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ORIGINAL ARTICLE

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

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ABSTRACT

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

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

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

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

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Background

The ototoxic side effect of Cisplatin Based ChemoTherapy (CBCT) is well known and has been documented in numerous studies, mainly based on pure-tone audiometry or self-reports in questionnaires [1–9]. CBCT affects hearing primarily in the high frequencies and there are studies, particularly from pediatric patients, suggesting that ototoxic damage can progress over several years after treatment [9–14]. However, there are few long-term studies on ototoxicity in survivors after adult-onset cancer who have undergone CBCT, and to the best of our knowledge, only two with 2–3 decades follow-up [15,16].

The reported incidence of CBCT related ototoxicity varies greatly depending on the diagnostic criteria used. The highest incidence (up to 80%) is reported in studies which, based on pure tone audiometry, define ototoxicity as hearing loss at one single frequency, most often within the high frequency range [3,7–9,17]. The clinical relevance of such solitary high-frequency loss (HFL) can be questioned on the background of the much lower prevalence of self-reported hearing loss (20–30%) [9,18,19].

Pure tone audiometry is a useful tool for detecting ototoxic damage both during and after CBCT. The pure tone average (PTA) refers to the average of hearing thresholds at the frequencies most important for speech perception. Although PTA provides an indication of expected speech perception, which is a clinically important outcome, PTA does not assess speech perception directly. Thus, specific tests are needed. Further, speech perception is different in quiet and in noisy conditions. Speech audiometry is a test of word recognition, often performed together with pure tone audiometry. Both are performed in quiet conditions and thus do not

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match real life conditions. Difficulties with speech perception in noise is a common problem among patients with high-frequency hearing loss, experienced both after CBCT and with Age-Related Hearing Loss (ARHL). Comparative studies are therefore needed to evaluate the true impact of CBCT on long-term hearing and speech perception. However, studies reporting long-term speech perception after adult-onset cancer are lacking.

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

Material and methods

Patients

This study is based on the third round of a longitudinal, national multicenter, long-term follow-up survey of TCS treated in Norway between 1980 and 1994 (Norwegian Testicular Cancer Project 1998: NorTeCaP-1998) [11,13,17,18,20–26]. The three surveys (S1 [1998-2001]; S2 [2007/2008]; S3 [2016/2017]) included questionnaires, clinical examination, and blood sampling. Surviving patients who had participated in the preceding round were invited to participate in the subsequent round. At S3, patients participated in a comprehensive hearing test panel including pure tone audiometry, basic speech audiometry, and tests of hearing in background noise and quiet conditions. Due to financial restrictions, only patients living in our health-care region were invited for extended audiological testing.

Controls

We constructed a study-specific age-matched control group consisting of 30 males. They were initially randomly identified from the LiRe project, where individuals >18 years living in the Norwegian county Lier were invited to participate in a public health survey [27]. However, after having tested 19 Controls, we could no longer justify inviting healthy persons to the hospital due to the SARS-Cov-2 situation. We therefore supplemented with 11 age-matched male healthcare workers including nurses, doctors and radiographers since these were already working in the hospital.

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

Treatment

Patients were staged according to the Royal Marsden Hospital staging system, and treatment followed protocols of either the Swedish-Norwegian Testicular Cancer Project or the European Organization for Research and Treatment of Cancer Genito-Urinary Group [28–31]. Patients with metastatic disease received three or four cisplatin-based cycles, most often CVB (cisplatin, vinblastine, bleomycin) or BEP (bleomycin, etoposide, cisplatin) with a standard cisplatin dose of 100 mg/m^2 per cycle [32]. A few patients, those treated during the early eighties, received higher per-cycle cisplatin doses [33]. Patients with recurring disease typically had >4 cycles. Two cycles of CBCT were given as adjuvant therapy after primary removal of retroperitoneal lymph node metastases [34]. No patients had supradiaphragmatic radiotherapy.

