



## Original Article

# Comparison of acute toxicities in patients of Head and Neck Cancer treated by 3D-CRT v/s IMRT

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## Abstract

**Background:** Radiotherapy plays a critical role in the management of many patients with head and neck cancer. In recent decades, the treatment for head and neck cancer has moved from two-dimensional radiotherapy to three-dimensional conformal radiotherapy (3D-CRT) and recently also to intensity-modulated radiotherapy (IMRT). In this study we aim to demonstrate difference of toxicity profile between 3D-CRT and IMRT in patients of head and neck cancer.

**Material and Methods:** A total of 60 patients of head and neck cancer were randomly selected divided into two groups of 30 patients in each. Patients of group A received 3D-CRT and group B received IMRT. Patients of both arms received concurrent chemoradiation, were assessed weekly for local disease response & development of any acute skin or mucosal reactions. Xerostomia was assessed at the end of treatment, 1 month, 3 month and 6 month post radiotherapy. Xerostomia was also assessed and graded as per the CTCAE guidelines at 6 months follow up after treatment completion.

**Results:** The median age in the 3D-CRT arm was 50.5 years with range of 21 to 70 years while the median age in IMRT arm was 38 years with range of 18 to 64 years. Male patients were more common in both arms than female patients (90% in 3D-CRT arm and 80% in IMRT arm). In 3D-CRT arm 83.3% patients and in IMRT arm 76.6% patients suffered from grade II acute skin reactions during treatment duration or at the end of treatment. In 3D-CRT arm 80% patients were with grade II and 10% patients were with grade III acute stomatitis while in IMRT arm 86.6% patients were with grade II and no patient was with grade III acute stomatitis during treatment or at end of treatment. There was no statistically significant difference in incidence and severity of both acute skin reaction and stomatitis during or at the end of treatment in both arms. At the end of treatment, 1 month, 3 month and 6 month post radiotherapy there was no significant

*difference in incidence or RTOG grade of xerostomia between both the arms. While on assessing with CTCAE criteria there was significant difference in occurrence of grade III xerostomia at 6 months post radiotherapy between the two arms (63.3% in 3D-CRT arm v/s 30% in IMRT arm, p value = 0.009). There was no significant difference in the two arms in respect to treatment response*

**Conclusion:** *This study concluded that there was no significant difference in acute skin toxicity and stomatitis in head and neck cancer patients treated by either 3D-CRT or IMRT but there was significant difference in occurrence of higher grade xerostomia at 6 months in favor of IMRT. So, IMRT should be considered in treatment of head and neck cancers to prevent higher grade xerostomia.*

## Introduction

Cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012.<sup>(1)</sup> The projected numbers for the year 2030 are 20-26 million new cases and 13-17 million deaths due to malignancies.

On the Indian scene, 1.1 million new cancer cases were estimated, indicating India as a single country (of the 184 countries) contributing to 7.8% of the global cancer burden; mortality figures were 682830, contributing to 8.33% of global cancer deaths in 2012.

Head and neck malignancies are the sixth most common malignancies, worldwide<sup>(2)</sup> with an annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year.<sup>(3)</sup>

It is the third most common malignancy in India (2nd most common in males while 4th most common in females).<sup>(4)</sup>

Male to female ratio ranges from 2:1 to 4:1. Among females, the age-adjusted rates of India are the highest in the world. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC) probably due to their higher indulgence in risk factors such as alcohol and tobacco consumption.

As per the estimate provided by the GLOBOCAN, head and neck cancers account for almost 166,708 new cases annually in females and 477,161 new cases in males. The mortality rates are staggering, with almost 262,242 males and 89,498 females dying from the disease annually worldwide.<sup>(4)</sup>

Over 200,000 new cases of head and neck cancers are registered every year in India.<sup>(5)</sup>

Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1.<sup>(6)</sup> This probably accounts for the higher probability of the males getting exposed to the risk factors i.e. tobacco and alcohol.

