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Post Concurrent Chemo-Radiotherapy Hearing Loss in Patients of Oral Cavity Cancers

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ABSTRACT

Treatment of head and neck squamous cell carcinoma (HNSCC) includes wide local surgical excision followed by adjuvant therapy. **Objectives:** To determine the frequency of hearing loss in patients who underwent concurrent chemo-radiation therapy (CCRT) treatment after surgical removal of tumour of the oral cavity. **Methods:** This cross-sectional study was conducted at the Department of ENT and Head and Neck Surgery, Liaquat National Hospital, Karachi, from March 2025 to August 2025. Using non-probability consecutive sampling, 133 patients aged 18–70 years with histopathologically confirmed grade III or higher oral cavity malignancies planned for post-surgical CCRT were enrolled. Hearing was assessed using pure-tone audiometry pre-surgery, two weeks post-surgery, and three months post-CCRT, and categorised by severity. Data were analysed with SPSS version 26.0, using descriptive statistics and chi-square tests, with $p<0.05$ considered significant. **Results:** Among 133 post-surgical CCRT patients, 94 (70.7%) were male, and the median age was 48.0 (39.0–58.0) years. T4 disease was present in 114 (85.7%) patients. Hearing loss occurred in 15 (11.3%), highest in >60 years 5 (33.3%, p=0.016), and most frequent in tongue malignancy 10 (66.7%). By CCRT cycles, loss was seen in 1–2 cycles 3 (20.0%), 3–4 cycles 12 (10.5%), and none in >4. Severity of hearing loss was found to have a significant association with cancer, stating (p=0.031). **Conclusions:** Hearing loss following CCRT for oral cavity malignancies occurred in around one in ten patients, with most cases being mild and associated with older age, tongue primary site, and advanced T stage.

INTRODUCTION

Head and neck cancers (HNC) represent the third most common cancer worldwide, with 1,464,550 new cases and 487,993 deaths, accounting for 7.6% of all cancers and 4.8% of all cancer-related deaths [1,2]. In Pakistan, after lung cancer, HNC is the second most common cancer, and in females, it is after breast cancer [3]. Karachi is the city with the largest population in this country and hence bears a hefty load of head and neck tumours; its annual incidence from a community-based study in the district of South Karachi is 4.1 per 100,000 among male and 4 per 100,000 among female, making Karachi the first city with the highest incidence of oral squamous cell carcinoma [3].

Treatment of head and neck squamous cell carcinoma (HNSCC) includes wide local surgical excision followed by adjuvant therapy (radiotherapy with or without chemotherapy). Patients tend to present in the late stages, hence, around 46% to 85% of those having surgical removal require adjuvant therapy, also known as concurrent chemo-radiation therapy (CCRT). The regimen for CCRT in HNC is 66-68 gray in 33-34 fractions of radiotherapy; each session has a dose of 2 gray, together with cisplatin 100 mg/m2 every three weeks for up to three cycles [4]. Concurrent cisplatin and radiation lead to an absolute gain of 6.5% in five-year overall survival and better locoregional

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control [5]. However, this gain should be weighed against the additional toxicity it implies, as well as potential compromise in the quality of life (QoL). Radiotherapy encompasses the level of the base of the skull up to the clavicle, with various strategies adopted to protect the sensitive structures during organ preservation strategies. Leading to damage to the eustachian tube, it causes hearing loss. Radiotherapy can have deleterious and detrimental effects on the nervous system because of the limited capacity for repair and regeneration of the nervous tissues. While not as common as other adverse effects in HNCs, neuropathies leave a long-lasting compromise in the patients' well-being. Radiation-induced neuronal damage in HNC manifests mainly as sensorineural hearing loss (SNHL) and minorly as alterations in taste and smell sensory functions. Chemotherapy includes cisplatin, which is a chemotherapeutic drug. Neurotoxicity is the most serious cisplatin toxicity. Cisplatin ototoxicity typically presents as a bilateral high-frequency SNHL that may progress to profound loss of hearing [6]. Literature shows that almost 70% of patients experience a symmetrical, permanent loss greater than 15 decibels (dB) in the 4000 to 8000 Hertz (Hz) range, with nearly all patients affected when extended high-frequency hearing (>8000 Hz) is measured [7]. Incidence rates of SNHL following cisplatin-based chemo-radiotherapy range between 17-88% [8]. Evidence points out that higher cumulative cisplatin is associated with greater risk and severity of SNHL, and a sharp rise beyond ~300 mg/m^2 is reported; moderate–to–severe loss clusters in the 300–400 mg/m^2 range, and risk continues to increase at higher totals. Weekly lower-dose regimens tend to produce less ototoxicity than tri-weekly high-dose schedules at similar totals [9]. Post-CCRT changes in hearing loss in patients with oral cavity cancers have been conducted in various studies, providing data regarding the type of chemotherapeutic agent being used and the amount of radiation being given, leading to their effects on hearing [8].

