Volume - 13 | Issue - 02 | February - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARATIVE STUDY OF SENSORINEURAL HEARING LOSS IN PATIENTS OF HEAD AND NECK CANCERS TREATED WITH 2-D CRT VS 3-D CRT

Oncology/Radiotherapy

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ABSTRACT

Aim / Objective- The prospective and follow up study aims to compare incidence and severity of the hearing loss in the 2D vs 3D radiotherapy modalities in the head and neck cancer cases. **Material & Methods-** A Prospective cohort study of 50 head and neck cancer patients, 25 of them treated with 2D- CRT and 25 of them treated with 3D-CRT from November 2020 to December 2021. All patients of arm A and arm B followed after 2 years. Baseline pure tone audiometry both for air conduction and bone conduction, was performed at 250, 500, 1000, 2000, 4000, and 8000Hz along with Impedance audiometry before the commencement of treatment. These tests are repeated after completion of treatment and after 3 months post-completion of treatment. A decrease of 20 dB in an isolated frequency or of 10 dB in two or more successive frequencies was set as a criterion for reduction in auditory acuity (ASHA criteria). After 2 years of treatment, both arms followed and a pure tone audimetry test was done for evaluation of SNHL. The statistical test, the Chi-square test was used to investigate whether the distribution of categorical variables differs from one another. The p-value was taken as significant when less than then0.05($p<0.05$) and a confidence interval of 95% was taken. **Observations And Results -** In Conventional (2-D) radiotherapy-induced hearing loss in group A, 44% of subjects had no hearing loss and 16% of subjects had mild hearing loss, 36% of subjects had moderate hearing loss, 4% of subjects had moderate severe hearing loss, no any subject had severe hearing loss. In Conformal (3-D) Radiotherapy induced hearing loss in group B, 68% of subjects had no hearing loss and 20% of subjects had mild hearing loss,12% of subjects had moderate hearing loss, No subjects had moderate-severe hearing loss, no subject had severe hearing loss. **Conclusion-** 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.

KEYWORDS

Radiotherapy, head and neck cancer, sensory neural hearing loss

INTRODUCTION

The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year. Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC)[1]. HNSCC include malignant tumours that arise in lip, oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx.

Radiotherapy has long been the standard treatment modality for loco-regional treatment of head and neck cancer apart from surgery. It is use either in the definitive setting or in the adjuvant setting after surgery when indicated. The auditory apparatus, of which cochlea is the most sensitive to radiation, is often in the field of irradiation and sensorineural hearing loss (SNHL) is a possible sequel of it.

The top three head-and-neck functional impairments (HNFI) mentioned by nasopharyngeal carcinoma survivors were problems with salivation (71%), hearing (51%), and swallowing (45%). The effects of radiation on hearing function have not received much attention unlike other sequel (xerostomia, mucositis) which is extensively studies. SNHL is potentially more disabling for the patient, since it has a chronic and often Progressive natural history. The experimental radiobiological data on SNHL are With modern conformal radiation techniques, the incidence of radiation induced SNHL is expected to decline, due to a better visualization of the organs at risk (OARs) on the planning CT images and a better capability to spare the inner ear. Newer technologies like intensity modulated radiotherapy (IMRT) help us in giving dose constraints to sensitive organs and more or less can be achieved. Various published data clearly state that the dose to cochlea can be significantly reduced by technologies like IMRT and prevent the development of SNHL even when concurrent cisplatin is used. Cisplatin (cis-diamine-dichloro-platinum) is extensively used as a radiosensitiser in radiotherapy.

Since both cisplatin and radiotherapy seem to affect primarily the organ of Corti in the cochlea, and both modalities have their most pronounced effect in the high-frequency area, there has been some interest in determining their additive ototoxicity.

Though human beings can typically hear up to 20,000 Hz, testing is usually done from 250 to 8,000 Hz. Audiometry is a technique used by an audiologist or an otolaryngologist to measure hearing. There are two components of hearing loss: (a) conductive hearing loss, which is usually due to effects of radiation on the external and middle ears; (b) sensorineural hearing loss, which is related to radiation effects on the cochlear and retro cochlear region.

