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Comparison of Clinical Outcome and Dosimetric Parameters of Three-Dimensional Conformal Radiotherapy Versus Intensity Modulated Radiotherapy in Patients with Head and Neck Squamous Cell Carcinoma: A Prospective Two Armed Observational Study

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ABSTRACT

This study aimed to compare the clinical outcomes and dosimetric parameters of three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) in treating patients with head and neck squamous cell carcinoma (HNSCC). According to NCCN Guideline, 'Head and Neck cancer' refers to cancer of the upper aero-digestive tract, arising from the lip, oral cavity, pharynx, larynx, paranasal sinuses., salivary gland cancers, mucosal melanoma and occult primary cancers. Squamous cell carcinoma is the histological type in >90% of all Head and Neck tumors. Worldwide, Squamous cell carcinoma of Head and Neck is the 7th most common cancer, having an annual incidence of 7, 00,000 (approximately) and mortality rate of 3, 50,000 in 2018. To study the response and dosimetric parameters after radical treatment in patients with Head and Neck Squamous Cell carcinoma undergoing radical concomitant chemoradiation with either Three-Dimensional Conformal Radiotherapy (3-DCRT) or Intensity modulated radiotherapy (IMRT). This is two tailed, open labeled, comparative, single institutional observational study. Place of study is R. G. Kar Medical College and Hospital, 1, Khudiram Bose Sarani. Kolkata- 700004. The study duration is from January 2021-August 2022 and Sample Size is 100patients. The functional status was assessed as per ECOG (Eastern Cooperative Oncology Group) Performance status. The distribution of the patients in both the arms according to their Performance status were also comparable (p value=0.144). In studies comparing Three-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity-Modulated Radiotherapy (IMRT) for treating head and neck squamous cell carcinoma (HNSCC), IMRT generally demonstrates superior dosimetric advantages, offering improved target coverage and sparing of surrounding healthy tissues. IMRT's ability to more precisely conform the radiation dose to the tumor shape reduces the risk of damage to critical structures such as the salivary glands, spinal cord and oral cavity.

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Key Words
Radiotherapy, cell carcinoma, IMRT

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INTRODUCTION

According to NCCN Guideline, 'Head and Neck cancer' refers to cancer of the upper aerodigestive tract, arising from the lip, oral cavity, pharynx, larynx, paranasal sinuses., salivary gland cancers, mucosal melanoma and occult primary cancers. Squamous cell carcinoma is the histological type in more than 90% of all Head and Neck tumors. Worldwide, Squamous cell carcinoma of Head and Neck is the 7th most common cancer, having an annual incidence of 7, 00,000 (approximately) and mortality rate of 3, 50,000 in 2018[1]. In Europe, between years 2000-2007, the annual crude incidence rate was 4.6/ 1,00,000 for laryngeal squamous cell carcinoma, 3.5/1,00,000 for oral cavity SCC, 3.3/1,00,000 for oropharyngeal SCC and 1.3/1,00,000 for hypopharyngeal SCC, corresponding to 90,000 new cases per year[2]. The important etiological factors for head and neck SCC include-tobacco chewing (specially for oral cavity cancers), alcohol consumption, Human Papilloma Virus (HPV16) infection (specially for Oropharyngeal cancer), Epstein Barr Virus (for Nasopharyngeal cancer), environmental and occupational exposure to carcinogenic agents, poor nutritional status, bad dentition etc. Patients of head and neck cancer have an increased risk for developing Second Primary Tumor (SPT), either within head-neck region or in other sites (e.g. esophageal and lung cancers)[3]. Currently, concurrent chemo-radiation is the most commonly used treatment protocol for head and neck SCC[4], although, surgery is the primary treatment option for oral cavity cancers (if operable) followed by concurrent chemo-radiation. The radiation delivery techniques has been evolved from 2D planning to 3D conformal planning and now, modified and more precise form of 3-DCRT, i.e. IMRT is being used largely for its capability to distribute more homogeneous radiation dose within the PTV(planning target volume), sharp fall off PTV boundary and better sparing of adjacent critical normal tissue. Classically, 3-DCRT process is based on 'Forward Planning'. Here, the radiation beam parameters i.e. directions, apertures and their margins, beam weights, beam modifiers are specified and, dose distributions are computed. The beam parameters can be modified, if necessary, to achieve more acceptable dose distribution. Whereas, IMRT uses 'Inverse Planning'. Here, the desired dosimetric and clinical objectives are stated mathematically and then it determines the beam shapes and fluence patterns in a best way to achieve the dosimetric goals[5,6].

