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A Prospective Comparative Study of Sensorineural Hearing Loss in Patients with Head and Neck Cancers Treated with 2D RT vs. 3D CRT

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Background and objective: Sensorineural hearing loss (SNHL) is a disabling condition for patients due to its chronic and often progressive nature. While conductive hearing loss (often observed after radiotherapy) is primarily reversible, SNHL is irreversible.

Material and methods: This prospective randomized study was conducted in the Department of Radiation Oncology at S.P. Medical College in Bikaner, Rajasthan, India. The study was conducted from November 2020 to October 2021. After obtaining informed consent, 50 patients with biopsy-proven squamous cell carcinoma of the head and neck region were randomly assigned to two groups: Group A (receiving 2D RT at 2 Gy/fraction for 30 to 35 fractions over 6 to 7 weeks) and Group B (receiving 3D CRT at 2 Gy/fraction for 30 to 35 fractions over 6 to 7 weeks).

Results: SNHL assessment was performed at the completion of treatment and 3 months later. At the completion of treatment, SNHL for speech frequencies was 15% in Group A (2D RT) and 8% in Group B (3D CRT), while high-frequency hearing loss was 45% and 28%, respectively. At 3 months post-treatment, SNHL for speech frequencies was 27.5% in Group A and 12% in Group B, and high-frequency hearing loss was 62.5% and 32%, respectively.

Conclusion: High-frequency hearing loss can significantly impact quality of life by affecting speech discrimination. Conventional radiotherapy (2D RT) resulted in greater hearing loss compared to 3D conformal radiotherapy (3D CRT).

Introduction

Global cancer burden using the GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer. Worldwide, about 19 million new cancer cases and approx. 10 million cancer deaths have been seen in 2020 [1]. In India approximately 1.3 million new cancer cases were observed, indicating India contributed to 10.43% of the global cancer burden; mortality figures were 8,51,678 contributed to 7.05% of global cancer deaths in 2020. GLOBOCAN 2020 (India) [1]. Mostly head and neck cancer diagnosed in locally advanced stage (66.6%) [2]. Two types of hearing loss are there:- first is conductive hearing loss, which is seen because of radiation effects on the external and middle ears; second is sensorineural hearing loss, which is due to radiation effects on the cochlear and retro cochlear region. Pure-tone audiometry (PTA) is a standard procedure to measure the threshold of audibility. Therefore, this study is done to determine the radiation dose received by the inner ear and to know the SNHL in head and neck cancer patients. sensorineural hearing loss is irreversible, whereas conductive hearing loss (as often found after radiotherapy) is mainly reversible [3]. Radiotherapy in the acute phase, leads to transient conductive hearing loss as a result of inflammation, oedema, and/or fibrosis of the middle ear and/or eustachian tube. Sensorineural hearing loss can be an acute or a late complication of radiotherapy (RT) to the inner ear and may be irreversible. It is caused most likely by vascular insufficiency and radiation induced lesions to the inner ear or acoustic nerve [4]. Destruction of the organ of Corti and vestibulocochlear nerve atrophy after radiation to the temporal bone have been demonstrated [5]. Furthermore, loss of OHCs, loss of spiral ganglion cells in the basal turn of the cochlea, atrophy of the stria vascularis, changes in vasa nervosum and damage to organ of Corti, macula of the utricle & the cristae of the semi-circular canals, have been found in post-mortem examination of the human temporal bone in patients treated with RT [6,7]. Cisplatin induced SNHL may start in the acute phase of treatment and is characterized by bilateral, irreversible, and progressive high frequency loss [8]. Patients who received radiotherapy and concurrent/adjuvant chemotherapy using cisplatin experienced greater SNHL compared to patients treated with radiotherapy alone, especially to high-frequency sounds in the speech range [9]. Our aim is to evaluate incidence and severity of hearing loss between 2D RT and 3D CRT.

Materials and Methods

This prospective randomized study was conducted in Department of Radiation Oncology, S P medical college Bikaner, Rajasthan. The study was done from November 2020 to October 2021. After taking informed consent total of 50 patients of biopsy proven squamous cell carcinoma of head and neck region randomly distributed among Group A who received 2D RT (2Gy/Fr in 30 to 35 fractions for 6 to 7 weeks) and Group B who received 3D CRT (2Gy/fr) in 30 to 35 fractions for 6 to 7 weeks).

