Original Article

DOI: 10.7860/JCDR/2021/51787.15736

Oncology Section

A Prospective Cohort Study Analysing 3-Dimensional Conformal Radiotherapy and Salivary Glands Preserving Intensity Modulated Radiotherapy with/without Concomitant Cisplatin Chemotherapy in Head and Neck Malignancies

M SANTOSH KRISHNA[1], BHASKAR VISHWANATHAN[2], B NAVEEN[3], GEETA S NARAYANAN[4]

ABSTRACT

Introduction: Most common toxicity of radiotherapy in head and neck malignancy patients is xerostomia. Xerostomia can be prevented by using salivary gland sparing Intensity Modulated Radiation Therapy (IMRT) technique.

Aim: To compare Dose Volume Histogram (DVH) of salivary glands in IMRT and 3-Dimensional Conformal Radiation Therapy (3DCRT) and evaluation of xerostomia, mucositis and dysphagia in both groups.

Materials and Methods: The present study was a prospective cohort study in which 30 patients were selected. Patients of head and neck cancer reporting to Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India were included. Duration of study was one year (January 2013 to December 2013). Fifteen patients treated with IMRT and 15 patients with 3DCRT to a dose of 60-70 Gy in 30-35 fractions, with or without concomitant cisplatin. The DVH of salivary glands and incidence of xerostomia, mucositis and dysphagia was compared in both the groups. Patients were assessed during the course of radiotherapy and three months postradiotherapy.

Results: Mean dose to contralateral parotid was 19.48 Gy in IMRT when compared to 47.31 Gy in 3DCRT. Mean dose to contralateral submandibular was 44.06 Gy in IMRT when compared to 67.63 Gy in 3DCRT. At three, six and seven weeks there was a difference in number of patients having reduced severity of mucositis in IMRT when compared to 3DCRT. There was no significant difference in dysphagia between both groups at three, six and seven weeks and one month after the treatment. No significant difference in xerostomia between both the groups at seven week and one month after treatment. At three months after treatment the difference in xerostomia was significant between both groups ($p<0.05$) favouring IMRT. No tumour response benefit was seen with IMRT.

Conclusion: Radiation dose received by salivary glands by IMRT was significantly less when compared to 3DCRT, thereby reducing the incidence, severity and duration of xerostomia. IMRT helps in reducing the severity and duration of dysphagia and mucositis in comparison to 3DCRT during radiotherapy of head and neck cancer.

Keywords: Dose volume histogram, Dysphagia, Mucositis, Parotid glands, Submandibular glands, Xerostomia

INTRODUCTION

Head and neck cancer is the predominant subsite in India and constitutes 30% of all cancers as opposed to 3-4% in the Western World [1]. The high incidence of head and neck carcinoma in Indian subcontinent is due to widespread and prevalent use of tobacco [2]. Head and neck carcinoma are more frequently present and diagnosed in a locally advanced stage. Treatment of locally advanced head and neck carcinoma is very challenging. Radiotherapy with concomitant chemotherapy is the standard treatment of the locally advanced head and neck cancer [3]. The treatment related toxicities of chemoradiotherapy include mucositis, dysphagia, dermatitis, weight loss, xerostomia, mucosal infections, subcutaneous tissue fibrosis, dental caries and neuropathic pain [4,5]. A 3DCRT treatment planning is a manually optimised process in which beams parameters, number and directions of beams, field size and shapes, weightage, wedge angle etc. are selected manually. The IMRT is an advanced form of 3DCRT with features of non uniform intensity of the radiation beams and computerised inverse planning. It is of particular value for concave or complex shapes tumour target volumes with close proximity to Organs at Risks (OARs). The IMRT is a very sophisticated and more conformal approach than 3DCRT to the planning and delivery of radiation therapy. The IMRT allows higher doses to tumour while sparing normal and critical organs by modulating the intensity of the radiation beam. The IMRT has shown beneficial effects by reducing late treatment related toxicities such as xerostomia compared to 3DCRT [6]. The advances of modern radiotherapy have emerged with the development of CRT techniques, such as the 3DCRT or the IMRT. CRT allows the delivery of higher doses to the tumour and by sparing the critical normal structures or OAR [7,8]. A 3DCRT is the use of Computerised Tomography (CT) based planning techniques to generate three Dimensional (3D) volumes of internal anatomy. Correct treatment planning computer software uses these volumes to shape various radiation beams conforming to the target in each Beam's Eye View (BEV). The 3DCRT allows delineation of tumour target as well as OARs with radiologic visualisation of their spatial relations in planning CT scan thus providing a potential therapeutic benefit of dose escalation to tumour tissue with reduced toxicity to normal tissues [7,8]. The clinical data is still limited to confirm the advantages and disadvantages of IMRT over 3DCRT with regards to acute toxicities and compliance to chemoradiotherapy treatment in locally advanced head neck cancer [8].

