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ORIGINAL RESEARCH ARTICLE

3-Dimensional Conformal versus Intensity Modulated Radiotherapy in Head and Neck Squamous Cell Carcinoma: Comparative Analysis of Compliance, Toxicities and Dosimetric Parameters

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ABSTRACT

Introduction: Advance radiotherapy conformal techniques have an advantage over conventional radiotherapy in delivering the dose more accurately to the target volume while limiting the doses to organs at risk. 3-dimensional conformal radiotherapy leads to sparing the surrounding normal tissue better than 2-dimensional radiotherapy, but it still causes significant volumes of normal tissue irradiation because RT is delivered in three dimensions with a uniform dose in each field. Intensity modulated radiotherapy is a refinement of 3-dimensional conformal radiotherapy, which modulates the radiation beams so that a high dose can be delivered to the tumor target while the dose to normal tissues can be reduced. The dose-modulating ability of IMRT gives a theoretical advantage over 3D-CRT, but it also has a drawback of delivering a higher dose outside the planning target volume (PTV) due to more number of fields used. The present study aims to analyze and compare dosimetric parameters, compliance, and toxicities of these two techniques.

Materials and methods: About 50 patients of head neck cancers presented in our department were treated with definitive concurrent chemoradiation after randomizing into two groups of twenty-five each- Group I (3DCRT) and Group II (IMRT). Inclusion Criteria**-** Histologically proven squamous cell carcinoma; age >18 years; Karnofsky performance status >70; normal hemogram, renal function test, liver function test and 2D ECHO. Exclusion Criteria **-** prior or synchronous malignancy or previous history of head and neck surgery; distant metastasis; previously treated patients with radiotherapy. Radiotherapy dose of 70 Gy in 35 fractions over 7 weeks, along with weekly cisplatin 35 mg/m^2, was given. Treatment compliance (overall treatment time and number of weekly chemotherapy cycles), toxicities (hematological and radiotherapy-induced), clinical response assessment and dosimetric parameters of PTV and organ at risk were compared. Statistical analysis was done using an unpaired t-test to compare the mean of two independent groups and a chi-square test for compliance and toxicities.

Results: The mean and median age in Group I is 57.2 years (35–77 years) and 60 years and in Group II is 62.08 years (42–76 years) and 63 years. The male-to-female ratio in groups I and II is 11.5 and 5.25, respectively. The majority of the cases were locoregionally advanced, 76% in Group I and 84% in Group II. There was no statistically significant difference in overall treatment time above 51 days in both groups (40 *vs* 24%) and patients receiving 5 to 7 cycles of chemotherapy (54 *vs* 46%). Similarly, there was no statistically significant difference in hematological and radiotherapy-induced toxicities. Complete response seen in both groups (80 *vs* 72%, $p = 0.51$). The PTV parameters were achieved in both groups, but were statistically better in IMRT. Dose constraints for OARs were achieved in most organs, though they were statistically better in IMRT.

Conclusion: Both techniques, 3-DCRT and IMRT, did not have any statistical difference in treatment compliance and toxicities. Dosimetric parameters were achievable, though they were better in IMRT. Different forward planning techniques may improve and make 3DCRT plans comparable to IMRT.

Keywords: Head and neck carcinoma, 3-dimensional radiotherapy, Intensity modulated radiotherapy.

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INTRODUCTION

Radiotherapy techniques have evolved from two-dimensional to three-dimensional to intensity modulated radiotherapy in the past few decades. Initially development of radiotherapy started from conventional radiotherapy techniques based on bony landmarks using two-dimensional data. Later, with the advent of three-dimensional imaging techniques, conformal techniques developed. Conformal techniques have an advantage over conventional techniques as they deliver the dose more accurately to the target volume while sparing normal tissues and organs at risk (OAR).

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It resulted in improved radiotherapy planning techniques such as 3-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT). In 3DCRT, the radiation beams are formed to fit to size and shape of the tumor better, using a multileaf collimator (MLC). This leads to sparing the surrounding normal tissue better than 2DRT, but it still causes significant volumes of normal tissue irradiation because RT is delivered in three dimensions with a uniform dose in each field. Manual optimization of beam orientation, beam weighting, and beam eye view (BEV) shaping can be done in 3DCRT. The problem of dose inhomogeneity and suboptimal conformity to the concave target volume is still unresolved.

IMRT is a refinement of three-dimensional conformal radiotherapy (3DCRT). It modulates the radiation beams so that a high dose can be delivered to the tumor target while the dose to normal tissues can be reduced. IMRT provides a degree of freedom by allowing dose intensity modulation within each beam. IMRT creates dose distributions shaped to concave nodal volumes satisfying the ICRU criteria.

3D-CRT and IMRT are technological advancements over conventional radiotherapy because they increase dose delivery accuracy while sparing surrounding normal tissues and organs at risk (OAR). The dose-modulating ability of IMRT gives a theoretical advantage over 3D-CRT.[1,2] IMRT demonstrates better dose conformity in tumors with complex anatomy that are near vital structures, but it also has a drawback of delivering a higher dose outside the planning target volume (PTV) due to more number of fields used. So. IMRT requires more complex quality assurance procedures.[3]

The present study aims to analyze and compare dosimetric parameters, compliance and toxicities of these two techniques- 3D CRT and IMRT in the treatment of head and neck squamous cell carcinoma patients.

