Factors Affecting Permanent Sensorineural Hearing Loss and Bone Conduction in Patients After Receiving Radiotherapy to the Head and Neck Region

Original Investigation

Birsen Yücel[1], Eda Erdiş[1], Seher Bahar[2], Ebru Akkaş Atasever[3], Mustafa Gürol Celasun[4], Emine Elif Altuntaş[5]

[1]Department of Radiation Oncology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey
[2]Department of Radiation Oncology, University of Health Sciences Turkey, Balıkesir Atatürk City Hospital, Balıkesir, Turkey
[3]Department of Radiation Oncology, University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[4]Department of Radiation Oncology, University of Health Sciences Turkey, Kütahya Evliya Çelebi Training and Research Hospital, Kütahya, Turkey
[5]Department of Otorhinolaryngology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Abstract

Objective: This study aimed to investigate the factors affecting permanent sensorineural hearing loss (SNHL) and causing changes in bone conduction (BC) thresholds over time in patients after receiving radiotherapy (RT) or chemoradiotherapy (CRT) to the head and neck region.

Methods: A total of 63 patients with irradiated HNC that were admitted to the Radiation Oncology Department between 2011 and 2018 were included in the study. All patients were assessed with pure tone audiometry at eight different time points (first before RT and last five years after completion of RT). A chi-square test was used to analyze the variables that affected permanent SNHL occurrence. Repeated measure analysis of variance was conducted to investigate the factors affecting change in the BC threshold at pure-tone average (0.5–2 kHz) and the air conduction (AC) threshold at 4 and 6 kHz frequencies over time.

Results: Median follow-up was 52 months (range, 12–110 months). SNHL was found in 18 (14%) of the 126 ears. According to the receiver operating characteristic analysis, the cut-off values of cochlear D_{mean} and D_{max} radiation doses were 40 Gy [p=0.017, area under the curve (AUC): 0.676] and 45 Gy (p=0.008, AUC: 0.695). D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} (≤45 Gy vs. >45 Gy) cochlear doses and age (≤40 vs. >40 years) were determined as factors affecting SNHL in the chi-square test. Repeated measures showed that BC thresholds between 0.5–2 kHz and AC thresholds at 4 and 6 kHz increased over time. Age (≤40 vs. >40 years), treatment of head and neck cancer (RT vs. CRT), cisplatin use, and D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} cochlear dose (≤45 Gy vs. >45 Gy) were important factors affecting the course of BC threshold over time.

Conclusion: D_{mean} and D_{max} cochlear doses and age were found to be associated with permanent SNHL. Conduction thresholds worsened over time at all frequencies, and this trend was affected by cochlear doses, age, CRT, and cisplatin use.

Keywords: Head and neck cancer, radiotherapy, chemoradiotherapy, side effect, hearing loss, radiation dose

ORCID IDs of the authors:

B.Y. 0000-0002-0083-6866;
E.E. 0000-0003-3003-6643;
S.B. 0000-0001-6933-1009;
E.A.A. 0000-0003-4164-7196;
M.G.C. 0000-0002-7186-0169;
E.E.A. 0000-0003-4503-3730.

Cite this article as: *Yücel B, Erdiş E, Bahar S, Akkaş Atasever E, Celasun MG, Altuntaş EE. Factors Affecting Permanent Sensorineural Hearing Loss and Bone Conduction in Patients After Receiving Radiotherapy to the Head and Neck Region. Turk Arch Otorhinolaryngol 2022; 60(4): 212-219.*

Corresponding Author:
Eda Erdiş;
dr.erdiseda@hotmail.com

Received Date: 09.06.2022
Accepted Date: 27.09.2022

DOI: 10.4274/tao.2022.2022-6-2

Introduction

Radiotherapy (RT) is a treatment method frequently used in head and neck cancers (HNC) and brain tumors. In HNC patients RT or chemoradiotherapy (CRT) can be definitive or adjuvant, and typically given in high doses. Many critical organs such as the medulla spinalis, the cochlea, the brain stem, the optic nerves, and the optic chiasm are located within the area targeted by RT. The side effects of RT in these organs can be observed in the early and late periods.

RT can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL). CHL, originating in the outer and middle ear, is usually observed in early periods of RT and temporary, while SNHL can be seen as a late and irreversible side effect of fractional RT. SNHL is probably caused by the changes induced by radiation in the retrocochlear component or the cochlea of the auditory system (1, 2). Schuknecht and Karmody (3) reported marked changes in soft tissue, stria vascularis degeneration, and spiral ligament and basilar membrane atrophy after RT.

Leach (4) found that the outer hair cells were destroyed, and atrophy developed in the eighth cranial nerve. Moretti (5) reported extensive degeneration of the outer hair cells in the Corti organ in guinea pigs after radiation to the inner ear. Furthermore, in postmortem studies of the human temporal bone, destruction of the Corti organ, atrophy of the audiovestibular nerve, loss of outer hair cells, loss of spiral ganglion cells, atrophy of the stria vascularis, changes in the nerve vessels, the macula of the utricle, and the cristae of the semicircular canals were observed after radiation (4-6).

