Effects of Chemoradiation on Hearing in Patients with Head and Neck Malignancies: Experience at a Tertiary Referral Care Hospital

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Abstract Hearing loss as a side effect in patients with head and neck malignancies with chemoradiation is frequently ignored. Its effects on auditory functions are less studied and there are studies done on animals which are less reliable. The present study was undertaken to identify the type of hearing loss and also to quantify the degree of hearing loss in these patients. A prospective, descriptive study was undertaken in histologically proven head and neck cancer patients treated with cobalt 60 teletherapy who received a dose of 60–66 Grays (Gy) over a period of 6–7 weeks with concurrent Cisplatin 30 mg/m² once weekly for 6 weeks. The study included 40 patients (80 ears) undergoing chemoradiation. A baseline pure tone audiometry and impedance audiometry was performed in all the cases prior to the therapy and the same was repeated immediately after the completion of treatment, at 8 and 16 weeks. The changes in pure tone level thresholds and impedance from baseline were correlated with the dose of radiation and chemotherapy. Sensori neural hearing loss (SNHL) and conductive hearing loss was observed in 82.5 and 17.5 % respectively. At the end of 16 weeks, SNHL was found in 27.5, 72.5 and 82.5 % at 2, 4 and 8 kHz respectively. In addition, Eustachian tube dysfunction and Otitis media with effusion was observed in 10 and 7.5 % of patients respectively which lead to conductive hearing loss. Further, it was noted that SNHL in patients with high risk site malignancy (81.8 %) was alarmingly higher compared

with low risk site malignancy (18.1 %). The hearing loss at 62, 64 and 66 Gy in comparison to 60 Gy was statistically significant. Hearing loss, specially SNHL was the predominant finding in our study with >80 % of patients showing the inner ear damage due to irradiation of head and neck malignancies. Although, all the frequencies like 2, 4 and 8 kHz were significantly affected, SNHL was more marked in the latter two frequencies. Nearly, 90 % of the patients who had SNHL belonged to high risk site category of head and neck malignancies. Increasing the radiation dosage was directly proportional to the degree of hearing loss with the dose more than 60 Gy causing significant injury to the middle and inner ear.

Keywords Hearing loss · Chemotherapy · Radiotherapy · Head and neck cancer

Introduction

Head and neck malignancies (including thyroid lesions) is third most common malignancy seen in both the sexes across the globe where as it constitutes the commonest malignancies in India [1]. In locally advanced inoperable head and neck malignancies, addition of chemotherapy and radiotherapy has improved the survival rate of patients in addition to preserving the organ. These patients who receive radiotherapy in and around acoustic structures are at extremely high risk of developing hearing loss. Cochlea hair cell death is implicated to be responsible for the radiation-induced sensorineural hearing loss (SNHL), which is one of the main complications of radiotherapy (RT) for head and neck cancers. The role of pathways of P53, reactive oxygen species (ROS) and c-Jun N-terminal kinase (JNK) have been proposed to be the processes leading

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to radiation induced hair cell death [2]. Similarly, the effects of radiation on middle ear includes otitis media due to transient Eustachian tube dysfunction leading to conductive hearing loss (CHL). In addition, Cisplatin, a chemotherapeutic drug used in head and neck cancers cause ototoxicity particularly for higher frequencies. The aim of the study was to identify the type and magnitude of hearing loss in chemoradiation.

Materials and Methods

The study was a prospective descriptive study conducted on patients attending the Department of ENT and Department of Radiation and Medical oncology at JLN hospital and Research Centre, Bhilai, Chattisgarh from November 2013 to October 2014. The aim of the study was to ascertain the effects of chemoradiation on the ear in patients with head and neck malignancies. Inclusion criteria were the biopsy proven newly diagnosed, inoperable cases of head and neck malignancies requiring concomitant chemoradiation. Patients of less than 6 years of age, those receiving ototoxic drugs other than cisplatin, preexisting middle ear pathologies and cases not having ear in the field of radiation were excluded from the study. A convenience sampling method was used. A total of 40 patients (80 ears) receiving concomitant chemoradiation were inducted into the study. Ethical committee clearance was obtained from the Institutional ethics committee and a valid informed consent was taken in all the cases.