MATERIALS AND METHODS

Fifty patients of head and neck cancers presented in the Department of Radiation Oncology in our institute and treated with definitive concurrent chemoradiation were randomized into two groups of twenty-five each- Group I (3DCRT) and Group II (IMRT)

Inclusion Criteria

Histologically proven locally advanced head and neck squamous cell carcinoma; age >18 years; Karnofsky performance status >70; normal hemogram, renal function test, liver function test and 2D ECHO

Exclusion Criteria

Patients with prior or synchronous malignancy or previous history of head and neck surgery; distant metastasis; previously treated patients with radiotherapy.

All patients were treated with concurrent chemoradiation with a standard radiotherapy dose of 70 Gy in 35 fractions over 7 weeks, along with weekly concurrent chemotherapy, cisplatin 35 mg/m^2.

Radiotherapy Planning and Technique

Immobilization

The patients who were planned for radiotherapy were immobilized using a fixed 5-point thermoplastic cast system.

Simulation

All patients underwent a contrast-enhanced CT (CECT) scan, radiotherapy planning (RTP).

- Contrast-enhanced CT Neck was performed with a flat table insert.
- CT images of the simulation were acquired with the patient in the supine and treatment position, along with fiducial markers.
- The axial images were obtained with a 3 mm slice thickness.
- These images were transferred through Digital Imaging and Communications in Medicine (DICOM-CT) into the Eclipse treatment planning system (Version 8.6.17, Varian Medical System, Inc., Palo Alto, CA, US).

Delineation of structures

A gross tumor volume (GTV), including the gross tumor and positive regional lymph nodes, was contoured. The clinical target volume (CTV) was defined as per RTOG Guidelines. The OARs were also contoured. A margin of 7 mm was taken for PTV. All the patients were planned for either 3DCRT or IMRT techniques. The total prescription dose was 70 Gy in 35 Fractions to the target mean.

Dosimetric Parameters

All plans were aimed to achieve a minimum dose of >95% and a maximum dose of <107% of the prescribed dose.

Patients were randomized into two groups (25 each) based on radiotherapy technique:

- *Group I*

Received radiotherapy by the 5 field 3DCRT technique.

- *Group II*

Received radiotherapy by the IMRT technique.

5 Field 3D CRT Technique

- Five fields were created for five different gantry angles.
- Plans were normalised for PTV.
- The completed plan was evaluated by isodose coverage and DVH. If the coverage of PTV and tolerance to OAR were not achieved, the beam angles and weightage were adjusted to achieve the goal.
- IMRT Technique
- Coplanar 7–9 fields around the isocenter using isotropic gantry angles were used.
- In the next step of fluence optimization, the parameters of PTV and OARs were defined (Table A).
- Plans were evaluated by DVH and Isodose distributions.
- All plans were aimed to achieve a minimum dose >95% and a maximum dose <107% of the prescribed dose.

Chemotherapy Administration

- Patients received Inj. cisplatin 35 mg/m^2 weekly
- Patients were adequately hydrated with 2 to 2.5 litres of IV fluids and supplemented with Inj.KCL, Inj. $MgSo_4$.
- Radiotherapy was delivered within 1-hour of the administration of cisplatin.
- Proper antiemetic therapy with 5-HT_3 antagonist, dexamethasone, and ranitidine was given prior to chemotherapy administration.

Patient Compliance

Compliance was calculated based on two parameters. Overall treatment time taken from the starting date of radiation to the completion of radiotherapy is normally taken as 49 to 51 days, depending on the weekday on which radiotherapy was started. The number of chemotherapy cycles is supposed to be received by the patient during the treatment (Normal: 5–7 cycles).

Assessment of Toxicity

- Radiation toxicity (skin, mucosal, salivary gland) was assessed by the Radiation Therapy Oncology Group (RTOG) acute and late morbidity scoring criteria.
- Acute RTOG morbidity criteria were applied from the day of commencement of radiotherapy till 90 days. Patients were assessed weekly during chemoradiation for assessment of acute radiation reactions.
- Late radiation reactions were assessed using RTOG late morbidity criteria that were applicable from 90 days onwards.
- Hemogram (Hb, TLC, DLC, Platelet) and kidney function and liver function were repeated in all patients before each cycle. These toxicities were graded according to the common toxicity criteria. During treatment, assessment was done on a weekly basis and thereafter monthly basis by Common Terminology Criteria for Adverse Effects (CTCAE) (v4.03).

Clinical Response Assessment

The patients were assessed for objective tumor response according to the WHO criteria:

Complete response (CR)

Total tumor regression for at least 4 weeks; Partial response (PR): 50% or more reduction in product of two major perpendiculars of the measurable tumor for at least 4 weeks; Stable disease (SD): Less than 50% or more reduction to less than 25% increase in cross product; Progressive disease (PD): Growth of measurable tumour by 25% or more or appearance of new lesion.

Dosimetric Assessment

Dosimetric parameters assessed in PTV (95–107%) were V95%, D95 (Gy), Dmax, Dmean, homogeneity index (HI), conformity index (CI), and integral doses (ID) received in both groups.

Dosimetric assessment of OARs was done by following Table 1.

The formula for calculating conformity and homogeneity indices was according to ICRU 83:

CI = Treated volume (TV)/Planning target volume (PTV), where TV is Treated volume, i.e., volume receiving 95% prescribed dose and PTV is planning target volume.

