Chapter 2

A prediction formula for hearing loss due to concurrent cisplatin chemoradiation in patients with head and neck cancer

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ABSTRACT

High-dose cisplatin chemoradiation is a common treatment modality for advanced head and neck cancer. Risk factors for hearing loss due to high-dose targeted concurrent cisplatin chemoradiation (acronym Radplat) for advanced squamous cell carcinoma of the head and neck (HNSCC) were determined in a previous study from our institute. The current report evaluates the feasibility of a formula predicting cisplatin chemoradiation-induced hearing loss prior to the applied treatment.

INTRODUCTION

High-dose cisplatin chemo-irradiation (CRT) is increasingly used in patients with advanced or high-risk head and neck cancer.[1] Recently, we have evaluated the incidence, degree and patterns of hearing loss in patients treated with high-dose concurrent cisplatin chemoradiation for HNSCC.[2,3,4] In a multivariate analysis, risk factors for ototoxicity were assessed and patient and treatment variables were evaluated for their predictive value for hearing loss due to treatment[3]. Cumulative cisplatin dose, cumulative radiation therapy dose, and young age were identified as risk factors for increased sensorineural hearing loss due to treatment. In addition, the pre-treatment hearing level of the concerning ear at frequencies vital for speech perception proved to be the only independent predictive factor for hearing capability after CRT. The more unfavourable the hearing level prior to therapy, the more unfavourable the hearing capability after high-dose cisplatin chemoradiation. Other patient and treatment variables (gender, age, subjective hearing loss, subjective tinnitus, right or left ear, cumulative cisplatin dose, and cumulative radiation dose) were potentially predictive, but not statistically proven to be of independent predictive value.

However, although sensorineural hearing loss (SNHL) is observed at speech frequencies in a vast majority of patients treated with Radplat[4,5], in individual patient counselling prior to therapy, the exact risk for clinically significant hearing loss is still unknown. Moreover, multiple pure tone audiograms are still needed during high-dose cisplatin CRT to discover patients in whom the treatment scheme may possibly be altered to reduce the risk for high-grade ototoxicity. The current study evaluates the feasibility of a prediction formula, based on patients and treatment characteristics, to determine hearing loss due to treatment prior to therapy.

PATIENTS AND METHODS

From 1997 to 2003, 146 patients with stage III/IV HNSCC were treated with intra-arterial high-dose cisplatin (150 mg/m^2; four courses in week 1,2,3 and 4) with sodium thiosulfate (STS) rescue and concurrent radiation therapy (RT) to 70 Gray in 35 fractions on tumor bearing areas (Radplat). Chemo-irradiation was applied to 112 men and 34 women, aged 54 years (median). A prospective analysis was performed for the total range of audible frequencies (0.125 to 16 kHz) obtained before, after each cisplatin infusion and median 7.5 weeks after treatment. In the audiograms up to 8 kHz 97-100% of the air-conduction thresholds were measured. The applied radiation dose to the inner ear was 13 Gy median (range 0-82 Gy). The patient population and the acquisition of audiometric and treatment related data have been described in detail in our preceding analysis[3].

Thirty-four patients with insufficient RT information were excluded for the statistical multivariate prediction analysis. Audiometric thresholds were logarithmically transformed

to obtain a normal distribution of data, after adding 10 dB. To predict PTA AC 1-2-4 kHz after the 4th cisplatin infusion, a repeated measurement analysis was used with arbitrary covariance matrix for the two thresholds. Multiple imputation[6] (5 imputations) based on the conditional Gaussian model with data augmentation[7] was used to deal with lacking explanatory variables. The results were combined using the methods of Barnard[8] and Rubin and Hesterberg[9]. These methods are used as implemented in the "missing" library of the statistical package S+ (version 6.2): ninety-one patients with known thresholds were used. Finally, the performance of the predictor was evaluated using leave-one-out cross-validation (LOOCV).[10]

RESULTS

From the statistical multivariate prediction model, patient and treatment variables were assembled in a formula to assess the hearing capability at PTA AC 1-2-4 kHz after the 4th infusion of cisplatin (in dB HL), per ear, as schematically expressed as in Figure 1. Mathematically, for a prediction prior to treatment, the formula is expressed as in Figure 2. As we used a natural logarithmic-transformation of the (audiometric measurement + 10 dB) in our statistics, this formula is written as an inverse LN-transformation (EXP) minus 10 dB in order to obtain outcome in dB HL. Dependent on the timing of prediction (prior to treatment or after the 1st , 2nd , 3rd , or 4th cisplatin infusion) this mathematical formula should be extended and adjusted with specific constant and coefficients.

In Figure 3, the observed hearing levels of individual ears (112 patients) were plotted against their LOOCV-predicted hearing levels. A margin of 10 dB (area within dotted straight lines) was plotted. In order to assess the formula referring to the ability of speech perception

Predicted PTA AC 1-2-4 kHz (in dB HL) =

constant + (gender + age + infusion side + cisplatin dose + radiation dose + left ear)

+

(pre-treatment values of both ears: hearing level, subjective hearing loss / tinnitus)

+

(values known after latest obtained audiogram of both ears: hearing level, subjective hearing loss / tinnitus)

Figure 1. Schematic reproduction of the formula predicting hearing capability (at Pure Tone Average AC 1-2-4 kHz) after the 4th cisplatin infusion (in dB HL) per ear. The model is built up of patient variables, treatment variables, pre-treatment values of both ears, and values of both ears known after the latest obtained audiogram.

PTA AC 1-2-4 kHz =

EXP [1.52 + (0.038*G) + (0.0010*A) + (-0.094*I) + (-0.104*DI) + (-0.055*C/100) + (0.0021*RT^i) + (0.0028*RT^c) + (-0.009*L)

+

0.477*LN(ACH^i_0+10) + 0.267*LN(ACU^i_0+10) + (-0.019*H^i_0) + (0.055*T^i_0) +

0.169*LN(ACH^c_0+10) + -0.17*LN(ACU^c_0+10) + (-0.005*H^c_0) + (-0.019*T^c_0)**]**

– 10 dB

G = gender (women = 1, man = 0), A = age (yrs), I = infusion side (ipsilateral = 0, contralateral = 1)
DI = double sided infusion (yes = 1, no = 0), C = cumulative cisplatin dose (mg), RT = cumulative radiation dose (Gray)
Superscript i = ipsilateral ear, superscript c = contralateral ear, L = Left Ear (yes = 1, no = 0)
LN = natural logarithm, ACH = PTA AC 1-2-4 kHz (in dB **HL**); ACU = PTA AC 8-10-12.5 kHz (in dB **SPL**)
H = Subjective Hearing loss = 1, no complaints = 0
T = Subjective Tinnitus = 1, no complaints = 0
Underscript 0 = obtained from pre-treatment audiogram

Figure 2. The formula of Figure 1, mathematically, with specific coefficients belonging to a prediction performed prior to treatment. As our statistical analysis used a natural logarithmic-transformation of the (audiometric measurement + 10 dB), the formula reflects an EXP minus 10 dB.

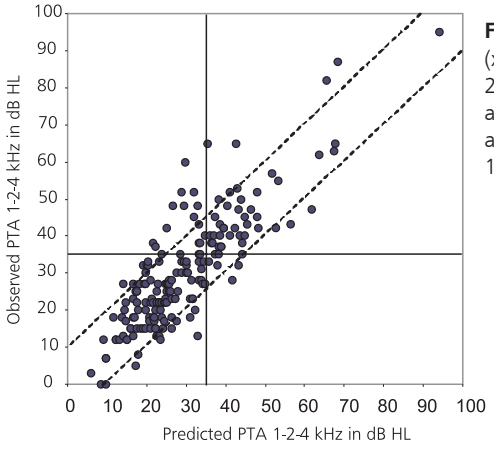

Figure 3. Observed (y-axis) against LOOCV-predicted (x-axis) Pure Tone Average AC 1-2-4 kHz in dB HL, 224 ears, with demarcation lines (solid straight lines) at 35 dB HL reflecting the qualification for a hearing aid. Area between dotted straight lines ressembles a 10 dB interval of confidence.

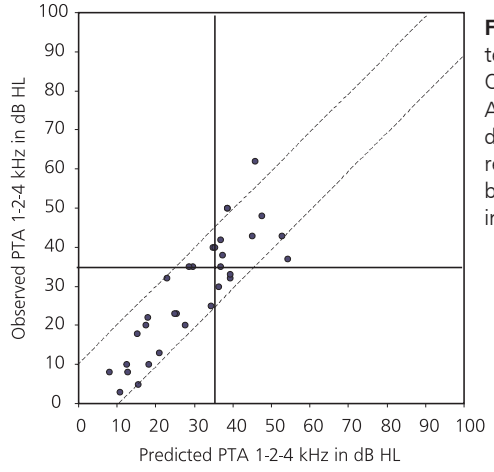

Figure 4. External validation of prediction formula tested on 16 extra patients treated with RADPLAT. Observed (y-axis) against predicted (x-axis) Pure Tone Average AC 1-2-4 kHz in dB HL, per ear (n=32), with demarcation lines (solid straight lines) at 35 dB HL reflecting the qualification for a hearing aid. Area between dotted straight lines ressembles a 10 dB interval of confidence.

in noise we set a demarcation line at 35 dB HL at PTA AC 1-2-4 kHz (straight solid lines) the criterium for reimbursement of hearing aids (HAs) in the Netherlands.

In this assessment, the sensitivity of the formula was 77%, as 61 ears were predicted to qualify for a HA (hearing level > 35 dB HL at PTA AC 1-2-4 kHz) of the 79 ears which were actually observed to qualify for a HA. The specificity of the formula is 92%, as 134 ears were predicted to remain ≤ 35 dB HL of the 145 ears which were indeed observed below that level. As we expected, performing the prediction formula at a later moment during therapy will increase the predictive power: Assessment after the 1st infusion of cisplatin resulted in a sensitivity of 83% and a specificity of 92% (not shown).

DISCUSSION

In the current study, various patient and treatment related variables were assembled in a formula to estimate treatment-induced hearing loss prior to the intended therapy. Thus, for use of the formula, a baseline pure tone audiogram is indispensable and certain numbers of the treatment scheme –e.g. the individual cumulative cisplatin dose and the inner ear radiation dose- have to be known beforehand.

With a sensitivity of 77% and a specificity of 92%, the risk for hearing loss > 35 dB HL at PTA AC 1-2-4 kHz due to treatment can be assessed in individual patient counselling prior to treatment. However, it can be debated whether audiometry after each cisplatin infusion -to identify patients in whom the treatment scheme may be altered to reduce the chance for high-grade hearing loss- can be omitted, as 18 of 152 ears were falsely predicted to remain below 35 dB HL. A limited improvement was seen performing a prediction after the first infusion of cisplatin, as 13 ears were falsely predicted to remain below 35 dB HL.

In addition, we performed an external validation on 16 extra patients (32 ears) treated with Radplat (Figure 4), resulting in a sensitivity of 86% and a specificity of 83%. Despite the limited number of patients, this result supports the main message of our report considering the predictive strength of various variables. Nevertheless, a more elaborated external validation is required to confirm our findings.

However, as the current analysis went along, final results were obtained from the phase III trial conducted in our institute comparing Radplat with intravenously administered high-dose cisplatin CRT (CRT-IV; 100 mg/m^2; three courses in week 1,4 and 7; and 70 Gy RT) without sodium thiosulphate.[11] The first clinical evaluation of this trial showed no significant difference in loco-regional control (62% and 68%, in Radplat and CRT-IV, respectively) or overall survival (61% and 63%, respectively) at two years follow-up, and therefore, in our institute, the Radplat protocol was halted. Hence, in the future, it is imperative to evaluate the feasibility of this prediction model in high-dose CRT-IV and in other cisplatin CRT regimens.

For that purpose, certain issues have to be addressed that may influence the final form and use of the predictive formula. Firstly, in Radplat, the cumulative dose of cisplatin (in mg) is relatively high compared to other cisplatin CRT schemes, while the use of STS is not present as a separate variable in the current formula. Logically, an underestimation of the predicted hearing capability can be expected when the formula described above is applied to other cisplatin CRT protocols without STS. Secondly, the presented formula was made to provide a prediction of hearing capability after the 4th infusion of cisplatin in Radplat (week 4), while at that point in time during CRT-IV the 3rd cisplatin infusion (week 7) is not yet administered. Therefore, again, a systematic underestimation of the prediction of hearing capability may be expected when the formula is applied to CRT-IV. Finally, while performing the multivariate prediction analysis once again and aiming to increase the practicability of the formula for other treatment regimens/protocols, it is desirable to investigate whether the formula can be simplified by reducing the number of variables used without devaluating its predictive power.

In conclusion, a prediction of Radplat-induced hearing loss at frequencies vital for speech perception has proven to be feasible using the presented formula. We propose to perform audiometry before and after therapy in the routine follow up of these patients. However, in the future, it is imperative to evaluate the feasibility of this prediction model in other cisplatin CRT regimens.

REFERENCES

1. Adelstein DJ, Recent randomized trials of chemoradiation in the management of locally advanced head and neck cancer. Curr Opin Oncol. 1998 May;10(3):213-8.
2. Zuur CL, Simis YJ, Lansdaal PE, Rasch CR, Tange RA, Balm AJ, Dreschler WA. Audiometric patterns in ototoxicity of intra-arterial cisplatin chemoradiation in patients with locally advanced head and neck cancer. Audiol Neurotol 2006;11(5):318-30.
3. Zuur CL, Simis YJ, Lansdaal PE, Hart AA, Rasch CR, Schornagel JH, Dreschler WA, Balm AJ. 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. 2007;68(5):1320-5.
4. Zuur CL, Simis YJ, Lansdaal PE, Hart AA, Schornagel JH, Dreschler WA, Rasch CR, Balm AJ. 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 2007;25(24):3759-65.
5. Madasu R, Ruckenstein MJ, Leake F, et al. Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1997;123(9):978-981.
6. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons Inc.; 1987.
7. Schafer JL. Analysis of incomplete multivariate data. London: Chapman and Hall; 1997.
8. Barnard J, Rubin DB. Small-sample degrees of freedom with multiple imputations. Biometrika 86:948-955, 1999.
9. Hesterberg TC. Combining multiple imputation t, chi-square, and f inferences. Seattle: MathSoft Inc.; 1998.
10. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. Statistics in Medicine 1990;9:1303-1325.
11. Rasch CRN, Balm AJM, Schornagel JH, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-institutional trial. ASTRO, 2006 (abstr)

Chapter 3

Audiometric patterns in ototoxicity of intra-arterial cisplatin chemoradiation in patients with locally advanced head and neck cancer

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Abstract

This study describes audiometric patterns of ototoxicity in a consecutive series of patients uniformly treated with intra-arterial high-dose cisplatin chemo-irradiation for advanced cancer of the head and neck. Air-conduction thresholds were measured from 0.125 to 16 kHz and bone-conduction thresholds were measured from 0.5 to 4 kHz. The overall audiometric pattern was characterised by maximum threshold shifts after the 2nd cisplatin infusion and a maximum total threshold shift at 8 kHz; irrespective of gender, age, pre-treatment sensorineural hearing loss (SNHL) or subjective complaints during therapy. A hearing deterioration gradient was observed from (ultra) high to low frequencies, worse with increasing pre-existent SNHL and with increasing cumulative dose of cisplatin chemoradiation. Cisplatin chemoradiation induced hearing loss seemed to reach a plateau at higher levels (75-80 dB HL) for frequencies above 8 kHz compared to frequencies up to 8 kHz (45-60 dB HL). Recovery of SNHL was found after therapy in 27 ears characterized by extensive hearing loss at frequencies 1, 2 and 4 kHz.

Introduction

Cis-diamminedichloroplatinum II (cisplatin), clinically the most powerful platinum chemotherapeutic agent since FDA approval in 1978, has demonstrated a significant antineoplastic activity against a variety of solid tumors in adults and children. It plays an important role in the treatment of locally advanced head and neck carcinomas, especially in combination with radiotherapy.[1,2] Cisplatin chemoradiation allows for organ preservation and in order to increase drug doses in the tumor while limiting systemic toxicity, a superselective intra-arterial administration protocol of high-dose cisplatin with sodium thiosulfate for neutralization with concurrent radiation therapy was developed for advanced carcinomas of the head and neck (acronym Radplat). Recent evaluations show favourable results.[3,4]

Although ototoxicity is known to be a major side effect of (high-dose) cisplatin and of radiation therapy [5-11], previous reports describing outcome of clinical trials with Radplat do not comment on the incidence and extent of hearing loss due to treatment [12-14]. Nevertheless, significant hearing loss due to Radplat was shown in studies of Madasu and Balm.[4,15] In a preceding analysis we described the degree of hearing loss and its predicting factors in high-dose cisplatin based chemo-irradiation in our patient population with inoperable carcinomas of the head and neck.[16]

Clinically, cisplatin ototoxicity has been described as a bilateral, cumulative, dose-related and usually permanent sensorineural hearing loss (SNHL), beginning at the higher frequencies and, with increasing doses or prolonged treatment, progressively extending to frequencies involved in speech perception.[17,18] The ototoxicity pattern seems related to age or pre-existent hearing loss, as studies regarding *low* dose cisplatin infusions described high-frequency hearing loss mainly in younger patients and an increasing risk of low frequency hearing loss in the elderly.[17,19] At high frequencies, a potential maximum of cisplatin induced hearing loss was considered.[6,8] In addition, case reports with recovery after low dose cisplatin have been described.[9,17,20] The variability in the individual human presentation was frequently ascribed to individual susceptibility to the adverse effects of cisplatin. However, the precise clinical pattern of hearing loss induced by cisplatin chemoirradiation remains unclear, as previous studies are characterized by heterogeneous populations, limited patient numbers or case reports, diverse in- or exclusion criteria, and various audiometric assessments.

The objective of the current study was to deduce the audiometric patterns of hearing loss at individual frequencies (125 Hz to 16 kHz) in this large group of uniformly treated patients.

Patients and Methods

Patient and treatment characteristics

From 1997 to 2003, 146 patients (112 men and 34 women, median age 54 years) with locally advanced squamous cell carcinoma of the head and neck were treated with chemoirradiation according to a protocol of intra-arterial infusion of high-dose cisplatin (150 mg/m^2, four courses on days 1, 8, 15 and 22) in the nutrient artery of the carcinoma (a branch of the external carotid artery) and concurrent RT (70 Gray) (acronym Radplat). Simultaneously with the intra-arterial infusion, sodium thiosulfate (9g / m^2 / 30min, followed by 12g / m^2 / 2h) was administered intravenously to provide effective cisplatin neutralization.

The 4 individual cisplatin infusions (150 mg/m^2) ranged from 248 mg to 264 mg and were applied ipsilateral or contralateral (49%) and bilateral (51%) to the measured ear. Four patients did not complete the treatment protocol, due to impaired physical condition.

The tumor was staged T3/4 in 98% of the patients and located in the oropharynx (62%), oral cavity (19%), hypopharynx (16%), and supraglottic larynx (3%).

Radiotherapy protocol and calculation of radiation dose on the inner ear

Patients received 70 Gray (Gy) fractionated RT in 35 daily sessions of 2 Gy. To determine the dose of RT to the inner ear we simulated patient models in whom the inner ear was either inside or outside the radiation field. Hence we were able to record the radiation dose at several points in the radiation field at a direct line to the boundary of the field. Thereafter, we measured distances from the inner ears to the boundary of the radiation field in our patients en translated these distances to the received amount of Gy according to the simulated patient models.

From 1999 to 2000, 97 patients were treated in the conventional way with 2 lateral radiation portals on the head and neck. As the portals were plotted on head and neck X-rays, we were able to determine in retrospect the distance of the ear to the radiation field by measuring the distance of the centre of the bony external auditory canal to the boundary of the field. By repeating this measurement we found an uncertainty of 3,2 mm median. In later years, radiation portals of 31 patients were set up on a CT scan. By reloading these scans and portals we were able to digitally measure the actual distance from the cochlea to the radiation field. By repeating the procedure twice, we found a median variation of 1.0 mm. In recent years, 18 patients were submitted to intensity-modulated radiation therapy RT. In intensity-modulated RT multiple portals in different angles are applied to the head and neck sparing the organs (ear) contralateral to the tumor. In these patients the RT dose to the ipsilateral and contralateral inner ear was computed digitally.

Audiometry and analysis of audiometric data

Audiometry was performed by trained speech therapists using a Madsen Electronics Orbiter 922/2 Clinical Audiometer in a sound proof booth. Telephonics TDH39P headphones

were used for the frequencies 0.125, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz**1**. Ultra-high audiometric thresholds (9.0, 10.0, 11.2, 12.5, 14.0 and 16.0 kHz) were obtained using Sennheiser HDA200 headphones**2**. During the audiometry session, pure tone air-conduction (AC) audiometry was performed first, followed by bone-conduction (BC) audiometry.

Audiometry was performed before therapy, after each infusion of cisplatin (days 1, 8, 15 and 22) and median 7.5 weeks after termination of therapy. AC thresholds were measured at 15 frequencies from 0.125 to 16 kHz and BC thresholds were measured at 0.5, 1, 2 and 4 kHz. Audiometric thresholds were analysed for each ear. In testing the ototoxic effect we used BC thresholds whenever possible (up to 4 kHz). To evaluate ototoxicity in terms of different aspects of hearing, Pure Tone Averages (PTAs) were computed to obtain the mean AC threshold at three frequency areas: the low frequency area related to speech perception in quiet (PTA 0.5-1-2 kHz), the high frequency area related to speech perception in noise (PTA 1-2-4 kHz) and the ultra-high frequency area related to the perception of high tones in music and/or in nature (PTA 8-10-12.5 kHz). Air-bone gaps (ABGs) were determined by the difference between AC and BC at 0.5-1-2 kHz. Thresholds are presented in dB Hearing Level (dB HL). For hearing thresholds above 8 kHz we used the calibration values of the audiometer / headphones.

In the audiograms up to 8 kHz 97-100% of the AC thresholds were measured. At ultra-high frequencies (9-16 kHz) and in particular in the course of time during therapy, many thresholds could not be measured. In a number of cases this was due to the fact that the patient was not fit enough to complete the full audiometry session. One may assume that these patients endured severe side effects of the cisplatin chemoradiation. Other patients had hearing thresholds beyond the maximum output of the audiometer. Excluding these patients may lead to an underestimation of hearing thresholds and threshold shifts during treatment. Nevertheless, a reconstruction of missing data (through intrapolation or extrapolation) would potentially interfere with the exact audiometric pattern of ototoxicity. Therefore, we decided to evaluate the actually measured audiometric data. In 4 patients the pre-treatment audiogram was not available.

Statistics

We pretested both baseline thresholds and threshold shifts at pure tones and PTAs to have a normal distribution. A Kolmogorov-Smirnov test showed that neither our plain data at baseline audiometry, nor our transformed data are likely to be normally distributed (maximum $p = 0.005$). Therefore, since certain residues of the population inhibit a normal distribution and since we aim to analyse patterns of hearing loss in patient subgroups, we performed

1 Telephonics TDH39 headphones were calibrated according to ISO 389-1[21], table 2 using B&K Artificial Ear Type 4153 (IEC 60318). Reference equivalent threshold sound pressure levels relative to 2 x 10^{-5} Pa are the following (in dB): 125 Hz: 45.0; 250 Hz: 27.0; 500 Hz: 13.5; 1 kHz: 7.5; 2 kHz: 9.0; 3 kHz: 11.5; 4 kHz: 12.0; 6 kHz: 16.0; 8 kHz: 15.5.

2 Sennheiser HDA 200 headphones were calibrated according to ISO 389-5[21] using B&K Artificial Ear Type 4153 (IEC 60318). Reference equivalent threshold sound pressure levels relative to 2 x 10^{-5} Pa are the following (in dB): 9 kHz: 18.5; 10 kHz: 22.0; 11.2 kHz: 23.0; 12.5 kHz: 28.0; 14 kHz: 36.0; 16 kHz: 56.0. In this work we refer to thresholds obtained with this calibration as hearing levels at the ultra-high frequencies.

nonparametric tests. The Mann-Whitney U test was used in case of independent samples. The Wilcoxon matched-pairs signed-ranks test was used in case of related samples.

Results

Audiograms of all 146 patients (n=292 ears) that underwent targeted chemoradiation from 1997 to 2003 were analysed to prevent selection bias. The percentages of patients undergoing the audiometry schedule were as follows: 96% before therapy, 91% after cisplatin infusion I, 91% after infusion II, 84% after infusion III, 59% after infusion IV and 62% after therapy.

The overall audiometric pattern

Hearing loss due to cisplatin chemoradiation is shown in the average AC pure tone audiogram for the whole population (Figure 1). After the first infusion of cisplatin the largest threshold shift was seen at 10 kHz (mean 5.4 dB, SD 11.5). For the total treatment, the largest total threshold shifts due to cisplatin chemoradiation were calculated to be 27 dB (SD 23.3) at 8 kHz (n=236 ears) and 23 dB (SD 19.9 and 19.3) at 9 and 10 kHz (n=202 ears and 213 ears). At frequencies higher than 12.5 kHz, however, mean hearing thresholds are affected by the maximum output of the audiometer, as patients with thresholds higher than the capacity of the audiometer could not be measured, resulting in an underestimation of the actual mean hearing level of the population at the concerning frequency and resulting in an upward trend of hearing levels above 12.5 kHz, as displayed in figure 1. A similar influence may be present at frequencies 11.2 kHz and 12.5 kHz, although not graphically visible.

Nevertheless, the *largest* threshold shifts at all (ultra) high frequencies (4 to 16 kHz) were found after the 2nd cisplatin infusion.

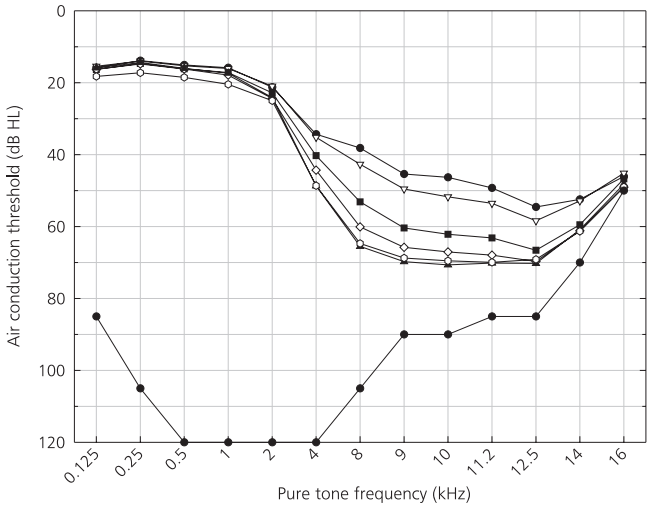

Figure 1. Mean hearing thresholds of all patients (146) (y-axis, air-conduction in dB HL) at low and (ultra-) high frequencies (x-axis) before targeted high-dose cisplatin chemoradiation (●), after the 1st, 2nd, 3rd and 4th cisplatin infusions (▽, ■, ◇ and ▲, respectively) and after therapy (○). Plotted is the maximum output of the audiometer (●).

The influence of pre-treatment hearing thresholds

In our previous work, we found that patients with good pre-treatment hearing were more susceptible to hearing loss and that pre-treatment hearing capability is an independent predictive variable for hearing deterioration due to therapy.[16]

In the current study, a *statistically* significant hearing deterioration of the whole population was found at all frequencies between 4 and 14 kHz after the 1st cisplatin infusion ($p<0.001$, Wilcoxon test). In addition, a significant shift at BC 0.5, 1 and 2 kHz was observed after the 2nd cisplatin infusion ($p<0.03$). As our previous study indicated that good pretreatment hearing capability appeared the most important predicting factor for a high degree of hearing loss, we analysed the role of pretreatment hearing capability at the onset of statistically significant hearing deterioration.[16] Therefore, we selected four patient groups (Quartiles) based on hearing capability before therapy. Quartiles 1, 2, 3 and 4 are characterized by a median pretreatment PTA AC 1-2-4 kHz of 8.3 dB HL (range 0 – 12), 16.7 dB HL (range 13 – 20), 26.7 dB HL (range 21 – 28) and 38 dB HL (range 29 - 68), respectively.

Patients with favourable hearing thresholds before treatment (Quartile 1) presented an earlier onset (after the first infusions of cisplatin) of statistically significant hearing loss *at all frequencies*, when we compared these patients to other patient subgroups with unfavourable (Quartiles 2 and 3) and adverse baseline hearing (Quartile 4): Figure 2 shows a consistent pattern (with only one exception for Quartile 2 at 2 kHz) that patients with relatively unfavourable hearing capability prior to therapy did not display statistically significant hearing loss until after a higher cumulative dose of cisplatin chemoradiation. For frequencies higher than 11.2 kHz we have to interpret results with reserve, as the number of ears measured at those frequencies declined (eventually to n = 18) when patients suffered higher hearing thresholds and therefore shifts of thresholds had to be larger to appear statistically significant.

Secondly, figure 3 illustrates the relative effects for different frequency areas when comparing the subjects from Quartile 1 to Quartile 3. Patients in Quartile 3 (with pre-existent SNHL) endured a small extent of hearing deterioration at PTA 8-10-12.5 kHz with respect to their hearing loss at PTA BC 1-2-4, in comparison with patients in Quartile 1 (with good baseline hearing) that suffered a relatively large extent of hearing deterioration at PTA 8-10-12.5 kHz with respect to their hearing loss at PTA BC 1-2-4 kHz.

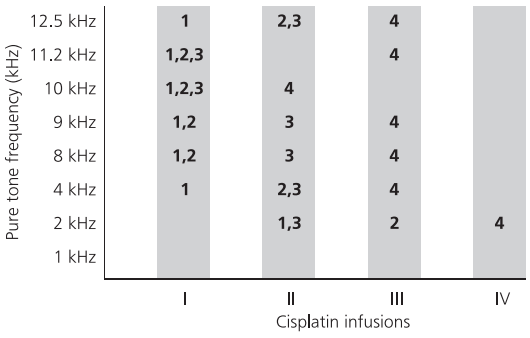

Figure 2. Timing (x-axis: audiograms obtained after cisplatin infusions) and location (y-axis: pure tone frequencies) of statistically significant hearing threshold shifts ($p<0.05$) of ears that were categorized on baseline hearing capability: Quartiles group 1, 2, 3 and 4 are characterized by median pre-treatment PTA AC 1-2-4 kHz of 8.3, 16.7, 26.7 and 38 dB HL, respectively.

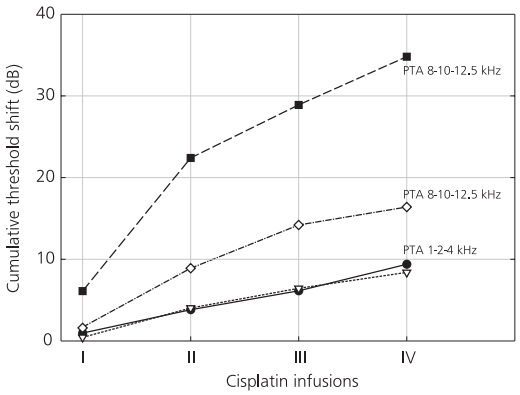

Figure 3. Mean cumulative threshold shifts (y-axis) measured after cisplatin infusion I, II, III and IV (x-axis), in patients with the most favourable pre-treatment hearing capability Quartile 1: PTA BC 1-2-4 kHz (●) and PTA 8-10-12.5 kHz (■), and in patients with an unfavourable pre-treatment audiogram Quartile 3: PTA BC 1-2-4 kHz (▽) and PTA 8-10-12.5 kHz (◇).

Increase in threshold shifts

In figure 4 we plotted the increase in hearing thresholds (AC) against the cisplatin infusions for individual frequencies. After the 1st infusion of cisplatin an increase in slope is found at all frequencies. This slope decreases again after the 2nd cisplatin infusion. At 12.5 kHz the slope approached 0 after the 3rd infusion of cisplatin.

Plateau

To determine a possible maximum hearing level ("plateau") due to cisplatin chemoradiation we analysed threshold shifts at individual frequencies. As the degree of total threshold shift is dependent on baseline hearing capability[16], we grouped ears with similar hearing thresholds at that frequency prior to therapy. In order to avoid bias effects, only those ears that underwent audiometry after all cisplatin infusions were included (figure 5).

At 12.5 kHz (figure 5d), the maximum obtained hearing level due to cisplatin chemoradiation seemed to convert towards a plateau value of approximately 75 dB HL. Ears with a pre-treatment hearing level of 75-80 dB did not suffer (extra) loss of hearing due to therapy.