MATERIALS AND METHODS

Type of Study: Two tailed, open labelled, comparative, single institutional observational study.

Place of Study: R. G. Kar Medical College and Hospital. 1, Khudiram Bose Sarani. Kolkata-700004.

Duration: January 2021-August 2022.

Sample Size: 100 patients.

Inclusion:

- All patients of histopathology proven squamous cell carcinoma of oral cavity, oropharynx, larynx and hypopharynx.
- Age: 18 years-70 years of age.
- Stage of disease: AJCC (8th ed.) stage T1-T4a, N0-N3b, M0 (AJCC stage group I-IVB) patients with pre-treatment tumor measurements clinically as well as CT/MRI scan.
- ECOG Performance Status 0-2.
- Normal baseline hematological and biochemical parameters (viz. Hb%≥10gm/dl, ANC≥1500/µl, Platelets≥1lakh/µl, Creatinine clearance ≥50ml/min, Normal liver functions).
- Patients willing to provide informed consent (with signature or left thumb impression) for the approval for inclusion in the study.

Exclusion:

- All patients of histopathology proven squamous cell carcinoma of oral cavity, oropharynx, larynx and hypopharynx.
- Age: 18 years-70 years of age.
- Stage of disease: AJCC (8th ed.) stage T1-T4a, N0 -N3b, M0 (AJCC stage group I-IVB) patients with pre-treatment tumor measurements clinically as well as CT/MRI scan.
- ECOG Performance Status 0-2.
- Normal baseline hematological and biochemical parameters (viz. Hb%≥10gm/dl, ANC≥1500/µl, Platelets≥1lakh/µl, Creatinine clearance ≥50ml/min, Normal liver functions).
- Patients willing to provide informed consent (with signature or left thumb impression) for the approval for inclusion in the study.

Statistical Analysis: For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0., SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests, which compare the means of independent or unpaired samples, were used to assess differences between groups. Paired t-tests, which account for the correlation between paired observations, offer greater power than unpaired tests. Chi-square tests (χ^2 tests) were employed to evaluate hypotheses where the sampling distribution of the test statistic follows a chi-squared distribution under the null hypothesis., Pearson's chi-squared test is often referred to simply as the chi-squared test. For

comparisons of unpaired proportions, either the chi-square test or Fisher's exact test was used, depending on the context. To perform t-tests, the relevant formulae for test statistics, which either exactly follow or closely approximate a t-distribution under the null hypothesis, were applied, with specific degrees of freedom indicated for each test. P-values were determined from Student's t-distribution tables. A p-value ≤ 0.05 was considered statistically significant, leading to the rejection of the null hypothesis in favour of the alternative hypothesis.