In the treatment of HNC, the use of cisplatin-based chemotherapy, simultaneously with RT, is also quite common. In animal experiments, cisplatin has been shown to cause injury to the outer hair cells in the Corti organ and in marginal cells in the stria vascularis (7-10). Cisplatin, like RT, causes irreversible SNHL, but unlike RT, usually starts acutely and occurs bilaterally (9-10).

The best way to protect patients from hearing loss due to RT to the head and neck region is to exclude the cochlea or retrocochlear region from the planned target region. In the past, it was not possible to exclude the cochlea from the target region, especially in nasopharyngeal and parotid cancers, but thanks to the technological advancements, normal tissues can be preserved completely or partially by three-dimensional (3D) contouring. Particularly with the availability of the intensity modulated radiotherapy (IMRT) technique it became possible to better preserve the cochlea and the retrocochlear region.

This study aimed to investigate possible factors causing SNHL and the changes in BC over time in patients who received RT or CRT to head and neck region.

Methods

This study was conducted at the Department of Radiation Oncology at Sivas Cumhuriyet University Hospital in Turkey, in accordance with the principles of the Declaration of Helsinki following the approval of Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2017-11/22, date: 8.11.2017). All patients provided written consent for the use of their information. A total of 118 patients (n=236 ears) with irradiated HNC that were admitted to the Radiation Oncology Department between 2011 and 2018 were included in the study. However, 55 patients were excluded because of insufficient data (e.g., without regular audiological tests, with short follow-up, etc.). Patients with tumor invasion into the external ear pathway, the middle ear, or the inner ear, 70 decibel (dB) or worse bone conduction (BC) thresholds, recurrent disease; a history of previous RT, and those who had used ototoxic drugs, had not completed RT, or were followed-up for less than twelve months were excluded from the study. Eventually, the data of 63 patients were analyzed. Each ear was evaluated independently for radiation doses and hearing status.

RT Techniques and Dose Fractionation

In all patients RT was administered using contrast-enhanced computed tomography (CT) or positron emission tomography-CT. Axial CT images were taken from the top of the head to the lower neck with patients in treatment position. In all cases slice thickness was 3 mm and the cochlea was contoured on the bone window of the CT. Figure 1 shows the contouring of the cochlea on CT (on the bone window) and T2-weighted magnetic resonance imaging.

RT was administered using a linear accelerator device (Varian Clinac DHX, Varian Medical Systems, Inc., Palo Alto, CA, USA) or TomoTherapy (Accuray, USA). The 3D-conformal radiation therapy (3D-CRT) planning was done using the Varian Eclipse treatment planning (Varian Medical Systems,

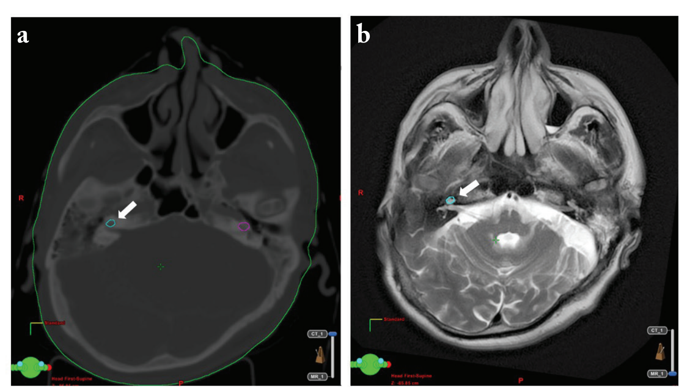

Figure 1. Contour of the cochlea on computed tomography and T2-weighted magnetic resonance imaging. a. The contour of the cochlea on computed tomography (white arrow). b. The contour of the cochlea on T2-weighted magnetic resonance imaging (white arrow)

Inc., Palo Alto, CA, USA), taking into account tissue inhomogeneity during dose calculation. IMRT planning was done using the TomoTherapy Planning Workstation (TomoTherapy Inc., Madison, WI, USA). RT was given with 6 MV photons on both devices. RT was prescribed to a total dose of 46–70 Gy at 1.8–2 Gy per fraction with 5 fractions per week.

Chemotherapy

Patients with locally advanced HNC received concurrent platinum-based chemotherapy (cisplatin 40 mg/m^2 were given every week during the radiation course). Induction CT and adjuvant CT were given with DCF protocol (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 and 5FU at 750 mg/m^2/day for five days every three weeks).

Audiological Evaluation

Pre- and post-RT audiological evaluations were done in the otolaryngology department of the same institution. Hearing data of all patients were obtained using an AC-40 Interacoustics Clinic Audiometer (Interacoustics, Assen, Denmark) at baseline (the start RT; T_1), completion of RT (T_2), six months after completion of RT (T_3), one year after completion of RT (T_4), two years after completion of RT (T_5), three years after completion of RT (T_6), four years after completion of RT (T_7) and five years after completion of RT (T_8) and retrieved from the audiological evaluation form of each patient.

