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Original paper

Dose-response relationship and normal-tissue complication probability of conductive hearing loss in patients undergoing head-and-neck or cranial radiotherapy: A prospective study including 70 ears

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ABSTRACT

Purpose: Head-and-neck (H&N) and cranial radiotherapy may cause hearing loss. Little has been published on the dose-response relationship and normal-tissue complication probability (NTCP) of the conductive subtype of hearing loss. The aims were to observe the incidence of hearing loss in patients undergoing non-intensity-modulated H&N or cranial radiotherapy, obtain the relationship between dose and conductive hearing loss (CHL) and test the current Lyman-Kutcher-Burman (LKB) NTCP model parameters.

Methods: The dose-response in the peripheral auditory system (PAS) of 35 patients (70 ears) was prospectively studied using mean dose and the current LKB model parameters. A wide dose range was obtained by conducting the study at a clinic without advanced treatment techniques. The patients underwent routine external-beam treatments following 3D treatment planning. Hearing status was evaluated by pure-tone audiometry one day before the start and one day and 30 days after the end of radiotherapy.

Results: Nineteen ears (27%) experienced hearing loss. Sixteen (23%) had CHL and three (4%) the sensorineural subtype. On average, mean doses of the PAS structures and V95%, V40Gy and V30Gy volumes of the middle-ear planning-organ-at-risk volume (PRV) were significantly greater in ears that suffered CHL. The modelled 50% NTCP of CHL occurred at approximately 30–40 Gy mean dose to middle ear planning organ-at-risk volume.

Conclusions: Incidence of conductive hearing loss in non-intensity-modulated radiotherapy of H&N and brain can be significant. CHL exhibits a dose-effect. This suggests that the PAS should be considered in treatment plan optimization. The LKB NTCP model was reasonably accurate but modifications are indicated.

1. Introduction

Hearing loss is one of the most common normal tissue complications of external-beam radiation therapy (RT) in the head-and-neck (H&N) and cranial region [1,2].

This type of toxicity has been categorized into conductive hearing loss (CHL), sensorineural hearing loss (SNHL), or a combination of these two types (mixed hearing loss). CHL is an acute effect. If it occurs, this typically happens within a few weeks after the start of RT and lasts until about four weeks after the end of the course. In contrast, SNHL is a long term effect usually lasting for months or years. The causes of CHL include damage to the outer (external) ear, tympanic membrane or middle ear, which can impair the conduction of sound waves from the middle to the inner ear. SNHL is caused by damage to the inner ear, which can adversely affect nerve conduction from the cochlea [3–9].

The risk of SNHL after RT is relatively well documented [10], whereas little has been published on the dose–response relationship and normal tissue complication therapy (NTCP) of the conductive subtype of hearing loss.

Moreover, the role of radiobiological modelling in the decision making and optimization process in treatment planning is increasing. Regarding the RT side effect of hearing loss, the parameters for the radiobiological models of SNHL are also better known than for CHL. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) publications have not covered CHL either [10]. There is, therefore, a need for studying the dose-response and NTCP of CHL, especially as hearing loss can have a negative effect on a patient's quality of life.

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The aims of this study were (i) to observe the incidence of hearing loss in patients undergoing non-intensity-modulated H&N or brain RT for whom at least one treatment field was incident on at least one part of the peripheral auditory system (PAS) (i.e., inner, middle or external ear), (ii) to obtain the relationship between CHL and mean dose to the inner, middle and external ear, and (iii) to test the current parameters of the Lyman-Kutcher-Burman (LKB) radiobiological model for estimating the NTCP of acute hearing loss against the incidence observed in patients. The incentive for carrying out this study was that the resulting information can be useful in assessing the need for considering the dose to any part of the PAS as organ-at-risk when optimizing treatment plans and can also provide supporting data for reliable implementation of radiobiological modelling in treatment planning decision making.

2. Patients and methods

2.1. Patients

This study was carried out prospectively on patients referred to the AK Hospital for H&N or cranial RT during 2014 and 2015. Forty six patients whose treatment fields included at least one beam incident on part or all of the PAS were entered into the study. The final study group included both ears of 35 patients (70 ears).