Pure-tone audiometry (PTA) is a standard procedure used in clinics to measure the threshold of audibility for pure tones presented to a listener over headphones and via bone vibrators held on mastoids.

The head and neck region embodies complex anatomical structures. The main stays of treatment are surgery, concurrent chemoradiation and radiotherapy. The treatment modality used depends on the tumour site, stage, radiological and histological characteristics and comorbidities of the patient.

Patients with stage I or II HNSCC are treated with surgery or radiotherapy alone. A combination of chemotherapy and radiation therapy is used in patients with inoperable or unresectable cancers [stage III and IV]. Cisplatin is the most commonly used drug for HNSCC given as concomitant therapy along with radiation.

Addition of a high dose, single agent cisplatin to conventional fractionated radiotherapy significantly improves the survival but also increases the toxicity[3].

Cisplatin causes side effects such as nausea, vomiting, ototoxicity, nephrotoxicity, neurotoxicity, and myelosuppression[2]. The severity of these side effects is dose dependant.

Several therapeutic compounds and modalities can cause ototoxicity. Antimalarial, antihypertensive, antibiotics, platinum-based chemotherapeutic agents, and radiotherapy applied on the head and neck area all may result in hearing loss[3]. This sensorineural hearing loss is irreversible, whereas conductive hearing loss (as often found after radiotherapy) is mainly reversible[4]. 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[5]. In 1969, Winther described an extensive degeneration of outer hair cells (OHCs) of the organ of Corti in guinea pigs after radiation of the inner ear[6]. Destruction of the organ of Corti and vestibulocochlear nerve atrophy after radiation to the temporal bone have been demonstrated[7]. 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 semicircular canals, have been found in post-mortem examination of the human temporal bone in patients treated with RT[8,9]. Cisplatin induced SNHL may start in the acute phase of treatment and is characterized by bilateral, irreversible, and progressive high frequency loss[10]. 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[11].

The incidence of post-RT sensorineural deficit has been reported to range from 0% to 50 % [12]. Kwong *et al.* reported a 24% incidence of sensorineural hearing loss particularly for higher frequencies, following radical radiotherapy for nasopharynx carcinoma[13]. Wai-kuen Ho in a prospective study reported a 31% incidence of deterioration of bone conduction threshold at 4 kHz[14]. Raaijmakers in a systematic review showed that at least one out of three patients, receiving a dose of 70Gy in 2Gy per fraction near the inner ear, can be expected to develop hearing impairment of 10db or more in the 4 kHz region[15].

Petsuksiri in a retrospective analysis of 68 nasopharyngeal carcinoma Patients reported the incidence of SNHL at high frequency (4 kHz). At pure tone average (PTA), the incidence of SNHL was 10.3%. For individual ear evaluation, the incidences of SNHL were 44% and 6% at 4 kHz and PTA, respectively[16].

Zuur in prospective analysis of hearing loss due to 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. Low-dose cisplatin chemo-irradiation (CRT) caused less acute hearing loss (31%), compared to high-dose cisplatin CRT (78%)[17].

Chan *et al.* in a longitudinal study on SNHL after treatment of nasopharyngeal carcinoma found that RT and chemo-radiotherapy resulted in 40% and 56.4% persistent SNHL, respectively, after a median follow-up of 2 years. 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[18].

At dose levels of fractionated radiotherapy given for most of head and neck cancers and intracranial brain tumours, the cochlea is the main organ affected. Mean dose to the cochlea (Dmean) is a statistically significant factor consistently identified across studies while determining the incidence and degree of hearing loss[19].

Pan *et al.* in prospective study found that an increase in the mean Radiation dose to the inner ear was associated with increased hearing loss[12].

Most recently, Merchant *et al.* studied 72 children treated with conformal RT and suggested that the average cochlear dose should be kept to < 32Gy to prevent hearing loss[20].

Ho *et al.* reported that SNHL is found between 1.5 – 2 years after RT and in 40% of the ears, recovery was evident at 2 years. With follow-up for 4.5 years, the probability of significant threshold deterioration increased with time.