However, there is no study available with data from the local region in this regard. The findings of this study would not only furnish the local data but also aid in further research for the adjustment of dose to prevent hearing loss and achieve better patient outcomes. This study aimed to determine the frequency of hearing loss in patients who underwent CCRT after surgical removal of a tumour of the oral cavity.

METHODS

This cross-sectional study was performed at the Department of ENT and Head and Neck Surgery, Liaquat National Hospital, Karachi, Pakistan, from March 2025 to August 2025, after obtaining approval from the ethical review committee of the institution (letter number: App # 1261-2025 LNH-ERC). A sample size of 133 was calculated using the Open Epi online sample size calculator with an anticipated frequency of hearing loss in patients who underwent CCRT after surgical removal of tumour of the oral cavity as 78.4% [10], with 95% confidence level, and 7% margin of error. Sampling selection was carried out using the non-probability consecutive sampling technique. The inclusion criteria were patients of any gender, aged 18-70 years, and who were histopathologically confirmed cases of oral cavity malignancies, with grade III or above disease according to TNM classification. Only those patients who were planned to receive post-surgery chemo-radiotherapy were considered for the study. The exclusion criteria were patients with primary tumours of any part of the auditory system and those with direct extension of primary tumour to any auditory system, a history of SNHL or CHL, tumours of the hard palate and soft palate, a history of receiving CCRT, or a history of operated oral cavity tumours. Written and informed consent was taken from each patient once the date was booked for the surgery, followed by a proper ear examination. The eligible subjects went through documentation of their demographics, such as age and gender. Disease-related information, such as the stage and grade of the tumor (as per biopsy findings), was noted. Diagnosis was established through incisional or excisional biopsy, reviewed by a consultant histopathologist. Preoperative staging was performed using contrast-enhanced cross-sectional imaging as part of routine clinical care. CT imaging was acquired using a multidetector CT scanner (Aquilion 64-slice, Canon Medical Systems, Japan), and magnetic MRI was performed on a 1.5 Tesla system (MAGNETOM Aera, Siemens Healthineers, Germany). Imaging protocols followed the institution's standard head-and-neck oncology protocols and were interpreted by consultant radiologists. CT and/or MRI findings were integrated with clinical and histopathological data to assign TNM stage according to the AJCC 8th edition. Only patients with grade III or above disease (T3 or T4 lesions) were included, as these cases typically require adjuvant concurrent chemoradiotherapy (CCRT) following surgical excision. Ear examination included general examination of the ear, and per speculum examination with an otoscope was performed for each patient. Hearing sensitivity was assessed using the pure-tone audiometer (PTA) by the certified audiologist of the institute. The machine used for performing PTA was the GSI STAR PRO 321UX. The cost of PTA was covered by the departmental funds throughout the study. The first PTA was conducted before surgery (baseline), the second two weeks after surgery and before the initiation of CCRT, and the third and final PTA was performed three months after completion of

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CCRT to assess post-treatment hearing outcomes. Hearing loss was assessed and categorized as mild (25-40 dB), moderate (41-70 dB), severe (71-90 dB), and profound (>91 dB) [11]. All the relevant data were recorded on a specifically designed proforma. Data were entered and analyzed using "IBM-SPSS Statistics" version 26.0. The qualitative variables were mentioned in the form of frequency and percentage. The normality of data was checked using the Shapiro-Wilk test. The quantitative data were expressed as mean and standard deviation (SD) if data were normally distributed, and if data were non-normally distributed, median and interquartile range (IQR) were computed. Effect modifiers, which included age, gender, chemo cycles, stage, and grade of tumour were controlled through stratification to see their effect on the outcome (hearing loss). A post-stratification chi-square test was applied, with a $p<0.05$ to mark significance.

