Study of Radiation Induced Xerostomia in Head and Neck Cancer in Conformal Versus Conventional Radiotherapy

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ABSTRACT

Introduction: Head and neck cancers are most common cancers in india. Radiotherapy is common modality of treatment. Xerostomia is most common late side effect of Radiotherapy. The aim is to compare it in conformal and conventional radiotherapy.
Materials and methods: Head and neck cancer patients presented to department of Radiotherapy in MNJ Institute of Oncology and RCC during period of 2013-2015 were recruited in present study.22 patients were allotted in conventional arm and 20 patients in IMRT arm.xerostomia after Radiation therapy was assessed subjectively by using xerostomia related questionnaire and objectively by comparing the salivaryglandfunctioningusing quantitative salivary gland scintigraphy(QSGS).
Results: Analysis of QOL related questionnaire showed mean score of 8.5in conventional arm and mean score of 4.8 in IMRT arm with p value=0.003. Analysis of EF% showed baseline EF% of 48.47 and follow up EF% of 3.86 in conventional arm whereas baseline EF% of 47.49 and follow up EF% of 15.36 in IMRT arm with pvalue of 0.001.
Conclusion: Xerostomia can be reduced with Conformal Radiotherapy like IMRT which improves the quality of life of patients after irradiation to Head and Neck region.

Keywords: Xerostomia, Conformal Radiotherapy, Salivary Scintigraphy.

INTRODUCTION

Cancer of the head and neck is one of the most common cancers in India affecting both males and females. In India, head and neck cancers constitute 25% to 30% in males and 15% in females.[1] Surgery and radiotherapy with or without chemotherapy are most frequently used therapeutic modalities in head and neck cancers. Surgery or radiotherapy has shown good comparable results in early stage cancers (T1, T2). For advance stage disease (stage III / IV) with large primary tumors, the primary curative modalities are surgery, radiotherapy and chemotherapy. The conventional RT to head and neck cancers typically involves irradiation of major salivary glands and large area of normal mucosa. It leads to mucositis, dysphagia and xerostomia. Xerostomia is most prevalent late side effect of head and neck malignancy. Also xerostomia is cited by patient as major cause of decreased quality of life.[2]
The main objective of this study wasto compare xerostomia subjectively by using xerostomia related questionnaire and to compare salivary gland functioning by using quantitative salivary gland scintigraphy (QSGS) in head and neck cancer patients receiving conventional RT / IMRT.

MATERIAL AND METHODS

Source of data: Patients presenting to the Department of Radiation oncology in MNJ Institute of Oncology and Regional Cancer Centre during 2013 to 2015.

Sample Size: 22 patients in conventional arm and 20 patients in IMRT arm based on inclusion/exclusion criteria.

Patient's inclusion criteria: Histologically confirmed SCC of the Head and Neck region, which are to be treated by Radiotherapy primarily or postoperatively with age between 15 to 70 years, with ECOG performance status 0-2.

Patient's exclusion criteria: Patients with previous head and neck irradiation, preexisting salivary gland disease, tumor involving parotid gland,concurrent illness that would compromise completion of treatment or follow up, patient taking any substitutes like pilocarpine and patients who have a disseminated disease.

Xerostomia related Questionnaire: We devised a 14 point questionnaire form. Each participant had to answer, first time during a baseline scintigraphy scanning, and later during the follow up scan. Each patient was scored based upon his or her responses, to a maximum possible score of 14.

1) Do you have a normal salivary secretion?
☐YES 0 ☐No 1
2) Has there been a change lately in saliva amount?
☐YES 1 ☐No 0
3) Is your mouth dry when you are not eating?
☐YES 1 ☐No 0
4) Do you have problem with your gums?
☐YES 1 ☐No 0
5) Do you have problem while speaking?
☐YES 1 ☐No 0
6) Do you drink water during the day because of dry mouth?
☐YES 1 ☐No 0
7) Do you have touble sleeping in the night due to dry mouth?
☐YES 1 ☐No 0
8) Do you drink water during the night because of dry mouth?
☐YES 1 ☐No 0
9) Do you have any problem while swallowing solid food?
☐YES 1 ☐No 0
10) Do you have a problem with the transport of grounded food through your mouth?
☐YES 1 ☐No 0