Bhandare *et al.* reported the median interval between RT and the development of persistent SNHL was 1.8 years (range, 0.5–5.9 years). For patients who received doses greater than or less than 60 Gy, the latency time was similar, indicating that the latency is not affected by the total dose received by the cochlear apparatus. When stratified by fractionation schedule, the median time interval for SNHL was 2.1 years for patients treated with once-daily fractionation compared to 1.45 years for those treated with twice-daily fractionation. The median latency for persistent SNHLamong 11 patients who received adjuvant chemotherapy combined with RT was 0.8 years, compared to 2.0 years for 38 patients who received RT alone[16].

Raaijmakers *et al.* in a systematic review showed an increasing loss with increasing dose starting at about 40 Gy applied in 2 Gy per fraction. Based on these reults one might argue that hearing loss becomes a substantial side effect in dose escalation studies.

Johannesen *et al.* in a study on late radiation effects on hearing, vestibular function, and taste in brain tumour patients found that adverse events (SNHL) do occur in patients treated with fraction doses less than 2 Gy to total doses of 53 to 54 Gy.

Bhandare *et al.* in study on ototoxicity after radiotherapy for head and Neck tumours reported an overall SNHL incidence of 14.7% for pts treated with once-daily fractionation and 15.7% for pts treated with twice-daily fractionation. The 5- 10-year actuarial estimates for freedom from clinically overt SNHL were 81% and 80%, respectively[16].

Bhandare N et al in 2007 observed that radiotherapy toxicity affects all parts of the auditory system with median doses for incidence varying between 60 Gy to 66 Gy and total dose to organ seems to be a significant factor that may contribute to ototoxicity[16].

Monika PPS study, in the study it was found the sensorineural hearing loss was more in higher frequencies. The hearing losses before and 6, 12 months after therapy and were found to be significant ($p<0.05$). It was found that hearing loss was persistent. The difference of proportions of hearing loss after RT and RT+CT ($p<0.05$) were found to be significant.

Jain et al (2016) states sensorineural 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. They found that all the frequencies like 2, 4 and 8 kHz were significantly affected, SNHL was more marked in the latter two frequencies.

Present study is being undertaken to evaluate the incidence and severity of hearing-loss in patients of HNSCC receiving radiotherapy, Also, the comparison of hearing loss in patients receiving 2D CRT (conventional radiotherapy) and 3D CRT (conformal radiotherapy) was done.

AIM / OBJECTIVE-

The prospective and follow up study aims to compare incidence and severity of the hearing loss in the 2D vs 3D radiotherapy modalities in the head and neck cancer cases.

MATERIALS AND METHODS

50 patients fulfilling the inclusion and exclusion criteria and giving informed, written consent divided into 2 groups - A and B of 25 each. Group A treated with 2D CRT (conventional radiotherapy) and group B with 3D CRT (conformal radiotherapy) therapy.

Inclusion criteria:

All newly biopsy proven cases of head and neck cancer and The patients with age group between 30-65 years

Exclusion criteria:

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 have previously been treated by chemoradiotherapy or another ototoxic drug,

Patients with diseases such as diabetes, renal failure, Patients not having ear in the field of radiation and Patients with bone conduction threshold >50db. The dose of radiotherapy in 2-D and 3-D regimen were as follows.

Treatment modality	Dose and regimen	Route	Duration of treatment
2-D RT	2Gy/day,5 fraction week(30-35 fraction)	EBRT	Over 6-7 weeks

Group B

Table 1: Treatment Modality In Group A And Group B

Treatment modality	Dose and regimen	Route	Duration of treatment
3-D RT	2Gy/day, 5 fraction/ week (30-35 fraction)	EBRT	Over 6-7 weeks

Tuning fork test done using 256, 512 and 1024 Hz Tuning forks. 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. And followed them for 2 years' 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 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.