All patients underwent a standard evaluation using pure-tone audiometry. This test was performed in a standardized, soundproofed and shielded room. Pure-tone thresholds were obtained for air conduction (AC) at 0.25–6 kHz and for BC at 0.5–2 kHz measured in the dB hearing level, respectively.

An increase in BC threshold of least 10 dB from baseline was considered significant (11). Permanent hearing loss was defined as a difference greater than 10 dB in hearing level results between two consecutive hearing threshold measurements done six months apart (11). Hearing levels of the left and the right ears were analyzed separately in each patient.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (IBM Corp. Armonk, NY, USA). Medians and frequencies were calculated for patient demographics. In RT techniques, the Mann–Whitney U test was used to compare the median of D_{mean} and D_{max} cochlear doses.

Receiver operating characteristic (ROC) analysis was used to determine the cut-off values of the cochlear D_{mean} dose and the cochlear D_{max} dose that affected hearing.

A chi-square test was used to analyze the variables that affected permanent SNHL occurrence. Repeated measures analysis of variance was conducted to investigate the factors (age, treatment of HNCs, use of cisplatin, D_{mean} and D_{max} cochlear doses) affecting change in the BC threshold at pure-tone average (0.5–2 kHz) and the AC threshold at 4 and 6 kHz frequencies over time. P values ≤0.05 were accepted as statistically significant.

Results

Demographic Features

The study group consisted of 51 (81%) male and 12 (19%) female patients. Their median age at the time of their cancer diagnosis was 52 years (range, 16–75 years). Fifteen (24%) of the patients were ≤40 years old, and 48 (76%) were >40 years old. Nineteen (30%) had at least one comorbid disease.

Ranked in order of frequency, the cancer classifications were head and neck (n=51, 81%) and central nervous system (n=12, 19%). Regions of head and neck tumors were nasopharynx (NPC) in 26 (41%) patients, oral cavity/oropharynx in 11 (18%), larynx/hypopharyngeal in 10 (16%), and salivary gland in 4 (6%) patients. The 12 brain tumors (18%, 24 ears) were: grade 1-2.

Staging of the HNCs were: stage I in 2 (4%) patients, stage II 11 (22%), stage III in 23 (45%), and stage IVA in 15 (29%) patients. Brain tumors were not staged.

Treatments

Surgical treatment was performed in 25 (40%) patients. A total of 17 (27%) patients were treated with postoperative RT, six (10%) patients with definitive RT, and a total of 40 patients (63%) were treated with concurrent CRT, seven (11%) patients with postoperative CRT, and 33 (52%) patients with definitive CRT. Induction chemotherapy was administered to five (8%) patients, and 16 (25%) patients received adjuvant chemotherapy.

The median treatment RT dose was 70 Gy (range, 46–70.2 Gy). From January 2011 to June 2015, a total of 37 (59%) patients (74 ears) were treated with 3D-CRT. From June 2015 to December 2018, 26 (41%) patients (52 ears) were treated with IMRT.

Median D_{mean} cochlear dose was 23.13 Gy (range, 0.52–71.60 Gy) and median D_{max} cochlear dose was 32.9 Gy (range, 0.58–74.80 Gy). Median D_{max} cochlear dose was 36.77 Gy (range, 0.58–73.67 Gy) in 3D-CRT and 26.95 Gy (range, 1.16–74.80) in IMRT (p=0.931). Median D_{median} cochlear dose was 32.48 Gy (range, 0.52–71.58) in 3D-CRT and 18.01 Gy (range, 1.14–71.60 Gy) in IMRT (p=0.886).

The median dose of cumulative cisplatin in all treatments (induction, adjuvant and simultaneously) was 435 mg (range, 200–980 mg).

Audiological Results

The median clinical follow-up was 52 months (range, 12–110 months). Permanent SNHL was observed in 18 (14%) of the 126 ears.

According to the ROC analysis, the cut-off values of cochlear D_{mean} and D_{max} radiation doses were 40 Gy (p=0.017, AUC: 0.676, range, 0.532–0.820) and 45 Gy (p=0.008, AUC: 0.695, range, 0.553–0.838), respectively (Figures 2, 3). The cut-off value was not found for the cisplatin dose.