Primary Objective

Was to find out the incidence of SNHL and CHL in patients receiving chemoradiation for head and neck malignancies and to ascertain the pattern of hearing loss in different frequencies.

Secondary Objectives

1. To evaluate the magnitude of SNHL in high risk and low risk site group of head and neck malignancies.
2. To ascertain the effect of higher doses of radiation on the hearing.

Treatment

Patients inducted received radiation with cobalt 60 teletherapy unit and a dose between 60 and 66 Gy as 2 Gy/fraction over 6–7 weeks. Concurrent with radiotherapy these patients also received Cisplatin 30 mg/m² once weekly for 6 weeks.

Auditory Status Evaluation

Baseline pure tone audiometry both for air conduction and bone conduction were performed at 250, 500, 1000, 2000, 4000 and 8000 Hz along with Impedance audiometry. These tests were repeated at the completion of treatment, 8 and 16 weeks following treatment. Ototoxicity was measured using intra subject audiogram comparisons. Each patient served as his/her control with the pretreatment audiogram serving as baseline.

Statistical Methods

Significance was assessed at 5 % level of significance. Student *t* test (two tailed, independent) was employed to find the significance of study parameters on continuous scale between two groups. Inter group analysis was assessed on metric parameters. Pearson correlation was used to find the relationship between radiation/cisplatin dose and magnitude of hearing loss.

Decrease of 20 dB in an isolated frequency or of 10 dB in two or more successive frequencies was set as criteria for reduction in auditory acuity (ASHA criteria).

Results

The study population included 34 men and 6 women with an average age of 60.2 years and the population age ranged from 30 to 76 years. Malignancies of oral cavity, oropharynx, nose and paranasal sinuses constituted 80 % (32 cases of 40) cases. In the study group, patients were stratified into high risk site (nasopharynx, paranasal sinuses, parotid, high level 2 metastatic node) and low risk site groups as per their risk of inner ear exposure to radiation and likelihood of developing increased hearing loss in follow up period. Important findings in the present study are as follows.

Hearing loss

Thirty-three patients (82.5 %) had SNHL and 7 patients (17.5 %) had CHL at the end of 16 weeks following treatment.

At 4 kHz, the SNHL was observed in 20 % of patients which at the completion of treatment rose to 39 and 72.5 % respectively at 8 and 16 week follow up period (Table 1). Similarly, at 8 kHz, the SNHL which was 42.5 % at the completion of treatment showed linear increase to 67.5 and 82.5 % at 8 and 16 week follow up period respectively. On the contrary at 2 kHz, SNHL which was seen in 15 % of patients at the completion of treatment saw an initial surge

Table 1 Number of patients with SNHL observed at different follow up periods of time at different frequencies

SNHL	Completion			8th week			16th week		
	2 kHz	4 kHz	8 kHz	2 kHz	4 kHz	8 kHz	2 kHz	4 kHz	8 kHz
Number of patients	6	8	17	13	18	27	11	29	33
Percentage of patients (Out of 40)	15	20	42.5	32.5	39	67.5	27.5	72.5	82.5

at 8th week follow up period (32.5 %) dropped to 27.5 % at 16 week follow up.

At completion of treatment, Eustachian tube dysfunction and Otitis media with effusion was observed in 5 and 2.5 % respectively which rose to 10 and 7.5 % at 16 week follow up (Table 2,3).

Among 40 patients, 62 ears had SNHL and the pure tone average (PTA) thresholds were analyzed for various frequencies (In comparison to baseline) at treatment completion, 8 and 16 weeks follow up (Table 4). The difference was statistically significant ($p < 0.05$) for the frequencies 2, 4 and 8 kHz at all the follow up periods with reference to the baseline.