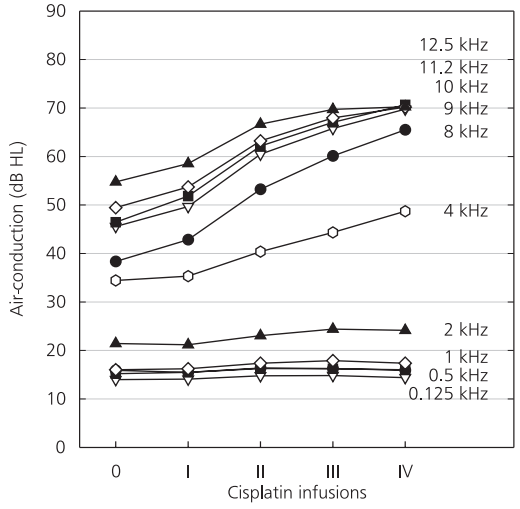

Figure 4. Mean hearing thresholds of all patients per individual frequency (y-axis, in dB HL) before therapy (0) and after cisplatin infusions I, II, III and IV (x-axis).

(The maximum output of the audiometer at AC 12.5 kHz is 85 dB HL). Interestingly, at lower frequencies BC 2 kHz, BC 4 kHz and AC 8 kHz (figure 5a-c) ears with pre-treatment hearing thresholds ≥ 45 dB HL, ≥ 60 dB HL and ≥ 80 dB HL, respectively, did not suffer hearing deterioration, suggesting an upper limit for a possible plateau at approximately 45 dB HL, 60 dB HL and 80 dB HL, at 2 kHz, 4 kHz and 8 kHz, respectively. (The maximum output of the audiometer at BC 2 kHz, BC 4 kHz and AC 8 kHz is 80, 85 and 90 dB HL, respectively). When we performed the same procedure for *AC* 2 kHz and *AC* 4 kHz, an upper limit for a possible plateau was found of approximately 40 dB HL and 60 dB HL, respectively (not shown).

Air-bone gap

About 14% of the patients suffered an ABG larger than 10 dB before therapy. During or after therapy, 30 ears (bilateral in 7 patients) developed an average air-bone gap ≥ 5 dB

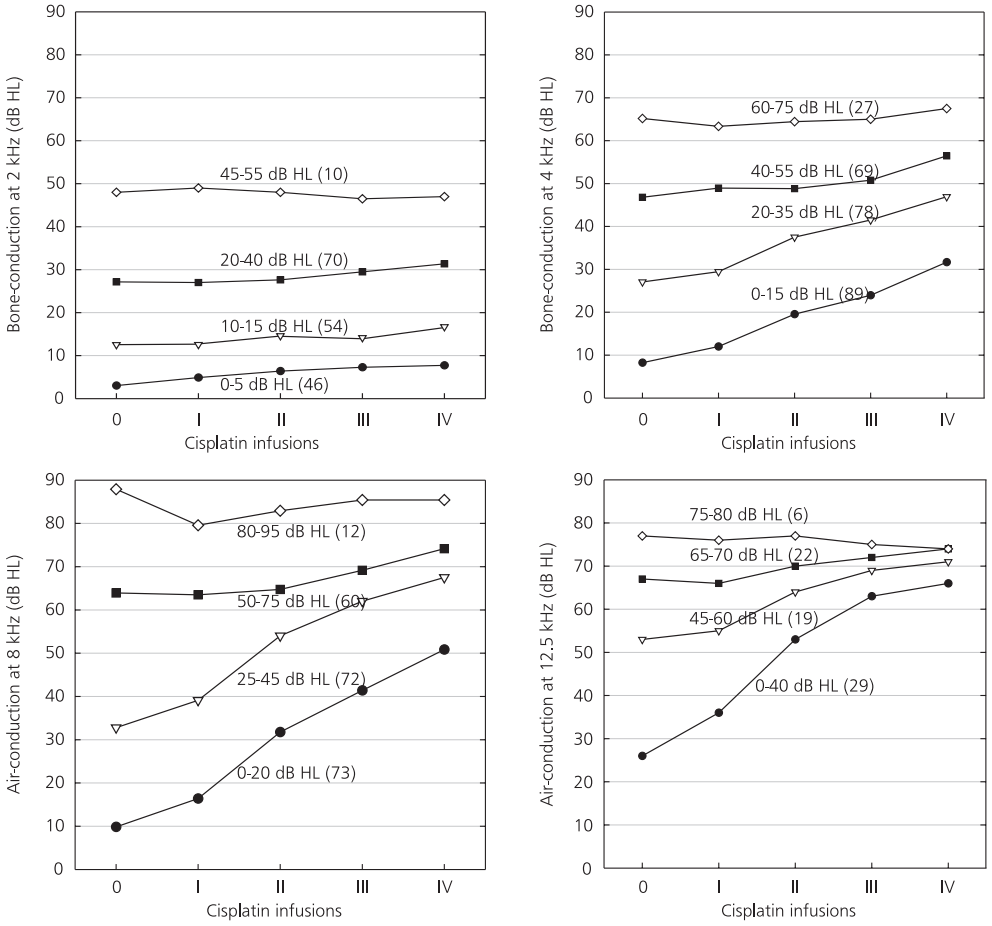

Figure 5. Mean hearing thresholds (y-axis, in dB HL) at frequency 2 kHz BC (figure 5a), 4 kHz BC (figure 5b), 8 kHz AC (figure 5c) and 12.5 kHz AC (figure 5d), before therapy (0) and after cisplatin infusions I, II, III and IV (x-axis). Only those ears that were measured after all cisplatin infusions were plotted with their specific range of pre-treatment hearing thresholds in dB HL and (the number of ears considered).

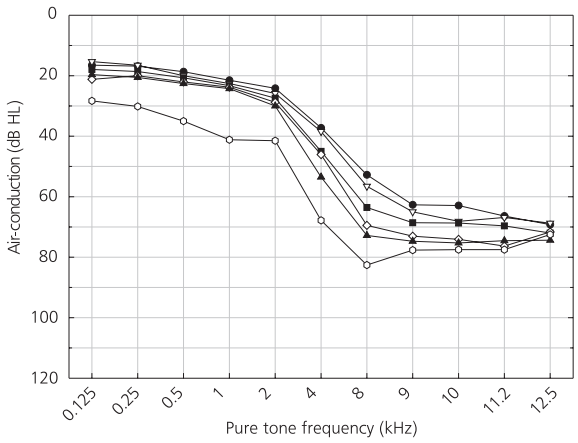

Figure 6. Pure tone audiogram (mean hearing thresholds) of 30 ears with the development of ABG during or after therapy ≥ 5 dB (mean 14 dB) at PTA 0.5-1-2 kHz, before targeted high-dose cisplatin chemoradiation (●), after the 1st, 2nd, 3rd and 4th cisplatin infusions (▽, ■, ◇ and ▲, respectively) and after therapy (○).

(mean 14 dB, SD 8.3) at PTA 0.5-1-2 kHz (figure 6). In ears that were measured at BC 1, 2, and 4 kHz pretreatment and after therapy (n=13), there was an increase in hearing threshold at PTA *BC* 1-2-4 kHz of 12.7 dB. In our previous study we hypothesized that the development of an ABG during therapy may be due to irradiation induced middle ear pathology, as ears ipsilateral to the tumor experienced a higher air-bone gap than ears contralateral to the tumor and a greater increase of ABG during or after therapy was found in patients with tumors of the pharynx.[16] A long-term follow up of these patients should reveal a possible reversibility of the ABG and SNHL in these patients, as shown in a study with radiation-induced hearing loss and a 2 years follow up.[22]

No hearing loss

Forty-nine ears showed hearing deterioration < 10 dB at both PTA AC 1-2-4 and 8-10-12.5 kHz during the chemoradiation. PTA 1-2-4 AC before therapy and after the 4th infusion of cisplatin were 30 dB HL (SD 12.2) and 34 dB HL (SD 11.6), respectively. PTA 8-10-12.5 AC before therapy and after the 4th infusion of cisplatin were 62 dB HL (SD 13.8) and 60 dB HL (SD 13.9), respectively. When we compared the audiometric thresholds of these patients with median thresholds for the same age and gender[23], we found that their mean pre-treatment at PTA AC 8-10-12.5 kHz and PTA AC 1-2-4 kHz proved to be 14.2 dB and 4.5 dB worse than in other patients of the same age and gender, respectively.

Patient subgroups

Gender

During therapy, the audiometric patterns of hearing loss in both men and women were characterised by a maximum threshold shift after the 2nd infusion of cisplatin and a largest total threshold shift due to therapy at 8 kHz. Before therapy, women were characterized by more favourable hearing levels than men at frequencies PTA 1-2-4 kHz and PTA 8-10-12.5 kHz ($p<0.001$, univariate analysis, Mann-Whitney test). After the first infusion of cisplatin, AC thresholds at 10 and 12.5 kHz became equal ($p>0.1$) and after the second infusion of cisplatin

AC thresholds at 8 kHz became equivalent (p=0.3). Hearing levels at 4 kHz (AC) became equal only after the 4th cisplatin infusion. Nevertheless, a multivariate analysis indicated that gender is not responsible for differences in hearing measurements, either before, during or after therapy (p=0.38).[16]

There was a trend that the ABG (PTA 0.5-1-2 kHz) increased slightly during (1.6 dB, SD 5.4) and after (3.4 dB, SD 9.5) therapy (p<0.001) in women but not in men; however, this difference between women and men appeared statistically not significant. Additionally, we found no differences in radiation dose or tumor site between men and women. Moreover, a revision of the data of a quality of life study concerning a similar patient population of our institute[24], could not reveal a correlation between gender and subjective complaints related to mucosa of the the upper airway or digestive tract.

Asymmetric pre-treatment hearing ability

In our study, 7 patients had an asymmetric hearing ability (average difference ≥10 dB between the right and left ear) at both 1, 2 ànd 4 kHz before treatment. In 2 patients, hearing thresholds at the left and right ear were symmetric after therapy. In 4 patients the ears tended to an equal hearing capacity after the 4th cisplatin infusion, as hearing thresholds at 4 kHz converged (hearing thresholds at 2 kHz to a lesser extend), indicating again that the unfavourable hearing ear suffered less hearing loss due to treatment at 2 kHz and 4 kHz than the better hearing ear. In 1 patient, no ototoxicity was found in either ear, leaving the asymmetric hearing intact.

Noise-Induced Hearing Loss

To study the effects of cisplatin chemoradiation in patients with pre-existent noise-induced hearing loss (NIHL), we studied 9 patients with bilateral SNHL with a typical dip. We considered that NIHL was present if the pre-treatment PTA AC 2-4-6 kHz was more than > 10 dB larger than the hearing thresholds at 1 kHz and 8 kHz, after correction for age and gender according to ISO 2000[23], resulting in a mean cPTA AC 2-4-6 kHz in NIHL patients of 24.4 dB HL (SD 12.1) and a mean cPTA AC 2-4-6 kHz in non NIHL patients of 10.9 dB HL (SD 15.6).

Remarkably, at all frequencies from 2 kHz to 8 kHz, NIHL patients suffered larger total threshold shifts due to therapy than patients without NIHL, thus resulting in a larger difference of hearing capability in NIHL patients versus non NIHL patients at PTA AC 2-4-6 kHz after treatment compared to before treatment. It is conceivable that cisplatin chemoradiation may initially interfere with different parts of the organ of Corti than exposure to noise does. In a previous study, a history of noise exposure was independently correlated to hearing loss due to therapy.[25]

In other literature, the phenomenon of summation of NIHL to *age* related SNHL has been described [26,27]: The age related threshold shift adds up to pre-existent NIHL related thresholds. As the total hearing loss at PTA 2-4-6 kHz in patients with NIHL was larger than in other patients, this study may support a hypothesis of summation of cisplatin chemoradiation induced hearing loss and pre-existent NIHL.

Tinnitus

Patients with (increased) subjective tinnitus after the first infusion of cisplatin (n=38) were characterised by good pre-treatment hearing (PTA AC 1-2-4 kHz 19 dB HL). They endured a greater extent of hearing loss after the 1st infusion of cisplatin at ultra-high frequencies (13 dB, SD 16.2 at 10 kHz and 11 kHz) when compared to other patients with similar baseline hearing levels. Nevertheless, these patients were characterized by similar hearing loss patterns when compared to the averaged total population: maximum threshold shifts after the second infusion of cisplatin and a maximum total hearing loss due to therapy at 8 kHz (44 dB, SD 23.7).

Recovery of SNHL measured after therapy

In our study, 27 ears (in 22 patients) experienced recovery (≥ 5 dB at PTA BC 1-2-4) after therapy (figure 7), as PTA BC 1-2-4 kHz improved from 27 dB HL (mean, SD 11.4) measured after the 4th cisplatin infusion, to 18 dB HL (mean, SD 10.4) measured after therapy ($p<0.01$, Wilcoxon test), leading to significant better hearing capability after therapy than others ears (27 dB HL, SD 14.8) ($p<0.01$, Mann-Whitney test).

Ears with recovery were characterised by a larger extent of hearing loss at PTA BC 1-2-4 kHz during therapy (8.9 dB, SD 7.4) compared to other ears (2.7 dB, SD 10.3) ($p<0.01$, Mann-Whitney test). However, between ears with and without recovery, the distribution of age, gender, pretreatment c-level at PTA BC 1-2-4 kHz and PTA AC 8-10-12.5 kHz, ABG before / during / after therapy, and cisplatin dose or radiation dose were equivalent ($p > 0.01$, Mann-Whitney test).

Deterioration of SNHL measured after therapy

Overall, 46 ears (in 29 patients) experienced a deterioration (≥ 5 dB at PTA BC 1-2-4) of hearing thresholds measured after therapy (figure 7), as PTA BC 1-2-4 kHz deteriorated from 19 dB HL (mean, SD 12.4) measured after the 4th cisplatin infusion to 32 dB HL (mean, SD 12.3) measured after therapy ($p<0.01$, Wilcoxon test).

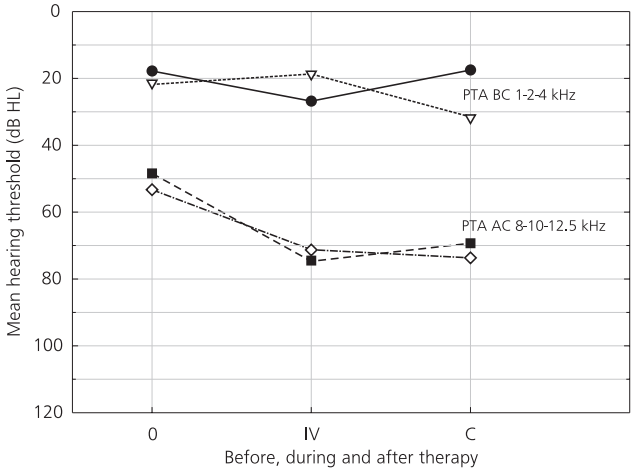

Figure 7. Mean hearing thresholds (y-axis, in dB HL) before therapy (0), after the 4th cisplatin infusion (IV) and after therapy (C) of 27 ears with recovery of hearing after therapy at PTA BC 1-2-4 kHz (●) and PTA 8-10-12.5 kHz (■), and 47 ears with deterioration of hearing after therapy at PTA BC 1-2-4 kHz (▽) and PTA 8-10-12.5 kHz (◇).

Ears with deterioration were characterised by smaller hearing loss at PTA BC 1-2-4 kHz during therapy compared to other ears ($p<0.01$, Mann-Whitney test), whereas after therapy the PTA BC 1-2-4 kHz becomes significantly higher than in other ears (23 dB HL, SD 18.2) ($p<0.01$, Mann-Whitney test). However, between ears with and without deterioration, the distribution of age, gender, pretreatment c-level at PTA BC 1-2-4 kHz and PTA AC 8-10-12.5 kHz, ABG before / during / after therapy, and cisplatin dose or radiation dose were equivalent ($p > 0.01$, Mann-Whitney test).

Discussion

This is the first analysis of hearing loss in a large group of patients uniformly treated with high-dose cisplatin based chemoirradiation to reveal the audiometric pattern of hearing loss at individual frequencies from 125 Hz to 16 kHz. The overall audiometric pattern was characterised by maximum threshold shifts after the 2nd infusion of cisplatin and a maximum total threshold shift due to treatment at 8 kHz in all patients, irrespective of gender, age, pretreatment SNHL or subjective complaints during therapy as tinnitus and hearing loss. A hearing deterioration gradient was observed from (ultra) high to low frequencies. Statistically significant threshold shifts at *higher* frequencies appeared after a lower cumulative dose of cisplatin chemoradiation, when compared to statistically significant threshold shifts at *lower* frequencies that appeared after a higher cumulative dose of cisplatin chemoradiation. Moreover, relatively larger threshold shifts at frequencies representing speech (PTA AC 1-2-4 kHz) appeared in ears with pre-existent SNHL, when we compared these threshold shifts (in dB) to their threshold shifts at ultra-high frequencies (8-10-12.5 kHz). However, gradually during therapy, the number of patients completing the audiometric assessment declined, mainly at ultra-high frequencies and especially in patients with extensive pre-existent SNHL. It was assumed that these patients exceeded the limited intensity range for the ultra-high frequencies between baseline threshold and maximum output of the audiometer, as these may have been patients with extensive hearing loss due to therapy. Therefore, the maximum equipment output is likely to have caused an underestimation of the mean threshold shift at ultra-high frequencies, increasingly in patients with SNHL after higher doses of cisplatin. This may give the impression of relatively greater threshold shifts at lower frequencies with increasing cisplatin chemoradiation dose, while the opposite may be true in some cases.

The emphasis on hearing loss at speech frequencies with increasing cumulative dose of chemoradiation and in patients with more extended pre-treatment SNHL is in agreement with previous studies regarding low-dose cisplatin infusions, that showed high frequency hearing loss (>10 kHz) mainly in younger patients and an increasing risk of low frequency hearing loss in the elderly.[17,19,28] In the current study, the largest threshold shift after the first cisplatin infusion was seen at 10 kHz.

The phenomenon that the audiometric hearing loss pattern was characterized by an ultra-high to low frequency gradient seems biologically explained by the finding that outer hair cells near the base of the cochlea are reportedly affected first by cisplatin, progressing to apical cells with increasing doseor time-interval after cisplatin injection.[29-32] In addition, the drug interferes with the morphology and function of the stria vascularis with special affinity for the marginal cells in the basal turn of the cochlea.[33-35] However, concerning mean hearing thresholds of our whole population, statistically significant threshold shifts were measured after the 1st infusion of cisplatin at low, high and ultra-high frequencies, a finding supported by a histopathological study of guinea pigs that showed degeneration in OHCs of all cochlear windings after a first infusion of cisplatin and a base-to-apex gradient concerning the number of OHCs affected by cisplatin.[29]

In our treatment protocol, cisplatin was administered directly in the nutrient artery of the carcinoma, allowing for higher drug concentrations in the tumor but limited adverse effects by simultaneous systemic infusion of sodium thiosulfate for cisplatin neutralization. In previous literature, animal models were used to test the otoprotective capacity of thiols before and after infusions of cisplatin.[36-38] To avoid a potential reduction of the tumoricidal effect of cisplatin, the chemoprotectant and chemotherapy treatment were separated in time and space; two-route administration protocols were designed. In the rat model, the vertebral arteries were perfused with cisplatin while sodium thiosulfate was applied intravenously. Depending on the timing of thiol administration, full otoprotection was observed.[37] In the guinea pig model, intracochlear application of sodium thiosulfate was found to protect the organ of corti while cisplatin was infused intravenously.[38]

However, in our treatment protocol, increasing cumulative dose of targeted cisplatin resulted in increasing hearing deterioration, despite the systemic sodium thiosulfate rescue. To determine the precise otoprotective role of sodium thiosulfate in our patient population, a control group of patients lacking sodium thiosulfate would be required, which is not justifiable in this regime with high-dose chemotherapy. In the future, it is imperative to compare ototoxicity in patients enduring RADPLAT to ototoxicity in patients treated with high-dose intravenously administered cisplatin chemoradiation without sodium thiosulfate.

We investigated the existence of a maximum hearing level ("plateau") induced by cisplatin chemoirradiation in a large number of patients receiving the same therapy. In a previous study, concerning high-dose cisplatin infusion, a plateau at 4 kHz and 8 kHz was described at 40 to 60 dB HL in 1 patient with normal hearing prior treatment.[6] Another study commented on a so-called "plateau" at 4 to 8 kHz of 75 dB HL in 7 patients, although the authors excluded patients with limited hearing loss from analysis and another 7 patients were described with increased hearing loss due to therapy (up to 95 dB HL at 8 kHz).[8] In a study concerning SNHL due to radiotherapy in patients with a nasopharynx carcinoma, ears with more pre-irradiation hearing loss than 60 dB HL at BC 4 kHz, were less likely to suffer deterioration at this frequency.[39]

Our analysis of hearing thresholds in individual frequencies after each infusion of cisplatin revealed a maximum of hearing deterioration or plateau at 8 kHz and 12.5 kHz

to approximately 80 and 75 dB HL, respectively, close to the maximum output of the audiometer at the concerning frequencies (90 and 85 dB HL, respectively). As the selection of patients required to reveal a possible plateau was based on their hearing levels at ultra-high frequencies being measured at all occasions, these were patients in whom hearing thresholds remained within the output range of the audiometer during treatment. Therefore, especially in case of proximity between the observed plateau and the maximum output of the audiometer, we may have excluded some patients developing hearing levels beyond the output capacity of the equipment due to (during) treatment, after having exceeded the suggested plateau. At 2 kHz and 4 kHz, an upper limit to a possible plateau was found to be 45 and 60 dB HL respectively, with a larger separation from the maximum output of the audiometer (80 and 85 dB HL, respectively).

The issues of a base-to-apex gradient in hearing loss and a dissimilar maximum SNHL in the base of the cochlea compared to the apex of the cochlea may have several explanations. Firstly, a differential drug access to and distribution within the cochlea. Scanning electron microscope studies of the cochlea of the rat after plastic injection into the vascular system showed the arteria cochlearis communis to divide into the arteria cochlea propria (to the apex cochlea) and the arteria vestibularis communis and ramus cochlearis (to the basis cochlea).[40] This would suggest a watershed area near the middle of the cochlea that, according to the anatomical frequency scale, represents the high frequency (2 kHz) perception area.[41] Hence, an impaired access of cisplatin to the watershed area may be conceivable. Secondly, a greater intrinsic susceptibility of basal hair cells to cisplatin may be responsible for a base-to-apex gradient in ototoxicity and an increased maximum SNHL in the base of the cochlea. Cisplatin binds to the antioxidant glutathione, a free-radical scavenger in the hair cell, that was found at a significantly lower level in basal outer hair cells compared with apical outer hair cells.[42,43] In tissue strips of the organ of Corti and whole-cochlea preparations apical outer hair cells remained significantly more viable than basal cells, suggesting an intrinsic difference in susceptibility to injury along the cochlear spiral related to the glutathion effect.[44] Finally, the phenomenon that different frequency areas displayed a dissimilar maximum hearing level induced by cisplatin chemoradiation, may be in agreement with a previous report describing outer hair cells functioning as a cochlear amplifier with a clear frequency specificity.[45] However, as we hypothesized that in humans a greater compression capacity is present at frequencies representing speech (1, 2 and 4 kHz), greater sensitivity to cisplatin at these frequencies would be conceivable.

Interestingly, reversibility of SNHL at speech frequencies (PTA BC 1-2-4 kHz) was seen after therapy in 27 ears with extensive hearing loss at these frequencies during therapy, while in previous reports restoration of hearing function after cessation of cisplatin infusions seemed a rare occurrence. Single patients with recovery after low dose cisplatin have been observed [17,20,32] and of these, two patients were documented with audiometric data. In agreement with our patient selection, they were characterized by extensive hearing loss during therapy. We have to approach this subject with care: especially in case of relatively high hearing thresholds after the 4th infusion of cisplatin, we expect a large (negative)

correlation with measurements after therapy (regression to the mean). In addition, a patients impaired physical condition may negatively influence audiometry after the 4th cisplatin infusion, resulting in improved hearing thresholds after therapy. However, in a guinea pig model, electrophysiological recovery of hair cell-related potentials was seen in an interval of 1 to 8 weeks after cisplatin ototoxicity and in the same animals a histopathological study indicated outer hair cell recovery 1 to 4 weeks after the last infusion of cisplatin.[46,47] In addition, electrocochleography in a similar animal model showed nearly complete recovery of thresholds at lower frequencies, but incomplete at high frequencies. In our study, a similar pattern was found: recovery of hearing function was seen mainly at frequencies 2 to 8 kHz and not at ultra-high frequencies. However, different hypotheses exist as to the regeneration of hair cell function or reversibility of function of the stria vascularis.[34,46,47] At present, the exact mechanisms of recovery of cochlear function are still unknown.

In addition, a substantial number of ears was characterized by deterioration of hearing capability measured after therapy at frequencies vital for speech perception (PTA BC 1-2-4 kHz). This deterioration took place during the last 3 weeks of treatment (RT without cisplatin infusions) and/or in the 7.5 weeks of median follow-up after therapy. In previous literature, radiation-induced SNHL has been found in short- and long-term after cranial irradiation without cisplatin [10,11,48] and both recovery of hearing function and deterioration of hearing loss were measured several years after therapy [39]. Long-term follow up is needed to determine the full ototoxic effect of cisplatin chemoradiation.

Conclusion

This is the first study describing the audiometric patterns of hearing loss in a large homogeneously treated group of advanced head and neck cancer patients treated with high-dose cisplatin chemoirradiation. The overall audiometric pattern was characterised by maximum threshold shifts after the 2nd infusion of cisplatin and a maximum total threshold shift due to treatment at 8 kHz in all patients, irrespective of gender, age, pre-treatment SNHL or subjective complaints during therapy. A hearing deterioration gradient was observed from (ultra) high to low frequencies with increasing pre-existent SNHL and with increasing cumulative dose of cisplatin chemoradiation. Cisplatin chemoradiation-induced hearing loss seemed to reach a plateau located at higher levels (75-80 dB HL) for frequencies above 8 kHz compared to frequencies up to 8 kHz (45-60 dB HL). Interestingly, reversibility of SNHL at speech frequencies (PTA BC 1-2-4 kHz) was seen after therapy in 27 ears with extensive hearing loss at these frequencies during therapy.

References

1 Pignon JP, Bourhis J, Domenge C, Designé L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. The Lancet 2000;355:949-955.

2 Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S: Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 1998;18(6B):4779-4786.

3 Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, Weir AB 3rd, Neill HB, Murry T, Ferguson R, Hanchett C, Vieira F, Bush A, Howell SB: Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. Head Neck 2000;22(7):687-693.

4 Balm AJ, Rasch CR, Schornagel JH, Hilgers FJ, Keus RB, Schultze-Kool L, Ackerstaff AH, Busschers W, Tan IB: High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 2004;26(6):485-493.

5 Evans WE, Yee GC, Crom WR, Pratt CB, Green AA: Clinical pharmacology of bleomycine and cisplatin. Head Neck Surg 1981;4(2):98-110.

6 Kopelman J, Budnick AS, Sessions RB, Kramer MB, Wong GY: Ototoxicity of high-dose cisplatin by bolus administration in patients with advanced cancers and normal hearing. Laryngoscope 1988;98(8 Pt 1):858-864.

7 Fleming S, Ratanatharathorn V, Weaver A, Peters G, Peppard S, Schumacher M, Al-Sarraf M: Ototoxicity from cis-platinum in patients with stages III and IV previously untreated squamous cell cancer of the head and neck. Am J Clin Oncol 1985;8(4):302-306.

8 Myers SF, Blakley BW, Schwan S, Rintelmann WF, Mathog RH: The "plateau effect" of cis-platinum-induced hearing loss. Otolaryngol Head Neck Surg 1991;104(1):122-127.

9 Laurell G, Jungnelius U: High-dose cisplatin treatment: Hearing loss and plasma concentrations. Laryngoscope 1990;100:724-734.

10 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 2002;65(1):1-7.

11 Johannesen TB, Rasmussen K, Winther FO, Halvorsen U, Lote K: Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 2002;53(1):86-90.

12 Michael II LM, Sorenson JM, Samant S, Robertson JH: The treatment of advanced sinonasal malignancies with pre-operative intra-arterial cisplatin and concurrent radiation. J Neuro-oncol 2005;72:67-75.

13 Regine WF, Valentino J, John W, Storey G, Sloan D, Kenady D, Patel P, Pulmano C, Arnold S, Mohiuddin M: High-dose intra-arterial cisplatin and concurrent hyperfractionated radiation therapy in patients with locally advanced primary squamous cell carcinoma of the head and neck: report of a phase II study. Head Neck 2000;22:543-549.

14 Kovács AF, Schiemann M, Turowski B: Combined modality treatment of oral and oropharyngeal cancer including neoadjuvant intraarterial cisplatin and radical surgery followed by concurrent radiation and chemotherapy with weekly docebaxel – three year results of a pilot study. J Cranio-Maxillofacial Surg 2002;30:112-120.

15 Madasu R, Ruckenstein MJ, Leake F, Steere E, Robbins T: Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1997;123(9):978-981.

16 Zuur CL, Simis YJ, Lansdaal PE, Hart AA, Rasch CR, Schornagel JH, Dreschker WA, Balm AJ. 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 2007;68(5):1320-5.

17 Aguilar-Markulis NL, Beckly S, Priore R, Mettlin C: Auditory effects of long-term cis-dichlorodiammineplatinum II therapy in genitourinary cancer patients. J Surg Oncol 1981;16(2):111-123.

18 Schweitzer VG: Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents.

Laryngoscope 1993;103(4 Pt 2):1-52.

19 Van Der Hulst RJ, Dreschler WA, Urbanus NA: High frequency audiometry in prospective clinical research of ototoxicity due to platinum derivates. Ann Otol Rhinol Laryngol 1988;97(2 Pt 1):133-137.

20 Vermorken JB, Kapteijn TS, Hart AA, Pinedo HM: Ototoxicity of cis-diamminedichloroplatinum (II): Influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol 1983;19(1):53-58.

21 International Organization for Standardization 1998, ISO/TR 389-1;5, 1998 ISO-1998 Acoustics: Reference zero for the calibration of audiometric equipment.

22 Anteunis LJ, Wanders SL, Hendriks JJ, Langendijk JA, Manni JJ, De Jong JM: A prospective longitudinal study on radiation-induced hearing loss. Am J Surg 1994;168(5):408-411.

23 International Organization for Standardization 2000, 2nd edition, Reference number ISO 7029:2000(E). International Standard. Acoustics – Statistical distribution of hearing thresholds as a function of age.

24 Ackerstaff AH, Tan IB, Rasch CR, Balm AJ, Keus RB, Schornagel JH, Hilgers FJ: Quality-of-life assessment after supradose selective intra-arterial cisplatin and concomitant radiation (RADPLAT) for inoperable stage IV head and neck squamous cell carcinoma. Arch Otolaryngol Head Neck Surg 2002;128(10):1185-1190.

25 Bokemeyer C, Berger CC, Hartmann JT, Kollmannsberger C, Schmoll HJ, Kuczyk MA, Kanz L: Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. Br J Cancer 1998;77(8):1355-1362.

26 International Organization for Standardization 1999. Acoustics: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ISO-1999. Geneva: Int Org Stand.

27 Dobie RA: Noise-induced hearing loss and Acoustic trauma: Interactions; in Dobie RA (ed): Medical-legal evaluation of hearing loss. New York, Van Nostrand Reinhold, 1993, pp 148-151.

28 Dreschler WA, Van Der Hulst RJ, Tange RA, Urbanus NA: Role of high-frequency audiometry in the early detection of ototoxicity. II. Clinical aspects. Audiology 1989;28(4):211-220.

29 Tange RA: Differences in the cochlear degeneration pattern in the guinea pig as a result of gentamicin and cis-platinum intoxication. Clin Otorhinolaryngol Allied Sci. 1984;9(6):323-327.

30 Van Ruijven MW, De Groot JC, Smoorenburg GF: Time sequence of degeneration pattern in the guinea pig cochlea during cisplatin administration. A quantitative histological study. Hear Res 2004;197(1-2):44-54.

31 Cardinaal RM, De Groot JC, Huizing EH, Veldman JE, Smoorenburg GF: Dose-dependent effect of 8-day cisplatin administration upon the morphology of the guinea pig cochlea. Hear Res 2000;144(1-2):135-146.

32 Laurell G, Bagger-Sjöbäck D: Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol 1991;20(3):158-167.

33 Tange RA, Vuzevski VD: Changes in the stria vascularis of the guinea pig due to cis-platinum. Arch Otorhinolaryngol 1984;239(1):41-47.

