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Assessment of Hearing Ability in Patients after Head and Neck Cancer Radiotherapy

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ABSTRACT

Introduction: The study assesses radiation-induced sensorineural hearing loss (SNHL) in head and neck cancer patients, highlighting the common occurrence of SNHL as a significant side effect of radiation therapy (RT) targeting the cochlea and acoustic pathways.
Material and Methods: The study included 34 patients (22 men, 12 women, mean age 40.13 ± 26.8 years) with head and neck cancers undergoing three-dimensional conformal radiation therapy (3D-CRT); 16 also had chemoradiotherapy (CRT). Pure-tone audiometry (PTA: 250-8000 Hz) was done before, immediately after, and three months post-RT for all patients. Hearing impairment was evaluated using the CTCAE 4.03 scoring system.
Results: According to the findings, 19% and 37% of ears experienced SNHL immediately post-RT and 3 months after RT, respectively. The mean cochlear dose was 25.48 ± 13.56 Gy. A significant correlation existed between the cochlear dose and SNHL incidence (P-value < 0.05). Regression analysis indicated the mean cochlear dose as a robust predictor of SNHL, particularly at 8000 Hz (β = 0.570, P-value = 0.0001). Highest SNHL incidence at 8000 Hz, 3 months post-RT. A significant difference in SNHL threshold was observed between men and women at the frequency of 1000 Hz (P-value = 0.024). There was a statistically significant difference in SNHL thresholds between patients who underwent CRT versus those treated with RT alone (P-value < 0.05).
Conclusion: RT commonly causes SNHL in head and neck cancer patients. Mean cochlear dose predicts SNHL, especially at higher frequencies.

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Introduction

Cancer is a major public health problem due to its rising incidence and fatality rates worldwide [1]. According to GLOBOCAN 2020 predictions, there were 10.0 million cancer-related deaths and 19.3 million new cases of the disease in 2020 [2]. Meanwhile, head and neck cancers (HNCs) are a class of tumors that account for over 350,000 annual deaths and rank as the sixth most prevalent kind of cancer globally [3]. HNCs are the third leading cause of mortality in Iran [4]. Despite significant advancements in diagnosis and treatment, the overall 5-year survival rate for HNC remains approximately 60% [5]. Most head and neck malignancies that develop in the larynx, mouth, or throat are indeed squamous cell carcinomas (SCCs) [6]. Surgical procedures, radiation therapy (RT), and chemotherapy are frequently used as treatment modalities for HNCs [7]. RT is a viable and commonly used treatment option for patients suffering from HNC, RT is administered to approximately 80% of all HNC patients during their illness, with a range between 73.9% and 84.4% [8, 9]. Despite being generally successful, RT has several serious short- and long-term side effects. Radiation side effects result in a decline in both survival rate and quality of life [10]. When head and neck tumors are treated with RT, radiation-induced ototoxicity is a well-known and significant side effect. Ototoxicity refers to damage to the structures of the inner ear or auditory nerve, leading to HL, as well as other symptoms such as vertigo and tinnitus [11]. The hearing loss (HL) caused by radiation exposure is classified according to which part of the ear is affected. Conductive hearing loss, known as "conductive HL," results from damage to middle ear structures like the ossicles or Eustachian tube, while cochlear damage leads to sensorineural hearing loss (SNHL) [12]. Radiation-induced SNHL is a delayed adverse effect that can become apparent anywhere from 3 months to 13 years after RT [13]. Exposing the cochlea to radiation during head and neck region treatment is a frequent occurrence, often resulting in SNHL; Preserving the cochlea while adequately treating the planning target volume (PTV) poses a considerable challenge [14]. With an α/β ratio of 2, the cochlea appears to be the most radiation-

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sensitive organ in patients with HNCs [15]. Cochlear hair cells and spiral ganglion neurons form the foundation of auditory function. Studies have shown that oxidative stress and inflammation in cochlear cells, stria vascularis endothelial cells, vascular endothelial cells, and spiral ganglion neurons are linked to radiation-induced SNHL [16]. Studies have demonstrated a correlation between SNHL and the average radiation dose received by the cochlea [17]. According to the study by Emami et al. [18], the incidence of HL is expected to be less than 15% if the average radiation dose reaching the cochlea is below 45 Gy (Dmean ≤ 45 Gy). According to the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), SNHL following RT for head and neck tumors is more likely to occur at higher frequencies than at lower frequencies [19]. According to studies, patients with HNC who get cisplatin-based chemotherapy may experience SNHL [20, 21]. In this study, we investigated SNHL following 3D conformal radiation therapy (3D-CRT) in individuals with head and neck malignancies.