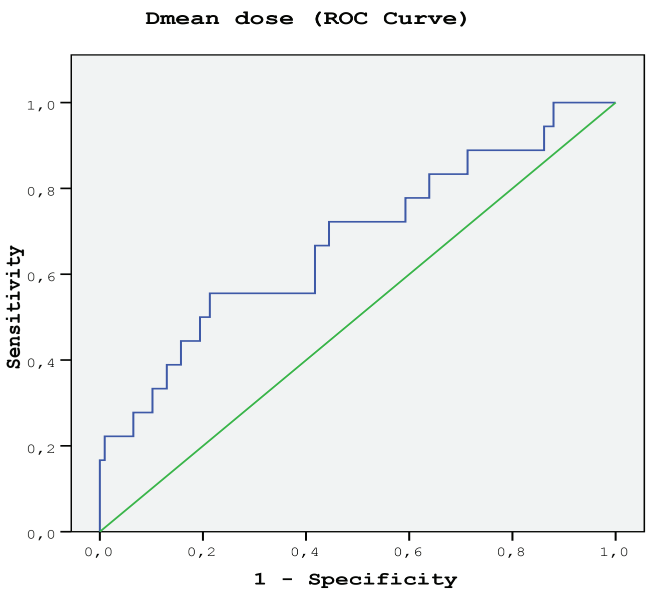

Figure 2. ROC analysis of D_{mean} radiation dose of cochlea
ROC: Receiver operating characteristic

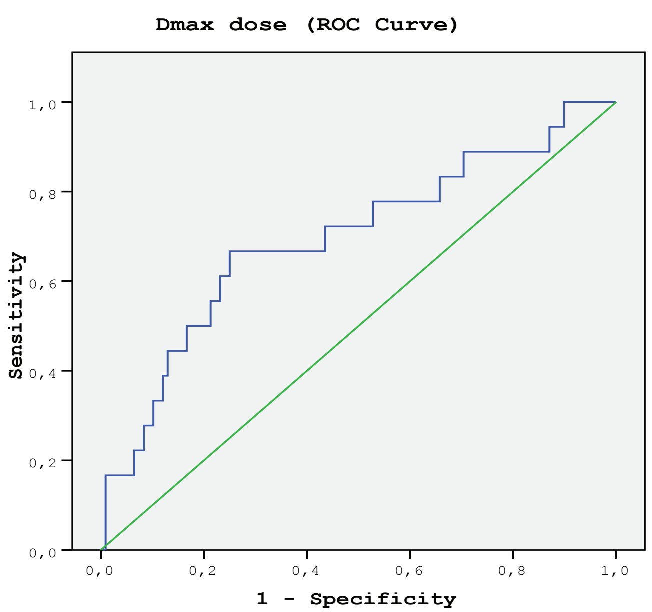

Figure 3. ROC analysis of D_{max} radiation dose of cochlea
ROC: Receiver operating characteristic

The chi-square test showed D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} (≤45 Gy vs. >45 Gy) cochlear dose and age (≤40 vs. >40 years) as factors affecting permanent SNHL. Gender, comorbidity, the localization of the disease (HNC vs. brain tumors), treatment of HNC (RT vs. CRT) and use of cisplatin, RT technique (3D-CRT vs. IMRT) and BC threshold at diagnosis (≤20 vs. >20 dB) did not affect the rate of SNHL (p>0.05). Table 1 shows the factors affecting permanent SNHL rates.

Table 1. Factors affecting the rate of permanent sensorineural hearing loss

Chi-square test	All ears n (%)	SNHL absent n=108 (86%)	SNHL present n=18 (14%)	p-value
D_{mean} cochlear dose				
≤40 Gy	93 (74)	85 (91)	8 (9)	0.004
>40 Gy	33 (26)	23 (70)	10 (30)	
D_{max} cochlear dose				
≤45 Gy	90 (71)	83 (92)	7 (8)	0.002
>45 Gy	36 (29)	25 (69)	11 (31)	
Gender				
Female	24 (19)	19 (79)	5 (21)	0.236
Male	102 (81)	89 (87)	13 (13)	
Age				
≤40 years	30 (24)	30 (100)	- (0)	0.005
>40 years	96 (76)	78 (81)	18 (19)	
Comorbidity				
No	89 (71)	75 (84)	14 (16)	0.339
Yes	37 (29)	33 (89)	4 (11)	
Localization of the disease				
HNC	102 (81)	86 (84)	16 (16)	0.286
Brain tumors	24 (19)	22 (92)	2 (8)	
Treatment of HNC				
RT	22 (22)	19 (86)	3 (14)	0.531
CRT	80 (78)	67 (84)	13 (16)	
RT techniques				
3D-CRT	74 (59)	64 (87)	10 (13)	0.481
IMRT	52 (41)	44 (85)	8 (15)	
Use of cisplatin				
No	46 (36)	41 (89)	5 (11)	0.290
Yes	80 (64)	67 (84)	13 (16)	
Cumulative dose of cisplatin				
≤435 mg	44 (55)	40 (60)	4 (31)	0.053
>435 mg	36 (45)	27 (40)	9 (69)	
BC threshold at diagnosis				
≤20 dB	106 (84)	91 (84)	15 (83)	0.575
>20 dB	20 (16)	17 (16)	3 (17)	

n: Number of ears, SNHL: Sensorineural hearing loss, HNC: Head and neck cancers, 3D-CRT: Three-dimensional conformal radiation therapy, RT: Radiotherapy, IMRT: Intensity modulated radiotherapy

In repeat measurements, it was observed that BC thresholds at 0.5–2 kHz and AC thresholds at 4 and 6 kHz increased over time. Table 2 shows that BC thresholds at 0.5–2 kHz and AC thresholds at 4 kHz and 6 kHz increased over time. Age (≤40 vs. >40 years), treatment of HNC (RT vs. CRT), use of cisplatin, and D_{mean} (≤40 Gy vs. >40 Gy) and D_{max} cochlear dose (≤45 Gy vs. >45 Gy) were important factors affecting the course of BC threshold over time. Table 3 shows the average BC threshold of these variables. Gender, comorbidity, the localization of the disease (HNC vs. brain tumors), and BC threshold at diagnosis (≤20 vs. >20 dB) did not affect the course of BC threshold over time (p>0.05).

