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"Three Dimensional Conformal Radiotherapy with Bilateral Wedge Fields versus Field in Field Technique in Operated Cases of Head and Neck Cancer, a Study from Rural Cancer Center of Maharashtra, India"

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ABSTRACT

OBJECTIVES: To study the treatment outcome in terms of, local control of disease, disease free survival, toxicities and to demonstrate dosimetric parameters in post operated cases of head and neck cancer undergoing 3DCRT with WF and FIF technique.

METHODOLOGY: 38 patients were enrolled in the study and randomly divided in two groups of 19 patients each. Group A received CTRT via FIF technique and Group B received treatment using WF technique. All the patients were assessed for RT and CT induced toxicities during and after the treatment completion based on RTOG guidelines and response was assessed according to RECIST v 1.1. Out of these 38 patients, a group of 20 patients were randomly selected for dosimetric analysis. For each of these 20 patients, two plans were generated on the same PTV, one of each with bilateral WF and FIF technique.

The dosimetric parameters like – maximum dose (D max), Conformity Index (CI), Homogeneity index (HI), mean dose (D mean) and PTV volume in percentage receiving 95% dose (D95%) were calculated.

RESULTS:

The clinical study of 38 patients did not show any statistical significance for the toxicity parameters. However, in the response evaluation depicted that at the end of 3 months, there was 100% CR, 86.8% CR by the end of 6 months and 57.9% CR on third follow up. Loss of follow up was seen for 18.4% of patients. There was no statistical difference for response between the two groups

In the current study, CR was observed in a total of 22 patients (57.89%). Disease progression was seen only in advanced stage patients (Stage III and Stage IV) and none of the early stage patients (Stage II) had disease progression. Out of 38 patients, a total of nine patients (23.63%), all belonging to locally advanced stage (Stage III, IV A and IV B) experienced disease progression out of which eight patients showed loco-regional recurrence and only one patient showed evidence of distant metastasis.

Dosimetric analysis showed statistically significant P value of HI, CI, Dmean, Dmax and PTV Volume in % at D95 indicating FIF had a better homogenous dose distribution for a given PTV and that it also decreases the chances of hotspot as compared to WF technique.

CONCLUSION:

The study revealed no significant difference between the early and late toxicities amongst the two arms. Response assessment showed that most of the patients with locally advanced disease experienced disease progression. The study helps us to establish that FIF is a better alternative to WF technique in terms of dose distribution to the PTV as well as normal tissue sparing in 3DCRT for post operated cases of head and neck carcinoma.

KEYWORDS: Three Dimensional Conformal Radiotherapy(3DCRT),Wedge field, Field – in – field technique, operated cases of head and neck carcinoma.

I. INTRODUCTION:

Head and neck carcinomas (HNCs) are malignant tumors of the upper aerodigestive tract including oral cavity, nasopharynx, oropharynx, hypopharynx, salivary glands, paranasal sinuses and larynx.[1] HNC is a common and aggressive malignancy with high morbidity and mortality profile. It is ranked as the 17th most common cancer in the world with more than 8,75,000 patients afflicted and around 4,40,000 deaths each year worldwide. In India, head and neck cancer ranks as the second most common cancer type with approximately 1.35 million patients diagnosed annually. It is the most common cancer among Indian men. [2] Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC).

In India, the incidence is higher in Assam, Manipur, Mizoram, Tripura, and Nagaland (54%).

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The possible reasons for the higher incidence of HNCs in India include extensive use of tobacco, pan masala (which include betel quid, areca nuts, and slaked lime), and gutkha.

Head and Neck Carcinoma (HNC) is multi-factorial in origin. It results due to a combination of genetic predisposition and environmental factors, such as exposure to carcinogens, often due to lifestyle habits. According to recent worldwide estimates, one billion men and 250 million women are cigarette smokers, 600-1200 million people chew betel quid, and two billion people consume alcohol.Tobacco use including smokeless tobacco (SLT), betel-quid chewing, excessive alcohol consumption, poor oral hygiene, nutrient-deficient diet, and sustained viral infections, like human papillomavirus (HPV) are some of the risks associated with the occurrence of oral cancer. Lack of knowledge, exposure to extreme environmental conditions, and behavioural risk factors are indicators of a wide variation in the global incidence. Periodontal diseases are also a cause for oral malignancy, and it has a higher incidence among the Indian population due to poor oral hygiene and habit of chewing paan[10].

The complexities of head and neck cancer (HNC) makes multidisciplinary team (MDTs) involvement with training not only in treatment but also in supportive care (considering swallowing, nutritional, dental, and voice impairment due to the effects of clinical intervention), a necessary approach. MDT should include not only an ear, nose, throat surgeon, radiation oncologist and medical oncologist, and radiologist but also a dietician, dentist, pain physician, and swallowing physician.

Treatment modalities available are – Surgery, Radiation therapy, Chemotherapy,Biological or targeted therapy. These modalities can be used alone or as a combined modality approach.

Treatment options are selected depending upon the stage of the disease and performance score of the patient. Data from recent clinical trials have led to the refinement of current therapies and new treatment options.

Surgery is a preferred choice in early stage, accessible disease and those who are less responsive to Radiation. Definitive Radiation therapy (RT) plays an important role in treatment of locally advanced head and neck cancers (LAHNC)

Head and neck radiotherapy treatment has been evolved from two dimensional (2D) to three dimensional conformal therapy (3DCRT) and intensity modulated radiation therapy (IMRT) and recently to the more efficient volumetric modulated arc therapy (VMAT) and Image Guided Radiation Therapy (IGRT).[11] Despite IMRT became the principle modality for treating head and neck tumors because of its ability to conform the dose on the tumor and to reduce the dose to the surrounding organs at risk (OAR) to high extent, also 3DCRT can do this task sufficiently through using some ”forward” planning with 3-D conformal techniques. 3DCRT gives the opportunity to the target and the organs at risk to be delineated in three dimensions and with the utilization of Multi-Leaf Collimator (MLC), the desired dose coverage can be shaped around the target, simultaneously the irradiated healthy tissues can be minimized [12]. Doses up to 70Gy with a conventional fractionation of 2Gy per fraction may be prescribed.