Materials and Methods

Study Design

This prospective cohort study was conducted at the radiotherapy ward of Imam Reza Hospital in Kermanshah for two years. The study included patients with HNCs who underwent 3D-CRT and had no prior history of HL. The study protocol was approved by the Faculty of Medicine of Kermanshah University of Medical Sciences, and informed consent was obtained from all participating patients.

Patients

In this prospective cohort study, we included 34 patients (12 men and 22 women) with head and neck malignancies who were referred to the radiotherapy ward of Tohid Hospital in Sanandaj between October 2016 and December 2017. The patients ranged in age from 16 to 60 years. This study was approved by Kermanshah University of Medical Sciences (Project code: 95320). The Declaration of Helsinki's ethical guidelines were strictly adhered to. The criteria for patients to enter the study were:

1. Patients with tumors in the head and neck and treated with external RT.
2. The hearing system of the patients was within the treatment fields.
3. Patients did not have any specific HL before starting treatment.
4. The maximum age of patients was 60 years.

Treatment planning & radiation therapy

In this study, we employed 3D-CRT as the treatment method. Patients were positioned supine and immobilized with a thermoplastic head and neck mask. CT scan images with a thickness of 3.75 mm were acquired from patients at the radiotherapy ward of Tohid Hospital in Sanandaj using a CT simulation machine (Light Speed RT 16, GE Healthcare). Subsequently, the CT images were imported into the ISOgray treatment planning system (version 4.1, Dosi Soft Company, France). A medical linear accelerator (Elekta, Synergy, England) was used to deliver the prescribed radiation doses to treatment volumes through the standard fractionated regimen (one fraction per day, and 5 days per week, with a dose per fraction of 180–200 cGy). The PTV and the left and right cochlea were delineated on each corresponding CT slice. Dosimetry calculations were performed using the collapsed-cone calculation method and the Point Kernel algorithm. The treatment planning system (TPS) was utilized to generate dose-volume histogram (DVH) diagrams for the PTV and organs at risk, such as the cochlea, for each patient.

Chemotherapy

Additionally, 16 patients received concurrent chemotherapy comprising at least three cycles of cisplatin, in conjunction with RT.

Audiometric Evaluation

Pure tone audiometry (PTA) was performed by audiology technicians before, immediately, and three months after the end of RT. In this investigation, an audiometer instrument (Inventise, Piccolo, Italy) was utilized. The measured frequencies were 250, 500, 1000, 2000, 4000, and 8000 Hz, which were measured for both ears. From the Common scoring system CTCAE (Common Terminology Criteria for Adverse Events) version 4.03 was used to score hearing damage (Table 1) [22].

Statistical Analysis

IBM SPSS Statistics (Version 25, IBM, USA) was employed for the statistical analyses. A significance level of p-value < 0.05 was adopted for all tests. The normality of the data was assessed using the non-parametric Kolmogorov-Smirnov (K-S) test.

Subsequently, the paired t-test and the Wilcoxon signed-rank test were conducted to evaluate differences in patients' hearing levels before, immediately, and three months after RT. The hearing levels of the RT and CRT (concurrent chemoradiotherapy) groups were compared using the Mann-Whitney test.

Table1. Grades of hearing impairment based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

Grade of impairment	Grade 1	Grade 2	Grade 3	Grade 4
Adverse event: Hearing impaired (based on CTCAE version 4.03)	Threshold shift of 15-25 dB averaged at 2 contiguous test frequencies in at least one ear	Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear	Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear	Threshold >80 dB hearing loss at 2 kHz and above; non-serviceable hearing

Additionally, regression analysis was performed to investigate the relationship between the average dose received by the cochlea and the change in hearing threshold at each frequency. Furthermore, the Mann-Whitney test was utilized to compare hearing thresholds between males and females.