Discussion

RT-induced ear toxicity is related to the anatomical location of the ear in the irradiation field. Radiation-induced ear toxicity can lead to a wide range of conditions from otitis media to SNHL. Similarly, the incidences of toxicity are also very different. Therefore, it is important to know the incidence and the factors causing permanent SNHL.

In their study, Wang et al. (12) analyzed 395 ears of 220 NPC patients who were followed-up for a median of 36 months (3–120 months) after completion of RT. The researchers found that 13.7% of the ears had an increase of at least 30 dB in BC threshold at low frequencies and 46.2% at 4 kHz. Bhandare et al. (13) retrospectively investigated ototoxicity in 325 patients who received RT for HNC between 1964 and 2000 and recorded 15.1% SNHL at low frequencies. Yilmaz et al. (14) reported a median loss of 22.6 dB at a rate of 47% at any frequency of BC threshold one year after the completion of RT in 19 HNC patients. Oh et al. (11) found that in 24 NPC patients who underwent CRT, SNHL was 44% at 4 kHz and 17% at low frequencies 40 months after completion of RT. The SNHL due to a retro-cochlea (cochlea nerve) damage may occur, although, this was relatively rare compared to the cochlea damage (15). Kwong et al. (16) reported that the patients with NPC (n=132) had 24.2% permanent SNHL in a median 30-month follow-up after completion of RT.

In our study, we investigated the factors affecting the occurrence of SNHL at low frequencies, and similarly

Table 2. Changes in bone conduction threshold at 0.5–2 kHz and air conduction thresholds at 4 and 6 kHz over time

Conduction thresholds	T_1 n=126	T_2 n=126	T_3 n=126	T_4 n=126	T_5 n=86	T_6 n=78	T_7 n=58	T_8 n=58	p-value
Bone (0.5–2 kHz)	15±7	15±6	16±6	16±16	16±16	18±17	18±17	19±19	0.005
Air (4 kHz)	35±23	37±24	38±22	41±22	44±23	46±23	48±25	48±25	<0.001
Air (6 kHz)	37±24	40±26	41±24	42±23	46±26	51±24	54±23	58±25	<0.001

T_1: Start of RT, T_2: Completion RT, T_3: Six months after completion of RT, T_4: One year after completion of RT, T_5: Two years after completion of RT, T_6: Three years after completion of RT, T_7: Four years after completion RT, T_8: Five years after completion of RT, n: Number of ears, RT: Radiotherapy

Table 3. Effects of age, treatment of head and neck cancers, use of cisplatin, D_{mean} and D_{max} cochlear doses on bone conduction threshold over time

	T_1 n=126	T_2 n=126	T_3 n=126	T_4 n=126	T_5 n=86	T_6 n=78	T_7 n=58	T_8 n=58	p-value
Age									
<40	11±12	11±13	12±13	12±13	13±14	13±14	14±15	16±17	0.002
≥40	44±14	43±13	43±13	43±13	43±11	46±10	46±16	40±21	
Treatment[1]									
RT	6±4	7±5	8±4	9±4	7±4	9±5	11±6	10±6	0.048
CRT	18±18	18±18	19±8	18±18	19±18	21±18	20±21	22±21	
Cisplatin									
No	6±4	7±5	8±4	9±4	7±4	9±5	11±6	10±6	0.048
Yes	18±18	18±18	19±18	18±18	21±18	21±18	20±21	22±21	
D_{mean}[2]									
≤40 Gy	12±12	12±12	13±12	12±12	13±12	14±12	13±12	15±14	0.037
>40 Gy	20±22	22±22	21±21	23±21	22±22	26±22	27±24	27±24	
D_{max}[3]									
≤45 Gy	12±12	12±11	13±11	13±11	13±12	14±12	13±12	15±14	0.030
>45 Gy	22±23	22±23	22±23	23±22	24±23	27±23	28±25	27±26	

T_1: Start of RT, T_2: Completion RT, T_3: Six months after completion of RT, T_4: One year after completion of RT, T_5: Two years after completion of RT, T_6: Three years after completion of RT, T_7: Four years after completion RT, T_8: Five years after completion of RT, n: Number of ears

Treatment[1]: Treatment of head and neck cancers, D_{mean}[2]: Mean radiation dose of cochlea, D_{max}[3]: Maximum radiation dose of cochlea to the above studies, found SNHL to be 14% at low frequencies.