In order to understand the function of salivary gland in postradiotherapy patients the present prospective cohort study was carried out to analyse if IMRT decreases the dose to salivary gland and thereby decreasing xerostomia, mucositis and dysphagia when compared to 3DCRT.

MATERIALS AND METHODS

A prospective cohort study conducted at Department of Radiation Oncology at Vydehi Institute of Medical Sciences and Research Centre (VIMS and RC) Bangalore, Karnataka, India. Thirty patients with head and neck cancer were included between January 2013 to December 2013. Sample size was calculated with 95% confidence interval and 5% marginal error. Patients were assessed during the course of radiotherapy and three months postradiotherapy. Study was reviewed by scientific review board and approved by Institutional Ethical committee. Informed consent was obtained from all patients.

Inclusion criteria: Selected patients were biopsy proven head and neck cancer with TNM (Tumour, Nodes, Metastasis) Stages from T1-4, N0-3, M0, Age 18 to 78 years and planned for curative radiation therapy with or without chemotherapy having performance status 0-2 (ECOG-Eastern Cooperative Oncology Group) [9].

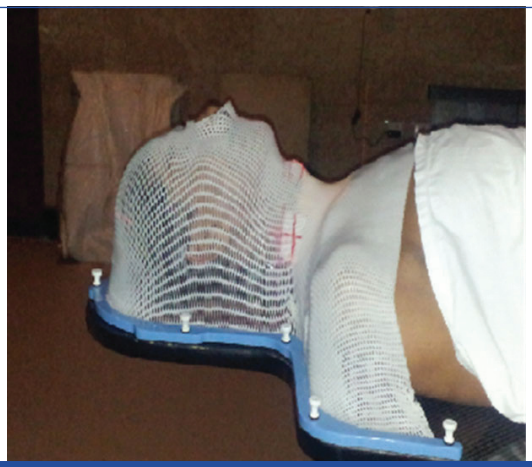
Exclusion criteria: Included metastatic disease, ECOG performance status more than 2, postoperative cases and patients who received neo-adjuvant chemotherapy.

Patients underwent complete clinical evaluation, biopsy for confirmation of malignancy, CT or Magnetic Resonance Imaging (MRI) with or without contrast was carried out for staging, X-ray Chest, Complete Blood Count (CBC) and Renal Function Tests were done.

Radiation Therapy Procedure

A. Conventional Radiotherapy Protocol

1. Immobilisation: The patients are immobilised in thermoplastic cast and orfit head rest [Table/Fig-1]. The patient was kept in supine position and shoulders were pulled down as far as possible. The head is extended depending on the site of tumour.



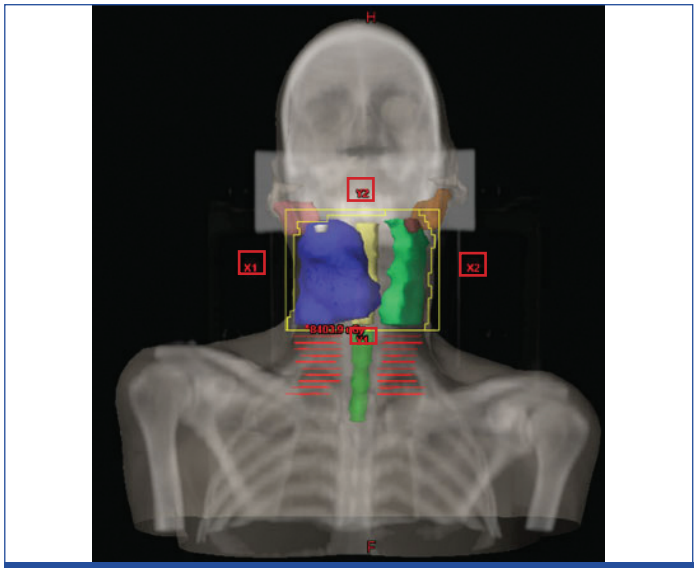
[Table/Fig-1]: Patient with the thermoplastic mask on the treatment couch.

2. Simulation: A 5 mm Contrast Enhanced Computed Tomography (CECT) axial cuts of the patient were acquired with immobilisation devices and fiducials. The CT images were exported to 3D- Eclipse planning system in Digital Imaging and Communications in Medicine (DICOM) format.

3. Energy: All patients were treated by Clinac Linear accelerator machine with Source to Axis Distance (SAD) 100 cm using 6MV energy.

