International Journal Of

Recent Scientific Research

ISSN: 0976-3031

Volume: 7(1) January -2016

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THE OFFICIAL PUBLICATION OF
INTERNATIONAL JOURNAL OF RECENT SCIENTIFIC RESEARCH (IJRSR)
http://www.recentscientific.com/ recentscientific@gmail.com

ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 1, pp. 8071-8074, January, 2016

International Journal of Recent Scientific Research

RESEARCH ARTICLE

HEARING LOSS AFTER CHEMO RADIOTHERAPY IN HEAD AND NECK CANCER- IS DOSE OF RADIATION THE ONLY FACTOR RESPONSIBLE?

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ARTICLE INFO

Article History:

Received 15th October, 2015
Received in revised form 21st November, 2015
Accepted 06th December, 2015
Published online 28st January, 2016

Key words:

Cochlea dose; radiotherapy hearing loss

ABSTRACT

Background; Hearing loss during chemo radiotherapy is a common problem encountered during the treatment of head and neck cancers. In this study, we try to understand the relationship of dose to hearing loss in a subset of patients treated for head and neck malignancies

Objectives: To assess hearing loss in patients receiving cisplatin based chemo-radiotherapy for head and neck cancers

Methods: Patients were treated with conformal radiotherapy either by 3 dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) with 6 MV photons from a medical linear accelerator. A weekly low dose of cisplatin was given concurrently with radiotherapy. Pure tone audiometry (PTA) was done at baseline and three weeks into radiotherapy as well as at the end of radiotherapy and three months later. The dose received by the cochlea was then correlated with the PTA values.

Results: The mean drop in the PTA values of the right ear when compared to base line was 3.77 at 3 weeks, 7.89 at completion of chemo radiation and 10.08 at the third month follow up. However, Pearson test did not show any statistically significant correlation between the dose and the hearing loss. The mean drop in PTA in the left ear was 1.13 at 3 weeks and 6.95 at completion of chemo radiation and 9.32 at the third month follow up. Here too, there was no correlation seen between the dose of radiation received by the cochlea and the hearing loss.

Conclusion: There was a drop in the pure tone audiometry values during the course of treatment which was found to b statistically significant in both the ears. However there was no statistically significant correlation between the dose of radiation and hearing loss in this study

INTRODUCTION

SNHL is traditionally defined as a clinically significant increase in bone conduction threshold (BCT) at the key human speech frequencies (0.5–4.0 kHz), as seen in pure-tone audiometry.

However, reports of SNHL after fractionated RT vary in terms of:

(a) the frequencies evaluated (e.g. 2 or 4 kHz alone (1,2) and/or pure tone average [PTA] of frequencies between 0.5–3.0 kHz) (3–5); (b) the control/standard used for comparison (e.g., pre-RT BCT of same ear or post-RTBCT of the contralateral ear , or age-specific standard (4); and (c) the change in BCT (DBCT) that is defined as clinically significant .The degree of hearing loss after RT for head-and-neck cancer is worse at higher frequencies

The cochleae typically reside within the high–RT dose–volume region of conformal RT plans when treating high-neck or base-of-skull malignancies, such as those in the nasopharynx, parotid, paranasal sinus, brain, or the area covering the parapharyngeal space and pterygo-palatine fossa. The RT dose to the cochleae can be reduced by specifically excluding this region from three-dimensional conformal treatment plans or by the placement of dose constraints for intensity-modulated RT (IMRT) plans. Permanent SNHL resulting from treatment effects has resulted in worsening of the quality of life and is correlated with cognitive impairment (1, 4, 6)

For primary tumors located in the base of skull, nasopharynx, paranasal sinuses, or high-neck disease, it is likely that the petrous bone or cochlea will receive a relatively high radiation dose compared with other primary sites in the head and neck. The IMRT technique can be used to deliver high doses to the high-risk tumor regions while sparing critical structures from

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potential radiation damage if dose constraints are placed on those critical structures. Although the cochleae have been recognized as organs at risk, it is not standard practice to place dose constraints on the cochleae. Cisplatin is a commonly used cytotoxic agent and radiation sensitizer for the treatment of squamous cell carcinoma of the head and neck as well as some other types of cancer. Cisplatin induces its toxic effects by targeting cellular DNA and is thought to act by activating apoptosis and alternating a number of other cellular parameters (7). One of the major side effects of cisplatin chemotherapy is ototoxicity that is probably caused by cisplatin-induced degeneration.