ASHA- NO: no hearing loss
YES: Threshold shift ≥20 dB shift at any frequency OR threshold ≥10 shift at two consecutive frequencies.
ASHA; =American Speech Language Hearing Association

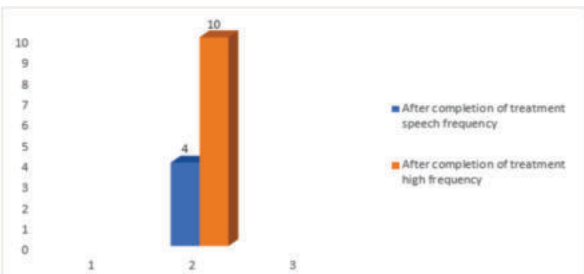
OBSERVATIONS AND RESULT:
Sensorineuronal Hearing Loss In Group A

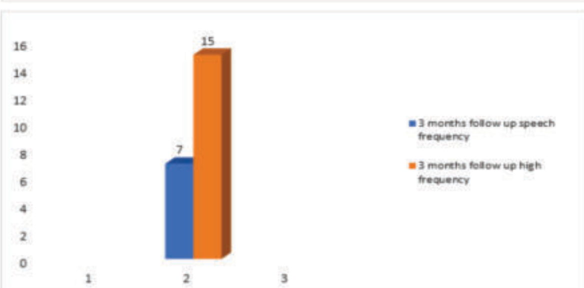
Table 2: Sensorineuronal Hearing Loss In Group A

	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 25)	4/15%	10/45%	7/27.5%	15/62.5%

The above table show that 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.

Sensorineuronal Hearing Loss At Different Frequencies Observed At Different Follow Up Period In Group A

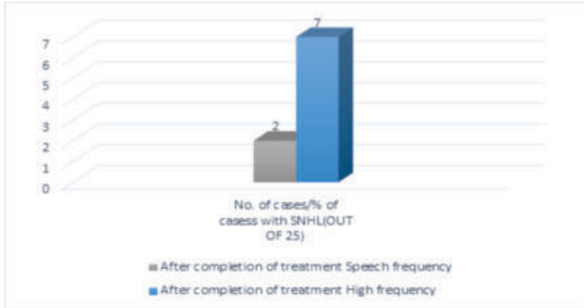


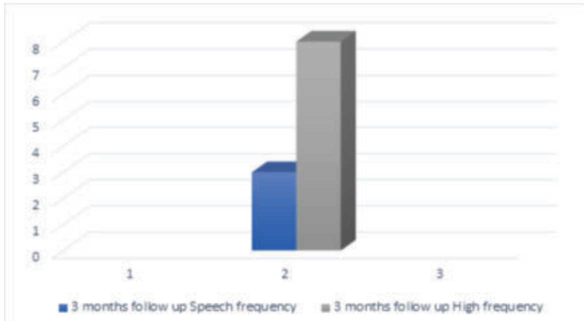


	After completion of treatment		3 months follow up	
	speech frequency	high frequency	Speech frequency	High frequency
no. of cases/% of cases with SNHL (out of 25)	4/15%	10/45%	3/12%	8/32%

Sensorineuronal Hearing Loss In Group- B
Table 2: Sensorineuronal Hearing Loss In Group B

The above table show that in group A, 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=15) patient had SNHL involving speech and high frequency respectively.





Severity Of Sensorineuronal Hearing Loss In Group A
Table 4: Severity Of Sensorineuronal Hearing Loss In Group A

HEARING LOSS	NO. OF SUBJECTS	PERCENTAGE
No hearing loss	11	44%
Mild	4	16%
Moderate	9	36%
Moderate severe	1	4%
Severe	0	0%
Total	25	100%

The above table show that 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.

Severity Of Sensorineuronal Hearing Loss In Group B
Table 5: Severity Of Sensorineuronal Hearing Loss In Group B

HEARING LOSS	NO. OF SUBJECTS	PERCENTAGE
No hearing loss	17	68
Mild	5	20
Moderate	3	12
Moderate severe	0	0
Severe	0	0
Total	25	100%

The above table show that 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 6

Cochlea volume(cc)	Number of ears	%
0.1-0.5	68	68
0.5-1	28	28
>1	4	4
Total	100	100

For analysis of SNHL both right and left (n = 100) parameters are combined. Volume of cochlea contoured on CT images varied from 0.1cc – 1.3c

Table 7: Dose Of Rt Verusus Impact On Hearing In

Cochlea dose(cGy)	Number of ears	%
Nil	10	10%
1-2000	44	44%
2001-4000	16	16%
4001-6000	24	24%
>6000	6	6%
Total	100	100%

Group-a

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

In group A 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.

