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Audiometric findings in patients with head and neck chemoradiotherapy and radiotherapy: short-term outcomes

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► ***Original article***

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ABSTRACT

Background*:** Hearing loss is a major concern in the patient with head and neck cancer (HNC) undergoing radiotherapy (RT) and/or chemotherapy (CHT). The present study aimed to assess the incidence of sensorineural hearing loss (SNHL) at 6 months follow-up after RT and/or concurrent Cisplatin-based CHT. ***Materials and Methods*:** In this prospective study, 60 patients with histopathologically proven HNC underwent three-dimensional conformal radiotherapy (3DCRT) (35 patients) and concurrent Cisplatin-based CHT and RT (25 patients). The status of the hearing was assessed pre-treatment (baseline), one day, 1, 3 and 6 months after treatment by pure tone audiometry (PTA) and other audiometric tests such as tympanometry (TM), acoustic reflex (AR), and speech audiometry (SA). ***Results: In the RT group, SNHL was observed in 18 patients and hearing loss occurred in 47 % (33 of 70 ears) of ears. In the chemo-radiotherapy (CRT) group, SNHL was discerned in 20 patients and hearing loss appeared in 88 % (44 of 50 ears) of ears. Perforation of the tympanic membrane occurred in 2/35 patients in the RT group and 1/25 patients in the CRT group. The AR threshold (ART) of patients with CRT significantly increased compared to the RT group at the end of 6 months after treatment ($P < 0.05$). Meanwhile, there was a significant difference in the speech discrimination score (SDS) and speech recognition threshold (SRT) between the CRT group and RT group at the 6 months after treatment ($P < 0.05$). ***Conclusion:*** The incidence of hearing loss in patients that underwent CRT was higher. The auditory system should be considered as a critical organ at risk (OAR) in treatment planning.

Keywords: *Sensorineural hearing loss, head and neck cancer, radiotherapy, cisplatin-based chemotherapy.*

INTRODUCTION

Head and neck cancers (HNC) are considered as one of the most common malignancies in both the sexes in the world [(1)]. To the treatment of HNC, there are several treatment strategies, including surgery, chemotherapy (CHT), and radiotherapy (RT), and multimodality approaches [(2-4)]. The choice of treatment strategy depends on the patient's condition, the size and location of the tumor, the disease stage, and, above all,

the goal of the treatment (i.e., curative or palliative) [5, 6]. RT of HNCs can destroy the structure of the hearing organ, from the external through the middle and inner ear that may lead to conductive, sensorineural or in combination hearing loss. The most serious complication is sensorineural hearing loss (SNHL) in the inner ear. SNHL can typically appear immediately or several months to years after RT [7, 8], and also it is characterized by degeneration and atrophy of the inner ear sensory structures, fibrosis and even ossification of the inner ear fluid spaces [9-11]. With advent of modern RT techniques such as three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), the incidence of radiation-induced hearing loss is expected to decrease, due to a better radiation dose sparing of auditory system, in particular cochlea [6, 12, 13].

Recently, the addition of cisplatin-based CHT and RT is standard treatment approach for patients with locally advanced HNC. Cisplatin is a cytotoxic agent and radiation sensitizer for the treatment of HNC. However, one of the main complications of cisplatin is SNHL. There is a synergistic effect between Cisplatin and RT that can result in increasing risk of SNHL [14-17].

The aim of the present study was to assess the incidence of SNHL at 6 months follow-up after RT alone and concurrent cisplatin-based CHT and RT. To the best of our knowledge, this is the first study that all patients not only underwent pure-tone audiometry (PTA) as a common audiometric test, but also other audiometric tests such as tympanometry (TM), acoustic reflex (AR), and speech audiometry (SA) were performed to evaluate the SNHL.

MATERIALS AND METHODS

Patients

Between October 2014 and April 2015, a total of 60 patients with head and neck malignancy participated in this prospective study. Thirty-five patients (70 ears) and 25 patients (50 ears) were treated with RT alone and chemo -radiotherapy (CRT), respectively. This study involved human participants, and it was conducted considering ethic responsibilities according to the World Medical Association and the Declaration of Helsinki. The study was approved by the ethics committee of Iran University of Medical Sciences, Tehran, Iran. Informed consent was obtained from all individual participants included in the study. The details of the patients under study according to the individual characteristics, type of cancer and treatment strategy are shown in table 1.

The inclusion criteria were patients with confirmed histopathologically HNC that were candidate to receive RT alone and/or concurrent CRT. The patients with primary or secondary tumors of any part of the auditory system, metastatic tumors, previous head and neck RT or cisplatin-based CHT, palliative RT, discontinued RT before treatment completion, hearing loss more than 70 dB in two continues frequencies in the pre-treatment audiometry test, and the use of ototoxic drugs at treatment and follow up time were excluded.