With cisplatin alone, there is a negligible risk of hearing loss at doses 90–360 mg/m2.The chief advantage of IMRT is its ability to precisely deliver radiation to the target tissue while relatively sparing the surrounding tissues, such as the cochlea and eighth cranial nerve (auditory apparatus). Radiation-induced SNHL has been shown to be a doserelated phenomenon with the threshold of injury occurring at doses of 50 to 60 Gy (8). Thibadoux *et al.* did not find any hearing loss in children receiving 24 Gy of cranial radiation for acute leukemia (9). In a series of nasopharyngeal carcinoma, Grau *et al.* reported a 7% rate of SNHL with doses less than 50 Gy, but this increased to 44% when the dose was increased above 59 Gy (8).

High-frequency hearing is generally more severely affected by radiation. (10) CDDP-induced ototoxicity is also well known; is characterized by bilateral, irreversible, and progressive high tone loss; and is directly related to dose and inversely related to age. (11) Although combined chemoradio therapy using CDDP has increasingly been used to treat advanced head and neck cancers, the synergistic ototoxic effect of radiation and CDDP has not been adequately studied.

MATERIALS AND METHODS

Source of Data

Patients with head and neck malignancies uncdergoing chemo-radiation at the Department of Radiotherapy, Father Muller Medical College hospital, Mangalore

Inclusion Criteria for Study Group

- Individuals with head and neck cancer undergoing chemo-radiotherapy, in which the temporal bone is included in the field of radiation.
- Individuals who could be followed up for timely hearing assessment.

METHOD OF DATA COLLECTION

Thirty patients having head and neck malignancies were enrolled in the study, selected using purposive sampling technique. They received concurrent chemo-radiation at the dose of 66-70 Gy given about 5 to 6 days a week. Each daily fraction delivered a dose of 2 Gy for 6 weeks to 7 weeks. Low dose weekly cisplatin at dose of 35mg/m^2 weekly was given for 6 weeks. Pre –therapy audiological evaluation was done in the form of pure tone audiometry. Standardized instruments were used for these tests. The tests were repeated at the end of chemo-radiotherapy and results were computed. Hearing thresholds were measured at frequencies of 500, 1000, 2000 and 4000 Hz. The readings were taken before the start of CTRT, 3 weeks after the onset of therapy, after the completion of therapy at 7 weeks and at 3 months. The results were drawn based on the audiometric studies done during this time period.

Table 1 Comparisom of Pure Tone Audiometry at 3 Weeks, 7 Weeks and 3 Months with Baseline

		N	Correlation	Sig.
Pair 1	R PTA 1 & R PTA 2	31	.888	<0.001
Pair 2	R PTA 1 & R PTA 3	31	.732	<0.001
Pair 3	R PTA 1 & R PTA 4	31	.773	<0.001
Pair 4	L PTA 1 & L PTA 2	31	.512	<0.003
Pair 5	L PTA 1 & L PTA 3	31	.694	<0.001
Pair 6	L PTA 1 & L PTA 4	31	.709	<0.001

Radiotherapy technique

Patients were treated with concurrent chemo radiation by either the conformal 3DCRT technique or the IMRT technique. A planning CT was done for all patients from the vertex to the T4 vertebral level and the gross tumour volume (GTV) was drawn by the radiation oncologist. The CTV was marked to cover all the risk areas for nodal metastases. The cochlea is a conical structure with its base resting anterior to the internal auditory canal and its apex pointed anteriorly, inferiorly, and laterally, toward the carotid artery. The vestibule is located posterior to the cochlea and lateral to the internal auditory canal. The internal auditory canal is a readily apparent landmark for identification of the cochlea and vestibule on CT and this was used to mark the cochlea. The patients were then planned on VARIAN ECLIPSE version 8.6 planning system. The IMRT plans were made using the inverse planning algorithm. Patients were all treated by 6 MV photons by CLINAC DBX- D-2300 CD linear accelerator.

