Article published online: 2025-02-06

Sensorineural Hearing Loss after Chemoradiotherapy with High-Dose Cisplatin in Patients with Head and Neck Cancer

Ryosuke Kitoh[1] Kota Hirose[1] Mariko Kasuga[1] Kentaro Hori[1] Yoh Yokota[1] Yoh-ichiro Iwasa[1] Yutaka Takumi[1]

[1] Department of Otorhinolaryngology-Head and Neck Surgery, Shinshu University School of Medicine, Matsumoto-shi, Nagano, Japan

Int J Pract Otolaryngol 2025;8:e8–e18.

Address for correspondence Ryosuke Kitoh, MD, PhD, Department of Otorhinolaryngology-Head and Neck Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto-shi, Nagano 3908621, Japan (e-mail: ryosuke@shinshu-u.ac.jp).

Abstract

Objective To investigate sensorineural hearing loss in patients with head and neck cancer receiving chemoradiotherapy (CRT) with a standard regimen of high-dose cisplatin, focusing on the acute changes before and after CRT with high-dose cisplatin (CDDP).

Materials and Methods A total of, 135 cases of head and neck cancer treated with high-dose cisplatin-based CRT between 2014 and 2023 were included in this retrospective study. The hearing threshold shifts at each frequency before and after each CDDP dose were used as an indicator to assess hearing impairment.

Results The CRT-induced hearing threshold shift was greater at frequencies >4,000 Hz, with a threshold increment of ~10 dB at 4,000 Hz and 20 dB at 8,000 Hz. The threshold after each course of CDDP was elevated at one week after CDDP administration, and the changes in the thresholds from one week after administration to just before the subsequent course were small. Total CDDP dose, radiation dose to the cochlea, and mean pretreatment hearing thresholds were identified as significant factors influencing the increase in hearing thresholds at 8,000 Hz.

Conclusion In patients with head and neck cancer receiving CRT with high-dose cisplatin, threshold increment was predominantly observed at frequencies >4,000 Hz, as previously reported. The threshold increment occurred immediately after CDDP administration, which might be relevant when considering the timing of future interventions.

Keywords
- sensorineural hearing loss
- chemoradiotherapy
- high-dose cisplatin
- head and neck cancer

Introduction

Chemoradiotherapy (CRT) with high-dose cisplatin (CDDP) is a major part of standard treatment for head and neck squamous cell cancer. However, this treatment may cause several adverse effects, including hearing impairment. Other effects include renal dysfunction and cytopenia, which are easily accessed through blood tests, as well as nausea and vomiting, which are common complaints from patients. However, patients are not usually tested for hearing impairment unless they report any symptoms.

Despite numerous reports on CDDP-induced hearing loss, previous studies (1) focused on treatment with CDDP alone (without concurrent radiation therapy), (2) used non-

received
August 20, 2024
accepted after revision
November 13, 2024

DOI https://doi.org/10.1055/s-0045-1802338.
ISSN 2569-1783.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

standardized CDDP regimens, and (3) performed almost no hearing tests during CDDP administration.

In this study, we characterized hearing impairment in patients receiving CRT with CDDP according to a standardized regimen, focusing on the acute changes observed before and after CDDP administration.

Materials and Methods

This retrospective study included patients with head and neck squamous cell cancer who underwent CRT with high-dose CDDP at our hospital between April 2014 and September 2023.

The following cases were excluded: patients with primary cancer of the external auditory canal and those who received induction chemotherapy; one pediatric case (age, 16 years); cases with severe unilateral hearing loss caused by other diseases (two ears); and cases with obvious conductive hearing loss (ten ears; eight with otitis media with effusion and two with chronic otitis media), based on previous reports stating that sensorineural hearing loss accounts for the majority of CDDP-induced hearing loss cases. None of the included ears in this study had otitis media with effusion before treatment or developed conductive hearing loss due to new-onset otitis media with effusion during treatment. In total, 135 patients (258 ears) were included.

The primary diseases were treated in accordance with the guidelines, with 100 mg/m^2 CDDP administered every three weeks for up to three courses. The doses were adjusted based on adverse reactions from the previous CDDP course and renal function. For radiotherapy, the radiation dose for lesions was 70 Gy. Opposing or non-opposing bilateral portal irradiation was performed in four cases before introducing volumetric modulated arc therapy (VMAT) and in seven pharynx T2 cases following the VMAT introduction. VMAT was used in the remaining cases. The radiation dose to the cochlea was evaluated only in cases where VMAT was used; in evaluable cases, the treatment plan was designed to minimize the dose as much as possible.

Hearing tests were carried out before treatment initiation, and after treatment initiation, the tests were carried out before chemotherapy administration (basically the day before or the morning of the day of administration) and one week after CDDP administration. Air conduction hearing thresholds were assessed at 125, 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz, whereas bone conduction thresholds were evaluated at 250, 500 1,000, 2,000, and 4,000 Hz.

Statistical analysis was conducted using SPSS Statistics ver. 27 q(SPSS Inc, Chicago, IL, USA). The *t*-test (Welch *t*-test for non-homogenous variances) and Kruskal–Wallis test were used. Multiple regression analysis was performed for multivariate analysis. The significance level was set at <0.05.

This study was approved by our hospital's ethics committee (approval date: 12 October 2020; approval no. 4209).