4. Target volume: Initial tumour volume consists of primary tumour, involved lymph nodes and possible subclinical disease. The irradiation field was reduced to include only the gross disease and involved lymph nodes by shielding the spinal cord after 40 Gy in 20 fractions.

5. Technique: Depending on the primary tumour site and draining lymph nodes, patients were treated with three field techniques {i.e., two parallel opposed lateral fields and a low neck field (AP- Antero-posterior)}. All patients were treated based on CT scan simulation and planning. The portal verification was done using Electronic Portal Imaging Device (EPID) generated image and compared with Digitally Reconstructed Radiographs (DRR) [Table/Fig-2].



[Table/Fig-2]: Digitally Reconstructed Radiography (DRR) in an IMRT patient. Yellow: Superior spinal cord; Dark green: Inferior spinal cord; Blue: PTV 1 (Planning target volume 1); Light green- PTV 2 (Planning target volume 2); Red: PTV 3 (Planning target volume 3); Pink: Right parotid gland; Orange: Left Parotid Gland; X1, X2, Y1, Y2-Asymmetric collimator jaws of linear accelerator

6. Dose fractionation: Ionising radiation via mega voltage was given with a total dose of 60-70 Gy (30-35 fractions), 2 Gy once daily, and five days per week (Monday-Friday) over a period 6-7 weeks. Radiotherapy was administered to patient by positioning them in supine position with thermoplastic mask. The spinal cord was shielded after 40 Gy in 20 fractions. The radiation dose delivered to the lower neck portal was 50 Gy in 25 fractions at 3 cm depth.

B. Intensity Modulated Radiotherapy Protocol (IMRT)

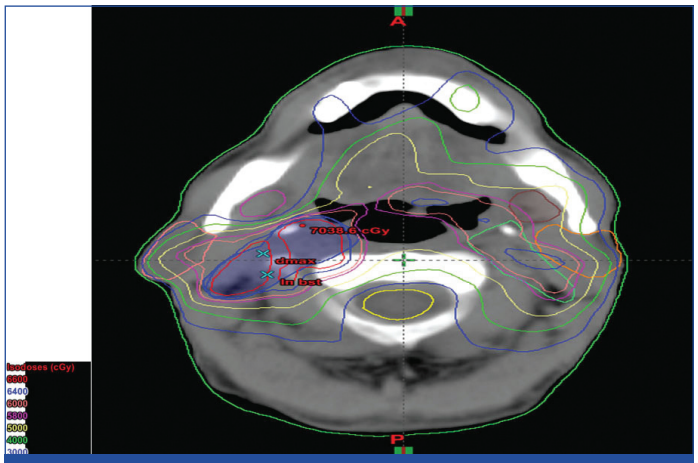
The IMRT planning procedure is technological evolution from the traditional 3DCRT planning. The inverse planning module to produce non uniform fluencies and delivery of higher dose gradients within short distances are the unique aspects of IMRT.

Contouring: This is one of the most important aspects in IMRT treatment planning. Present study followed the recommendations of ICRU 50 [10] and its supplement ICRU 62 [11]. At first the Gross Tumour Volume (GTV) is delineated. It includes both primary and nodal tumour volumes. Then the clinical target volume was contoured depending on the stage and site of the disease. In Simultaneous Integrated Boost-Intensity Modulated Radiation Therapy (SIB-IMRT), there are different clinical target volumes and they are named CTV (Clinical Target Volume) 1, CTV 2 and CTV 3. The CTV 1 is gross tumour (primary and enlarged nodes) with margins based on clinical and radiologic justification. The CTV 2 encompasses soft tissue and nodal regions adjacent to CTV 1. It includes generally ipsilateral adjacent lymph nodes which harbors high risk sub clinical disease. The CTV 3 includes elective nodal regions constituting ipsilateral, contralateral and retropharyngeal lymph nodes which contain low risk subclinical disease. After delineation of CTV, the Planning Target Volume (PTV) is generated. The PTV will provide a margin around each CTV to compensate for the uncertainties of treatment set-up and tissue deformation. An isotropic expansion of 5 mm is typically added around the CTV to define each respective PTV [12,13]. In our Institute, authors have used a margin of 5 mm around the CTV. Therefore, three PTVs, i.e., PTV 1, PTV 2 and PTV 3 are generated from CTV 1, CTV 2 and CTV 3, respectively.

IMRT- Target Volumes

The PTV 1 was prescribed to doses ranging from 66 Gy. The dose per fraction was from 2-2.2 Gy and the number of fractions was 30-33 fractions. The PTV 2 received doses ranging from 60 Gy. The dose per fraction was 2 Gy. The PTV 3 received doses from 54 Gy and dose per fraction was 1.8 Gy. The PTV 1, PTV 2 and PTV 3 were treated simultaneously, one fraction each day, five days a week for six and half weeks.