Patients with permanent SNHL (n = 1) or permanent CHL (n = 0) in at least one ear prior to RT were excluded from this study. Also, patients who had tumour invasion into the ear or had a recurrent disease (n = 2) were excluded. Further, patients who did not complete all three stages of hearing loss assessment for any reason were also excluded (n = 8). The patients' treatments followed the clinic's routine regimens and were not affected by this study, apart from the additional audiometry tests (paid for by research project funding). The study was approved by the University's Ethics Committee. Every patient completed an informed consent form.

2.2. Treatment planning and delivery

The treatment planning and delivery was carried out following the routine procedures in the clinic. All patients were CT scanned for 3D treatment planning. The planning CT slice thickness was 3 mm. The treatment planning was carried out on an Isogray version 4.1 system (Dosigray, France). The system had passed a national dosimetry audit using an inhomogeneous phantom. The same radiation oncologist contoured each gross tumour volume or clinical target volume, which was grown in 3D by 3–5 mm to obtain the planning target volume (PTV). For the purposes of this study, the inner ear, middle ear, and external ear were contoured separately as OARs, and each was grown by a 3 mm 3D margin to produce the corresponding planning organ-at-risk volume (PRV).

CT-based dose calculations were performed using the collapsed-cone convolution superposition algorithm. Because of the fairly small sizes of the OARs, the highest available dose calculation matrix resolution of $2 \times 2 \times 2\,mm^3$ was used. Prescribed doses were in the range 30–72 Gy, delivered 1.8–2.0 Gy per fraction. Relatively simple beam geometries involving three or two beams with conformal multileaf field shaping were planned. Forward plan optimization was carried out based on dose-volume histogram (DVH) data and inspection of isodoses such that the PTV was covered by the 95% isodose in the plans. OAR physical dose values such as mean, minimum and maximum doses as well as the DVHs and the V95%, V40Gy and V30Gy (volumes receiving 95% of the prescription dose, 40 Gy and 30 Gy, respectively) were recorded.

All patients had customized thermoplastic immobilization. The treatments were delivered with 6 MV, 10 MV and/or 15 MV photons of a single Elekta linear accelerator.

2.3. Audiometry

For each patient, threshold hearing assessment was carried out once before the commencement of RT and twice (one day and 30 days) after the end of the course of RT. Pure-tone audiometry assessments were performed by a specialist on all patients in a soundproof testing room at a single centre. Left and right ears were tested separately and analysed independently. Air conduction thresholds were measured at frequencies 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz and bone conduction thresholds at 0.5, 1, 2 and 4 kHz. Audiometric data were accessible in dB units.

Hearing loss was assigned a grade based on the widely used Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [11]. This system defines four degrees of hearing loss classified according to the hearing loss threshold in the sound frequencies of 1–8 kHz:

Grade 1: Threshold shift of 15–25 dB averaged at two contiguous frequencies in at least in one ear, or a subjective change in hearing.
Grade 2: Threshold shift of > 25 dB averaged at two contiguous frequencies in at least in one ear.
Grade 3: Threshold shift of > 25 dB averaged at three contiguous frequencies in at least in one ear.
Grade 4: Profound bilateral hearing loss (> 80 dB at 2 kHz and above).

2.4. NTCP modelling

To obtain NTCP values from the physical dose distributions, the well-established LKB model [10] included in the BioSuite software (version 12) was used [11]. NTCP can be calculated using the following set of equations:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \tag{1}$$

$$t = \frac{EUD - TD_{50}}{mTD_{50}} \tag{2}$$

$$EUD = \left(\sum_i v_i D_i^{1/n} \right)^n \tag{3}$$

where *EUD* is the equivalent uniform dose, *TD50* is, for a homogenous dose distribution, the dose to the organ at which 50% of patients are likely to experience the complication, *m* is the parameter related to the standard deviation of *TD50* describing the steepness of the dose-response curve, *n* is the parameter indicating the volume effect of the organ, D_i is the dose in bin *i*, and V_i is the fractional volume in bin *i* [12–15].

For each ear, the differential DVH files of the structures of interest, exported from the treatment planning in a comma delimited CSV format, were imported into BioSuite. Various parameters including total prescribed dose and number of fractions were also entered into the program. There is little data on the model parameters needed to calculate the NTCP of CHL. Here, the currently available parameters for acute hearing loss resulting from dose to middle and external ear were used in the LKB model. The parameters were as follows: *TD50* = 40 Gy, *m* = 0.15, *n* = 0.01. The computed values of EUD and NTCP were then individually displayed and recorded for each structure.