Inclusion criteria

Histopathological proven primary HNSCC of either sex, who had ECOG PS 0-2 included in the study.

Exclusion criteria

Patients with severe co-morbidities, pregnant and lactating women, those who had received prior radiotherapy, having bone conduction threshold >50 dl were excluded from the study.

Tuning fork test done using 256, 512 and 1024 Hz Tuning forks. In Nose examination anterior rhinoscopy done. Oral cavity examined and neck examination done to look for any enlarged lymph nodes and secondaries. Indirect Laryngoscopy performed using a 90°endoscope. Baseline pure tone audiometry both for air conduction and bone conduction performed at 250, 500, 1000, 2000, 4000 and 8000Hz along with Impedance audiometry before the commencement of treatment. These tests repeated: after completion of treatment and after 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 set as criteria for reduction in auditory acuity (ASHA criteria).

Data Analysis

The collected data entered in excel sheet and analysed using appropriate statistical methods with

SPSS 2. The significance of the outcome of the study was assessed by calculating the ‘P’ value a value less than 0.05 taken as significant.

Results

Our study consisted two groups, group A were subjected to conventional (2-D) radiotherapy while group B undergone conformal (3-D) radiotherapy, patients were selected from Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Centre, PBM hospital Bikaner. Total 50 patients were selected with mean age 47.17 in group A and 47.07 in group B (Table 1).

Characteristics	Group A (n = 25)	Group B (n = 25)	p-value
Mean age (yr.)	47.17	47.07	0.979
Gender			0.656
Male	21 (80)	20 (84)	
Female	4 (20)	5 (17)	
History of tobacco consumption	23 (87)	21 (93)	0.343
Co-morbidity			0.476
Diabetes	2 (6)	5 (16)	
Hypertension	4 (14)	4 (14)	
No comorbidity	24 (80)	21 (70)	
ECOG PS			0.943
0	5 (16)	9 (30)	
1	22 (74)	19 (64)	
2	3 (10)	2 (6)	
Primary site			
Oral cavity	11 (6)	6 (3)	0.643
Oropharynx	6 (46)	6 (43)	
Nasopharynx	2 (13)	5 (16)	
Hypopharynx	6 (33)	8 (36)	

Table 1. Baseline Patient Characteristics between arm A and arm B.

Patients are given concurrent cisplatin whenever required. Inner ear contoured as per guidelines given by Heather D. Pacholke [10]. Treatment was done by conventional techniques (2-D) on telecobalt machine and conformal technique (3-D) on 6MV linear accelerator. Dose on inner ear was calculated by dose volume histogram (DVH). Baseline audiological evaluation was done in all the patients and repeated at completion of treatment and at 3 months follow up. The difference of PTA thresholds were correlate with cochlea dose. In group A, 15% (n=4) and 45% (n=10) patient had SNHL at speech and high frequency respectively after completion of treatment. After 3 month follow up, 27.5% (n=7) and 62.5% (n=15) patient had SNHL involving speech and high frequency respectively. In group B, 8% (n=2) and 28% (n=7) patient had SNHL at speech and high frequency respectively after completion of treatment. After 3 month follow up,12% (n=3) and 32% (n=8) patient had SNHL involving speech and high frequency respectively (Table 2).

	Group A		Group B	
	Completion of RT	3-month flu	Completion of RT	3-month flu
Speech frequency	4/25	7/25	4/25	10/25
High frequency	10/25	15/25	3/25	8/25

Table 2. Sensorineural Hearing Loss.

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In Conventional (2-D) Radiotherapy induced hearing loss in group A ,44% subjects had no hearing loss and 16% subjects had mild hearing loss,36% subjects had moderate hearing loss,4% subjects had moderate severe hearing loss, no any subject had severe hearing loss. And In Conformal (3-D) Radiotherapy induced hearing loss in group B ,68% subjects had no hearing loss and 20% subjects had mild hearing loss,12% subjects had moderate hearing loss, no subjects had moderate severe hearing loss, no any subject had severe hearing loss (Table 3).