34 O'Leary SJ, Klis SF: Recovery of hearing following cisplatin ototoxicity in the guinea pig. Anticancer Res 2002;22(3):1525-1528.

35 Hamers FP, Wijbenga J, Wolters FL, Klis SF, Sluyter S, Smoorenburg GF: Cisplatin ototoxicity involves organ of Corti, stria vascularis and spiral ganglion: modulation by αMSH and ORG 2766. Audiol Neurotol 2003;8(6):305-315.

36 Dickey DT, Muldoon LL, Kraemer DF, Neuwelt EA: Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res 2004;193:25-30.

37 Dickey DT, Wu YJ, Muldoon LL, Neuwelt EA: Protection against cisplatin-induced toxicities by N-

acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol exp therapeut 2005;314:1052-1058.

38 Wang J, Faulconbridge RVL, Fetoni A, Guitton MJ, Pujol R, Puel JL: Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. Neuropharmacol 2003;45:380-393.

39 Ho WK, Wei WI, Kwong DL, Sham JS, Tai PT, Yuen AP, Au DK: Long-term sensorineural deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head Neck 1999;21(6):547-553.

40 Tange RA: Vascular inner ear partition: a concept for some forms of sensorineural hearing loss and vertigo. ORL J Otorhinolaryngol Relat Spec. 1998;60(2):78-84.

41 Schuknecht HF: The anatomic frequency scale; in Bussy RK, Lazar T, Klass FM, Spahr RN (eds): Pathology of the ear. Malvern, Pennsylvania, Lea & Febiger, 1993, pp 26-27.

42 Kopke RD, Liu W, Gabaizadeh R, Jacono A, Feghali J, Spray D, Garcia P, Steinman H, Malgrange B, Ruben RJ, Rybak L, Van De Water TR: Use of organotypic cultures of Corti's organ to study the protective effects of antioxidant molecules on cisplatin-induced damage of auditory hair cells. Am J Otol 1997;18(5):559-71.

43 Bose RN: Biomolecular targets for platinum antitumor drugs. Mini Rev Med Chem 2002;2:103-111.

44 Sha SH, Taylor R, Forge A, Schacht J: Differential vulnerability of basal and apical hair cells is based on intrinsic susceptibility to free radicals. Hear Res 2001;155(1-2):1-8.

45 Oxenham AJ, Bacon SP: Cochlear compression: perceptual measures and implications for normal and impaired hearing. Ear Hear 2003;24(5):352-366.

46 Stengs CH, Klis SF, Huizing EH, Smoorenburg GF: Cisplatin-induced ototoxicity; electrophysiological evidence of spontaneous recovery in the albino guinea pig. Hear Res 1997;111(1-2):103-113.

47 Cardinaal RM, De Groot JC, Huizing EH, Veldman JE, Smoorenburg GF: Cisplatin-induced ototoxicity: Morphological evidence of spontaneous outer hair cell recovery in albino guinea pigs? Hear Res 2000;144(1-2):147-156.

48 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 1991;21(3):723-728.

Chapter 4

Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer

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ABSTRACT

Purpose

Cisplatin concomitantly administered with radiotherapy is increasingly used in locally advanced head and neck squamous cell carcinoma. We aimed to compare the incidence of hearing loss between patients treated with intra-arterial high-dose cisplatin chemoradiation (CRT-IA) and intravenously administered high-dose cisplatin chemoradiation (CRT-IV).

Patients and Methods

We conducted a prospective analysis of hearing thresholds at low and (ultra-) high frequencies obtained before, during and after treatment in 158 patients. Patients were randomly assigned for either CRT-IA (150 mg/m^2, four courses) with sodium thiosulfate cisplatin neutralization or CRT-IV (100 mg/m^2, three courses) without rescue. All patients received concomitant radiation therapy (70 Gy).

Results

CRT-IA resulted in approximately 10% less hearing loss at frequencies vital for speech perception, compared with CRT-IV ($p<0.001$). In CRT-IA fewer ears qualified for hearing aids (36% versus 49%, $p=0.03$). However, in both treatment arms, the incidence expressed in CTCAEv3.0 did not deviate ($p>0.14$). Age, cumulative cisplatin dose, cumulative RT dose, and the considered frequency-area determine the degree of hearing loss ($p<0.001$). Cisplatin induced increasing hearing loss of 24% to 60% with increasing frequencies. RT induced hearing loss at speech frequencies of 9% to 12%.

Conclusion

Depending on the criteria used to assess hearing loss due to treatment, differences in ototoxicity between CRT-IA and CRT-IV were found in favour of CRT-IA. It is desirable to specify hearing loss criteria towards frequencies vital for speech perception and to refine grading scales, in order to reveal subtle and clinically relevant dissimilarities in ototoxicity between different treatment protocols.

INTRODUCTION

Chemoradiation has become increasingly important for treatment of head and neck squamous cell carcinoma (HNSCC).[1,2]

In the past, high-dose cisplatin chemotherapy schemes induced a 58% to 81% incidence of hearing loss at frequencies from 0.250 to 8 kHz.[3,4] Others reported an incidence up to 46% of notable hearing loss.[5] In addition, radiation-induced sensorineural hearing loss (SNHL) has been observed to an incidence of 49% immediately after treatment and to an incidence of 55% at 2 to 8 years after therapy of patients treated with cranial irradiation that exposed the inner ear.[6-14] In studies concerning the combined-modality treatment of intravenously applied high-dose cisplatin and radiotherapy a 53% incidence of SNHL more than 30 dB at 4 and 8 kHz and a 14% incidence of ototoxicity interfering with the chemotherapy regimen were described.[15-16] Others did not comment on ototoxicity.[17-19]

To increase drug doses in the tumor with minimal systemic toxicity, a superselective administration of intra-arterial high-dose cisplatin chemoradiation with sodium thiosulfate (CRT-IA) was designed. In this treatment model, cisplatin was directly infused in the nutrient artery of the tumor with concurrent intravenously administered sodium thiosulfate (STS) for cisplatin neutralization. Favorable results have been reported.[20-23] Nevertheless, in this treatment modality, incidence rates up to 60% of hearing loss ≥ 10 dB at frequencies vital for speech perception also have been described[24], and in individual patients hearing loss was the cause for treatment interruption.[25] Other reports on CRT-IA did not comment on hearing loss.[26-30]

The objective of this study was to compare the incidence of hearing loss in a phase III randomized trial comparing CRT-IA and intravenous high-dose cisplatin chemoradiation without STS (CRT-IV).[31]

PATIENTS AND METHODS

Patients and treatment characteristics

From 1999 to 2004, 162 patients with locally advanced head and neck squamous cell carcinoma participated in a randomized phase III trial in our center. Patients were assigned to either targeted intra-arterial cisplatin infusions (150 mg/m^2, cisplatin 1 mg/mL in saline, automatic pump 1-2 mL/second, four courses on days 1, 8, 15 and 22) with simultaneous intravenously administered STS (9g/m^2/30minutes, followed by 12g/m^2/2hours) for cisplatin neutralization, or to intravenously administered cisplatin infusions (CRT-IV, 100 mg/m^2 in 500 mL saline over 30 minutes, three courses on days 1, 22, 43) without rescue. All patients received concurrent radiation therapy (RT). Hundred-and-fifty-eight patients were included in our study (78 CRT-IA and 80 CRT-IV). Four patients were excluded from analysis; three patients did not receive high-dose cisplatin chemoradiation and in one patient audiometry was not performed.

RT and the inner ear radiation dose

All patients received 70 Gray (Gy) fractionated RT in 35 daily fractions of 2 Gy.

The inner ear radiation dose was determined by measuring the distance of the inner ear to the boundary of the radiation field. Thereafter, we converted these distances into Grays according to a computed tomography(CT)-simulated patient model with cochleas located at several distances to the field and the RT dose computed digitally. In patients treated in a conventional way (two lateral radiation portals and one anterior-posterior adjacent supraclavicular field with customized shielding) the planning x-rays were reviewed to measure the distance of the centre of the bony external auditory canal to the boundary of the field. By repeating this measurement twice we found a median uncertainty of 3,2 mm. In later years, radiation portals were planned at the time of a CT scan. By revision of these images we computed the distance from cochlea to the radiation field digitally. By repeating the procedure twice, we found a median variation of 1.0 mm.

In most recent years, patients received intensity-modulated radiation therapy (IMRT, based on digital planning of radiation portals in CT scans). The cochlea radiation dose was calculated directly.

Audiometry

Audiometry was performed before therapy, 1-6 days after each cisplatin infusion and median 8 weeks after termination of therapy. In two CRT-IA patients the post-treatment audiogram was performed 10 days before and 1.8 years after the end of treatment, respectively. Air-conduction (AC) thresholds were measured at frequencies 0.125 kHz to 16 kHz, and bone-conduction (BC) thresholds were measured at 0.5 kHz to 4 kHz. We calculated mean thresholds at three Pure Tone Averages (PTAs): 0.5-1-2 kHz (BC and AC), 1-2-4 kHz (BC and AC) and 8-10-12.5 kHz (AC), representing speech perception in quiet, in noise and perception of high-pitched sounds (e.g. music), respectively. Air-bone gaps (ABGs) were calculated by the difference between AC and BC at 0.5-1-2 kHz. Audiometric data are presented in dB Hearing Level (HL) 0.125 to 8 kHz and dB Sound Pressure Level (SPL) 8 to 16 kHz. All analyses were conducted per ear.

In the audiograms up to 8 kHz 69% to 96% of the AC thresholds were measured. At ultra-high frequencies (8-16 kHz) and particularly as the treatment progressed, many thresholds could not be measured, because the patient was not able to complete the audiometry session. At 8 kHz, 10 kHz and 12.5 kHz the number of ears measured in CRT-IA / CRT-IV patients were 67%/71%, 54%/64%, and 27%/29%, respectively. Excluding these patients may lead to an underestimation of hearing thresholds and to exclusion of patients with potentially the highest hearing threshold (shift) during chemoradiation. Therefore, we reconstructed missing thresholds by extrapolating with the same slope as was found on average in the audiograms of our patients that were actually measured at all (ultra-) high frequencies.

Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0)

The incidence of ototoxicity due to CRT-IA or CRT-IV was expressed in CTCAEv3.0 (for patients enrolled in a monitoring program).[32] Grade 1: threshold shift 15-25 dB averaged at ≥ 2 contiguous frequencies at least in one ear, òr subjective change in hearing. Grade 2: threshold shift > 25–90 dB, averaged at 2 contiguous frequencies at least in one ear. Grade 3: threshold shift > 25-90 dB, averaged at 3 contiguous frequencies, at least in one ear. Grade 4: threshold shift > 90 dB.

Statistics

Of 158 patients, nine were excluded for the multivariate analysis, leaving 76 in the CRT-IA and 73 in the CRT-IV arm. In six patients, no follow-up audiometry was performed, whereas in three patients no baseline audiogram was available.

Two statistical analyses were performed, in which hearing loss was defined as a percentage change in dB of pre-treatment hearing level: A comparison of hearing loss between CRT-IA and CRT-IV, and 2. an explanatory analysis to unravel the separate effects of patients and treatment variables. Repeated measurement analysis of covariance was performed using all PTA's per patient. A logarithmic transformation was applied to the audiometric (measurements + 10dB) to improve normality and constancy of variation. No structure was imposed on the variances and correlations of the 10 measurements per time point; based on Akaike's Information Criterion, the (co)variances of the same PTA at the same ear were assumed to be constant over time ("compound symmetry"). PROC MIXED of SAS® (8.2 for Windows) was used.

In the first analysis, the development over time of the PTAs was modelled by a second order polynomial during treatment and a separate difference between pre- and post-treatment value. The slopes during treatment were assumed to vary between patients according to a multivariate normal distribution. The coefficients of the polynomial as well as the pre-post difference were allowed to vary between thresholds as well as arms. In order to simplify interpretation, it was tested whether the quadratic components could be removed from the model. The analysis was adjusted for baseline measurement, the effect of which was allowed to vary over the PTAs.

In the second analysis, relations between quantitative variables (cisplatin and radiotherapy dose, time, age) and transformed PTA values were assumed to be linear. Other effects considered were ear at side of infusion (no, yes, intravenous), side of ear (right or left) and gender. The effect of cumulative cisplatin dose was allowed to vary with ear at side of infusion, age and gender. All effects were allowed to vary with type of PTA. The slopes against cumulative cisplatin dose were assumed to vary between patients following a multivariate Normal distribution. In view of the large number of effects evaluated, P-values < 0.001 were considered statistically significant. Hierarchical backward elimination (P>0.10) was applied to facilitate interpretation.

RESULTS

Patient and treatment characteristics

Patient and treatment characteristics are summarized in Table 1. Eleven CRT-IA patients received 1-3 infusions. Seven CRT-IV patients received 0-2 infusions. In 70 CRT-IA patients and in 67 CRT-IV patients we were able to review sufficient RT data to calculate the amount of Gray received in the inner ear. The median RT dose of the inner ear was higher in CRT-IV, due to skewness in distribution of RT doses within the CT scan-guided patients (CRT-IV: 19.2 Gy, CRT-IA 10.8 Gy).

Overall hearing loss

Figure 1 concerns mean AC hearing thresholds at all frequencies before, during and after therapy. In CRT-IV patient, a larger threshold shift after the 1st infusion of cisplatin at frequencies > 4 kHz is visible, compared with CRT-IA patients.

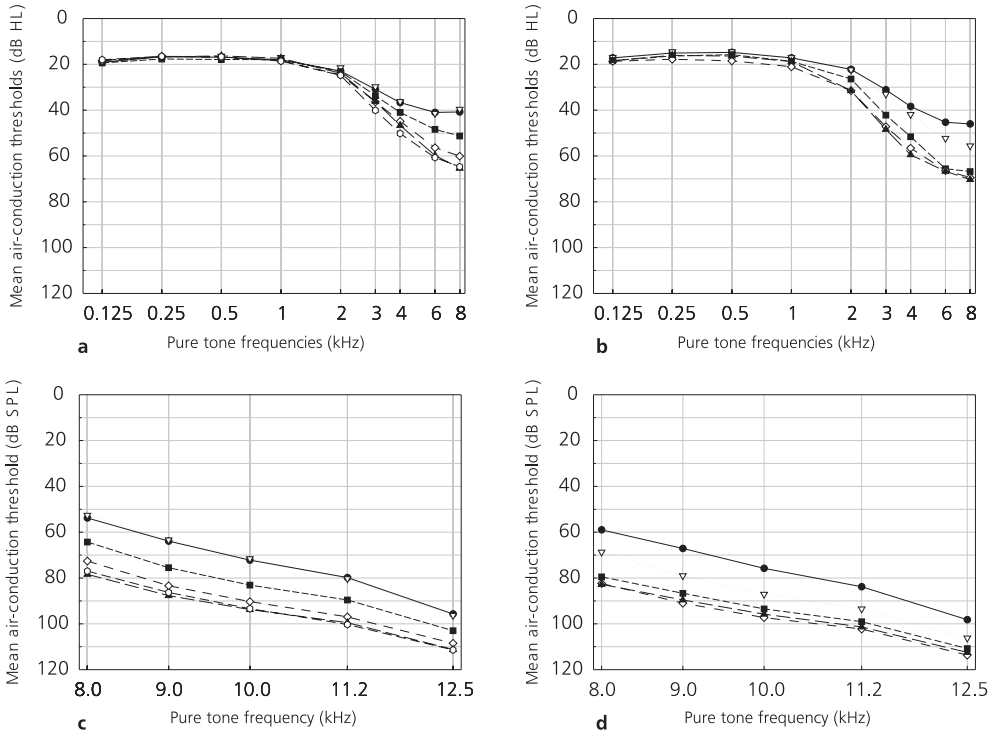

Figure 1. Mean hearing thresholds of CRT-IA (Figure 1a and c) and CRT-IV (figure 1b and d). Note: ultra-high frequencies in dB SPL. Pre-treatment (●), after the 1st, 2nd, 3rd cisplatin infusions (▽, ■, ◇, respectively), after the 4th cisplatin infusion of CRT-IA patients (▲), and after therapy (CRT-IA: 0, CRT-IV:▲).

Table 1. Patient, tumor and treatment characteristics CRT-IA / CRT-IV

Characteristics			Value
Patient number n			78 / 80
Age, median, y			55 / 56
Sex			
	male		78% / 75%
	female		22% / 25%
T classification			
	2		4 % (3) / 0
	3		36 % (28) / 31% (25)
	4		60 % (47) / 69% (55)
N classification			
	0		14 % (11) / 19% (15)
	1		19 % (15) / 10% (8)
	2		50 % (39) / 54% (43)
	3		15 % (12) / 18% (14)
	unknown		1 % (1) / 0
Tumor site			
	Oral cavity		12 % (9) / 18% (14)
	Oropharynx		64 % (50) / 66% (53)
	Hypopharynx		24 % (19) / 16% (13)
Radiation therapy dose to inner ear, median		10.8 / 16.3 Gray *	
Radiation protocol and inner ear dose, median	Conventional	14.3 / 14.0 Gray	27% / 24%
	CT scan guided	10.8 / 19.2 Gray *	49% / 59%
	IMRT	8.4 / 12.7 Gray	24% / 18%
Cisplatin, median dose per infusion in mg			267 / 180 *
Cisplatin dose intensity in mg/m^2/week			86 / 43 *, **, ***
Side of CRT-IA infusion with regard to measured ear	ipsi- or contralateral		43%
	bilateral cisplatin infusion		57%

* = difference between CRT-IA and CRT-IV, Mann-Whitney U test, $p < 0.05$
** = 600 mg/m^2/ in 7 weeks intra-arterially administered (CRT-IA)
*** = 300 mg/m^2/ in 7 weeks intravenously administered (CRT-IV)
Note: Numbers are percentages (patients), unless otherwise stated

Both treatment schemes induced increasing hearing loss with increasing frequency. Table 2 lists (sensorineural) hearing loss after the individual cisplatin infusions. Pre-treatment hearing capability at all PTAs was similar between the 2 patient groups (p=0.053 to 0.97, univariate analysis), as expected after the randomization procedure. Mean total threshold shifts at PTA BC 1-2-4 kHz were 5.3 dB and 8.9 dB for CRT-IA and CRT-IV), respectively, whereas mean total threshold shifts at PTA 8-10-12.5 kHz were 20.4 dB and 19.6 dB for CRT-IA and CRT-IV, respectively.

Table 2. Mean Pure Tone Average (PTA) CRT-IA / CRT-IV

	PTA BC 0.5-1-2 kHz	PTA BC 1-2-4 kHz	PTA AC 8-10-1.25 kHz
before therapy	16.6 / 16.3	22 / 22.2	69.5 / 73.3
after the 1st cisplatin infusion	17.1 / 15.5	21.1 / 21.0	69.3 / 83.0
after the 2nd cisplatin infusion	18.1 / 17.9	21.9 / 26.4	79.1 / 90.4
after the 3rd cisplatin infusion	18.1 / 21.2	23.1 / 30.0	86.4 / 93.5
after the 4th cisplatin infusion	18,4	25,9	90,1
after therapy	19.1 / 18.5	27.3 / 31.1	89.9 / 92.9

Note: Thresholds at PTAs 0.5-1-2 and 1-2-4 in dB HL, PTA 8-10-12.5 kHz in dB SPL

Table 3. Absolute hearing loss (%) due to treatment for CRT-IA and CRT-IV

	CRT-IA % (SE)	CRT-IV % (SE)
PTA AC 0.5-1-2 kHz **	4.9 (2.2)	15* (2.2)
PTA AC 1-2-4 kHz **	17.5* (2.3)	29* (2.2)
PTA AC 8-10-12.5 kHz	27.8* (1.6)	23.8* (1.6)
PTA BC 0.5-1-2 kHz **	4.2 (2.3)	15.1* (2.3)
PTA BC 1-2-4 kHz **	13.8* (2.8)	28.6* (2.8)

AC = Air-conduction, BC = Bone-conduction, PTA = Pure Tone Average
Note: *Statistically significant difference between post-treatment and baseline threshold: $p < 0.001$
Note: **Statistically significant difference of hearing loss between CRT-IA and CRT-IV: $p < 0.001$

Comparison of hearing loss during and after treatment between the two treatment arms

In both CRT schemes, hearing thresholds deteriorated during treatment at low frequencies (0.4%/day), high frequencies (0.7%/day), and ultra-high frequencies (1%/day) (all p-values <0.0005). No evidence was found for a difference between the two arms during treatment ($P \geq 0.34$).

After treatment, differences between the two arms were found to be about 10% in favour of CRT-IA for low and high frequencies ($P<0.001$). See Table 3. No difference was found at ultra-high frequencies.

The comparison of hearing loss during therapy took place at 4 weeks and therefore included in CRT-IA four doses of 150 mg/m^2 cisplatin, and included in CRT-IV 2 doses of 100 mg/m^2 cisplatin. It seems likely that after that period, hearing loss increased more in the CRT-IV arm, given that an additional cisplatin dose was administered at 7 weeks.

Eligibility for Hearing Aids

An AC threshold > 35 dB HL at speech frequencies (PTA 1-2-4 kHz) is considered the criterion for reimbursement of hearing aids (HAs) in the Netherlands. Fewer ears qualified for Has after CRT-IA (51 of 143 measured ears, 36%) compared with CRT-IV (72 of 148 measured patients, 49%) ($p=0.03$, Chi-square test). In 2007, 55% of all ears that qualified for HAs (of the 25% of patients that were still alive and in our follow-up), actually received (or

planned to receive) a hearing aid, given that they suffered dysfunctional hearing capability after treatment.

CTCAEv3.0

Between both treatment arms, the incidence of CTCAE grades[32] was similar (p=0.72, linear-by-linear association trend test, Table 4). In total, 76 CRT-IA patients and 73 CRT-IV patients were assessed. Seven CRT-IA patients (9%) and nine CRT-IV patients (12%) had threshold shifts < 15 dB in both ears and no subjective changes in hearing due to treatment.

When we left out ultra-high frequencies (>8 kHz), a redistribution of ototoxicity grades was observed (Table 4). Eighteen CRT-IA patients (24%) and fifteen CRT-IV patients (21%) had threshold shifts < 15 dB in both ears and no subjective changes in hearing due to treatment. Again, in both treatment schemes the incidence of hearing loss was equal (p≥0.36).

Air-Bone Gap

Overall, 20 ears developed an ABG > 10 dB during or after therapy, equally distributed between CRT-IA and CRT-IV patients.

Table 4a. Common Terminology Criteria for Adverse Events v3.0. Audiogram up to 16 kHz

Grade	1	2	3	4	5	total incidence
CRT-IA 76	15 (20%)	6 (8%)	48 (63%)	0	-	69 (91%)
CRT-IV 73	10 (14%)	3 (4%)	51 (70%)	0	-	64 (88%)

Note: numbers are patients

Table 4b. Common Terminology Criteria for Adverse Events v3.0. Audiogram up to 8 kHz

Grade	1	2	3	4	5	total incidence
CRT-IA 76	20 (26%)	16 (21%)	22 (29%)	0	-	58 (76%)
CRT-IV 73	15 (21%)	18 (25%)	25 (34%)	0	-	58 (79%)

Note: numbers are patients

Explanatory analysis

Over all patients (CRT-IA and CRT-IV together), age, cumulative cisplatin dose, cumulative RT dose, and the type of hearing loss considered (the three PTAs, AC and BC) determine the extent of hearing loss due to cisplatin chemoradiation (p<0.0001), while age also modifies the effect of cumulative cisplatin dose (P<0.0001). The younger the patient, the more vulnerable he or she was to hearing loss due to high-dose cisplatin chemoradiation. A cumulative cisplatin dose of 1050 mg induces increasing (sensorineural) hearing loss with increasing frequencies (at low, high and ultra-high frequencies from 24% to 60%) and a cumulative dose of 15 Gy RT is associated with an increase in hearing loss at low and high frequencies PTA 0.5-1-2 of 9% (BC) and 12% (AC), and hearing loss at PTA 1-2-4 of 9% (BC) and 9% (AC).

Averaged over all frequencies and patients, the degree of hearing loss was not influenced by the "treatment arm" (whether intra-arterial cisplatin injection with STS was applied) (p=0.11) Nevertheless, the effect of cumulative cisplatin dose was found to be higher in CRT-IV (63%) than in CRT-IA (24%).

DISCUSSION

Recently, it was found, that the benefit in survival of chemotherapy added to the loco-regional treatment1,2 is accompanied by an increase of 37% to 43% of acute adverse effects (CTC-grade ≥ 3) for cisplatin added to radiotherapy.17,18 The current study reports on a prospective analysis of ototoxicity within a randomized phase III trial comparing CRT-IA with CRT-IV. The first clinical evaluation of this trial showed no significant difference between CRT-IA and CRT-IV in loco-regional control (62% and 68%, respectively) or overall survival (61% and 63%, respectively) at two years follow-up.31 Whether differences in ototoxicity between CRT-IA and CRT-IV were revealed, depended on the criteria used to assess the incidence and/or degree of hearing loss due to treatment.

When we expressed hearing loss in a percentage change of baseline hearing (in decibels), differences in hearing loss after treatment between CRT-IA and CRT-IV were about 10% in favor of CRT-IA at frequencies vital for speech perception (p<0.001). No difference of hearing loss after therapy was found at ultra-high frequencies. In correspondence, CRT-IA resulted in fewer ears that qualified for HAs after therapy (36%) compared with CRT-IV (49%). These results are in agreement with the report on DNA-adduct formation of our group, which observed less DNA damage in healthy tissue in CRT-IA patients compared with CRT-IV patients,[33] assuming that a higher dose of cisplatin leads to increased adduct formation. Given that we did not measure serum cisplatin concentrations in our patients, the potential effect of the mode of cisplatin application on its serum level cannot be identified. However, from our previous study on cisplatin, it became evident that hearing loss correlated better with cisplatin dose than with serum level.[34]

In our explanatory analysis, the effect of an equal dose of cisplatin was found to be larger in the CRT-IV arm than in the CRT-IA arm. A protective effect of CRT-IA may be explained by a first-pass extraction of the tumor area in intra-arterial infusion of cisplatin,[35] and / or the infusion of STS. In previous studies, the otoprotective capacity of thiols was tested in animal models.[36-38] The chemoprotectant and chemotherapy treatment were separated in time and space to avoid a potential reduction of the tumoricidal effect of cisplatin: in a rat model, vertebral arteries were perfused with cisplatin whereas STS was applied intravenously. Depending on the timing of thiol administration, full otoprotection was observed.[37] In the guinea pig model, intracochlear application of STS was found to protect the organ of corti when cisplatin was infused intravenously.[38] In the future, it may be desirable to

examine additional possibilities for two-route administration schemes for chemotherapy and otoprotective drugs in humans.

We could not find a major confounding effect of RT imbalance in our conclusion of cisplatin-induced ototoxicity, given that the different RT doses in CRT-IV subgroups (13.4 Gy in IMRT/Conventional versus 19.2 Gy in CT-guided; p<0.002, Mann Whitney U test) were related to equal hearing losses at PTA BC 1-2-4 kHz (10.0 dB versus 9.2 dB, respectively, p=0.840). Moreover, between treatment schemes, a similar discrepancy in hearing deterioration was found in patients with CT-guided therapy with RT imbalance (9.2 dB in CRT-IV therapy and 3.3 dB in CRT-IA therapy; discrepancy 5.9 dB) versus IMRT/conventional therapy without RT imbalance (10.0 dB in CRT-IV and 3.3 dB in CRT-IA; discrepancy 6.7 dB).

The incidence of significant hearing loss expressed in CTCAEv3.0 criteria[32] was equal in both treatment arms. When we applied these criteria to frequencies up to 8 kHz (not 16 kHz), a decrease in the total incidence of 91% to 76% in CRT-IA and 88% to 79% in CRT-IV was found, and a redistribution of patients towards lower CTCAE grades. This was expected, as the mean ultra-high frequency hearing loss (at PTA 8-10-12.5 kHz) was larger than the mean high frequency hearing loss (at PTA 1-2-4 kHz). Evidently, CTCAE grades 2 and 3 are too coarsely defined and do not allow for (subtle) differences in hearing loss between both treatment arms. Nevertheless, the incidence of CTCAEv3.0 grade 2 to 3 ototoxicity up to 8 kHz (50% and 59% in CRT-IA and CRT-IV, respectively) is in accordance with previous studies concerning high-dose cisplatin CRT reporting up to 60% of ≥ 10 dB hearing loss at speech frequencies and 62% > 10 dB hearing loss at 4-8 kHz.[15,24,39]

To evaluate the effect of treatment on hearing function in future studies, we suggest that hearing loss per ear be reported at frequencies of ultra-high sounds (PTA AC 8-10-12.5 Hz) for the early detection of ototoxicity; at PTA AC 1-2-4 kHz for hearing loss at frequencies vital for speech perception in noise; and at PTA 0.5-1-2 kHz for analysis of conductive hearing impairment. Furthermore, hearing loss criteria should be defined as threshold shifts relative to the pre-treatment audiogram and may be graded as 0-10 dB, 15-25 dB, 30-50 dB and > 50 dB. A pre-treatment and post-treatment audiogram is indispensable. In addition, the impact of hearing loss on a patients daily life performance may be reflected as whether a patient will qualify for a HA after treatment (PTA AC 1-2-4 kHz > 35 dB HL). To improve future study methodology we suggest that researchers focus on IMRT to obtain the most accurate assessment of the inner ear and retrocochlear RT dose. [40-44]

REFERENCES

1. Sankaranarayanan R, Masuyer E, Swaminathan R, et al: Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 18(6B):4779-4786, 1998
2. Pignon JP, Bourhis J, Domenge C, et al: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355:949-55, 2000
3. Markman M, D'Acquisito R, Iannotti N, et al : Phase-1 trial of high-dose intravenous cisplatin with simultaneous intravenous sodium thiosulfate. J Cancer Res Clin Oncol 117:151-55, 1991
4. Myers SF, Blakley BW, Schwan S, et al: The "plateau effect" of cis-platinum-induced hearing loss. Otolaryngol Head Neck Surg 104(1):122-127, 1991
5. Laurell G, Jungnelius U. High-dose cisplatin treatment: Hearing loss and plasma concentrations. Laryngoscope 100:724-734, 1990
6. Anteunis LJC, Wanders SL, Hendriks JJT, et al: A prospective longitudinal study on radiation-induced hearing loss.Am J Surgery 168:408-411, 1994
7. Ho WK, Wei WI, Kwong DLW, et al: Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head and Neck 21:547-553, 1999
8. Kwong DLW, Wei WI, Sham JST, et al: Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Rad Oncol Biol Physiol 36:281-289, 1996
9. 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 65(1):1-7, 2002
10. Oh YT, Kim CH, Choi JH, et al: Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. Radiotherapy and oncology 72:79-82, 2004
11. Palazzi MP, Guzzo M, Tomatis S, et al: Improved outcome of nasopharyngeal carcinoma treated with conventional radiotherapy. Int J Rad Oncol Biol Physiol 60:1451-1458, 2004
12. Wang LF, Kuo WR, Ho KY, et al: A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Olot Neurotol 25:168-173, 2004
13. Pan CC, Eisbruch A, Lee JS, et al: Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Rad Oncol Biol Physiol 61(5):1393-1402, 2005
14. Johannesen T, Rasmussen K, Winther FO, et al: Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 53(1):86-90, 2002
15. Pearson SE, Abby C, Meyer BS, et al: Decreased hearing after combined therapy for head and neck cancer. Am J Otolaryngol 27:76-80, 2006
16. Langenberg M, Terhaard CHJ, Hordijk GJ, et al: Simultaneous radio- and chemotherapy for squamous cell carcinoma of the head and neck in daily clinical practice: 5 years experience in a university hospital. Clin Otolaryngol 29:729-734, 2004
17. 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 Eng J Med 350:1937-44, 2004
18. Adelstein DJ, Li Y, Adams GL, et al: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemotherapy in patients with unresectable squamous cell head and neck cancer. JCO 21:92-98, 2003
19. Bernier J, Domenge C, Ozsahin M, et al: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Eng J Med 350(19):1945-52, 2004
20. Robbins KT, Storniolo AM, Kerber C, et al: Phase I study of highly selective supradose cisplatin infusions for advanced head and neck cancer. J Clin Oncol 12:2113-2120, 1994

21. Robbins KT, Vicario D, Seagren S, et al: A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. Am J Surg 168(5):419-422, 1994

22. Robbins KT, Kumar P, Wong FS, et al: Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. Head and Neck 22(7):687-693, 2000

23. Balm AJM, Rasch CRN, Schornagel JH, et al: High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head and Neck 26(6):485-493, 2004

24. Madasu R, Ruckenstein MJ, Leake F, et al: Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 123(9):978-981, 1997

25. Hiesiger EM, Green SB, Shapiro WR, et al: Results of a randomised trial comparing intra-arterial cisplatin and intravenous PCNU for the treatment of primary brain tumors in adults: Brain tumor cooperative group trial 8420A. J Neuro-Oncol 25:143-154, 1995

26. Regine WF, Valentino J, John W, et al: High-dose intra-arterial cisplatin and concurrent hyperfractionated radiation therapy in patients with locally advanced primary squamous cell carcinoma of the head and neck: report of a phase II study. Head Neck 22:543-549, 2000

27. Foote RL, Kasperbauer JL, Okuno SH, et al : A pilot study of high-dose intraarterial cisplatin chemotherapy with concomitant accelerated radiotherapy for patients with previously untreated T4 and selected patients with T3N0-N3M0 squamous cell carcinoma of the upper aerodigestive tract. Cancer 103:559-68, 2005

28. Michael II LM, Sorenson JM, Samant S, et al: The treatment of advanced sinonasal malignancies with pre-operative intra-arterial cisplatin and concurrent radiation. J Neuro-oncol 72:67-75, 2005

29. Kovács AF, Schiemann M, Turowski B: Combined modality treatment of oral and oropharyngeal cancer including neoadjuvant intraarterial cisplatin and radical surgery followed by concurrent radiation and chemotherapy with weekly docetaxel – three year results of a pilot study. J Cranio-Maxillofacial Surg 30:112-120, 2002

30. Madajewicz S, Chowhan N, Tfayli A, et al : Therapy for patients with high grade astrocytoma using intraarterial chemotherapy and radiation therapy. Cancer 88:2350-6, 2000

31. CRN Rasch, AJM Balm, JH Schornagel, et al: Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-institutional trial. ASTRO, 2006 (abstr)

32. Cancer Therapy Evaluation Programm, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (http://ctep.cancer.gov). publ date: December 12, 2003.