2.5. Statistical analysis

Statistical analyses of the physical parameters, degree of hearing loss, type of complication, clinical factors, etc. were performed using the IBM SPSS software version 16 in consultation with a statistician. Depending on the required statistical analysis, the tests carried out were Kruskal-Wallis H, Chi Square, Mann-Whitney, Friedman or T-test. A p-value < 0.05 was considered statistically significant.

Table 1
Summary of the patients and their treatments.

Characteristic	Value
Total number of patients and ears	35 and 70
Sex	
Male	22 (62.9%)
Female	13 (37.1%)
Age (years)	
Mean, range	52.6, 24–81
Tumour sites	
Brain	18 (51.4%)
Nasopharynx	4 (11.4%)
Oropharynx	5 (14.3%)
Oral cavity	1 (2.9%)
Pituitary gland	3 (8.6%)
Skin	4 (11.4%)
Stage	
Nonmalignant	3
I/II	10
III	12
IV	10
Treatment	
RT alone	18 (51.4%)
RT + cisplatin chemotherapy	17 (48.6%)

3. Results

3.1. Patient results

Table 1 summarizes the characteristics of the patients' cancers and their treatments. They included T1-T4, N0-N3, M0 diseases.

The mean age of patients was 52.6 years (range 24–81 years). The mean age of the patients who experienced hearing loss was 56.5 years, and for patients who did not suffer this complication, it was 49.9 years. However, there was no statistically significant difference in age between the two groups of patients ($p = 0.201$). There was no statistically significant difference in hearing loss between the male and female patients either ($p = 0.238$).

Seventeen patients (48.6%) also received chemotherapy (cisplatin-based) as part of their treatment (nine patients concurrently, five prior to RT and three following RT). However, there was no statistically significant difference between the occurrence of hearing loss and treatment with or without chemotherapy ($p = 0.226$). The percentage of patients having chemotherapy was not equal among the different tumour sites (50% for brain and 30–100% for the other sites). Among the ears included in the study, the site of tumour also had no statistically significant influence on the occurrence of hearing loss ($p = 0.338$).

Table 2 summarizes the number of $0.6 \times 0.6 \times 3\,mm^3$ CT image voxels and $2 \times 2 \times 2\,mm^3$ dose calculation elements contained in each structure of interest in a typical patient. Inner ear was the smallest but still typically included more than 60 dose elements and 460 image voxels.

Table 2
The number of $0.6 \times 0.6 \times 3\,mm^3$ CT image voxels and $2 \times 2 \times 2\,mm^3$ dose calculation elements contained in each structure of interest in a typical patient's treatment plan.

Structure	Volume (cm^3)	Voxels	Dose elements
External ear	2.2	2037	275
External ear PRV	11.3	10,463	1413
Middle ear	0.7	648	88
Middle ear PRV	4.1	3796	513
Inner ear	0.5	463	63
Inner ear PRV	2.5	2315	313

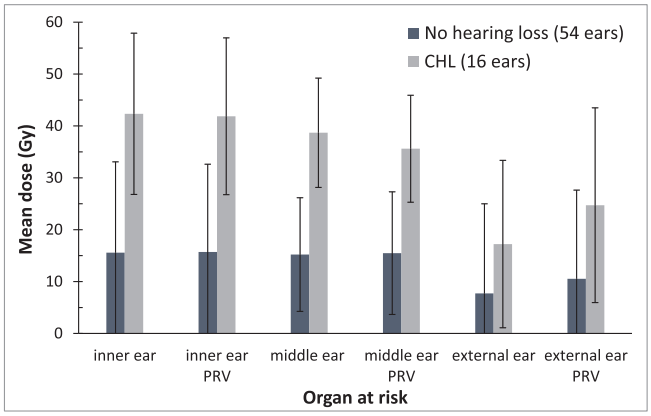

Fig. 1. Mean doses to the auditory organs-at-risk and their PRVs averaged over the patients, showing no hearing loss ears versus those suffering from CHL. Error bars indicate one standard deviation.

Out of the 70 ears studied, 19 ears (27%) suffered hearing loss. Sixteen ears (23%) had CHL and three ears (4%) the sensorineural subtype ($p < 0.05$). All hearing losses were of Grade 1.