Radiotherapy and Chemotherapy

Computed tomography (CT)-images were imported into the CorePlan (version 3.5.0.5, Seoul C&J Co., South Korea) treatment planning software (TPS) for 3DCRT treatment planning. Dose calculations were computed using the equivalent tissue to air ratio algorithm. All CT-scans were obtained using a multislice CT-scanner with a slice thickness of 2 mm, and dose calculations were performed using a dose voxel size of 2 × 2 × 2 mm^3. TPS was initially validated using thermos-luminescence dosimeters (TLDs) embedded in Alderson Rando phantom. The bilateral cochlea and the other organs at risks (OARs) were outlined on each slice of the CT-scans. Dose-volume histograms (DVHs) of both cochleae were computed. The prescribed doses were between 60 Gy and 72 Gy at 1.8-2 Gy/fraction in 5 consecutive days per week. The patients in CRT group, concurrent with RT also received Cisplatin 40 mg/m^2 once weekly for 6 weeks (at least five cycles of cisplatin concurrent RT [18].

Audiometric testing

All Patients were first referred to an otolaryngology specialist to evaluate the presence of hearing complaints, and then they had been followed by audiometry evaluation at the audiology service. The basic functional tests (PTA, TM, AR, and SA) were performed pre-

treatment as baseline measurement and then followed up immediately (one day after treatment), 1, 3 and 6 months after treatment. Each individual ear was evaluated separately for hearing status.

PTA test at a range of frequencies 0.25-12 KHz was used. In the current study, significant threshold shifts were defined using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. of the National Cancer Institute [19]. Clinically significant SNHL was defined as a ≥15-dB increase at two consecutive frequencies.

Middle ear function was evaluated by the AR and TM. The TM was performed by using a 226 Hz probe tone that sound pressure in the cavity between the probe tip and the tympanic membrane as the pressure within the cavity is changed from about +200 to -300 decapascals (daPa). The equivalent ear canal volume (ECV) estimates the volume of air medial to the probe, which comprises the volume between the probe and the tympanic membrane when the tympanic membrane is undamaged, or the volume of the ear canal and the middle ear space if the tympanic membrane is perforated [20]. Middle ear pressure (MEP) measures the pressure of ear canal at which the peak of the tympanogram occurs [21]. The static compliance (SC) is the greatest amount of acoustic energy absorbed by the middle ear system (the vertical peak of the tympanic tracing) [22]. The ECV and SC are expressed in milliliter (ml) and MEP is expressed in decapascal (daPa).

The AR thresholds (ARTs) were measured at the frequencies of 0.5, 1, 2, and 4 KHz. The ART was performed at a bilateral reflex, ipsilateral (ipsi) and contralateral reflexes obtained for each ear [23]. The speech audiometry (SA) tests such as the speech recognition threshold (SRT), speech discrimination score (SDS) and most comfortable level (MCL) were measured. The SRT and MCL are expressed in dBHL and the SDS is expressed in percentage [24].

Statistical analysis

The data processing and statistical analysis were done by using a commercially available statistics software package (SPSS for Windows version 19, Chicago, USA) and Microsoft Excel software version 2013. In this study, the results are presented as mean ± standard deviation, and P-value < 0.05 was considered statistically significant difference.

The paired sample t-test was used to show the presence of hearing loss in pre- and post-treatment. The chi-square association test or Fishers' exact t-test was used to identify a relationship between independent variables and hearing loss. The following analyses were performed using Friedman's test to compare four-time intervals (0, 1, 3 and 6 months) within each frequency, separately. If significant results were obtained in Friedman's test, pair-wise comparisons were made using Wilcoxon's Signed Rank test.

Table 1. Distribution of patients according to the characteristics, primary cancer, and type of treatment (n=60 patients).

Malignant tumor site	Mean Age/Gender/No. of Patient (percentage)	Treatment method	Treatment volume (cm^3)	Tumor total dose (Gy)	Dmean of cochlea (Gy)
Nasopharynx	47Y/15M-6F/21(35%)	11 RT–10 CRT	1128-2304	60-72	28.6-69.5
Oropharynx	58Y/11M-4F/15(25%)	9 RT–6 CRT	992-2858	60-72	33-71.7
Larynx	63Y/9M-4F/13(22%)	8 RT–5 CRT	1060-2044	60-72	28.4-70.0
Parotid gland	52Y/4M-1F/5(8%)	3 RT–1 CRT	768-1411	60	21.44-58.78
Oral cavity	68Y/2M/2(3%)	2 RT	1160-1844	60-72	25.09-72
Submandibular gland	49Y/2M/2(3%)	1 RT–1 CRT	768-1411	60-70	24.34-68.93
Nasal cavity	73Y/2F/2(3%)	1 RT–1 CRT	862-1201	60-72	28-69.09
Hypopharynx	38Y/1M/1(1%)	1 CRT	1940	72	28.81-70.35