RESULTS

A total of 133 patients with histopathologically confirmed oral cavity malignancies who underwent post-surgical concurrent chemoradiotherapy (CCRT) were included. The median age was 48.0 years (IQR 39.0–58.0; range 21–70 years), with 59 (44.4%) patients each in the 18–45 and 46–60-year categories, and 15 (11.3%) aged >60 years. Most participants were male (n=94, 70.7%) and resided in urban areas (n=94, 70.7%). The buccal mucosa was the most common tumour site (n=62, 46.6%), followed by the tongue (n=50, 37.6%), alveolus (n=6, 4.5%), cheek (n=5, 3.8%), lip (n=5, 3.8%), and other sites (n=5, 3.8%). The majority presented with T4 disease (n=114, 85.7%), while T3N0 and T3N1 were seen in six (4.5%) patients each, T3N2 in five (3.8%), and T2N2B and T3 in one (0.8%) patient each (Table 1).

Table 1: Characteristics of Oral Cavity Malignancy Patients (n=133)

Characteristics		n (%)
Gender	Male	94 (70.7%)
	Female	39 (29.3%)
Age	18-45	59 (44.4%)
	46-60	59 (44.4%)
	>60	15 (11.3%)
Residence	Urban	94 (70.7%)
	Rural	39 (29.3%)
Malignancy Diagnosis	Buccal Mucosa	62 (46.6%)
	Tongue	50 (37.6%)
	Alveolus	6 (4.5%)
	Cheek	5 (3.8%)
	Lip	5 (3.8%)
	Others	5 (3.8%)
Cancer Stagging	T2N2B	1 (0.8%)
	T3	1 (0.8%)
	T3N0	6 (4.5%)
	T3N1	6 (4.5%)
	T3N2	5 (3.8%)
	T4	114 (85.7%)

The post-CCRT hearing loss was observed in 15 (11.3%) patients. Age group was significantly associated with hearing loss (p=0.016), with the highest prevalence in patients aged >60 years (n=5, 33.3%), compared with 18–45 years (n=5, 33.3%) and 46–60 years (n=5, 33.3%). No significant associations were noted for gender (male: 10/94 (10.6%) vs female: 5/39 (12.8%), p=0.717) or residence (urban: 8/94 (8.5%) vs rural: 7/39 (17.9%), p=0.117). Hearing loss occurred most frequently in patients with tongue malignancy (n=10, 66.7%), followed by buccal mucosa (n=3, 20.0%), cheek (n=1, 6.7%), and lip (n=1, 6.7%), with no cases among alveolus or other sites (p=0.129). Although most patients with hearing loss had T4 stage disease (n=14, 93.3%), the association between stage and hearing loss was not statistically significant (p=0.857) (Table 2).

Table 2: Comparison of Baseline Characteristics of Oral Cavity Malignancy Patients with Post CCRT Hearing Loss (n=133)

Characteristics		Post CCRT Hearing Loss		p-value
		Yes (n=15)	No (n=118)	
Gender	Male	10 (66.7%)	84 (71.2%)	0.717
	Female	5 (33.3%)	34 (28.8%)	
Age	18-45	5 (33.3%)	54 (45.8%)	0.016
	46-60	5 (33.3%)	54 (45.8%)	
	>60	5 (33.3%)	10 (8.5%)	
Residence	Urban	8 (53.3%)	86 (72.9%)	0.117
	Rural	7 (46.7%)	32 (27.1%)	
Malignancy Diagnosis	Buccal Mucosa	3 (20.0%)	59 (50.0%)	0.129
	Tongue	10 (66.7%)	40 (33.9%)	
	Alveolus	–	6 (5.1%)	
	Cheek	1 (6.7%)	4 (3.4%)	
	Lip	1 (6.7%)	4 (3.4%)	
	Others	–	5 (4.2%)	
Cancer Stagging	T2N2B	–	1 (0.8%)	0.857
	T3	–	1 (0.8%)	
	T3N0	1 (6.7%)	5 (4.2%)	
	T3N1	–	6 (5.1%)	
	T3N2	–	5 (4.2%)	
	T4	14 (93.3%)	100 (84.7%)	

Analysis of CCRT cycles showed that hearing loss occurred in 3 (20.0%) of the 15 patients receiving 1–2 cycles, 12 (10.5%) of the 114 patients receiving 3–4 cycles, and none of the two patients receiving >4 cycles (p=0.604). The majority of patients without hearing loss had received 3–4 cycles (n=102, 86.4%), compared with 14 (11.9%) receiving 1–2 cycles and two (1.7%) receiving >4 cycles (Figure 1).