The timing pattern of the observed hearing losses was as follows. Ten ears (belonging to eight patients) had CHL one day after the end of the course of RT that recovered 30 days later. Three ears (belonging to three different patients) did not have CHL one day after the end of RT but had it 30 days later. Also, three ears (belonging to three different patients) had CHL at both tested time points.

The observed incidences of hearing loss in the different sound frequency ranges were as follows: 14 at the high frequency range (4–8 kHz), five at the medium range (1–2 kHz) and two at the low range (0.25–0.5 kHz). Five ears suffered hearing loss at both high and medium frequency ranges.

Fig. 1 shows the mean doses of the inner, middle and external ear and their PRVs, averaged over the patients showing no hearing loss versus those experiencing CHL. On average, the mean doses of all of the OARs shown were higher in those ears that suffered hearing loss ($p < 0.05$). There were also statistically significant differences between the mean doses in the studied auditory structures in patients with and without CHL a day, 30 days, and both a day and 30 days following the end of RT ($p < 0.05$(. In contrast, there was no statistically significant relationship between the mean doses and the timing of the occurrence of CHL ($p > 0.05$).

Table 3 compares the average V95, V40 and V30 volumes of the middle ear PRV between the group of patients who suffered CHL and those who did not.

The observed cumulative incidence of CHL as a function of mean dose to the middle and external ears and their PRVs are shown in Fig. 2. The dose values were grouped into 10 Gy bins. The incidences are plotted as a percentage of the total number of ears in this study. It can be seen that in the majority of the cases, the same probability of incidence corresponds to higher mean doses to the middle ear than to the external ear (the curves for the middle ear are shifted to the right of the external ear).

Table 3
The V95%, V40Gy and V30Gy volumes of the middle ear PRV averaged over the patients suffering from CHL and the group without complication ($p = 0.001$).

Parameter	No CHL (cm^3)	CHL (cm^3)
V95%	0.52	2.28
V40Gy	0.47	2.25
V30Gy	0.74	2.52

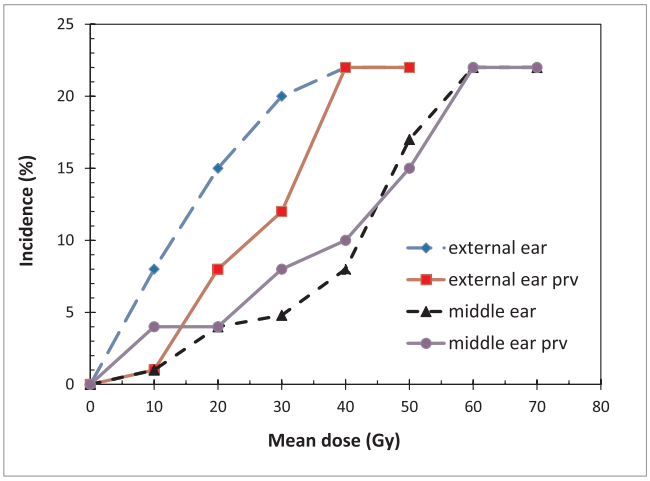

Fig. 2. The observed cumulative incidence of CHL (in percentage of the total number of ears in the study) as a function of mean dose to the middle and external ears and their PRVs.

3.2. NTCP model results

The calculated hearing loss NTCPs produced by the LKB model are shown in Fig. 3 as a function of mean dose to the middle ear PRV for all the 70 ears in this study. The scatter in the data points are due to the fact that the NTCP values are plotted as a function of mean dose (not EUD; to facilitate a direct comparison with the observed data) as well as differences in total prescription dose and dose per fraction among the patients. Fig. 4 shows the same NTCP data plotted as a function of EUD, exhibiting a better sigmoid relationship as expected, as well as a wide and reasonable distribution of dose-effect points from the ears in this study.