33. Hoebers FJ, Pluim D, Verheij M, et al: Prediction of treatment outcome by cisplatin-DNA adduct formation in patients with stage III/IV head and neck squamous cell carcinoma, treated by concurrent cisplatin-radiation (RADPLAT). Int J Cancer 119(4):750-6, 2006

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

35. Sileni VC, Fosser V, Maggian P, et al: Pharmacokinetics and tumor concentration of intraarterial and intravenous cisplatin in patients with head and neck squamous cell cancer. Cancer Chemother Pharmacol 30(3):221-5, 1992

36. Dickey DT, Muldoon LL, Kraemer DF, et al: Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res 193:25-30, 2004

37. Dickey DT, Wu YJ, Muldoon LL, et al: Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol exp therapeut 314:1052-1058, 2005

38. Wang J, Faulconbridge RVL, Fetoni A, et al: Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. Neuropharmacol 45:380-393, 2003

39. Dropcho EJ, Rosenfeld SS, Morawetz RB, et al : Preradiation intracarotid cisplatin treatment of newly diagnosed anaplastic gliomas. J Clin Oncol 10:452-458, 1992

40. Bohne BA, Marks JE, Glasgow GP, et al: Delayed effects of ionising radiation on the ear. The Laryngoscope 95:818-828, 1985

41. Greene JS, Giddings NA, Jacobson JT: Effect of irradiation on guinea pig ABR thresholds. Otolaryngol Head Neck Surg 107:763-768, 1992

42. Lau SK, Wei WI, Sham JST, et al: Early changes of auditory brain stem evoked reponse after radiotherapy for nasopharyngeal carcinoma – A prospective study. J Laryngol Otol 106:887-892, 1992

43. Leighton SEJ, Kay R, Leung SF, et al: Auditory brainstem responses after radiotherapy for nasopharyngeal carcinoma. Clin Otolaryngol 22:350-354, 1997

44. Low WK, Burgess BSc, Fong KW, et al: Effect of radiotherapy on retro-cochlear auditory pathways. The Laryngoscope 115:1823-1826, 2005

Chapter 5

Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer

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ABSTRACT

Background and Purpose

Cisplatin based chemo-irradiation is increasingly used for head and neck squamous cell carcinoma. We aimed to assess hearing deterioration due to low-dose cisplatin chemoradiation and to compare the observed hearing loss with hearing loss in our previously described high-dose cisplatin CRT cohort.

Materials and Methods

A prospective analysis of hearing thresholds at low and (ultra-)high frequencies obtained before and after treatment in 60 patients. Patients received low-dose cisplatin (6 mg/m^2, daily infusions, 20-25 days) with concomitant accelerated radiotherapy (70 Gy).

Results

Audiometry up to 16 kHz was performed before therapy and 31 days (median) after treatment. The total incidence of ototoxicity in CTCAEv3.0 was 31% in audiograms up to 8 kHz, and 5% of ears tested qualified for HAs due to treatment. The mean hearing loss at speech frequencies was 2.6 dB (SD 5.7) and 2.3 dB (SD 9.2) at PTA 1-2-4 kHz air-conduction and bone-conduction, respectively. The mean hearing loss at ultra-high frequencies (PTA AC 8-10-12.5 kHz) was 9.0 dB (SD 8.1). Low-dose cisplatin CRT caused less acute hearing loss (CTCAE 31%), compared to high-dose cisplatin CRT (CTCAE 78%).

Conclusions

Low-dose cisplatin chemo-irradiation for HNSCC is a relatively safe treatment protocol with respect to ototoxicity.

INTRODUCTION

Head and neck cancers are responsible for 12% of male and 7% of female cancers in the developing world and over 70% of these patients present with advanced stage III-IV disease.[1] The management of these stage III/IV carcinomas is characterised by the limited response to RT leading to an increasing need for organ preservation in case of resectable disease. Meta-analyses on the impact of adding chemotherapy to RT proved an 8% increase in the 2- and 5-years survival when chemotherapy was administered concomitantly.[2] Since then, concurrent cisplatin-based chemoradiation (CRT) has been widely adopted as the treatment of preference in advanced head and neck squamous cell carcinoma (HNSCC) in primary setting or adjuvant to curative surgery.[3,4] However, although various CRT schemes have been evaluated with respect to clinical outcome and tolerability, a consensus about the optimal schedule has not been reached yet.

The addition of high-dose cisplatin (100 mg/m^2, 3 infusions in 7 weeks) to RT induces an increase in acute adverse effects CTC grade $\geq$ 3 from 52% to 89%[3] and from 34% to 77%[4] , whereas intermediate-dose cisplatin (cisplatin 20 mg/m^2, daily infusions for 1 or 2 weeks) resulted in acute toxicities of 40% and 63%.[5,6] When weekly infusions of 40 mg/m^2 cisplatin were combined with RT, an incidence of 86% CTC grade >3 was found.[7] Comparing single-modality RT to RT with concomitant cisplatin of 6 mg/m^2 (daily infusions, 7 weeks), the 42% incidence of acute side-effects was reported to remain unaltered.[8] In addition, comparing daily cisplatin 6 mg/m^2 with concurrent conventional RT (7 weeks) to daily cisplatin 10 mg/m^2 with concurrent hypofractionated RT (week 1, 4 and 7), similar acute toxicity was observed.[9]

Cisplatin is well-known to induce mostly irreversible sensorineural hearing loss (SNHL), increasing with increasing frequencies and depending on cisplatin dose-intensity.[10,11] In addition, cranial irradiation has shown a 49% incidence of hearing loss directly post-treatment and a 55% incidence of hearing loss 2-8 years after therapy.[12-19] In contrast, detailed information about ototoxicity remains scarce in reports on acute toxicity after concurrent chemoradiation. Following our previous studies on hearing loss due to high-dose cisplatin chemo-irradiation[20-22], this article focusses on hearing loss after low-dose cisplatin CRT and compares results with findings of a previously described high-dose cisplatin CRT cohort from our institute.

MATERIALS AND METHODS

Patients and treatment characteristics

From 2002 to 2006, 60 patients with locally advanced HNSCC not eligible for the randomised high-dose cisplatin CRT trial[23], received low-dose cisplatin chemo-irradiation[24]. The treatment consisted of radiotherapy, with a 4-6 MV photon linear accelerator (Elektra, Sweden). Target volume included the primary tumor and the bilateral neck to a dose of

46 Gray (Gy) in 23 fractions. Tumor bearing area received 70 Gy and a boost of 24 Gy (12 fractions) was given to the microscopic tumor extensions at the primary tumor site and lymph node metastases. RT was delivered in an accelerated fractionation scheme. Twenty-eight patients received conventional RT by a standard 3-field technique (2 opposing laterals for the upper neck region, with an adjacent supraclavicular field for the lower neck). In thirty-two patients, intensity-modulated radiation therapy (IMRT) was given, in which multiple portals at different angles were applied in order to spare the organs at risk (ie parotid gland). Cisplatin was given at a dose of 6 mg/m^2 in 2 minutes infusion daily, for a total number of 20 to 25 doses in 51 patients and 9 patients respectively, 1-2 hours prior to irradiation. Treatment was delivered on an outpatient basis.

Inner ear radiation dose

In conventional RT, radiation portals were planned at a CT scan. The inner ear radiation dose was determined by revision of these images. Firstly, the distance of the inner ear (cochlea) to the boundary of the radiation field was measured. By repeating the procedure twice, we found a median variation of 1.0 mm. Secondly, we converted these distances into Grays according to a CT-simulated patient model with cochleas located at several distances to the boundary of the radiation field (both inside and outside the field), in which the applied inner ear radiation dose had been computed digitally. In IMRT, the inner ear radiation dose was computed directly in the planning system. In 33 ears RT data were not sufficient to assess the radiation dose.

Audiometry

Audiometry was performed before therapy and 31 days (median) post-treatment. In two patients the audiogram was performed 2.2 and 3.5 years after the end of treatment. Air-conduction (AC) thresholds were measured at frequencies 0.125 kHz to 16 kHz and bone-conduction (BC) thresholds were measured at 0.5 kHz to 4 kHz. We calculated mean thresholds at five Pure Tone Averages (PTAs): 0.5-1-2 kHz (BC and AC), 1-2-4 kHz (BC and AC) and 8-10-12.5 kHz (AC), representing speech perception in quiet, speech perception in noise and perception of high-pitched sounds e.g. music, respectively. Air-bone gaps (ABGs) were calculated by the difference between AC and BC at 0.5-1-2 kHz. Audiometric data are presented in dB Hearing Level (HL). All analyses were conducted per ear.

Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0)

The incidence of ototoxicity was also expressed in CTCAEv3.0.[25] Grade 1: threshold shift 15-25 dB averaged at ≥ 2 contiguous frequencies at least in one ear, òr subjective change in hearing. Grade 2: threshold shift > 25–90 dB, averaged at 2 contiguous frequencies at least in one ear. Grade 3: threshold shift > 25-90 dB, averaged at 3 contiguous frequencies, at least in one ear. Grade 4: threshold shift > 90 dB. No specific frequencies or frequency ranges are given.

Statistics

The limited number of patients in this study combined with the large number of patient and treatment variables studied did not allow for a meaningful multivariate analysis. A one-sample Kolmogorov-Smirnov test showed that our data cannot be regarded as a sample from a normal distribution (PTA AC/BC 0.5-1-2 kHz $p<0.008$; PTA BC 1-2-4 kHz $p=0.005$; PTA AC 1-2-4 kHz $p=0.067$; PTA 8-10-12.5 kHz $p=0.951$). Therefore, nonparametric statistics were performed. The Mann-Whitney U test was performed to evaluate differences between 2 independent samples and the Wilcoxon signed-rank test was used to determine differences between dependent samples. Spearman rank-order correlation coefficients for non-symmetrical data were obtained to identify significant relations between 2 variables.

RESULTS

Patient and treatment characteristics

Patient and treatment characteristics are summarized in Table 1. In 4 patients the chemotherapeutic scheme was halted due to neutropenia, anorexia and cerebrovascular ischemia The median cisplatin dose per infusion was 10.9 mg. On average, 20.4 infusions were given, resulting in a cumulative median cisplatin dose of 220 mg (range 78 to 300 mg).

Overall hearing loss

Hearing loss of patients treated with low-dose cisplatin CRT is plotted in Figure 1, concerning mean AC hearing thresholds at all frequencies before and after therapy. In the audiograms up to 8 kHz 92% of the air-conduction thresholds were measured. At ultra-high frequencies (8-16 kHz) and particularly as the treatment went along, many thresholds could not be measured, due to the fact that the patient was not fit enough to complete the audiometry session. At 10 kHz and 12.5 kHz the number of ears measured was 73% and 36%, respectively.

The largest threshold shift was seen at ultra-high frequencies: 9.9 dB (SD 12.6) and 9.5 dB (SD 11.1) at 11.2 kHz and 12.5 kHz, respectively. At frequencies vital for speech perception (1, 2 and 4 kHz), hearing deterioration was limited and completely caused by SNHL, as shown in Table 2 summarizing mean (sensorineural) hearing capability at speech frequencies and ultra-high frequencies, before and after treatment.

Eligibility for Hearing Aids

An air-conduction threshold > 35 dB HL at speech frequencies (PTA 1-2-4 kHz) is considered as the criterion for reimbursement of hearing aids (HAs) in the Netherlands. Six of 120 ears (5%) qualified for HAs due to treatment.

Table 1 Patient and treatment characteristics (n = 60)

Age (in years) average (SD), median		**61**	
Gender	male	41 (68%)	
	female	19 (32%)	
Follow-up (in days, median)		31	
T classification			
	0	0	
	1	2 (3%)	
	2	9 (15)%	
	3	22(37)%	
	4	25(42)%	
	unknown	2 (3%)	
N classification			
	0	23(38)%	
	1	9(15)%	
	2	22(37)%	
	3	5(8)%	
	unknown	1 (2%)	
			Inner ear RT dose: mean (SD), median
Primary tumor site	sinus	1 (2%)	23.7 Gy
	cavum oris	13 (22%)	15.0 (11.9), 9.5 Gy
	oropharynx	25 (42%)	17.3 (18.7), 9.9 Gy
	hypopharynx	15 (25%)	14.3 (8.0), 11.7 Gy
	larynx	3 (5%)	9.1 (6.1), 8.9 Gy
	neck	1 (2%)	49.4 Gy
	lung	1 (2%)	
	oesofagus	1 (2%)	
Overall inner ear RT dose (Gray) mean (SD)		16.4 (14.6) Gy	
median		11.3 Gy	
range		3-99 Gy	
Overall conventional radiation therapy dose (Gray) median		10.5 Gy	
Overall IMRT dose (Gray) median		12.0 Gy	
Cisplatin dose per infusion (mg) median		10.9 mg	

Note: Numbers are patients, unless otherwise stated

Air-Bone Gap

Of 81 ears measured at AC and BC PTA 0.5-1-2 kHz or PTA 1-2-4 kHz before and after therapy, 10 ears (12%) developed an (increase in) ABG > 10 dB due to treatment, in patients with tumors of the cavum oris (3 ears), oropharynx (5 ears), hypopharynx (1 ear), and neck (1 ear).

Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0)

In Table 3 auditory CTCAE criteria version 3.0 are described for our patients treated with low-dose cisplatin chemoradiation. Considering audiograms including ultra-high frequencies (up to 16 kHz) an increased total incidence of ototoxicity was seen with a redistribution towards higher CTCAE grades, compared to when the criteria were applied to audiograms including frequencies up to 8 kHz.

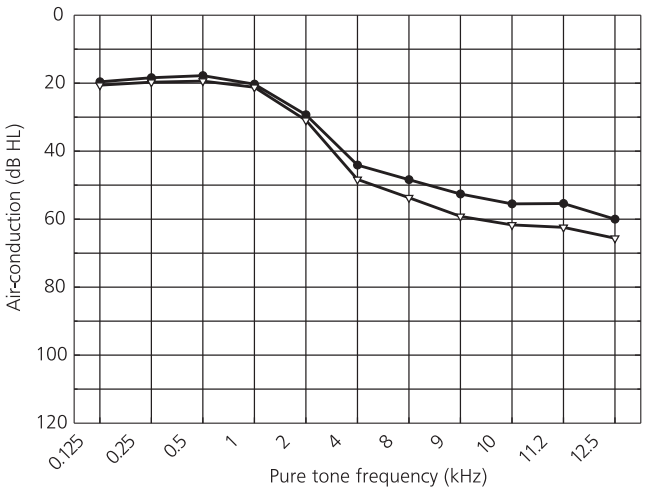

Figure 1. Mean hearing thresholds (air-conduction in dB HL) of all patients treated with low-dose cisplatin chemo-irradiation, before (●) and after (∇) treatment at pure tone frequencies 0.125 kHz to 12.5 kHz.

Table 2 Mean hearing thresholds of the whole population before and after therapy

	PTA AC 1-2-4 kHz mean (SD)	PTA BC 1-2-4 kHz mean (SD)	PTA AC 8-10-12.5 kHz mean (SD)
Before therapy	30.9 (19.1)	24.4 (14.9)	42.8 (18.5)
After therapy	33.1 (20.7)*	28.2 (17.1)*	48.2 (18.7)*

AC = air conduction, BC = bone conduction, SD = standard deviation
PTA 1-2-4 kHz = Mean threshold at 1, 2 and 4 kHz (in dB Hearing Level)
PTA 8-10-12.5 kHz = Mean threshold at 8, 10 and 12.5 kHz (in dB Hearing Level)
* statistically significant increase during treatment, $p<0.01$, Wilcoxon test

Univariate analysis

We found no significant difference in treatment induced hearing loss at AC/BC PTA 0.5-1-2 kHz and 1-2-4 kHz, and PTA 8-10-12.5 kHz ($p>0.250$) between women and men. Age and hearing loss had a significant relationship at AC 1-2-4 kHz with a coefficient of 0.219 ($p<0.05$), but not at AC 8-10-12.5 kHz (coefficient 0.010, $p=0.950$). Pre-treatment hearing capability at PTA AC 1-2-4 kHz or PTA 8-10-12.5 kHz had no influence on treatment induced hearing loss at PTA 1-2-4 kHz and PTA 8-10-12.5 kHz ($p>0.218$). RT dose, cisplatin dose, number of cisplatin infusions or cumulative cisplatin dose were not statically correlated with hearing loss at PTA BC/AC 1-2-4 kHz and PTA 8-10-12.5 kHz ($p>0.099$).

Table 3 Common Terminology Criteria for Adverse Events v3.0 for low-dose cisplatin CRT

Grade	1	2	3	4	5	total incidence
Audiogram up to 8 kHz	14 (23%)	2 (3%)	3 (5%)	0	-	19 (31%)
Audiogram up to 16 kHz	14 (23%)	4 (7%)	10 (17%)	0	-	28 (47%)

Note: numbers are patients

Table 4 Comparison between low-dose* and high-dose** cisplatin CRT

	low-dose cisplatin (60 patients)	high-dose cisplatin (158 patients)
CTCAE up to 8 kHz, % of patients		
grade 1	23%	23%
grade 2	3%	23%
grade 3	5%	32%
grade 4	0	0
Hearing Aids due to treatment, % of ears	5%	15%
Hearing loss during treatment, mean dB (SD)		
PTA BC 1-2-4 kHz	2.6 dB (5.7)	8.0 dB (10.5)
PTA AC 1-2-4 kHz	2.3 dB (9.2)	9.1 dB (12.3)
PTA 8-10-12.5 kHz	9.0 dB (8.1)	21.5 dB (17.6)

* = cisplatin dose 6 mg/m^2, daily, 20-25 days, with concurrent RT
**= 2 patient groups pooled [20], that received cisplatin 100-150 mg/m^2, 1 infusion per week, 3-4 infusions, and concurrent RT

DISCUSSION

In this study, the total incidence of significant hearing loss expressed in CTCAEv3.0 criteria[25] was 31% in audiograms up to 8 kHz, but was increased and characterised with a redistribution of patients towards higher CTCAE grades, when we applied these criteria to frequencies up to 16 kHz (total incidence 47%). This was expected, as the mean ultra-high frequency hearing loss at PTA 8-10-12.5 kHz was larger (5.6 dB) than the mean high frequency hearing loss at PTA 1-2-4 kHz (3.6 dB). These percentages were relatively high, compared to the 5% percent of patients suffering CTC grade 2 and 4 hearing loss that received RT to a cumulative dose of 69.9 Gy and concomitant cisplatin 40 mg/m^2 weekly in a phase I/II trial. (Hearing loss grade 1 was not commented on).[8] The difference could be explained by the use of another pure tone frequency area, since CTCAEv3.0 criteria lack a specific frequency definition.

In our series, the low-dose cisplatin based CRT regimen caused less acute ototoxicity compared to our previously studied high-dose cisplatin (see Table 4). For the comparison to hearing loss following high-dose cisplatin chemoradiation, we pooled two previously studied patient groups[20] and recalculated hearing loss for the high-dose cisplatin CRT cohort as a

whole. Total CTCAE toxicity increased from 31% in case of the low-dose to 78% in case of the high-dose cisplatin, in audiograms up to 8 kHz. Low-dose cisplatin CRT resulted in less hearing loss at speech frequencies and ultra-high frequencies, and less ears qualifying for HAs due to treatment. In both low-dose and high-dose CRT populations, patients age and median applied RT dose were similar, only the percentage of women was higher in the low-dose group (32% versus 23%). In our univariate analysis we confirmed that gender is not an important predictive factor for hearing loss due to cisplatin CRT.[22] However, our low-dose population was characterized by relatively favourable baseline hearing capability compared to our high-dose cohort.[20] Although the current univariate analysis did not recognize the influence of pre-treatment hearing levels on hearing loss due to therapy, good pre-treatment hearing capability was proven to be the main predictive factor increased hearing deterioration due to high-dose cisplatin CRT.[22] Therefore, the favourable baseline hearing of the low-dose group is unlikely to be related to the relatively limited hearing loss observed in this study. The limited hearing deterioration in the low-dose cohort, compared to the high-dose cohort, is probably a result of the limited admistered cisplatin dose.

In previous literature, radiation-induced SNHL has been found after cranial irradiation with or without cisplatin, and both partial recovery of hearing function and deterioration of hearing loss were measured several years after therapy.[14,16,21,26-27] Also after low-dose cisplatin chemotherapy (without RT), partial recoveries have been described.[11,28-29] As these patients were characterised with extensive hearing loss due to treatment, it is uncertain whether partial recovery of cisplatin (chemoradiation) induced hearing loss can be expected in our low-dose cisplatin CRT population. Long-term follow up is needed to determine the full ototoxic effect of cisplatin chemoradiation.

In conclusion, this study indicates that low-dose cisplatin chemo-irradiation for head and neck SCC is a relatively safe treatment protocol with respect to ototoxicity, as the incidence of hearing loss > 25 dB at 2 or more frequencies up to 8 kHz was 8% (CTCAE grade 2 and 3), and 5% of ears qualified for HAs due to treatment. Long-term follow-up is needed to assess the full effect of cisplatin chemoradiation on hearing capability.

REFERENCES

[1] Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J, Whelan S. Head and neck cancer: a global perspective on epidemiology and prognosis. Anticancer Res 1998;18(6B):4779-4786.

[2] Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949-55.

[3] Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-98.

[4] 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 Eng J Med 2004;350:1937-44.

[5] Vega de la FA, Vera Garcia R, Dominguez D, et al. Hyperfractionated radiotherapy and concomitant cisplatin for locally advanced laryngeal and hypopharyngeal carcinomas. Am J Clin Oncol 2003;26(6):550-557.

[6] Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. Head and Neck 2006;28:189-196.

[7] Beckmann GK, Hoppe F, Pfeundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. Head and Neck 2005;27:36-43.

[8] Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily cisplatin chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-3548.

[9] Bartelink H, Bogaert van den W, Horiot JC, Jager J, Glabbeke van M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial. Eur J Cancer 2002;38:667-673.

[10] Aguilar-Markulis NL, Beckly S, Priore R, Mettlin C. Auditory effects of long-term cis-dichlorodiammineplatinum II therapy in genitourinary cancer patients. J Surg Oncol 1981;16(2):111-123.

[11] Schweitzer VG. Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 1993;103(4 Pt 2):1-52.

[12] Anteunis LJC, Wanders SL, Hendriks JJT, et al. A prospective longitudinal study on radiation-induced hearing loss.Am J Surgery 1994;168:408-411.

[13] Ho WK, Wei WI, Kwong DLW, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head and Neck 1999;21:547-553.

[14] Kwong DLW, Wei WI, Sham JST, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Rad Oncol Biol Physiol 1996;36:281-289.

[15] 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 2002;65(1):1-7.

[16] Oh YT, Kim CH, Choi JH, et al. Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. Radiotherapy and oncology 2004;72:79-82.

[17] Palazzi MP, Guzzo M, Tomatis S, et al. Improved outcome of nasopharyngeal carcinoma treated with conventional radiotherapy. Int J Rad Oncol Biol Physiol 2004;60:1451-1458.

[18] Wang LF, Kuo WR, Ho KY, et al. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.

[19] Pan CC, Eisbruch A, Lee JS, et al. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Rad Oncol Biol Physiol 2005;61(5):1393-1402.

[20] Zuur CL, Simis YJW, Lansdaal PEM, 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, 2007;25(24):3759-65.

[21] Zuur CL, Simis YJW, Lansdaal PEM, et al. Audiometric patterns in ototoxicity of intra-arterial cisplatin chemoradiation in patients with locally advanced head and neck cancer. Audiol Neurotol 2006;11(5):318-30.

[22] Zuur CL, Simis YJW, Lansdaal PEM, 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 2007;68(5):1320-5.

[23] CRN Rasch, AJM Balm, JH Schornagel, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-institutional trial. ASTRO, 2006 (abstr)

[24] Hoebers FJP, Heemsbergen W, Balm AJM, Zanten van M, Schornagel JH, Rasch CRN. Concurrent chemoradiation with daily low dose cisplatin for advanced stage head and neck carcinoma. Radiotherapy and Oncology 2007;in press.

[25] Cancer Therapy Evaluation Programm, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (http://ctep.cancer.gov). publ date: December 12, 2003.

[26] Johannesen TB, Rasmussen K, Winther FO, Halvorsen U, Lote K. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 2002;53(1):86-90.

[27] 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 1991;21(3):723-728.

[28] Vermorken JB, Kapteijn TS, Hart AA, Pinedo HM. Ototoxicity of cis-diamminedichloroplatinum (II): Influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol 1983;19(1):53-58.

[29] Laurell G, Bagger-Sjöbäck D. Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol 1991;20(3):158-167.

Chapter 6

Risk factors for hearing loss in head-and-neck cancer patients treated with Intensity-Modulated Radiation Therapy

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Submitted

ABSTRACT

Purpose:
Radiation therapy (RT) is a common treatment for head and neck carcinomas. The objective of this study was a prospective multivariate assessment of the dose-effect relationship between Intensity-Modulated RT and hearing loss.

Methods and materials:
Pure-tone audiometry at 0.250 kHz to 16 kHz was obtained before and after treatment in 101 patients (202 ears). All patients received full-course Intensity-Modulated RT (range 56 to 70 Gray), with a median cochlear dose of 11.4 Gy (range 0.2 to 69.7 Gy).

Results:
Audiometry was performed 1 week before and median 9 weeks (range 1 to 112 weeks) after treatment. The mean hearing deterioration at pure-tone average (PTA) air-conduction (AC) 1-2-4 kHz was small (from 28.6 to 30.1 dB HL). However, individual patients showed clinically significant hearing loss, as the incidence of 10 dB threshold shifts at PTA AC 1-2-4 kHz and PTA 8-10-12.5 kHz was 13% and 18%, respectively. Post-treatment hearing capability was unfavourable in case of higher inner ear radiation doses ($p<0.0001$), unfavourable baseline hearing capability ($P<0.0001$), green-eyed patients ($P<0.0001$), and older age ($p<0.0001$). Based on the multivariate analysis, a prediction of individual hearing capabiltity after treatment was made.

Conclusions:
Radiotherapy-induced hearing loss in the mean population is modest. However, clinically significant hearing loss was observed in older patients with green eyes and unfavourable pre-treatment hearing. In these patients, the intended radiation dose may be adjusted according to the proposed prediction model, aiming to decrease the risk for ototoxicity.

INTRODUCTION

Radiation therapy (RT), as single-modality treatment or adjuvant to surgery, is a common treatment modality for head and neck cancer. Adverse effects of radiotherapy involving the ear are (chronic) external otitis, stenosis of the external ear canal, and atrophy or ulceration of the skin. The most common reaction in the middle ear is otitis media due to dysfunction of the Eustachian tube.[1] Delayed radiation effects may be osteoradionecrosis of the temporal bone or mastoiditis.[1,2] Radiation-induced sensorineural hearing loss (SNHL) has been observed to an incidence of 49% directly post-treatment and to an incidence of 67% at 2-8 years after therapy of patients treated with RT fields exposing the inner ear, as described in studies concerning tumors of the nasopharynx and parotid gland.[3-10] In addition, sensorineural hearing loss has been observed in up to 47% of patients treated with other head and neck carcinomas, depending on the pure tone frequency that was considered.[11] SNHL due to RT affects mainly the high-frequency area at 4 kHz and 8 kHz and may be transient.[2-7,9,11]

In previous literature, various threshold radiation doses for clinically significant hearing loss have been suggested of 32 Gy, 45-50 Gy, 60 Gy, and 65 Gy.[10,12-14] In a study of patients treated with concurrent cisplatin infusions, ears receiving > 48 Gy RT experienced an increased risk for SNHL.[15] In addition, multivariate analyses showed a 50% risk of 15 dB SNHL in ears receiving 24.2 Gy to 45.3 Gy, depending on age, the pure tone frequency and follow-up period considered[16] and, in another study, the inner ear radiation dose producing a 15% risk for perceptive hearing loss was reported to depend on the patients age and individual pre-therapeutic hearing capability.[17] In addition, Pan et al. found that patients with older age or good pre-treatment hearing capability suffered more hearing loss.[11]

The objective of this study was a prospective multivariate analysis of radiation-induced hearing loss concerning various patient and treatment variables, in order to reveal individual risk factors for ototoxicity in a group of consecutive patients treated with (postoperative) Intensity-Modulated RT for head and neck tumors. None of the patients received chemotherapy. Pure tone audiometry at low, high and ultra-high frequencies was obtained before and after treatment.

METHODS AND MATERIALS

From 2003 to 2006, 101 patients received (postoperative) Intensity-Modulated RT in our institution for carcinomas of the head and neck. The patients were treated for a malignancy of the facial skin (3), the nasal cavity (4), sinus (3), oral cavity (17), oropharynx (22), hypopharynx (2), larynx (28), and carcinoma or recurrent / irradically excised pleomorphic adenoma of the parotid gland (9 and 8, respectively). Other patients suffered lymphnode metastases in the

neck of unknown primary origin (1), recurrent regional neck disease (1), carcinoma of the thyroid gland (2), and carcinoma of the submandibular gland (1).

Intensity-Modulated Radiaton Therapy protocol

Computer tomogram-generated treatment plans were made for all patients. An axial CT-scan series in treatment position was taken from the bottom of the frontal sinus to the lower neck. The slice thickness was 3 mm. The CT datasets were transferred to the treatment planning systems (Um-plan version 3.38, University of Michigan, USA and Pinnacle version 7.3, Philips, Best, the Netherlands); three-dimensional treatment planning systems (TPS) that has the possibility to design Intensity-Modulated RT plans. The Clinical Target Volumes (CTVs) and the organs at risk (OARs) were outlined on each relevant CT slice. The CTVs were defined as the primary tumor (surgical bed if applicable) and the lymph nodes on both sides. A 5 mm expansion from CTV to Planning Target Volume (PTV) was applied. The following OARs were outlined: the parotid glands, the oral cavity, the brain stem, and the spinal cord. No additional margins were set around the OARs.

An Intensity-Modulated RT technique was used to deliver multisegmental, (non)-coplanar fields. The dose distribution in the PTV should be according to the ICRU Report-62 recommendations: 99% of the volume should receive ≥ 95% of the prescribed dose, and maximum 1% of the volume may receive a dose ≥ 107% of the prescribed dose. In addition the oral cavity mean dose should be ≤ 26 Gray (Gy) with a maximum of 1% of the volume to get 30 Gy. Spinal cord and brainstem should receive a dose ≤ 50 Gy.

The calculation of applied dose on the inner ear

Three-dimensional dose distributions were calculated and dose-volume histograms were derived, after delineation of the target organ (cochlea) as shown in Figure 1. Dose calculation and DVH calculation were the same as performed for the 3D conformal plan using the Um-plan and the Pinnacle treatment planning system, with a superposition-convolution algorithm using a 2 mm gridsize.

