Original Research Article

To Investigate the Incidence and Severity of Hearing Loss Caused By Chemoradiotherapy in Head and Neck Cancer Cases

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Abstract

Background: In head and neck oncology, treatment-induced hearing loss has been reported in patients treated with high-dose cisplatin chemoradiotherapy (CRT). The present study was conducted to investigate the incidence and severity of hearing loss caused by chemoradiotherapy in Head and Neck cancer cases. **Materials & Methods:** All patients with head and neck cancers who visited the Department of Otorhinolaryngology and Head and Neck surgery and undergone treatment, after histological confirmation, at the Department of Radiation Oncology at Sardar Patel Medical College, Bikaner, Rajasthan from November 2019 to October 2020 were taken up for the study. 80 patients were included in the study out of which 40 undergone concurrent chemoradiation. Patients with concurrent chemoradiotherapy were selected for the study. Data was entered in Microsoft Excel and was subsequently imported to Statistical package for the social sciences (SPSS) free version 21.0 and Epi info version 3.0 for analysis. **Results:** 80 patients were included in the study out of which 40 undergone concurrent chemoradiation. Hearing levels were documented before starting of treatment, after completion of treatment and 3 months of follow up. Our study consisted of 80 subjects out of which 52 (65%) were male and 28 (35%) females. The age of the subjects ranged from 30 to 60 years, with highest number of patients belonged to the age group of 51-60 (57.5%) years. In our study, majority of the patients had carcinoma oral cavity (35%) followed by Larynx (28.75%), Hypopharynx (16.25%), Oropharynx (8.75%), Nose & PNS (6.25%), Nasopharynx and Occult primary with secondary neck (each 2.5%). In patients having RT+CT , 45% had conductive hearing loss after completion of treatment which declined to 30% after 3 months follow up. Otitis media with effusion and Eustachian tube dysfunction are temporary and reversible side effects of the irradiation of the ear. Conductive hearing loss develops as a reversible side effect of radiation of the ear. The impact of radiation dose on hearing loss was studied and was found that patients with radiation dose less than 60 Gy showed no hearing loss. Dose of the radiation is proportional to development of ototoxicity. Total radiation dose of minimum 60 Gy is required to produce noticeable ototoxic effects.**Conclusion:** Thus, we conclude that patients who received concomitant chemoradiation experienced greater hearing loss. Hearing loss was evident after 1 month of therapy and was persistent. The incidence and severity of hearing loss increased with time and higher frequencies were affected predominately. High-frequency hearing loss can have a significant impact on quality of life because it affects speech discrimination. It is recommended to perform a pre-treatment and post-treatment audiological evaluation with special emphasis on high frequencies.

Keywords: Ototoxicity, Chemoradiation, Audiological.

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Introduction

Radiation therapy or radiotherapy uses ionizing radiation, generally as part of cancer treatment to control or kill malignant cells and normally delivered by a linear accelerator.

It is commonly applied to the cancerous tumour because of its ability to control cell growth and works by damaging the DNA of cancerous tissue leading to cellular death[1]. Radiation therapy works by damaging the DNA of cancerous cells. This DNA damage is caused by one of two types of energy, photon or charged particle. This damage is either direct or indirect ionization of the atoms which make up the DNA chain. Indirect ionization happens as a result of the ionization of water, forming free radicals notably hydroxyl radicals, which damages the DNA[1]. Radiotherapy in the head and neck region leads to fatigue, xerostomia, oral mucositis, salivary gland dysfunction, painful epidermioloysis and ototoxicity[2]. Several therapeutic compounds and modalities can cause ototoxicity. Antimalarial, antihypertensive, antibiotics, platinum-based chemotherapeutic agents and radiotherapy applied on the head and

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neck area all may result in hearing loss[3-5]. In the cochlea, ototoxicity characteristically starts at the basal (perception of ultra-high frequency tones) and then progresses to the apical end (perception of the low frequency tones). This sensorineural hearing loss is irreversible, whereas conductive hearing loss (as often found after radiotherapy) is mainly reversible[6]. The present study was conducted to investigate the incidence and severity of hearing loss caused by chemoradiotherapy in Head and Neck cancer cases.