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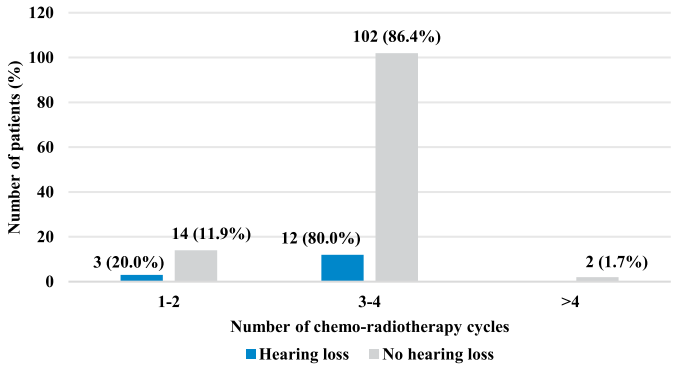

Figure 1: Comparison of Hearing Loss Following CCRT with Respect to Chemo-Radiotherapy Cycles (n=133)

Out of those with post CCRT hearing loss (n=15), 9 (60.0%) had mild, 4 (26.7%) had moderate, and 2 (13.3%) had severe impairment. There was no statistically significant association between hearing loss severity and gender (p=0.472) or age (p=0.165). Patients aged 18–45 years accounted for nearly half of mild cases (n=4, 44.4%), while moderate loss was most common in the 46–60-year group (n=3, 75.0%), and severe loss was equally distributed between the 46–60 and >60-year groups (n=1 each, 50.0%). The majority of cases across all severity categories occurred in urban residents, although differences by residence were not significant (p=0.978). Tongue malignancy predominated across severity groups, accounting for 6/9 (66.7%) mild, 3/4 (75.0%) moderate, and 1/2 (50.0%) severe cases (p=0.077). Cancer stage was significantly associated with severity (p=0.031), with all mild and moderate cases arising from T4 disease, while one severe case occurred in T3N0 and the other in T4 disease (p=0.031), and the details are shown (Table 3).

Table 3: Association of Post CCRT Hearing Loss Severity with Baseline Characteristics of Patients with Oral Cavity Malignancy (n=15)

Characteristics		Post CCRT Hearing Loss Severity			p-value
		Mild (n=9)	Moderate (n=4)	Severe (n=2)	
Gender	Male	6 (66.7%)	2 (50.0%)	2 (100%)	0.472
	Female	3 (33.3%)	2 (50.0%)	–	
Age	18-45	4 (44.4%)	1 (25.0%)	–	0.165
	46-60	1 (11.1%)	3 (75.0%)	1 (50.0%)	
	>60	4 (44.4%)	–	1 (50.0%)	
Residence	Urban	5 (55.6%)	2 (50.0%)	1	0.978
	Rural	4 (44.4%)	2 (50.0%)	1	
Malignancy Diagnosis	Buccal Mucosa	3 (33.3%)	–	–	0.077
	Tongue	6 (66.7%)	3 (75.0%)	1 (50.0%)	
	Cheek	–	–	1 (50.0%)	
	Lip	–	1 (25.0%)	–	
Cancer Stagging	T3N0	–	–	1 (50.0%)	0.031
	T4	9 (100%)	4 (100%)	1 (50.0%)	