HI = [D2(Gy) -D98(Gy)] / D50 (Gy), where D2 is dose received by 2% PTV, D98 is dose delivered to 98% PTV and D50 is dose delivered to 98% PTV.

ID of whole body (Gy.cc) = Dmean Body (Gy) x Volume of whole Body (cc), where ID is integral dose of body, calculated by multiplying Dmean of body in Gy and volume of body in cc.

Follow Up

The patients were followed up at least for a period of 6 months from the day of completion of treatment.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS). An unpaired t-test was used to compare the mean of two independent groups. Chi-square test was used for statistical analysis of compliance and toxicities. *p-value* <0.05 was considered statistically significant.

Table 1: Dose constraints of OARs

Organ	*Whole organ*	*Dose constraints*	*Criteria*
PRV Spine	Partial organ	Dmax≤ 50	QUANTEC
Mandible	Whole organ	Point Dose<70	Emami 2013
		1cc<75	RTOG
Brainstem	Whole organ	Dmax<54	QUANTEC
		D1-10 cc ≤ 59	QUANTEC
		Dmax<64 (Pointdose<1cc)	QUANTEC
Parotid gland (right &left)	Unilateral whole gland	Mean dose <20	QUANTEC
	Bilateral Whole gland	Mean dose <25	QUANTEC
	Bilateral Whole gland	Mean dose <26	QUANTEC
Cochlea (right &left)	Whole organ	Mean dose ≤45	QUANTEC
Lips		Dmean<30	RTOG
Optic nerve (right &left)/optic chiasma	Whole organ	Dmax<55	RTOG
		52 Gy when the target is the oropharynx	QUANTEC

RESULTS

Fifty patients with head and neck cancer were randomized into two groups based upon radiotherapy technique: Group I treated by the 5 Field 3DCRT technique and Group II by the IMRT technique. Treatment was given in the form of Chemoradiotherapy:70 Gy in 35 Fractions, over 7 weeks, 2 Gy per fraction, along with concurrent weekly cisplatin (35 mg/m^2) in both groups.

Patient Characteristics

The mean and median age in Group I is 57.2 years (35–77 years) and 60 years, and in Group II is 62.08 years (42–76 years) and 63 years. Almost 3/4th cases in the study are above 50 years of age. The male-to-female ratio in groups I and II is 11.5 and 5.25, respectively. About 88% of cases are male in the present study.

Table 2 shows primary tumor site distribution in both groups.

Staging

Early T stage lesions (T1, T2) were 03(12%) and 06(24%) in Group I. In Group II, none of the patients was T1, while T2 cases were 08 (32%). Maximum lesions were T3 (more than 4 cm); 12 (48%) in each arm. 04 (16%) in Group I and 05 (20%) in Group II had moderately advanced local disease (T4a).

Eleven (44%) in Group I and 10 (40%) in Group II were Node negative. Node positive cases were 14 (56%) in Group I and 15 (60%) in Group II. N1, N2, and N3, respectively, as 16, 36, and 4% in Group I and 12, 40, 08% in Group II.

Table 3 shows the AJCC group staging of both groups. The majority of the cases were locoregionally advanced, 19 (76%) in Group I and 21 (84%) in Group II.

Compliance with treatment

Overall treatment time exceeded 51 days in 10 (40%) patients in Group I and 06 (24%) patients in Group II. Further, 27 (54%) patients received 5 to 7 cycles of concurrent chemotherapy, and in 23 (46%), fewer than 5 cycles were administered due to various reasons. No statistical difference was seen in compliance in both groups in terms of overall treatment time and number of chemotherapy cycles administered.

Hematological toxicities

Grade 3 Anemia (Hb<8 g/dl) was seen in 01 (04%) in each arm. Grade 3 Neutropenia (ANC 500–1000/mm^3) was seen in 01 (04%) in Group I and 05 (20%) in Group II. Grade 3 and 4 thrombocytopenia (25,000–50,000) was seen in 02 (08%) in Group I and 03 (12%) in Group II. No Grade 3 or 4 toxicity was seen in KFT and LFT. The difference was not statistically significant.

Radiation-induced toxicities

03 (12%) in Group I and 04(16%) in Group II had confluent Grade 3 or 4 mucositis. 02 (08%) in Group I and 01 (04%) in Group II had moist desquamation of irradiated skin. At 6 months post-treatment, 03 (12%) in Group I and 01 (04%) in Group II had complete dryness of the mouth, leading to frequent erosions and disturbed quality of life. Grade 1 and 2 radiation-induced dermatitis at 6 months was seen in 24 and 12%. The difference in acute and late toxicities was not statistically significant.

Response to treatment

Complete response in group I was seen in 20 (80%) patients and in group II, 18 (72%) patients; the difference was not statistically significant (p = 0.51).

Table 2: Primary tumor site wise distribution

SITE	Group I n (%)	Group II n (%)	*p-value*
Oral cavity	03 (12%)	04 (16%)	0.25
Oropharynx	15 (60%)	10 (40%)	
Hypopharynx	06 (24%)	06 (24%)	
Larynx	01 (04%)	05 (20%)	

Table 3: AJCC group staging (AJCC 8TH)

Stage	*Group I*	*Group II*	*p-value*
Stage I	0	0	0.21
Stage II	06 (24%)	04 (16%)	
Stage III	09 (36%)	05 (20%)	
Stage IV	10 (40%)	16 (64%)	

Table 4 shows the comparison of various dosimetric parameters of PTV and OARs in both groups.