As people age, the rate of SNHL increases as a result of the loss of the characteristics of the vessels of the ear, the deterioration of the auditory nerve and the decrease in the function of the hearing center in the brain (17, 18). Some studies have shown that the probability of SNHL occurrence is more common in elderly patients who received RT or CRT (12, 19). In the study conducted by Wang et al. (12), age was associated with significant loss at BC threshold at low frequencies in logistic regression analysis. In the study by Chan et al. (19), SNHL at low frequency was associated with patient's age, and SNHL at high frequency was associated with simultaneous cisplatin dose. Kwong et al. (16) reported that older patients were more susceptible to SNHL. In their series, permanent SNHL was 0% in patients under 30 years, 17.2% in patients 30–50 years, and 37.4% in patients over 50 years of age. However, unlike the above studies, Zuur et al. (20) reported that younger patients who underwent CRT with high-dose cisplatin were more susceptible to hearing loss.

In our study, while none of the patients aged under 40 years had SNHL, 19% of the patients aged over 40 years had permanent SNHL. Moreover, an advanced age had more statistically significant negative impact on the course of BC threshold over time. This suggests that care should be taken to better protect the cochlea when planning RT for elderly patients.

Many authors have identified a relationship between the occurrence of SNHL and high cochlear radiation doses (10, 19, 21-23). This, however, has not been demonstrated in some other studies (21, 24). In most studies, increased incidence of SNHL was reported in patients with a median cochlear dose of 45–55 Gy (10, 19, 21-23). Bhandare et al. (13) reported the five-year and 10-year actuarial risk of clinically overt SNHL as 3% at cochlear doses below 60.5 Gy and 37% at doses above 60.5 Gy. In a study conducted by Chan et al. (19) on NPC patients, they found that high-frequency SNHL was associated with the mean cochlear dose (>46 Gy). Chen et al. (22) audiologically followed up 22 patients who underwent CRT due to NPC for 29 months (range, 12–76 months). They reported that the occurrence of SNHL was higher in patients with D_{mean} cochlear dose >48 Gy at all frequencies. Petsuksiri et al. (23) examined the factors affecting SNHL in 68 NPC patients who received CRT. The researchers separately investigated the roles of mean cochlear dose, inner ear (cochlear and vestibule) and internal auditory canal (IAC) in SNHL opposite to other studies. In the study, the univariate analysis showed that the D_{mean} cochlear dose ≤50 Gy, the D_{mean} inner ear dose ≤45 Gy and the D_{mean} IAC dose ≤50 Gy appeared to lead to a lower incidence of SNHL at high frequency (4 kHz). However, they could not identify an important factor affecting the incidence of SNHL at low frequencies. The researchers further reported that in the bivariate analysis, the D_{mean} IAC dose >50 Gy tended to lead to a higher rate of SNHL at higher frequencies (relative risk 2.02).

Unlike the results of Petsuksiri et al. (23), in our study the D_{mean} cochlear dose >40 Gy at low frequencies was found to be a risk factor for SNHL. The cochlear D_{max} dose >45 Gy was also found to be a risk factor for SNHL. Analysis of the audiological tests done at eight different time points showed that the D_{mean} cochlear dose >40 Gy and the D_{max} cochlear dose >45 Gy negatively affected the course of BC thresholds at low frequencies over time. Compared to other studies, in our study the D_{mean} cochlear dose affecting SNHL was lower than 45–55 Gy. Therefore, the cochlear dose should be lower in RT planning.

Cisplatin-induced ototoxicity is observed at high frequencies and in the form of SNHL, which is due to the damage done by cisplatin to the outer hair cells and the stria vascularis of the organ of Corti (7-10, 25). Cisplatin CRT is frequently used in HNC patients due to better survival results with CRT. It is logical that the use of two ototoxic agents, RT and cisplatin, causes increased ototoxicity. However, this has not been demonstrated, especially in studies using weekly low-dose cisplatin (12, 15, 21). As shown in studies reported to date, high-dose cisplatin appears to increase the risk of SNHL (19, 26). Rezaeyan et al. (27) investigated rates of SNHL in 60 HNC patients in the short term (over a six-month period). The researchers applied RT or CRT with 3D-CRT to the head and neck regions of the patients and compared the SNHL incidence rates of these two applications. The result of the study showed that 47% of the patients that received RT and 88% of the patients that received CRT had SNHL. In their analysis of 17 studies, Schmitt and Page (26) reported that CRT with low-dose cisplatin (30–40 mg/m^2 weekly) could be associated with lower hearing loss incidences and lower severity of hearing loss. Chan et al. (28) investigated the effect of cisplatin in 142 patients who received RT or CRT for nasopharyngeal cancer. The researchers reported that the hearing loss in CRT patients tended to be seen in the first three months and at high frequencies, and that the severity of toxicity was higher compared to RT alone. They also reported that there was no significant hearing toxicity in patients who received only RT in the first two years. In their 2007 report of the study on HNC patients, Bhandare et al. (13) stated the results of univariate and multivariate analysis showed that age, cochlear dose and CRT were factors affecting SNHL. In their study, they determined that the five-year and ten-year actuarial risk of clinically overt SNHL was 18% in RT and 30% in CRT. In Chan et al.'s (19) study, pure-tone audiogram and tympanometry were performed on 87 NPC patients at the start of RT and then every six months. The researchers reported that patients receiving CRT had a higher rate of persistent SNHL at 4 kHz compared to low frequencies (51.2% vs. 9.4%). They showed that SNHL at low frequency was related to patient age, and SNHL at high frequency was associated with simultaneous cisplatin dose (>1.008 mg/m^2) and mean cochlear dose (>46 Gy). Further, in the study conducted by Zuur et al. (20), a cumulative 1,050 mg dose of cisplatin was shown to cause SNHL with increasing frequency.