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11) Do you have problem during swallowing solid food?
☐YES 1 ☐No 0
12) Do you have problem during swallowing grounded food?
☐YES 1 ☐No 0
13) Do you experience dry mouth during meals?
☐YES 1 ☐No 0
14) Do you need to drink water to swallow your food?
☐YES 1 ☐No 0

Salivary Scintigraphy Scan

Every patient had to undergo a baseline salivary scintigraphy scan before the initiation of radiation therapy. They were also required to come for a follow up scan after three months from the date of completion of the last fraction of radiation. The maximum delay time allowed for follow up visit was 2 months from the due date.

Tracer used: Technetium pertechnetate ($^{99m}Tc\text{-}TcO_4^-$).

Dose administered: 5 mCi, Intravenously.

Sialagogue used: Concentrated lime juice, approximately 1ml, administered orally over tongue at the end of 15 min from the beginning of the scan.

Acquisition technique: Image acquisition was performed using a millennium MG Dual Head gamma camera, equipped with low energy collimators. Dynamic imaging was performed at a capture rate of 1 min per frame for 30 min, after an intravenous injection of 5mCi of $^{99m}Tc\text{-}TcO_4^-$.15 min post injection of the tracer, 1 ml of lemon juice administered orally as a sialagogue to induce excretion of saliva. The patient was told to distribute lemon juice around his mouth and then swallow it. The pre and post syringe images were acquired for quantification purposes.

Quantitative analysis: Four oval regions of interest (ROIs) were drawn over both parotids as well as submandibular glands. One banana shaped ROI was also drawn around right clavicle region. Percentage excretion fraction (EF%) was determined using time activity curves.

The quantification of salivary gland excretion is done by calculating fraction of maximal excretion to maximal uptake of each salivary gland and is called as salivary excretion fraction. Reduction in salivary gland function after (chemo) radiotherapy was described by the relative SEF or SEF ratio. SEF ratios on follow-up at 3 months were correlated with mean parotid doses.

STATISTICAL ANALYSIS

The analysis of the data was done by chi-square test using Statistical software SPSS 20.0 and OPEN EPI.

RESULT

The mean age in conventional arm was 43.31±21years. The mean age in IMRT arm was 44.7±26.72 years. The number of male and females in the conventional arm was nineteen(86%) and three (14%)respectively. The number of male and female in the IMRT arm was fifteen (75%) and five (25%) respectively. The distribution of patients in conventional arm according to stage: two were stage II, eleven were stage III and nine were stage IV and in the IMRT arm, two patients were stage II, eleven patients were stage III and eight patient were stage IV.

As only 16 patients in conventional arm and 14 patients of IMRT arm were available for follow up, the results of xerostomia related questionnaire and results of salivary ejection fraction measured by Quantitative salivary scintigraphy were analysed only in these patients. Also the mean doses to parotid received in were compared in these patients.

Mean Dose of Parotid Glands

Mean dose to ipsilateral parotid was 57.39 ± 4.81 Gy (±1sd) andmean dose to contra lateral parotid was 50.77GY ± 10.06 Gy (±1sd) in conventional arm patients. Mean dose to ipsilateral parotid was 33.28 ± 10.99 Gy (±1sd) and mean dose to contralateral parotid was 23.92 ± 3.12 Gy (±1sd) in IMRT patients (figure-1)

Xerostomia related QOL questionnaire

Analysis of the mean scores obtained in questionnaire for the two arms was done, for a total possible score of 14 points. The conventional arm had a mean score of 8.5 ± 2.47(±2sd) whereas the IMRT arm had a mean score of 4.8 ± 3.8 with p value=0.003 which is significant (table-1).