DISCUSSION

Treatment planning for advanced head and neck cancer is a problem due to the complex shape of the target, which commonly has an irregular concave shape and the need to spare critical organs. The conformal radiotherapy techniques like 3D-CRT and IMRT have advantages over conventional techniques in terms of increased dose delivery accuracy while sparing normal tissues and OARs.

IMRT technique is better than 3D-CRT in delivery better doses, but is not without disadvantages, which include an increased chance of geographical miss, which is seldom seen in conventional technique, and an increase in treatment costs.

This study aimed to compare 3DCRT with IMRT in terms of compliance, toxicities and dosimetric parameters and to analyze their clinical correlation.

Compliance

Ferreira B.C *et al*.[4] conducted a study from 2007 to 2013 and included a total of 359 patients divided into two groups: either those into received RT as prescribed or interrupted or suspended RT. The cumulative incidence of locoregional control (LRC), disease-free survival (DFS) and overall survival was determined. Major causes for treatment interruptions were toxicity (41.7%) and public holidays (30.1%). 10% interrupted treatment for 3–9 days. Significant differences in LRC (19%) were found in patients with N2–3 tumours. Treatment breaks larger than two days had around a fourfold increase risk of poorer LRC and DFS. They suggested in their study that treating patients on public holidays would be an effective measure to minimize RT breaks. For HNC, patient compliance is mostly limited by RT side effects. They concluded that major causes for treatment interruptions in head and neck cancer patients were treatment-related toxicities (41.7%) and public holidays (30.1%).

In our study, compliance was measured in terms of overall treatment time (OTT), which was 46 to 56 days in Group I and 49 to 57 days in Group II. Mean OTT in

Table 4: Comparison of dosimetric parameters

	Dosimetric Parameter	*Group I*	*Group II*	*p-value*
PTV	V95(%)	90.66 ± 4.28	98.97 ± 0.9	<0.001
	D95(Gy)	64.2 ± 2.66	68.37 ± 0.69	<0.001
	Dmax	77.16 ± 1.0	73.94 ± 1.04	<0.001
	Dmean	70.66 ± 0.89	70.15 ± 0.61	0.024
	Homogenity index	0.23 ± 0.07	0.064 ± 0.018	<0.001
	Conformity index	1.41 ± 0.32	1.122 ± 0.096	<0.001
OAR's Dmax	PRV spine	43.44 ± 3.54	37.51 ± 3.67	<0.001
	Mandible Dmax	73.69 ± 4.52	71.38 ± 2.49	0.03
	MANDIBLE 1cc	71.34 ± 6.24	69.56 ± 3.65	0.224
	Brainstem	38.01 ± 11.27	37.66 ± 12.92	0.92
	Optic chaisma	2.14 ± 0.89	3.02 ± 3	0.16
	Optic nerve right	2.04 ± 0.88	3.22 ± 3.4	0.1
	Optic nerve left	2.18 ± 1.21	4.58 ± 8.82	0.18
OAR's Dmean	Parotid right	58.19 ± 9.25	35.52 ± 7.3	<0.001
	Parotid left	53.85 ± 9.71	36.01 ± 10.76	<0.001
	Combined parotid	55.79 ± 9.19	35.03 ± 6.31	<0.001
	Cochlea right	20.99 ± 18.25	10.26 ± 11.21	0.016
	Cochlea left	17.14 ± 13.48	9.62 ± 12.29	0.045
	Lips	14.34 ± 12.35	22.88 ± 13.13	0.026
Whole Body	Integral dose (Gy.cc)	162.35 ± 27.69	163.79 ± 43.69	0.89

group I vs Group II (51.56 vs 51.12) days. 10 (40%) patients in group I had treatment exceeding 51 days, in which 4(16%) had a treatment break due to gazetted holidays and 6 (24%) patients due to treatment-associated toxicities. In group II, 6 (24%) had treatment beyond 51 days. In 04 (16%) patients, due to gazetted holidays and in 02 (08%) due to treatment-associated toxicities. Hence, the major causes of treatment interruptions were the same as in the study by Ferreria BC *et al.*[4], with the number of days when treatment was interrupted also being the same (3–9 days).

Toxicity Profile

Analysis of Clinical toxicity during radiotherapy

The study by Santa Cruz O *et al* [5] showed that the overall incidence of acute grade ≥3 toxicities was mucositis 32%, pain 11%, xerostomia 7%, dysphagia 53%, radiodermatitis 44%, and osteonecrosis 1%. Late grade ≥3 toxicities were fibrosis 6%, dysphagia 21%, fistula 1%, and skin necrosis 1%.

Our study also showed similar rates of acute toxicity; the overall incidence of acute grade ≥3 toxicities was mucositis 28 %, radiodermatitis 12%. Late grade ≥3 toxicities were xerostomia in 16 %.

Acute grade ≥3 mucositis was higher (8% in 3DCRT and 16% in IMRT) as patients were not regular with the oral hygiene regimen and gargling as advised. Grade ≥3 radiodermatitis was seen in only 1 patient in IMRT and no patient in 3DCRT. In late toxicities, grade ≥3 dysphagia was present in 12% patients in 3DCRT vs 8% in IMRT at 6 months follow-up.