In 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.

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.

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.

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 tumor dose, treatment completion and 3 months follow up and changes in absolute PTA threshold values are analyzed 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 (p = <0.001**, 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 month follow up is statistically significant only for 8000Hz (p=0.023).

DISCUSSION

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 age of the patients in this study ranged from 30-60 years among which majority of patients were in 51-60 years (32 patients, 64%) followed by 31-40 years (14 patients, 28%) and 41-50 years (4 patients, 8%). The mean age of the study group was 49.5 years.

A similar was observed by Upadhya et al. where maximum number of patients suffering from head and neck carcinoma were in the age group of 51–70 years, similar by Seyedeh Mahtab et al. mean age was found to be 57.1 years, similar study by Monika PPS, mean age was found to be 52 years and while in a study by Abhineet Jain et al. mean age of 60.2 years was reported. As expected, and as per concept, malignant disease process in Head and Neck is generally noted beyond 40 years of age and the same has been found to be true in approximately 82.5% of our patients. Thus, above all indicates that head and neck carcinomas mostly occur in 5th and 6th decade of life. The gender wise data was pooled from the proforma, and it was observed that there was male predominance in overall study. Out of 50 subjects, 80% were male and 20% were female. Male to female ratio was 4:1 which was again consistent with study done by Monika PPS65, where male to female of 2:1 in RT group and 1.8:1 in RT+CT group was observed. A high male predominance has also been seen by Sankaranarayanan et al

Coplan J et al. in their study of hearing loss after radiotherapy revealed thickening of the tympanic membrane[21] while Bhandare et al. found erythema (congestion) or opacification of the tympanic membrane as one of the signs of middle ear inflammation resulting from radiation induced middle ear damage. 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 following radiotherapy serous otitis media and Eustachian tube dysfunction can occur as temporary and reversible side effects. These can occur as early as immediately following radiotherapy to up to 3months 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. in which 25.71% had type B tympanogram immediately after RT which decreased to 5.71% after 6 months ns post RT while 42.85% had type C tympanogram immediate post RT which de which declined to 31.42% after 6 months post RT. Among these 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[52]. 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[52]. Similarly, in group B receiving conformal(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. The 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. 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[9].

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[22].

The present study has been taken up to compare SNHL in conventional and conformal modality of radiotherapy. Because this was an epidemiologic type of study, the primary factors of interest were the exposure (radiation dose to cochlea) and the SNHL consequence. The primary site of the malignancy was of little interest to the interpretation of the results except to say that oral cavity primaries might be less likely to result in sensorineural hearing impairment than other head-and-neck sites because they were less likely to receive doses to the cochlea. The majority of the studies on SNHL are published for nasopharyngeal carcinoma.

Merchant et al. studied the effects of 3DCRT on children with median age of 9.5 years. Hua et al. also studied hearing loss after radiotherapy for pediatric brain tumors with median age of 6.5 years. The median age of the present study is 49.5 years (Mean ± SD: 49.23±13.03). Age is considered as a risk factor for SNHL following radiotherapy. On univariate and multivariate analysis age has been reported to an independent risk factor with increase in SNHL as the age increases. In the present study on multivariate analysis age and male gender are predictors for SNHL at 4000 Hz and 8000 Hz.

Johannesen *et al.* found no relation between patient age and increased risk of developing hearing impairment[37].