RESULTS AND DISCUSSIONS

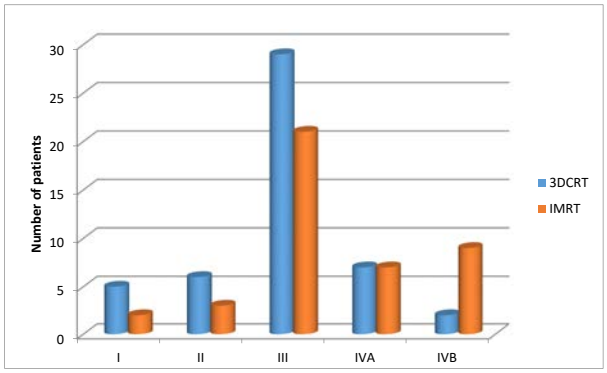

Fig. 1: Distribution According to Stage Grouping

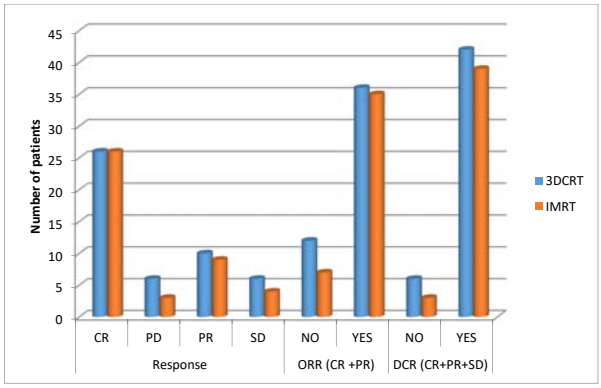

Fig. 2: Response Assessment

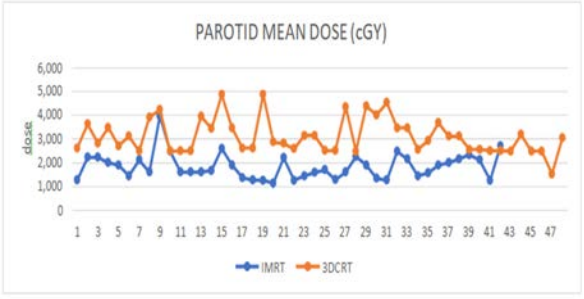

Fig. 3: Graphical Representation of Mean Dose to Parotid

As per addiction history, 34.44% of the study population have chewing habit., 67.66% have Smoking habit and 17.77% consume alcohol. Smoker vs Non-smoker ratio-[2.1:1] History of chewing and alcohol intake is significantly less than Smoking. Differences in prevalence of different types of addiction between both of the study arms are not statistically significant. Prevalence of Hypertension and Diabetes are found to be comparable between two arms. The functional status was assessed as per ECOG (Eastern Cooperative Oncology Group) Performance status. The distribution of the patients in both the arms according to their Performance status were also comparable (p value=0.144). B.O.T=Base of tongue., F.O.M.=Floor of mouth., PFS=Pyriform sinus., GBS=Gingivo buccal sulcus., RMT=Retromolar trigone. In terms of different subtypes, both the arms are comparable. Most prevalent subsite for this study population is-Supraglottic larynx [31.2% of cases in 3DCRT arm and 38.1% of cases in IMRT arm]. 2nd most prevalence seen for Buccal mucosa cancers [16.7% in 3DCRT arm and 11.9% in IMRT arm]. F.O.M. and RMT are the 2 least prevalent subsites in the study population [having only 2 patients of each sunsite, only in IMRT arm]. Total 45 patients, i.e.- 50% of the study population show Pathological Grade 2 disease, followed by 38.89% with Grade 1 disease., least prevalent is Grade 3 disease (only 11.11%). No significant difference between two arms. No significant difference in disease stages between two arms. Stage III disease cases are most prevalent in both arms [60.4% and 50% cases in 3DCRT and IMRT arms, respectively]. Among 90 patients, 52 patients acquired complete response., 19 acquired partial response., 10 had stable disease and 9 had progressive disease. The response rates were found to be similar in both arms. This needs to be highlighted that unlike literature review, our study period was short, which might have not translated into improved locoregional control rates in favour of IMRT. Also none of the patients of IMRT had SIB (Simultaneous Integrated Boost) as their protocol. Among 90 patients, 52 patients acquired complete response., 19 acquired partial response., 10 had stable disease and 9 had progressive disease. The response rates were found to be similar in both arms. This needs to be highlighted that unlike literature review, our study period was short, which might have not translated into improved locoregional control rates in favour of IMRT. In 3DCRT arm, CI found to be 0.49±0.09., HI found to be 1.01±0.01 In IMRT arm, CI found to be 0.95±0.09., HI found to be 1±0. Both the parameters show significant p values, confirming that the IMRT arm achieved better CI and HI than 3DCRT arm. In 3DCRT arm, maximum PTV dose=70.51±2 Gy., minimum dose=54.52±8 Gy In IMRT arm, maximum PTV dose=72.65±4 Gy., minimum dose=49.90±12 Gy. The maximum dose coverage to PTV is better (i.e.