Y=years, M=male, F=female, RT=radiotherapy, CRT=chemoradiotherapy

RESULTS

Patients and radiotherapy plans characteristics

Table 1 lists the details of the patients under study according to the individual characteristics, type of cancer and treatment strategy. Out of 60 patients, 35 (58%) received RT alone and 25 (42%) received concurrent CRT. The age of patients ranged from 25-79 years with a median of 61 years. The total RT dose varied between 60.0 Gy and 72.0 Gy with a median dose of 62.0 Gy. We found treatment volume at a variation of 768- 2,858 cm^3 - mean of 1,683 cm^3, and median of 1,592 cm^3.

Pure tone audiometry

We examined audiometric test for the 120 ears of our 60 patients. PTA of baseline and other follow up periods are shown in table 2. As shown in figure 1, the hearing threshold was significantly increased after RT and CRT at 6 months' follow-ups in comparison with pre-treatment (*t-test* two-paired, P <0.05). After treatment, the difference was larger at high frequencies.

In the RT group, according to CTCAE, SNHL was observed in 18 patients (51 %) and hearing loss occurred in 47 % (33 of 70 ears) of ears. SNHL mostly occurred at high frequencies. Based on CTCAE, SNHL was discerned in 20 patients (80 %) and hearing loss appeared in 88 % (44 of 50 ears) of ears. The probability of hearing loss increased in the patients who had concurrent cisplatin-based CRT.

Hearing thresholds on PTA were analyzed by Friedman's test to compare the various time intervals, as outlined in table 3. There was a statistically significant difference in all frequencies. Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at p<0.0125. It showed a significant difference in most of the time interval pairs at all frequencies (table 3).

In the RT group, there was a significant difference for follow-ups at 0.25, 0.5, 1, 6, 8, 10 and 12 KHz compared to pre-treatment. In one day after RT, hearing loss occurred at frequencies 0.25, 10 and 12 KHz, and 6 months after RT hearing loss occurred in all frequencies except for 4 KHz. In the CRT group, there was a significant difference in all frequencies for follow -ups in comparison with pre-treatment. In one day after CRT, hearing loss observed in frequencies 0.25, 0.5, 6, 8, 10 and 12 KHz, and 6 months after CRT hearing loss occurred in all frequencies.

Tympanometry

The TM data were obtained from the 120 ears of 60 patients. Perforation of the tympanic membrane occurred in 2/35 patients in the RT group and 1/25 patients in the CRT group. Other patients had a normal Type A tympanogram. Table 4 displays the results of the TM test in term of ECV, MEP and SC in different follow-ups. As shown in table 4, there was a significant difference between ECV pre-treatment and 6 months after treatment in both groups (p<0.05). At the end of 6 months after treatment, the ECV and SC were significantly larger in the CRT group than that in the RT group, but they were in a normal range of TM test.

Acoustic reflexes

ART was measured for all patients in both groups. The mean ARTs of the 120 ears are shown in table 5. Both pre-treatment ipsilateral and contralateral reflexes were normal at all frequencies for all patients. At 6 months after treatment, ART significantly increased at all frequencies in the CRT group, while it significantly increased at 4 KHz for patients in the RT group. In the CRT group, the ART of 6 patients were absent at all frequencies. In the RT group, 4 patients had no response to acoustic reflex at all frequencies. The ART of patients with CRT significantly increased compared to the RT group at the end of 6 months after treatment (p<0.05).

Speech audiometry

Table 6 shows the results of the SA in various follow-ups. The speech audiometry parameters such as SRT and MCL significantly increased at 1, 3 and 6 months after RT and CRT, and the SDS significantly reduced at the same periods

($p<0.05$). Meanwhile, there was a significant difference in the SDS and SRT between the CRT group and RT group at the 6 months after treatment ($p<0.05$).

Radiation doses to cochlea and incidences of SNHL

The cochlea dose ranged between 21.4–72.0 Gy, and average and median dose to the cochlea were 48.5 Gy and 51.1 Gy, respectively. The mean dose (Dmean) of the cochlea in the RT and CRT group were 52.0 Gy and 40.0 Gy, respectively. As shown in table 7, an increase in the SNHL is seen with increasing radiation dose to the cochlea.

Table 2. PTA at different frequencies and time intervals.