Results

Patient Characteristics

The data for all patients included in this study are summarized in ►**Table 1**. Among the patients, the most common tumor location was the oropharynx, followed by the hypopharynx, nasopharynx, and larynx; these four locations accounted for 90% (123/135) of the cases. Three, two, and one CDDP courses

Table 1 Patient characteristics

Number of patients	**135**
Number of evaluated ears	258
Sex	
Male	111
Female	24
Age	
Mean (years)	63.01 ± 9.11
Range (years)	34–76
Primary site	
Nasopharynx	21
Oropharynx	47
Hypopharynx	29
Larynx	26
Paranasal cavity	10
Oral cavity	2
Staging	
T stage	
1	24
2	64
3	24
4a/4b	23
N stage	
0	34
1	41
2a/2b/2c	55
3	5
Stage	
I	18
II	31
III	28
IVa/IVb	58
Cisplatin administration	
Number of courses	
1	1
2	29
3	105
Dose	
Average (mg/m^2)	259.9 ± 45.7

(*Continued*)

Table 1 (*Continued*)

Number of patients	135
Median (mg/m^2)	280
Radiotherapy	
Irradiation method	
Opposing/non-opposing bilateral portal irradiation	11
Volumetric modulated arc therapy (VMAT)	124
Radiation dose to the cochlea (226 ears)	
Mean radiation dose in evaluable ears (Gy)	18.9 ± 13.7
Range (Gy)	0–69.8

were administered in 105, 29, and 1 case, respectively. The average CDDP dose was 259.9 ± 45.7 mg/m^2, with a median dose of 280 mg/m^2. The mean radiation dose to the cochlea in all evaluable ears was 19.3 ± 13.7 Gy (range, 0–68.8 Gy).

Hearing Threshold Shifts

The air conduction hearing thresholds measured at various frequencies for the left and right ears during the pretreatment and final examinations were compared across all cases (►**Table 2**). The pretreatment hearing thresholds were slightly elevated at higher frequencies, possibly because of the patient's age. After treatment, the thresholds at these higher frequencies became even more pronounced. Comparison of the pre- and post-treatment thresholds showed increases at all frequencies evaluated, with significant differences except at 125 and 250 Hz in the right ear. The mean increases in thresholds up to 2,000 Hz were modest, ranging from 1 to 4 dB; however, those at 4,000 and 8,000 Hz were 10 and 20 dB, respectively, indicating that the threshold primarily increased in the higher frequency range (►**Fig. 1**).

Hearing Threshold Shifts for Each Course

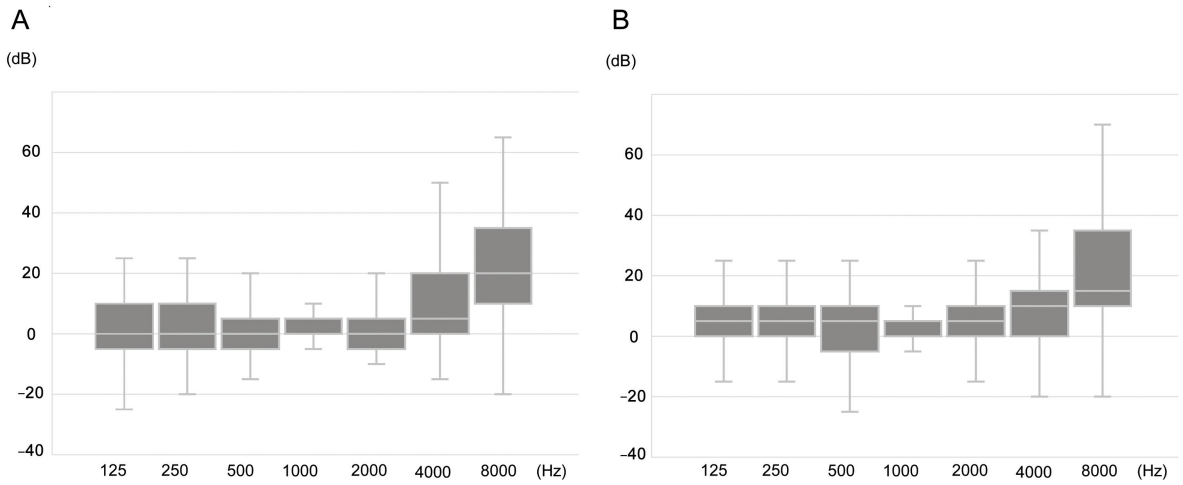
In this study, 10 patients who did not undergo some hearing tests during treatment were excluded; thus, 125 cases were included. The threshold shifts at 8,000 Hz, where the largest increases were observed, after the first, second, and third courses compared with thresholds before respective courses were 10.56 ± 13.39, 8.86 ± 11.78, and 5.22 ± 8.96 dB, respectively, with significant differences between the third course and the first or second course (►**Fig. 2**). The thresholds between the end of the first course and the beginning of the second course and between the end of the second course and the beginning of the third course were −1.79 ± 9.10 and −0.27 ± 8.57 dB, respectively, indicating that the thresholds remained unchanged or improved slightly during the intervals between the courses. To rule out any effects of dose differences among the courses, the patients who completed all three courses without a dose reduction (i.e., received CDDP at 100 mg/m^2 in all three courses) were extracted, and the increases in hearing threshold during each course for 103 ears of these patients were determined. The mean increases in the threshold during the first, second, and third courses were 10.8 ± 15.5, 13.1 ± 12.6, and 6.4 ± 9.6 dB, respectively, showing significant differences between the third course as well as the first and second courses.