Audiometry and analysis of audiometric data

Pure-tone audiometry was conducted in all patients 1 week before and median 9 weeks (mean 31 weeks, range 1 to 112 weeks) after treatment. We obtained a post-treatment audiogram within 3 months and within 1 year after treatment in 54% and 78% of the patients, respectively. Air-conduction (AC) thresholds were measured at frequencies 0.125 to 16 kHz and bone-conduction (BC) thresholds were measured at 0.5 to 4 kHz. Pure Tone Averages (PTAs) were computed to obtain the mean AC threshold at three frequency areas: the low frequency area (PTA 0.5-1-2 kHz) related to speech perception in quiet, the high frequency area (PTA 1-2-4 kHz) related to speech perception in noise and the ultra-high frequency area (PTA 8-10-12.5 kHz) related to the perception of high tones as in music and/or in nature. Air-bone gaps (ABGs) were determined by the average differences between AC and BC at 0.5-1-2 kHz. Analyses were performed per ear. In the audiograms up to 8 kHz

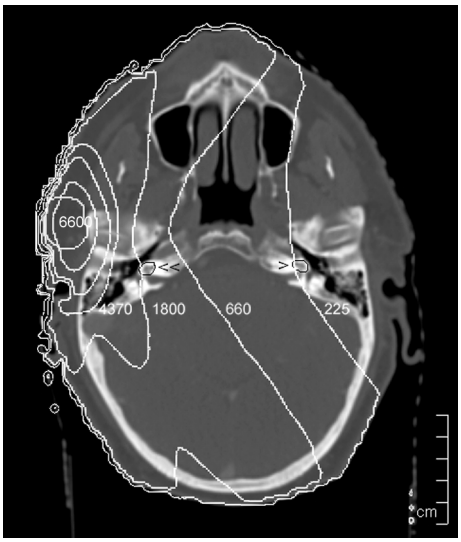


Figure 1. An axial computed tomography scan of a patient treated for parotid gland disease. Intensity-Modulated Radiation Therapy resulted in an isodose distribution indicated with lines 6600 cGy, 4370 cGy, 1800 cGy, 660 cGy, and 225 cGy. The left cochlea (>) and the right cochlea (<<) were delineated to assess the locally applied radiation dose.

96% of the air-conduction thresholds were measured. However, at ultra-high frequencies 9-16 kHz, increasing numbers of thresholds were not measured with increasing frequency (minimum 8%, maximum 93%), either because patients were not fit enough to complete the audiometry session, or because the actual threshold exceeded the maximum output of the audiometer.

Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0)

The incidence of ototoxicity was also expressed in CTCAEv3.0.[18] Grade 1: threshold shift 15-25 dB *averaged* at ≥ 2 contiguous frequencies at least in one ear, òr subjective change in hearing. Grade 2: threshold shift > 25–90 dB, averaged at 2 contiguous frequencies at least in one ear. Grade 3: threshold shift > 25-90 dB, averaged at 3 contiguous frequencies, at least in one ear. Grade 4: threshold shift > 90 dB. No specific frequencies or frequency ranges are given.

Statistics

The main goal was to assess the dose-effect relationship between radiation dose and hearing capability after treatment at PTA AC and BC 0.1-2-4 and 1-2-4 kHz, and at PTA 8-10-12.5 kHz, for both ears simultaneously, giving 10 outcome variables per patient. The effects of the following patient and treatment variables on these outcomes were studied in this multivariate analysis: pre-treatment hearing capability, RT dose, age, gender, ear (left or right), eye color (brown, blue, green, unknown) and time of post-treatment audiogram in days after start of treatment (FU time). An added effect of the multivariate approach was that a patient was automatically used as his/her own control comparing the two ears. From the 101 patients, 97 were included for the analysis, as in 4 patients the radiation dose to the inner ear could not be retreived. To obtain a normal distribution of data, audiometric

thresholds were logarithmically transformed after adding a constant of 10 dB. P-values < 0.001 were considered statistically significant.

The statistical analysis did acknowledge the correlations between the maximally 10 post-treatment measurements within a patient (PTA AC and BC 0.5-1-2 kHz, PTA AC and BC 1-2-4 kHz, PTA 8-10-12.5 kHz, both ears). No structure was imposed on the covariance matrix of these 10 measurements, that is they may have all unequal SD's and arbitrary correlations. The relation between PTA and RT dose was assumed to be a linear one, where the patient (except side of ear) and treatment variables were allowed to affect the slope as well as the intercept. Effects of baseline PTA, age and FU time were also initially assumed to be linear. In addition, post-treatment PTA was allowed to depend on the side of ear (left, right). All effects were allowed to depend on medium (air or bone) and frequency area. A maximum likelihood approach was used for the estimation. This method imputes missing outcome values automatically from known outcome values and covariates, but takes this into account when calculating p-values and confidence intervals. The overall effect of a variable on posttreatment hearing was assessed by simultaneously testing all main effects and interactions containing that variable. Hierarchical backward elimination (p>0.10) was applied to facilitate interpretation. P-values were calculated from approximate type III F-tests, confidence intervals from approximate t-distributions. The number of patients defined the denominator degrees of freedom for between-patients factors and the number of measurements for the within-patient factors. Detection of violations of the model, especially linearity and non-constancy of the SD, was examined by scatter plots of residuals against the covariates. To be able to test linearity of the relation between post-treatment PTA and RT dose, age, FU time, and baseline PTA more formally, the model had first to be reduced. This was done using hierarchical backward elimination, with all remaining p values<0.10 as stopping criterion. Backward elimination means that the in each step the (eligible) main factor or interaction with the highest P-value is removed from the (remaining) model. Hierarchical means that main factors and interactions, which are included in higher order interactions still in the model, are not eligible for removal. Linearity was then tested in the reduced model using likelihood ratio tests comparing the linear model with a nonlinear model based on natural splines.[19] Number and placement of knots were defined as recommended by Harrell. P-values > 0.05 were used as criterion for linearity. PROC MIXED of SAS® (9.1 for Windows) was used.

Results were expressed in terms of percentage differences in post-treatment PTAs. Where possible, results were back-transformed to the decibel scale.

RESULTS

Overall hearing loss in the averaged population

Radiation therapy was applied to 101 patients (66 men and 35 women) with a median age of 60.8 years. All patients received full-course RT (56 to 70 Gy, 200 cGy/fraction/per day) to the primary tumor site. The overall RT dose applied to the inner ear varied from 0.2 to 69.7 Gy (median of 11.4 Gy). In 4 patients the RT dose to the inner ear could not be calculated due to missing data. Patient, tumor, and treatment characteristics are summarized in Table 1.

To visualize hearing capability before and after RT, we plotted the mean pre-treatment and post-treatment hearing thresholds of all 101 ears in Figure 2. Small threshold shifts are visualized at 0.5 kHz to 12.5 kHz. At ultra-high frequency PTA 8-10-12.5 kHz the threshold shift is statistically significant (Wilcoxon signed-rank test, univariate non-parametric analysis). Mean pre- and post-treatment hearing capability at PTA AC and BC 1-2-4 kHz and PTA 8-10-12.5 kHz are shown in Table 2.

However, in individual patients clinically significant threshold shifts were found. The incidence of ≥ 10 dB hearing loss at 4 kHz (AC and BC) and AC 8 kHz was 21%, 13% and 26%, respectively. The incidence of ≥ 10 dB hearing loss at PTA 1-2-4 kHz (AC and BC) and PTA 8-10-12.5 kHz was 13%, 6% and 18%, respectively.

Air-bone gap

Of all ears measured pre-treatment ànd post-treatment at PTA AC ànd BC 0.5-1-2-4 (n=180), 21 (12%) ears developed an (increase in) ABG ≥ 10 dB due to treatment. The inner ears of these ears received higher radiation doses (median 34.4 Gy), compared to other ears (median 10.7 Gy) (Mann-Whitney U test). Tumor site distribution and tumor side (ipsi- or contralateral to tumor) were similar in both groups (p 0.134 and 0.734, Pearson Chi-square test), as were T stage, gender, age and follow-up time (p= 0.024 to 0.313, Mann-Whitney U test).

Subjective complaints

Before therapy, subjective hearing loss and tinnitus were experienced in 25% and 7% of the ears, respectively. After treatment, increased subjective hearing loss and tinnitus were noted in 20% and 10% of the ears, respectively.

Eligibility for Hearing Aids

Of 149 measured ears without an indication for a hearing aid before therapy, 15 ears (10%) were under consideration for a hearing aid after therapy, as they developed an AC > 35 dB HL at frequency PTA 1-2-4 kHz, considered the criterium for reimbursement of hearing aids in the Netherlands.

Table 1. Patient and treatment characteristics (n = 101)

Characteristics			
Age (in years) average (stdev), median		61.3 (12.2), 60.8	
Gender	male	66	
	female	35	
Eye color	brown	20	
	blue	56	
	green	8	
	unknown	17	
Follow-up weeks after termination of RT (median)		9	
Primary tumor site (101)* with inner ear RT dose (Gy)			Gy mean (stdev), median
	skin / face	3	26.1 (25.0), 15.7
	cavum nasi	4	28.2 (12.4), 26.9
	sinus	3	16.4 (15.6), 14.0
	cavum oris	17	14.5 (9.6), 13.1
	oropharynx	22	19.8 (11.7), 17.4
	hypopharynx	2	7.6 (4.7), 7.6
	larynx	28	7.8 (3.1), 7.4
	parotid gland*	17	23.3 (19.3), 12.9
	Other†	5	14.4 (18.1), 8.0
T classification (93)			
	0 (recurrent disease N+)	2	
	1	21	
	2	45	
	3	8	
	4	14	
	x (unknown primary)	1	
	unknown	2	
N classification (93)			
	0	60	
	1	17	
	2	11	
	3	4	
	unknown	1	
Radiation therapy indication	primary radiotherapy	42	
	adjuvant radiotherapy	59	
Overall RT dose to inner ear (Gy)	mean (stdev)	16.2 (14.1)	
	median	11,4	
	range	0.2-69.7	

Note: Numbers are patients, unless otherwise stated * of whom 8 patients with recurrent or irradically excised pleomorphic adenoma (T and N stage not applicable) † lymphnode metastases in the neck (2), thyroid gland carcinoma (2), and submandibular gland carcinoma (1)

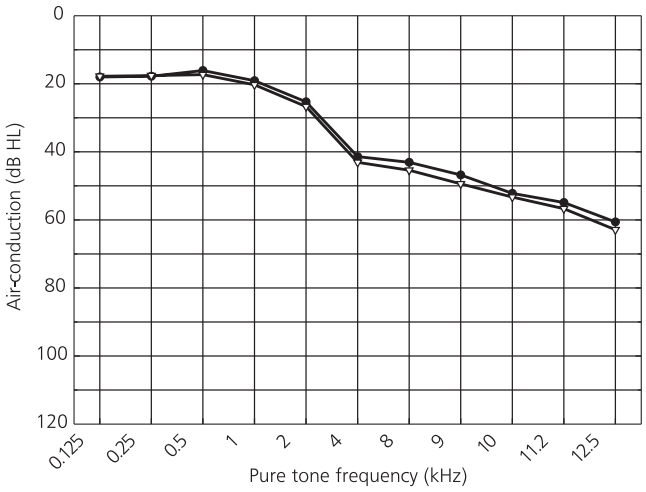


Figure 2. Mean hearing thresholds before (●)and after treatment (∇) of 101 patients (202 ears) treated with Intensity-Modulated Radiation Therapy.

Table 2. Mean hearing thresholds (101 patients, 202 ears)

	PTA BC* 1-2-4 kHz† mean (stdev) median	**PTA AC* 1-2-4 kHz†** mean (stdev) median	**PTA AC* 8-10-12.5 kHz††** mean (stdev) median
Before therapy	24.1 (14.1) 21.7	28.6 (16.9) 25.0	43.7 (17.6) 46.7
After therapy	23.3 (14.4) 21.7	30.1 (19.6) 25.0	46.4 (18.2) 48.3§

*AC = air conduction, BC = bone conduction
†PTA 1-2-4 kHz = Mean threshold at 1, 2 ànd 4 kHz (in dB Hearing Level)
††PTA 8-10-12.5 kHz = Mean threshold at 8, 10 ànd 12.5 kHz (in dB Hearing Level)
§significant difference between pre- and post-treatment hearing level, p< 0.001, Wilcoxon test

Common Terminology Criteria for Adverse Events v3.0 (CTCAEv3.0)

In Table 3 hearing loss is expressed in auditory CTCAE criteria version 3.0 criteria. Considering audiograms including ultra-high frequencies (up to 16 kHz) an increased total incidence of ototoxicity was seen, compared to when the criteria were applied to audiograms including frequencies up to 8 kHz.

Table 3 Common Terminology Criteria for Adverse Events v3.0 for 101 patients treated with Intensity-Modulated Radiotherapy

Grade	**1**	**2**	**3**	**4**	**total incidence**
Audiogram up to 8 kHz	13 (13%)	1 (1%)	10 (10%)	0	24 (24%)
Audiogram up to 16 kHz	28 (28%)	1 (1%)	14 (14%)	0	43 (43%)

Note: numbers are patients

Multivariate analysis

No apparent violations against linearity of the relation between PTA and RT dose was found. Post-treatment PTA was proven to depend on baseline hearing capability (p<0.0001), RT dose (p<0.0001), age (p<0.0001) and colour of the eye (p<0.0001). There was also

some evidence of an effect of follow-up time on post-treatment hearing, depending on the frequency area considered (p=0.0028).

A difference in radiation dose of 15 Gy in the mean population (eye colour brown 25%, blue 65%, green 10%, unknown 18%, age 56 year, baseline at PTA 0.5-1-2-4-8-10-12.5 kHz is 25 dB, 24% women, 1 year FU) resulted in a difference in hearing loss (defined as a percentage difference in (dB+10)) at low frequencies BC and AC of 0.6% (95% confidence interval: –4.5% – 6.1%) and 3.5% (95% CI: -1.9% – 9.1%), respectively, whereas the difference in hearing loss at high (BC and AC) and ultra high frequencies was 3.2% (95% CI: -0.3% – 6.8%), 5% (95% CI: 0.9% – 9.2%) and 10.4% (95% CI: 4.4% – 16.8%), respectively.

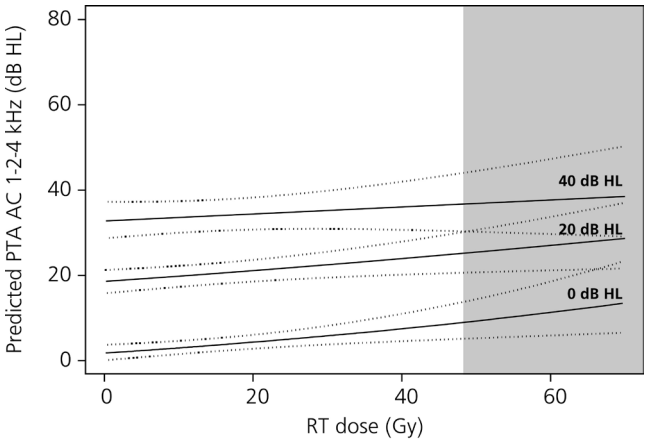
The relative increase in hearing loss (in %) due to radiation therapy was larger in older patients than in younger patients (p<0.0001). Patients with green eyes suffered more hearing loss at all frequencies, compared to patients with blue or brown eyes (p<0.0001). Finally, when patients were characterised with an excellent pre-treatment hearing capability, the relative hearing deterioration was larger, compared to patients with relatively unfavourable pre-treatment hearing (p<0.0001).

Following the multivariate analysis a prediction of post-treatment hearing capability at speech frequencies PTA AC 1-2-4 kHz, 3 months after treatment, was performed and shown in Figure 3. For the mean population, predicted hearing capability (y-axis in dB HL, data back-transformed) and RT dose (x-axis) are shown in figure 3a, containing three curves that represent patients with a pre-treatment hearing capability of 0 dB HL, 20 dB HL and 40 dB HL, respectively. From this figure the predicted post-treatment hearing level in dB HL (with 95% interval of confidence) can be read out, once the baseline hearing level and the intended RT dose are known. At the right side of the x-axis, the confidence intervals (CIs) of the three curves start to overlap, due to the fact that limited number of patients received relatively high radiation doses, and results become less meaningful. Therefore, at the point where the CIs of curves 20 dB HL and 40 dB HL start to overlap, figure 3 was shaded.

The effect of radiation dose on hearing loss in our 8 patients with green eyes (16 ears evaluated), is graphically presented in Figure 3b. Compared to the averaged population presented in Figure 3a, the slopes of the curves belonging to patients with 0 dB HL, 20 dB HL and 40 dB HL pre-treatment hearing capability at PTA AC 1-2-4 kHz are larger, meaning that an equal RT dose increase resulted in an increased hearing loss after therapy (in dB HL) in patients with green eyes, compared to other patients.

Also, in Figure 3, two additional effects are visualized.

Firstly, although patients with good pre-treatment hearing were described above to suffer relatively more hearing deterioration (calculated in percentages), these patients were characterised by less radiation-induced hearing loss in absolute numbers (dB), compared to patients with unfavourable hearing capability prior to treatment. This is clearly illustrated in Figure 3b, as the slope of the 0 dB HL curve is less steep than the slope of the 40 dB HL



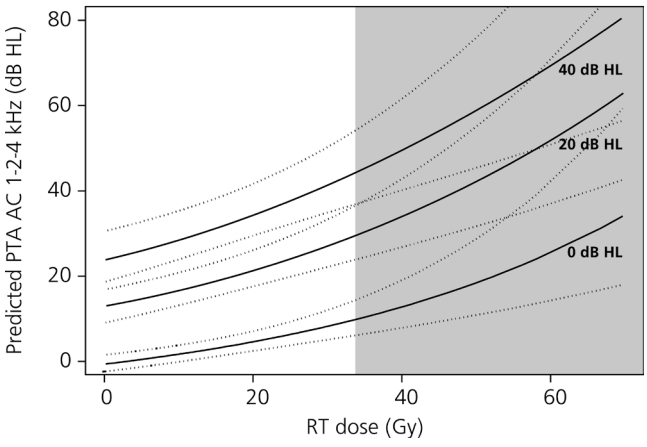


Figure 3. Predicted hearing level (dB HL) 3 months after radiation therapy at PTA AC 1-2-4 kHz, for the whole population (3a), and patients with green eyes (3b). Each figure contains 3 lines for ears with excellent pre-treatment hearing at PTA AC 1-2-4 kHz (0 dB HL), moderate pre-treatment hearing loss (20 dB HL), and severe pre-treatment hearing loss (40 dB HL), respectively. Dotted lines represent the 95% confidence intervals (CIs). Shaded area is part of the figure where CIs started to overlap.

curve, meaning that in patients with good pre-treatment hearing levels an equal increase in radiation dose resulted in less increase in dB hearing loss. The explanation of the discrepancy between a high %-change and a small change of absolute dBs, and the inverse, is, obviously, that a high percentage-change of low pre-treatment hearing levels results in a limited increase in absolute dB, whereas a small percentage-change of high pre-treatment hearing levels results in large increase in absolute dB.

The second additional effect visualized in Figure 3 is that in patients with pre-treatment audiograms of poorer hearing thresholds (40 dB HL), the post-treatment hearing level was favourable compared to the pre-treatment hearing level, in case lower radiation doses were applied. This was explained by regression-to-the-mean (combined with the rather modest effect of the radiotherapy): patients that were measured to have 40 dB HL prior to therapy, probably have more favourable hearing levels at that point in time. Another more theoretical explanation is that pre-treatment hearing problems might partly be cancer related. Radiotherapy may then have even had a beneficial effect on hearing. To test this hypothesis,

the statistical model as described in the Methods section was expanded to include the possibly frequency-dependent effect of the side of the tumor (homolateral or contralateral to the measured ear) including the interaction with RT dose. An overall likelihood ratio test showed no effect of tumor side (p=0.47).

Finally, a relation was found between post-treatment hearing and follow-up time, depending on the frequency area considered (p=0.0028). In general, post-treatment hearing capability at AC and BC PTA 0.5-1-2 kHz and 1-2-4 kHz tended to be constant or to worsen somewhat in the first few months (3-6 months), after which a gradual recovery of hearing occurred (up to 18 months) after which hearing thresholds seemed to stabilize up to our follow-up of 24 months. At ultra-high frequencies, a deterioration of hearing was stabilized at 6 months post treatment. In case of unfavourable pre-treatment hearing capability (40 to 100 dB HL), post-treatment hearing capability at 3 months follow-up was seen to have improved to below baseline hearing level, especially at higher frequencies. At 1 year follow-up, this phenomenon was even stronger.

DISCUSSION

Radiation-induced hearing loss in this study was rather modest, receiving a median inner ear radiation dose of 11.4 Gy. Hearing deteriorated at frequencies vital for speech perception from 28.6 to 30.1 dB HL, and at ultra-high frequencies from 43.7 to 46.4 dB HL. In comparison, other head-and-neck cancer populations treated with multi-modality treatment regimens as high-dose cisplatin chemoradiation, endured mean threshold shifts at PTA 1-2-4 kHz and PTA 8-10-12.5 kHz of 9 dB (SD 12) and 22 dB (SD 18), respectively.[20] In addition, when auditory adverse effects were expressed in CTCAE criteria (applied to audiograms up to 8 kHz) the incidence of ototoxicity in Intensity-Modulated RT was 24%, compared to 78% in high-dose cisplatin chemoradiation. The phenomenon that the extent of (sensorineural) hearing loss due to RT in the current population increased with increasing frequencies, was in agreement with earlier reports.[2-7,9,11]

Nevertheless, within our patient group we found several ears actually suffering clinically significant hearing loss, as 13% and 18% of the ears suffered ≥ 10 dB hearing loss at speech frequencies and ultra-high frequencies, respectively, and 10% of the ears qualified for a hearing aid due to therapy. In our multivariate analysis, risk factors for unfavourable post-treatment hearing were higher radiation dose (p<0.0001), unfavourable baseline hearing capability (p<0.0001), green eyes (p<0.0001), and older age (p<0.0001), which may explain the earlier reported various threshold doses of 24.2 to 60 Gy found in various patient populations.[12-17] In the current study, threshold radiation doses that caused clinically significant hearing loss

(depending on pre-treatment hearing capability) were graphically presented for the mean population and -more specifically- for the subgroup of 8 patients with green eyes.

As far as we know, this is the first clinical study demonstrating an increased sensitivity to radiation-induced sensorineural hearing loss in patients with green eyes. In agreement, a descriptive analysis comparing our green-eyed patients to the whole population showed that other risk factors for increased hearing loss were not present: In our patients with green eyes the median age was 59 years, the median received inner ear radiation dose was 12.1 Gy, and the median pre-treatment hearing capability at PTA BC / AC 1-2-4 kHz and PTA 8-10-12.5 kHz was 20.0 dB HL, 24.2 dB HL, and 47 dB HL, respectively. (for comparison see Tables 1 and 2). As patients with green eyes and unfavourable baseline hearing bear a higher risk for clinically significant hearing deterioration, the radiation dose distribution may be adjusted according to the proposed model, aiming to decrease the risk for treatment-induced hearing loss.

A relation between eye colour and ototoxicity was described in earlier studies concerning intravenously adiministered cisplatin, wherein patients with dark eyes suffered more hearing loss.[21,22] In experimental models, a high-dose of cisplatin reduced the density of melanin in the high frequency region of the cochlea in guinea pigs and thereby reduced the auditory brain stem responses at 30 kHz, suggesting a relation between melanin content and hearing status.[23]

In the current study patients with pigmented (brown) and non pigmented (blue) eyes suffered less treatment related hearing loss, compared to patients with green eyes. It may be that patients with green eyes have a specific composition of cochlear pigment resulting in decreased prevention of cochlear injury or relatively ineffective repair of radiation damage. Although the phenomenon of increased ototoxicity in green eyed patients was highly significant in the current study, we propose confirmation of this finding in a large patient group.

As demonstrated by others in nasopharynx carcinoma[24], a relation between post-treatment hearing and follow-up time after therapy was found, although not statistically significant. At frequencies vital for speech perception (both AC and BC), post-treatment hearing capability tended to be constant or to worsen somewhat in the immediate post radiotherapy period with a gradual recovery of hearing up to 18 months. This can be recovery at the level of the middle and/or inner ear, or improvement of clinical condition. From neuro-oncological literature is known that sensorineural hearing loss may occur immediately, months or years after cranial irradiation with possible (partial) reversibility.[2,6,25,26] The cumulative risk of significant persistent SNHL seemed to stabilize within 2 years, whereas for severe SNHL (>30 dB) the cumulative risk increases through the 3rd and 4th year.[27] Long-term follow-up study of (chemo)irradiated head and neck cancer patients may possibly unravel the prognostic indicators for potential (partial) reversibility or deterioration of hearing capability.

Finally, in this analysis, radiation resulted in less SNHL at speech frequencies, compared to the radiation effect observed in a previous multivariate analysis of our institute concerning

concurrent high-dose cisplatin chemoradiation.[28] On the other hand, at ultra-high frequencies, the effect of RT in the current study was larger than observed in our high-dose cisplatin CRT, as the radiation effect in the CRT regimen may have been masked by the extensive adverse effect of cisplatin at ultra-high frequencies.[28] While radiation-induced vascular insufficiency has been proposed by several authors as the etiology of SNHL,[29,30] in animal models, radiation and cisplatin both affected similar targets in the cochlea as hair cells, stria vascularis and afferent nerve endings, from basal to apical windings with increasing dose.[29-41] Hence, it may be that cisplatin reinforces the adverse effects of radiation on the inner ear. However, a potential synergy of RT and cisplatin can only be proven by a comparison of patients treated with single-modality radiation therapy, chemoradiation, ànd cisplatin mono-chemotherapy.

In conclusion, radiotherapy-induced hearing loss in mean population is rather modest. However, patients with green eyes and unfavourable pre-treatment hearing bear a higher risk for clinically significant hearing loss and, consequently, in these patients the intended radiation dose may be adjusted according to the proposed prediction model, aiming to decrease the risk for treatment-induced hearing loss.

REFERENCES

1. Jereczek-Fossa BA, Zarowski A, Milani F, et al. Radiotherapy-induced ear toxicity. Cancer Treatm Rev 2003;29:417-430.
2. Johannesen TB, Rasmussen K, Winther FO, et al. Late radiation effects on hearing, vestibular function, and taste in brain tumor patients. Int J Radiat Oncol Biol Phys 2002;53(1):86-90.
3. Anteunis LJC, Wanders SL, Hendriks JJT, et al. A prospective longitudinal study on radiation-induced hearing loss. Am J Surgery;168:408-411, 1994.
4. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head Neck 1999;21(6):547-553.
5. Kwong D, Wei W, Sham J, 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 1996;36(2):281-289.
6. 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 2002;65(1):1-7.
7. Oh YT, Kim CH, Choi JH, et al. Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. Radiotherapy and Oncology 2004;72:79-82.
8. Palazzi MP, Guzzo M, Tomatis S, et al. Improved outcome of nasopharyngeal carcinoma treated with conventional radiotherapy. Int J Rad Oncol Biol Phys 2004;60:1451-1458.
9. Wang L, Kuo W, Ho KY, et al. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.
10. Schot LJ, Hilgers FJ, Keus RB, et al. Late effects of radiotherapy on hearing. Eur Arch Otorhinolaryngol 1992;249(6):305-8.
11. Pan CC, Eisbruch A, Lee JS, et al. Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2005;61(5):1393-1402.
12. Merchant TE, Gould CJ, Xiong X, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. Int J Radiat Oncol Biol Phys 2004;58(4):1194-1207.
13. Putten L van der, Bree R de, Plukker JT, et al. Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. Head Neck 2006;28:903-908.
14. Chen WC, Liao CT, Tsai HC, et al. Radiation-induced hearing impairments in patients treated for malignant parotid tumor. Ann Otol Rhinol Laryngol 1999;108:1159-1164.
15. Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 2006;106:820-9.
16. Herrmann F, Dörr W, Müller R, et al. A prospective study on radiation-induced changes in hearing function. Int J Radiat Oncol Biol Phys 2006;65(5):1338-1344.
17. Honoré HB, Bentzen SM, Möller K, et al. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiother Oncol 2002;65:9-16.
18. Cancer Therapy Evaluation Programm, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (http://ctep.cancer.gov). publ date: December 12, 2003.
19. Harrell F. Regression modelling strategies:with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001. p. 24.
20. 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 2007;25(24):3759-65.
21. Todd NW, Alvarado CS, Brewer DB. Cisplatin in children: hearing loss correlates with iris and skin pigmentation. J Laryngol Otol 1995;109:926-929.

22. Barr-Hamilton RM, Matheson LM. Ototoxicity of cis-platinum and its relationship to eye colour. J Laryngol otol 1991;105:7-11.

23. Laurell G, Ekborn A, Viberg A, et al. Effects of a single high dose of cisplatin on the melanocytes of the stria vascularis in the guinea pig. Audiol Neurotol 2007;12:170-178.

24. Low WK, Toh ST, Wee J, et al. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: A single, blinded, randomized study. J Clin Oncol 2006;24(12):1904-1909.

25. Huang E, The BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys 2002;52(3):599-605.

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

27. Grau C, Overgaard J. Postradiation sensorineural hearing loss: A common but ignored late radiation complication. Int J Radiat Oncol Biol Phys 1996;36(2):515-517.

28. 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 2007;68(5):1320-5.

29. Gamble JE, Peterson EA, Chandler JR. Radiation effects on the inner ear. Arch Otolaryng 1968;88:64-69.

30. Winther FQ. X-ray irradiation of the inner ear of the guinea pig. Acta Otolaryngol 1969;68:98-117.

31. Hultcrantz M. Correlation between auditory brainstem recordings and morphology as seen through the scanning electron microscope. Scanning Microscopy 1988;2(3):1125-1131.

32. Hultcrantz M, Anniko M, Borg E. The influence of prenatal gamma irradiation on the ageing of the cochlea. Acta Otolaryngol (Stockh) 1989;108:414-423.

33. Kim CS, Shin S. Ultratsructural changes in the cochlea of the guinea pig after fast neutron irradiation. Otolaryngol Head Neck Surg 1994;110:419-27.

34. Tokimoto T, Kanagawa K. Effects of x-ray irradiation on hearing in guinea pigs. Acta Otolaryngol (Stockh) 1985;100:266-272.

35. Tange RA, Vuzevski VD. Changes in the stria vascularis of the guinea pig due to cis-platinum. Arch Otorhinolaryngol 1984;239(1):41-47.

36. Tange RA. Differences in the cochlear degeneration pattern in the guinea pig as a result of gentamicin and cis-platinum intoxication. Clin Otorhinolaryngol Allied Sci. 1984;9(6):323-327.

37. Van Ruijven MW, De Groot JC, Smoorenburg GF. Time sequence of degeneration pattern in the guinea pig cochlea during cisplatin administration. A quantitative histological study. Hear Res 2004;197(1-2):44-54.

38. Cardinaal RM, De Groot JC, Huizing EH, et al. Dose-dependent effect of 8-day cisplatin administration upon the morphology of the guinea pig cochlea. Hear Res 2000;144(1-2):135-146.

39. Laurell G, Bagger-Sjöbäck D. Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol 1991;20(3):158-167.

40. O'Leary SJ, Klis SF. Recovery of hearing following cisplatin ototoxicity in the guinea pig. Anticancer Res 2002;22(3):1525-1528.

41. Hamers FP, Wijbenga J, Wolters FL, et al. Cisplatin ototoxicity involves organ of Corti, stria vascularis and spiral ganglion: modulation by αMSH and ORG 2766. Audiol Neurotol 2003;8(6):305-315.

Chapter 7

The role of otoacoustic emissions in the monitoring of hearing loss in patients treated with radiation therapy or concurrent cisplatin chemoradiation for head and neck cancer

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ABSTRACT

Objectives:

The aim of the current work was to study the feasibility of using otoacoustic emissions (OAE) in a hearing loss monitoring program for ototoxicity. We studied the relation between pure-tone threshold levels and otoacoustic emission levels in a large population of adults and elderly, prior to, during and after exposure to cisplatin chemotherapy and/or radiation therapy. We also investigated the relation between pure-tone threshold shifts and otoacoustic emission level changes during therapy.

Design:

In total, 264 patients were included in this study. Audiometry and otoacoustic emission recordings were obtained before and after therapy. For a subpopulation op 59 patients undergoing high-dose cisplatin chemoradiation (CRT), audiometry and otoacoustic emissions were recorded also during therapy. The relation between pre-therapy audiometry and otoacoustic emissions was studied performing Receiver-Operator-Characteristics (ROC) analyses. The subpopulation of 59 patients was also followed longitudinally.