The median age at diagnosis is in the sixth decade of life, studies have shown that infection with certain strains of human papilloma virus (HPV) is linked to the development of HNSCC. HPV infection accounts for the increasing incidence of HNSCC in younger people.<sup>(7)</sup>

Radiotherapy plays a critical role in the management of many patients with head-and-neck (H&N) cancer. In recent decades, the treatment for H&N cancer has moved from two-dimensional radiotherapy to three-dimensional conformal radiotherapy (3D-CRT) and recently also to intensity-modulated radiotherapy (IMRT). High rates of local tumor control can be achieved with 5-year survival greater than 80% for stage I and II and 60-70% for stage III and IV tumors<sup>(8)</sup>; however, long-term sequelae of radiotherapy are highly prevalent and have severe adverse effects on quality of life (QoL)<sup>(9,10)</sup>.

In radiotherapy for head and neck cancer, the major salivary glands frequently receive a high radiation dose. A high dose on the salivary glands results in a reduction in amount and quality of salivary output and a change in its composition.<sup>(11,12)</sup> Radiation induced xerostomia is the most commonly reported late side-effect of radiotherapy to head and neck. Lack of saliva affects swallowing and speaking, loss of taste, and dental caries, with a direct impact on patient quality of life (QoL).<sup>(13)</sup>

Intensity-modulated radiotherapy (IMRT) is a conformal radiotherapy which allows

simultaneous geometric and intensity modulation of radiation beams allows delivery of non-uniform fluence from any given position of the treatment beam to optimize the composite dose distribution. Thus, with greater control on dose distribution within the target, IMRT allows much higher possibility to sculpt radiation dose thereby improving the therapeutic ratio.<sup>(14,15)</sup>

In head and neck radiotherapy there are many clinical situations where radiosensitive normal tissues lie within a concavity surrounded by the planning target volume (PTV). The clinical target volume (CTV) often includes a midline target and bilateral cervical lymph nodes, producing a horseshoe-shaped PTV with the spinal cord within the concavity.<sup>(16)</sup> Homogeneous irradiation of these PTVs to radical doses (50-66 Gy) with conventional external-beam radiotherapy is difficult. Typically parallel-opposed photon portals are matched to electron beams. This technique leads to dose inhomogeneity at the photon-electron match-line, and may under dose the posterior cervical and deep cervical lymph nodes close to the spinal cord. Such under dose may result in failure to achieve local tumour control.

This shape of PTV can be treated homogeneously using IMRT without the need for electrons. IMRT using highly conformal dose distributions and ability to generate concave dose distributions should translate into reduction in organ at risk doses and reduced toxicity. Second, the ability to reduce the volume of normal tissue to be irradiated allows the opportunity to deliver higher radiation doses in an attempt to increase local tumour control. Thus, Head and Neck is one of the ideal site for IMRT because of complex geometry of this area and substantial radiation related acute and late toxicities, usually distance between Clinical Target Volume (CTV) and critical structures such as salivary glands, optic apparatus, inner ear and brainstem is within few millimeters. Currently, a modest but significant improvement in salivary flux parameters and subjective xerostomia has been confirmed in randomized

trials, with only parotid gland sparing.<sup>(17-19)</sup> Small phase 2 studies have shown that a reduction in radiation dose to parotid glands (to 24-26 Gy) through IMRT aids early recovery of saliva flow<sup>(20-22)</sup>.

The purpose of above mentioned study is to compare IMRT with 3D conformal radiotherapy with respect to acute toxicity profile.

### Material and Methods

A total of 60 newly diagnosed histopathologically proven squamous cell carcinoma patients of head and neck region with any stage except M1, 18-70 years age group, ECOG score 0-2, normal base line organ function (normal CBC, RFT, RBS and LFT) and with informed consent were randomly selected and allotted in 3D-CRT or IMRT arm at Acharya Tulsi Cancer Treatment and Research Institute. Distant metastases, evidence of second malignancies, history of previous treatment with any of the following modalities- radiotherapy, chemotherapy, surgery in head and neck region, pregnant and lactating woman, associated other severe comorbid diseases, pre-existing salivary gland disease, tumor involvement of parotid glands, prophylactic use amifostine or pilocarpine and recurrent disease were criteria for exclusion in this study.

GTV, CTV, PTV were contoured as per ICRU 50 and 62 GUIDELINES.