4. Discussion

Although CHL is an acute side effect that is often reversible, it can affect a patient's quality of life for a number of weeks. The primary aim of this study was to obtain further patient data and clinical evidence on the dose-response relationship regarding CHL. Our data (Figs. 1 and 2) provide further clinical evidence on the existence of a dose effect for this treatment complication. The patients that developed CHL on average received 2.2–2.7 times higher mean doses to their PAS compared to those who did not ($p < 0.05$). As mentioned previously, one of the aims of this study has been to quantify the dose-effect relationship for CHL, a little-studied deterministic effect of ionizing radiation. For deterministic effects, if the doses are very low (below the threshold) or very high (in the plateau or saturation region), doubling or even

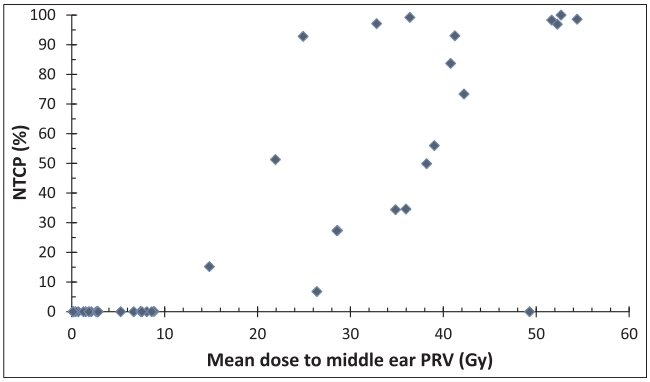

Fig. 3. NTCP values for acute hearing loss for all 70 ears calculated by using the LKB model, plotted as a function of mean dose to the middle ear PRV.

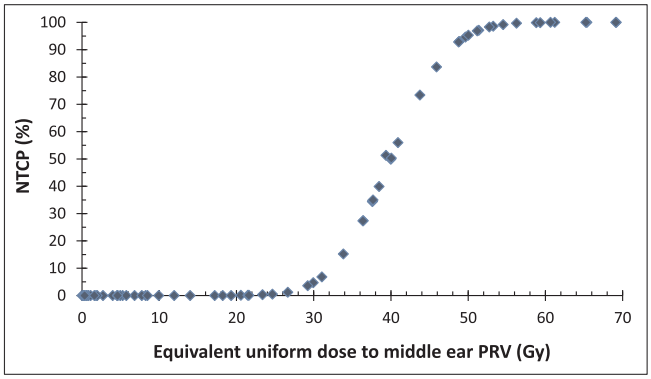

Fig. 4. NTCP values for acute hearing loss for all 70 ears calculated by using the LKB model, plotted as a function of EUD to the middle ear PRV.

tripling the dose may not lead to much difference in the observed effect. The results of this study provide clinical evidence that, for the range of doses shown, there is a clear increase in CHL if mean dose to middle ear is higher by a factor of about 2.5.

The 27% hearing loss in patients' ears represents the added burden attributable predominantly to RT dose, because patients who already suffered from hearing loss of any kind had been excluded from the study and also, the probability of age-related hearing loss occurring within the typically 2.5 months duration of this study per patient is very small. More frequent and longer follow-up PTA may have slightly increased this percentage but that was impractical due to limitations in patient co-operation. Of course, if patients with other causes of hearing loss are also considered, the percentage of patients who undergo RT while experiencing hearing impairment is greater than this 27% figure.

In a recently published paper, an incidence rate of 18% for hearing loss was reported in H&N cancer patients treated with RT (with or without temodal chemotherapy) [16]. The relatively small discrepancy from the 27% finding in the present study may be due to differences in doses to the PAS (stemming from differences in patient selection criteria and the RT technique used) as well as the chemotherapy regimen.

Nearly half of the patients included in our study had cisplatin-based chemotherapy as part of their treatment. Cisplatin-based chemotherapy has been reported to have damaging effects in the inner ear, notably on the hair cells of the cochlea, that can lead to SNHL [17]. We, however, found no statistically significant difference in the incidence of CHL with or without chemotherapy. This may be explained by the fact that CHL is caused by effects in the middle and external ear rather than the inner ear.

CHL accounted for 84% of the hearing losses in our study. The predominance of CHL over SNHL within the follow-up period of 30 days after the end of RT is as expected due to the acute nature of CHL.

