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A Prospective Analysis of Dosimetric and Acute Toxicity Profile Between Three Dimensional Conformal Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) in Locally Advanced Head and Neck Cancer Patients

[1]Dr. P. Masthan Basha, [2]Dr. B.V. Subramanian, [3]Dr. Pranabandhu Das, [4]Dr. Swapna Jilla, [5]Dr. B. Manilal, [6]Dr. Amit Kumar Chowhan, [7]Mr. S. Balaraju

[1]Assistant Professor, [2]Professor , [3,4,5,6]Associate Professor, [7]Lecturer in Radiological Physics/RSO
[1,2,3,4,7]Department of Radiation Oncology, [5]Department of Surgical Oncology, [6]Department of Pathology
Sri Venkateswara Institute Of Medical Sciences (SVIMS), Tirupati

***Corresponding Author:**
Dr. Pranabandhu Das
Associate Professor, Department of Radiation Oncology, Sri Venkateswara Institute Of Medical Sciences (SVIMS), Tirupati

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Abstract

Background:

Definitive chemo radiotherapy is the contemporary standard of care in non-surgical management of locally advanced head-neck carcinoma. Conformal radiation delivery techniques advances from three dimensional conformal radiotherapy (3D-CRT) to intensity modulated radiotherapy (IMRT). We have conducted a study to evaluate the dosimetric and acute toxicity profile of IMRT compared to 3D-CRT in locally advanced head and neck region.

Materials And Methods:

66 patients enrolled between March 2017 and June 2018 in this prospective randomized study. 33 patients treated with 3D-CRT and 33 patients treated with IMRT techniques. Concurrent chemotherapy with weekly cisplatin 40 mg/m2 was given to patients in both the arms who were medically fit for chemotherapy. All patients were assessed weekly during chemoradiotherapy treatment and after 6-8 weeks of the treatment.

Results:

Final analysis was done in 62 patients (30 patients in 3D-CRT and 32patients in IMRT). There was a significant dose coverage for tumor volume (V90%: 98.24% 3D-CRT vs 99.69% IMRT, P= <0.0001; V95%: 96.04% 3D-CRT vs 98.42% IMRT, P=<0.0002) along with significant dose reduction for organs at risk (OAR's) in IMRT arm compared to 3D-CRT arm. Acute toxicities were significantly less in IMRT arm than those of 3D-CRT arm. Grade 2 or more mucositis (59.37% IMRT vs 93.33% 3D-CRT, p=0.001), Grade 2 or more skin reactions were (56.25% IMRT vs 79.99% 3D-CRT, P=0.045). Acute grade 2 or more dysphagia was (53.12% IMRT vs 86.66% 3D-CRT, P=0.004). Complete response rates were 90% in 3D-CRT and 96.87% in IMRT, but there was no statistically significant difference (P= 0.275) between the two arms.

Conclusion:

IMRT can be a better radiotherapy technique compared to 3D-CRT both in terms of tumor coverage and sparing organs at risk with reduced incidence of acute toxicities especially in complex anatomical regions like head and neck cancers.

Keywords: Dosimetric, 3D-CRT, Head and neck cancers, IMRT, Toxicity profile

Introduction

Head and neck cancers are the commonest neoplasm seen in India accounting for significant morbidity and mortality. According to GLOBOCAN 2020, worldwide incidence and mortality of head and neck cancers are 4.6% (8,78,348 cases) and 4.47%(4,44,347) respectively.[1] According to GLOBOCAN 2020 Indian data, incidence 17.72% (2,33,2691) and mortality 15.19%(1,30,371) respectively. The contemporary standard of care in non-surgical, curative-intent management of head and neck squamous cell carcinoma (HNSCC) is definitive radiotherapy (RT) with or without concurrent chemotherapy[2]. There is advances in techniques of radiation treatment delivery from two dimensional radiotherapy (2D) to three dimensional conformal radiotherapy(3D-CRT) with geometric modulation of beam shape, that conform as closely as possible to the target volume and then to intensity modulated radiotherapy (IMRT).[3,4] The IMRT technique gives the ability to create treatment fields with varying beam intensity using inverse planning and optimization algorithms.[5] The irradiation beam can be adjusted to the irregularly shaped target volumes with high precision while reducing the radiation delivered to the surrounding healthy tissue and critical structures.[6,7,8] Hence IMRT is an optimal technical approach for treating head and neck cancer because of the anatomical complexity of the cancer site with many critical and radiation sensitive structures in close proximity to the targeted cancer tissue.[9] However, at the same time technical errors in delivery of IMRT may lead to increased risk of treatment-related morbidity and recurrence. Some studies shows that IMRT correlates with decreased toxicity of organs at risk(OARs) without compromising local tumor control compared to 3D-CRT.[10,11]. Hence we have conducted a study to compare dosimetric and acute toxicity profile between IMRT and 3D-CRT techniques in squamous cell carcinomas of locally advanced head and neck region(Oropharynx, Hypopharynx, Larynx).