Table 1: Comparison of Pattern of Addiction, Co-Morbidity Profile, ECOG PS

Parameters		ARMS				
		3DCRT		IMRT		
		Count	Column N %	Count	Column N %	P-value
Chewing	**No**	28	58.30%	31	73.80%	0.123
	Yes	20	41.70%	11	26.20%	
Smoking	**No**	13	27.10%	16	38.10%	0.265
	Yes	35	72.90%	26	61.90%	
Alcohol	**No**	40	83.30%	34	81.00%	0.768
	Yes	8	16.70%	8	19.00%	
HTN	**No**	38	79.20%	30	71.40%	0.394
	Yes	10	20.80%	12	28.60%	
Diabetes	**No**	43	89.60%	37	88.10%	0.823
	Yes	5	10.40%	5	11.90%	
ECOG PS	**1**	31	64.60%	33	78.60%	0.144
	2	17	35.40%	9	21.40%	

Table 2: Sub Site Wise Distribution and Distribution as Per Pathological Grade

Parameters		ARMS				
		3DCRT		IMRT		
		Count	Column N %	Count	Column N %	P-value
SUBSITE	**B.O.T**	2	4.20%	4	9.50%	0.106
	Buccal mucosa	8	16.70%	5	11.90%	
	F.O.M	0	0.00%	2	4.80%	
	GBS	3	6.20%	0	0.00%	
	Glottis	3	6.20%	2	4.80%	
	Hard Palate	5	10.40%	1	2.40%	
	PFS	5	10.40%	2	4.80%	
	RMT	0	0.00%	2	4.80%	
	Soft palate	2	4.20%	1	2.40%	
	Supraglottic larynx	15	31.20%	16	38.10%	
	Oral tongue	5	10.40%	3	7.10%	
	Tonsillar fossa	0	0.00%	4	9.50%	
HPE	**MD-SCC**	22	45.80%	24	57.10%	0.455
	PD-SCC	5	10.40%	5	11.90%	
	WD-SCC	21	43.80%	13	31.00%	
PATH- GRADE	**1**	21	43.80%	14	33.30%	0.598
	2	22	45.80%	23	54.80%	
	3	5	10.40%	5	11.90%	

Table 3: Response Assessment

Response assessments		ARMS				
		3DCRT		IMRT		
		Count	Column N %	Count	Column N %	P-value
Response	CR	26	54.20%	26	61.90%	0.787
	PD	6	12.50%	3	7.10%	
	PR	10	20.80%	9	21.40%	
	SD	6	12.50%	4	9.50%	
ORR (CR+PR)	NO	12	25.00%	7	16.70%	0.334
	YES	36	75.00%	35	83.30%	
DCR (CR+PR+SD)	NO	6	12.50%	3	7.10%	0.398
	YES	42	87.50%	39	92.90%	

Table 4: Comparison of Conformity and Homogeneity Index., Maximum and Minimum Dose

ARMS		CI (TV/PTV)	HI(5%/95%)	PTV5% (cc)	PTV95% (cc)	MAXD (cGy)	MIND (cGy)
3DCRT	**N**	48	48	48	48	48	48
	Median	0.48	1.01	95	94	6996	5544
	Mean	0.499	1.0115	145.44	142.21	7051.77	5452.23
	S.D	0.097	0.01458	120.74	115.321	270.08	837.224
IMRT	**N**	42	42	42	42	42	42
	Median	1	1	223.5	214.5	7341.5	5350.5
	Mean	0.952	1	274.5	270.21	7265.4	4990.02
	S.D	0.0917	0	241.946	237.242	479.603	1206.022
Total	**N**	90	90	90	90	90	90
	Median	0.67	1	143.5	142	7132.5	5490
	Mean	0.71	1.0061	205.67	201.94	7151.47	5236.53
	S.D	0.2463	0.01206	197.124	192.55	394.932	1045.933
	P-value	0	0	0.002	0.001	0.01	0.036

Table 5: Comparison of Doses to Important OARs (in cGy)

ARMS		BSTM DMAX	SPCD DMAX	PRTD DMEAN	OPN DMAX	CSM DMAX
3DCRT	N	48	48	48	48	48
	Median	4357.5	4502	2875.5	163	176.5
	Mean	4056.92	4473.29	3083.02	549.33	471
	Std. Deviation	1258.232	370.689	734.657	1136.149	1014.205
	Minimum	1316	2699	1500	26	22
	Maximum	5551	5106	4846	5247	4958
IMRT	N	42	42	42	42	42
	Median	2826	4180	1664	5	4
	Mean	3031.76	4121.02	1815.1	232.57	218.6
	Std. Deviation	1044.825	660.334	542.308	837.259	784.266
	Minimum	1092	1980	1120	2	2
	Maximum	4878	5080	3940	5437	5095
Total	N	90	90	90	90	90
	Median	3565	4435	2467	145	123
	Mean	3578.51	4308.9	2491.32	401.51	353.21
	Std. Deviation	1266.274	551.97	908.363	1014.823	917.923
	Minimum	1092	1980	1120	2	2
	Maximum	5551	5106	4846	5437	5095
	P value	0.000*	0.002*	0.000*	0.141	0.195