On follow up at 16th weeks, 10 % ($n = 4$) & 7.5 % ($n = 3$) had OME and ET dysfunction (Type B/Type C tympanogram) respectively.

Distribution Pattern of SNHL Among Patients Between High and Low Risk Sites

Out of 30 high risk category of patients 27 patients (90 %) had SNHL whereas it was observed in 6 (60 %) out of 10 low risk category patients at the end of 16 weeks. The frequency wise distribution depicts that majority of the patients affected were in 4 and 8 kHz at the end of 16 weeks follow up (Table 5).

Relation Between Radiation/Cisplatin Dose and Hearing Thresholds Difference (Table 6)

No statistical significance in the hearing threshold was observed in terms of dosage of cisplatin (<300 mg and >300 mg) with the dose of radiation given from 60 to 66 Gy.

Relationship Between the Dose of Radiation and Hearing Loss at Various Frequencies (Table 7)

Increase in SNHL magnitude (difference between baseline to 16th weeks in dB) was observed at 4 and 8 kHz (p value < 0.01 and p value < 0.05 respectively) when RT dose increased from 60 to 64 Gy and 60 to 66 Gy and was statistically significant. Similarly, there was also a significant SNHL at 2 kHz (p value < 0.02) when RT dose was increased from 60 to 66 Gy.

Discussion

The relative contributions of radiation and chemotherapy to ototoxicity in patients undergoing combined chemoradiation for head and neck cancers has not been previously defined in detail. Majority of the studies on SNHL in such patients were published on nasopharyngeal carcinoma patients receiving radiation [3–8] except few studies [9–11]. However, there is still uncertainty prevailing regarding the pattern of hearing loss, the frequencies affected and the dose of chemoradiation effects on the hearing. The present study aims to address these issues which could lead to understanding of the effects of chemoradiation on the inner ear.

SNHL is considered as a late complication following radiotherapy. Few studies have reported the median interval for development of persistent SNHL as ranging from immediate follow up period up to 48 months [5, 12]. However, our study was consistent with one of those studies with the onset of SNHL noted from immediate post chemoradiation to 4 months follow up period.

Chemoradiation is associated with varying types and degree of hearing loss. Goel et al. [13] in prospective study

Table 2 Number of patients with CHL observed at different follow up periods of time at different frequencies

Conductive hearing loss	Completion		8th week		16th week	
	ET dysfunction	OME	ET dysfunction	OME	ET dysfunction	OME
Number of patients	2	1	3	3	4	3
Percentage (Out of 40)	5	2.5	7.5	7.5	10	7.5

Table 3 Type of tympanogram observed in patients with CHL at different follow up periods

Type of tympanogram	Baseline		Completion		8th week		16th week	
	n	%	n	%	n	%	n	%
Type A	4	57.14	3	42.86		0		0
Type B		0	1	14.29	3	42.86	4	57.14
Type C		0	2	28.57	3	42.86	3	42.86
Type A+C	2	28.57		0		0		0
Type As		0		0		0		0
Type A+As	1	14.29	1	14.29	1	14.29		0

Table 4 Difference in the hearing threshold (PTA) from baseline to different follow up periods of time (dB)

Time periods	250 Hz	500 Hz	1 kHz	2 kHz	4 kHz	8 kHz
Completion	0.7	4.89	3.79	7.82	8.1	8.12
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$
8th weeks	0.85	2.62	3.51	8.47	15.18	11.81
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.01$	$p < 0.001$	$p < 0.001$
16th weeks	1.56	4.69	2.74	7.63	13.93	14.39
	$p > 0.05$	$p > 0.05$	$p > 0.05$	$p < 0.01$	$p < 0.001$	$p < 0.001$

Table 5 Number of SNHL observed in high and low risk site category groups at various follow up periods of time