Gupta T *et al.*[6] in a systematic review and meta-analysis showed that the use of IMRT was associated with a 36% relative showed that k reduction in grade 2 acute xerostomia (RR = 0.64, 95%CI = 0.49–0.84; $p = 0.001$) compared to 2D/3D-RT. IMRT also significantly reduced the risk of grade 2 late xerostomia (RR = 0.44, 95%CI = 0.34–0.57; $p = 0.00001$) compared to non-IMRT techniques.

Our study also shows that IMRT was associated with 12 % reduced relative risk in grade 2 radiodermatitis ($p = 0.43$), mucositis ($p = 0.42$) and 4% reduced xerostomia ($p = 0.31$) in acute settings, but the *p-values* were not significant where whereas the risk of grade 2 late xerostomia was 4% more in IMRT compared to 3D CRT.

The benefit of IMRT is with regard to acute toxicities. The assessment was done by RTOG criteria, which is observer-based and perhaps a larger sample of patients may give significant results.

Another randomized control trial done by Gupta T *et al.*[7] showed that the proportion [95% confidence intervals (CI)] of patients with RTOG grade 2 or worse acute salivary gland toxicity was significantly lesser in the IMRT arm [19 of 32 patients (59, 95% CI: 42–75%)] as compared to 3D-CRT [25 of 28 patients (89, 95% CI: 72–97%; $p = 0.009$)]. Late xerostomia and subcutaneous fibrosis were also significantly lower with IMRT. There was significant recovery of salivary function over time in patients treated with IMRT (*p-value* for trend = 0.0036). At 3 years, there were no significant differences in locoregional control or survival between the two arms.

In this study, RTOG grade 2 or worse acute salivary gland toxicity was less in the IMRT arm [03 of 25 patients (12, 95%) as compared to 3D-CRT [04 of 25 patients (16%, $p = 0.31$]. Xerostomia at 6 months post-treatment was present in 1 of 25 patients (4%) in the IMRT group and in no patient in the 3DCRT. Complete response at 6 months was seen in 20 of 25 patients (95%) in 3DCRT and 18 of 25 patients (72%) in IMRT, hence no significant difference was seen in treatment response at 6 months in both groups ($p = 0.049$).

In a retrospective study done by Ghosh G.[8] the 3D-CRT group demonstrated significantly more acute toxic effects compared with the IMRT. Acute Grade 3 or greater toxic effects to the skin occurred in 5 of 40 (12.5%) patients in the 3D-CRT group compared with 3 of 40 (7.5%) patients in the IMRT group. Acute Grade 3 or greater toxic effects to the mucous membranes occurred in 23 of 40 (57.5%) patients in the 3D-CRT group and only 16 of 40 (40%) patients in the IMRT group. Statistically significant dysphagia developed in 34 of 40 (85%) patients in the 3D-CRT group, compared with 23 of 40 (57.5%) patients in the IMRT group, while statistically significant xerostomia developed in 29 of 40 patients in the 3D-CRT group (72.5%), compared with 18 of 40 (45%) patients in the IMRT group.

Whereas in our study, RTOG acute grade ≥3 toxicities to the skin occurred in none of 25 patients in the 3D-CRT group compared with 1 of 25 (4%) patients in the IMRT group. Acute Grade 3 or greater toxic effects to the mucous membranes occurred in 3 of 25 (12%) patients in the 3D-CRT group and only 4 of 25 (16%) patients in the IMRT group. Acute xerostomia developed in 1 of 25 (4 %) in both groups.

In a study by Spiotto MT *et al.*[9] patients treated with IMRT+SIB had lower rates acute toxicity according to Grade 3 or greater mucositis (3D-CRT: 44.0% vs. IMRTseq: 36.7% vs. IMRT+SIB: 22.4%; p .0001), dermatitis (3D-CRT: 44.0% vs. IMRTseq: 20.0% vs. IMRT+SIB: 7.5%; p .0001) and feeding tube placement during radiotherapy (3D-CRT: 80.0% vs. IMRTseq: 50.8% vs. IMRT+SIB: 44.0%; p .0001) as well as late toxicity as measured by feeding tube use (p -0.0001) and tracheostomy use (p -0.0001). On multivariate analysis, IMRT+SIB predicted less mucositis, dermatitis and feeding tube use compared to 3DCRT and less dermatitis compared to IMRT seq. Compared to 3D-CRT and IMRTseq, IMRT+SIB provided similar

outcomes and potentially less toxicity, indicating it is a feasible technique for chemoradiation in locally advanced head and neck cancer.

The findings of our study are contrary to the study by Spiotto *et al*[9] as there was no significant difference in the number of patients having grade 3 or more mucositis in both groups. In our study, acute toxicity according to Grade 3 or greater mucositis (3D-CRT: 12% vs. IMRT: 16%; $p = 0.43$), dermatitis (3D-CRT: 0% vs. IMRT: 4, $p = 0.42$)

Analysis of hematological toxicity

A study by Kruser TJ *et al*.[10] showed that acute mucositis grades did not significantly differ between 3DCRT, IMRT, and tomotherapy patients. Through six weeks of chemo radiotherapy, the median decline in hemoglobin was 15.6%, the median decline in platelets was 30.6%, and the median decline in leukocytes was 51.5%, but these drops were not significantly different between treatment cohorts. Chemotherapy was discontinued or held secondary to hematologic toxicity in 12% of 3D-CRT patients, 5% of IMRT patients and 15% of tomotherapy patients ($p = 0.14$).