In our study, the chi-square test showed that the use of cisplatin and RT vs. CRT did not affect the occurrence of SNHL; however, the use of CRT adversely affected the course of BC threshold over time at low frequencies. In our study, although no relation was found between cisplatin dose (cumulative cisplatin dose >435 mg) and SNHL, this relationship was close to being statistically significant. Since we used weekly low-dose cisplatin in our study, a strong relationship between ototoxicity and cisplatin dose could not be demonstrated. Previous studies have shown quite different results regarding the relationship between SNHL and CRT. It seems, however, that CRT, especially with high doses of cisplatin (cumulative ~1000 mg), increases the likelihood of SNHL occurrence, especially at high frequencies.

It is known that IMRT provides better protection of normal tissue than 3D-CRT. By providing lower cochlear doses with IMRT, it may be possible to reduce the risk of SNHL. In fact, some studies reported lower rates of SNHL with IMRT. In the study conducted by Petsuksiri et al. (23), the incidence of SNHL was 48.75% at 4 kHz and 5% at low frequencies with conventional RT and 37% at 4 kHz and 7.4% at low frequencies with IMRT. Zhu et al. (29) reported that the incidence of SNHL was 8% at low frequency and 36% at high frequency in 70 patients who were irradiated with the IMRT technique due to NPC. Nutting et al. (30) compared 3D-CRT and IMRT techniques in terms of SNHL in 110 parotid cancer patients treated between 2008 and 2013. The researchers detected a statistically significant difference between the techniques in terms of cochlear doses; however, at one year after RT, they did not find any difference in hearing loss of ≥10 dB.

Like Nutting et al. (30), no relationship was found between RT techniques and SNHL occurrence in our study. This may be due to the lack of difference in the D_{mean} and D_{max} cochlear doses among RT techniques. In the IMRT technique, however, lower cochlear doses were used compared to 3D-CRT.

The limitations of the study are the small number of patients and the heterogeneity of the group, and the lack of BC threshold measurements at 4 kHz, which means that the factors related to high frequency SNHL have not been investigated.

Conclusion

In our study, SNHL occurred at lower D_{mean} cochlear radiation doses at low frequencies than in other studies (>40 Gy vs. 45–55 Gy). Moreover, D_{mean} and D_{max} cochlear doses and age were found to be associated with permanent SNHL. Regardless of SNHL, in the patients who receive RT in the brain and the head and neck region, conduction thresholds worsen over time at all frequencies, and this poor trend is affected by cochlear doses, age, CRT, and cisplatin use.

Ethics Committee Approval: This study was conducted at the Department of Radiation Oncology at Sivas Cumhuriyet University Hospital in Turkey, in accordance with the principles of the Declaration of Helsinki following the approval of Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (decision no: 2017-11/22, date: 8.11.2017).

Informed Consent: All patients provided written consent for the use of their information.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.E.A., Concept: E.E.A., Design: B.Y., E.E., Data Collection and/or Processing: E.E., S.B., E.A.A., M.G.C., Analysis and/or Interpretation: B.Y., E.E., Literature Search: B.Y., E.E., Writing: B.Y.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- In this study, a relationship was found between radiation dose and hearing impairment.
- Bone and air conduction hearing deteriorates over time in the area of radiotherapy to the head and neck region.
- Patient age is an effective factor in the deterioration of hearing.

References

1. Bhide SA, Harrington KJ, Nutting CM. Otological toxicity after postoperative radiotherapy for parotid tumours. Clin Oncol (R Coll Radiol) 2007; 19: 77-82. [Crossref]
2. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. Cancer Treat Rev 2003; 29: 417-30. [Crossref]
3. Schuknecht HF, Karmody CS. Radionecrosis of the temporal bone. Laryngoscope 1966; 76: 1416-28. [Crossref]
4. Leach W. Irradiation of the ear. J Laryngol Otol 1965; 79: 870-80. [Crossref]
5. Moretti JA. Sensori-neural hearing loss following radiotherapy to the nasopharynx. Laryngoscope 1976; 86: 598-602. [Crossref]