A single observer contoured the following OAR on each scan: parotid glands (PG), thyroid gland (TG), constrictor muscles (CM), sternocleidomastoid muscles (SCM), masticatory muscles (MM), larynx (L), and spinal cord(SC), brachial plexus(BP).

Both arms patients were irradiated by linear accelerator (Make: Varian, Model: 2300CD with multileaf collimators having 40 pairs of leaves and each leaf having 1cm width at isocentre) with concurrent chemotherapy in form of weekly cisplatin.

CT imaging was done for each patient prior to start of the treatment. All patients underwent head-and-neck immobilization with a thermopl-

astic mask and CT simulation according to standard procedures. Target volumes and normal structures were manually contoured on the axial slices of the planning CT scan.

**Group A:** This group consisted of randomly selected previously untreated 30 patients of squamous cell carcinoma of head and neck. These patients received 3D conformal radiotherapy. The control group was irradiated by 6MV photon obtained by LINAC teletherapy machine, MLC shaped fields from three to five beams to achieve homogeneity.

The lower neck nodes were treated using lower anterior photon field.

This group was irradiated by 2 Gy/#, 1#/day, 5 days a week in 33 fractions. Total tumor dose was 66Gy. After 46Gy (2Gy/#) off-cord reduction was made and the posterior cervical nodes were treated, if necessary, with electrons.

**Group B:** This group consisted of randomly selected previously untreated 30 patients of squamous cell carcinoma of head and neck region. These patients received irradiation by Intensity Modulated Radiation Therapy (IMRT) [through inverse planning performed in Eclipse Treatment Planning System(T.P.S) version 13.7] by isocentric technique, by 6MV photon obtained by

LINAC teletherapy machine. The treatment plan was delivered in RV mode (record and verify). 95% of the Planning Target Volume (PTV) received 95% of the prescribed dose. The maximum dose allowed to the spinal cord was 46 Gy.

The aim was to reduce the mean dose to 26 Gy or less for at least one parotid gland. If this was not achievable, the lowest possible mean dose, whilst maintaining target coverage, was accepted. Sparing of the submandibular glands or oral cavity was not attempted. Treatment setup consisted of five to seven beams. Radiotherapy plan for this group was as following:

**PTV1**

Dose: 2.11Gy/#, 1#/day, 5days a week

Total dose: 69.63Gy

Total number of fractions: 33

**PTV2**

Dose: 1.63Gy/#, 1#/day, 5days a week

Total dose: 54Gy

Total number of fractions: 33

The schedule for IMRT arm was planned by equating the Biological Effective Dose calculations taking conventional value of  $\alpha/\beta=10$  for acute effects.

$$BED = D [1 + d / (\alpha/\beta)]$$

where D is the total dose and d is dose per fraction.

**BED Calculation for 3DCRT arm:**

$$\begin{aligned} \text{BED for early effect} \\ (\text{for GTV}) &= 2 \times 33(1 + 2/10) \\ &= 79.2\text{Gy} \end{aligned}$$

**BED Calculation for IMRT arm:**

$$\begin{aligned} \text{BED for early effects} \\ (\text{for PTV1}) &= 2.11 \times 33(1 + 2.11/10) \\ &= 84.32 \text{ Gy} \end{aligned}$$

Patients (both 3D-CRT and IMRT arm) received concurrent chemoradiation, were assessed weekly for local disease response & development of any acute skin or mucosal reactions. Treatment response was assessed as per the RECIST Criteria. Xerostomia was assessed as per the RTOG guidelines during treatment, at the end of treatment, 1 month 3 month and 6 month post radiotherapy. Xerostomia was also assessed and graded as per the CTCAE guidelines at 6 months follow up after treatment completion.