In our study, through five weeks of chemo radiotherapy, the decline in hemoglobin was 12% in 3DCRT and 8% in IMRT, the decline in platelets was 16% in IMRT, no decline in platelets was in 3DCRT and the decline in leukocytes was 8% in 3DCRT and 24% in IMRT, but these drops were not significantly different between treatment cohorts (CTCAE v4.03). This is in concordance with the findings of the study of Kruser TJ *et al*.[10]

This decline in haemoglobin and platelets was seen in patients whose age was more than 60 years and concurrent chemotherapy was administered, which led to bone marrow suppression. The cause of decline in haemoglobin was also related that as the weeks progressed, mucositis increased, which led to decreased oral intake.

Dosimetric Parameters

Cozzi *et al* (2003)[11] compared dosimetric and technical parameters in 3DCRT vs IMRT. The study included twenty-six head-and-neck cancer patients who were irradiated with IMRT. Dose plans were evaluated in terms of physical quantities based on dose volume histograms (DVH) and isodose distributions. Each IMRT plan was also compared to a reference 3DCRT. IMRT target volumes coverage improved compared to 3DCRT, that is, V95 increased from 85% to 93% with $p < 0.001$, and V90 is 98 *vs* 93% with a statistical significance of $p < 0.001$. Dose received by 2/3rd volume(D2/3rd) of parotid gland reduced from 59 to 41 Gy significantly ($p < 0.001$) and for spinal cord, the maximum dose (Dmax) reduced from about 40 to 30 Gy significantly ($p < 0.001$). They concluded that comparison of dosimetric data at plan level between treated IMRT and reference 3DCRT dose showed benefit of IMRT in terms of both target coverage (minimum doses to target, V90, V95, or EUD and organs at risk (spinal cord and parotids) sparing; however, the data suggested further improvement in parotid sparing.

This finding was reciprocating in our study, where V95 was 90.66 ± 4.28 vs 98.97 ± 0.9 (in 3DCRT vs IMRT) ($p < 0.001$) showing better coverage in IMRT but improvement in coverage may be attained by increasing in number of subfields and manual iteration between the beam weights, The mean dose to the combined parotid is not achieved in the IMRT arm which is same in the above study. The parotids combined received (55 vs 35 Gy) in 3DCRT vs IMRT this shows that parotid dose constraint was not achieved in IMRT arm even though there is significance this can be explained by the fact that in locally advanced head and neck cancers the volumes of target would be large which may include major volume of parotids and patients who received single PTV 70 Gy in IMRT arm were 15 that is about 60%. Thus, the doses of parotid combined are high; this is the single most important reason for not achieving dose constraints even in the IMRT arm.

Lee N *et al*. (2004),[12] proposed a forward planning multisegment technique (FPMS) as an alternative treatment method for patients who are not suitable for inverse planned IMRT (IP-IMRT) head and neck region and situations where IMRT is not available. Patients were treated with 7 gantry angles, including an anterior, 2 lateral, 2 anterior oblique, and 2 posterior oblique beams with a 13 beam shapes in total formed by MLC, called MLC segments. The lower neck nodes and the supraclavicular nodes were treated with a split-beam anterior field, matched to the inferior border of the FPMS plan at the isocenter. The results of patients treated with FPMS are retrospectively compared to results for similar patients treated with IP-IMRT. With FPMS, the GTV was prescribed to 70 Gy (2.12 Gy/fraction), whereas the CTV received a dose of 59.4 Gy (1.8 Gy/fraction). GTV dosimetric parameters D99 (68.9 Gy vs 69.3 Gy), D95 (70.2 vs 71.2 Gy), V93 (0.2cc vs 0.1cc), CTV dosimetric parameters D99 (50.23Gy vs 54.3 Gy), D95 (58.9 vs 60.6), V93 (15cc vs 9cc) for FPMS vs IP-IMRT, respectively, suggesting no statistical significance.

In the present study, a total of 5 fields were used in 3DCRT, which was delivered in a phase manner in which 50 Gy was delivered in phase I and 20 Gy in phase II by using conventional opposing fields. When the dosimetric parameters are compared in our study, there is a statistically significant benefit for the IMRT arm in V95 (90,66 vs 98.97% $p < 0.001$). Whereas in Lee *et al*[14] study,

it is insignificant. This may be due to the fact difference in the number of fields they used 7 fields 13 segments. This mandates the fact that further studies are required, in which an increase in the number of sub-fields can be done, followed by manual iterations, which may result in comparable plans to IP-IMRT.

In Lee *et al.*[12] study, Dmax to the brainstem and spinal cord was below 54 vs 45 Gy and 45 *vs* 43 Gy, respectively, in which FPMS is comparable to IP-IMRT. Dmax to mandible 73.3 *vs* 71.6 Gy and the Mean dose to the parotid glands was 32 Gy with FPMS *vs*. 26 Gy with IP-IMRT, where there is no statistical significance.