	Hearing loss in the RT group (dB) (n=70 ears)					Hearing loss in the CRT group (dB) (n=50 ears)				
Frequency (KHz)	Pre-treatment of RT	At 1 day post-RT	At 1 months post-RT	At 3 months post-RT	At 6 months post-RT	Pre-treatment of CRT	At 1 day post-CRT	At 1 months post-CRT	At 3 months post-CRT	At 6 months post-CRT
0.25	5.03±0.12	5.27±0.09	5.97±0.21	6.22±0.19	6.5±0.24	4.82±0.95	5.76±1.01	6.5±1.33	6.95±1.44	7.65±1.86
0.5	5.25±0.19	5.36±0.22	6.11±0.25	7.21±0.25	7.95±0.23	5.54±1.26	6.54±1.4	7.2±1.94	8.33±2.02	9.21±2.13
1	5.35±0.21	5.44±0.18	7.17±0.28	8.2±0.3	9.34±0.28	5.97±1.07	7.12±1.9	8.5±1.99	9.84±2.09	11.44±2.04
2	6.1±0.31	6.39±0.26	8.25±0.85	10.56±1.02	13.8±1.43	6.34±1.32	8.21±1.91	13.52±2.17	16.5±2.33	21.19±2.69
3	8.08±0.85	8.89±1.2	10.12±1.43	15.67±1.85	19.75±2.5	8.62±2.09	12.45±2.53	20.81±2.88	28.94±3.46	35.09±3.71
4	17.05±1.34	18.45±1.14	21.45±1.78	25.81±1.9	27.81±1.55	15.84±3.58	21.63±4.65	28.5±3.96	35.33±3.58	42.14±4.52
6	22.1±1.03	24.53±1.2	30.49±1.54	33.22±1.85	36.74±1.9	24.074.23±	27.5±3.81	32.28±3.49	39.81±4.01	44.94±3.9
8	22.78±2.2	28.6±3.37	35.82±2.78	39.51±3.77	44.33±3.16	27.28±4.13	37.4±4.27	44.82±3.87	51.54±4.62	57.24±4.58
10	34.62±2.87	39.51±3.92	43.62±3.74	49.63±3.55	53.94±3.19	37.64±3.95	46.8±4.2	57.56±4.29	64.55±5.87	72.92±6.41
12	40.58±3.11	47.6±3.01	52.45±3.14	59.7±3.59	67.8±3.87	42.5±4.76	51.51±4.56	62.88±5.41	74.54±6.88	85.53±8.56

The hearing loss data presented as mean ± SD. RT: Radiotherapy, CRT: Chemo-radiotherapy.

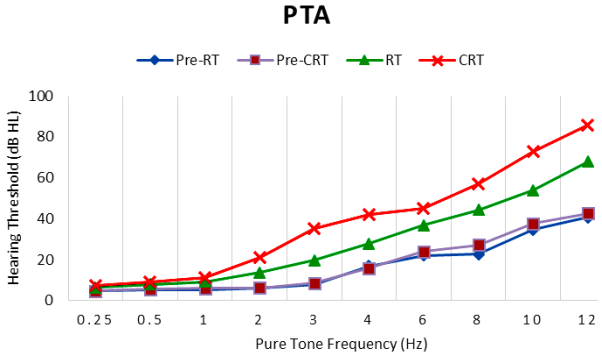

Figure 1. Mean hearing thresholds before and 6 months after treatment for 60 patients (120 ears) treated with RT and CRT. (dB HL: decibel hearing level, Pre-RT: Pre-Radiotherapy, Pre-CRT: Pre-Chemo-radiotherapy, RT: Radiotherapy, CRT: Chemo-radiotherapy).

Table 3. Friedman's test and Wilcoxon's signed rank post hoc for comparison of different frequencies and time intervals.

Frequency (KHz)	χ^2	Z value in RT group				χ^2	Z value in CRT group			
		1st day and pre-RT	1st month and pre-RT	3rd month and pre-RT	6th month and pre-RT		1st day and pre-CRT	1st month and pre-CRT	3rd month and pre-CRT	6th month and pre-CRT
0.25	69.417^a	3.379^b	3.215^b	4.571^b	4.168^b	83.104^a	3.153^b	3.726^b	3.653^b	4.062^b
0.5	45.084^a	2.461	3.578^b	3.642^b	4.688^b	78.840^a	4.177^b	3.695^b	4.622^b	4.744^b
1	54.355^a	2.880	1.946	2.473	3.386^b	53.824^a	3.086	2.634	3.730^b	3.545^b
2	46.705^a	2.780	1.749	2.655	2.268	61.680^a	2.492	2.522	3.976^b	3.783^b
3	65.887^a	2.796	2.524	2.583	2.838	54.304^a	2.750	2.344	3.432^b	3.983^b
4	64.639^a	2.652	2.653	1.457	2.878	49.600^a	2.500	3.027	3.766^b	3.878^b
6	73.320^a	2.393	4.469^b	3.804^b	3.718^b	85.408^a	3.306^b	4.497^b	3.552^b	4.213^b
8	73.391^a	3.016	3.124^b	3.951^b	3.244^b	92.064^a	4.892^b	3.777^b	4.653^b	4.244^b
10	88.297^a	3.837^b	4.347^b	3.684^b	3.203^b	92.000^a	3.153^b	3.971^b	4.622^b	4.309^b
12	77.129^a	4.379^b	3.832^b	3.033^b	4.789^b	94.816^a	4.177^b	3.668^b	4.730^b	3.747^b