Group A:		
No. of patient	Total dose of RT	SNHL at 3 months post RT
20	60-70	9/20 (44%)
5	Less than 60	0/5 (0%)
Group B:		
No. of patient	Total dose of RT	SNHL at 3 months post RT
21	60-70	6/21 (15%)
4	Less than 60	0/4 (0%)

Table 3. Dose of RT and Impact on Hearing.

In group A 20 patients who received radiation dose between 60-70Gy, 9 patients (44%) had SNHL after 3 months post radiotherapy while 5 patients receiving radiotherapy with radiation dose less than 60Gy showed no hearing loss. The above table shows that in group B, 21 patients who received radiation dose between 60-70Gy, 6 patients (15%) had SNHL after 3 months post radiotherapy while 4 patients receiving radiotherapy with radiation dose less than 60Gy showed no hearing loss (Table 4).

		Baseline	Completion of treatment	Follow up 3 months
Mean threshold (dB)	Speech frequency	23.76 (dB)	26.29 (dB)	31 (dB)
	High frequency	24.26 (dB)	32.9 (dB)	37.18 (dB)
Mean threshold (dB)	Speech frequency	21.46 (dB)	23.76 (dB)	26 (dB)
	High frequency	21.26 (dB)	30.86 (dB)	35.78 (dB)

Table 4. Mean Bone Conduction Threshold at Different Frequency in Hearing Loss Patients.

Group A, patient developed around 2.4dB average hearing loss immediately post radiotherapy and 6.34 dB average hearing loss after 3 months post radiotherapy. Here average hearing threshold is average of hearing threshold at 500,1000 and 2000kHz frequencies. The above table shows that in group A, patient developed around 8.9dB average hearing loss immediately post radiotherapy and 15.11 dB average hearing loss after 3 months post radiotherapy. Here average hearing threshold is average of hearing threshold at 8000kHz frequencies. The above table shows that in group B, patient developed around 1.8 dB average hearing loss immediately post radiotherapy and 4.86 dB average hearing loss after 3 months post radiotherapy. Here average hearing threshold is average of hearing threshold at 500,1000 and 2000kHz frequencies. The above table shows that in group B, patient developed around 5.34 dB average hearing loss immediately post radiotherapy and 11.24 dB average hearing loss after 3 months post radiotherapy. Here average hearing threshold is average of hearing threshold at 8000kHz frequencies.

The absolute PTA threshold values for various frequencies at baseline, 40Gy tumour dose, treatment completion and 3 months follow up and changes in absolute PTA threshold values are analysed from baseline to 40Gy tumor dose, treatment completion and 3 months follow up. Change in absolute PTA threshold values are significant for 8000Hz at 40Gy tumor dose, treatment completion and 3months follow up (0.002, 0.006 respectively). Change in the PTA threshold >10db is considered as significant hearing loss. According to this criterion, in patients receiving 2-D RT 50%, 15% and 45% patients had significant hearing loss for 4 kHz and 8 kHz respectively at the completion of treatment and 27.5%, 62.5% patients had significant hearing loss for 4 kHz and 8 kHz respectively at 3 month follow up. Significant SNHL (> 10 db loss) is observed for 8 kHz at cochlear dose levels of more than 40Gy at completion of treatment and at 3 months follow up. For 4 kHz significant SNHL is noted at cochlear doses of more than 60Gy at 3 months follow up. The difference of absolute PTA threshold values from baseline to completion of treatment and 3 months follow up is correlated with various levels of cochlea dose across all frequencies. The difference in absolute PTA threshold values from baseline to completion is not statistically significant for any frequency. The difference in absolute PTA threshold values from baseline to 3 months follow up are noted for 4000 Hz and 8000 Hz but it is statistically significant for 8000 Hz. (p = 0.046) only. The difference in the absolute PTA threshold values from baseline to treatment completion and baseline to 3 months follow up are analysed according to use of modality of radiotherapy. Difference from baseline to treatment completion is statistically significant for 500 Hz (0.037), 2000 Hz (0.002), 4000 Hz (0.018) and 8000 Hz (<0.001). Difference from baseline to 3 months follow up is statistically significant only for 8000Hz (p = 0.023).