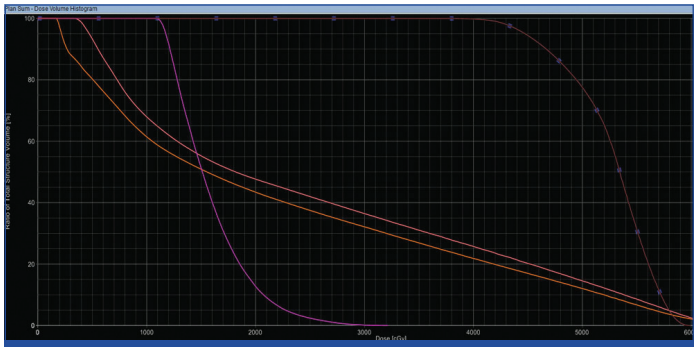
Then, the surrounding critical structures are delineated. All the critical structures are delineated slice by slice and 3D volume was generated. The structures like parotid, submandibular gland, mandible, spinal cord and brainstem are delineated depending on the primary disease. DVH must be generated for all critical structures and unspecified tissues. Normal tissue and OAR dose-constraints were prescribed as per the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines [14]. Dose volume objectives (dose constraints) for OAR were prescribed as Spinal cord Dmax <44 Gy, Brain stem Dmax <54 Gy, Mandible Dmax <70 Gy and Parotid glands Dmean <26 Gy, Oral cavity Dmean <40 Gy. The prescription isodose is the isodose line that encompasses at least 95% of the PTV. The IMRT plan objectives were to achieve no more than 20% of any PTV volumes could receive >110% of its prescribed dose, no more than 1% of any PTV volume would receive <93% of prescribed dose [Table/Fig-3].



[Table/Fig-3]: PTV 1 and PTV 2 with parotid and submandibular glands dose distribution in an IMRT patient.
Isodoses (cGy): Red: 6600; Dark blue: 6000; Pink: 5800; Yellow: 5000; Green: 4000; Sky blue: 3000; Organs At Risk (OAR): In bst: Integrated boost; Yellow: Spinal cord; Pink: Right submandibular gland; Brown: Left submandibular gland; Orange: Left parotid gland; Light pink: Right parotid gland; Dmax: Maximum dose at depth

Plan evaluation: At first- the maximum, minimum and mean doses were evaluated in each CT scan slice as well as using DVH [Table/Fig-4]. In inverse IMRT, the plan acceptance criteria was compared with the existing plan. If the criteria are met, further dose distribution is displayed in each CT slices and dose conformity, hot spot and cold spots were same. If the criteria were not met, one should find out what the key limiting factors are. The first step was to examine whether there are dose constraints that are physically impossible to achieve. It was useful to remember that most achievable dose gradient for a single beam is approximately 10% per millimeter. Scatter doses from other beams in a treatment plan that uses multiple beams and the leakage dose from the multileaf collimator make the dose gradient shallower than 10% per millimeter [10].

Plan acceptance criteria: It should be developed among attending physicians, planners and therapists according to clinical requirements, physical limitations and practical limitations.



[Table/Fig-4]: Dose Volume Histograms (DVH) of an IMRT patient showing sparing of both the parotids and contralateral submandibular gland.
DVH showing contralateral submandibular gland (Pink isodose line) receiving less dose in comparison to ipsilateral submandibular gland (Brown isodose line); Both parotid glands (Orange isodose line and Light Pink isodose line) with better sparing ability

Quality Assurance (QA) for Intensity Modulated Radiation Therapy (IMRT): Ongoing QA after the system is released to the clinic, it is important to establish routine QA program. It is separated into patient specific QA and equipment QA.

1) Patient specific QA: Because of complexity of irregular field shape, small field dosimetry and time dependent deliverable leaf sequence, it is recommended by the American Association of Physicists in Medicine (AAPM) and American Society for Radiation Oncology (ASTRO) that patient specific QA should be performed as a part of the IMRT management process: I) Patient set-up is considered a key step in ensuring accurate IMRT treatment in our institute we have used liquid chamber based electronic portal imaging for setup verification; II) The most reliable and practical technique for IMRT Monitor Units (MU) verification is ion chamber-based point dose measurement in a phantom which is also done for all the patients before the start of treatment. It is usually performed through a process called the "Hybrid phantom plan". In this plan, all the beam angles and deliverable intensity pattern for a patient plan are transferred to the phantom, and doses in the phantom are computed for QA; III) Relative dosimetry is performed with radiographic films in our Institute. The film measurements are primarily for investigating the relative dosimetric agreement between the planned and measure dose distribution.