Materials And Methods:

A prospective randomized study was conducted on patients of head and neck cancers presenting to the radiotherapy out-patient department, at our institute during the time period between March 2017 to June 2018, after obtaining approval from institutional ethics committee. A total of 66 patients were recruited into the study and were randomly assigned to two arms, arm A (3D-CRT) and arm B (IMRT). Out of 33 patients in arm A (3D-CRT), 1 patient could not complete treatment due to toxicities, 2 patients lost follow up after treatment. In arm B (IMRT), out of 33 patients 1 patient lost for follow up after treatment. Sixty two patients were considered in final analysis, 30 patients in arm A and 32 in arm B. Inclusion criteria were histopathologically proven squamous cell carcinoma of head and neck (oropharynx, hypopharynx and larynx), patients with Stage III to stage IVB according to American Joint Committee on Cancer (AJCC) staging manual, 7th edition[12], Eastern Co-operative Oncology Group (ECOG) performance status: 0 – 2.[13] and patients who are willing to give approved informed consent. Exclusion Criteria were, patients previously treated with surgery or radiotherapy or induction chemotherapy, ECOG performance status 3-4, patients with distant metastasis, pregnant women and lactating mothers. Before enrolling to study all patients were assessed with history and physical examination, haemogram, renal function test, liver function test, contrast enhanced computed tomography (CECT) of head & neck, magnetic resonance imaging (MRI) to know local extent of tumor and for staging purpose, indirect laryngoscopy to know about the mobility of vocal cords and other structures involvement, chest radiograph and ultrasound abdomen as part of metastatic work up.

Study Procedure:

Sample size of 33 patients in each group was taken with 80% power and alpha error of 0.05. Randomization was done using computer generated random number table in to two arms. A total of 66 patients were taken into the study.33 patients were taken in each arm. Patients assigned to arm A were planned and treated with three dimensional conformal radiotherapy (3D-CRT). Patients assigned to arm B were planned and treated with intensity modulated radiotherapy (IMRT). All the patients were treated with Elekta synergy linear accelerator (Elekta, Stockholm) with 6MV photons. All the patients are planned to receive external beam radiotherapy dose of 66 to 70 Gy in 33 to 35 fractions at the rate of 2 Gy per fraction 5 fractions per week over 6 to 7 weeks with or without concurrent weekly cisplatin chemotherapy 40mg/m² .

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The objectives of the present study were to compare dosimetric parameters such as V90% of PTV (volume receiving 90% of prescribed dose of planning target volume) , V95% (volume receiving 95% of prescribed dose) of PTV, V107% (volume receiving 107% of prescribed dose of PTV) , Mean dose to ipsilateral parotid gland , Mean dose to contralateral parotid gland, Maximum dose to spinal cord, Mean dose to pharyngeal constrictors. Acute toxicities were assessed for dermatitis, mucositis, dysphagia once weekly while on treatment and monthly for 2 months post-treatment and graded according to the Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [14]. Response rates were assessed using the response evaluation criteria in solid tumors (RECIST) version 1.1 [15] after 6-8 weeks of completion of treatment both clinically and radiologically.

Statistical Analysis:

Data was collected in a pre-designed proforma and recorded in microsoft excel 2013 (Microsoft Corp, Redmond, WA). Dosimetric parameters between the two groups are compared by Mann- Whitney U test. Pearson's Chi-Square test was performed to assess the association of grade 2 or more toxicities between two arms. Proportions of complete responses between the two arms compared using Z test. Statistical tests were performed using IBM SPSS Software version 21 and p value < 0.05 is taken to denote statistically significant relationship.

Results:

Total 66 patients were enrolled into two arms of the study i.e 3D-CRT and IMRT arm. Sixty two patients were considered for final analysis ; 30 patients in 3D-CRT arm and 32 in IMRT arm. There were 53 men and 9 women in this study with a median age of 57 years (37–77 years) at presentation. There were no significant differences in the baseline tumor characteristics between the two arms. Baseline patient characteristics were shown in the Table-1 and tumor characteristics were shown in the Table- 2. Patients in both arms were planned to receive external beam radiotherapy of dose 66 to 70 Gy. Most of the patients in both the arms received chemotherapy with weekly cisplatin 40mg/m2 for 1 – 5 cycles.