Based on the above results, the ears were divided into two groups to examine the associations between the hearing thresholds measured before each CDDP course and the increases in thresholds after each course: ears with a threshold of <50 dB HL at 8,000 Hz before each course and those with a threshold of ≥50 dB HL at 8,000 Hz before each course. The results of the comparisons between the two groups are summarized in ►**Table 3A**. Comparisons between the <50-

Table 2 Average hearing thresholds at various frequencies for the left and right ears pretreatment and at the final examination

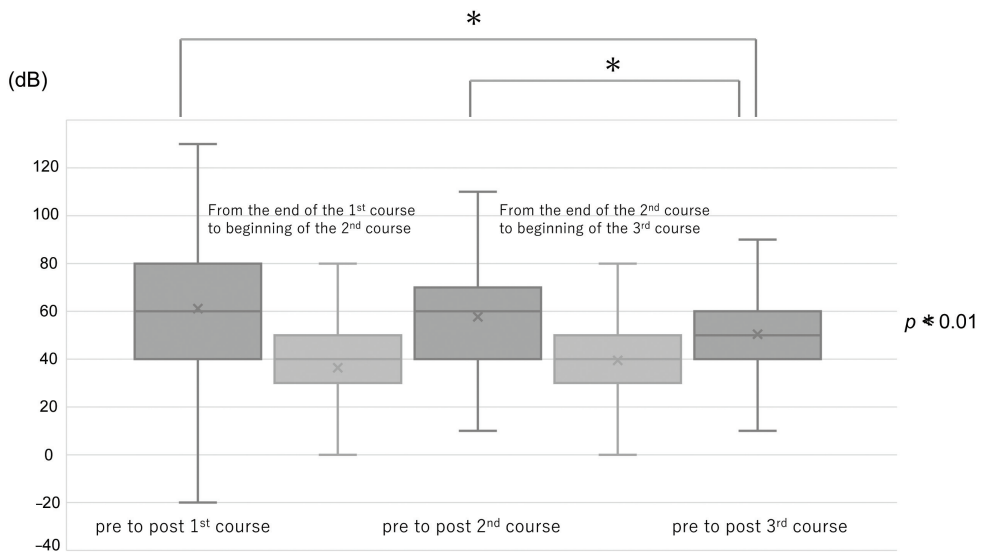
	Frequency (Hz)	Pretreatment (dB)	Final examination (dB)	*p*-Value
Right ear	125	24.4 (SD = 11.2)	25.6 (SD = 11.6)	0.170
	250	24.5 (SD = 11.4)	25.7 (SD = 11.7)	0.175
	500	23.3 (SD = 11.2)	25.0 (SD = 12.1)	**0.036**
	1,000	19.3 (SD = 11.9)	21.1 (SD = 12.5)	**0.005**
	2,000	24.2 (SD = 15.1)	27.6 (SD = 15.7)	<**0.001**
	4,000	34.1 (SD = 20.7)	45.7 (SD = 19.3)	<**0.001**
	8,000	42.8 (SD = 23.4)	64.8 (SD = 18.5)	<**0.001**
Left ear	125	22.3 (SD = 9.7)	26.3 (SD = 11.5)	<**0.001**
	250	22.8 (SD = 9.9)	25.9 (SD = 11.9)	<**0.001**
	500	22.6 (SD = 10.7)	25.5 (SD = 11.4)	<**0.001**
	1,000	19.2 (SD = 11.4)	21.6 (SD = 12.5)	<**0.001**
	2,000	24.0 (SD = 16.8)	27.6 (SD = 16.1)	<**0.001**
	4,000	36.1 (SD = 21.5)	46.4 (SD = 19.4)	<**0.001**
	8,000	43.7 (SD = 23.9)	64.6 (SD = 18.1)	<**0.001**

Note: Significant increases were observed at all frequencies except for 125 and 250 Hz in the right ear.



	Frequency (Hz)						
	125	250	500	1,000	2,000	4,000	8,000
Δ Right ear (dB)	1.18 (SD = 9.76)	1.19 (SD = 9.94)	1.64 (SD = 8.89)	1.88 (SD = 7.5)	3.32 (SD = 9.40)	11.60 (SD = 15.59)	21.95 (SD = 18.99)
Δ Left ear (dB)	4.02 (SD = 9.68)	3.03 (SD = 9.07)	2.95 (SD = 9.14)	2.40 (SD = 6.57)	3.66 (SD = 10.19)	10.27 (SD = 16.64)	20.83 (SD = 18.57)

Fig. 1 Hearing threshold shifts at the final evaluation compared with pretreatment levels in the left and right ears across various frequencies. The vertical axis represents increases in the threshold, whereas the horizontal axis denotes frequencies. (A, right ear; B, left ear) The average increases in the threshold up to 2,000 Hz were modest, ranging from 1 to 4 dB. However, those at 4,000 and 8,000 Hz were ∼10 and 20 dB, respectively, indicating an increased hearing threshold mainly in the higher frequency range.



	Before and after the 1st course	From the end of the 1st course to beginning of the 2nd course	Before and after the 2nd course	From the end of the 2nd course to beginning of the 3rd course	Before and after the 3rd course
Number of ears examined	239	237	237	182	182
Mean increase in threshold (dB)	10.6 ± 13.4	−1.8 ±9.1	8.9 ± 11.8	−0.3 ± 8.6	5.2 ± 9.0

Fig. 2 Mean increases in hearing threshold at 8,000 Hz after each course of CDDP administration were calculated from the level before each course (from after to before a course) and during the intervals between treatment courses (from the end of a course to the beginning of the next course). Threshold shifts were observed after the first, second, and third courses compared with the thresholds before the respective courses, whereas the thresholds remained virtually unchanged during the intervals between courses. The increase in the threshold after the third course was significantly smaller than that after the first and second course (*t*-test, $p < 0.01$).