2) Equipment Quality Assurance (QA): The IMRT delivery system is equipment specific, which usually requires special design of QA procedures. Many of the sources of uncertainties in RT and IMRT application has been discussed in AAPM report [15].

Treatment delivery: The plan is then approved and exported to treatment machine. On the first day, the patient is placed in linear accelerator treatment room and lasers are aligned to the fiducials. Then the center is moved to the new isocenter and marked on the thermoplastic mask. The setup verification is done using the EPID generated portal imaging. This image is taken and matched with the set-up fields in DRR. Anterior, posterior and lateral portal imaging is done in order to look for vertical, horizontal and anterior displacements. The patient is then re-aligned only if the displacement is more than 5 mm in any direction.

Chemotherapy protocol: The drug cisplatin was used as a single agent concomitantly with the radiotherapy. The dosage used was 70-100 mg/msq (Meter Square) 3 weekly for 2-3 cycles. The patient was started on chemotherapy after adequate hydration and premedication. Cisplatin was administered with normal saline and given over 2 to 3 hours Intravenous (i.v.) infusion. It is followed by radiotherapy within one hour after completion of infusion. Myelosuppression and renal toxicities are evaluated by doing complete haemogram, blood urea and serum creatinine weekly.

Cisplatin Regimen

Injection- Ranitidine 50 mg.

Injection- Dexamethasone 8 mg in 100 mL normal saline over 15 minutes.

Injection- Palonosetron 0.25 mg.

Injection cisplatin 70 mg/msq (Meter Square) over 2 to 3 hours infusion.

i.v. Normal saline+Injection KCL (Potassium chloride) 5 cc.

i.v. Normal saline+Injection $MgSO_4$-2 cc.

Patient evaluation: During treatment, the patient was explained about the care of irradiated site, precautions, and diet modifications. The weight of the patient was then checked on a weekly basis. Acute reactions like mucositis, xerostomia, pharyngitis, laryngitis, secondary infections, and skin reactions are watched on weekly basis. The grading of acute reaction was done as in RTOG-acute reaction morbidity criteria [16]. The patient was managed according to the toxicity profile. At the end of radiotherapy and subsequently on follow-up, acute and sub-acute reactions were noted.

Mean follow-up period, three months after radiotherapy, the chronic reactions like xerostomia, trismus, and dysphagia were noted. They were subsequently managed as per severity of reactions. Tumour response was noted clinically whenever feasible at the end of treatment and subsequently on follow-up based on WHO criteria [17]. On follow-up, the patient also undergoes CECT of head and neck, nasopharyngoscopy and direct laryngoscopy depending on site.

STATISTICAL ANALYSIS

The sample size has been estimated in consultation with a biostatistician and was calculated with 95% confidence interval and 5% marginal error. The sample size suggested was 30 [18].

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Standard Deviation) (Min-Max) and results on categorical measurements are presented in number (%). Significance was assessed at 5% level of significance. The following assumptions on data were made, assumptions: Dependent variables should be normally distributed. Cases of the samples should be independent.

Student's t-test (two tailed, dependent) has been used to find the significance of study: Parameters on continuous scale within each group.

p-value <0.05 was considered statistically significant.

+ Suggestive significance (p-value: 0.05 <p<0.10)

* Moderately significant (p-value: 0.01 <p≤0.05)

** Highly significant (p-value: p≤0.001).

The Statistical software namely SAS 9.2, Statistical Package for the Social Sciences (SPSS) 22.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.11.1 were used for the analysis of the data and MS Word and Excel have been used to generate graphs, tables etc.

RESULTS

A total of 30 patients with locally advanced head and neck cancer were recruited and analysed prospectively either by 3DCRT or IMRT technique from January 2013 to December 2013. Fifteen patients with SIB-IMRT with concomitant cisplatin chemotherapy served as cases. Fifteen patients with 3DCRT and concomitant cisplatin chemotherapy served as controls. Median age of the patients was 53 years [Table/Fig-5]. Twenty nine patients were males and only one patient was female. A total of 26 patients (87%) gave history of using tobacco and or alcohol. Oropharynx was the most affected primary site [Table/Fig-6]. Twenty three patients had clinically stage IV carcinoma [Table/Fig-7].

Age range (years)	No. of patients	%
18-49	10	33
50-59	12	40
60-78	8	27

[Table/Fig-5]: Age distribution.

Site	No. of patients	%
Oral cavity	4	13
Oropharynx	14	47
Hypopharynx	10	33
Nasopharynx	2	7

[Table/Fig-6]: Primary site distribution.

T-stage	No. of patients	%	N-stage	No. of patients	%	TNM stage	No. of patients	%
T2	2	7	N0	4	13	II	1	3
T3	11	37	N1	6	20	III	6	20
T4	17	56	N2	20	67	IV	23	77

[Table/Fig-7]: Showing TNM stage distribution.