SNHL (n = 33)	High risk (n = 27)			Low risk (n = 6)		
	Completion N (%)	8th week N (%)	16th week N (%)	Completion N (%)	8th week N (%)	16th week N (%)
2 kHz	5 (18.519)	12 (44.444)	10 (37.037)	1 (16.667)	1 (16.667)	1 (16.667)
4 kHz	6 (22.222)	16 (59.259)	26 (96.296)	2 (33.333)	2 (33.333)	3 (50)
8 kHz	14 (51.852)	22 (81.481)	27 (100)	3 (50)	5 (83.33)	6 (100)

of 30 patients with Carcinoma larynx undergoing concomitant radio chemotherapy observed that the average hearing loss ranged between 5 and 15 dB and the frequency range commonly affected was 4000–8000 Hz. SNHL was observed in 43.33 % of patients and 16.67 % had mixed hearing loss 6 months post treatment. Dell'Aringa et al. [14] observed that 17 patients with extra cranial head and neck malignancies included in the study presented with auditory damage with 70.5 % of them with having auditory alteration; 55.8 % with change higher than 20 dB in a unique frequency and 14.7 % with reduction of 10 dB in at least two consecutive frequencies. However, in the present study at the end of 16 weeks, 72.5 and 82.5 % of patients had SNHL at 4 and 8 kHz frequencies respectively which was clearly much above than the previous two studies. This could be attributed to old conventional method of radiotherapy (Cobalt) associated with significant unwanted radiation exposure of the inner ear.

Conductive hearing loss was because of acute otitis media with effusion and ET dysfunction as a result of injury to the ET tube ciliated epithelium, tubal swelling, and fibrosis that blocks the lumen. Acute OME usually occurs within a few weeks after RT. It is associated with transient hearing loss. Bhandare et al. [12] reported acute OME in 11.5 % of patients in their series. No association was noted between occurrence of acute OM and persistent SNHL. In the present study of 40 patients, conductive hearing loss was present in 7 patients (17.5 %) at the end of 16 weeks of follow up. Prospective studies conducted on patients with carcinoma larynx undergoing chemoradiation have found no correlation between chronic OME and associated persistent SNHL after a follow up period of up to 6 months [5, 13]. Yet another study reported low prevalence of middle ear complications at 10 year following RT for patients with carcinoma larynx [15].

Table 6 Relationship between the dose of radiation and chemotherapy on mean PTA difference at various follow up periods of time (Only one low frequency and two high frequencies have been shown for the convenience)

		500 Hz		<i>p</i> value	4 kHz		<i>p</i> value	8 kHz		<i>p</i> value
60		Mean	SD	$p > 0.05$ NS	Mean	SD	$P > 0.05$ NS	Mean	SD	$p > 0.05$ NS
	≤300	2.86	2.67		5	4.08		16.43	5.56	
	>300	3.33	2.89		10	5		16.67	2.89	
62		Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS
	≤300	8.75	2.5		6.25	4.79		16.25	2.5	
	>300	7.5	3.54		7.5	3.54		17.5	3.54	
64		Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS
	≤300	1	2.24		14	4.18		20	7.91	
	>300	1.25	2.5		17.5	6.45		22.5	2.89	
64		Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS	Mean	SD	$p > 0.05$ NS
	≤300	2.5	2.74		19	4.18		18.33	5.16	
	>300	3.33	3.54		21.1	6.01		20.56	6.82	

Table 7 Effect of increasing dose of radiation on the hearing threshold differences (baseline to 16 weeks) at various frequencies