To obtain a good level of information on the dose-response curve and NTCP of an OAR in a prospective study, it is desirable to have a wide range of low to medium to high probabilities in the occurrence of the complication in question. In our study, this in turn necessitated that the group of patients entered into the study represented a wide range of doses to the PAS. The patient group in this study included various tumour sites (brain, oropharynx, nasopharynx, skin, pituitary gland and oral cavity) with a wide range of PTV volumes (36.6 cm^3 to 1405.9 cm^3). While patients nowadays benefit from an increasing use of advanced RT techniques and the consequently better conformal avoidance of critical structures, acquisition of scientific/clinical data on the effects of high doses on OARs have become more and more difficult due to ethical concerns [18]. This hinders studies that aim to gain insight into the dose-response and NTCP modelling of such organs. Therefore, this study was carried out at a clinic that, at the time of the study, did not have access to IMRT but instead, had the required patient treatment planning and delivery capabilities to perform 3D-planned RT.

As the routine techniques in the clinic were used, in terms of the design of the study, the required dose range was therefore ethically available. Of course, as advanced techniques offer the capability of sparing OARs from high doses and inducing side effects, direct clinical relevance of the results of this and other similar studies somewhat diminishes. However, such studies can still be of interest because (i) inclusion or exclusion of an OAR as an objective in inverse planning optimization depends on the knowledge of the expected severity of the effect and its relative importance in the possible dose range, and (ii) studying dose-effect relations are scientifically informative in terms of further understanding the biological effects of ionizing radiation and its mathematical modelling.

In all of the patients that experienced hearing loss in this study, the complication was of Grade 1. Eustachian tube edema and secretory otitis media have been found to be the main causes of CHL in early stages and CHL has been reported to be mostly reversible [9,19,20] Our data also showed that the condition is usually reversible. Only three ears showed CHL both one day and 30 days after the end of RT, while 10 ears recovered from CHL during the first post-RT month. CHL can, however, be permanent if atrophy caused by inflammation or necrosis of bone of the middle ear or narrowing of the external auditory canal occur [21].

CHL can be caused by radiation dose to the middle and external ears. It has been reported that up to 40% of patients have acute middle ear side effects during radical irradiations that include the PAS [17]. The most common reaction is otitis media due to transient edema and dysfunction of the Eustachian tube. These are caused by tumefaction of the mucosa and blockage within the cartilaginous part or at the pharyngeal orifice of the Eustachian tube [22]. The chronic inflammatory response in the mucosal lining of the middle ear and Eustachian tube may lead to chronic CHL [1,19]. If the function of the Eustachian tube does not return to normal, and the negative pressure in the middle ear becomes sufficiently high, transudation from the engorged capillaries of the mucous membrane will occur. The presence of effusion in the middle ear cleft can further irritate the mucosa, resulting in metaplasia of the normal epithelium into pseudostratified, columnar ciliated epithelium with an increased number of mucus-secreting cells. Due to mucus secretion, the originally liquid transudate transforms into a glue-like deposit. As a result, CHL occurs [1].

Apart from ionizing radiation, hearing loss can occur due to other causes such as age or noise, which mostly belong to the SNHL category. Age-related hearing loss can occur due to nerve synapse degeneration in the cochlea followed by hair cell damage and loss. In noise-induced hearing loss, synaptic connections between the auditory nerve and the hair cells can be affected [23].

In this study, hearing deterioration was mostly observed at high sound frequencies. SNHL is known to occur mainly at high frequencies. Different structures in the cochlea have different sensitivities to radiation. The basal cells of the cochlea (responsible for the higher frequencies) are more sensitive than the surrounding cells and this could be why SNHL occurs at higher frequencies [24]. Therefore, various RT techniques to reduce dose to the cochlea have been investigated [25]. As for CHL, detailed reasons for this tendency require further investigation.

We considered left and right ears of an individual as two independent organs. The same strategy has been used in several other studies [24,26–28]. On the other hand, in a study conducted around the same time as this investigation, CHL was assessed based on air conduction and using a statistical analysis method that considered the correlation between paired organs [16]. While a correlation between paired organs can be important in some diseases, we believe that it is a reasonable assumption that CHL can be considered independently in each ear of a person, due to the local and mechanical nature of conductive hearing and the fact that the position of the tumour and the selected beam geometry can result in substantially different doses to a patient's two ears.

In the present study, only two patients experienced CHL in both ears. This number is too small to draw any conclusions on whether having CHL in one ear increases the susceptibility of the other ear to this complication.