Mean dose received by ipsilateral parotid gland was more in 3DCRT (51.84 Gy) patients in comparison to IMRT (33.27 Gy) patients. Mean dose received by contralateral parotid gland was more in 3DCRT (47.31 Gy) patients in comparison to IMRT (19.48 Gy) patients. Mean dose received by submandibular glands (ipsilateral submandibular gland mean dose in 3DCRT – 69.63 Gy, contralateral submandibular gland mean dose in 3DCRT – 67.63 Gy) in patients treated with 3DCRT was more then 60 Gy when compared to IMRT (Mean dose to ipsilateral submandibular gland was 48.06 Gy, mean dose to contralateral submandibular gland was 44.06 Gy).

All the patients in 3DCRT group developed various grades of mucositis at 3rd, 6th and 7th week follow-up compared to lesser number of affected patients in IMRT group [Table/Fig-8].

The severity of dysphagia in patients of both groups at 3rd, 6th and 7th week follow-up is tabulated in [Table/Fig-9].

Duration	Technique	Grade 1	%	Grade 2	%	Grade 3	%	p-value
Week 3	IMRT	4	27	11	73	0	0	0.032
	3DCRT	0	0	15	100	0	0	
Week 6	IMRT	1	6	10	67	4	27	<0.0001
	3DCRT	0	0	0	0	15	100	
Week 7	IMRT	0	0	11	73	4	27	<0.0001
	3DCRT	0	0	0	0	15	100	

[Table/Fig-8]: Mucositis analysis (at week 3, 6 and 7).
Chi-square test is used for calculation of p-value

Duration	Technique	Grade 1	%	Grade 2	%	Grade 3	%	p-value
Week 3	IMRT	1	7	14	93	0	0	0.142
	3DCRT	4	27	11	73	0	0	
Week 6	IMRT	0	0	10	67	5	33	0.525
	3DCRT	0	0	8	53	7	47	
Week 7	IMRT	0	0	8	53	7	47	0.136
	3DCRT	0	0	4	27	11	73	

[Table/Fig-9]: Dysphagia analysis (at week 3, 6 and 7).
Chi-square test is used for calculation of p-value

During radiotherapy 65% patients had grade 3 xerostomia in 3DCRT group when compared to 35% patients with grade 3 xerostomia in IMRT group. One month post radiation therapy 2 (13%) patients had grade 3 xerostomia in 3DCRT group when compared to no patients with grade 3 xerostomia in IMRT group. Three months after completion of radiation therapy 67% patients had grade 3 xerostomia in 3DCRT group when compared to no patients with grade 3 xerostomia in IMRT group [Table/Fig-10].

Duration	Technique	Grade 0	%	Grade 1	%	Grade 2	%	Grade 3	%	p-value
7 weeks	IMRT	0	0	0	0	11	73	4	27	0.258
	3DCRT	0	0	0	0	8	53	7	47	
1 month	IMRT	0	0	10	67	5	33	0	0	0.189
	3DCRT	0	0	6	40	7	47	2	13	
3 months	IMRT	0	0	11	73	4	27	0	0	<0.0001
	3DCRT	0	0	0	0	5	33	10	67	

[Table/Fig-10]: Xerostomia analysis at 7th week, 1 month and 3 months of RT.
Chi-square test is used for calculation of p-value

On assessing the tumour response [Table/Fig-11], at three months postradiotherapy, complete response was seen in 13 patients and partial response in two patients in 3DCRT group in comparison to complete response in all 15 patients in IMRT group. On subsequent follow-up, tumour recurrence was seen in two patients in 3DCRT group in comparison to one patient in IMRT group.

Duration	Technique	CR*	%	PR±	%	PD‡	%	p-value
7 Weeks	IMRT	6	40	9	60	0	0	0.741
	3DCRT	4	27	11	73	0	0	
1 Month	IMRT	12	80	3	20	0	0	0.490
	3DCRT	9	60	6	40	0	0	
3 Months	IMRT	15	100	0	0	0	0	0.893
	3DCRT	13	87	2	13	0	0	

[Table/Fig-11]: Tumour response.
Chi-square test is used for calculation of p-value; *: Complete response; ±: Partial response; ‡Persistent disease

DISCUSSION

In present study, mean dose received by ipsilateral and contralateral parotid gland was more in 3DCRT patients when compared to IMRT. Mean dose to submandibular gland was more in 3DCRT group when compared to IMRT. Patients who were treated with 3DCRT had significantly more grade 3 acute toxicities such as mucositis, dysphagia and xerostomia in comparison to patients who were treated with IMRT for head and neck cancer.