A hearing decrement of ≥10 dB was considered clinically significant in the present study as reported by Pan *et al.* According to this criterion, in patients receiving 2-D RT only 15% and 45% patients had significant hearing loss for 4 kHz and 8 kHz respectively at the completion of treatment; 27.50% and 62.5% patients had significant hearing loss for 4 kHz and 8 kHz respectively at 3 months follow up. Kwong et al. reported a 24% incidence of sensorineural hearing loss particularly for higher frequencies, following radical radiotherapy for nasopharynx carcinoma. Wai-kuen Ho in a prospective study reported a 31% incidence of deterioration of bone conduction threshold at 4 kHz. Bhandare et al observed SNHL in 15.1% patients. Merchant *et al.* found the rate of permanent hearing loss ranged from 24.2% to 36% for doses approaching 60Gy[23]. Zuur in prospective analysis of hearing loss due to 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. Compared to high-dose cisplatin CRT (78%).18Chan *et al.* in a longitudinal study on SNHL after treatment of nasopharyngeal carcinoma found that RT alone and chemo-radiotherapy resulted in 40% and 56.4% persistent SNHL, respectively, after a median follow-up of 2 years. 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. For such a small structure, the accuracy and consistency of the extracted dose data are strongly dependent on the accuracy in cochlea contouring. 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. 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 statisticallysignificant 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 ($p = 0.079$).

Grau *et al.* found significantly greater SNHL for cochlear doses >50Gy.2 Pan *et al.* in prospective study, reported SNHL for cochlear doses ≥ 45 Gy.

Hua *et al.* reported that the probability is very low for Dmean of 30 Gy or less and increases at 40–45Gy[24].

Chen *et al.* reported that *Dmean* threshold of 48 Gy was found to be statistically significant in predicting SNHL.

Petsuksiri *et al*. reported that, cochlea mean dose ≤ 50Gy appeared to have lower incidences of SNHL and the incidences of SNHL tended to be higher if they received mean radiation dose of > 50 Gy to the cochlea[25].

Honore *et al.* found lower frequencies, no statistically significant dose-response relationship could be demonstrated. The result of the multiple linear regressions at 4000 Hz with dose, as independent variable has shown a loss of 0.306 dB[26]. SNHL is considered as a late complication following radiotherapy. SNHL in the present study is noted for 8000Hz at treatment completion and at 3 months follow up. For 4000 Hz SNHL is noted at 3 months follow up only. The onset of SNHL following radiotherapy is noted for higher frequencies and at longer follow ups. The present study has 3 months follow up for 2 years.

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

Kwong *et al.* reported the median time to documentation of SNHL was 4 months postirradiation, ranging from immediate postirradiation to 48 months. Bhandare *et al.* reported the median interval between RT and the development of persistent SNHL was 1.8 years (range, 0.5–5.9 years).

Grau *et al.* and Chan *et al.* reported that most of SNHL was first noted 12 months after RT completion. Pan *et al* Johannesen *et al.* did not find any time association between hearing loss and RT.

CONCLUSION AND SUMMARY

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 was in accordance with many prior studies

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.

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REFERENCES

1. Jemal et al.. Global cancer statistics. CA Cancer J Clin 2011; 61(2):69-90.
2. 2@Goncalves MS, Silveira AF, Teixeira AR, Hyppolito MA. Mechanisms of cisplatin ototoxicity: theoretical review. J Laryngol Otol.Jun 2013;127(6):536-541.
3. 3@Obasikene G, Adobamen P, Okundia P, Ogusi FO. Prevalence of ototoxicity in University of Benin Teaching Hospital, Benin city: a 5-year review. Niger J Clin Pract. Oct-Dec 2012;15(4):453-457.