Table 3 Relationship between hearing thresholds before CDDP administration and threshold shifts (*t*-test)

A. 8,000 Hz				
Course no.	**Hearing threshold before CDDP administration**	**Number of ears (%)**	**Hearing threshold shifts after each course from that before the course (dB)**	***p*-Value**
1	<50dB HL	139 (57.9%)	16.29 ± 12.77	<0.001
	≥50dB HL	101 (42.1%)	2.57 ± 9.61	
2	<50dB HL	88 (37.0%)	14.94 ± 12.88	<0.001
	≥50dB HL	150 (63.0%)	5.23 ± 9.40	
3	<50dB HL	36 (19.7%)	10.97 ± 10.41	<0.001
	≥50dB HL	147 (80.3%)	3.78 ± 7.97	
B. 4,000 Hz				
Course	**Hearing threshold before CDDP administration**	**Number of ears (%)**	**Hearing threshold shifts after each course from that before the course (dB)**	***p*-value**
1	<50dB HL	160 (66.7%)	5.73 ± 8.92	<0.001
	≥50dB HL	80 (33.3%)	0.56 ± 7.79	
2	<50dB HL	148 (62.2%)	7.59 ± 8.73	<0.001
	≥50dB HL	90 (37.9%)	1.17 ± 7.50	
3	<50dB HL	106 (57.9%)	6.80 ± 9.56	<0.001
	≥50dB HL	77 (42.1%)	1.75 ± 6.63	

Note: When the hearing thresholds before CDDP administration were divided into the <50 dB HL and ≥50 dB HL groups, the threshold shifted across all frequencies, and all courses were significantly greater in the < 50 dB group. The percentage of ears in the <50-dB HL group decreased noticeably at 8,000 Hz as the number of courses increased, whereas the percentage decreased only slightly at 4,000 Hz.

and ≥50dB HL groups based on course revealed significantly greater increases in the threshold for the < 50dB HL group. The results of similar comparisons of thresholds at 4,000 Hz are presented in ►**Table 3B**.

Factors Influencing Threshold Shift

Initially, univariate analysis was performed to assess whether the threshold shifts at 8,000 Hz, where the increases were greatest, were associated with patient and disease backgrounds and treatment details (►**Table 4**). The result showed significant differences in seven factors, including age, mean pretreatment hearing threshold, and creatinine clearance.

Based on the above findings, multiple regression analysis was performed on the threshold shifts at 2,000, 4,000, and 8,000 Hz. The threshold shifts from pre-treatment to post-treatment were considered as dependent variables, while radiation dose to the cochlea and the seven significant factors from the univariate analysis were considered as independent variables (►**Table 5**). Multiple regression analysis identified the mean pretreatment hearing threshold, total CDDP dose, and radiation dose to the cochlea as factors significantly associated with threshold shifts at 8,000 Hz. Similarly, the mean pretreatment hearing threshold, radiation dose to the cochlea, T stage, and age were associated with threshold shifts at 4,000 Hz and the mean pretreatment hearing threshold and T stage were associated with threshold shifts at 2,000 Hz.

In addition, ROC analysis calculations using a threshold elevation at 8,000 Hz of 30 dB as a cut-off value derived a mean pretreatment hearing threshold of 19.375 dB, a total CDDP dose of 270 mg/m^2, and a radiation dose to the cochlea of 15.235 Gy as cut-off values (►**Fig. 3**).

Discussion

In this study, the hearing threshold shifts at different frequencies in the left and right ears were evaluated, focusing on the acute changes before and after CDDP administration. Although hearing threshold shifts from pre- to post- treatment were obtained at various frequencies, the shifts at ≤2,000 Hz frequencies were small (range: 1–4 dB), whereas those that primarily occurred at 4,000 and 8,000 Hz were significant.

Previous reports on CDDP-induced hearing impairment are unsuitable for direct comparison with the conditions of the present study because those studies included patients who did not receive CRT and/or those who received CRT with low-dose CDDP (40 mg/m^2). Nevertheless, high-frequency hearing loss was a common feature observed for all patients in the present and previous studies.

Threshold Shifts for Each Course

The present study focused on 8,000 Hz, where particularly significant increases in the threshold induced by CDDP were observed. The results revealed an increase in the threshold at one week after each course compared with that before the course; practically, the threshold values between courses

Table 4 Univariate analysis of hearing threshold elevation at 8,000 Hz and various candidate factors