higher) in IMRT arm and, Minimum achieved dose is also better (i.e. lower) in IMRT arm. Results are significant., p value 0.01 and 0.036 for maximum and minimum doses, respectively. Mean dose to parotid gland is 30±7 Gy in 3DCRT arm and 18±5 Gy in IMRT arm., p value is <0.0001, which is statistically significant, supports the fact shown in previous literature reviews that , better parotid sparing can be achieved by IMRT than 3DCRT.

In this study, total 100 patients with biopsy proven squamous cell carcinoma of head and neck, attending Radiotherapy Departmental OPD during the period of January 2021 to December 2021, were recruited (as per our abovementioned inclusion and exclusion criteria)., all of them received definitive treatment with concurrent chemo-radiation. 50 patients among them received radiotherapy with IMRT technique and the other 50 patients received radiotherapy by 3DCRT technique. All the eligible patients received weekly concurrent Injection Cisplatin (40mg/m2) during the radiation period. During the treatment, thorough clinical examinations were done weekly (and also in between whenever required), to assess acute toxicities. Unfortunately, only 48 (out of 50) patients in 3DCRT arm and 42 (out of 50) patients completed the treatment and were eligible for statistical analysis. Of these 90 patients, 79 were male and 11 female, clearly showing male preponderance and there is no significant difference in gender-wise distribution between two arms. Mean of the total study population was 55 years. There was no significant difference in mean age, height, weight between the two study arms. ECOG performance status was found to be comparable in both arms., 71.11% of the patients have ECOG PS 1. Prevalence of common comorbidities, i.e. Hypertension and Diabetes were almost similar in both of the study arms. Addiction history of smoking (67.66%), chewing (34.44%) and alcohol consumption (17.77%) was taken., with no significant statistical difference between two arms. Smoking has been found to be most prevalent habit., smoker versus non-smoker ratio was 2.1:1. As per sub site wise occurrence, most prevalent sub site for this study population was Supraglottic larynx (total 34.44%., 31.2% in 3DCRT arm vs. 38.1% in IMRT arm), followed by Buccal mucosa (total 14.44%., 16.7% in 3DCRT arm vs. 11.9% in IMRT arm) . Whereas, Globocan 2020 data shows that among head and neck cancers, highest numbers of cases have been recorded of Lip and Oral Cavity, followed by Larynx, Nasopharynx, Oropharynx and Hypopharynx. Between our two study arms, there was no significant difference in subsite wise distribution. 50% of the population was having initial pathological Grade 2 disease, 38.89% had Grade 1 disease and only 11.11% had Grade 3 disease., the two arms showed similar distribution. According to group staging, most of the cases were of Stage III (60.4% and 50% in 3DCRT and IMRT arms, respectively), also showing no significant difference. As per the observation on concurrent chemotherapy, mean dose received by the IMRT arm patients, is slightly more than that received by 3DCRT arm [approx.-255mg vs. 242mg respectively]. No statistically significant difference of number of chemotherapy cycles and cumulative Cisplatin dose, between the two arms was found. Among 90 patients, 52 patients acquired complete response., 19 acquired partial response., 10 had stable disease and 9 had progressive disease. Response assessment was done in terms of-Overall response rate (ORR=CR+PR) and Disease control rate (DCR=CR+PR+SD). ORR in 3DCRT arm was 75% and in IMRT arm was 83.3%., DCR in 3DCRT arm was 87.5% and in IMRT arm was 92.9%., no significant difference between the two arms. Acute radiation induced