4. 4@Zuur CL, Simis YJ, Lansdaal PE, et al. Audiometric patterns in ototoxicity of intra-arterial Cisplatin chemoradiation in patients with locally advanced head and neck cancer. Audiol Neurootol. 2006;11(5):318- 330.
5. 5@Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. Int J Radiat Oncol Biol Phys. Mar 1 2010;76(3 Suppl):S50-57.
6. 6@Winther FO. X-ray irradiation of the inner ear of the guinea pig. Early degenerative changes in the cochlea. Acta Otolaryngol. Jul-Aug 1969;68(1):98-117.
7. 7@ Moretti JA. Sensori-neural hearing loss following radiotherapy to the nasopharynx. The Laryngoscope. Apr 1976;86(4):598-602.
8. 8@ Li JJ, Guo YK, Tang QL, et al. Prospective study of sensorineural hearing loss following radiotherapy for nasopharyngeal carcinoma. J Laryngol Otol. Jan 2010;124(1):32-36.
9. 9@Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol. Mar 2004;25(2):168-173
10. 10@Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer. Jun 1990;61(6):927- 931.
11. 11@Wong KL, Song TT, Joseph W, Stephanie M.C.F, and De YW. Sensorineural Hearing Loss After Radiotherapy and Chemoradiotherapy: A Single, Blinded, Randomized Study. J Clin Oncol. April 2006; 24:1904-1909.
12. Charlie C. Pan, Avraham Eisbruch, Julia S. Lee, Rhonda M. Snorrason, Randall K.Ten Haken Paul R. Kileny, et al. Prospective Study of Inner Ear Radiation Dose andHearing Loss in Head-and-Neck Cancer Patients. Int. J. Radiation Oncology Biol.Phys.2005; 61(5):1393-1402.
13. Dora L. W. Kwong, William I. Wei, Jonathan S. T. Sham, W. K. Ho, P. W. Yuen Daniel T. T. Chua, et al. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: A prospective study of the effect of radiation and cisplatin treatment. Int. J. Radiation Oncology Biol. Phys. 1996; 36:281–289.
14. Ho WK, Wei WI, Kwong DL, et al. Long-term sensorineural hearing deficitfollowing radiotherapy in patients suffering from nasopharyngeal carcinoma:A prospective study. Head Neck 1999; 21:547–553.Esther Raaijmakers and Antoine M.
15. Engelen. Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. Radiotherapy and Oncology.2002; 65:1–7.
16. Niranjan Bhandare, Patrick J. Antonelli, Christopher G. Morris, Robert S. Malayapa and William M. Mendenhall. Ototoxicity after radiotherapy for head and neck tumors. Int. J. Radiation Oncology Biol. Phys.2007; 67(2):469–479.
17. Charlotte L. Zuur, Yvonne J. Simis, Emmy A. Lamers, Augustinus A. Hart, Wouter A. Dreschler, Alfons J. Balm, et al. Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. Int. J. Radiation Oncology Biol. Phys.2009; 74(2):490–496.
18. S. H. Chan, W. T. Ng, K. L. Kam, Michael C. H. Lee, C. W. Choi, T. K. Yau, et al.Sensorineural hearing loss after treatment of nasopharyngeal Carcinoma: a longitudinal analysis. Int. J. Radiation Oncology Biol. Phys.2009; 73(5):1335–1342.
19. Lisa van der Putten, Remco de Bree, John T. Plukker, Johannes A. Langendijk, Cas Smits, Fred R. Burlage, et al. Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. Wiley Periodicals, Inc. Head Neck 2006; 28: 902–908.
20. William C. Chen, Andrew Jackson, Amy S. Budnick, David G. Pfister, Dennis H. Kraus, Margie A. Hunt, et al. CANCER.2006;106(4):820-829.
21. Coplan J, Post E, Richman R, Grimes C. Hearing loss after therapy with radiation. Am J Dis Child. 1981 [PubMed] [Google Scholar]
22. Monika PPS. Prospective study of sensorineural hearing loss in patients of head and neck cancers after radiotherapy and chemotherapy. J Otolaryngol ENT Res. 2018;10(4):207□211.
23. Thomas E. Merchant, Ciara J. Gould, Xiaoping Xiong, Nicole Robbins, Junhong Zhu, David L. Pritchard, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. Int. J. Radiation Oncology Biol. Phys.2004; 58(4):1194–1207.
24. Chiaho Hua, Johnnie K. Bass, Raja Khan, Larry E. Kun, and Thomas E. Merchant. Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. Int. J. Radiation Oncology Biol. Phys.2008; 72(3):892–899.
25. Janjira Petsuksiri, Achariyaporn Sermsree, Kullathorn Thephamongkhol, Phawin Keskool, Kanthong Thongyai,Yaowalak Chansilpa et al. Sensorineural hearing loss after concurrent chemoradiotherapy in nasopharyngeal cancer patients. Radiation Oncology. 2011; 6:19.
26. Henriette B. Honore, Søren M. Bentzen, Kitty Moller, Cai Grau. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiotherapy and Oncology.2002; 65:9–16.