	Number of ears evaluated	Mean increase in the hearing threshold at 8000 Hz (dB)	*p*-Value
Age (years)			
<55	39	28.1 ± 21.1	$<$**0.001**
55–64	94	26.6 ± 20.1	
≥ 65	125	15.4 ± 14.8	
Sex			
Male	212	21.5 ± 19.1	0.712
Female	46	20.98 ± 17.4	
History of hypertension			
Yes	82	21.27 ± 18.9	0.888
No	176	21.64 ± 18.6	
History of diabetes mellitus			
Yes	17	12.05 ± 17.3	**0.036**
No	241	22.05 ± 18.7	
Mean pretreatment hearing threshold (mean of measurements at four frequencies)			
<25 dB	143	28.53 ± 18.1	$<$**0.001**
≥ 25 dB, <40 dB	77	16.29 ± 14.3	
≥ 40 dB	38	4.86 ± 15.3	
Creatinine clearance			
<50 mL/min	10	8.5 ± 15.6	**0.014**
$\geq 50, <60$ mL/min	25	16 ± 12.4	
$\geq 60, <100$ mL/min	185	21.7 ± 19.3	
≥ 100 mL/min	38	26.84 ± 18.5	
Primary site			
Nasopharynx	38	25.39 ± 21.79	0.142
Oropharynx	90	20.16 ± 16.73	
Hypopharynx	57	18.94 ± 20.0	
Larynx	51	19.5 ± 17.3	
Paranasal cavity	18	30 ± 18.1	
Oral cavity	4	31.25 ± 26.6	
Positional relationship between the primary lesion and ear evaluated			
Affected side	100	19.75 ± 19.3	0.554
Unaffected side	107	21.63 ± 17.6	
Both sides	51	24.11 ± 20.0	
Staging			
T stage			
1	47	25.63 ± 21.1	**0.032**
2	124	17.9 ± 18.4	
3	47	22.55 ± 15.6	
4a/4b	40	25.87 ± 19.0	
N stage			
0	65	24.69 ± 20.0	**0.036**
1	80	17.43 ± 17.4	
2a/2b/2c	104	21.82 ± 18.2	
3	9	27.77 ± 23.5	

(*Continued*)

Table 4 (*Continued*)

	Number of ears evaluated	Mean increase in the hearing threshold at 8000 Hz (dB)	*p*-Value
Cisplatin dose (mg/m^2)			
<200 mg/m^2	14	8.21 ± 14.9	$<$**0.001**
≥ 200 mg/m^2, <300 mg/m^2	133	18.61 ± 16.9	
300 mg/m^2	111	26.40 ± 19.91	
Mean radiation dose to the cochlea			
<20 Gy	133	20.1 ± 17.7	0.056
≥ 20 Gy, <40 Gy	71	25.2 ± 19.8	
≥ 40 Gy	21	27.1 ± 20.5	

Note: Among patient and disease background factors, age, history of diabetes mellitus, mean pretreatment hearing threshold, creatinine clearance, and T and M stages were significantly associated. Among treatment-related factors, the total doses of CDDP and radiation to the cochlea showed significant associations.

Table 5 Multiple regression analysis to identify factors associated with increases in hearing threshold at various frequencies (using the forward selection method)

A. 8,000 Hz: Forward selection R = 0.566				
	Unstandardized coefficient (B)	**Standard error**	**Standardized coefficient**	***p*-Value**
Mean pretreatment hearing threshold	−0.723	0.084	−0.491	$<$**0.001**
Total CDDP dose (mg/m^2)	0.092	0.024	0.314	$<$**0.001**
Radiation dose to the cochlea	0.191	0.077	−0.186	**0.013**
N stage	−1.000			0.078
Pretreatment creatinine clearance (mg/dL)	−0.087			0.155
T stage	0.081			0.153
Age	0.022			0.724
History of diabetes mellitus	0.016			0.779
B. 4,000 Hz: Forward selection R = 0.559				
	Unstandardized coefficient (B)	**Standard error**	**Standardized coefficient**	***p*-Value**
Mean pretreatment hearing threshold	−0.708	0.083	−0.529	$<$**0.001**
Radiation dose to the cochlea	0.223	0.069	0.182	**0.002**
T stage	2.993	0.997	0.174	**0.003**
Age	0.267	0.113	0.151	**0.019**
Total CDDP dose (mg/m^2)	0.078			0.175
Pretreatment creatinine clearance (mg/dL)	0.105			0.177
History of diabetes mellitus	0.056			0.329
N stage	−0.054			0.351
C. 2,000 Hz: Forward selection R = 0.354				
	Unstandardized coefficient (B)	**Standard error**	**Standardized coefficient**	***p*-Value**
Mean pretreatment hearing threshold	−0.218	0.046	−0.283	$<$**0.001**
T stage	2.418	0.62	0.231	$<$**0.001**
Pretreatment creatinine clearance (mg/dL)	−0.085			0.164
N stage	0.081			0.173
Radiation dose to the cochlea	0.073			0.220
Age	0.08			0.233
History of diabetes mellitus	−0.04			0.511
Total CDDP dose (mg/m^2)	−0.036			0.548