DISCUSSION

The frequency of hearing loss observed in the present study following post-surgical CCRT for oral cavity malignancies was 11.3%, with the majority of cases being mild (60.0%), followed by moderate (26.7%) and severe (13.3%) impairment. A study reported 22% patients developing conductive loss during treatment for head and neck malignancies [12]. Regional data shows 50% of patients developed SNHL following chemoradiotherapy, with 55% mild, 35% moderate, and 10% severe impairment [13]. Another study using IMRT with concurrent cisplatin documented significant hearing loss in 37.1% of patients and demonstrated a dose-response relationship with cochlear dosimetry [14]. The lower incidence in the present study may reflect differences in patient selection, treatment sequencing, and radiation exposure to the cochlea. All patients underwent surgical resection before CCRT, which may have reduced target volumes and enabled better sparing of the auditory apparatus. The radiation techniques used in the current setting may also have delivered lower mean and minimum cochlear doses, although this could not be confirmed in the absence of dosimetric data. Another factor could be the relatively short follow-up period of three months post-CCRT. In some studies, follow-up extended to six months or longer, and late ototoxicity was observed to progress over time, suggesting that the present incidence may underestimate the true long-term burden [13,14]. Cisplatin-related SNHL can manifest or worsen months to years after therapy, and a longer surveillance window would be required to capture delayed-onset cases [15]. The association between age and hearing loss in the present cohort was statistically significant (p=0.016), with the highest prevalence in those aged >60 years (33.3%). Age-related susceptibility to ototoxicity has been reported previously. A study from India noted that older patients were more prone to developing SNHL during and after chemoradiotherapy for head and neck malignancies [13]. Ageing cochlear hair cells may be more vulnerable to cumulative damage from cisplatin and radiation, which can explain the higher incidence among older adults [16]. Some researchers observed that their cohort, which had a predominance of patients aged 61–70 years, showed a statistically significant deterioration in pure-tone thresholds after CCRT, particularly at higher frequencies [17]. Cancer stage was significantly associated with the severity of hearing loss (p=0.031) in this cohort, with all mild and moderate cases and one severe case occurring in patients with T4 disease. This association between advanced tumour stage and higher hearing loss severity aligns with observations from India, where a greater incidence and persistence of SNHL in patients with advanced-stage head and neck

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cancers receiving concomitant chemoradiotherapy was reported compared to those treated with radiotherapy alone [18]. The higher dose volumes required for advanced disease likely expose the cochlea and surrounding auditory structures to increased radiation doses, potentiating ototoxicity [19]. The number of chemoradiotherapy cycles did not show a statistically significant association with hearing loss in the present study, although the highest proportion was observed among those receiving 1–2 cycles (20.0%). In contrast, some others noted that the majority of SNHL cases (60%) developed mid-therapy, indicating that cumulative cisplatin exposure plays a role in ototoxicity [13]. The lack of a clear dose-response relationship in the current series may reflect the relatively small number of patients in the 1–2 cycle group, limiting statistical power. It is also possible that individual susceptibility, influenced by genetic predisposition or baseline cochlear reserve, may contribute to variability in response to cumulative cisplatin exposure [20, 21]. From a clinical perspective, the relatively lower incidence of hearing loss in this cohort compared to several published series may reflect the combined effect of surgical tumour debulking before CCRT, potentially smaller treatment fields, and possibly greater use of advanced radiation planning. This suggests that a multimodality approach incorporating surgery followed by adjuvant therapy might reduce auditory toxicity compared to primary chemoradiation in select cases, without compromising oncological outcomes [22-24]. The results also reinforce the importance of baseline and serial audiometric assessment, particularly in older adults and those with tongue primaries, to allow for timely intervention with hearing rehabilitation strategies [25].

Short post-CCRT follow-up (three months) may have underestimated late-onset or progressive cisplatin-related ototoxicity. Additionally, the lack of cochlear dosimetric data and genetic susceptibility assessment limited evaluation of dose–response relationships and individual variability in hearing loss risk. Long-term prospective studies incorporating serial audiometry and cochlear dosimetric analysis are recommended to better characterize delayed and dose-dependent hearing loss after CCRT.

CONCLUSIONS

Hearing loss after post-surgical CCRT for oral cavity malignancies was observed in a minority of patients and was predominantly mild in severity. Older age, tongue primary site, and advanced tumor stage were significantly associated with greater auditory impairment. These findings highlight the need for targeted auditory monitoring in high-risk patients undergoing multimodality treatment.

Authors' Contribution

Conceptualization: SA, AA
Methodology: RT, SA, DS, AA[1], SAA, AA[2], AB
Formal analysis: RT
Writing and Drafting: RT, SK
Review and Editing: RT, SA, DS, AA[1], SK, SAA, AA[2], AB

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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