		2 kHz				4 kHz			8 kHz		
A	RT(Gy)	N	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value
	60	10	6.5	4.849	>0.05 NS	6.5	4.328	>0.05 NS	16.5	5.027	>0.05 NS
	62	6	5.83	5.45		6.67	4.51		16.67	2.796	
B	RT(Gy)	N	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value
	60	10	6.5	4.849	>0.05 NS	6.5	4.328	<0.01 HS	16.5	5.027	<0.05 HS
	64	9	8.33	5.96		15.56	5.274		22.05	6.272	
	60	10	6.5	4.849	>0.05 NS	6.5	4.328	<0.01 HS	16.5	5.027	<0.05 HS
	64	9	8.33	5.96		15.56	5.274		22.05	6.272	
C	RT(Gy)	N	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value	Mean	SD	<i>p</i> value
	60	10	6.5	4.849	0.02 HS	6.5	4.328	0.001 HS	16.5	5.027	<0.05 HS
	66	15	12.67	6.403		20.27	5.38		22.1	6.234	

Table 8 Mean difference in PTA from baseline to 16 weeks at different frequencies following Chemoradiation

Study	High risk side SNHL incidence			Low risk site SNHL incidence		
	2 kHz (%)	4 kHz (%)	8 kHz (%)	2 kHz (%)	4 kHz (%)	8 kHz (%)
Hitchcock et al.	40	50	50	21	32	30
Our study	44	59.25	81.48	16.66	33.33	50

In the present study, at 27 (90 %) out of 30 high risk site and 6 out of 10 low risk site patients had SNHL. Our incidence of significant SNHL at 2/4/8 kHz as per high/low risk sites at 1st follow up (8th week) were higher compared to a similar study conducted by Hitchcock et al. where in 21 patients of Head and neck cancer received radiation alone (Table 8).

Cisplatin based chemotherapy is widely used with concomitant RT for loco-regional, advanced head and neck cancers. There are still arguments about the dosage of

cisplatin used in concomitant chemoradiation for head and neck cancers despite several very large, prospective, randomized trials using cisplatin at 100 mg/m² proving to have better survival rate than RT alone. Oh et al. [16] reported that low dose cisplatin had no additive effect on ototoxicity in nasopharyngeal carcinoma patients who received one cycle of neoadjuvant 5-FU (1000 mg/m²) and cisplatin (20 mg/m²) followed by low dose cisplatin every 3 weeks for 2–3 cycles concurrently during RT. They maintained that the cisplatin dose was too low to induce

SNHL by itself. Ho et al. [17] reported that the mean dose of 275 mg/m² was not associated with increased hearing threshold. In the present study, total cumulative dose of cisplatin received ranged from 210 to 372 mg. Most of the patients received concurrent cisplatin with dose of 30 mg/m² and no significant change was observed (p value > 0.05) for SNHL at 2/4/8 kHz with variation of dosage of cisplatin (<300 mg and >300 mg) at all follow up periods.

The present study signifies relationship between increased dose of radiation and risk of hearing loss at higher frequencies specially at 4 and 8 kHz. This view is also supported by Petsuksiri et al. [6] who reported that the mean dose less than 50 Gy of radiation appeared to have lower chances of SNHL and the incidence was higher when the dose was more than 50 Gy to the cochlea. In addition, a retrospective study by Honore et al. [18] inferred that SNHL at 4000 Hz after irradiation of the inner ear showed a statistically significant dose response relationship which was not the case with low frequencies. The result of the multiple linear regressions at 4000 Hz with dose, as independent variable has shown a loss of 0.306 dB.

Although, short term follow-up of the study is the drawback of the present study, most of the inner ear damage is irreversible and minimal variations in the findings can be expected with respect to the SNHL.

Conclusion

Hearing loss, specially SNHL was the predominant finding in our study with >80 % of patients showing the inner ear damage due to irradiation of head and neck malignancies. Although, all the frequencies like 2, 4 and 8 kHz were significantly affected, SNHL was more marked in the latter two frequencies. Nearly, 90 % of the patients who had SNHL belonged to high risk site category of head and neck malignancies. Increasing the radiation dosage was directly proportional to the degree of hearing loss with the dose more than 60 Gy causing significant injury to the middle and inner ear.

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