In the present study, Dmax to PRV spinal cord is (43.4Gy *vs* 37.5Gy) in group I&II which is statistically significant (p <0.001). Dmax to brainstem is (38.01 *vs* 37.66) in group I&II, which is statistically insignificant (p = 0.92). Optic chiasma, Optic nerve (right and left), and lips received better dose in 3DCRT (Optic chiasma 2.14 Gy *vs* 3.02 Gy, p = 0.16, right optic nerve 2.04 *vs* 3.22 Gy, p = 0.1, left optic nerve 2.18 Gy *vs* 4.58 Gy, p = 0.18. As the maximum doses of serial neural structures (PRV spine, Brain stem, Optic Nerves, Optic chiasma) in both techniques are in agreement with QUANTEC and RTOG criteria, the 3DCRT plans can be used. Statistical significance can be reduced only by manual iterations of fields and increasing subfields, which requires planning time and labour. They would be forming the scope for future studies. There is one patient in IMRT who received high left optic nerve(16.2 Gy). Right optic nerve(7.6Gy) and optic chiasma dose (15.3Gy) compared to other patients. This can be explained by the fact that the patient has a primary disease extending into Infra infratemporal fossa, which resulted in PTV approximating the OARs. There is another patient in IMRT who received PRV spine max dose of 49.7. This is due to the fact that the patient has cancer oropharynx with positive nodes staging T4N3bM0, which required irradiation of the posterior pharyngeal wall and retropharyngeal group of lymph nodes and the beam arrangement was such that there is close approximation of PTV and PRV. There is only a single PTV that received a dose of 70 Gy.

Mandible mean Dmax doses in both the groups were on the higher side, with a statistical benefit for IMRT (73.69 *vs* 71.38 Gy; p = 0.03) and 1cc volumes received (71Gy *vs* 69Gy), which did not attain statistical significance. This can be explained by the fact that most of the cases in the study were oropharyngeal, that is, about 60% which results in irradiation of the mandible and are higher stages with resulting in single PTV volumes of 70 Gy in the IMRT arm. 15 out 25 patients in the IMRT arm were given 70 Gy to a single PTV. Another dose constraint defined by QUANTEC 1 cc<75 Gy was achieved in both groups.

With respect to parallel structures other than parotids (Lips and Cochlea) the mean lip doses were achieved in both techniques according to criteria but the doses of IMRT arm were significantly high compared to 3DCRT arm (14,34 Gy *vs* 22.88; p = 0.026) This can be explained by that in IMRT multiple beams are used which may result in dose dumping from the lips to achieve the PTV coverage. Clinically, it is important as the Lip mucosal reactions may result in decreased nutrition of patients and may lead to treatment breaks.

Mean doses of right and left cochlea for 3DCRT and IMRT were (20.99 Gy *vs* 10 Gy; p=0.016) (17.14 *vs* 13.48 Gy; p = 0.045), respectively, which satisfied the QUANTEC criteria[14]. Further reducing the doses of 3DCRT to make it comparable to IMRT requires creating more multisegment fields, which may result in better shielding of the cochlea. There is one patient in the 3DCRT arm who received 59.6 Gy to the right cochlea. This is due to the fact that there was a level II lymph node positive, which required inclusion of the retrostyloid group within the CTV, resulting in unilateral high dose to the cochlea. There are 2 patients in IMRT who also received high doses in comparison with others i.e., 37.2 to 40.3 Gy. Both cases have extension of their CTV up to pterygoid plates and required retropharyngeal and retrostyloid irradiation and a single PTV of 70Gy, which resulted in high doses to the cochlea.

In a study by Abotaleb *et al*.[13] (2017), conformity and homogeneity Indices were measured for HNC patients treated with 3DCRT. In this study, a total of 15 patients were included and for each patient, five plans were made using four planning techniques: The conformity indices of various plans were Field-in-Field (1.46±0.16), Bellinzona (1.47±0.16), Conpas(1.52±0.18), FMPS (Multiple energies) (1.564 ± 0.20), FPMS (single energy)1.58± 0.21 (S).

In our study, the conformity index of the 3DCRT technique was 1.41, which is in agreement with all the above 3DCRT forward planning techniques. As asserted by RTOG that CI between 1 and 2 comply treatment to the treatment plan. There are 2 cases in the 3DCRT arm where there is a minor violation of (0.9–1.0). And there are 6 patients with minor violation in the IMRT arm of the range (0.98–0.99). This shows that even though there is a significant difference in conformity index with benefit in IMRT arm, there are more minor violations in IMRT compared to 3DCRT. And present study shows have better value of 1.41 compared with all 5 techniques of forward planning.

In the same study by Abotaleb *et al*., [13] Homogeneity index were FPMS(M) 0.187 ± 0.014, FPMS(S) 0.193 ± 0.011, FIF0.196 ± 0.031, Conpas 0.202 ± 0.017, Bellinzona 0.219 ± 0.02, respectively. The FPMS technique, either using multiple or single energy, has the highest conformity

and homogeneity, followed by the FIF technique. For conformity, Conpas ranks third, followed by the Bellinzona technique. For homogeneity, Bellinzona ranks third, followed by the Conpas technique.

Our study showed better homogeneity index in IMRT arm compared to 3DCRT (0.23 *vs* 0.06) with a significant p =<0.001. The results of this 5-field are comparable to Bellinzona, which also uses 5 fields, ConPas which uses 7 fields and FPMS, which is 7 fields and 13 segments with single or multiple energies. Homogenous dose distribution by obtained either by increasing more fields with subfields.

As a notion that IMRT received a higher integral dose compared to 3DCRT due to an increase in the number of beam angles, in our doses, integral doses assessed showed that there is no significant difference between whole body integral doses (162.35 Gy *vs* 163.79 Gy; p = 0.89).