**Results**

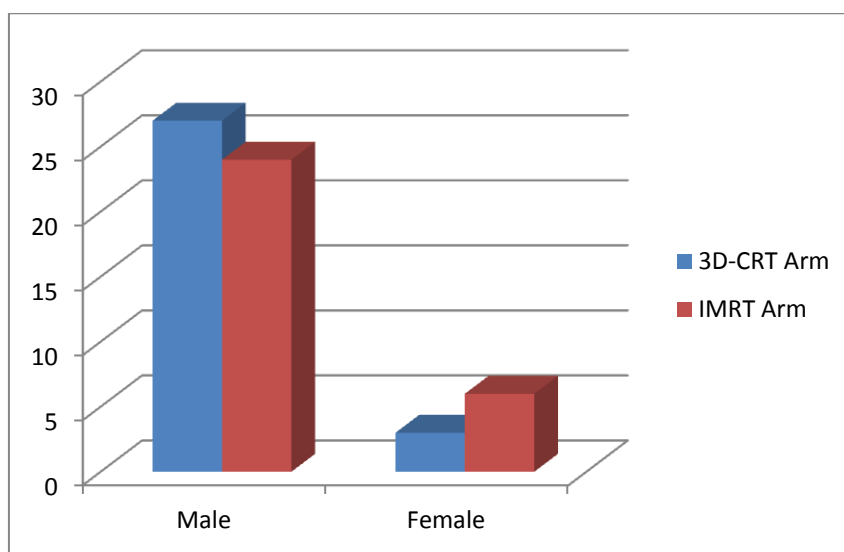
The age distribution of the patients enrolled in the study is shown in the table 1. The median age of the patients in the 3D CRT arm was 50.5 years with range 21 years to 70 years while the median age in the IMRT arm was 38 years with range of 18 years to 64 years. Total number of patients in each group was 30. The majority of patients were in their 5<sup>th</sup> decade of life. Chi-square test was performed to analyze for the possibility of age distribution as a confounding factor. However, the p value was insignificant signifying equitable distribution of patients in both the groups.

**Table 1** Age Distribution of the Patients Enrolled in the study

S. No.	Age Group (years)	3D-CRT Arm	IMRT Arm
1	18-20	0	4(13.3%)
2	21-30	3(10%)	4(13.3%)
3	31-40	1(3.3%)	2(6.6%)
4	41-50	8(26.6%)	7(23.3%)
5	51-60	9(30%)	11(36.6%)
6	61-70	9(30%)	2(6.6%)
	<b>Total</b>	30(100%)	30(100%)

Sex distribution of patients enlisted in both arms is shown in figure 1. In 3D-CRT arm 90% patients were of male sex and 80% patients were of female

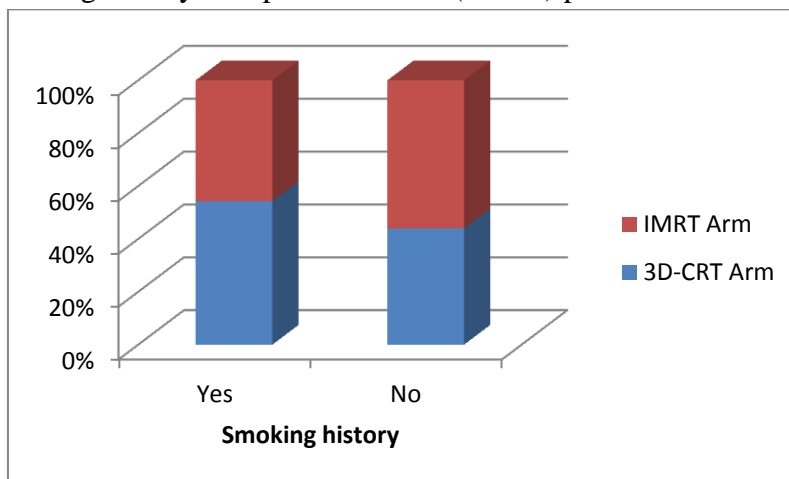
sex while in IMRT arm 80% patients were of male sex and 20% patients were of female sex.



**Figure 1** Sex Distribution of Patients Enrolled in the Study

Smoking history of patients included in the study is shown in figure 2. Smoking history was present

in 19 (63.3%) patients of 3D-CRT arm and 16 (53.3%) patients of IMRT arm.