Results:

For transient-evoked OAE (TEOAE), the best discrimination between normal hearing and hearing loss could be made by defining hearing loss as an audiometric threshold exceeding α = 30 dBHL averaged for 1-2-4 kHz. The corresponding cut-off TEOAE level was -6.85 dBSPL. The area under the ROC curve corresponding to 30 dBHL was 0.857, indicating moderate test accuracy. The cut-off value of 30 dBHL was in agreement with previous ROC studies for TEOAE and hearing level by other groups. For distortion-product OAE (DPOAE) at 4 kHz, an area under the ROC curve of 0.858 was found for a cut-off value for hearing levels of 25 dBHL, again indicating a moderately accurate test. The corresponding cut-off value for an optimal combination of sensitivity and specificity was –8,80 dBSPL. In terms of sensitivity as well as specificity, DPOAE turned out to be a better diagnostic tool than TEOAE. We performed a follow up of patients treated with high-dose cisplatin CRT schemes based on DPOAE levels.

Conclusions:

ROC analyses showed that both TEOAE and DPOAE level recordings enable to discriminate between normal and deteriorated hearing (defined as hearing thresholds exceeding 30 dBHL for 1-2-4 kHz average and 25 dBHL at 4 kHz respectively) with moderate accuracy. When applying DPOAE in the longitudinal follow up, the very small number of surviving ears however was an indication that, although rather sensitive and specific, follow up with DPOAE is not a very efficient method of monitoring for this combination of population and high-dose cisplatin CRT. For a population with initially better hearing thresholds and/or in the case of a less toxic treatment scheme longitudinal follow up using DPOAE cut-off levels based on baseline recording values may be useful though.

INTRODUCTION

Otoacoustic emissions (OAE) yield a promising instrument in the monitoring of ototoxicity since the emissions are generated by the outer hair cells (OHC) in the cochlea, which are assumed to be the most vulnerable site of otoxicity due to cisplatin[1-3] and radiotherapy (RT)[5-10]. Recording of OAEs does not require the cooperation of the patient tested and does not necessarily require a soundproof room. The emissions are a by-product of the so-called cochlear amplifier. Under the influence of inner hair cell (IHC) generated nerve activity, outer hair cell (OHC) motility generates local amplification of cochlear fluid motion leading to both extra gain for low level stimuli and enhanced frequency resolution. The cochlear fluid motion generated by the OHC activity is radiated backwards through the middle and outer ear and can be recorded as a faint sound in the external ear canal. For more details on the mechanism see e.g. the review on OAEs, their origin, and clinical use by Kemp.[11]

Detectable OAEs for cochlear hearing loss exceeding 30 dB are rare. OAEs are normally very stable over a long time period. Hence, a longitudinal approach, in which individual changes of emission levels are studied over time, may be a promising way to apply OAEs. It should be noted here that cochlear damage may be reflected not merely by a decrease of OAE amplitude but by any change of amplitude. This is due to the fact that OAE generation is based on the presence of imperfections that are even present in the healthy cochlea.[11-12]

Various types of OAEs can be distinguished, based on the evoking stimulus. For clinical use of OAEs, most often click-evoked (transient-evoked, TEOAE) and distortion product (DPOAE) are applied. TEOAE are evoked by repetitive broad-band clicks. The broad-band character of the stimulus causes a substantial part of the cochlea to respond. TEOAE response turns out to be strongest in the frequency 1-4 kHZ. TEOAE are considered to be very sensitive to cochlear damage and may show changes in the spectrum before audiometric threshold shifts can be recorded.[11]

DPOAE are generated by two simultaneous continuous tonal stimuli with typically a frequency ratio $f_1 / f_2 = 1\text{-}1.5$. The nonlinear behavior of the ear generates distortion products of frequencies $f = f_1 - N(f_2 - f_1)$. Particularly the $N=1$ DPOAE ($2 f_1 - f_2$) causes a recordable emission, reflecting the status of the cochlea at the basilar membrane location corresponding to f_2. DPOAE are less sensitive to minor cochlear insult than TEOAE.[11] At the same time, DPOAE are recordable for higher hearing thresholds than TEOAE.[13] Although the frequency specific stimulation in DPOAE may suggest so, DPOAEs do not provide better frequency specificity than TEOAE when applied to monitoring cochlear status.[14] Both recording techniques reflect the intrinsic frequency resolution of the cochlea, which is roughly one-quarter octave.[11]

Locoregional radiation therapy (RT) is a common treatment modality for head and neck squamous cell carcinoma (HNSCC). In addition, concurrent cisplatin chemo-irradiation has proven a benefit in survival and locoregional control.[15-18] However, considerable acute adverse effects due to treatment were reported with a 58% to 81% incidence of hearing loss at frequencies 0.250 to 8 kHz.[17-20] Ototoxicity manifests as tinnitus and/or hearing loss, usually bilateral, irreversible and progressive with increasing cumulative dose. Hearing loss

becomes manifest first in the highest frequencies and with increasing dose starts to affect the thresholds at lower frequencies, gradually compromising speech intelligibility.[19,21,22]

Therefore, prevention and early diagnosis of ototoxicity has become an issue. At the same time there is need for fast and easy audiological diagnostics, also suitable for patients who are too ill to perform pure tone audiometry at the audiology department. The aim of the current work is to study the feasibility of using OAE in a hearing loss monitoring program for HNSCC patients treated with (high-dose) cisplatin CRT or single modality RT.

Previous to this study, otoacoustic emissions were applied for the monitoring of ototoxicity in a number of studies, e.g. focusing on ototoxicity in children during treatment with aminoglycosides[23], cisplatin[24-27] and carboplatin.[28] In many of these studies focusing on children and some studies of adults populations[29] otoacoustic emissions replaced standard pure-tone audiometry in the monitoring. Studies focusing on OAE monitoring during cisplatin treatment in adults are often not longitudinal and most studies are based on relatively small populations, with very diverse types of diseases and treatment protocols. Audiometric follow up is not uniform for all patients. Of the few studies having a longitudinal character most involve small numbers of patients.[30-32] A well-designed, systematic, longitudinal study, based on a substantial adult population (N=66), was carried out by Ress et al.[33] There is little uniformity, over studies, in the way of interpreting emissions and analyzing results. In a number of studies OAEs are reported to serve as an early identifier of ototoxicity, revealing (subclinical) damage to the cochlea prior to the presentation of audiometric hearing loss.[23,25,30,31,34]

In this paper we addressed the following research questions: What is the relation between pure-tone threshold levels and otoacoustic emission levels in a large population of adults and elderly, exposed to (high-dose) cisplatin chemotherapy and/or radiation? What is the relation between pure-tone threshold shifts and otoacoustic emission level changes in the current population of adults and elderly during therapy? Rationale for this was firstly the fact that OAEs monitor cochlear (more specifically OHC) status, which is thought to be a main focus of cisplatin-induced ototoxicity. Secondly, OAEs are considered less demanding to chemoradiation patients with deteriorated physical conditions. It was not the aim of this paper to study the differences in ototoxicity induced by the oncological treatments our patients were subjected to, neither it was to study the effect of dosage on OAE levels.

PATIENTS AND METHODS

Patients

Audiometry and otoacoustic emission recordings were obtained from a total of 264 patients. The median age of the total population was 59,4 years (range 25-93), 66% percent of the total population was male. The age of patients within each group was normally distributed

Group	Therapy	N (patients)	% male	Age (median, range)
I	CRT-IA	36	67	56,2 (35-82)
II	CRT-IV	23	83	58,7 (25-78)
III	CRT-LD	69	68	60,9 (33-85)
IV	RT	136	62	61,1 (32-93)
Total		264	66	59,4 (25-93)

Table 1: population: therapy protocol, age and gender

(Kolmogorov-Smirnov, $p > 0.05$ for all groups). All ears were included in the study, irrespective of pre-existent sensorineural hearing loss (SNHL) or middle ear pathology. Between various treatment groups, introduced below, there were no significant age differences (T-test, $P< 0.05$).

Treatment

The patients (see Table 1) were divided into four groups based on disease and treatment. Group I consisted of 36 patients with a locally advanced HNSCC treated with high dose intra-arterial cisplatin chemoradiation (CRT-IA, four courses of cisplatin (150 mg/m^2 per course on days 1, 8, 15, 22) with sodium thiosulfate cisplatin rescue)**1**. Group II involved 23 HNSCC patients, treated with high-dose intravenous cisplatin chemoradiation (CRT-IV, three cisplatin infusions (100 mg/m^2 per course on days 1, 22, 43) without rescue). 69 HNSCC patients in group III were treated with low dose cisplatin chemoradiation. Cisplatin was given at a dose of 6 mg/m^2 daily, 20-25 days. Group IV consisted of 136 patients with various types of malignancies treated with intensity modulated radiation therapy only (IMRT).

All CRT patients received radiotherapy. Target volume included the primary tumor and the bilateral neck to a dose of 46 Gray (Gy) in 23 fractions. Tumor bearing areas received 70 Gy RT. Since the aim of the present work was to study the applicability of OAE recordings in the monitoring of ototoxicity in the population, we did not exclude patients with middle ear pathology, and/or a history of otological disease, noise exposure or preexistent hearing loss of any kind, realizing that these pathologies influence OAE outcomes. No otoscopy and tympanometry were conducted before the audiometry sessions.

Methods

Behavioral pure tone audiometric thresholds, transient-evoked otoacoustic emissions, and distortion product otoacoustic emissions were recorded prior to start of therapy and median 60 (range 25-754) days after termination of therapy in for all four patient groups. For the CRT-IA and the CRT-IV patients (group I and II) the same audiometric tests were performed

1 From 1999 to 2004, our centre participated in a multicentre phase III randomized trial of intra-arterial supradose cisplatin chemoradiation (RADPLAT) versus intravenously administered high-dose cisplatin chemoradiation for irresectable squamous cell carcinoma of the head and neck.35 The current work is part of a series of papers studying the incidence of hearing loss for various treatment modalities.

after each infusion of cisplatin. Analyses were conducted per ear. Unless stated otherwise, all pure tone thresholds are air conduction thresholds.

Method used for Pure Tone Audiometry

Audiometric thresholds were obtained by trained speech therapists using the standard (manual) Hughson-Westlake technique (ANSI S3.21-1978) on a Madsen Electronics Orbiter 922/2 Clinical Audiometer in a sound proof booth. Telephonics TDH39P headphones were used for the frequencies 0.125, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 kHz**2**. Ultra-high audiometric thresholds (9.0, 10.0, 11.2, 12.5, 14.0 and 16.0 kHz) were recorded using Sennheiser HDA200 headphones**3**. During the audiometry session, pure tone air-conduction (AC) audiometry was performed first, followed by bone-conduction (BC) audiometry (0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 kHz). Occasionally speech audiometry and tympanometry were carried out. For reasons described above, no ears were excluded from the study.

Method and interpretation used for OAE

Both TE- and DPOAEs were recorded using Otodynamics ILO Echoport USB equipment in a quiet though not sound-treated room. OAEs were recorded immediately after pure tone audiometry. For Transient Evoked emissions (TEOAE) the equipment was used in the nonlinear mode, with 84 dBSPL (target) clicks, with duration 80 microseconds and 50 Hz repetition rate. Response rejection level was fixed at 49 dBSPL for all recordings and for all patients. After probe fit check, 260 responses below rejection level were recorded. For five half-octave frequency bands, centered around 1, 1.4, 2, 2.8 and 4 kHz response and noise levels were recorded. Distortion product otoacoustic emissions (DPOAE) were recorded as so-called DP-grams, for each ear, immediately after TEOAE recording, leaving the probe in position. Recording settings used were a fixed frequency ratio f2/f1 = 1.22 with sound pressure levels L_1=65 dBSPL and L_2=55 dBSPL. All equipment options for automatic response detection (based on critical S/N ratios) were switched off. Instead, DPOAE recording for each ear was performed during 120 seconds. DP emission levels lower than –10 dBSPL were all automatically set to –30 dBSPL.

The analysis of OAE data is fundamentally different from that of audiometric thresholds since prior to judging the outcome of the recording one needs to establish the quality of the measure. We propose, for a longitudinal approach of studying OAE results, to formulate three criteria to be used sequentially in the process of data analysis:

2 Telephonics TDH39 headphones were calibrated according to ISO 389-1, Table 2 (ISO/TR 389-1, 1998) using B&K Artificial Ear Type 4153 (IEC 60318). Reference equivalent threshold sound pressure levels relative to 2 x 10-5 Pa are the following (in dB): 125 Hz: 45.0; 250 Hz: 27.0; 500 Hz: 13.5; 1 kHz: 7.5; 2 kHz: 9.0; 3 kHz: 11.5; 4 kHz: 12.0; 6 kHz: 16.0; 8 kHz: 15.5.

3 Sennheiser HDA 200 headphones were calibrated according to ISO 389-5 (ISO/TR 389-5, 1998) using B&K Artificial Ear Type 4153 (IEC 60318). Reference equivalent threshold sound pressure levels relative to 2 x 10-5 Pa are the following (in dB): 9 kHz: 18.5; 10 kHz: 22.0; 11.2 kHz: 23.0; 12.5 kHz: 28.0; 14 kHz: 36.0; 16 kHz: 56.0. In this work we refer to thresholds obtained with this calibration as hearing levels at the ultra-high frequencies.

1. *Inclusion criteria* based on pre-therapy recordings on the basis of which one decides to continue follow up with OAE for this ear or not.**4** The inclusion criteria for both TEOAE and DPOAE levels for ears to be included in the longitudinal follow up in the current study were chosen to be equal to the quality criteria.

2. *Quality criteria* for (baseline as well as) follow-up OAE recordings on the basis of which one determines if the actual OAE recording can be used for diagnostics.
   The quality criteria for a TEAOE recording to fulfill in order to be incorporated in the analysis were (a) 260 recordings below noise rejection level, (b) a stimulus intensity exceeding 80 dBSPL, (c) TEOAE noise level not exceeding the group average noise level plus one standard deviation (after selecting for previous quality criteria), unless TEOAE signal-to-noise ratio (S/N) was positive.
   DPOAE quality criteria were formulated as follows. If DPOAE levels were lower than –10 dB, both emission level and noise level were set to –30 dBSPL by the recording equipment. Since low DPOAE levels can be due to either failed recording or to poor cochlear status, the application of the quality criteria needs to discriminate/separate between these two causes. In order to do so we first applied the following quality criteria: (a) Stimulation levels $L_1 \geq 55$ dBSPL and $L_2 \geq 45$ dBSPL in each frequency band considered (b) recording time of at least 100 seconds. With these criteria we omitted DPOAE recordings with low emission results due to inadequate stimulation due to e.g. poor probe fitting or to incomplete testing. Next, we selected all recordings with noise levels exceeding –30 dBSPL, i.e. all ears for which actually DPOAE emissions > -10 dB were found. For these ears we calculated the average noise level and standard deviation for DPOAE recordings. Thereafter, all ears with noise levels exceeding the average level plus one standard deviation were filtered out. The remaining ears, and the ears for which both emission and noise were set to –30 due to poor response were used for further analysis.

3. *The choice of the outcome measure* that will be used to assess (changes in) OAE outcomes. Outcome measures in this study for both TEOAE and DPOAE are OAE levels in dBSPL.

RESULTS

Due to a poor physical condition, frequently patients could not be tested with OAEs after completing audiometry. See completeness of data tables for the four main treatment groups, Table 2.

4 In a single-recording setup, the inclusion criterion is trivial so that only the second and third criteria need to be formulated. For example in a newborn hearing screening program based on OAE, all newborns are screened, recordings are considered valid if S/N ratio is sufficiently high in a predetermined number of frequency bands (quality) and the outcome measure is 'OAE is present or not'.

CRT-IA (N=72 ears)	Audiometry	TEOAE	DPOAE
Pre therapy	70	**62**	**62**
After 1st infusion	60	46	42
After 2nd infusion	66	47	47
After 3rd infusion	62	40	41
After 4th infusion	50	43	43
After therapy	62	48	46

Table 2a: completeness of audiometry, Transient Evoked Otacoustic Emissions (TEOAE) and Distortion Product Otoacoustic emissions (DPOAE) for the intraarterial cisplatin chemoradiation therapy (CRT-IA) group

CRT-IV (N=46 ears)	Audiometry	TEOAE	DPOAE
Pre therapy	46	36	36
After 1st infusion	38	26	26
After 2nd infusion	42	28	27
After 3rd infusion	28	24	24
After therapy	40	28	28

Table 2b: completeness of audiometry, TEOAE and DPOAE for the intravenous cisplatin chemoradiation therapy (CRT-IV) group

CRT-LD (N=138 ears)	Audiometry	TEOAE	DPOAE
Pre therapy	136	113	114
After therapy	68	49	49

Table 2c: completeness of audiometry, TEOAE and DPOAE for the low-dose chemoradiation therapy (CRT-LD) group

RT (N=272 ears)	Audiometry	TEOAE	DPOAE
Pre therapy	258	236	232
After therapy	188	135	133

Table 2d: completeness of audiometry, TEOAE and DPOAE for the single modality radiation therapy (RT) group

The relation between pure-tone threshold levels and otoacoustic emission levels

TEOAE

In Figure 1 we have plotted individual pre-therapy audiometric thresholds vs. OAE levels at 1, 2, and 4 kHz and for the average values of 1, 2, and 4 kHz, for all ears in this study for which both audiometric data and OAE levels were recorded at baseline and the TEOAE recordings fulfilled the quality criterion.

For all three individual frequency bands and for the frequency average, audiometric thresholds and OAE levels are significantly correlated (1 kHz: n=382 ears, α= -0,44; 2 kHz: n=394 ears, α= -0,47; 4 kHz: n=413 ears, α= -0,50; 1-2-4 kHz: n=388 ears, α= -0,59; Pearson correlation, $p < 0,0001$). The amount of explained variance (R^2) by the linear correlation increases with frequency and is highest for the frequency average 1-2-4 kHz (1 kHz: R^2= 0,19; 2kHz: R^2= 0,23; 4 kHz: R^2= 0,25; 1-2-4 kHz: R^2= 0,34).

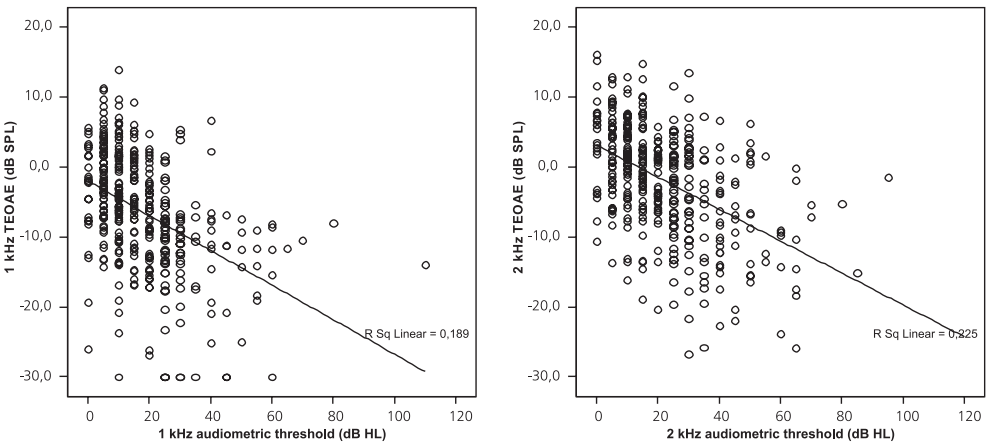

Fig 1 a-b. Audiometric thresholds versus TEOAE levels at 1 and 2 kHz.

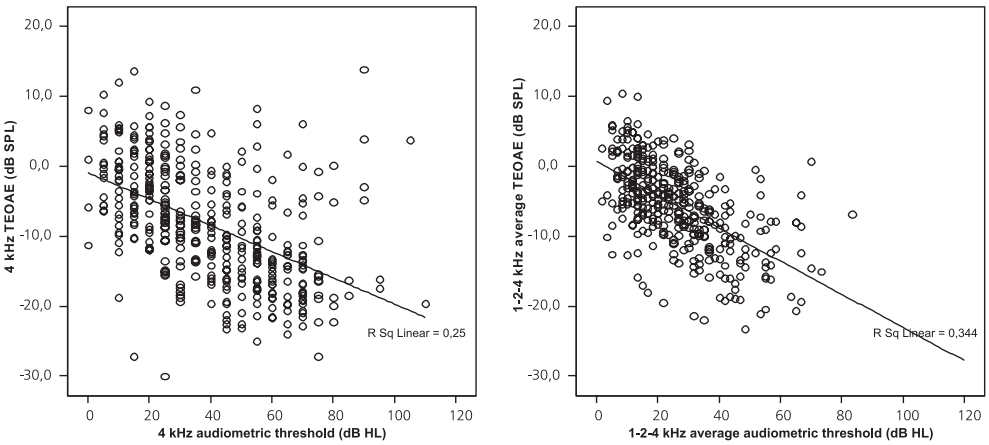

Fig 1 c-d. Audiometric thresholds versus TEOAE levels at 4 kHz and for the frequency average 1-2-4 kHz.

When comparing frequency averaged (1-2-4 kHz) thresholds and otoacoustic emissions in Fig. 1, OAEs seem to be a highly sensitive but not very specific instrument for identifying hearing levels beyond approx 30 dB at a criterion for TEOAE of about 0 dBSPL (Figure 1.d). Comparing bone conduction audiometric thresholds rather than air conduction thresholds did not lead to a clear improvement of specificity (not shown).

Sensitivity and specificity of TEOAE as a diagnostic tool for hearing level were investigated in more detail by a Receiver-Operator-Characteristics (ROC) analysis. Aim of this analysis was to find for which combination of hearing level α, and TEOAE level β, optimal sensitivity and specificity are obtained. The analysis was performed for audiometric pure tone average threshold at 1-2-4 kHz (PTA 1-2-4) and the frequency average TEOAE level at the same frequencies. This was chosen because for the frequency combination the relation between OAE and audiometric threshold the amount of explained variance (R2) is larger than for any of the individual test frequencies, see Fig. 1. Incorporated in the analysis were 388 ears for which PTA 1-2-4 was determined and TEOAE at 1, 2 and 4 kHz were measured and met the quality criteria formulated above. For values of α ranging from 15 to 65 dBHL we calculated ROC curves. The individual curves represent sensitivity versus 1-specificity for values of β ranging from the minimum TEOAE level to the maximum TEOAE level recorded in the

α	Area under ROC curve	St. error	Siginificance	95 % confidence interval	
				Lower boundary	Upper boundary
15	0.778	0.025	< 0.000	0.730	0.827
20	0.793	0.023	< 0.000	0.749	0.837
25	0.805	0.022	< 0.000	0.762	0.849
30	0.856	0.020	< 0.000	0.816	0.895
35	0.848	0.023	< 0.000	0.803	0.892
40	0.844	0.026	< 0.000	0.793	0.895
45	0.818	0.034	< 0.000	0.751	0.885
50	0.779	0.043	< 0.000	0.694	0.864
55	0.784	0.051	< 0.000	0.685	0.884
60	0.754	0.071	< 0.003	0.615	0.892
65	0.706	0.096	< 0.046	0.519	0.893

Table 3. Transient Evoked Otoacoustic Emissions, listing of area under the Receiver-Operator-Characteristics (ROC) curve for various audiometric criteria α. Null hypothesis for significance was "true area under the curve = 0.5".

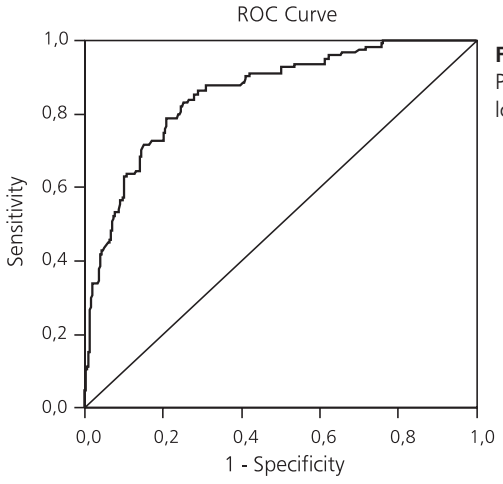

Fig 2. Receiver-Operator-Characteristic for criterion PTA 1-2-4 kHz > 30 dB defined as positive for hearing loss.

population. The area under the curve represents the probability that the TEOAE result for a randomly chosen ear with PTA 1-2-4 > α is smaller than the TEOAE for a randomly chosen ear with PTA 1-2-4 ≤ α. Hence, the value of α for which the maximum area is found represents the hearing loss for which TEOAE are best suitable for discriminating between normal and deteriorated hearing. The maximum area under the ROC curve was found for α=30 dBHL, see Table 3, the concerning curve is shown in Figure 2. Of the 388 ears incorporated in the ROC analysis, 264 (68%) had PTA 1-2-4 ≤ 30 dBHL and 124 had PTA 1-2-4 > 30 dBHL during pre-therapy audiometry.

Further analysis of the curve for α=30 dBHL learns that 100% sensitivity is reached by adopting β=0.65 dBSPL as the TEOAE value for discriminating between normal hearing and audiometric hearing thresholds exceeding 30 dBHL at PTA 1-2-4 kHz. For this choice of β, the percentage ears correctly diagnosed as normal hearing is 24% (64/264 ears) and the false positive percentage is 76% (200/264 ears). When demanding 100% specificity, corresponding to β= -19.95 dBSPL, for only 5% (6/124) ears hearing loss > 30 dB is correctly identified whereas 95% (118/124) with PTA 1-2-4 > 30 dB are misdiagnosed as normal hearing. The optimum value of β corresponds to the point in the ROC curve closest to the upper-left corner of the plot, where the product of sensitivity and specificity reaches its maximum value. For the current ROC plot the optimum value for β is -6.85 dBSPL. When adopting this value to discriminate between normal and deteriorated hearing using TEOAE at 1, 2 and 4 kHz averaged, 79% specificity is found, i.e. 209/264 of the ears is correctly identified as normal hearing. Furthermore, 21% (55/264) of normal hearing ears is misdiagnosed as having hearing loss (false alarm), 21% (26/124) of the ears with hearing loss is misdiagnosed as normal hearing and sensitivity is found to be 79%, i.e. 98/124 of ears with hearing loss is correctly identified.

DPOAE

Scatterplots of DPOAE levels versus audiometric thresholds are shown in Fig.3.a-d for frequencies 1, 2 and 4 kHz, and for the average outcomes at 1-2-4 kHz. Note that DPOAE levels set to –30 due to low-level emission are not shown in the plots but were taken into account in the ROC analysis presented below. Ears for which the DPOAE level was set to –30 due to poor recording were excluded on the basis of the quality criteria (see methods). For all three frequency averages as well as for the frequency average 1-2-4 kHz, Pearson correlation between DPOAE level and pure tone threshold were significant ($p < 0{,}0001$): 1 kHz: n=233 ears, α= -0,26; 2 kHz: n=263 ears, α= -0,41; 4 kHz: n=153 ears, α= -0,58; 1-2-4 kHz: n=108, α= -0,49. The amounts of explained variance (R^2) by the linear correlation were 1 kHz: R^2= 0,07; 2kHz: R^2= 0,17; 4 kHz: R^2= 0,34; 1-2-4 kHz: R^2= 0,24.

A ROC analysis of sensitivity and specificity of DPOAE based on three frequency average could not be performed because the –30 values did not enable to calculate a correct average for all ears. Instead, a ROC analysis for DPOAE levels in the 4 kHz band was performed

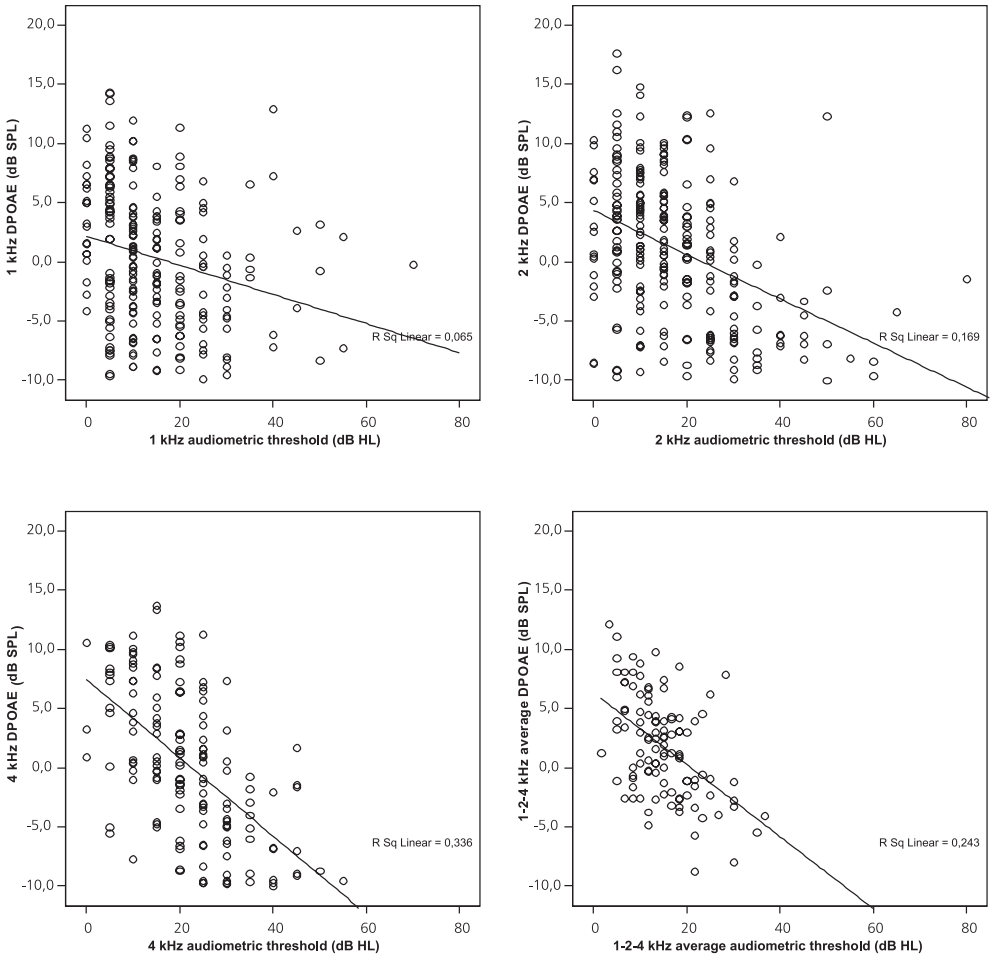

Fig. 3. a-d. Audiometric thresholds versus DPOAE levels at 1, 2 and 4 kHz and for the frequency average 1-2-4 kHz.

(because this is clinically the most relevant frequency for ototoxicity**5** and because the amount of explained variation, based on all values > -30 dBSPL, is larger than for the other frequencies, see Fig. 3.c.). After applying the quality criteria as outlined above, 359 ears were left for further analysis. ROC curves were calculated for values of α ranging from 15 to 65 dBHL. For α=25 dBHL the area under the sensitivity vs. 1- specificity curve was maximal, see Table 4. The curve is shown in Fig 4. Optimal sensitivity and specificity were found to be 0,886 and 0,771 respectively for a DP criterion of –8,80 dBSPL. Of all 359 ears included, 131 ears had an audiometric threshold of 25 dB or smaller in the baseline audiometric session.

5 An ROC analysis for DPOAE in the 1 kHz band was also performed (not shown). The audiometric criterion for which sensitivity and specificity were optimal was found to be 55 dBHL. This is not a clinically relevant criterion for hearing loss at 1 kHz.

α	Area under ROC curve	St. error	Siginificance	95 % confidence interval	
				Lower boundary	Upper boundary
15	0,835	0,032	< 0.000	0,772	0,899
20	0,852	0,026	< 0.000	0,8	0,904
25	0,861	0,023	< 0.000	0,816	0,907
30	0,852	0,022	< 0.000	0,808	0,896
35	0,833	0,022	< 0.000	0,789	0,877
40	0,815	0,023	< 0.000	0,771	0,86
45	0,796	0,023	< 0.000	0,752	0,841
50	0,779	0,023	< 0.000	0,733	0,824
55	0,753	0,025	< 0.000	0,703	0,802
60	0,737	0,027	< 0.000	0,683	0,79
65	0,724	0,031	< 0.000	0,664	0,784

Table 4. Distortion Product Otoacoustic Emissions, listing of area under the Receiver-Operator-Characteristics (ROC) curve for various audiometric criteria α. Null hypothesis for significance was "true area under the curve = 0.5".