Results

Patient Characteristics

The study included 68 ears from 34 patients (12 males and 22 women), with an average age of 40.13 ± 26.8 years. Table 2 displays these patients' clinical and demographic characteristics.

Audiometric findings

We assessed SNHL in 34 patients at three different time points: before, immediately after, and three months after RT. Before RT, no cases of SNHL were detected. However, following RT, 19% of patients experienced SNHL, which increased to 37% three months post-RT. Statistical analysis revealed a significant difference in SNHL thresholds immediately after RT and three months after RT compared to before RT across all PTA frequencies (p-value = 0.001).

Figure 1 illustrates the incidence of SNHL immediately after RT and three months after RT across PTA frequencies. SNHL was observed across all frequencies with varying degrees, with significantly higher prevalence in high frequencies. Notably, the frequency of 8000 Hz exhibited the highest prevalence of SNHL both immediately and three months after RT (Figure 1).

The audiometric results of patients, categorized according to CTCAE Version 4.03 to determine the degree of damage, are presented in Figure 2 for both the immediate and three-month post-RT time points.

Table 2. Characteristics of the patients who participated in the present study

Characteristic	Value
Number of patients	34
Number of ears	68
Age (Years)	
Mean (± SD)	40.13 ± 26.8
Range	16-60
Gender, No. (%)	
Male	12(35%)
Female	22(65%)
Tumor sites, No. (%)	
Nasopharynx	16(47%)
oral cavity	5(15%)
Parotid	3(9%)
Paranasal sinuses	7(20%)
Hypopharynx	2(6%)
Larynx	1(3%)
Surgery, No. (%)	14(41%)
Chemotherapy, No. (%)	16(47%)

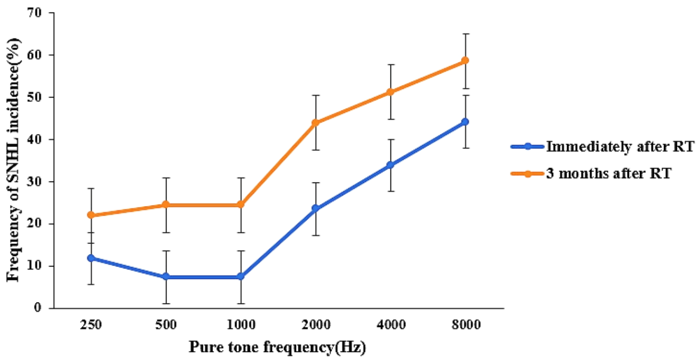

Figure 1. Frequency of SNHL incidence immediately and 3 months after RT at pure-tone audiometry (PTA) frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz)

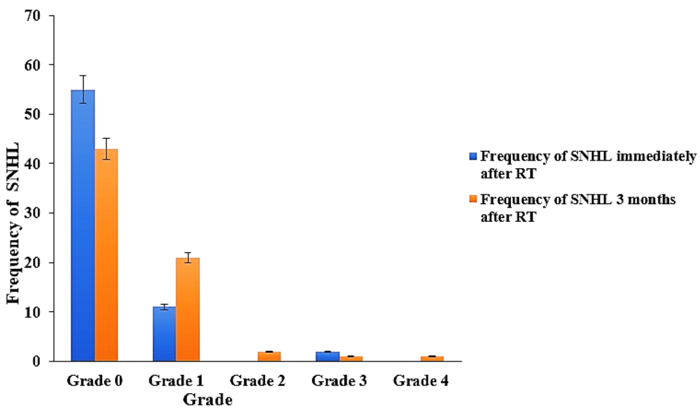

Figure 2. The frequency of SNHL developed in the patients according to the degree of damage or grades of hearing impairment (Grade: from 0 to 4)

The figure illustrates that, three months after RT, a total of 25 ears experienced SNHL, with the majority categorized as grade 1 (21 ears), followed by grade 2 (2 ears), grade 3 (1 ear), and grade 4 (1 ear).

Effect of Patient Variables

Age

Logistic regression analysis showed that age is not a significant determinant of SNHL (P-value > 0.05). To assess the influence of age, patients were stratified into two groups: under 40 and over 40 years old. The results of the Mann-Whitney test revealed no significant differences in SNHL between the two age groups across all tested frequencies in the PTA (p-value > 0.05).