Chi-square ($\chi 2$) values obtained from Friedman's test for comparison of four-time intervals. Z values obtained from Wilcoxon's Signed Rank Test for pair-wise comparison of different time interval post-treatment. a Significant at 0.05 level, b Significant at 0.0125 level

Table 4. Tympanometry follow-ups in the RT and CRT groups (n=120 ears).

	RT group			CRT group		
	Tympanometry			Tympanometry		
	ECV(ml)	MEP(daPa)	SC(ml)	ECV(ml)	MEP(daPa)	SC(ml)
Pre-treatment	0.87±0.09	-20.06±21.76	0.99±0.33	0.85±0.05	-20.5±15.4	0.86±0.43
At 1 day post-RT	0.87±0.09	-21.61±19.75	0.86±0.42	0.86±0.09	-22.5±16.5	0.92±0.51
At 1 months post-RT	0.91±0.05	-14.85±19.92	1.01±0.43	0.92±0.08	-45.6±21.45	1±0.48
At 3 months post-RT	0.97±0.05	-39.34±27.45	1.13±0.54	1.1±0.12	-49.5±31.7	1.16±0.52
At 6 months post-RT	1±0.07 [a]	-32±24.65	1.21±0.48	1.38±0.11 [a]	-43.5±28.6	1.25±0.58

Values are expressed in mean±SD. P<0.05, statistically significant comparison between before and after treatment. ECV: equivalent ear canal volume, MEP: middle ear pressure, SC: static compliance. a Significant at 0.05 level

Table 5. Distribution of acoustic reflex thresholds at different time intervals (n=120 ears).

		RT group			CRT group		
	Frequencies (KHz)	Pre-RT	1month post-RT	6months post-RT	Pre-CRT	1month post-CRT	6months post-CRT
Reflex thresholds	**0.5**	87.4±7.8	90±5.9	90.85±8.25	87.3±6.9	91.95±9.15	103.5±4.5 [a, b]
	1	86.3±6.4	89±7.1	92.65±6.79	86.3±7.4	92.8±9.85	108.45±5.75 [a, b]
	2	85.4±5.9	88±6.35	93.58±7.56	88.4±6.6	95.75±8.95	109.55±7.85 [a, b]
	4	89.2±8.1	92±7.45	109.65±7.35 [a]	89.7±7.5	92.35±8.45	110.85±8.15 [a, b]

Values are expressed in mean±SD. a Significant at 0.05 level in comparison with pre-treatment in each group, b Significant at 0.05 level in the between RT and CRT groups at 6th month. RT: radiotherapy, CRT: chemoradiotherapy.

Table 6. Speech audiometry follow-ups in the RT and CRT groups (n=120 ears).

	RT group			CRT group		
	Speech Audiometry			Speech Audiometry		
	SRT(dB)	MCL(dB)	SDS(%)	SRT(dB)	MCL(dB)	SDS(%)
Pre-treatment	5.90±2.02	33.45±5.65	95.45±2.55	6.36±2.35	34.45±6.85	95.15±2.40
1 day post-RT	5.92±2.12	33.09±8.61	95.35±2.10	6.12±2.56	34.09±8.61	95.25±3.15
1 months post-RT	13.96±2.23 [a]	42.56±7.56 [a]	92.67±3.14 [a]	17.12±5.42 [a]	48.56±8.66 [a]	88.45±2.56 [a]
3 months post-RT	12.45±2.98 [a]	43.54±8.15 [a]	84.65±3.12 [a]	16.35±6.03 [a]	47.12±6.85 [a]	81.68±2.85 [a]
6 months post-RT	15.34±2.80 [a]	43.62±7.56 [a]	83.43±2.75 [a]	19.41±5.38 [a,b]	50.42±6.58 [a]	77.53±2.57 [a,b]

Values are expressed in mean±SD. a Significant at 0.05 level in comparison with pre-treatment in each group, b Significant at 0.05 level in the between RT and CRT groups at 6th month. RT: radiotherapy, CRT: chemoradiotherapy. SRT: speech recognition threshold, MCL: most comfortable level, SDS: speech discrimination score.