Audiometry

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

To rule out conductive hearing loss (which is not likely to be related to ototoxicity), bone conduction thresholds, which reflect the inner ear function, were measured if air conduction thresholds exceeded 20 dB HL at any frequency. The pure tone average (PTA) of air conduction thresholds at; 0.5, 1, 2 and 3 kHz was calculated. PTA, and absolute thresholds for 4, 6 and 8 kHz were adjusted for age-related hearing loss (ARHL) by using age-matched data from the general male population in Norway, obtained from the HUNT-II study [35,36]. Age-adjusted hearing thresholds were calculated by subtracting the expected ARHL from the absolute threshold. Hence, negative values were obtained for patients with hearing thresholds better than the age-matched general population. Age-adjusted hearing loss was defined as an age-adjusted threshold >20 dB at any frequency. Basic speech audiometry according to validated Norwegian standards (ISO 8253-3) was performed routinely for each ear following pure-tone audiometry. This test evaluates the perception of standardized monosyllabic words in quiet conditions.

Hearing in Noise Test (HINT)

A widely used test of speech perception in noise in clinical practice is the Hearing in Noise Test (HINT) [37,38].

Normative data from young adults with normal hearing are reported for several languages including Norwegian [39,40]. To the best of our knowledge, no normative data for elderly people has been published in any language to date.

Speech perception in noise was assessed in all participants with the Norwegian version of HINT [40]. Testing was performed in an anechoic chamber under headphones using the HINT Pro SW Bio-logic® in which the source locations were simulated for speech and noise. Three noise conditions were used: Noise Front (NF, 0°), Noise Right (NR, 90°) and Noise Left (NL, 270°) with sentences always presented from the front (0°) (Figure 1). The noise level was fixed at 65 dBA, whereas the speech level varied according to the listener's response on the previous sentence [37]. The resulting score represents the ratio between the speech level and noise level, the signal-to-noise ratio (SNR) expressed dB SNR. The test estimates the SNR at which the listener can repeat 50% of the sentences correctly. Increasing SNR values reflect worse speech perception, negative values mean that speech can still be understood although noise is louder. For the noise conditions, the HINT score is expressed as dB SNR. Additionally, speech perception in quiet was assessed, using the same procedure but without noise (HINT Q) and hence the score represents the speech reception threshold (SRT) in quiet, expressed in decibels (dBA) at which 50% of the sentences are repeated correctly.

Questionnaire

All Cases completed a comprehensive questionnaire which included the validated Scale for Chemotherapy-Induced Neurotoxicity (SCIN) [18]. All participants scored their hearing ability based on two questions: 'Do you suffer from reduced hearing?' and 'Do you suffer from reduced hearing in noisy environments?' Alternative responses were: 0= 'Not at all'; 1= 'A little'; 2= 'Quite a bit'; and 3= 'Very much'. Self-reported hearing loss was defined as a score ≥2.

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

Statistical analyses

Data were analyzed using SPSS® software for PC version 25 (IBM Corp Chicago, IL). All tests were two sided. p-values $<.05$ were considered statistically significant and no correction for multiple testing was performed as the study was considered exploratory. Continuous variables were described with median and range and categorical variables with counts and proportions.

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

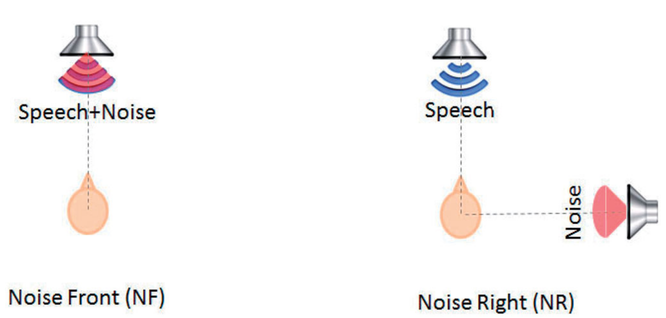

Figure 1. Setup of Hearing In Noise Test (HINT).