toxicities were documented and classified according to the CTCAE version 5. We found that, Grade 3 toxicities (dermatitis, oral mucositis, dydphagia, xerostomia and nausea-vomiting) are more in 3DCRT arm than IMRT. Incidence of Grade 3 oral mucositis, dysphagia and xerostomia are significantly reduced with use of IMRT technique, with the p value of 0.001, 0.021 and 0.009 respectively. This result supports various literatures discussed previously[7,8] and puts weight on the fact that with the use of IMRT, we can save the parotid function >3DCRT. Late toxicities (occurring beyond 90 days) are found to be almost similar in all patients. All of them developed different grades of Dysphagia and Dryness of mouth (Xerostomia) with thickened saliva. No case of Osteoradionecrosis was reported. Different target volumes were comparable between two arms. In 3DCRT arm, CI was found to be 0.49±0.09., HI was found to be 1.01±0.01. In IMRT arm, CI found to be 0.95±0.09., HI found to be 1±0. Both the parameters show significant p values, confirming that the IMRT arm achieved better CI and HI than 3DCRT arm. The maximum PTV dose coverage was better in IMRT arm and minimum PTV dose coverage was better (i.e. lower) in IMRT arm [p values 0.01 and 0.036 for maximum and minimum doses, respectively]. Dose received by 2%, 50% and 98% of PTV volumes are clearly found to be better in IMRT arm., with strongly significant p value. Coming to the OARs, dose to brainstem, spinal cord, parotids, optic nerve and optic chiasm were observed., it was found that, maximum dose to brainstem and spinal cord are significantly lower in IMRT arm, i.e. better sparing of brainstem and spinal cord by IMRT than 3DCRT. Mean dose to parotid gland is 30±7 Gy in 3DCRT arm and 18±5 Gy in IMRT arm., p value is <0.0001, which is statistically significant, supports the fact shown in previous literature reviews that, better parotid sparing can be achieved by IMRT than 3DCRT. This result also correlates one of our previous observations, that there are lower incidences of xerostomia in patients of IMRT arm. Maximum dose to optic nerve and chiasm are although similar in both arms (not significant p values). The mean treatment span (for each case, in days) for 3DCRT arm is 58 days and for IMRT arm is 52 days. From our previous observation, we can conclude that, due to higher incidence of grade 3 toxicities in 3DCRT arm (as shown in table 46), there was statistically significant treatment delay. Disease progression was found in 13 patients of 3DCRT arm and 8 patients of IMRT arm. Calculation of PFS was a little difficult due to very short time of follow up., The mean PFS for 3DCRT was 37.98-49.17 weeks, for IMRT was 49.14-63.07 weeks., Median PFS for 3DCRT was 45 weeks (28.42-61.58 weeks)., median PFS was not reached by the IMRT arm. This problem could be overcome if we got a more prolonged follow up period.

CONCLUSION

Accepting all the limitations, this single institutional prospective two-armed comparative study on Head and Neck squamous cell carcinoma, managed to produce some significant results. 42 patients in 3DCRT arm and 48 patients in IMRT arm completed the whole treatment plus the follow up period. There was similar distribution of gender, tobacco addiction, cancer sub sites, stages and pathological grades of the disease. The primary endpoint was to compare clinical outcome., in terms of response rates of both arms. The Overall Response Rate (ORR) and Disease Control Rate (DCR) both were found to be slightly better in IMRT arm (75% and 87.5% in 3DCRT arm, vs. 83.3% and 92.9% in IMRT arm), but, these differences are not statistically significant. The secondary endpoints of our study were the comparison of different dosimetric parameters and toxicity profile. Significantly better Conformity Index (CI) and Homogeneity Index (HI) were achieved by the IMRT arm, concluding its better target delineation, OAR sparing and homogenous dose distribution within the target volumes. IMRT arm also shows better percentage of PTV volume coverage and maximum achieved dose to PTV. The IMRT arm shows significant reduction of grade 3 oral mucositis, xerostomia and dysphagia., whereas, due to more prevalence of all grade 3 toxicities, 3DCRT arm shows more treatment delay (more gaps during treatment due to adverse events). In IMRT arm, maximum dose to brainstem and spinal cord are significantly lower and, mean Parotid dose is also significantly lower, supporting the previous conclusion of lesser degree of xerostomia in IMRT arm. By considering all these cumulative results, we can say that , for head and neck cancer patients, 3DCRT and IMRT technique are comparable in terms of clinical response and, IMRT technique can be preferable than 3DCRT, for providing better target delineation and better critical organ preservation thereby reducing acute radiation induced toxicities.

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