Final analysis was done for the percent excretion fraction (EF%) in the salivary scintigraphy scans between baseline and first follow up after completion of radiotherapy, for patients in both conventional and IMRT arms (figure-2)

Patients in the conventional arm had a baseline EF% of 48.47 ± 11.51 versus a follow up EF% of 3.86 ± 6.98. In the IMRT arm baseline EF% was 47.49 ± 17.03 whereas follow up EF% was 15.36 ± 12.91 with p value of 0.001 which is clinically significant (figure-3)

DISCUSSION

Head and neck cancers are implicated as a major contributor to the burden of cancer of India.[1] Radiotherapy plays a significant role in management of head and neck cancer as the primary treatment modality. One of the most frequent and debilitating long-term side effects of radiotherapy (RT) for head and neck cancer is xerostomia.[2]

The radiation induced adverse events manifest as either acute reactions (i,e occurring within 90 days of RT) or late/delayed reactions (i.e occurring months to years after RT).The acute reaction includes mucositis, difficulty in swallowing and xerostomia. The delayed effects include xerostomia, nocturnal dry mouth, difficulty in swallowing, speech, dental caries, periodontitis and osteoradionecrosis. This would compromise on the outcome of the patient with respect to the long term physiological functioning and quality of life[3]

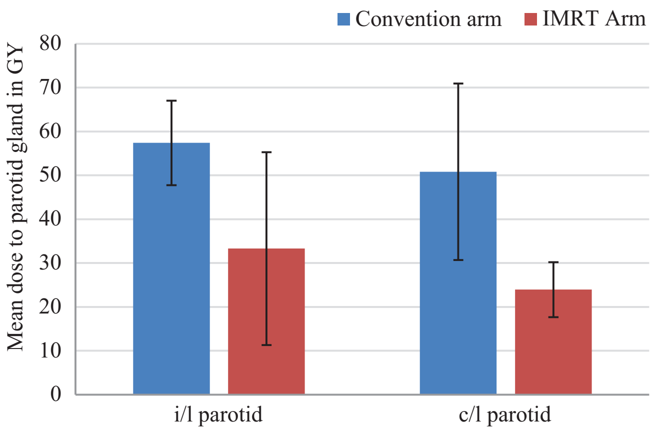

Figure-1: Mean dose to ipsilateral and contralateral parotid gland in both arm ±2SD

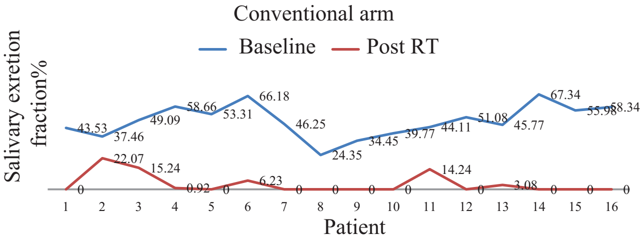

Figure-2: Baseline and Post radiotherapy time activity curve in a salivary gland scintigraphy in a patient receiving conventional radiation

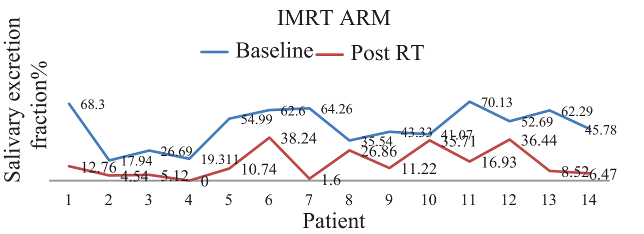

Figure-3: Baseline and post radiotherapy time activity curve in a salivary gland scintigraphy in a patient receiving IMRT.

Patient number	Conventional arm	IMRT arm
Patient 1	7	3
Patient 2	7	2
Patient 3	8	3
Patient 4	9	7
Patient 5	10	9
Patient 6	6	4
Patient 7	10	5
Patient 8	10	4
Patient 9	8	7
Patient 10	9	5
Patient 11	10	6
Patient 12	8	5
Patient 13	8	3
Patient 14	8	5
Patient 15	9	-
Patient 16	9	-

Table-1: Total xerostomia related QOL score in conventional and IMRT arms in each patient.