Results

Cases

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

Hearing

Pure tone audiometry and self-reported hearing/tinnitus

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

Hearing loss was reported by 22 Cases (23%) compared to 2 Controls (7%) (p =.007). Hearing difficulties in background noise were reported by 44 Cases (46%) and 5 Controls

Table 1. Patient characteristics.

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

Table 2. Hearing and tinnitus.

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

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

(17%) (p =.001). Tinnitus was reported by 36 Cases (38%) and 3 Controls (10%) ($p < .001$), and it correlated significantly with worse hearing thresholds at 4, 6 and 8 kHz ($p < .05$) both before and after age-adjustment. Reported tinnitus was also correlated to self-reported hearing difficulties ($p < .001$; data not shown).

Hearing in Noise Test (HINT)

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

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

Discussion

To the best of our knowledge, this is the first evaluation of CBCT-related long-term ototoxicity assessed by speech perception tests in survivors after adult-onset cancer. We found no significant differences in HINT scores between the 95 TCSs and the 30 age-matched male Controls with speech and noise from the front (HINT NF). Cases scored slightly, yet significantly, worse than Controls with speech from front and noise from either side. In quiet conditions (HINT Q), we found no significant difference between Cases and Controls. In multiple linear regression analyses, increasing age and increasing PTA (mid-frequencies) were associated with worse speech perception both in quiet and with noise from the front. In this model, cisplatin treatment provided three decades previously was not significantly associated with HINT scores, although it was associated with high-frequency hearing loss.

Reduced speech perception, especially in noisy surroundings, is one of the most common challenges in daily life for people with hearing loss. Studies have shown that speech perception can also worsen with increasing age irrespective