Present study results were similar to the trial conducted by Gupta T et al., [19]. In the randomised trial comparison was done between 3DCRT and IMRT in 60 patients, grade 1 and grade 2 mucositis were similar between both the groups but incidence of grade 3 mucositis was reduced by IMRT. In this trial, four of 28 patients (14.5%) in 3DCRT compared with two of 32 patients (6%) in IMRT developed grade 3 mucositis. In the present study, 100% patients vs 27% developed grade 3 mucositis in the 3DCRT and IMRT group, respectively [19].

Present results are similar to the trial done by Kucha N et al., [5], which was prospective, non randomised, comparative observational study, comparison done between 3DCRT and IMRT in 78 patients, 38.4% patients versus 20.51% developed grade 3 mucositis in the 3DCRT and IMRT group respectively ($p \leq 0.001$).

Our results are comparable with results of a non randomised, retrospective study, performed on prospectively collected data by Vergeer MR et al., [20] between IMRT (91 patients) and 3DCRT (150 patients). The authors found a significant difference in acute mucositis in favour of IMRT in weeks 3, 4, 5 and 12 after treatment (p-value ranging from 0.006 to 0.016).

Present results was comparable with the results of a retrospective study done by Ghosh G et al., in which 80 patients toxicity profile of IMRT with 3DCRT was studied [21]. They found grade 3 mucositis in 34 of 40 (85%) patients vs 23 of 40 (57.5%) patients in 3DCRT and IMRT arm respectively.

Parotid gland sparing by IMRT technique helps in reducing incidence of xerostomia. In present study. At week 7 of the treatment, 47% patients in 3DCRT group vs 27% in IMRT group had grade 3 xerostomia. At three months after completion of radiotherapy 67% patients had grade 3 xerostomia in 3DCRT group in comparison to no patients developing grade 3 xerostomia in IMRT group ($p<0.0001$). These results were similar to trial by Gupta T et al., where the authors concluded that the proportion of patients with grade 2 or worse acute xerostomia was significantly smaller after IMRT (19 of 32 patients, 59%) compared with 3DCRT (25 of 28 patients, 89%) (p=0.009) [19]. Kucha N et al., evaluated the incidence of xerostomia in 3DCRT and IMRT groups and they found that at 7th week of the treatment 87.1% patients versus 61.53% patients developed grade 2 xerostomia in 3DCRT and IMRT group, respectively [5]. At three months postradiotherapy, 7.6% patients in 3DCRT group vs no patient in IMRT group had grade 3 xerostomia (p=0.006) [5]. Ghosh-Laskar S et al., also evaluated the incidence of grade 2 or worse acute xerostomia eight weeks after parotid-sparing radiotherapy and they found significantly lower proportion of patients with grade 2 or worse xerostomia after IMRT than after 3DCRT (24% vs. 53%; p=0.024) [22].

Present study did not show any benefit for tumour response due to IMRT. Spiotto MT and Weichselbaum RR compared 3DCRT patients with IMRT+SIB, they found similar local control (p=0.51), regional control (p=0.26) [23]. Similarly, compared to IMRT sequential, patients treated with IMRT+SIB had similar local control (p=0.59) and regional control (p=0.10). A 3DCRT, IMRT sequential and IMRT+SIB has similar rates of 2-year local control (p=0.78), 2-year regional control (p=0.24). Vlacich G et al., evaluated the local, regional or distant recurrence and they found no difference between both the groups [24].

Limitation(s)

The present study was a single centre study. Larger multicentre studies are required.

CONCLUSION(S)

The IMRT definitely has a role in protecting salivary glands in head and neck cancer patients undergoing radiotherapy. It also has a significant role in reducing the incidence of severity of acute and chronic xerostomia in patients undergoing radiotherapy in addition to decreased incidence of mucositis. Though, IMRT did reduce incidence of severity of dysphagia slightly it was not very effective in preventing dysphagia altogether. The IMRT was generally well tolerated and offered a safe and effective means of salivary gland sparing in head and neck cancer patients.

The IMRT protects normal tissue from acute and late radiation damage without protecting the tumour. The increasing body of preclinical and clinical data justifies the use of IMRT in order to provide improved therapeutic efficacy. The IMRT has shown reduction in incidence and severity of acute toxicities for patients both during and after radiation therapy. Hence, authors recommend the usage of IMRT in head and neck cancer patients.