Discussion

Our Study consisted of 50 subjects with carcinoma Head and Neck region which were treated by radiotherapy alone or radiotherapy and cisplatin chemotherapy who visited to Department of Radiation Oncology PBM Hospital, Bikaner, Rajasthan. 50 patients were selected belonging to age group 30-60 years who fulfilled the inclusion and exclusion criteria. Informed consent was taken from study population and subjects were selected by simple random sampling. The aim of the study was to investigate and compare the incidence and severity of hearing loss caused by Conventional and conformal radiotherapy in Head and Neck cancer cases and compare the severity of hearing loss in these two modalities. The mean age of the study group was 47.17 years in group A and 47.07 in group B. Numbers of studies have been done on nasopharyngeal and parotid cancer because of involvement of otological structures in radiation field. We also included hypopharyngeal malignancies to see effects on otological structures involvement in Head and Neck malignancies. Today, most of the oral cavity/pharynx patients present with locally advanced disease therefore chemotherapy and radiation therapy combination is used. Hence, such cases who received concomitant chemoradiation were also included in the study to see for any synergistic effects, if any. Common complaints after irradiation were ear heaviness, earache, decreased hearing, tinnitus, and dizziness. Bohne et al. [11] in their study have mentioned that slight pain or discomfort in the ear as well as tinnitus resulting due to ionizing radiation of the ear. As a result of radiotherapy tympanic membrane become dull, retracted, bulged, congested, or may remain normal. This change were transient and reversible. Borsanyi et al. [12] & Evans et al. [13] told that tinnitus was an occasional, early but temporary complaint in the affected ear. Coplan J et al. [14] in their study revealed thickening of the tympanic membrane while Bhandare et al. [4] found erythema (congestion) of the tympanic membrane as one of the signs of middle ear inflammation. Patients in group A receiving conventional (2-D) radiotherapy, on completion of treatment type B tympanogram was observed in 20% which decreased to 12.5% on 3 months follow up while type C tympanogram was observed in 30% which declined to 25% after 3 months follow up. Above data shows that after radiotherapy serous otitis media and Eustachian tube dysfunction are mostly temporary and reversible adverse effects. These can occur immediately or up to 3 months following radiotherapy. At 3 months post radiotherapy number of patients with serous otitis media and Eustachian tube dysfunction decreased significantly as compared to immediate post radiotherapy. However longer study period is needed to prove such findings as shown by Upadhya et al. [15] in which 25.71% had type B tympanogram immediately after RT which decreased to 5.71% after 6 months post RT while 42.85% had type C tympanogram immediate post RT which declined to 31.42% after 6 months post RT. Among our 25 cases, 50% cases developed conductive deafness immediately post-radiotherapy which decreased to 37.5% after 3 months follow up showing that conductive deafness resulting from effects of radiotherapy is reversible in nature. Similar results were found by Upadhya et al. where 28.57% cases regained normal hearing within 6 months of radiotherapy i.e., conductive deafness resulting from effects of radiotherapy was reversible in 28.57% of cases within 6 months following radiotherapy. Similarly, in group B receiving conformal

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(3-D) radiotherapy, on completion of treatment type B tympanogram was observed in 15% which decreased to 10% on 3 months follow up while type C tympanogram was observed in 20% which declined to 15% after 3 months follow up. Among these 25 cases, 14% cases developed conductive deafness immediately post radiotherapy which decreased to 18% after 3 months follow up. In our study, in group A patients out of 25 patients who were subjected to incidence of SNHL was seen in 15% involving speech frequency after completion of treatment which rose to 27.5% after 3 months follow up while incidence of SNHL involving higher frequency (8000 Hz) was seen in 45% after completion of treatment which increased to 62.5