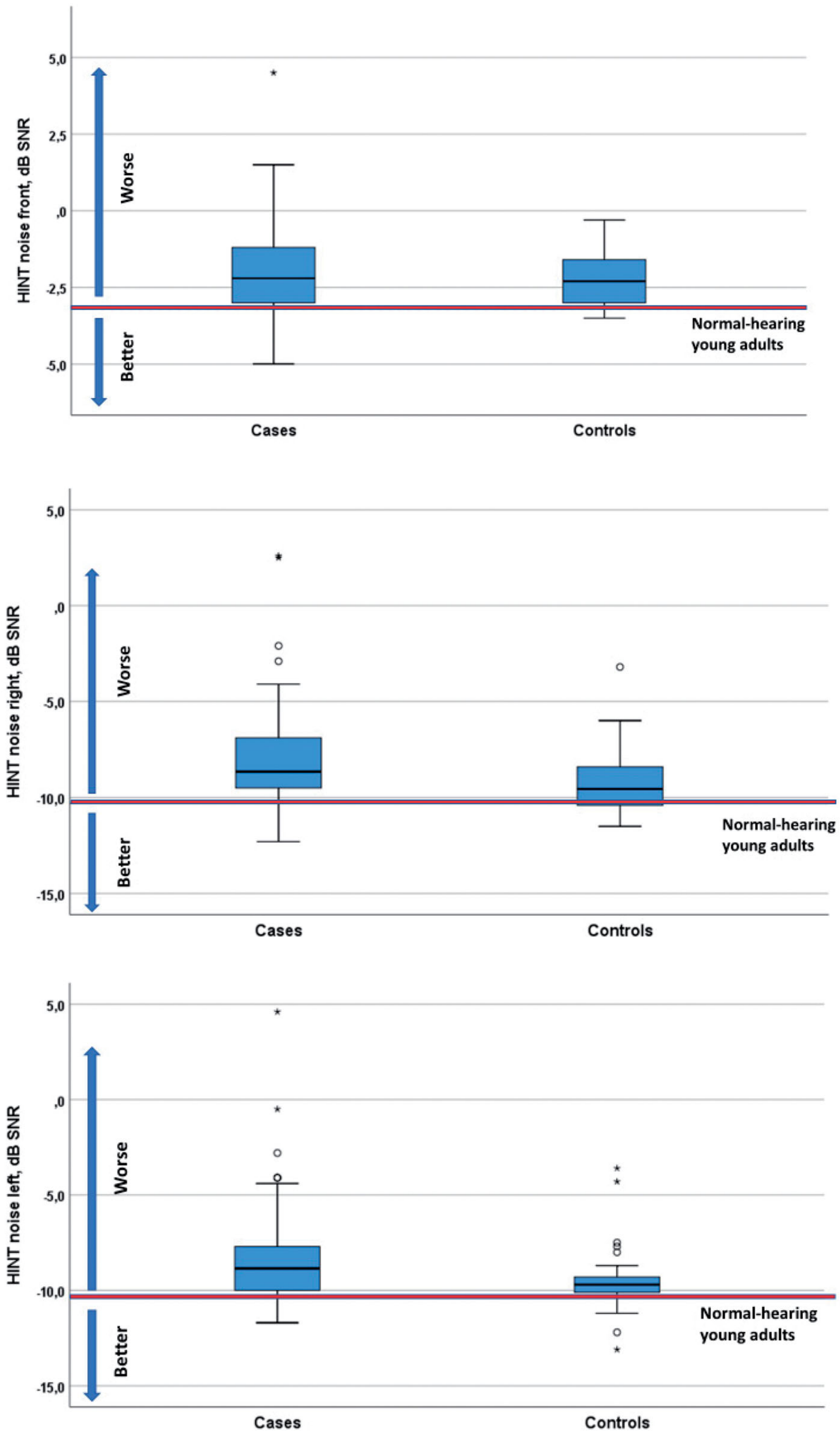

Figure 2. Boxplot of HINT scores for Cases and Controls (red line indicates mean score for normal-hearing young adults, median age 28 years). Results are presented as dB SNR for HINT noise front, noise right and noise left, and as dBA for HINT quiet.

of hearing thresholds, probably due to decreased cognitive ability [41–43]. However, long-term studies which evaluate speech perception related to CBCT-induced high-frequency hearing loss, which is an important and clinically relevant end point, have been lacking.

The ototoxic effect of CBCT is well documented by pure-tone audiometry displaying treatment-induced hearing loss in the high frequencies [3,7–9,13,15,44]. This was confirmed by a previous long-term follow-up of TCS by our group, where we also documented that hearing thresholds of TCS approached those of the age-matched males from the general population 30 years after CBCT [15]. We now document that HINT scores in TCS 30 years after treatment are rather similar to those of the Controls, in spite of worse high-

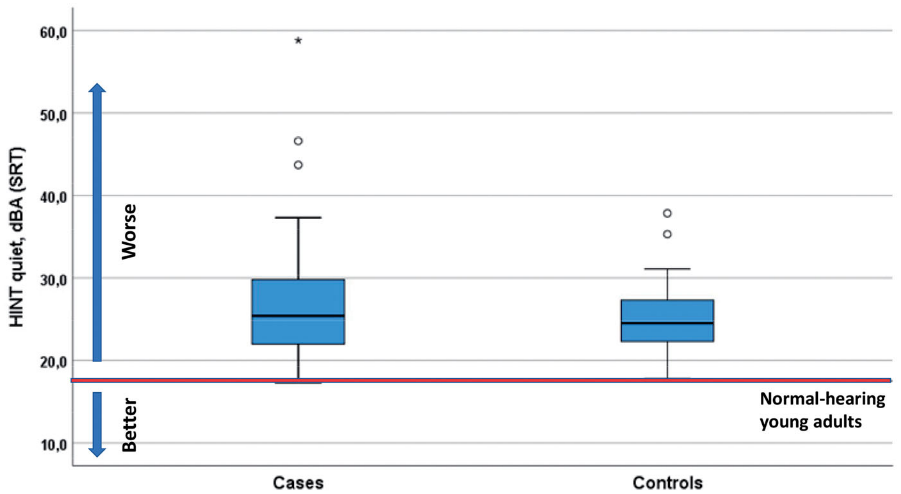

Figure 2. (Continued).