Gender

Logistic regression analysis demonstrated that gender was associated with SNHL (P-value < 0.05). Patients were divided into 'female' and 'male' groups based on gender. The results of the Mann-Whitney test revealed a statistically significant difference in SNHL between genders only at the frequency of 1000 Hz after RT, with a p-value of 0.024.

Chemotherapy

Figure 3 illustrates the average change in hearing threshold at various PTA frequencies for both the RT and CRT groups. The findings suggest that the CRT group experienced a greater change in hearing threshold compared to the RT group. Furthermore, the results of the Mann-Whitney test indicate a significant difference in SNHL thresholds between the two groups specifically three months after RT. Significant differences were observed at frequencies of 2000 Hz (p-value = 0.004), 4000 (p-value = 0.002), and 8000 Hz (p-value = 0.002).

Average values of cochlea mean doses for patients

The mean dose delivered to all 68 cochleae, right cochleae, and left cochleae was estimated to be 25.48Gy (range: 6.21-56.01Gy), 26.85 (range: 3.72-58.38 Gy) and 24.11 Gy (range: 0.78-54.60) Gy respectively (Table 3).

Table 4 presents the results of regression analysis performed to determine the relationship between the average dose received by the cochlea and the change in hearing threshold at various frequencies.

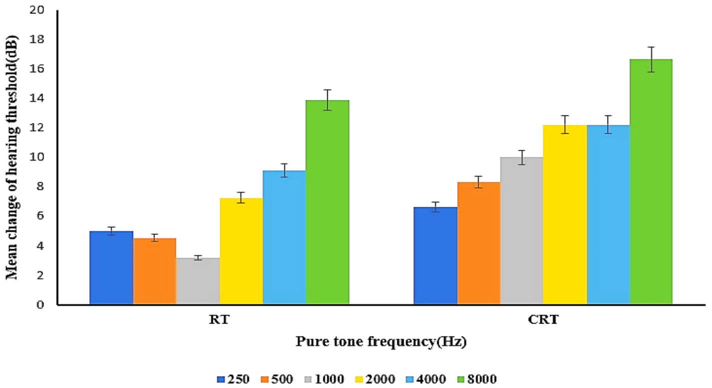

Figure 3. Mean change of hearing threshold (dB) three months after RT at pure-tone audiometry (PTA) frequencies (250, 500, 1000, 2000, 4000, and 8000 Hz) in RT and CRT groups

Table 3. The mean radiation dose received by the cochlea in the patients with HNCs in the present study

Organ	Mean radiation dose (±SD) (Gy)	Range (Gy)
Total 68 cochleae	25.48 ± 13.56	6.21 - 56.01
Right cochleae	26.85 ± 15.91	3.72 - 58.38
Left cochleae	24.11 ±15.1	0.78 - 54.60

Table 4. Results of regression analysis for correlation between mean cochlear dose and hearing threshold changes at PTA frequencies

Frequency (Hz)		β	p-value
250	Post-RT	0.109	0.018
	3 months after RT	0.192	0.099
500	Post-RT	0.079	0.047
	3 months after RT	0.227	0.039
1000	Post-RT	0.094	0.02
	3 months after RT	0.329	0.003
2000	Post-RT	0.241	0.002
	3 months after RT	0.435	0.001
4000	Post-RT	0.257	0.002
	3 months after RT	0.576	0.001
8000	Post-RT	0.281	0.0001
	3 months after RT	0.570	0.0001

The results from Table 4 indicate that the average cochlear dose serves as a robust predictor for sensorineural hearing loss induced by RT.

Table 5. The results of Pearson correlation analysis for the correlation between the average cochlear dose and changes in hearing threshold at PTA frequencies

Frequency (Hz)		Pearson correlation (r)	p-value
250	Post-RT	0.258	0.009
	3 months after RT	0.261	0.049
500	Post-RT	0.242	0.024
	3 months after RT	0.324	0.02
1000	Post-RT	0.281	0.01
	3 months after RT	0.447	0.002
2000	Post-RT	0.371	0.001
	3 months after RT	0.507	0.0001
4000	Post-RT	0.368	0.001
	3 months after RT	0.511	0.0001
8000	Post-RT	0.576	0.0001
	3 months after RT	0.576	0.0001

Table 5 indicates a significant and positive correlation between the average cochlear dose and SNHL across all frequencies of PTA both post-RT and three months after RT. The strongest correlation was observed at the frequency of 8000 Hz (r = 0.576).