**Figure 2** Smoking History of Patients Enrolled in the Study

Primary site wise distribution of patients is given in table 2. The most common primary site of

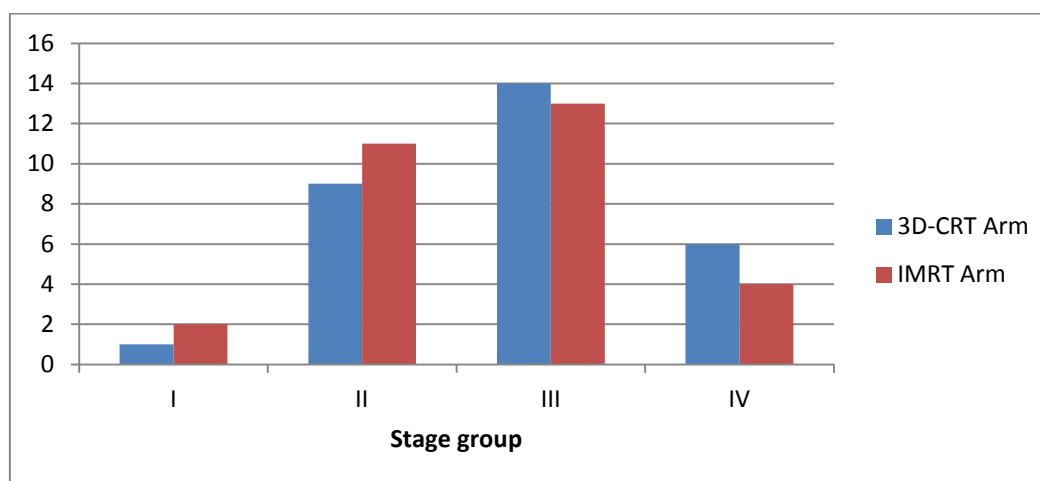
tumor was oropharynx and oral cavity in both the arms.

**Table 2** Primary site wise distribution of patients

S. No.	Primary Site	3D-CRT Arm	IMRT Arm
1.	Oral cavity	8(26.6%)	12(40%)
2.	Nasopharynx	4(13.3%)	5(16.6%)
3.	Oropharynx	16(53.3%)	12(40%)
4.	Larynx	2(6.6%)	1(3.3%)
	<b>Total</b>	30(100%)	30(100%)

In 3D-CRT arm 1 (3.3%) patient was in stage I, 9 (30%) patients were in stage II, 14 (46.6%) patients were in stage III and 6 (20%) patients were in stage IV while in IMRT arm 2 (6.6%)

patients were in stage I, 11 (36.6%) patients were in stage II, 13 (43.3%) patients were in stage III and 4 (13.3%) patients were in stage IV.



**Figure 3** Stage Grouping of patients included in the Study

Table 3 shows the distribution of patients in the two arms according to the highest grade of acute skin reaction found during the treatment duration

or at the end of treatment. No significant difference was found between the two arms with respect to skin toxicity.

**Table 3** Incidence of Acute Skin Reactions

Grade of Skin Toxicity	3D-CRT Arm	IMRT Arm	P value
I	5(16.6%)	7(23.3%)	0.99
II	25(83.3%)	23(76.6%)	
III	0	0	
IV	0	0	
<b>Total</b>	30(100%)	30(100%)	

Table 4 shows the distribution of the patients in the two arms according to the highest grade of acute mucosal reaction found during the treatment

duration or at the end of the treatment. No significant difference was found between the two arms as the p value was 0.71.

**Table 4** Statistical Calculation of Stomatitis Comparing the Two arms

Stomatitis Grade	3D-CRT Arm	IMRT Arm	P value
I	3(10%)	4(13.3%)	0.71
II	24(80%)	26(86.6%)	
III	3(10%)	0	
IV	0	0	
<b>Total</b>	30(100%)	30(100%)	

Table 5 represents the actual incidence of different RTOG grades of xerostomia reported by patients at 26<sup>th</sup> day of treatment, end of treatment, at 1

month, 3 month and 6 month follow up after treatment.

**Table 5** Incidence of Xerostomia

Treatment Duration	3D-CRT Arm Grade – Xerostomia				IMRT Arm Grade – Xerostomia			
	0	I	II	IV	0	I	II	IV
Day 26 (week 6) of Treatment	0	0	30	0	0	1	29	0
End of Treatment	0	0	30	0	0	0	30	0
One month after Treatment	0	1	29	0	0	1	29	0
Three month after Treatment	0	4	26	0	1	2	27	0
Six month after Treatment	0	7	23	0	1	12	17	0

On the 26<sup>th</sup> day of treatment all 30 patients of 3D-CRT arm were having grade II xerostomia while 1 patient of IMRT arm had grade I xerostomia rest all 29 patients were having grade II xerostomia. Hence occurrence of xerostomia at 26<sup>th</sup> day of treatment between the two arms was not significant. None of the patients enrolled in the study was free from xerostomia by the time of treatment completion.