Table 2 Paired Samples Test showing comparison between the PTA at different time points

		Paired Differences		T	df	Sig. (2-tailed)
		95% Confidence Interval of the Difference				
		Lower	Upper			
Pair 1	Right Ear 1 - Right Ear 2	-6.0508053	-1.4975818	-3.386	30	<0.002
Pair 2	Right Ear 1 - Right Ear 3	-11.8965286	-3.8989553	-4.034	30	<0.001
Pair 3	Right Ear 1 - Right Ear 4	-13.5596001	-6.6055612	-5.922	30	<0.001
Pair 4	Left Ear 1 - Left Ear 2	-6.5205523	4.2541007	-.430	30	<0.671
Pair 5	Left Ear 1 - Left Ear 3	-11.5336712	-2.3772965	-3.103	30	<0.004
Pair 6	Left Ear 1 - Left Ear 4	-13.6521410	-4.9891494	-4.395	30	<0.001

RESULTS

When the pure tone audiometry results are compared there is a statistically significant reduction in the hearing of all patients treated. This decrease was consistent when the baseline values i: e. PTA 1 (the PTA done before starting treatment) was compared with the values during or after the completion of treatment. This correlation of drop in hearing was consistent in both the ears. In the table given above one can see that there is a drop in the hearing of the patients during each of the PTA in

both the right as well as the left ear. All values are statistically significant except the left ear baseline compared to the left ear PTA at 3 weeks of RT. This shows that all patients had drop of hearing during the course of RT. The mean drop in the PTA of the right ear values at baseline to the value at 3 weeks of RT was 3.77. The mean drop in the PTA of the right ear from baseline to the 7 th week i: e after completion of radiation was 7.89 .The mean drop in the PTA of the right ear from baseline to 3 months post chemoradition was 10.08. However, when Pearson correlation was applied to the statistical analysis of dose compared to drop in hearing, no significant association was found between the dose of radiation delivered and the drop in the PTA values during as well as after treatment.

The mean drop in the PTA of the left ear from baseline to 3 weeks post start of RT , at completion of chemo radiation and 3 months post completion of treatment was 1.13 6.95 and 9.32 respectively . However, when Pearson correlation was applied to the statistical analysis of dose compared to drop in hearing, no significant association was found between the dose of radiation delivered and the drop in the PTA.

DISCUSSION

Definitions of SNHL are variable, and decreases from 10 to 20 dB after RT or chemo radiation are reported (4). Clinically, hearing loss between 500 and 8,000 Hz is more substantial, and hearing loss within these frequencies could affect patient's quality of life, particularly in long-term cancer survivors (1, 12, 13) Chen *et al* (2) suggested a D mean threshold of 48 Gy based on Fisher's exact test on 44 ears from 22 adult patients diagnosed with nasopharyngeal cancer receiving chemo radiotherapy along and platinum- based conconcurrent chemotherapy. The probability of developing sensorineural hearing loss at 4,000 Hz was 61% for patients receiving greater than 48 Gy compared with 24% for patients receiving 48 Gy or less.

Van der Putten *et al* (14) concluded that a mean dose greater than 50 Gy to the cochlea should be avoided based on data from 52 adult patients with parotid cancer receiving only radiotherapy. According to their logistic regression analysis, the dose corresponding to a normal tissue complication probability of 10% for the inner ear was 42 Gy. All patients given a D mean greater than 50 Gy to the cochlea had an asymmetrical hearing loss of greater than 10 dB.

Pan *et al* in his study on 31 unilateral neck–treated patients that received a median dose of 47.4 Gy to the ipsilateral inner ear demonstrated that a threshold for cochlear radiation tolerance dose was 45 Gy which was the dose that was most likely to cause hearing impairment at higher frequency ranges. An increase in the radiation dose to the cochlea was associated with clinically greater SNHL at the higher frequencies than at the lower frequencies (1). However, on further analysis, cumulative radiation dose, effect of age at the time of radiation, and the administration of radiation sensitizers with chemotherapy could have confounded their results.