Dose coverage for tumor volume significantly improved in IMRT arm (V90%: 98.24% 3D-CRT vs 99.69% IMRT, p= <0.0001; V95%: 96.04% 3D-CRT vs 98.42% IMRT, p=<0.0002) {Table-3} with significant sparing of surrounding OARs especially contralateral parotid (43.78Gy 3D-CRT vs 25.76Gy IMRT, p=<0.0001) {Table-4}

Grade 2 or more acute toxicities were significantly less in IMRT arm compared to 3D-CRT arm. None of the patients developed grade 4 toxicity. Grade 2 or more acute mucositis seen in 28 (93.33%) patients of 3D-CRT and 19 (59.37%) patients of IMRT with significant p value = 0.001. Grade 2 or more acute dermatitis seen in 24 (79.99%) patients of 3D-CRT and 18 (56.25%) patients of IMRT with significant p value = 0.045. Grade 2 or more acute dysphagia seen in 26 (86.66%) patients of 3D-CRT and 17 (53.12%) patients of IMRT with significant p value = 0.004{Table-5}

27 (90%) patients of 3D-CRT arm and 31(96.87%) patients of IMRT arm achieved complete response. But there was no statistically significant difference (P= 0.275) between the two arms {Table-6}

Discussion:

Definitive(chemo) radiotherapy, i.e., radical radiotherapy with or without concurrent systemic chemotherapy is the contemporary standard of care in non-surgical management of locally advanced head-neck squamous cell carcinoma (HNSCC).[16] The increasing use of computed tomography (CT) imaging for target volume delineation coupled with widespread availability of computer-controlled treatment planning and delivery systems have progressively led to conformation of radiation dose to the target tissues while sparing surrounding normal tissues i.e. three-dimensional conformal radiotherapy (3D-CRT). Intensity-modulated radiation therapy (IMRT) is an advanced form of 3D-CRT with high-precision of conformity that uses non-uniform radiation beam intensities determined through computer-based optimization to achieve the desired dose-distribution, has revolutionized contemporary radiotherapy practice.

Our study showed that, the coverage V90%, V95%, V107% of planning target volume (PTV) significantly better in IMRT arm compared to 3D-CRT arm. The results were comparable to studies

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conducted by Barbara Longobardi et al[17] and Cozzi.et al. [18] Mean dose to ipsilateral and contralateral parotids is reduced in IMRT arm patients compared to 3D-CRT arm. These results were similar with results of studies conducted by Barbara Longobardi et al[17] and Cozzi.et al[18] and a Phase III randomized controlled trial by Tejpal Gupta,et al[19]and PARSPORT trial[20]

IMRT can do significant partial sparing of the uninvolved swallowing structures compared to 3D-CRT, our study showed significant difference of mean doses of pharyngeal constrictors (PC) between 3D-CRT and IMRT arms(3D-CRT:66.19 vs IMRT:61.02; P <0.001).

IMRT technique can limit the dose to the spinalcord compared to 3D-CRT (48.94Gy 3D-CRT vs 43.15Gy IMRT; P <0.0001). Our study showed a significant dose difference between IMRT and 3D-CRT arms comparable to results of Barbara Longobardi et al[17] and Cozzi.et al[18]

Grade 2 or more acute toxicities were significantly less in IMRT arm compared to 3D-CRT arm. None of the patients developed grade 4 toxicity. Grade 2 or more acute mucositis seen in 28 (93.33%) patients of 3D-CRT and 19 (59.37%) patients of IMRT with statistically significant P value = 0.001. Grade 2 or more acute dermatitis seen in 24 (79.99%) patients of 3D-CRT and 18 (56.25%) patients of IMRT with significant P= 0.045. Grade 2 or more acute dysphagia seen in 26 (86.66%) patients of 3D-CRT and 17 (53.12%) patients of IMRT with significant P value=0.004. All of these results of reactions were similar with results of studies conducted by Lohia S.et al[21]. and Lambrechet, et al[22]. and Gopa Ghosh et al[23]. and a Phase III randomized controlled trial by Tejpal Gupta,et al[19].

27 (90%) patients of 3D-CRT arm and 31(96.87%) patients of IMRT arm achieved complete response. But there was no statistically significant difference (P= 0.275) between the two arms. It also indirectly indicates better tumor coverage in IMRT arm{Table-7}

Conclusion:

Based on our study report, we can conclude that , there was a significant dose coverage for tumor volume (V90%, V95% of PTV) with IMRT technique compared to 3D-CRT technique. Incidence of grade 2 or more toxicities are significantly reduced with IMRT technique due to reduced radiation dose to surrounding organs at risk (OAR's). Though statistically not significant tumor response rates also superior in IMRT arm. Hence, we can consider that IMRT is a better modality of technique for treatment delivery compared to 3D-CRT both in terms of tumor coverage and sparing organs at risk with reduced incidence of severe toxicities and good response rates in locally advanced head and neck cancers. But it was a single institution based randomized study with a small number of patients and short followup time. A large scale, multicentric, randomized trials are recommended to validate the results of our study.