Clinically, xerostomia has been reported with as little as two or three doses of 2 Gy, although many changes occurring with less than 60 Gy are reversible. However, doses greater than 30 Gy can cause permanent xerostomia.[4] Damage to the salivary glands results in reduced salivary flow, changes in the electrolyte and immunoglobulin composition of saliva, reduction of salivary pH, and repopulation of cariogenic micro flora. When the major salivary glands are included in the radiation field, salivary function often decreases by 50% to 60% in the first week, with basal salivary flow reaching a measurable minimum 2 to 3 weeks. The extent of glandular change is directly related to the dose of radiation to the salivary glands, with the most severe and irreversible salivary dysfunction resulting from damage to (or) loss of salivary acinar cells.[4]

Xerostomia symptoms are usually permanent, which illustrates the importance of prevention. Recent advances in conformal radiation therapy like IMRT, enable us to spare the parotid glands while providing adequate dosimetric coverage of tumour targets, and have provided a new avenue to prevent xerostomia.

Mean Dose of Bilateral Parotid Glands

Intensity-modulated radiotherapy (IMRT) optimizes the delivery of irradiation to irregularly shaped volumes and has the ability to produce concavities in radiation treatment volumes. It can deliver different doses to different target volumes simultaneously sparing the parotid glands and the spinal cord. In this study mean dose to ipsilateral parotid was 57.39 Gy and mean dose to contralateral parotid was 50.77GY in conventional arm patients. Mean dose to ipsilateral parotid was 33.28 GY and mean dose to contralateral parotid was 23.92 in IMRT patients.

Xia et al (2000) compared the treatment plans involving IMRT for nasopharyngeal carcinoma. In their series, the coverage to the GTV as well as the CTV was superior with the inverse planned IMRT plans. In addition, when using proper dose constraints to the normal structures, inverse planned IMRT plans achieved the least dose delivered to organs at risk. There was substantial reduction of the mean parotid dose to as low as 21.4 Gy.[5]

The results of present study were also consistent with the above trial. The mean dose to the parotid glands was less than 26Gy in IMRT arm indicating the superiority of IMRT in head and neck cancer patients receiving Radiation treatment.

Eisbruch et al reported that a mean dose of 26 Gy or above to the parotid gland shows significant decrease or immeasurable salivary flow upon stimulation. The radiation-induced xerostomia is an irreversible complication of the parotid glands which has received radiation with a mean dose of 26 Gy or above.[6]

Xerostomia can be defined and graded both subjectively according to patient's symptoms (severity of dryness and/ or response on stimulation) as well as objectively using quantified saliva production or excretion (salivary flow and/ or scintigraphy).So in our study we have assessed xerostomia in patients subjectively using questionnaire method and objectively by using 99m Tcpertechnetate salivary scintigraphy. The parotid glands produce maximum saliva during meals whereas submandibular glands are said to be responsible for lubrication in rest. In our study first eight questions in xerostomia questionnaire are related to xerostomia in rest and the latter six questions are related to xerostomia during meals. The aim was to spare at least one of the parotid gland and reducing the mean dose to less than 26Gy in the IMRT group.

Van Rii et al published a study which concluded that Parotid gland sparing IMRT for head and neck cancer patients improves xerostomia related quality of life compared to conventional radiation both in rest and during meals.[7] This study used questionnaire on xerostomia (based on the EORTC HandN 35 Questionnaire, Eisbruchs Questionnaire on xerostomia and an additional trial specific questionnaire).[8-9] Patients treated with IMRT experienced less chewing and swallowing difficulties. They also reported less problems with eating and speaking.

Edmond H. Pow etal in a study compared directly the effect of intensity-modulated radiotherapy (IMRT) vs. conventional radio- therapy (CRT) on salivary flow and quality of life (QoL) in patients with early-stage nasopharyngeal carcinoma.[10] Stimulated whole (SWS) and parotid (SPS) saliva flow were measured and Medical Outcomes Short Form 36 (SF-36), European Organization for Research and Treatment of Cancer (EORTC) core questionnaire, and EORTC head-and-neck module (QLQ-HandN35) were completed at baseline and 2, 6, and 12 months after radiotherapy. They concluded that in the IMRT group, there was consistent improvement over time with xerostomia-related symptoms significantly less common than in the Conventional RT group at 12 months post radiotherapy.[10]

Alexander. L.IN, M.D., et al did a prospective longitudinal study of head-and-neck cancer patients receiving multi segmental static IMRT.[11]