Table 7. The incidences of SNHL and the cochlear mean radiation dose (3DCRT)

Cochlea mean dose	Total ear	SNHL
RT group	70	
>52 Gy	45	25/45
≤52 Gy	25	8/25
CRT group	50	
>40 Gy	20	20/20
≤40 Gy	30	14/30

RT: Radiotherapy, CRT: Chemo-radiotherapy,
SNHL: Sensorineural hearing loss.

DISCUSSION

To date, several studies reported the incidence of SNHL to be 0% to 43% after RT and 17% to 88% after CRT overall measured frequencies [14, 25, 26]. Our study showed that the incidences of SNHL were 47% (33/70 ears) directly after RT and 88% (44/50 ears) directly after CRT. The data of the present study are concordant with other reports. However, each study was differed in sample size, tumor site, follow-up time, radiation delivery techniques and cisplatin dose.

As both RT to the head and neck region and Cisplatin-based CHT induce SNHL, the combination of these treatment modalities for the management of HNCs has a synergistic impact on hearing loss. The findings from the current study and other previous studies demonstrated that cisplatin-based CRT will increase the incidence of SNHL more than RT alone [14, 26]. As shown in table 2, hearing loss in the CRT group at high frequencies (≥4 kHz) and the time interval between 3 and 6 months tended to change more than the RT group. In the present study, the hearing thresholds based on pure tune frequency have a maximum slope of changes between 6 kHz and 12 kHz in the CRT group and 3 kHz and 12 kHz in the RT group. However, the study by Wang and colleagues found no significant differences in SNHL between patient treated with CRT and RT alone. In their study, it is important to note that two groups were unequal in the number of patients (7 treated with RT alone and 213 treated with CRT). In addition, the data of baseline audiogram were not available. Therefore, these possible biases have influenced the results of the study by Wang *et al*. [27].

From our results, it can be seen that there is an association between the mean dose to the cochlea and the incidence of SNHL. Although, a work by Zuur *et al*. found no correlation between the dose to the cochlea and SNHL [28], but overall findings of studies show that the incidence of SNHL will raise when the cochlea exposes to a dose of 47 Gy or more The radiation dose for the cochlea should be preferable as less 45 Gy as possible [26], although a precise safe threshold is still unavailable. Previous studies showed that SNHL levels increase with moderate doses of the cochlea > 45-50 Gy [26, 29-32]. In this study, it was also found that the probability of hearing loss was very low when the Dmean of cochlea was less than 30 Gy. However, it increased for the dose of 50 Gy. In the CRT group, the threshold dose for SNHL was 20 Gy in patients who had cisplatin-based chemo-radiotherapy (details of the results are not shown). Therefore, high conformal radiation delivery techniques such as IMRT can be an effective way to spare the cochlea from high radiation doses, and result in reducing the risk of SNHL. Reports have been shown that the structure of the cochlea has a different sensitivity to the radiation. The sensitivity of Basal turn of the cochlea (that is implicated to be responsible for the detection of high-frequency sounds) to radiation is higher than other regions of the cochlea, and this may address the question why SNHL occurs at high-frequency sounds [33, 34].

The state of the middle ear was obtained by TM and AR test, and these don't evaluate hearing ability. In our study, perforation of the tympanic membrane occurred in 2/35 patients in the RT group and 1/25 patients in the CRT group. Compared to the RT group, the ARs of patients received CRT increased significantly at the end of 6 months of post-treatment ($P < 0.05$). The SA is considered as a fundamental tool in hearing-loss evaluation, and also it confirms PTA results. From our data, it can be seen that there is a statistically significant difference in the SDS and SRT between the RT and CRT group at 6 months follow-up.

From a radiobiological point of view, death of cochlea hair cell is regarded to be responsible for the radiation-induced SNHL. There are several processes that can lead to radiation-induced cochlea hair cell death, including the role of pathways of P53, reactive oxygen species (ROS) and c-Jun N-terminal kinase (JNK) [35]. Also, radiation induced-conductive hearing loss occurs by the effects of radiation on the middle ear [36]. In the present study, perforation of the tympanic membrane as a radiation induced-conductive

hearing loss occurred in 3/50 patients.

With regard to quality of life (QOL), the SNHL can have a different range of effects on the patient's QOL based on type of occupation, physical health status, etc. For some persons such as vision-impaired, teachers, musicians, hearing loss can disturb working capability. Therefore, it is necessary to the radiation oncologists inform the patient of this possible adverse event before starting treatment [25].