Discussion

RT aims to deliver a sufficient radiation dose to the target tumor while minimizing damage to surrounding healthy tissues, thus mitigating the potential side effects of radiation [23]. RT is a crucial component of treatment for head and neck malignancies. However, exposure of the cochlea to radiation during RT can lead to SNHL [16]. The objective of this study was to assess the impact of RT on SNHL in patients diagnosed with HNCs. In our study, we observed that 19% of ears experienced SNHL after RT, which increased to 37% three months post-RT. These findings align with previous studies, as reported by Mujica-Mota et al. [24], and Theunissen et al. [25]. However, it is noteworthy that most studies have reported an incidence rate of SNHL exceeding 50%. The lower rate observed in our study may be attributed to the relatively shorter follow-up time compared to these studies [26]. According to Figure 1, SNHL is more pronounced in high frequencies, a trend observed both immediately after RT and three months after RT. This finding corroborates the results reported in studies by Bachtiary et al. [27], Saluja et al. [28], and Das et al. [29]. From a biological perspective, the heightened susceptibility of hair cells at the base of the cochlea to radiation may account for the greater impact on high frequencies. These cells are responsible for detecting sound at higher frequencies, thus rendering them more vulnerable to the effects of radiation [16]. In our study, 16 patients underwent concurrent CRT, and a significant difference in hearing threshold change was observed compared to the group receiving RT alone (p-value < 0.05). This finding is consistent with several other studies, including those conducted by Theunissen et al. [25], Malgonde et al. [30], Cheraghi et al. [31], and Hwang et al. [32], which also reported a similar impact of concurrent cisplatin-based chemotherapy on SNHL. The average cochlear dose among the patients in our study was estimated to be 25.48 ± 13.56 Gy. This value falls within the threshold recommended by Emami et al. [18], which suggests that the mean cochlear dose should be less than or equal to 45 Gy. This consistency further supports our findings According to previous studies, the mean dose of the cochlea is considered the primary factor in hearing damage. In our study, we observed a significant and positive correlation between the mean cochlear dose of patients and SNHL at PTA frequencies (p-value < 0.05). Furthermore, regression analysis revealed that the mean cochlear dose was a strong predictor of SNHL [33-36]. Based on the results of this study and other research, it is evident that the majority of hearing damage occurs at frequencies of 4000 Hz and above. Therefore, predicting damage in these frequencies can be particularly beneficial for clinical assessment and intervention [29, 37]. This finding was further confirmed through regression analysis, with a significant coefficient (β = 0.570, p-value = 0.0001). In this study, a statistically significant relationship was observed between SNHL and gender at the frequency of 1000 Hz after RT (p-value = 0.024). However, the study conducted by Pandav et al. revealed no significant relationship between gender and hearing loss in HNC patients undergoing radiation and chemotherapy. This highlights the nuanced nature of factors influencing hearing outcomes in this particular patient cohort [38]. In our study, no significant difference was found between SNHL and the age of patients. This finding contradicts the results reported by Huang et al. [32], who observed an increase in SNHL with age among individuals treated with RT for HNCs. Several factors may contribute to these differing findings, including variations in study populations, sample sizes, study methodologies, and the specific characteristics of the treatment regimens used. Additionally, differences in patient demographics, tumor characteristics, and underlying health conditions may also influence the relationship between age and hearing loss in patients undergoing radiation therapy for HNCs the findings regarding the impact of RT on hearing underscore the importance of proactive monitoring and management of hearing health in patients undergoing this treatment, particularly those with head and neck cancers. Given the potential for RT to induce SNHL, regular assessments of hearing function before, during, and after treatment are crucial for early detection of any changes and timely intervention.

Conclusion

According to our research, patients with HNC undergoing RT experience a considerable SNHL. Indeed, both the average cochlear dose and cisplatin-based chemotherapy are critical factors contributing to SNHL in such patients.

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