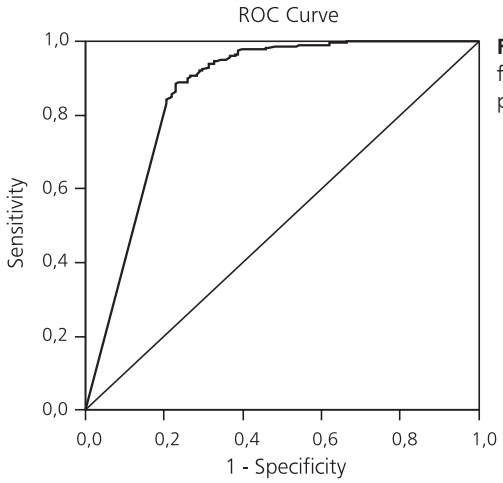

Fig. 4. DPOAE Receiver-Operator-Characteristic for audiometric criterion 4 kHz > 25 dB defined as positive for hearing loss.

('normal hearing'). The remaining 228 ears had a threshold exceeding 25 dBHL ('hearing impaired'). Specificity was 77%, meaning that 101 out of 131 normal hearing ears were correctly identified and 30 ears were tested false positive (normal hearing ears with DPOAE < -8.80 at 4 kHz). Sensitivity of DPOAE at 4 kHz for audiometric thresholds exceeding 25 dB was found to be 89%: out of 228 'hearing impaired' ears a number of 202 was correctly identified ('hits') and 26 hearing impaired ears were missed (11%).

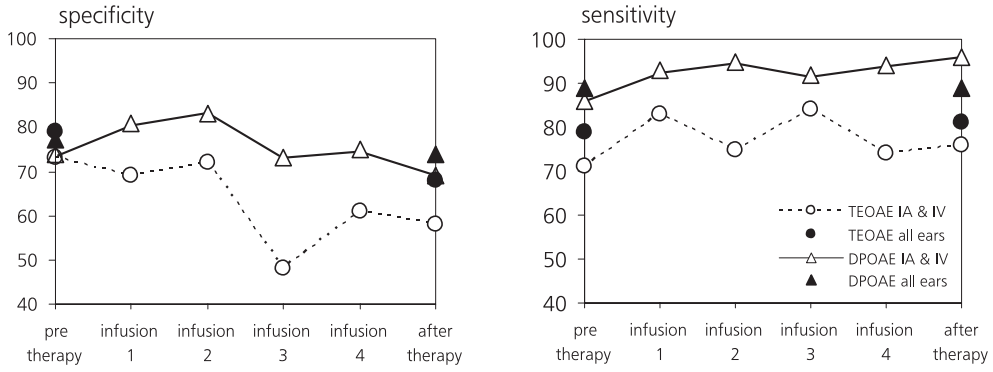

Fig. 5. Specificity and sensitivity of TEOAE and DPOAE during high-dose cisplatin chemoradiation treatment.

The relation between pure-tone threshold shifts and otoacoustic emission level changes

TEOAE

Based on pre-therapy OAE and audiometric data of the complete population, optimal sensitivity and specificity for the use of the 1-2-4 kHz average TEOAE level for the detection of hearing levels at 1, 2 and 4 kHz averaged of 30 dBHL or more was found for a TEOAE cut-off level of -6,85 dBSPL.

Follow up audiometric and TEOAE recordings in patients undergoing high dose cisplatin CRT schemes (combining groups I and II, i.e. the patients who had audiological assessment after each infusion of cisplatin) and for all ears grouped together (pre- and post therapy values only) were judged on the basis of the cut-off values for TEOAE and audiometric thresholds mentioned above. Sensitivity and specificity were plotted as a function of number of infusion in Fig. 5. Average sensitivity and specificity for follow up TEOAE recordings for high-dose cisplatin CRT groups were 77.2% and 63.5% respectively.

DPOAE

Optimal sensitivity and specificity for the use of DPOAE levels at 4 kHz for the detection of hearing levels at 4 kHz exceeding 25 dB was found to be –8.80 dBSPL. Hereafter we refer to this level as the cut-off level for DPOAE at 4 kHz. Follow up audiometric and DPOAE at 4 kHz recordings in the patients enduring high-dose cisplatin CRT (i.e. the patients who had audiological assessment after each infusion of cisplatin) were judged on the basis of the cut-off level. Sensitivity and specificity are plotted as a function of number of infusion in Fig. 5. Average sensitivity and specificity for follow up DPOAE at 4 kHz recordings for high-dose cisplatin groups were 92.7% and 75.8% respectively.

When applying the cut-off criteria retrieved from the baseline recordings of audiometric threshold and otoacoustic emissions, DPOAE at 4 kHz turned out to be both more sensitive

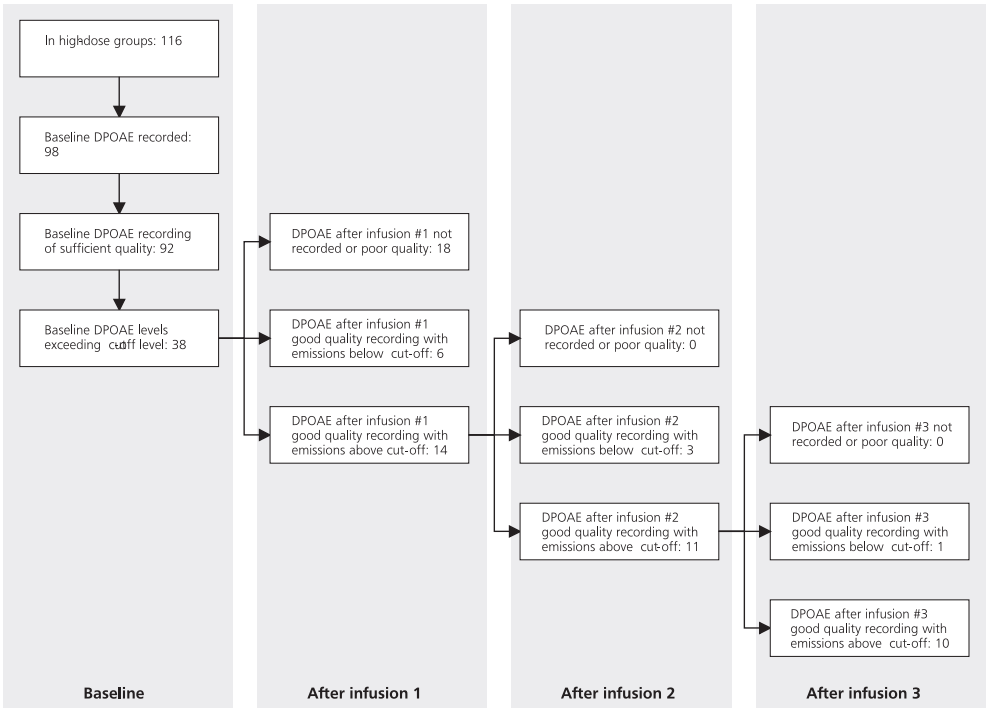

Fig. 6.a. Flow chart of follow up with DPOAE for IA and IV population until after infusion #3.

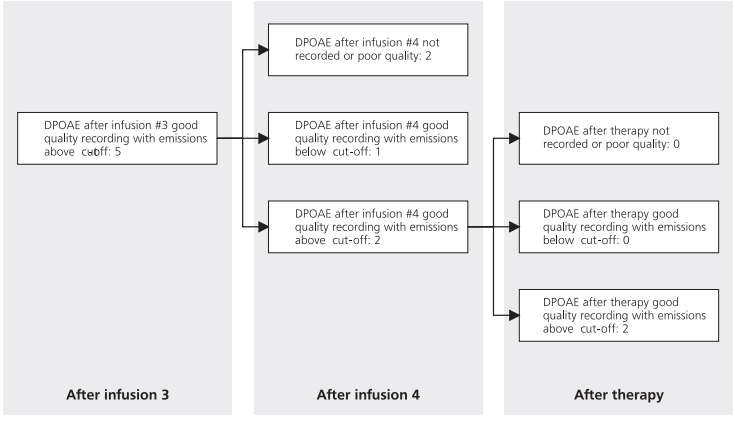

Fig. 6.b. Flow chart of follow up with DPOAE of CRT-IA population after infusion #3.

and more specific for the detection of hearing loss than TEOAE at 1-2-4 kHz. In the following we therefore applied DPOAE at 4 kHz to select, after subsequent infusions of cisplatin for the high-dose therapy groups, the ears that were not (yet) significantly affected by cisplatin induced hearing loss. Fig. 6.a. and b. show flow charts of the follow up with DPOAE at 4 kHz of patients undergoing treatment within one of the high-dose cisplatin treatment schemes (CRT-IA and CRT-IV, group I and II).

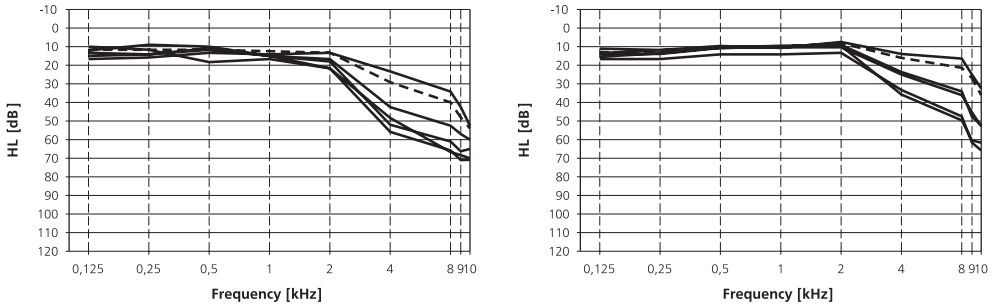

Fig 7.a. Average audiogram after subsequent infusions of cisplatin in high-dose chemoradiation groups I and II. Left panel shows ears (N=6) that had DPOAE at 4 kHz below the cut-off level (-8.80 dB SPL) after first (dashed line) cisplatin infusion (but had DPOAE above this level at baseline). Right panel shows ears (N=14) with DPOAE above the cut-off level after first infusion (dashed line).

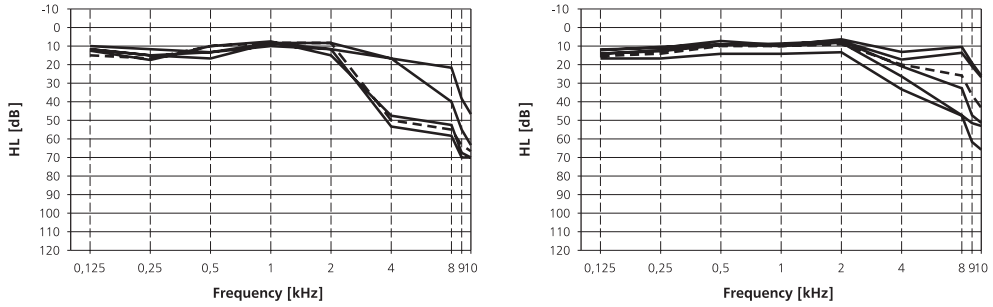

Fig 7.b. Average audiogram after subsequent infusions of cisplatin in high-dose chemoradiation groups I and II. Left panel shows ears (N=3) that had DPOAE at 4 kHz below the cut-off level (-8.80 dB SPL) after second (dashed line) cisplatin infusion (but had DPOAE above this level after the first infusion). Right panel shows ears (N=11) with DPOAE above the cut-off level after second (dashed line) infusion.

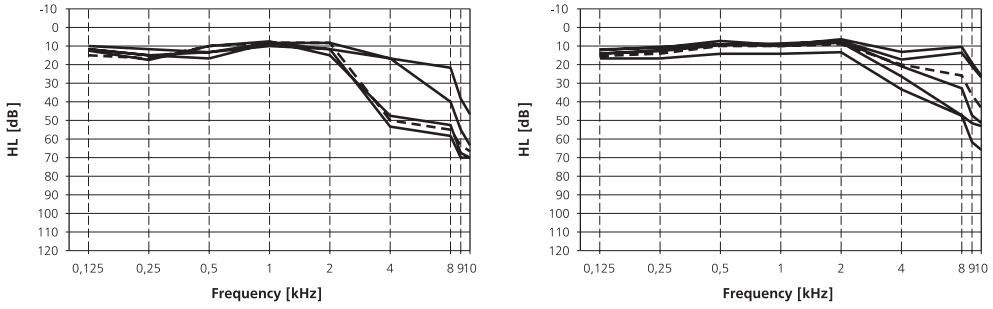

Fig 7.c. Average audiogram after subsequent infusions of cisplatin in high-dose chemoradiation groups I and II. Left panel shows one ear that had DPOAE at 4 kHz below the cut-off level (-8.80 dB SPL) after third (dashed line) cisplatin infusion (but had DPOAE above this level after the second infusion). Right panel shows ears (N=10) with DPOAE above the cut-off level after third (dashed line) infusion.

In the first column of Fig. 6.a. ('baseline') it is shown that a total of 118 ears were involved in these patient/treatment groups. For 98 ears baseline DPOAE at 4 kHz was recorded, 92 of these recordings fulfilled the quality criteria for DPOAE previously formulated (see methods). Of these 92 ears, 38 showed DPOAE levels at 4 kHz above the cut-off level.

In the second column ('after infusion 1'), referring to the situation after the first infusion of cisplatin, of these 38 ears, 18 were lost to follow up because no DPOAE at 4 kHz was recorded or because the recording did not fulfil the quality criteria. Of the ears for which qualitatively good DPOAE at 4 kHz was obtained, 6 ears did no longer have DPOAE at 4 kHz above cut-off level, and 14 still had DPOAE above the cut-off level. Corresponding average audiometry is shown in Fig. 7.a.

In the third column ('after infusion 2') it is shown that after the second infusion for all of these 14 ears qualitatively good DPOAE recordings at 4 kHz were retrieved, 3 ears showed DPOAE levels below the cut-off level, 11 ears had DPOAE levels exceeding this level. Corresponding average audiometry is shown in Fig. 7.b. In the fourth column ('after infusion 3'), referring to the situation after the third infusion, 10 out of 11 ears still had DPOAE above cut-off level and for one ear DPOAE at 4 kHz had dropped below the cut-off level. Corresponding average audiometry is shown in Fig. 7.c.

A fourth infusion of cisplatin was administered only to the CRT-IA patients (group I). A flow chart of DPOAE testing as of the third infusion for this group of patients is shown in Fig. 6.b. After the third infusion, five ears with good quality DPOAE above cut-off level were left (see first column of Fig. 7., 'after infusion 3'). The second column of this figure ('after infusion 4') shows that after the fourth (final) infusion of cisplatin, 2 ears with good quality DPOAE above cut-off level were left, whereas no or no good quality recording was obtained for another two ears and one ears had a good quality DPOAE below cut-off level. The third column ('after therapy') shows that the two remaining ears after the final cisplatin infusion did not deteriorate in terms of the DPOAE cut-off value during the weeks after therapy.

DISCUSSION

It seems tempting to analyze OAE data in a similar way as audiometric data, i.e. by comparison of individual scores (emission strength, signal to noise ratio or (band) reproducibility**6** to an average or standard. A fundamental difference between audiometry and OAEs regards the way the quality of the recording should be judged. We want to stress that judging OAE *quality* is an essential step in OAE monitoring, which should precede the assessment of the OAE *outcome*. Very often though, both steps are taken in one, because both are based on

6 For both OAE types none of the outcome measures show a strong correlation with behavioral audiometric thresholds. Although emissions for cochlear hearing losses exceeding roughly 30 dB are rare, the spread in emission levels is large.[13]

the same outcome measure, e.g. signal-to-noise ratio or reproducibility. We advocate not to use OAE signal-to-noise ratio or (band) reproducibility as outcome measures. An outcome measure should, as much as possible, reflect the status of the system tested. It should, as little as possible, be influenced by incidental, ambient or patient related factors (like breathing noise). Whereas non-patient related ambient noise could be limited by testing in a sound-proof booth**7**, it is not possible to eliminate patient noise. On the contrary: one may expect, especially during a treatment for head and neck disease involving irradiation, patient noise to increase in the course of therapy.

Although we advocate not to use OAE signal-to-noise ratio (or reproducibility) as an outcome measure, it may serve as an inclusion criterion of quality criterion. In that case, accidental noise may compromise the number of ears to be analyzed but it does not affect the results**8**.

TEOAE at baseline

Significant correlations between TEOAE levels and audiometric thresholds were found for the frequencies 1, 2 and 4 kHz and for the frequency average 1-2-4 kHz. However, the amount of explained variance by the linear correlation was low for all frequency combinations. This may be partially caused by some outliers in the TEOAE levels. TEOAE in the higher frequencies were present for a number of ears with audiometric thresholds far beyond 30 dBHL. This can reflect either a missed stimulus artifact or it can be a consequence of auditory nerve pathology. The association between hearing thresholds and TEOAE levels in the current study, in terms of the correlation coefficient α and the amount of explained variance R^2, is in very good agreement with the association found by Engdahl et al.[36] in a study of the relation between hearing levels and OAE involving 6415 unscreened adults. The difference between their and our values of the coefficients mentioned for the frequencies 1, 2 and 4 kHz was in all cases smaller than 0.05.

From a Receiver-Operator-Characteristic analysis we found that the best discrimination between normal hearing and hearing loss could be made by defining hearing loss as an audiometric threshold exceeding α = 30 dBHL averaged for 1-2-4 kHz. The corresponding cut-off TEOAE level was -6.85 dBSPL. The area under the ROC curve corresponding to 30 dBHL was 0.857, indicating a moderate test accuracy according to Swets.[37] This optimal value of α corresponds to a clinical relevant level for discriminating between normal hearing and hearing loss and indicates that TEOAE maybe useful in diagnosing hearing loss. The cut-off value of 30 dBHL is in agreement with previous ROC analyses for TEOAE and hearing level, e.g. 20-30 dBHL[38] and 35-45 dBHL[36].

7 Testing in a booth will cancel one of the potential advantages of using OAE.

8 Note that an effect may occur though, as adopting an inclusion or a quality criterion on the basis of OAE S/N or reproducibility may introduce a bias towards less-noisy patients, who may be suffering less from therapy than patients producing too much respiratory noise to produce an acceptable signal-to-noise ratio.

DPOAE at baseline

For DPOAE the recording at 4 kHz was chosen to be the most suitable for a ROC analysis with an area under the ROC curve of 0.858, indicating a moderately accurate test according to Swets.[37] A cut-off value for hearing levels of 25 dBHL turned out to optimally discriminate between normal and impaired hearing at 4 kHz. The corresponding cut-off value for an optimal combination of sensitivity and specificity was –8,80 dBSPL. Our results concerning DPOAE sensibility and specificity are comparable to those found by Steinhart et al.[13]. Although they used a signal-to-noise ratio rather than emission strength as an outcome measure for DPOAE, similar areas under the ROC curve (i.e. similar test accuracy) for a audiometric cut-off valued 20-30 dBHL were found. The fact that, for their population, the optimal cut-off threshold was found to be 50 dBHL probably reflects the, on average, larger hearing loss at 4 kHz in their population. In other studies lower cut-off values for hearing level were found, e.g. Engedahl et al.[36] found optimal performance for DPOAE when for cut-off hearing thresholds between 35 and 40 dBHL (depending on frequency) and Gorga et al.[39] for values corresponding closely to our result, namely between 20 and 30 dBHL.

TEOAE and DPOAE follow up

The cut-off criteria, derived from the base-line recordings, for audiometric thresholds and OAE levels discussed above were applied to the follow-up recordings of OAE and thresholds. When comparing pre- and post therapy values for the complete population and the high dose-groups (I and II, CRT-IA and CRT-IV) it became clear that the initial cut-off criteria for hearing and OAE levels lead to similar sensitivity and specificity throughout the treatment period, although hearing and OAE levels deteriorated. Note that the drop in specificity after the third infusion may be due to the fact that the number of CRT-IV patients, and especially patients with hearing levels < 30 dBHL, showing up for testing was significantly lower than at other test moments.

In terms of sensitivity as well as specificity, DPOAE turned out to be a better diagnostic tool than TEOAE. By choosing DPOAE as the instrument for performing a longitudinal follow up, hearing loss at 4 kHz was defined to be present for thresholds exceeding 25 dBHL. Although this is a rather low value, potentially leading to classify a relatively high number of ears as hearing impaired, we think that in a monitoring program a low value is to be preferred for reasons of precaution.

Figures 7.a-c- show, after each of the cisplatin infusions 1-3, the average audiogram for the ears that still did and the ears that did no longer have DPOAE at 4 kHz exceeding the cut-off level of -8.80 dBSPL. From this figure it is clear that with a cut-off level for DPOAE at 4 kHz of -8.80 dBSPL DPOAE recordings enable to discriminate between ears that do suffer hardly and ears that do suffer more from ototoxicity in terms of audiometric hearing loss. Qualitatively, DPOAE level recordings seem to be an instrument that may be used to follow-up “surviving ears” during ototoxic treatment. The very small number of surviving ears however is an indication that, although rather sensitive and specific, follow up with DPOAE is

not a very efficient method of monitoring for this combination of population and (high-dose) treatment modalities. For a population with initially better hearing thresholds (e.g. children) and/or in the case of a less toxic treatment scheme longitudinal follow up using DPOAE cut-off levels based on baseline recording values may be useful though. However, a longitudinal setup of a monitoring program in which each patients' individual baseline recordings serve as a reference for follow up diagnostics seems to be a more generally applicable method to incorporate OAE in a monitoring program. We will address this topic in future work.

CONCLUSIONS

In our patient groups treated with single-modality RT or high-dose cisplatin CRT, we have demonstrated that, based on pre-therapy audiometric and OAE data, the relations between audiometric thresholds and OAE levels in our population are similar to those in previously studied populations.[13-36] Furthermore we have shown that, although both audiometric thresholds and DPOAE levels are subject to change due to therapy, the relation between both remains the same in the sense that pre-therapy established cut-off criteria for hearing and DPOAE levels did not lead to significant changes in sensitivity and specificity of testing over time. Having established this, we performed a follow up of patients treated with the high-dose cisplatin treatment schemes (CRT-IA and CRT-IV) based on DPOAE levels. From this follow up we conclude that DPOAE may be useful in the follow-up during ototoxic treatment but that it is of limited value in an elderly population treated with a drug which is known to lead to significant hearing loss. The reason for this is the fact that the number of surviving ears is too low to significantly reduce time for audiometric diagnostics, assuming one wishes to continue the follow up of ears without or with low DPOAEs with conventional audiometry. For this reason our next study on the same population will focus on the development of methods for monitoring based on individual, rather than group criteria for OAE deterioration.

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REFERENCES

1. Tange, R.A. (1984) Differences in the cochlear degeneration pattern in the guinea pig as a result of gentamicin and cis-platinum intoxication. *Clin Otolaryngol Allied Sci*, 9(6), 323-327
2. Van Ruijven, M.W., de Groot, J.C., Smoorenburg, G.F. (2004) Time sequence of degeneration

pattern in the guinea pig cochlea during cisplatin administration. A quantitative histological study. *Hear Res*, 197(1-2):44-54

3. Cardinaal R.M., De Groot J.C., Huizing E.H. et al. (2000) Dose-dependent effect of 8-day cisplatin administration upon the morphology of the guinea pig cochlea. *Hear Res,* 144(1-2), 135-146.
4. Laurell G., Bagger-Sjöbäck D. (1991) Dose-dependent inner ear changes after i.v. administration of cisplatin. J Otolaryngol, 20(3), 158-167
5. Hultcrantz, M. (1988) Correlation between auditory brainstem recordings and morphology as seen through the scanning electron microscope. *Scanning Microscope,* 2 (3), 1725-1737
6. Hultcrantz, M., Anniko, M., Borg, E. (1989) The influence of prenatal gamma irradiation on the ageing of the cochlea. *Acta Otolaryngol*, 108(5-6), 414-423
7. Kim, C.S., Shin, S.O. (1994) Ultrastructural changes in the cochlea of the guinea pig after fast irradiation. *Otolaryngol Head Neck Surg,* 110, 419-427
8. Tokimoto, T., Kanagawa, K. (1985) Effects of X-ray irradiation on hearing in guinea pigs. *Acta Otolaryngol*, 100(3-4), 266-272
9. Winther, F.O. (1969) X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the cochlea. *Acta Otolaryngol* 68(1), 98-117
10. Wright, C.G., Schaefer, S.D. (1982) Inner ear histopathology in patients treated with cis-platinum. *Laryngoscope*, 92, 1408-1413
11. Kemp, D.T. (2002) Otoacoustic emissions, their origin in cochlear function, and use. *Br Med Bull*, 63, 223-241
12. Cevette, M.J., Drew, D., Webb, T.M. et al. (2000) Cisplatin ototoxicity, increased DPOAE amplitudes, and magnesium deficiency. Distortion product otoacoustic emissions. *J Am Acad Audiol*, 11(6), 232-239
13. Steinhart, H., Bohlender, J.E., Bentzien, S. et al. (2001) Clinical relevance of distortion product emissions by means of receiver operating characteristic (ROC) analysis. *Scand Audiol* 30, 131-140
14. Murnane, O.D., Kelly, J.K. (2003) The effect of high-frequency hearing loss on low-frequency components of the click-evoked otoacoustic emission. *J Am Acad Audiol*, 14-9, 525-533
15. Pignon, J.P., Bourhis, J., Domenge, C. et al. (2000) 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*, 355, 949-955
16. Bernier, J., Domenge, C., Ozsahin, M. et al. (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Eng J Med,* 350(19), 1945-1952
17. Cooper, J.S., Pajak, T.F., Forastiere, A.A., et al (2004) Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Eng J Med*, 350, 1937-1944
18. Adelstein, D.J., Li, Y., Adams, G.L. et al. (2003) 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*, 21, 92-98
19. Madasu, R., Ruckenstein, M.J., Leake, F. et al. (1997) Ototoxic effects of supradose cisplatin with sodium thiosulfate neutralization in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg,* 123(9), 978-981
20. Zuur, C.L., Simis, Y.J., Lansdaal, P.E. et al. (2007) 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*, 25(24):3759-65.
21. Zuur, C.L., Simis, Y.J., Lansdaal, P.E. et al. (2006) Audiometric patterns in ototoxicity of intra-arterial cisplatin chemoradiation in patients with locally advanced head and neck cancer. *Audiol Neurootol*, 11(5), 318-330

22. Markman, M., D'Acquisto, R., Iannotti, N. et al. (1991) Phase-1 trial of high-dose intravenous cisplatin with simultaneous intravenous sodium thiosulfate. *J Cancer Res Clin Oncol,* 117, 151-155.

23. Stavroulaki, P., Vossinakis, I.C., Dinopoulou, D. et al. (2002) Otoacoustic emissions for monitoring aminoglycoside-induced ototoxicity in children with cystic fibrosis. *Arch Otolaryngol Head Neck Surg*, 128, 150-155

24. Allen, G.C., Tiu, C., Koike, K. et al. (1998) Transient-evoked otoacoustic emissions in children after cisplatin chemotherapy. *Otolaryngol Head Neck Surg,* 118, 584-588

25. Stavroulaki, P., Apostolopoulos, N., Segas, J. et al. (2001) Evoked otoacoustic emissions – an approach for monitoring cisplatin induced ototoxicity in children. *Int J Pediatr Otorhinolaryngol*, 59, 47-57

26. Toral-Martiñón, R., Shkurovich-Bialik, P., Collado-Corona, M.A. et al. (2003) Distortion product otoacoustic emissions test is useful in children undergoing cisplatin treatment. *Arch Med Res*, 34, 205-208

27. Dhooge, I., Dhooge, C., Geuskens, S., et al. (2006) Distortion product otoacoustic emissions: an objective technique for the screeening of hearing loss in children treated with platin derivatives. *Int J Audiol,* 45(6), 337-343

28. Smits, C., Swen, S.J., Goverts, S.T. et al. (2006) Assessment of hearing in very young children receiving carboplatin for retinoblastoma. *Eur J Cancer*, 42, 492-500

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

30. Beck, A., Maurer.J, Welkoborsky, H.J. et al. (1992) Changes in transitory evoked otoacoustic emissions in chemotherapy with cisplatin and 5FU. *HNO*, 40(4), 123-127

31. Ozturan, O., Jerger, J., Lew, H. et al. (1996) Monitoring of cisplatin ototoxicity by distortion-product otoacoustic emissions. *Auris Nasus Larynx*, 23, 147-151

32. Lonsbury-Martin, B.L., Martin, G.K. (2001) Evoked otoacoustic emissions as objective screeners for ototoxicity. *Seminars in Hearing*, 22(4), 377-391

33. Ress, B.D., Sridhar, K.S., Balkany, T.J. et al. (1999) Effects of cis-platinum chemotherapy on otoacoustic emissions: the development of an objective screening protocol. *Otolaryngol Head Neck Surg*, 121, 693-701

34. Plinkert, P.K., Krober, S. (1991) Early detection of cisplatin-induced ototoxicity using evoked otoacoustic emissions. *Laryngorhinootologie*, 70(9), 457-462

35. Rasch, C.R.N., Balm, A.J.M., Schornagel, J.H. et al. (2006) Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-institutional trial. *ASTRO 2006* (abstract)

36. Engdahl, B., Tambs, K., Borchgrevink. H.M et al.. (2005) Otoacoustic emissions in the general adult population of Nord-Trondelag, Norway: III. Relationships with pure-tone hearing thresholds. *Int J Audiol,* 44(1), 15-23

37. Swets, J.A. (1988) Measuring the accuracy of diagnostic systems. *Science* 240, 1285-1293

38. Hussain, D.M., Gorga, M.P., Neely, S.T. et al. (1998) Transient evoked otoacoustic emissions in patients with normal hearing and in patients with hearing loss. *Ear Hear,* 19(6), 434-449

39. Gorga, M.P., Neely, S.T., Ohlrich, B. et al. (1997) From laboratory to clinic: a large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss. *Ear Hear*, 18(6), 440-450

Summary

Summary

This thesis addresses a number of issues in cisplatin and radiation induced hearing loss in head and neck cancer patients. The main objective of the research presented was to reveal patient and treatment related risk factors for hearing loss and to find a method to predict treatment induced hearing loss prior to the applied therapy. In addition, we aimed to evaluate and describe hearing loss in ototoxic treatment schemes and to make recommendations for refining ototoxicity criteria. Finally, the purpose of this thesis was to evaluate the feasibility of using otoacoustic emissions for monitoring hearing loss in the described treatment regimes.

Hearing loss in cisplatin chemoradiation

In 2000, Pignon performed three meta-analyses on the impact of adding chemotherapy to radiotherapy and proved an absolute 8% increase in 2- and 5-years survival when chemotherapy was administered concomitantly.[1] Since then, concurrent cisplatin chemoradiation (CRT) is increasingly used as primary therapy in locally advanced squamous cell carcinoma of the head and neck (HNSCC)[2,3], or in adjuvant setting after curative surgery of in high-risk HNSCC[4]. Various cisplatin CRT schedules have been evaluated with respect to their tolerability, showing incidence rates of 40% to 89% of non auditory acute adverse events in low (cisplatin 6-10 mg/m^2 daily)[5,6], intermediate (cisplatin 20 mg/m^2 daily for 1-2 weeks or 40 mg/m^2 weekly)[3,7,8], and high-dose (cisplatin 100-150 mg/m^2 weekly)[3,4,9] cisplatin CRT protocols. A consensus about the optimal CRT schedule has not been reached yet.

Cisplatin is well-known to induce sensorineural hearing loss (SNHL), increasing with increasing frequencies and depending on cisplatin dose-intensity[10,11]. In addition, cranial irradiation has shown a 49% incidence of hearing loss directly post-treatment and a 55% incidence of hearing loss 2-8 years after therapy.[12-14] In contrast, detailed information about ototoxicity remains scarce in reports on concurrent chemoradiation.

The first study of this thesis describes a prospective assessment of hearing loss in patients with HNSCC, engaged in a phase II (and part of a phase III) trial conducted in our institution concerning intra-arterial administration of high-dose cisplatin CRT (acronym: Radplat; 4 courses cisplatin of 150 mg/m^2, RT 70 Gy) using sodium thiosulfate (STS) for cisplatin neutralization (see **Chapter 1**). After treatment, 23% of the ears qualified for hearing aids due to therapy. In addition, a multivariate analysis revealed patient and treatment related variables predisposing for CRT induced hearing loss. Cumulative cisplatin dose, cumulative radiation dose, and young age displayed a positive relationship with increased sensorineural hearing loss (SNHL). In addition, it was illustrated that patients with good hearing capability prior to therapy suffered larger CRT induced threshold shifts than patients with unfavourable pre-treatment hearing, which may be (partly) explained by regression-to-the-mean. Nevertheless, in the multivariate prediction analysis, unfavorable baseline hearing level was identified as an independent predictive factor for unfavorable hearing capability after therapy.