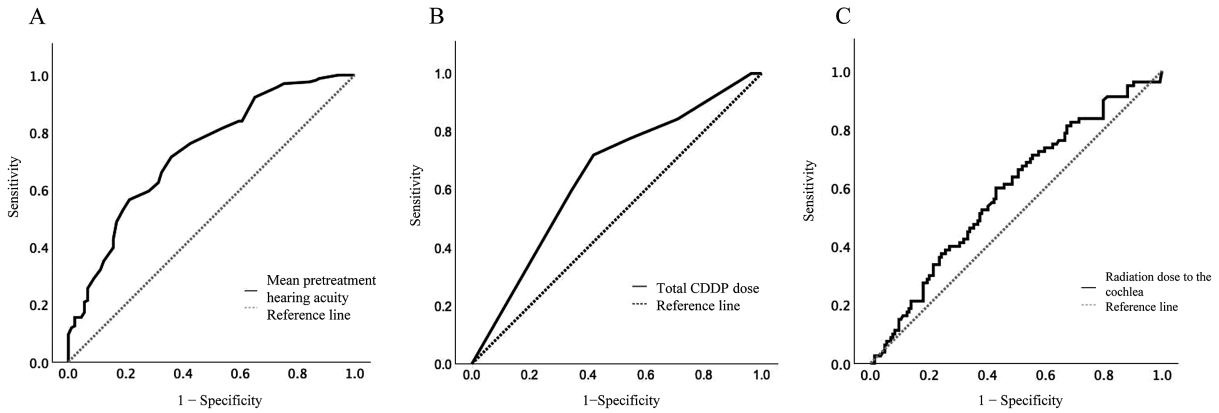


Fig. 3 ROC analysis of factors associated with an increase in hearing thresholds at 8,000 Hz. An increase in the threshold by ≥30 dB was used as a cutoff for the analysis. (A) The cutoff value for the pretreatment hearing threshold was 19.4 dB (sensitivity, 71.6%; specificity, 64%; AUC, 0.73). (B) The cutoff value for the total CDDP dose was 270 mg/m^2 (sensitivity, 71.9%; specificity, 58.0%; and AUC, 0.649). (C) The cutoff value for the radiation dose to the cochlea was 15.2 Gy (sensitivity, 60.0%; specificity, 56.6%; and AUC, 0.587).

remained unchanged, and the increase in the threshold during the third course was smaller than that in the first or second course.

Limited studies have reported progress during drug administration. In a report by Pandav et al,[1] patient was evaluated thrice after radiation at 10, 42, and 60 Gy during treatment, with 30%, 40%, and 63% of the patients having a hearing impairment at 8,000 Hz, respectively, based on American Speech-Language-Hearing Association (ASHA) criteria, and showing an upward trend. However, the study included only 30 patients treated with CRT, and the present study merits its inclusion of a large number of cases. The detection of acute increases in the threshold one week after CDDP administration compared with the threshold measured immediately before CDDP administration was considered highly significant in terms of its potential for preventive interventions.

The threshold increase during the third course was milder than that in the first and second courses. This was initially thought to be due to the reduction in CDDP dose in the third course. In fact, the mean CDDP doses per body surface area in the first, second, and third courses were 98.9 ± 4.5, 92.0 ± 13.2, and 88.4 ± 15.1 mg/m^2, respectively, showing significant progressive decreases. However, a significant difference remained in the threshold shift between the third course and the first or second course when only the patients who could complete the three courses without dose reduction (i.e., received CDDP 100 mg/m^2 in all three courses) were included in the analysis. Therefore, the CDDP dose differences cannot fully explain the smaller threshold shift in the third course than that in the first and second courses.

Previous animal experiments have reported that CDDP primarily damages the outer hair cells in the inner ear.[2,3] The outer hair cells contribute to increased sensitivity and generation of frequency selectivity in auditory reception through local amplification of basilar membrane vibrations. The magnitude of the contribution is greater at lower input sound levels, but decreases as the input sound level increases. Thus, damage to the outer hair cells is considered to raise the threshold by 50 dB. In other words, the threshold increment caused by CDDP ototoxicity is expected to decrease as the threshold before CDDP administration approaches 50 dB HL. Therefore, threshold shifts were compared between ears with a threshold of <50 dB HL at 8,000 Hz before each course and those with a threshold of ≥50 dB HL at 8,000 Hz before each course. As shown in ►**Table 3A**, 100/239 (41.8%) of the ears examined had a hearing threshold of ≥50 dB HL before the first course of CDDP, whereas 149/237 (62.9%) and 146/182 (80.2%) had a hearing threshold of ≥50 dB HL before the second and third courses, respectively. These results suggest that the prevalence of hearing thresholds of ≥50 dB HL before CDDP administration increased with the number of CDDP courses. Furthermore, the increase in the threshold for the <50 dB HL group was significantly greater than that for the ≥50 dB HL group in each course. The threshold shifts at 4,000 Hz in the first, second, and third courses were 4.0 ± 8.9, 5.2 ± 8.8, and 4.7 ± 8.8 dB, respectively, showing no significant differences. Furthermore, when the ears were divided into the two groups with thresholds of <50 or ≥50 dB HL before CDDP administration, the increases in the threshold differed significantly between them in all courses (►**Table 3B**). The results at 4,000 Hz were different from those at 8,000 Hz because the threshold increases at 4,000 Hz were milder; therefore, the percentage of ears with a threshold of ≥50 dB HL before CDDP administration did not increase with the number of CDDP courses (first course, 80/239 [33.3%]; second course, 90/237 [37.9%]; and third course, 77/182 [42.1%]).

Factors Influencing Increases in Threshold

A multivariate analysis conducted to identify factors associated with threshold elevation at various frequencies showed that the total CDDP and radiation doses to the cochlea were the factors associated with threshold elevation at 8,000 Hz, and only the radiation dose to the cochlea was associated with the threshold elevation at 4,000 Hz; however, none of these factors were significantly associated with the threshold at 2,000 Hz. Previous studies have also documented that

CDDP- or radiotherapy-induced hearing loss occurs primarily at 4,000 Hz and higher frequencies. In this respect, our results support previous findings.