Materials & methods

All patients with head and neck cancers who visited the Department of Otorhinolaryngology and Head and Neck surgery and undergone treatment, after histological confirmation, at the Department of Radiation Oncology at Sardar Patel Medical College, Bikaner, Rajasthan from November 2019 to October 2020 were taken up for the study. 80 patients were included in the study out of which 40 undergone concurrent chemoradiation. Patients with concurrent chemoradiotherapy were selected for the study. All newly biopsy proven cases of head and neck cancer, the patients with age group between 30-60 years were included in the study. Patients with pre-existing ear diseases such as otitis media with effusion, tympanic membrane perforation, otosclerosis with conductive hearing loss or who have undergone ear surgeries, Patients who previously being treated by chemoradiotherapy or ototoxic drug, Patients with diseases such as diabetes, renal failure, Patients not having ear in the field of radiation, Patients with type of tympanogram other than type A curve were excluded from the study. Patient details such as demographic information, site of cancer and biopsy report were recorded. Routine investigations such as complete blood picture, renal function tests, liver function tests, blood sugar and viral markers were done and recorded. The dose of chemotherapy (cisplatin and 5-fluorouracil) regimen used were as follows:

Table 1: Regimen used in present study

Treatment modality	Dose & regimen	Route	Days
Concurrent chemoradiotherapy			
Cisplatin	80-100 mg/m^2/cycle (3 cycles)	Intravenous over 6-8 hours	0,3,6 weeks
	Alternatively, 40 mg/m^2/cycle (7 cycles)	Intravenous over 6-8 hours	0,1,2,3,4,5,6 weeks
5-fluorouracil	500-1000 mg/m^2 weekly	Intravenous over 6-8 hours	0,4,7 weeks
Radiotherapy	2 Gy/d, 5 fractions/week (30-35 fractions)		

It is generally understood that 5-fluorouracil is not ototoxic. Therefore, in this study we only observed the relation between administration of cisplatin and development of hearing loss. A complete ENT examination was done: Otoscopic examination using Welch allyn Otoscope was performed and tympanic membrane status was seen. Any active discharging ear, tympanic membrane perforations or healed perforations were excluded from the study. Tuning fork test was done using 256, 512 and 1024 Hz Tuning forks. In Nose examination anterior rhinoscopy was done. Oral cavity was examined, and neck examination was done to look for any enlarged lymph nodes and secondaries. Indirect Laryngoscopy was performed using a 90° endoscope. Audiological evaluation was done using LABAT AUDIOLAB audiometer calibrated to ANSI S3. 6-1996,1969 and impedance audiometry was done using OSCILLA TSM400 tympanometer by a single audiologist. Baseline pure tone audiometry both for air conduction and bone conduction was performed at 250, 500, 1000, 2000, 4000 and 8000 Hz along with Impedance audiometry before the commencement of treatment. These tests were repeated: after completion of treatment and 3 months post completion of treatment. Decrease of 20 dB in an isolated frequency or of 10 dB in two or more successive frequencies was taken as criteria for reduction in auditory acuity (ASHA criteria). Descriptive statistics was performed by calculating mean and standard deviation for the continuous variables. The statistical tests used were: Chi-square test was used to investigate whether distributions of categorical variables differ from one another. The p-value was taken significant when less than 0.05 and a confidence interval of 95% was taken. Fisher Exact Probability Test was performed using the Freeman-Halton extension of the Fisher exact probability test for a two-rows by three-columns contingency table. Data was entered in Microsoft Excel and was subsequently imported to Statistical package for the social sciences (SPSS) free version 21.0 and Epi info version 3.0 for analysis.

Results

80 patients were included in the study out of which 40 undergone concurrent chemoradiation. belonging to age group 30-60 years.

Table 2 shows that in this study age of the subjects ranged from 31-60 years. The mean age of the study group was 55.5 years. The commonest age group was from 51-60 years of age with 46 (57.5%) patients.

There was male predominance in overall study. Out of 80 subjects, 65% were male and 35% were female. Male to female ratio was 1.85.

Table 4 shows that most of the subjects were farmers by occupation. The distribution of subjects according to their occupation was 57.5% were farmers, 30% were labourers, 2.5% were shopkeepers, 1.25% were carpenters and 8.75% others.