In the RT, the inter-fraction setup errors can have a crucial effect on the radiation dose actually received by organs [37], in particular small structures such as cochlea. It can be said that CT planning is a snapshot of patient or tumor position, and radiation dose evaluation on the treatment planning based on CT planning prior to starting RT can provide an estimation of the actual dose delivered to the cochlea. Therefore, mean dose to the cochlea may be an important risk factor than maximum dose to the cochlea in the incidence of SNHL because it is less sensitive to the setup errors. Another challenge is about delineation of cochlea that influences on the computed dose-volume parameters.

Authors consider several potential limitations of the current study. First, the follow-up time was short. Several studies have investigated SNHL at longer follow-up. However, it should be noted that hearing can reduce due to natural causes such as presbycusis (age-related hearing loss), with longer follow-up time [25]. Second, patients treated with 3DCRT while IMRT can better spare cochlea. However, study showed that hearing loss is independent of RT technique or RT regime when Dmean of the cochlea exceeds 45 Gy [38]. Third, the number of the patients enrolled in the study is limited.

CONCLUSION

Patients with locally advanced HNC submitted to concurrent Cisplatin-based CHT and RT have high occurrence of SNHL. Therefore, radiation dose to the cochlea should be kept as low as possible, preferably less than 45 Gy. SNHL threatens the QOL of patients undergoing CRT or RT for HNC. Meanwhile, the auditory system should be considered as a critical OAR in treatment planning. Our study focused on short-term SNHL post-treatment thus further long-term prospective study will be required to report SNHL.

Conflicts of interest**:** *Declared none.*

REFERENCES

1. Hunter KD, Parkinson EK, Harrison PR (2005) Profiling early head and neck cancer. *Nat Rev Cancer, **5**: 127-35*.
2. Chen H, Huang H, Li G, *et al.* (2017) Application of computed tomography and magnetic resonance imaging fusion images for delineating gross tumor volume in three-dimensional conformal radiotherapy of nasopharyngeal carcinoma. *Int J Radiat Res, **15**: 251-257*.
3. Kaizu H, Hata M, Takano S, *et al.* (2018) Treatment outcomes of (chemo) radiotherapy for oropharyngeal cancers: influence of the use of 15 MV X-rays in radiation boost. *Int J Radiat Res, **16**: 257-267*.
4. Cognetti DM, Weber RS, Lai SY (2008) Head and neck cancer: an evolving treatment paradigm. *Cancer, **113**: 1911-1932*.
5. Hitchcock YJ, Tward JD, Szabo A, *et al.* (2009) Relative contributions of radiation and cisplatin-based chemotherapy to sensorineural hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys, **73**: 779-88*.
6. Schultz C, Goffi-Gomez MVS, Liberman PHP, *et al.* (2010) Hearing Loss and Complaint in Patients With Head and Neck Cancer Treated With Radiotherapy. *JAMA Otolaryngol Head Neck Surg, **136**: 1065-1069*.
7. Grau C and Overgaard J (1996) Postirradiation sensorineural hearing loss: a common but ignored late radiation complication. *Int J Radiat Oncol Biol Phys, **36**: 515-7*.
8. Raaijmakers E and Engelen AM (2002) Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. *Radiother Oncol, **65**: 1-7*.
9. van Hasselt CA and Gibb AG (1999) Related ear problems. In: van Hasselt CA, Gibb AG (eds.), Nasopharyngeal Carcinoma. 2nd ed. The Chinese University Press: Hong Kong, *297-308*.
10. Jereczek-Fossa BA, Zarowski A, Milani F, *et al.* (2003) Radiotherapy-induced ear toxicity. *Cancer Treat Rev, **29**:417-30*.
11. Abdollahi H, Mostafaei S, Cheraghi S, *et al.* (2018) Cochlea CT radiomics predicts chemoradiotherapy induced sensorineural hearing loss in head and neck cancer patients: A machine learning and multi-variable model ling study. *Phys Med, **45**: 192-197*.