A systematic review by Theunissen et al examined various factors, including age, hearing acuity before drug administration, and sex. They state that the impact of age was reported in many studies; however, studies that focused on hearing acuity before drug administration and sex were limited.[4]

Many studies have shown an association between the CDDP dose and hearing impairment. Among four papers analyzing the association between the CDDP dose and hearing loss, which were included in the above systematic review, three showed that the cumulative CDDP dosage was significantly correlated with the incidence of hearing loss and the severity of threshold elevation.[5–7] A recent study reported on a threshold elevation prediction model, showing that every 100 mg/m^2 increase in CDDP dose leads to a 2.92 dB increase in the threshold.[8] In addition, in a deintensification trial of postoperative CRT for HPV-related oropharyngeal cancer, Lee et al[9] compared a conventional three-course regimen of CDDP at 100 mg/m^2 with a single-administration regimen of CDDP at 100 mg/m^2. The study revealed that the incidence rate of common terminology criteria for adverse events (CTCAE) grade $\geq$2 hearing impairment with the latter regimen (5%) was significantly lower than that with the former regimen (46%).[9] In this study, the dose per administration was analyzed in addition to the total dose. In a retrospective analysis, Gamez et al[10] compared the incidence of hearing impairment between weekly CDDP administration at 40 mg/m^2 and the conventional three-course regimen of CDDP administration at 100 mg/m^2 every three weeks. The final incidence rates of grade $\geq$3 hearing impairment with the weekly administration regimen and the triweekly three-course regimen were 13% and 56%, respectively, indicating a significant difference.[10] For postoperative radiation, the JCOG1008 trial compared the weekly administration at 40 mg/m^2 with the triweekly three-course regimen at 100 mg/m^2, reporting that hearing impairment of any grade occurred in 9 (7%) cases in the former group and 22 (17%) in the latter group.[11] Based on these findings, the weekly 40 mg/m^2 administration regimen is currently adopted for postoperative CRT, and the incidence of hearing impairment may decrease in the future.

Many studies have shown a link between the radiation dose to the cochlea and the severity of hearing impairment in CRT or RT alone. According to the normal tissue dose tolerance reported by QUANTEC, the incidence of hearing impairment was $<$30% when fractionated up to 45 Gy.[12] A recent meta-analysis on radiation and ototoxicity showed that the mean radiation dose was associated with hearing impairment and that intensity-modulated radiotherapy significantly reduced the risk of hearing impairment compared with conventional radiation regimens.[13] Specifically, hearing impairment occurred in 27% of cases with a radiation dose to the cochlea of 30–40 Gy, and the incidence increased to 35% with a dose of 50–60 Gy. With the advancements in radiation dose settings, such as intensity-modulated radiotherapy, the use of radiation doses to the cochlea of $<$30 Gy has recently been recommended to prevent hearing impairment. In the present study, the threshold calculated through ROC analysis using an increase in the 8,000 Hz hearing threshold of $\geq$30 dB as a cut-off was 15.2 Gy, suggesting that the dose settings to prevent hearing impairment in CRT would be even lower.

Regarding age, some studies have reported that the incidence of hearing loss is lower in younger patients, whereas others have shown that the incidence is higher in younger patients. Chan et al reported that the hearing ability at lower frequencies (mean of 500, 1000, and 2,000 Hz) was less affected in younger patients, and age was not significantly associated with the hearing ability at higher frequencies (4,000 Hz).[7] Zurr et al showed a positive correlation between age and threshold elevation; however, the correlation coefficient was small.[14] In both studies, treatment heterogeneity appeared to prevent a reliable analysis of whether age influences CRT-related ototoxicity; for example, some patients received RT alone with high and low doses of CDDP. The present study identified age as a significant factor only for threshold elevation at 4,000 Hz. Our results indicate that the pretreatment hearing threshold as a more direct factor may have a stronger association than age.

Methods and Timing of Evaluating CDDP-induced Hearing Impairment

Previous studies of CDDP-induced hearing loss have used a variety of assessment criteria in addition to threshold shifts at different frequencies. The specific grading criteria mentioned in these reports include: (1) CTCAE,[15] (2) ASHA,[16] and (3) TUNE grading system.[17] We will not detail these evaluation methods for hearing impairment because of the use of ototoxic drugs; however, the primary difference is whether the evaluation criteria are based on hearing threshold measurements rather than the severity of subjective symptoms and threshold elevation.[18] The purpose of evaluating drug-induced hearing impairment is not just to objectively evaluate ototoxicity but also to provide functional evaluation at an early and clinically important stage for the development of appropriate intervention and treatment strategies. Many grading methods are effective for the former purpose but are suboptimal to be useful for the latter because of variations in pretreatment hearing thresholds. In that regard, the TUNE grading system appears useful for intervention in clinical practice because subjective symptoms, such as tinnitus without threshold shifts, are used to define grade 1a ototoxicity and absolute means of pure tone audiometry results are used to define grade 3 and 4 ototoxicity. However, events would be rated as grade 1 or 2 even if the hearing threshold was $>$35 dB before drug administration (i.e., the patient had a pretreatment hearing threshold equivalent to grade 3) and increased by 10–20 dB, reaching 50 dB. As in this example, patients with thresholds requiring intervention are potentially considered to have grades 1 and 2 hearing impairments. Therefore, it is challenging to determine the appropriate timing of initiating intervention solely based on grade-related information.

These various grading methods also complicate the interpretation of the incidence rates of hearing impairment

induced by CDDP. A systematic review by Theunissen et al[4] showed that the incidence rates of hearing loss based on the CTCAE or ASHA criteria vary depending on the frequency band tested (79–89%), and the incidence rates of hearing loss based on an increase in bone conduction threshold of ≥15 dB were 56% when the 4,000 Hz test results were used and 9% when the mean values of thresholds at 500, 1000 and 2000 Hz were used, differing noticeably. In the present study, the incidence of grade ≥1 hearing impairment was 54.8% (grade 1, 23.0%; grade 2, 15.6%; and grade 3, 16.3%) and 86.7% based on the CTCAE and ASHA criteria, respectively, which differed significantly depending on the assessment method (to be precise, these are not accurate incidence rates because CTCAE v5.0 requires hearing tests at 3,000 and 6,000 Hz).