REFERENCES

[1] Dandekar M, Tuljapurkar V, Dhar H, Panwar A, DCruz AK. Head and neck cancers in India. J Surg Oncol. 2017;115(5):555-63.
[2] Tuljapurkar V, Dhar H, Mishra A, Chakraborti S, Chaturvedi P, Pai PS. The Indian scenario of head and neck oncology- Challenging the dogmas. South Asian J Cancer. 2016;5(3):105-10.
[3] Seiwert TY, Cohen EEW. State-of-the-art management of locally advanced head and neck cancer. Br J Cancer. 2005;92(8):1341-48.
[4] Sroussi HY, Epstein JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, et al. Common oral complications of head and neck cancer radiation therapy: Mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med. 2017;6(12):2918-31.
[5] Kucha N, Soni TP, Jakhotia N, Patni N, Singh DK, Gupta AK, et al. A prospective, comparative analysis of acute toxicity profile between three-Dimensional Conformal Radiotherapy (3DCRT) and Intensity-Modulated Radiotherapy (IMRT) in locally advanced head and neck cancer patients. Cancer Treatment and Research Communications. 2020;25:100223.
[6] Teh BS, Woo SY, Butler EB. Intensity Modulated Radiation Therapy (IMRT): A new promising technology in radiation oncology. The Oncologist. 1999;4(6):433-42.
[7] van der Veen J, Nuyts S. Can intensity-modulated-radiotherapy reduce toxicity in head and neck squamous cell carcinoma? Cancers (Basel). 2017;9(10):135.
[8] Tubiana A, Eschwege F. Conformal radiotherapy and intensity- modulated Radiotherapy: Clinical data. Acta Oncol. (Madr). 2000;39(5):555-67.
[9] Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) score for cancer patients by oncology healthcare professionals. Case Rep Oncol. 2019;12:728-36.
[10] Monti AF, Ostinelli A, Frigerio M, Cosentino D, Bossi A, Cazzaniga LF, et al. An ICRU 50 radiotherapy treatment chart. Radiother Oncol. 1995;35(2):145-50.
[11] Landberg T, Chavaudra J, Dobbs J, Gerard JP, Hanks G, Horiot JC, et al. ICRU report 62, prescribing, recording and reporting photon beam therapy (Supplement to ICRU Report 50). J ICRU. 1999;32(1):1-52.
[12] Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTVP) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol. 2018;126:3-24.
[13] Grégoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, et al., CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. Radiother Oncol. 2003;69(3):227-36.

[14] Marks LB, Yorke ED, Jackson A, Haken RKT, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiation Oncology Biol Phys. 2010;76(S3):S10-19.
[15] Ezzell GA, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, et al. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM radiation therapy committee. Med. Phys. 2003;30(8):2089-115.
[16] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-46.
[17] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47:207-14.
[18] Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks/Cole; 2011.
[19] Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, et al. Three-dimensional Conformal Radiotherapy (3D-CRT) versus Intensity Modulated Radiation Therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomised controlled trial. Radiother Oncol. 2012;104(3):343-48.
[20] Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: Results of a nonrandomised prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys. 2009;74(1):01-08.
[21] Ghosh G, Tallari R, Malviya A. Toxicity profile of IMRT vs 3D-CRT in head and neck cancer: A retrospective study. J Clin Diag Res. 2016;10(9):XC01-03.
[22] Ghosh-Laskar S, Yathiraj PH, Dutta D, Rangarajan V, Purandare N, Gupta T, et al. Prospective randomised controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: Long-term results. Head Neck. 2016;38(S1):E1481-87.
[23] Spiotto MT, Weichselbaum RR. Comparison of 3D conformal radiotherapy and intensity modulated radiotherapy with or without simultaneous integrated boost during concurrent chemoradiation for locally advanced head and neck cancers. PLOS ONE. 2014;9(4):e94456.
[24] Vlacich G, Stavas MJ, Pendyala P, Chen SC, Shyr Y, Cmelak AJ. A comparative analysis between sequential boost and integrated boost intensity modulated radiation therapy with concomitant chemotherapy for locally advanced head and neck cancer. Radiation Oncology. 2017;12:13.

PARTICULARS OF CONTRIBUTORS:
1. Consultant, Department of Radiation Oncology, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India.
2. Professor, Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India.
3. Assistant Professor, Department of Radiation Oncology, VTSM Peripheral Cancer Centre, Kidwai, Kalaburagi, Karnataka, India.
4. Professor/Head, Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. B Naveen,
S/O B Jayaram, H. No. 5, Radha Krishna Nilay Banashankari Colony, Near Luqman Pharmacy College, Old Jewargi Road, Kalaburagi-585102, Karnataka, India.
E-mail: naveenbellutagi@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 07, 2021
- Manual Googling: Oct 25, 2021
- iThenticate Software: Nov 26, 2021 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Aug 06, 2021**
Date of Peer Review: **Aug 31, 2021**
Date of Acceptance: **Nov 06, 2021**
Date of Publishing: **Dec 01, 2021**