6. Bhandare N, Mendenhall WM, Antonelli PJ. Radiation effects on the auditory and vestibular systems. Otolaryngol Clin North Am 2009; 42: 623-34. [Crossref]

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

8. Riedemann L, Lanvers C, Deuster D, Peters U, Boos J, Jürgens H, et al. Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Pharmacogenomics J 2008; 8: 23-8. [Crossref]

9. Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer 1990; 61: 927-31. [Crossref]

10. Bhandare N, Jackson A, Eisbruch A, Pan CC, Flickinger JC, Antonelli P, et al. Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys 2010; 76: S50-7. [Crossref]

11. Oh YT, Kim CH, Choi JH, Kang SH, Chun M. Sensory neural hearing loss after concurrent cisplatin and radiation therapy for nasopharyngeal carcinoma. Radiother Oncol 2004; 72: 79-82. [Crossref]

12. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004; 25: 168-73. [Crossref]

13. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. Int J Radiat Oncol Biol Phys 2007; 67: 469-79. [Crossref]

14. Yilmaz YF, Aytas FI, Akdogan O, Sari K, Savas ZG, Titiz A, et al. Sensorineural hearing loss after radiotherapy for head and neck tumors: a prospective study of the effect of radiation. Otol Neurotol 2008; 29: 461-3. [Crossref]

15. Low WK, Toh ST, Wee J, Fook-Chong SM, Wang DY. Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. J Clin Oncol 2006; 24: 1904-9. [Crossref]

16. Kwong DL, Wei WI, Sham JS, Ho WK, Yuen PW, Chua DT, 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: 281-9. [Crossref]

17. Mościcki EK, Elkins EF, Baum HM, McNamara PM. Hearing loss in the elderly: an epidemiologic study of the Framingham Heart Study Cohort. Ear Hear 1985; 6: 184-90. [Crossref]

18. Soucek S, Michaels L, Frohlich A. Evidence for hair cell degeneration as the primary lesion in hearing loss of the elderly. J Otolaryngol 1986; 15: 175-83. [Crossref]

19. Chan SH, Ng WT, Kam KL, Lee MC, Choi CW, Yau TK, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. Int J Radiat Oncol Biol Phys 2009; 73: 1335-42. [Crossref]

20. Zuur CL, Simis YJ, Lansdaal PE, Hart AA, Schornagel JH, Dreschler WA, 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: 3759-65. [Crossref]

21. Zuur CL, Simis YJ, Verkaik RS, Schornagel JH, Balm AJ, Dreschler WA, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. Radiother Oncol 2008; 89: 38-43. [Crossref]

22. Chen WC, Jackson A, Budnick AS, Pfister DG, Kraus DH, Hunt MA, Stambuk H, Levegrun S, Wolden SL. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 2006; 106: 820-9. [Crossref]

23. Petsuksiri J, Sermsree A, Thephamongkhol K, Keskool P, Thongyai K, Chansilpa Y, et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. Radiat Oncol 2011; 6: 19. [Crossref]

24. Wakisaka H, Yamada H, Motoyoshi K, Ugumori T, Takahashi H, Hyodo M. Incidence of long-term ipsilateral and contralateral ototoxicity following radiotherapy for nasopharyngeal carcinoma. Auris Nasus Larynx 2011; 38: 95-100. [Crossref]

25. Theunissen EA, Zuur CL, Yurda ML, van der Baan S, Kornman AF, de Boer JP, et al. Cochlea sparing effects of intensity modulated radiation therapy in head and neck cancers patients: a long-term follow-up study. J Otolaryngol Head Neck Surg 2014; 43: 30. [Crossref]

26. Schmitt NC, Page BR. Chemoradiation-induced hearing loss remains a major concern for head and neck cancer patients. Int J Audiol 2018; 57: S49-54. [Crossref]

27. Rezaeyan AH, Ghaffari SH, Mahdavi SR, Nikoofar AR, Najafi M, Koosha F, et al. Audiometric findings in patients with head and neck chemoradiotherapy and radiotherapy: short-term outcomes. Int J Radiat Res 2019; 17: 633-41. [Crossref]

28. Chan SL, Ng LS, Goh X, Siow CH, Goh HL, Goh BC, et al. Time course and clinical characterization of cisplatin-induced ototoxicity after treatment for nasopharyngeal carcinoma in a South East Asian population. Head Neck 2018; 40: 1425-33. [Crossref]

29. Zhu W, Chen F, Li J, Wang W, Zhang H, Yang G, et al. Dosimetric parameters associated with conductive or sensorineural hearing loss 5 years after intensity-modulated radiation therapy in nasopharyngeal carcinoma. Acta Otolaryngol 2019; 139: 263-8. [Crossref]

30. Nutting CM, Morden JP, Beasley M, Bhide S, Cook A, De Winton E, et al. Results of a multicentre randomised controlled trial of cochlear-sparing intensity-modulated radiotherapy versus conventional radiotherapy in patients with parotid cancer (COSTAR; CRUK/08/004). Eur J Cancer 2018; 103: 249-58. [Crossref]