Thus, this study instigates further studies of multiple field 3DCRT, which can obtain comparable or may be better than IMRT. As of now, IMRT in head and neck cancers remains standard. But multiple field 3DCRT may be an option for the centres where IMRT is not available and is also cost-effective.

Treatment response at 6 months

A study by Ferreira B.C *et al*.[5] significant differences in survival distributions of the LRC, up to 19 %, in the subgroup of patients with N2–3 tumours, for post-operative RT and for concomitant RT. Treatment breaks larger than two days had an almost fourfold increased risk of poorer LRC and DFS. But there are no significant differences in local control and survival rates.

Similarly, in our study, 20 patients in 3DCRT (95%) had a complete response and 18 in IMRT (76%) had complete response, 5 patients (20%) in IMRT had partial response and 2 patients (8% in IMRT had progressive disease where 1 patient (4%) in 3DCRT had stable disease according to WHO response Criteria. The differences in techniques resulted in different toxicity profiles but no effect on local control.

CONCLUSION

Both techniques, 3-DCRT and IMRT, did not have any statistical difference in treatment compliance, hematological or radiation-induced toxicities, and response assessment. All dosimetric parameters of PTV were achieved and were similar for OARs, though they were better in IMRT. An increasing number of beams, subfields and manual iterations may improve and make 3DCRT plans comparable to IMRT. The present study may form the basis for further studies where different forward planning techniques can be used. This ideology may be useful in centres where an IMRT facility is not available, and the 3DCRT technique is also cost-effective in comparison to IMRT.

REFERENCES

1. Fatema, Joseph Benjamin Gandi, Bala Sankar Ramavath, John Winkle Medida, Macha Kiran Kumar. Study of radiation-induced xerostomia in head and neck cancer in conformal versus conventional radiotherapy. International Journal of Contemporary Medical Research 2016;3(8):2367-2371.
2. Aseem Rai Bhatnagar, Rameshwaram Sharma, Prashant Kumbhaj .Improvement In Xerostomia Related Quality Of Life Of Oral Cavity And Oropharyngeal Squamous Cell Carcinoma Patients Treated With IMRT Compared To Conventional RT.National Journal Of Medical Research. Vol 3 Issue 4 Oct-Dec 2013.
3. Yu JB, Soulos PR, Sharma R, Makarov DV, Decker RH, Smith BD, *et al*. Patterns of care and outcomes associated with intensitymodulated radiation therapy versus conventional radiation therapy for older patients with headandneck cancer. Int J Radiat Oncol Biol Phys 2012;83:e1017.
4. Ferreira B. C., Couto, Lopes M. C.,Khouri L. Compliance to radiation therapy of head and neck cancer patients and impact on treatment outcome.Clinical Transl Oncol 2015; VOL:1417-5
5. Santa Cruz O, Tsoutsou P, Castella C, Khanfir ,Anchisi S, Oscar Matzinger Ozsahin M. Locoregional Control and Toxicity in Head and Neck Carcinoma Patients following Helical Tomotherapy-Delivered Intensity-Modulated Radiation Therapy Compared with 3D-CRT Data.Oncology 2018; Vol : 1-8
6. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP (2018) Systematic review and meta-analyses of intensity-modulated radiation therapy versus conventional two-dimensional and/or or three-dimensional radiotherapyin curative-intent management of head and neck squamouscell carcinoma. PLoS ONE 2018; 13(7): 1-15
7. Gupta T,Agarwal JP,Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, Murthy V, Budrukkar A, Dinshaw K, Prabhash K, Chaturvedi P, D'Cruz A Three-dimensional conformal (3D-CRT) versus intensity modulated radiotherapy(IMRT) in squamous cell carcinoma of the head and neck; A randomized controlled trial radiotherapy and oncology 2012;104;343-348
8. Ghosh G Tallari R Malviya A, Toxicity profile Vs.3DCRT in head and neck cancer: A retrospective study journal of clinical and diagnostic research 2016;10(9):1-12
9. 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. 1-8
10. Kruser TJ, Rice SR, Cleary KP, Geye HM, Tome WA, Harari PM, Kozak KR. Acute hematologic and mucosal toxicities in head and neck cancer patients undergoing chemoradiotherapy: a comparison of 3D-CRT, IMRT, and helical tomotherapy. Technol Cancer Res Treat. 2013 Oct;12(5):383-9. doi: 10.7785/tcrt.2012.500332. Epub 2013 Mar 26. PMID: 23547974; PMCID: PMC4469949.
11. Cozzi L, Fogliata A, Lomax A, Bolsi A. A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced

head and neck tumours. Radiother Oncol 2003;69:267–275.
12. Lee N, Akazawa C ,M Jeanne, Tang C, Verhey LJ, Xia P. A forward planned treatment technique using multisegments in the treatment of head and neck Int. J. Radiation Oncology Biol. Phys.2004. Vol. 59, No. 2, pp. 584–594
13. Abotaleb HA, Maarouf E,El-Hossary FM, Raaif M and Kelany M. Conformity and Homogeneity Indices for Head and Neck Cancer Patients using 3DCRT Sohag J. Sci.2017; 2, No. 1, 1-7
14. Cancer. Int. J. Radiation Oncology Biol. Phys.2004. Vol. 59, No. 2, pp. 584–594