Table 5 shows that majority of the subject i.e., 28 subjects (35%) had carcinoma Oral cavity, 23 subjects (28.75%) had carcinoma Larynx, 13 subjects (16.25%) had carcinoma Hypopharynx, 7 subjects (8.75%) had carcinoma Oropharynx, 5 subjects (6.25%) had carcinoma Nose & PNS, 2 subjects (2.5%) had carcinoma Nasopharynx and 2 subjects (2.5%) had Occult primary with secondary neck.

Table 6 shows that 62.5% subjects had moderately differentiated SCC, 12.5% had Well differentiated SCC and 25% had Poorly differentiated SCC.

Table 7 shows that after completion of Chemoradiotherapy, 20 % (n = 8) & 25 % (n = 10) had OME and ET dysfunction (Type B/Type C tympanogram) respectively. After 3 months follow up, 20% (n=8) had ET dysfunction and 10 % (n=4) had OME.

Table 8 shows that, 15% (n=6) and 45% (n=18) patients had SNHL at speech and high frequency respectively after completion of treatment. After 3 months follow up, 27.5% (n=11) and 62.5% (n=25) patients had SNHL involving speech and high frequencies respectively.

Table 9 shows that in chemoradiotherapy induced hearing loss in group B, 37.5% subjects had no hearing loss and 62.5% subjects had hearing loss, among which 37.50% subjects had moderate, 17.5% subjects had mild grade hearing loss and 7.5% had moderately severe hearing loss.

Table 10 shows that, patients developed around 8.13 dB average hearing loss immediately post chemoradiotherapy and 16.47 dB average hearing loss after 3 months post chemoradiotherapy. Here average hearing threshold is average of hearing threshold at 500, 1000 and 2000 Hz frequencies.

Table 11 shows that, patients developed around 18.96 dB average hearing loss immediately post chemoradiotherapy and 22.97 dB average hearing loss after 3 months post chemoradiotherapy. Here average hearing threshold is average of hearing threshold at 8000 Hz frequency.

Table 2: Age Distribution

Age group (years)	Total	Percentage
31-40	14	17.5%
41-50	20	25%
51-60	46	57.5%
Total	80	100%

Table 3: Gender Distribution

Gender	No. of subjects	Percentage
Female	28	35%
Male	52	65%
Total	80	100%

Table 4: Occupation of Subjects

Occupation	No. of subjects	Percentage
Farmers	46	57.5%
Labourers	24	30%
Carpenter	1	1.25%
Others	7	8.75%
Total	80	100%

Table 5: Site of Cancer

Site of cancer	No. of subjects (group A)	No. of subjects (group B)	Total
Oral cavity	15	13	28
Larynx	11	12	23
Hypopharynx	7	6	13
Oropharynx	4	3	7
Nasopharynx	-	2	2
Nose and PNS	3	2	5
Occult primary with Secondary neck	-	2	2
Total	40	40	80

Table 6: Histopathological Differentiation of SCC

Histopathology	No. of subjects	Percentage
Well differentiated SCC	10	12.5%
Moderately differentiated SCC	50	62.5%
Poorly differentiated SCC	20	25%
Total	80	100%

Table 7: Type of Tympanogram Observed in Patients At Different Follow Up Periods

Type of tympanogram	Completion of treatment		3 Months follow up	
	n	%	n	%
Type A	22	55%	28	70%
Type B	08	20%	04	10%
Type C	10	25%	08	20%
Total	40	100%	40	100%

Table 8:Sensorineural Hearing Loss

	After completion of treatment		3 months follow up	
	Speech frequency	High frequency	Speech frequency	High frequency
No of cases/% of cases with SNHL (out of 40)	6/15%	18/45%	11/27.5%	25/62.5%

Table 9:Severity of Sensorineural Hearing Loss

Hearing loss	No. of subjects	Percentage
No hearing loss	15	37.5%
Mild	7	17.5%
Moderate	15	37.50%
Moderately severe	3	7.5%
Severe	-	-
Total	40	100%

Table 10: Mean Bone Conduction Thresholds At Different Frequencies In Hearing Loss Patients

	Speech Frequency		
	Baseline	Completion of treatment	Follow up 3 months
Mean threshold (dB)	22.42 (dB)	30.55 (dB)	38.89 (dB)

Table 11: Mean Bone Conduction Thresholds at High Frequency In Hearing Loss Patients

	High Frequency		
	Baseline	Completion of treatment	Follow up 3 months
Mean threshold (dB)	22.32 (dB)	41.28 (dB)	45.29 (dB)

Discussion

Our Study consisted of 80 subjects with carcinoma Head and Neck region in which 40 were treated by radiotherapy and cisplatin chemotherapy.