This study has limitations. The threshold shifts were evaluated only during treatment. Hearing acuity was monitored for three to six months after treatment in many previous reports and even several years after treatment in some cases. Shetty et al reported that hearing loss, based on the ASHA criteria, was noted in 85/140 ears (60.7%) immediately after treatment; however, the incidence increased to 93/140 ears (66.4%) one month after treatment.[19] However, the difference was not statistically significant, and the incidence rate at three months remained unchanged from the rate at one month. Chan et al followed up on the patients for up to two years after treatment and reported that the hearing threshold shift stabilized three months after treatment with CRT.[20] In the present study, CRT-induced hearing impairment may not have been fully evaluated because post-treatment hearing threshold shifts were unconfirmed. Nevertheless, this study revealed that CDDP-induced hearing impairment primarily occurred immediately after drug administration, indicating that any threshold elevation following the completion of the treatment may reflect different pathological changes.

Finally, recent studies have reported that genetic factors, including genes related to CDDP metabolism, such as *GST* and oxidative stress-related genes, are associated with elevated hearing thresholds. Therefore, future studies on these factors, including their relationships with the factors analyzed in this study, are necessary.[21]

Conclusion

This study characterized hearing impairment in patients who received CRT at our hospital. The results showed that hearing thresholds at many frequencies were significantly higher than those measured before treatment, especially at 4,000 and 8,000 Hz.

The temporal relationship analysis between each CDDP course and hearing threshold elevation showed that the threshold increases from pretreatment levels occurred one week after CDDP administration, with no particular changes observed from one week after CDDP administration to the beginning of the next course. The increase in the hearing threshold for the third course was the smallest, probably because of the higher percentage of cases where the threshold reached 50 dB HL by the second course. The pretreatment hearing threshold, total CDDP dose, and radiation dose to the cochlea were identified as factors influencing CDDP-induced threshold elevation, particularly at 8,000 Hz.

Conflict of Interest
None declared.

References

1 Pandav R, Yadav V, Bhagat S, Sharma DK. Ototoxicity in patients of advanced head and neck malignancies receiving chemoradiation versus radiation alone: comparative study. Indian J Otolaryngol Head Neck Surg 2022;74(suppl 3):3927–3932
2 Morita I, Hosokawa S, Hiraide F, Inouye T. Cisplatin ototoxicity. Pract Otorhinolaryngol 1985;78:561–568
3 Laurell G, Engström B. The ototoxic effect of cisplatin on guinea pigs in relation to dosage. Hear Res 1989;38(1–2):27–33
4 Theunissen EA, Bosma SC, Zuur CL, et al. Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: a systematic review of the literature. Head Neck 2015;37(02):281–292
5 Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. J Clin Oncol 2007;25(24):3759–3765
6 Chen WC, Jackson A, Budnick AS, et al. Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 2006;106(04):820–829
7 Chan SH, Ng WT, Kam KL, et al. Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. Int J Radiat Oncol Biol Phys 2009;73(05):1335–1342
8 Schuette A, Lander DP, Kallogjeri D, et al. Predicting hearing loss after radiotherapy and cisplatin chemotherapy in patients with head and neck cancer. JAMA Otolaryngol Head Neck Surg 2020; 146(02):106–112
9 Lee DS, Mahal RS, Tharakan T, et al. Hearing outcomes in a deintensification trial of adjuvant therapy for HPV-related oropharyngeal squamous cell carcinoma. Otolaryngol Head Neck Surg 2023;168(05):1089–1096
10 Gamez ME, Blakaj DM, Bhateja P, et al. Audiological outcomes of weekly vs. triweekly cisplatin in head and neck cancer with cochlear-sparing intensity-modulated radiation therapy. Cancers (Basel) 2024;16(12):2228
11 Kiyota N, Tahara M, Mizusawa J, et al; Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG) Weekly cisplatin plus radiation for postoperative head and neck cancer (JCOG1008): a multicenter, noninferiority, phase II/III randomized controlled trial. J Clin Oncol 2022;40(18):1980–1990
12 Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(suppl 3)S10–S19
13 Huang Y, Zhou H, An F, et al. The relevance of ototoxicity induced by radiotherapy. Radiat Oncol 2023;18(01):95
14 Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. Radiother Oncol 2008;89(01):38–43
15 National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services. Common Terminology Crtieria for Adverse Events (CTCAE), Version 5.0. pp13, 2017
16 American Speech-Language-Hearing Association (ASHA) Guidelines for the audiologic management of individuals recieving cochleotoxic drug therapy. ASHA 1994;36:1–19
17 Theunissen EA, Dreschler WA, Latenstein MN, et al. A new grading system for ototoxicity in adults. Ann Otol Rhinol Laryngol 2014; 123(10):711–718
18 Crundwell G, Gomersall P, Baguley DM. Ototoxicity (cochleotoxicity) classifications: a review. Int J Audiol 2016;55(02):65–74

19 Shetty S, Bhandary SK, Bhat V, Aroor R, Shetty J, Dattatreya T. Role of otoacoustic emission in early detection of cisplatin induced ototoxicity. Indian J Otolaryngol Head Neck Surg 2022;74 (suppl 1):164–169
20 Chan SL, Ng LS, Goh X, 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(07):1425–1433
21 Hong DZ, Ong TCC, Timbadia DP, et al. Systematic review and meta-analysis of the influence of genetic variation on ototoxicity in platinum-based chemotherapy. Otolaryngol Head Neck Surg 2023;168(06):1324–1337