Subjects were followed for degree of xerostomia at one month, three month and six month after treatment completion. At 1 month follow up 1 patient of each arm had grade I xerostomia and 29 patients of each arm were with grade II xerostomia. There was no difference in occurrence of xerostomia at 1 month follow up after treatment.

At 3 month follow up after treatment completion 4 patients were having grade I and 26 patients were having grade II xerostomia in 3D-CRT arm whereas 1 patient had grade 0, 2 patients were having grade I and 27 patients were having grade II xerostomia in IMRT arm but there was no significant difference between two arms.

There was no patient was without xerostomia, 7 patients were with grade I and 23 patients were with grade II xerostomia in 3D-CRT arm while 1 patient was without xerostomia, 12 patients were with grade I and 17 patients were with grade II xerostomia in IMRT arm at six month follow up. Although there is 20% higher occurrence of grade II xerostomia in 3D-CRT arm (76.6%) compared

to IMRT arm (56.6%), this difference is not statistically significant (p value = 0.69).

Table 6 describes the incidence of xerostomia according to CTCAE grading at 6 month follow up after treatment completion. In 3D-CRT arm 1 patient had grade I, 10 patients had grade II whereas 19 patients had grade III xerostomia at 6 month. In IMRT arm 2 patients had grade I, 19 patients had grade II and 9 patients had grade III xerostomia at 6 month follow up. There is 33.3% higher incidence of grade III xerostomia in 3D-CRT arm compared to IMRT arm which was statistically significant (p value = 0.009).

**Table 6** Incidence of CTCAE Grade – Xerostomia 6 month after Treatment

Grade	3D CRT Arm	IMRT Arm
I	1(3.3%)	2(6.6%)
II	10(33.3%)	19(63.3%)
III	19(63.3%)	9(30%)

There was no significant difference in terms of disease response at 6 months in the two arms. At 6 months after treatment completion 23 patients were in complete response (CR) and 7 patients were in partial response (PR) in 3D-CRT arm. Out of these 7 patients 4 patients had disease at nodal region, 2 patients had disease at both primary as well as nodal site and 1 patient had disease at primary site only. In IMRT arm 24 patients were in CR, 5 patients were in PR (2 patients had disease at node and 3 patients had disease at primary site) and 1 patient was in stable disease status (SD).

## Discussion

Radiotherapy has played a significant role in the treatment of head and neck cancers. More than two third of head and neck cancer patients need to undergo either definitive or post-operative radiation therapy.<sup>(23)</sup> Conventional radiotherapy is associated with significant acute and late toxicities and to overcome this, newer techniques have evolved with the aim of delivering cancericidal dose to tumor while delivering minimum dose to surrounding normal tissues.

As compared to conventional radiotherapy, IMRT/3D-CRT technique offers better sparing of normal tissue thus minimising toxicity. The IMRT technique gives the ability to create treatment fields with varying beam intensity by using inverse planning and iterative optimization algorithms.<sup>(24)</sup> The radiation beam can be adjusted to the irregularly shaped target volumes with extremely high precision while reducing the radiation delivered to the surrounding healthy tissue and critical structures e.g., spinal cord, brain stem, parotid glands, eyes etc., in case of head and neck cancer.<sup>(25,26)</sup>

The ability of delivering lower doses of radiation to normal tissue while maintaining or increasing the dose in the target volume makes IMRT the most appropriate treatment option compared to conventional radiotherapy.<sup>(27-29)</sup>

In this study we analysed acute toxicities such as skin reactions, stomatitis and xerostomia during treatment duration and at the end of treatment in both 3D-CRT and IMRT arm. We found almost similar rates of acute toxicities in both the arms with insignificant p value.