Hence, in patient counseling, the attending physician should be aware that young patients with favorable pre-treatment audiograms seem to be more vulnerable for relatively larger CRT induced threshold shifts, compared to patients with unfavourable baseline hearing. The more decibels to lose, the larger the CRT induced threshold shifts may be. Nevertheless, although patients with pre-existent SNHL due to presbyacusis or other types of SNHL in general seem to suffer smaller threshold shifts due to treatment (in dB), they are characterized by worse hearing capability after treatment in (dB HL).

Secondly, in order to predict post-treatment hearing capability at frequencies vital for speech perception prior to the applied therapy, the prediction model of Chapter 1 was formulated and tested for its feasibility (see **Chapter 2**). The formula was shown to have a sensitivity of 77% and a specificity of 92%, indicating that a prediction of hearing loss prior to Radplat is indeed feasible using the presented model. However, simultaneously with our evaluation of the formula, the phase III trial conducted in our institute comparing Radplat with intravenously administered high-dose cisplatin CRT (CRT-IV; 3 courses cisplatin of 100 mg/m^2, RT 70 Gy, without STS) was completed. As the first analysis on clinical outcome of this trial showed no significant difference in loco-regional control or overall survival at two years follow-up, the Radplat protocol was halted[14]. Therefore, although the presented multivariate prediction model seemed promising, it is imperative, in the future, to employ the prediction model to other cisplatin CRT protocols (e.g.CRT-IV). Other limitations of the presented formula are discussed in detail in chapter 2.

The audiometric patterns of hearing loss due to ototoxicity in a large group of consecutive patients uniformely treated with Radplat were described in **Chapter 3**. In agreement with previous literature, a hearing deterioration gradient was observed from (ultra) high to low frequencies, with increasing pre-existent SNHL and with increasing cumulative dose of cisplatin chemoradiation. Interestingly, while in previous reports (partial) recovery of SNHL was described only in individual cases, in our Radplat population partial recovery of hearing after therapy was found in a number of ears. This may also be related to a regression-to-the-mean effect, although in animal models electrophysiological and histopathological evidence was found for hair cell recovery several weeks after cisplatin infusion.

In addition, it was investigated whether cisplatin CRT is confined to induce hearing deterioration up to a certain hearing level or so-called “plateau” at individual frequencies. In a selection of patients, a plateau of approximately 80 and 75 dB HL was found at 8 kHz and 12.5 kHz, respectively, while the maximum output of the audiometer was 90 and 85 dB HL for the respective frequencies. At 2 kHz and 4 kHz, an upper limit to a possible plateau was found to be 45 and 60 dB HL respectively, with maximum output of the audiometer of 80 and 85 dB HL, respectively. It may be that the assessment of the so-called plateau of treatment induced hearing loss at ultra-high frequencies was biased due to proximity of the restricted output of the audiometer. Nevertheless, the maximum treatment related hearing

loss at 2 and 4 kHz was found at lower hearing levels, with a larger separation from the maximum equipment output.

A comparison of hearing loss between cisplatin CRT regimens was presented in **Chapter 4**, concerning the evaluation of hearing loss the a randomized phase III trial comparing Radplat (here called CRT-IA) and CRT-IV. Whether hearing loss differences were revealed, depended on the ototoxicity criteria used. Hearing loss expressed as a percentage change of baseline hearing resulted in favour of CRT-IA. In correspondence, in CRT-IA less ears qualified for hearing aids after therapy (36%), compared to CRT-IV (49%). Moreover, our multivariate analysis showed that the effect of cisplatin was found to be larger in CRT-IV than in CRT-IA. A protective effect of CRT-IA may be explained by the infusion of STS, as previously demonstrated in guinea pigs, where the chemoprotectant and chemotherapy treatment were separated in time and space to avoid a potential reduction of the tumoricidal effect of cisplatin.

However, the incidence of significant hearing loss expressed in CTCAEv3.0 criteria was equal in both treatment arms. Evidently, CTCAE grades 2 and 3 are too coarsely defined and do not allow for (subtle) differences in hearing loss between both treatment arms. Future perspectives are to compose new hearing loss criteria, defined in terms of specific frequency areas of clinical familiar situations: PTA AC 1-2-4 kHz for speech perception in noise, and PTA AC 8-10-12.5 kHz for the early detection of ototoxicity and the perception of ultra-high sounds in nature (e.g. birds singing). In general, a pre-treatment and post-treatment audiogram is indispensable.

Finally, we aimed to assess hearing deterioration due to low-dose cisplatin CRT (daily cisplatin 6 mg/m^2 for 20-25 days, RT 70 Gy) and to compare the observed hearing loss with hearing loss in our previously described high-dose cisplatin CRT cohorts (**Chapter 5**). In low dose CRT, the total incidence of ototoxicity was 31% (CTCAEv3.0, audiograms up to 8 kHz) and 5% of ears tested qualified for hearing aids due to treatment. For a comparison to hearing loss in high-dose cisplatin CRT, we pooled the CRT-IA and CRT-IV patients studied in chapter 4, and calculated the overall incidence of hearing loss in those patients to be 78% (CTCAEv3.0, audiograms up to 8 kHz). This study indicated that low-dose cisplatin CRT for HNSCC is a relatively safe treatment protocol with respect to ototoxicity.

Hearing loss in Intensity-Modulated RT

Radiation therapy, as single-modality treatment or adjuvant to surgery, is a common treatment modality for head and neck cancer. The objective of this study was a prospective assessment of the dose-effect relationship between Intensity-Modulated RT and hearing loss (**Chapter 6**). Radiotherapy-induced hearing loss in the averaged population was rather modest. However, individual patients endured clinically significant threshold shifts and 10% of the ears qualified for a hearing aid due to treatment. In a multivariate analysis, post-treatment hearing capability was proven to depend on RT dose, baseline hearing capability,

eye colour, and age. Following this analysis, a model was presented to predict post-treatment hearing capability at speech frequencies, depending on radiation dose and baseline hearing. Older patients with green eyes and unfavourable pre-treatment hearing bear a higher risk for unfavorable hearing capability after RT and, consequently, the intended radiation dose may be adjusted according to the proposed model, aiming to decrease the risk for treatment-induced hearing loss. However, this is the first study showing an increased sensitivity to radiation-induced SNHL in patients with green eyes. Before routine application, it is safe to seek for confirmation of this finding in a larger patient group.

The feasibility of OAEs in monitoring hearing loss in head and neck cancer patients

OAEs are produced in the cochlea as a by-product of the cochlear amplifier (OHC function) and in **Chapter 7**, TEOAEs and DPOAEs were tested on their feasibility in monitoring treatment induced hearing loss in our populations, as both radiation and cisplatin exert detrimental effects on outer hair cells. In addition, OAEs are normally stable over long time periods (analogous to fingerprints) which makes them potentially suitable for follow-up. However, before OAEs were evaluated on their outcome, we concluded that it is essential to subject the OAE recordings to specific quality criteria, to exclude recordings with low emissions due to inadequate stimulation, probe fitting, or incomplete testing.

Then, firstly, the relation between pure-tone threshold levels and OAE levels was evaluated. Receiver-Operator-Characteristics (ROC) were used to determine for which combination of hearing level and OAE level optimal sensitivity and specificity were achieved. To discriminate between normal hearing and hearing loss, OAE emission levels of –6.85 dB HL (in TEOAE) and –8.8 dB HL (in DPOAE), respectively, corresponded to hearing losses of 30 dB HL at AC 1-2-4 kHz (with TEOAE) and 25 dB HL at 4 kHz (with DPOAE). Secondly, for follow-up of patients during treatment, the relation between pure-tone threshold shifts and OAE level changes was addressed in our populations of high-dose cisplatin CRT. As test accuracy at baseline was highest in DPOAEs, cut-off levels of DPOAEs were used for follow-up during therapy, showing similar sensitivity and specificity throughout the follow-up period. Thus, qualitatively, DPOAEs seem to be an instrument feasible for follow-up. Nevertheless, in our population, after the 1st cisplatin infusion only 15% of ears exceeded the DPOAE cut-off level, leading to a vast majority of patients still in need of pure-tone audiometry monitoring.

In the future, we will focus on longitudinal follow up using DPOAE cut-off levels in populations with initially better hearing thresholds (e.g. children) or less toxic treatment schemes. In addition, a longitudinal setup of a monitoring program, in which each patients' individual baseline recordings serve as a reference for follow up diagnostics, seems to be more generally applicable and may enhance the sensitivity of the monitoring of the hearing status in an individual patient.

References

1. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949-55.
2. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-98.
3. Vega de la FA, Vera Garcia R, Dominguez D, et al. Hyperfractionated radiotherapy and concomitant cisplatin for locally advanced laryngeal and hypopharyngeal carcinomas. Am J Clin Oncol 2003;26(6):550-557.
4. 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 Eng J Med 2004;350:1937-44.
5. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily cisplatin chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-3548.
6. Bartelink H, Bogaert van den W, Horiot JC, Jager J, Glabbeke van M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial. Eur J Cancer 2002;38:667-673.
7. Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. Head and Neck 2006;28:189-196.
8. Beckmann GK, Hoppe F, Pfeundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. Head and Neck 2005;27:36-43.
9. Robbins KT, Vicario D, Seagren S, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. Am J Surg. 1994;168(5):419-422.
10. Aguilar-Markulis NL, Beckly S, Priore R, Mettlin C. Auditory effects of long-term cis-dichlorodiammineplatinum II therapy in genitourinary cancer patients. J Surg Oncol 1981;16(2):111-123.
11. Schweitzer VG. Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 1993;103(4 Pt 2):1-52.
12. Kwong DLW, Wei WI, Sham JST, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Rad Oncol Biol Physiol 1996;36:281-289.
13. Ho WK, Wei WI, Kwong DLW, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head and Neck 1999;21:547-553.
14. Wang LF, Kuo WR, Ho KY, et al. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.

Samenvatting

Samenvatting

Dit proefschrift beschrijft slechthorendheid door cisplatine chemo-radiotherapie of door radiotherapie in patiënten die behandeld zijn voor een plaveiselcelcarcinoom van het hoofd-halsgebied. Het doel van de studie was patiënt- en therapiegebonden risicofactoren voor slechthorendheid op te sporen, en een model te maken dat het gehoorverlies op voorhand kan voorspellen. Slechthorendheid werd beschreven in soort en getal, en aanbevelingen voor toekomstige ototoxiciteit criteria werden opgesteld. Tot slot werd de waarde van otoacoustische emissies geëvalueerd voor (vroeg)diagnostiek van gehoorverlies tijdens behandeling.

Gehoorverlies in cisplatine chemoradiatie

In 2000 werd een meta-analyse verricht die aangaf dat er een 8% toename in 2- en 5-jaars overleving werd waargenomen door het toevoegen van chemotherapie aan radiotherapie voor een plaveiselcelcarcinoom van het hoofd- halsgebied, op voorwaarde van synchroniciteit van beide behandelingsmodaliteiten.[1] Sinds die tijd wordt concomitante cisplatine chemo-radiotherapie (CRT) toegepast als primaire therapie voor plaveiselcel carcinomen van een vergevorderd stadium[2,3], en als adjuvante therapie na chirurgie in geval van hoogrisico maligniteiten[4]. Verschillende studies werden verricht om de fysieke tolerantie van een aantal cisplatine chemoradiatie protocollen te boordelen, zoals lage dosis cisplatine CRT (cisplatine 6-10 mg/m^2 dagelijks)[5,6], intermediaire dosis cisplatine CRT (cisplatine 20 mg/m^2 dagelijks gedurende 1-2 weken of 40 mg/m^2 wekelijks)[3,7,8] en hoge dosis cisplatine CRT (cisplatine 100-150 mg/m^2 wekelijks)[3,4,9]. Hierbij werden acute bijwerkingen met incidenties van 40% tot 89% waargenomen. Een consensus met betrekking tot het optimale behandelschema werd nog niet bereikt.

Het is algemeen bekend dat cisplatine chemotherapie een meestal irreversibele perceptieve slechthorendheid veroorzaakt, die groter is bij hogere frequenties en toeneemt met de cisplatine dosis-intensiteit.[10,11] Radiotherapie van het hoofd- halsgebied veroorzaakt een 49% incidentie van gehoorverlies direct na therapie en een 55% incidentie van gehoorverlies 2 tot 8 jaar na behandeling.[12-14] Desalniettemin is precieze informatie over slechthorendheid tijdens of door concomitante cisplatine CRT zeldzaam.

De eerste studie van dit proefschrift beschrijft een prospectieve beoordeling van slechthorendheid in patiënten met een plaveiselcelcarcinoom van het hoofd- halsgebied, die werden betrokken in een fase II (en deels fase III) trial voor een behandeling met intra-arterieel toegediend hoge dosis cisplatine chemoradiatie (CRT-IA of acronym Radplat, 4 infusies cisplatine 150 mg/m^2, RT 70 Gy) met intraveneus toegediend natrium thiosulfaat om het cisplatine te neutraliseren (**Hoofdstuk 1**). Na behandeling komen 23% van de oren in aanmerking voor een hoortoestel. De multivariabele analyse toonde aan dat cumulatieve cisplatine dosis, cumulatieve radiotherapie dosis, en jonge leeftijd een positieve relatie hebben met perceptieve slechthorendheid na behandeling. Ook werd geïllustreerd dat patiënten met

een goed uitgangsgehoor een grotere gehoordrempel verschuiving doormaken dan patiënten met een ongunstig uitgangsgehoor, hetgeen (ten dele) verklaard kan worden door regression-to-the-mean. Dus, jonge patiënten met een goed gehoor lijken gevoeliger voor een grotere gehoordrempel verschuiving door CRT: Hoe meer decibels te verliezen, hoe meer absoluut verlies er optreedt. Echter, in de multivariabele analyse werd bewezen dat een ongunstig uitgangsaudiogram een onafhankelijke voorspeller is voor een relatief ongunstig gehoor na therapie; Patiënten met een preëxistente perceptieve slechthorendheid (zoals presbyacusis) lijken dus gekenmerkt door een minder grote gehoordrempel verschuiving (in dB), maar eindigen desondanks wel met het meest ongunstige gehoor na behandeling (in dB HL).

Met als doel het gehoor na Radplat op voorhand te voorspellen, werd het voorspellingsmodel van hoofdstuk 1 geformuleerd en getest op zijn klinische toepasbaarheid (**Hoofdstuk 2**). De formule toonde een sensitiviteit van 77% en een specificiteit van 92%. Echter, tijdens deze studie werden de resultaten van de fase III trial bekend, waarin CRT-IA werd vergeleken met CRT-IV (3 infusies intraveneus cisplatine 100 mg/m^2, RT 70 Gy, zonder natrium thiosulfaat). De eerste analyse toonde geen significant verschil in de 2-jaars loco-regionale controle of overleving. Om die reden werd CRT-IA in ons ziekenhuis tot nadere analyse gestaakt.[14] In de toekomst is het van belang om het voorspellingsmodel te converteren naar cisplatine CRT-IV schema's. Andere beperkingen van het voorspellingsmodel zijn in dit hoofdstuk in detail beschreven.

Patronen van slechthorendheid door CRT zijn beschreven in **hoofdstuk 3**. In overeenstemming met de literatuur, werd een gradiënt waargenomen van (ultra) hoge naar lage frequenties, met een toenemende cisplatine CRT dosis en met een toenemend preëxistent perceptief gehoorverlies. In onze populatie werd van een aantal oren een gedeeltelijk herstel van het gehoor vastgesteld na therapie. Hoewel dit kan berusten op regression-to-the-mean, is ook werkelijk herstel een reële mogelijkheid. In eerder bestudeerde diermodellen werden elektrofysiologische en histopathologische aanwijzingen gevonden voor haarcel herstel enkele weken na cisplatine infusie.

In dit hoofdstuk werd ook beschreven of cisplatine CRT onbeperkt slechthorendheid kan veroorzaken, of dat er sprake is van een zogenaamd verzadigingseffect ("plateau"). Op 8 kHz en 12.5 kHz werd in geselecteerde patiënten een plateau waargenomen van respectievelijk 80 dB HL en 75 dB HL. Het kan zijn dat dit plateau veroorzaakt werd door de nabijheid van de maximale output van de audiometer op deze frequenties (90 dB HL en 85 dB HL, respectievelijk). Echter, de maximale behandelingsgerelateerde slechthorendheid op 2 kHz en 4 kHz werd geschat op respectievelijk 45 dB HL en 60 dB HL, bij een grotere afstand tot de grenzen van het instrument (respectievelijk 80 dB HL en 85 dB HL).

Hoofdstuk 4 beschrijft slechthorendheid door cisplatine CRT in een fase III trial waarin patiënten werden gerandomiseerd voor een behandeling van intra-arterieel cisplatine CRT (Radplat of CRT-IA, met natrium thiosulfaat om het cisplatine te neutraliseren) of intraveneus

cisplatine CRT (CRT-IV, zonder natrium thiosulfaat). Afhankelijk van de criteria die werden gebruikt voor ototoxicteit, werd een verschil in slechthorendheid tussen CRT-IA en CRT-IV vastgesteld. Na CRT-IA kwamen minder oren in aanmerking voor een hoortoestel dan na CRT-IV (36% versus 49%) en in onze multivariante analyse werd het ongunstige effect van cisplatine op het gehoor in CRT-IV groter bevonden dan in CRT-IA. Dit kan worden verklaard door een beschermend effect van het natrium thiosulfaat op het gehoor in CRT-IA, zoals ook eerder beschreven werd in diermodellen. Echter, de incidentie van slechthorendheid uitgedrukt in CTCAEv3.0 criteria was gelijk voor CRT-IA en CRT-IV.

Uit onze studie blijkt dat CTCAE graad 2 en 3 te breed gedefinieerd zijn om een subtiel verschil tussen verschillende behandelingsmodaliteiten te kunnen vaststellen. Bovendien is het van belang om de criteria die worden gebruikt om slechthorendheid vast te stellen overeen komen met situaties die voor de patiënt herkenbaar zijn, zoals spraakverstaan in ruis (PTA 1-2-4 kHz) en het beluisteren van hoge tonen in de natuur en in muziek (PTA 8-10-12.5 kHz). In het algemeen geldt dat een uitgangsaudiogram van groot belang is. Andere aanbevelingen voor het opstellen van ototoxicteit criteria werden in dit hoofdstuk beschreven.

Tot slot werd in **hoofdstuk 5** het gehoorverlies ten gevolge van lage dosis cisplatine CRT (dagelijks cisplatine 6 mg/m^2, 20-25 dagen, RT 70 Gy) bepaald en vergeleken met hoge dosis cisplatine CRT (CRT-IA en CRT-IV). In lage dosis cisplatine CRT was de totale incidentie van slechthorendheid 31% (CTCAEv3.0 in audiogrammen tot 8 kHz) en 5% van de oren kwam ten gevolge van therapie in aanmerking voor een hoortoestel. Dit in vergelijking met een overall incidentie in hoge dosis cisplatine CRT van 78%. De conclusie is dan ook dat lage dosis cisplatine CRT een relatief veilige behandeling is met betrekking tot ototoxiciteit.

Slechthorendheid door Intensity-Modulated RT

Radiotherapie (RT) is een belangrijke behandelingsmodaliteit voor plaveiselcelcarcinomen van het hoofd- halsgebied. De slechthorendheid die ontstaat door intensity-modulated RT is in het algemeen zeer beperkt. (**Hoofdstuk 6**). Desalniettemin zijn er individuele patiënten die wel een klinisch significante gehoordrempel verschuiving doormaken en 10% van de oren komt in aanmerking voor een hoortoestel door de behandeling. De multivariabele analyse toonde aan dat het gehoor na therapie afhankelijk is van de RT dosis, het uitgangsgehoor, de oogkleur en de leeftijd. Vervolgens werd vanuit deze analyse een model weergegeven om de therapiegebonden slechthorendheid op voorhand te voorspellen. Oudere patiënten met groene ogen en een ongunstig uitgangsgehoor lijken een groter risico op RT geïnduceerde slechthorendheid te hebben. Bij deze patiënten zou de voorgenomen RT dosis aangepast kunnen worden op geleide van het voorspellingsmodel om het risico op slechthorendheid terug te dringen. Dit is de eerste studie die aangeeft dat er een verhoogde gevoeligheid bestaat bij patiënten met groene ogen voor RT gerelateerde slechthorendheid. Het lijkt verstandig de uitkomsten eerst te valideren in een grotere patiënten populatie, alvorens over te gaan op een klinische toepassing van het voorspellingsmodel.

Otoacoustische Emissies (OAEs)

De werkbaarheid van Distortion-Product OAEs en Transient-Evoked OAEs bij de monitoring van het gehoor tijdens RT en CRT wordt besproken in **hoofdstuk 7**, waarbij de OAEs eerst werden onderworpen aan voorgestelde kwaliteitscriteria om niet adequaat afgenomen emissies te kunnen excluderen.

Eerst werd de relatie bestudeerd tussen conventionele toonaudiometrie gehoordrempels en OAE levels. Receiver-Operator-Characteristics (ROC) werden gebruikt om te bepalen voor welke combinatie van gehoordrempel en OAE level een optimale sensitiviteit en specificiteit werd bereikt. Voor het onderscheid tussen een goed gehoor en gehoorverlies werden OAE emissie levels van –6.85 dB HL (TEOAE) en –8.8 dB HL (DPOAE) gevonden die overeenkwamen met een slechthorendheid van 30 dB HL op AC 1-2-4 kHz (in geval van TEOAE) en 25 dB HL op 4 kHz (in geval van DPOAE).

Vervolgens werd de relatie bestudeerd tussen gehoordrempelverschuivingen in het toonaudiogram en veranderingen in OAE levels tijdens cisplatine CRT. DPOAEs bleken het meest accuraat en toonden gelijke sensitiviteit en specificiteit gaandeweg de behandeling c.q. follow-up. Echter, na de eerste infusie van cisplatine was nog slechts 15% van de oren te vervolgen met DPOAEs. Hierdoor bleef het overgrote deel van ons hoge dosis cisplatine CRT cohort toch nog afhankelijk van conventionele toonaudiometrie. Dit hoofdstuk besluit met gezichtspunten over toekomstige onderzoeksvragen met betrekking tot het gebruik van OAEs bij het monitoren van slechthorendheid tijdens andere ototoxische behandelingsmodaliteiten.

References

1. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949-55.
2. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92-98.
3. Vega de la FA, Vera Garcia R, Dominguez D, et al. Hyperfractionated radiotherapy and concomitant cisplatin for locally advanced laryngeal and hypopharyngeal carcinomas. Am J Clin Oncol 2003;26(6):550-557.
4. 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 Eng J Med 2004;350:1937-44.
5. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily cisplatin chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-3548.
6. Bartelink H, Bogaert van den W, Horiot JC, Jager J, Glabbeke van M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial. Eur J Cancer 2002;38:667-673.
7. Lau H, Brar S, Hao D, MacKinnon J, Yee D, Gluck S. Concomitant low-dose cisplatin and three-dimensional conformal radiotherapy for locally advanced squamous cell carcinoma of the head and neck: analysis of survival and toxicity. Head and Neck 2006;28:189-196.
8. Beckmann GK, Hoppe F, Pfeundner L, Flentje MP. Hyperfractionated accelerated radiotherapy in combination with weekly cisplatin for locally advanced head and neck cancer. Head and Neck 2005;27:36-43.
9. Robbins KT, Vicario D, Seagren S, et al. A targeted supradose cisplatin chemoradiation protocol for advanced head and neck cancer. Am J Surg. 1994;168(5):419-422.
10. Aguilar-Markulis NL, Beckly S, Priore R, Mettlin C. Auditory effects of long-term cis-dichlorodiammineplatinum II therapy in genitourinary cancer patients. J Surg Oncol 1981;16(2):111-123.
11. Schweitzer VG. Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 1993;103(4 Pt 2):1-52.
12. Kwong DLW, Wei WI, Sham JST, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Rad Oncol Biol Physiol 1996;36:281-289.
13. Ho WK, Wei WI, Kwong DLW, et al. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: a prospective study. Head and Neck 1999;21:547-553.
14. Wang LF, Kuo WR, Ho KY, et al. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004;25:168-173.y

General discussion

General discussion

The main concern of physicians and head and neck cancer patients for treatment-induced hearing loss lies in high-dose cisplatin chemo-irradiation, showing a 78% ototoxicity incidence expressed in CTCAE criteria (version 3.0, in audiograms up to 8 kHz). Compared to these high-dose CRT schemes, single-modality RT and low-dose cisplatin CRT are relatively safe treatment protocols, showing 24% to 31% incidence rates of CTCAE graded auditory adverse effects, respectively. Nevertheless, it is important to critically monitor the effects of hearing loss because of its large impact on quality of life.

From this point of view, it is desirable to dedicate the first future studies on finding methods to decrease the incidence of high-dose cisplatin CRT. Interestingly, in the multivariate analysis comparing the two high-dose cisplatin CRT regimens, the adverse effect of cisplatin was found to be larger in CRT-IV than in CRT-IA. This could be explained by a significant extraction of cisplatin by the tumor in CRT-IA, as cisplatin was infused in the nutrient artery of the carcinoma, leaving a lower concentration of systemic cisplatin to induce ototoxicity, when compared to CRT-IV. However, another likely explanation is that the intravenous infusion of sodium thiosulfate (STS, for cisplatin recue, applied only in CRT-IA) indeed partly prevented the adverse effects of systemic cisplatin. In animal models, a significant otoprotective effect of STS was observed when the applications of cisplatin and rescue drugs were separated in space (e.g. intra-arterial, intravenous, or intra-cochlear). Therefore, in the future, we will examine possibilities for a two-route administration scheme for chemotherapy and otoprotective drugs in humans, aiming to increase the inner ear concentration of STS while avoiding a potential reduction of the tumoricidal effect of cisplatin.

In this thesis, prediction models were presented to assess post-treatment hearing capability at frequencies vital for speech perception prior to the applied therapy. In high-dose intra-arterial administered cisplatin CRT (CRT-IA / Radplat), a prediction of hearing loss was feasible using the presented formula, with a sensitivity and specificity of 77% and 92%, respectively. While in previous literature dissimilar hearing loss between patients was frequently ascribed to “individual vulnerability to ototoxicity” without further details, we may have succeeded to capture the greater part of this vulnerability in distinct patient and treatment variables. However, future work should address several important limitations of the formula, aiming to extend its use to other cisplatin CRT regimens and to enlarge its applicability in daily practice. The first priority is to convert the formula to patients treated with intravenously administered high-dose cisplatin CRT (CRT-IV), as this therapy is nowadays considered the standard high-dose cisplatin CRT regimen in our institute. In addition, these patients will benefit from a prediction of hearing loss prior to the applied therapy, as the large number of audiograms obtained per patient in routine audiometric follow-up are to be reduced if successful prediction is achieved.

Another prediction analysis was performed in patients enduring Intensity-Modulated RT. Although in the averaged population radiation induced hearing loss seemed of no clinical significance, in individual subjects significant hearing loss was observed, depending on baseline hearing capability, age, eye color, and radiation dose. Therefore, there is no such thing as a universal radiation threshold dose for ototoxicity, as this radiation threshold dose differs per patient population studied.

Nevertheless, we are the first study group to report on the positive relationship between green eyes and increased radiation induced hearing loss. Therefore, future work should comprehend a larger subset of patients treated with RT to confirm the findings described above, before the prediction model can be integrated in routine RT planning systems. Moreover, if we are able in the future to define relatively save radiation threshold doses for ears of specific patients, it may be wise to first evaluate the effect of possible radiation dose reduction of the inner ear in high-dose cisplatin CRT schemes. The reason for this is, that the results of the research presented in this thesis suggested a synergistic effect for cisplatin and radiation: In concurrent high-dose cisplatin CRT an equal radiation dose resulted in larger hearing deterioration, compared to a similar radiation dose in single-modality RT.

Throughout the research presented, mainly short term follow up was conducted. From previous literature we know that partial reversibility is likely to occur (years) after termination of RT, while in cisplatin induced hearing loss only single cases with partial recovery have been described. In our population enduring high-dose cisplatin CRT, several patients with partial reversibility of hearing loss were observed. These were patients characterized with extensive hearing loss due to treatment, and therefore, the "recovery" may actually be ascibed to regression-to-the-mean. On the other hand, previous experiments in guinea pigs show electrophysiological and hair cell recovery. In our Intensity-Modulated RT patients a (partial) recovery of hearing after treatment was found, although this trend was not considered statistically significant. To assess a potential improvement or deterioration of hearing capability after treatment induced hearing loss, it is imperative to perform long-term follow up studies.

Finally, quality criteria were described for OAEs in monitoring ototoxicity in head-and-neck cancer patients and cut-off levels of emission levels were assessed to discriminate between normal hearing and hearing loss. Thereafter, the feasibility of longitudinal follow-up with OAEs was first evaluated in high-dose cisplatin CRT, aiming to examine whether the large numbers of audiograms performed in our standard monitoring of auditory adverse events (5-6 per patient) in these regimens could be reduced or substituted by OAEs. In this analysis, the use of OAEs appeared not feasible, mainly due to the small number of ears that could still be evaluated with OAEs already after the 1st infusion of cisplatin. Nevertheless, future OAE perspectives are to focus on longitudinal follow up in populations with initially better hearing thresholds (e.g. children) or less toxic treatment schemes (e.g. low dose cisplatin CRT or single-modality RT). If so, we suggest to focus on DPOAEs as these have shown a good

pre-treatment test accuracy and similar sensitivity and specificity throughout the follow-up period.

However, at present, conventional pure-tone audiometry remains the main diagnostic in monitoring hearing loss in head-and-neck cancer patients. In addition, we still consider ultra-high frequency audiometry as the proper audiometric test to be used for an early detection of treatment induced hearing loss, as patterns of hearing loss in the described treatment modalities are characterised by a gradient from ultra-high to low frequencies with increasing cisplatin or radiation dose. In our opinion, it is important to report on PTA AC 1-2-4 kHz and PTA AC 8-10-12.5 kHz in routine auditory monitoring in order to evaluate clinical familiar situations as speech perception in noise and perception of ultra-high sounds as in music or nature. Ototoxicity grading systems should be confined to reasonable grading steps (of 10 to 20 dB threshold shifts) and analyses should be conducted per ear. The results of this study suggest that the CTCAEv3.0 ototoxicity criteria are defined too broadly and need to be adjusted to meet these recommendations.

In my impression, the main contribution of this thesis is that we came to realize that head and neck cancer patients with favorable pre-treatment audiograms may suffer significant treatment related hearing loss, indicating the need of future research for the prevention of ototoxicity. We have determined the extent of hearing loss in various treatment schemes and we have given specific recommendations to improve ototoxicity criteria. In addition, we were able to capture the individual patient and treatment related variables needed for an accurate prediction of post-treatment hearing capability, thereby creating future opportunities to decrease the number of audiograms needed per patient during therapy. Finally, it became clear in what treatment regimens the use of OAEs in auditory monitoring is feasible, provided that specific quality criteria are taken into account.

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Dankwoord

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Curriculum Vitae

De auteur van dit proefschrift is geboren op 5 juni 1972 te Utrecht. In 1990 behaalde zij haar gymnasium β diploma aan de Bataafse Kamp in Hengelo. Van 1988 tot 1991 studeerde zij piano aan het Koninklijk Conservatorium in Den Haag en later het Sweelinck Conservatorium in Amsterdam bij Marcel Baudet. Haar artsexamen behaalde ze in 1999 aan de Universiteit van Utrecht. In 1997 deed zij onderzoek op de afdeling experimentele cardiologie van de universiteit van Syracuse, New York (Professor J Jalife). Van 1999 tot 2000 was zij arts-assistent op de afdeling Hoofd Hals Oncologie van het Antoni van Leeuwenhoek Ziekenhuis te Amsterdam (Prof FJM Hilgers, Prof AJM Balm). Van 2001 tot 2006 werd zij opgeleid tot Keel-, Neus- en Oorarts in het AMC Amsterdam (Prof dr PF Schouwenburg, Prof dr GJ Nolst Trenité, Prof dr WJ Fokkens). Sinds 2006 is zij fellow Hoofd Hals Oncologie en Chirurgie in het VUMC te Amsterdam (Prof CR Leemans). Lotje Zuur is getrouwd met Erik Grimmelikhuysen. Zij hebben twee zoontjes, Servaas (2004) en Philip (2005).