Kwong *et al* (3) did a prospective study to assess the pattern of SNHL after post primary treatment for nasopharyngeal carcinoma. Among 132 patients and 227 ears evaluated, 24.2% of ears developed persistent SNHL. At a median follow-up 30-month time period, 5.2% to 8.5% of ears had SNHL at lower frequencies and 22% to 34.5% at higher frequencies. The median time to development of SNHL was about 4 months, some transient SNHLs did recover within 6 to 12 months; however radiation doses to the cochleae were not reported in this study. These investigators found that older age, male, and post-irradiation serous otitis media were poor prognostic factors associated with persistent SNHL. Without dose-volume histogram information, the association between RT dose and cochlea SNHL in this study cannot be analysed after RT, some patients do experience middle ear infection with effusion. This infection could affect hearing status and audiogram results. Thus, further investigation should take into account this factor of middle ear effusion that can affect the hearing of the patients

Although both cisplatin and RT may cause ototoxicity (13), the combined effects of the two are unclear. Severe post-RT hearing loss in pediatric patients has been attributed to the synergistic effects of these 2 modalities (11). Atrophy of stria vascularis and loss of inner and outer hair cells with reduced spiral ganglion cells have been reported in patients receiving cisplatin, RT, or the two combined (15). Cisplatin ototoxicity may be dose dependent (16) and sequence dependent, with increased ototoxicity if given after RT compared to pre-RT administration (11).

Ying *et al* in their study found that radiation doses of less than 40 Gy to the cochlea did not result in clinically significant hearing loss. Cisplatin-based chemotherapy significantly impaired high frequency hearing when doses of 100 mg/m2 were used. They also found that the use of lower-dose cisplatin- based chemotherapy with RT decreased the risk of clinically significant hearing loss when compared to high dose cisplatin. The threshold cochlear dose for hearing loss with combined cisplatin chemotherapy and RT was predicted to be 10 Gy. As long as tumor control will not compromised, they recommend that placing dose constraints on the cochlea when using IMRT treatment planning may help reduce the ototoxicity of radiotherapy , and their study endorsed the weekly lower-dose cisplatin regimens over higher dose administrations as it was found to be less ototoxic.(17)

In the current study it was found that there was a decrease in the pure tone audiometry values during the course of radiation therapy as well post chemo radiation. However, the decrease in hearing could not be correlated with the dose of radiotherapy as the pearson test applied did not show any statistical correlation between the dose of radiation used and the hearing loss as diagnosed by pure tone audiometery. However the pure tone audiometry values seen above show a decline during the course of treatment. The reason for this could be that other factors like the use of cisplatin may have also contributed to the hearing loss and the hearing loss could not just be attributed to the dose of radiation being delivered to the cochlea.

CONCLUSION

The standard of care for treatment of head and neck malignancies except oral cavity tumors is organs preservation

strategy that include neoadjuvant chemotherapy followed by chemoradiation or definitive radical intent chemo radiation, especially for oropharynx , nasopharynx, hypopharynx and laryngeal malignancies. With the advent of neoadjuvant chemotherapy in advanced head and neck cancer that also includes high dose cisplatin the hearing of patients need to be assessed prior to starting chemotherapy and also prior to chemo radiation as cisplatin will also be used concurrently with radiation as this drug is known to be ototoxic and is known to cause high frequency hearing loss. With advent of IMRT planning dose constraints can be given to the cochlea in order to spare it during treatment if it does not compromise on the coverage of the target volume. As the quality of life gets greatly affected by this morbidity more attention needs to be paid to this factor when planning patients for chemo radiation. Hearing loss was found in the current study but could not be directly correlated with the dose of radiation delivered. Further study needs to be done on a larger sample size to more clearly define the role of dose of radiation to hearing loss in patient undergoing concurrent chemo radiation with low dose cisplatin as widely used in India.

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How to cite this article:

Rohit Dominic Jawahar Rebello. *et al*, 2016, Hearing Loss After Chemo Radiotherapy In Head And Neck Cancer- Is Dose of Radiation The Only Factor Responsible?. *Int J Recent Sci Res.* 7(1), pp. 8071-8074.

TSSN 0976-3031