12. Pearson SE, Meyer AC, Adams GL, *et al.* (2006) Decreased hearing after combined modality therapy for head and neck cancer. *Am J Otolaryngol,* ***27****: 76-80*.
13. Theunissen EAR, Zuur CL, Yurda ML, *et al.* (2014) 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,* ***43****:30-30*.
14. Low WK, Toh ST, Wee J, *et al.* (2006) Sensorineural hearing loss after radiotherapy and chemoradiotherapy: a single, blinded, randomized study. J Clin Oncol, **24**:1904-9.
15. Eleonoor ART, Wouter AD, Merel NL, et al. (2014) A New Grading System for Ototoxicity in Adults. *Ann Otol Rhinol Laryngol,* ***123****: 711-718*.
16. Wei Y, Zhou T, Zhu J, *et al.* (2014) Long-term outcome of sensorineural hearing loss in nasopharyngeal carcinoma patients: comparison between treatment with radiotherapy alone and chemoradiotherapy. *Cell Biochem Biophys,* ***69****: 433-7*.
17. Yasui N, Adachi N, Kato M, *et al.* (2014) Cisplatin-induced Hearing Loss: The Need for a Long-term Evaluating System. *J Pediatr Hematol Oncol,* ***36****: e241-e245*.
18. Tsan D-L, Lin C-Y, Kang C-J, *et al.* (2012) The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. *Radiat Oncol,* ***7****: 215*.
19. Common Terminology for Criteria for Adverse Events, version 4.03; (2010) Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06,14_QuickReference_8.5x11.pdf. Accessed on June 14, 2010.
20. Fowler CG, Shanks JE (2002) Tympanometry. In: Katz J, ed. Handbook of clinical audiology 5th ed. Baltimore: Lippincott Williams & Wilkins*, pp. 175 - 204*.
21. Margolis RH, Hunter LL (200) Acoustic Immittance Measurements. In: Roeser RJ, Valente M, Hosford-Dunn H, eds. Audiology diagnosis. New York: Thieme Medical Publishers, Inc, *pp. 381-423*.
22. Onusko E (2004)Tympanometry. Am Fam Physician, ***70****: 1713 - 1720*.
23. Bess FH and Humes L (2008) Audiology: The Fundamentals: Lippincott Williams & Wilkins.
24. Gelfand SA (2016) Essentials of Audiology: Thieme.
25. Theunissen EA, Bosma SC, Zuur CL, *et al.* (2015) Sensorineural hearing loss in patients with head and neck cancer after chemoradiotherapy and radiotherapy: a systematic review of the literature. *Head Neck,* ***37****: 281-92*.
26. Chan S, Ng W, Kam K, *et al.* (2009) Sensorineural hearing loss after treatment of nasopharyngeal carcinoma: a longitudinal analysis. *Int J Radiat Oncol Biol Phys,* ***73****: 1335-1342*.
27. Wang LF, Kuo WR, Ho KY, *et al.* (2004) A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. *Otol Neurotol,* ***25****: 168-73*.
28. Zuur CL, Simis YJ, Verkaik RS, *et al.* (2008) Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol,* ***89****: 38-43*.
29. Chen WC, Jackson A, Budnick AS, *et al.* (2006) Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. *Cancer,* ***106****: 820-829*.
30. Pan CC, Eisbruch A, Lee JS, *et al.* (2005) Prospective study of inner ear radiation dose and hearing loss in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys,* ***61****: 1393 -1402*.
31. Bhandare N, Jackson A, Eisbruch A, *et al.* (2010) Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys,* ***76****: S50-S57*.
32. Cheraghi S, Nikoofar A, Bakhshandeh M, *et al.* (2017) Normal tissue complication probability modeling of radiation-induced sensorineural hearing loss after head-and-neck radiation therapy. *Int J Radiat Biol,* ***93****:1-26*.
33. Hua C, Bass JK, Khan R, *et al.* (2008) Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. *Int J Radiat Oncol Biol Phys,* ***72****: 892-899*.
34. Gupta T, Mohanty S, Kannan S, *et al.* (2014) Prospective longitudinal assessment of sensorineural hearing loss with hyperfractionated radiation therapy alone in patients with average-risk medulloblastoma. *Neuro-Oncology Practice,* ***1****: 86-93*.
35. Tan PX, Du SS, Ren C, *et al.* (2013) Radiation-induced Cochlea hair cell death: mechanisms and protection. *Asian Pac J Cancer Prev,* ***14****: 5631-5*.
36. Jain A, Banerjee PK, Manjunath D (2016) Effects of Chemoradiation on Hearing in Patients with Head and Neck Malignancies: Experience at a Tertiary Referral Care Hospital. *Indian J Otolaryngol Head Neck Surg,* ***68****: 456-461*.
37. Mahdavi SR, Jazayeri Gharehbagh E, Mofid B, *et al.* (2017) Accuracy of the dose delivery in prostate cancer patients-using an electronic portal imaging device (EPID). *Int J Radiat Res,* ***15****: 39-47*.
38. Scobioala S, Parfitt R, Matulat P, *et al.* (2017) Impact of radiation technique, radiation fraction dose, and total cisplatin dose on hearing : Retrospective analysis of 29 medulloblastoma patients. *Strahlenther Onkol,* ***193****: 910-920*.