The age of the patients in this study ranged from 30-60 years among which majority of patients were in 51-60 years (46 patients, 57.5%) followed by 41-50 years (20 patients, 25%) and 31-40 years (14 patients, 17.5%). The mean age of the study group was 55.5 years, similar was observed by by Monika PPS[7], mean age was found to be 52 years and while in a study by Abhineet Jain et al.[8], mean age

of 60.2 years was reported.

The gender wise data was pooled from the proforma, and it was observed that there was male predominance in overall study. Out of 80 subjects, 65% were male and 35% were female. Male to female ratio was 1.85 which was again consistent with study done by Monika PPS[7], where male to female of 2:1 in RT group and 1.8:1 in RT+CT group was observed.

Among the 80 cases of Head and Neck malignancies, oral cavity lesions contributed the largest group (28 patients, 35%) followed by Laryngeal (23 patients, 28.75%) and Hypopharyngeal cancers (13 patients, 16.25%). Next in order were Oropharyngeal, Nasopharyngeal, Nose and PNS tumours. Smallest group was of occult primary with secondaries in neck with 2.5% (2 patients) of cases.

All the selected patients had histopathological proved carcinoma of head and neck region, among which 62.5% had moderately differentiated SCC, followed by poorly differentiated (25%) and well differentiated (12.5%) SCC.

Common complaints experienced by the patients after irradiation was ear heaviness, earache, decreased hearing, tinnitus and dizziness. Bohne et al[9]. in their study have mentioned slight pain or discomfort in the ear as well as tinnitus as symptoms of serous otitis media resulting due to ionizing radiation of the ear.

Patients receiving concurrent chemoradiation, on completion of treatment type B tympanogram was observed in 20% which decreased to 10% on 3 months follow up while type C tympanogram was observed in 25% which declined to 20% after 3 months follow up. Among these 40 cases, 45% cases developed conductive deafness immediately post- chemoradiotherapy which decreased to 30% after 3 months followup.

The incidence of SNHL involving higher frequency (8000 Hz) was seen in 30% after completion of treatment which increased to 37.5% at 3 months follow up.

The observation that higher frequency hearing was generally more affected than lower frequency hearing is consistent with findings from other studies[10-12]. The significant variation in SNHL after RT in different studies may be attributed to factors including the study design, patient selection, total dose, fraction, size, length of follow up and variation in evaluation and interpretation[13].

The patients who were treated with concurrent chemoradiation the incidence of significant SNHL in speech frequency was 15% which rose to 27.5% after completion of treatment and follow up after 3 months respectively while at higher frequency (8000 Hz) incidence of SNHL was 45% which rose to 62.5% after completion of treatment and 3 months follow up respectively. Similarly, in a study by Abhineet Jain et al.[8], SNHL at higher frequency was 42.5% at the completion of treatment showed linear increase to 67.5 and 82.5% at 8 and 16 weeks follow up period respectively whereas at low frequency SNHL was reported in 15% at the completion of treatment and 32.5% after 8 weeks follow up period.

SNHL at higher frequency was 42.5% at the completion of treatment showed linear increase to 67.5 and 82.5% at 8 and 16 weeks follow up period respectively whereas at low frequency SNHL was reported in 15% at the completion of treatment and 32.5% after 8 weeks follow up period. Monika PPS[65] also in her study found that incidence of significant hearing loss was 67.64% after 1 month and increased to 70.58% after 6 months in patients who received concurrent chemoradiation.

In the present study it was found that patients in the chemoradiotherapy group experienced greater sensorineural hearing damage than patients in the radiotherapy group and the results were statistically significant($p<0.05$). Similar results were reported by Monika PPS[7] and Bhandare et al[13].

Conclusion

Thus, we conclude that patients who received concomitant chemoradiation experienced greater hearing loss. Hearing loss was evident after 1 month of therapy and was persistent. The incidence and severity of hearing loss increased with time and higher frequencies were affected predominately. High-frequency hearing loss can have a significant impact on quality of life because it affects speech discrimination. It is recommended to perform a pre-treatment and post- treatment audiological evaluation with special emphasis on high frequencies.

Conflict of Interest: Nil Source of support: Nil

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