Radiobiological models can be useful for examining the dose-response relationship in tissues, as they attempt to include the biological effects of the physical dose distribution. We, therefore, tested the current best-estimate model against our observed data from the patients. Applying the current LKB model parameters to the middle ear PRVs, an NTCP of 50% for the endpoint of CHL occurred at 40 Gy EUD (Fig. 4) and approximately 30–40 Gy mean dose (Fig. 3). The corresponding curve in the patients' observed cumulative incidence of CHL (Fig. 2) shows that an approximately 40 Gy mean dose to the middle ear PRV resulted in an incidence half of the maximum observed rate (for very high doses). So there is some level of agreement between the model's prediction in this respect and the observed data.

Our data on the observed cumulative incidence of CHL versus mean dose to the auditory structures (Fig. 2) showed no distinct threshold dose, although incidences generally exhibited a fairly sharp increase above 10–20 Gy mean dose. Following statistical analysis, it was found that the lowest mean dose that caused CHL was 5.6 Gy to the middle ear, 5.7 Gy to the middle ear PRV, 2.8 Gy to the external ear and 2.9 Gy to the external ear PRV. The NTCP model results indicated a threshold mean dose to the middle ear PRV in the range 9–15 Gy (about 25 Gy EUD). These findings suggest that the model predicts a higher threshold dose for CHL than we observed.

Within the studied parameters, we found no differences between the characteristics of the patients who experienced CHL with mean dose of < 20 Gy to middle ear PRV and those for whom a > 20 Gy dose was required to cause this complication. For instance, there was no statistically significant difference in age between the two sub-sets of patients (59 years versus 51 years, respectively; $p = 0.334$).

We used mean organ dose to represent the dose to each part of the PAS in this study. This seems reasonable due to the fairly small sizes of these structures and the usually low dose gradients. Moreover, if we consider the middle and external ear as having a more parallel structure with regards to conductive hearing, mean dose becomes even more representative [29]. On the other hand, the small value of the volume effect parameter ($n = 0.01$) currently available for acute hearing loss, which was also used in the LKB NTCP model here, assumes a highly serial structure. The volume effect in PAS structures with respect to CHL requires further investigation.

In addition to mean dose, on average, the volumes of V95%, V40Gy and V30Gy were also higher in the middle ear PRVs of those ears that suffered hearing loss ($p = 0.001$). The V95% index was chosen to represent the volume of the OAR that was part of the ICRU50 treated volume (the volume of tissue receiving at least 95% of the prescription dose). The V30Gy and V40Gy indices were selected as these dose are lower- and upper-bound values of the mean dose range in which 50% NTCP was observed. This suggests that the mean dose and the dose-volume indices agree. In contrast, there was no statistically significant difference between the mean volume of the middle ear PRV structure itself in the CHL and the group without complication ($p = 0.111$).

Ideally, to reduce uncertainties in delineation of the fairly small OARs in this study, carrying out intra- and inter-observer reproducibility studies would have been preferable. That approach was practically outside the scope of this study. Instead, the contours were drawn carefully by an experienced radiation oncologist using an atlas as a reference [30]. To achieve better consistency in contouring between different patients, all contours were drawn and later reviewed by the same radiation oncologist.

As previously mentioned, according to CTCAE4, Grade 1 hearing loss constitutes a certain threshold shift in PTA or a subjective change in hearing. Thus, any patients with only subjective hearing impairment should be included in the statistics. We based our assessments on PTA (the current gold standard) but did not conduct a separate quantitative

evaluation of subjective hearing impairment. However, no patient with normal PTA subjectively complained of hearing impairment in their weekly clinical examinations.

Radiobiological model parameters have to be obtained from fitting their predictions with experimental data [12,31–33]. At this stage, the number of patients studied is not sufficiently high to try fitting the LKB model with our patient data in order to derive a new set of model parameters. To that end, a study is underway to obtain hearing loss data for a larger group of patients.

5. Conclusions

This study provides dose-response information for CHL with a wide range of mean doses to the structures in the PAS. Our results add further evidence that the incidence of CHL in the range of doses that patients receive in non-intensity-modulated RT for H&N or brain cancer is significant. Given the effects on the patients' quality of life, this suggests that the auditory system should also be considered in treatment plan optimization. This study also provides further clinical evidence on the existence of a dose effect for CHL. Finally, the LKB model parameters provided a reasonably accurate NTCP curve although some modelling aspects require further study and improvement.

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Declaration of conflict of interest

The authors declare that they have no competing interests.

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