% at 3 months follow up. It was observation that higher frequency hearing was generally more affected than lower frequency hearing, is consistent with findings from other studies. 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. LF Wang et al. [7] in their study concluded that hearing deterioration may begin as early as 3 months after completion of radiotherapy and the effect of radiation on hearing tended to be chronic and progressive while the early changes may be transient. In the present study we observed that hearing loss can be noticed by 1 month following treatment which is similar from study by Monika PPS, who reported incidence of post RT sensorineural hearing loss in 45.45% at 1 months and increased to 51.51% after 6 and 12 months. In the group B where patients were treated with conformal radiotherapy the incidence of significant SNHL in speech frequency was 8% which rose to 12% after completion of treatment and follow up after 3months respectively while at higher frequency (8000 Hz) incidence of SNHL was 28% which rose to 32% after completion of treatment and 3 months follow-up respectively. The present study is comparing SNHL in conventional and conformal modality of radiotherapy. For the study only 3 months follow up after completion of treatment was considered. Kwong et al. [16] reported a 24% incidence of sensorineural hearing loss particularly for higher frequencies post RT for carcinoma of nasopharynx. Merchant et al. [17] found the rate of permanent hearing loss was from 24.2% to 36% for doses of 60Gy. Zuur et al [3] in prospective analysis of hearing loss by using concurrent daily low-dose cisplatin chemo-radiation for locally advanced head and neck cancer reported a total incidence of ototoxicity in CTCAEV3.0 as 31% in audiograms up to 8 kHz. SNHL at a high frequency was more frequent in the chemoradiotherapy group than in the RT-alone group (55% vs. 33.3%), but not at a low frequency. The dose received by the cochlea is the most important determinant for the development of SNHL following radiation to the head and neck cancers. In our series, all the cochlea doses were calculated in three dimensions using the Prowess treatment planning system. The actual dose distribution received by the cochlea could also be somewhat different from the calculated one owing to contouring errors and small setup errors. To avoid these uncertainties, in the present series we have used median cochlear dose, which is usually least affected by such uncertainties (Figure 1).

Figure 1. Isodose Distribution of Head and Neck Primary with Right and Left Cochleae.

In the present study SNHL (> 10 dB loss) is noted for cochlear doses of 40 Gy and above for higher frequencies. Significant SNHL (> 10 dB loss) is observed for 8 kHz at cochlear dose levels of more than 40Gy at completion of treatment and at 3 months follow up. For 4 kHz significant SNHL is noted at cochlear doses of more than 60Gy at 3 months follow up. In present study, we found that changes in absolute PTA thresholds are statistically significant at all points of time, however when the difference in PTA thresholds is correlated with cochlear dose, significant SNHL is noted only for 8000 Hz at 3 months follow up ($p = 0.046$*). There was trend for SNHL at 4000 Hz but not statically significant ($p = 0.079$). Cochlear hair cells are arranged such that each hair cell is sensitive to a limited frequency range. Several investigators have shown post radiation hearing loss to affect higher frequencies preferentially. Chemotherapy-related damage begins in the first row of outer hair cells at the base of the cochlea where high frequency sounds are processed. Hence, use of platinum compounds can result in sensorineural hearing loss, which initially involves the higher frequencies (4000–8000 Hz).

In conclusion, this study was a prospective comparative study carried out at ATRCTRI, Bikaner with aim of comparison of hearing loss in head and neck cancers treated on 2D (group A) Vs 3D (group B) CRT. 50 patients without any cause of deafness were selected randomly (statistical test applied was chi-square test and Fisher exact probability test) belonging to age group 30-60 years to receive 66Gy/33 fractions, 5 fractions per week, with concurrent cisplatin 40mg/m^2 based on fitness of patients, wherever applicable. On comparison, significant difference in proportions of hearing loss was observed between both the arms. After completion of treatment in group A, 45% developed significant hearing loss (>10db from baseline) whereas in group-B 30% had significant hearing loss. After 3 months follow up, 62.5% and 37.5% developed significant hearing loss in 2-D RT and 3-D RT group respectively (p value <0.001). Therefore, we conclude that patients who received conventional radiotherapy experienced greater hearing loss as compared to patients treated with conformal radiotherapy and hearing loss was predominately of sensorineural type. 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. Incidence of radiation induced SNHL increased with concurrent use of cisplatin chemotherapy and increasing follow up duration. Combined modality treatments particularly affect higher frequencies (4 kHz and 8 kHz). The results of this study were in accordance with many prior studies. In conclusion 3DCRT was better in sparing sensorineural hearing loss with compared to conventional 2D RT. More conclusive result would hence require further evaluation in terms of large sample size, longer follow up, other toxicity profiles and effect of different concurrent chemotherapy on SNHL.

Conflict of interest

There are no conflicts of interest.

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