A validated xerostomia questionnaire and head and neck cancer questionnaire were given to patients. The questionnaires and measurements of salivary output from the major glands were completed before RT started (pre-RT) and at 3, 6, and 12 months after RT. They concluded that after parotid-sparing IMRT, a statistically significant correlation was noted between patient-reported xerostomia and each of the domains of QOL: Eating, Communication, Pain, and Emotion. Both xerostomia and QOL scores improved significantly over time during the first year after therapy.[11]

This study results showed xerostomia related QOL questionnaire scores were better in IMRT patients than conventional RT patients.In the current study the total mean score of xerostomia related QoL was 8.5 in conventional arm vs4.5 in IMRT arm.

The radiation induced injury of the salivary gland functioning with irradiation has already been reported in literature by measuring salivary flow rates or quantitative salivary scintigraphy. Dynamic quantitative pertechnetatescintigraphy has emerged as a simple, reproducible and minimally invasive test for quantification of post radiotherapy salivary function of individual major salivary glands. It provides quantitative estimates of parenchymal and excretory function of individual major salivary glands. It can be a suitable alternative to salivary flow rate measurements for quantification of post radiotherapy salivary dysfunction.[12]

The salivary glands possess an iodide-trapping mechanism and 99mTc-pertechnetate (99mTc), like radioiodine, is concentrated in the intralobularductule cells by means of this trapping-mechanism with subsequent ductal epithelium secretion and discharge into the excretory ducts. This agent is particularly useful for scintigraphic analysis of the function of the salivary glands after irradiation. Salivary excretion of 99mTc-pertechnetate can be induced by local stimulation (e.g., by ingestion of citric acid) or by parasympathetic stimulation (e.g., by subcutaneous administration of carbachol).[13]

By salivary scintigraphy, the major salivary glands can be examined noninvasively, simultaneously, and continuously over a period of time. This technique has gained widespread acceptance in evaluating a variety of salivary glandular disorder and its usefulness to evaluate salivary function after radiotherapy has been demonstrated in patients with head and neck malignancies.[13] In this study, we compared the salivary glandular scintigraphy results using 99mTc-pertechnetate in a group of patients who had received conventional radiotherapy with group of patients receiving Intensity Modulated Radiotherapy.

A comparison of the EF% values for each patient, at baseline and post radiotherapy was done in both the arms. In the conventional arm about 62.5% (10 out of 16 patients) showed zero EF% post radiotherapy. In the IMRT arm, only one patient showed zero EF%. This shows that there is better salivary excretion function when there is sparing of the parotid gland in the IMRT arm.

For the change in relative saliva excretion rate before and after treatment, the fall in excretion fraction from baseline to post radiotherapy at 3months was analysed. The fall in salivary excretion fraction from baseline to post radiotherapy at 3 months was 45% in conventional arm whereas in IMRT arm is around 32%.It means the excretion percentage was better in the IMRT arm compared to the conventional arm.

Maria Golen et al. conducted a study where Pre- and post-treatment SEFs were measured in 31 patients treated by IMRT and in 9 patients treated by conventional RT. Salivary excretion fraction (SEF) was lower by 52% at six weeks and 35.5% at 6months in conventional arm vs. 34% at six weeks and 29.3% at six months in the IMRT arm.[14]

A similar study done by Tejpal Gupta et al at Tata memorial cancer institute where salivary excretion fraction percent was performed before and after receiving radiation.[15] It showed in IMRT patients the median SEF ratios (IQR) of the parotid glands were 25.7% at 3months, 38.2% at 12 months, 59.0% and 65.3% at 24-months indicating substantial recovery of salivary function over time, mostly within the first two years of follow up.[15] But in our study scintigraphy was performed only at first follow up at 3 months.

CONCLUSION

Due its conformity, IMRT reduces the mean dose to bilateral parotid glands and related xerostomia. The subjective assessment of xerostomia through Quality of life questionnaire clearly showed better scores in IMRT arm than conventional arm. The objective assessment by quantitative salivary scintigraphy also clearly showed better salivary gland functioning in IMRT arm than conventional arm implying the usefulness of IMRT in head and neck cancer patients for sparing parotids and less xerostomia symptoms and better quality of life.

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