Table 1: Patient Characteristics

	ARM A (3D-CRT) N = 30	ARM B (IMRT) N = 32
AGE (YEARS)		
<40	1	4
41-50	5	3
51-60	12	8
>60	12	17
SEX		

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MEN	26	27
WOMEN	4	5

3D-CRT = Three dimensional conformal radiotherapy, IMRT = Intensity modulated radiotherapy

Table 2: Tumor Characteristics

	ARM A (3D-CRT)	ARM B (IMRT)
PATHOLOGY		
WDSCC	16	18
MDSCC	14	14
T STAGE		
T2	4	11
T3	17	11
T4A	9	10
N STAGE		
N0	15	9
N1	9	10
N2	6	11
N3	0	2
STAGE GROUP		
STAGE III	19	14
STAGE IVA	11	16
STAGE IVB	0	2
SUB SITE		
OROPHARYNX	3	6
HYPOPHARYNX	7	11
SUPRAGLOTTIS	10	12
GLOTTIS	10	3

3D-CRT = Three dimensional conformal radiotherapy, IMRT= Intensity modulated radiotherapy

Table 3: Comparison of V90%, V95%, V107% of PTV

Parameters	Arms	No of patients	Mean (%)	Std., deviation	P value	Remarks
V90%	ARM A	30	98.24	1.223	0.0001	significant
	ARM B	32	99.69	0.452		

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V95%	ARM A	30	96.04	2.121	0.0002	significant
	ARM B	32	98.42	1.324		
V107%	ARM A	30	2.12	2.206	0.0006	significant
	ARM B	32	0.47	0.690		

V90% (volume receiving 90% of prescribed dose) of planning target volume(PTV)

V95% (volume receiving 95% of prescribed dose) of PTV

V107% (volume receiving 95% of prescribed dose) of PTV

Table 4: Comparison of mean doses of ipsilateral and contralateral parotids, maximum dose to spinal cord, mean dose to constrictors

Parameters	Arms	No of patients	Mean (Gy)	Std., deviation	P value	Remarks
Mean dose to ipsilateral parotid	ARM A	30	48.42	7.437	0.320	Not significant
	ARM B	32	46.58	7.602		
Mean dose to contralateral parotids	ARM A	30	43.78	7.044	0.0001	Significant
	ARM B	32	25.76	2.918		
Maximum dose to spinalcord	ARM A	30	48.94	1.68	0.0001	Significant
	ARM B	32	43.15	2.92		
Mean dose to constrictors	ARM A	30	66.19	3.075	0.00001	significant
	ARM B	32	61.02	5.201		

Table 5: Acute toxicity profile of mucous membrane, skin, pharynx between two arms

GRADE	ARM A (3D-CRT) (N= 30)	ARM B (IMRT) (N= 32)	P VALUE (for grade 2 or more toxicities)
MUCOSITIS			
0	0 (0%)	3 (9.38%)	0.001
1	2 (6.66%)	10 (31.25%)	
2	19 (63.33%)	14 (43.75%)	
3	9 (30%)	5 (15.62%)	
DERMATITIS			
0	0 (0%)	4 (12.5%)	

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1	6 (20%)	10(31.25%)	
2	16 (53.33%)	14 (43.75%)	0.045
3	8 (26.66%)	4 (12.5%)	
DYSPHAGIA			
0	0 (0%)	3 (9.38%)	
1	4 (13.33%)	12 (37.5%)	
2	18 (60%)	13 (40.62%)	0.004
3	8 (26.66%)	4 (12.5%)	

Table 6 : Response assessment between two arms

Response	ARM A (3D-CRT)	ARM B (IMRT)	P value (for complete response)
Complete Response	27 (90%)	31 (96.87%)	0.275
Partial Response	3 (10%)	1 (3.12%)	

Table 7 : Comparison of present study with other studies

Parameters	Barbara Longobardi et al.		Cozzi, et al.		Tejpal Gupta,et al.		Present study	
	3D-CRT	IMRT	3D-CRT	IMRT	3D-CRT	IMRT	3D-CRT	IMRT
V90%	94.3	98.1	93.9	98.2	-	-	98.24	99.67
V95%	-	-	85.4	92.9	-	-	96.04	98.49
Mean dose to ipsilateral parotid	-	-	-	-	56.2	39.8	48.42	46.58
Mean dose to contralateral parotid	-	-	-	-	49.8	28.8	43.78	25.76
Mean dose to constrictors	-	-	-	-	-	-	66.19	61.02
Max dose to spinalcord	43.8	40.9	40	30	-	-	48.94	43.15
Acute mucositis					93%	77%	93.33%	59.37%

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Acute dermatits					96.5%	94%	79.99%	56.25%
Acute dysphagia					71.5%	59.5%	86.66%	53.12%

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