Table 3. Multiple linear regression for HINT scores.

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

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

frequency hearing thresholds among the TCS. Our linear regression model revealed that PTA significantly affected speech perception both in noise and quiet. Although hearing loss at 4, 6 and 8 kHz was not significantly associated with HINT scores in our regression model, high-frequency thresholds are highly correlated with PTA thresholds and might therefore have confounded the results.

Importantly, some Cases had quite poor HINT scores both in noise and quiet, indicating that individual patients may experience severe problems with speech perception. Cases had slightly, but statistically significant worse HINT scores with speech from front and noise from either side. This slight difference is likely due to the worse high-frequency thresholds among Cases, leading to a poorer sound localization and Spatial Release from Masking (SRM). SRM refers to the ability to utilize that speech and noise come from different directions. An important part of SRM is the head-shadow effect: with HINT NR/NL the sound reaches each ear at slightly different times and volumes. The brain uses these differences to localize the sound and to hear in background noise. The effect of a difference in volume is most pronounced in the higher frequencies because the shorter wavelengths of high-frequency sounds are more blocked by the human head than those of lower frequencies [45]. Hence, directional hearing and hearing in noise may be slightly poorer among TCS, for example identifying what is said from whom and where in a noisy environment.

Both Cases and Controls (median age 60 and 61 years, respectively) had worse HINT NF scores (higher values) than the Norwegian reference population consisting of normal-hearing young adults (median age 28 years) (−2.2 dB SNR and −2.3 dB SNR vs −3.2 dB SNR, respectively). This is consistent with studies showing that speech perception in noise declines with age [41,42,46]. One dB worse HINT NF score equals approximately 10% poorer speech perception. The association between age and HINT scores (NF/Q) was also seen in our linear regression model.

CBCT 30 years previously was not associated with poorer HINT scores in our regression model.

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

Overall, our results indicate that reduced speech perception is a limited problem for the vast majority of TCS 30 years after CBCT. It is however important to identify the few patients who struggle with hearing problems after CBCT. The detection and the following aural rehabilitation of these patients are utterly important since hearing impairment is a known risk factor for social isolation, decreased quality of life, and possibly dementia [47–52]. The finding that only four TCS (4%) used hearing aids (another three were referred based on the results), further strengthens the view that most patients having received CBCT experience limited problems with hearing in daily life. A previous long-term study by our group showed that only 5% of patients treated with Cisplatin for malignant ovarian germ cell tumor used hearing aids, while a large study from the US found that 1.2% of TCS were using hearing aids [8,9]. While cost might explain the low percent the latter study, economical limitations are not valid for Norwegian patients as hearing aids are fully reimbursed by the government. We conclude that for most patients, standard pure-tone audiometry seems to be a sufficient examination, but selected patients will benefit from speech perception tests.

Limitations of our study should be recognized. The relatively small sample size is related to financial restrictions and associated with limited power. Further, it is important to recognize that during the 30 years follow-up there is inevitably some degree of positive selection among patients as discussed in previous studies, although this bias is unlikely to be directly related to hearing loss [53,54]. The size of the control group and the fact that it was supplemented by some health-care professionals is a limitation, but the small inter-individual variation of HINT scores among controls indicates that the two parts of the control group did not differ and that they were representative. As discussed in a previous article by our group, test conditions for both Cases and Controls were slightly better than those for the age-matched controls from HUNT II [15]. This will result in negative age-adjusted values for some frequencies, since our participants may reach slightly better thresholds with better test conditions. However, in our view, this will not affect the relative differences in age-adjusted thresholds. A strength of this study is the follow-up of 30 years. The comprehensive audiological work-up including pure-tone audiometry, speech perception, objective HINT testing and self-reported hearing is unique. We consider the participation rate (101 of 119 eligible) as very satisfactory, considering the long follow-up and the extent of testing required from participants.

Conclusions

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

Disclosure statement

The authors have declared no conflicts of interest.

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