In our study we observed grade  $\geq 2$  mucositis of 90% in 3D-CRT arm and 86.6% in IMRT arm. The difference between the arms was insignificant which was comparable to the study of S Clavel, et al.<sup>(29)</sup> in which they reported Grade 2 or greater acute mucositis of 75% with IMRT while it was 77% with 2-3D CRT. Pow EH et al.<sup>(19)</sup> also reported dry mouth and sticky saliva as acute toxicity were problems in both groups 2 months after treatment.

At treatment completion all patients suffered from xerostomia of atleast RTOG grade 2 in both the arms. At 6 months post radiotherapy higher number of patients were with RTOG grade 2 xerostomia in 3D-CRT arm (76.6%) whereas comparatively lower number of patients were with grade 2 xerostomia in IMRT arm (56.6%).

On comparing our study with Christopher M Nutting et al.<sup>(18)</sup> who conducted PARSPORT study we also got lesser incidence of RTOG grade 2 xerostomia at 6 months post treatment completion in IMRT arm compared to 3D-CRT arm as stated earlier but this difference was not statistically significant. This may be due to smaller number of patients and shorter duration of follow up. In PARSPORT study patients were followed also on 1 and 2 year post treatment completion and significant results were found in favor of IMRT whereas our results were of 6 month follow up.

In PARSPORT study they found that at 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (29% vs 83%;  $p < 0.0001$ ). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry mouth specific and global quality of life scores.

Pow EH et al.<sup>(19)</sup> compared directly the effect of IMRT vs conventional radiotherapy (CRT) on salivary flow and QoL in patients with early stage nasopharyngeal carcinoma (NPC). At 12 months post radiotherapy, 50% and 83% in IMRT group had recovered at least 25% of pre-radiotherapy stimulated whole saliva (SWS) and stimulated parotid saliva (SPS) flow respectively, compared with 4.8% and 9.5%, respectively in CRT group.

We also assessed unstimulated salivary flow rate and graded xerostomia according to CTCAE guidelines at 6 months after treatment completion. The incidence of CTCAE grade  $\geq 2$  xerostomia in IMRT arm (93.3%) compared to 3D-CRT arm (96.6%) at 6 months post radiotherapy was also similar. But on assessing whether patients were



having grade 3 or grade 2 xerostomia at 6 months we found higher number of patients with grade 3 xerostomia in 3D-CRT arm (63.3%) compared to IMRT arm (30%). This difference was statistically significant with p value of 0.009. The sub-group analysis revealed that patients getting IMRT were having higher incidence of lesser grade i.e. CTCAE grade 2 xerostomia at 6 months post RT compared to patients getting 3D-CRT (63.3% vs 33.3%).

Eisbruch A et al.<sup>(21)</sup> assessed long term xerostomia in patients receiving parotid sparing radiation therapy for head and neck cancer and concluded an improvement over time in xerostomia, occurring in tandem with rising salivary production from spared major salivary glands, suggests a long term clinical benefit from their sparing. The oral cavity mean dose, representing radiotherapy effect on minor salivary glands, was found to be a significant, independent predictor of xerostomia. Thus, in addition to the major salivary glands, sparing the uninvolved oral cavity should be considered as a planning objective to further reduce xerostomia.

This was the limitation of our study that we did not consider mean dose to oral cavity affecting minor salivary glands which was found to be significant in above mentioned study.

We are conscious that the results of the present study are influenced by several limitations. The first limitation regards the population of the study: the sample size is small, and moreover, we analysed the patients with different primary disease sites in head and neck region and subsequently with different treated volume. Another important limitation is that we did not take care of dose to the salivary glands other than parotid gland which produce about 20-30% salivary volume in a stimulated state such as during meal.

It is necessary to follow the study population further till 1 or 2 year post radiotherapy to get more accurate results regarding recovery of saliva secretion like PARSPORT study.

## Conclusion

This study concluded that there was no significant difference in acute skin toxicity and stomatitis during or at the end of treatment in head and neck cancer patients treated by either 3D-CRT or IMRT but there was significant difference in occurrence of higher grade xerostomia at 6 months in favor of IMRT. So, IMRT should be considered in treatment of head and neck cancers to prevent higher grade xerostomia.

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