In 3DCRT, various techniques have been developed, of which Field in Field (FIF) and bilateral wedge field technique are the ones most widely used to improve dose distribution to planning target volumes (PTVs) and OARs.All treatment plans are evaluated according to the dose-volume histogram (DVH). Various dosimetric parameters evaluated on DVH are the D-mean, maximum dose (D-max), Conformity Index (CI) and Homogeneity index (HI) to assess the effectivity of the plans before delivering treatment to the patients.

II. MATERIALS AND METHODOLOGY:

Thirty eight consecutive histologically proven operated cases of head and neck carcinoma patients (25-70 years) attending radiation oncology OPD between October 2019 to May 2021 fulfilling the inclusion criteria were included. All the patients were planned for adjuvant radiotherapy (RT) either using bilateral wedge fields (WF) or Field – in – Field (FIF) technique. All the patients were immobilized in supine position using perforated head and neck mould (thermoplastic cast) which is a 4 clamp orfit with proper head and neck support mounted on carbon fiber board that allowed proper patient positioning. Head and neck patients are also given proper shoulder traction for proper coverage of lower neck and to keep shoulders out of the field. At the time of simulation, external fiducial markers are placed over the bony landmarks of the orfit before obtaining CT scan. Radiotherapy planning CT scan with contiguous 2mm slice thickness were obtained on Siemens CT Scan Machine with intravenous contrast and was transferred to the ECLIPSE 15.6.8 treatment planning system contouring stations using Digital Imaging and Communications in Medicine

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(DICOM) protocol, where delineation of target and normal structures were performed on each axial slice using Radiation Therapy Oncology Group (RTOG) contouring guidelines.
After the treatment completion, patients were assessed for toxicity according to Radiation Therapy Oncology Group (RTOG) toxicity criteria and response was assessed based on Response Evaluation Criteria In Solid Tumors v 1.1 (RECIST 1.1).

Out of a total of 38 patients, twenty patients were randomly selected for dosimetric analysis. For each of these 20 patients, two plans were generated on the same PTV, one of each with bilateral WF and FIF technique. The dosimetric parameters like – maximum dose (D max), Conformity Index (CI), Homogeneity index (HI), mean dose (D mean) and PTV volume in percentage receiving 95% dose (D95%) were calculated and compared between the two groups.

III. RESULTS AND OBSERVATIONS:

General parameters of the patients enrolled in the study has been illustrated in Table 1. The clinical study of 38 patients did not show any statistical significance for the toxicity parameters.

TABLE 1: General Parameters of the patients enrolled in the study

Age group (in years)	30-50 51-70	16 22
Gender	M F	30 08
Site of Primary	Tongue Buccal mucosa GBS Lower alveolus Lower lip Floor of mouth Tonsil	14 12 04 04 01 01 02
Histopathology	WDSCC MDSCC PDSCC	12 18 08
Stage	II III IV A IV B	11 15 05 07

Groupwise and Stagewise response has been illustrated in the tables 2 and 3 respectively:

TABLE 2: Follow Up Of The Patients

FOLLOW UP		FIF	WF	Total
Response At 1st F/up (3 months)	CR	19	19	38 (100%)
Response At 2nd F/up (6 months)	CR PD (Nodal recurrence) PD (distant metastasis)	16 02 01	17 02 00	33 (86.8%) 04 (10.5%) 01 (2.63%)
Response At 3rd F/up (9 months to 12 months)	CR PD (Nodal recurrence) PD (Recurrence at primary) PD (distant metastasis) Loss of follow up	12 03 01 01 02	10 03 01 00 05	22 (57.9%) 06 (15.7%) 02 (5.26%) 01 (2.63%) 07 (18.4%)

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TABLE 3: Stagewise Response assessment using RECIST 1.1 Criteria						
	CR	**PD (Nodal recurrence)**	**PD (Recurrence at primary)**	**PD (Distant metastasis)**	**Loss of Follow up**	**Total**
EARLY STAGE (Stage II)	10 (90.9%)	0	0	0	1 (9.09%)	11
LOCALLY ADVANCED (Stage III, IV A and IV B)	12 (44.4%)	6 (22.22%)	2 (7.4%)	1 (3.70%)	6 (22.22%)	27

Dosimetric analysis showed statistically significant P value of HI, CI, Dmean, Dmax and PTV Volume in % at D95 indicating FIF had a better homogenous dose distribution for a given PTV and that it also decreases the chances of hotspot as compared to WF technique. It has been illustrated in the table below:

TABLE 4: Dosimetric Analysis						
S.No			**Mean ± SD**	**Median**	**Mini-Max**	**P value**
1	HI	FIF	0.16±0.05	0.14	0.11-0.31	0.011
		WF	0.20±0.06	0.19	0.14-0.34	
2	CI	FIF	1.01±0.04	0.99	0.96-1.09	0.002
		WF	1.12±0.13	1.08	0.97-1.40	
3	Dmean	FIF	101.14±1.06	101.10	99.5-103.5	0.0003
		WF	99.32±1.97	99.15	96.3-102.7	
4	Dmax	FIF	109.74±0.92	109.55	108.4-111.6	0.0001
		WF	110.84±0.67	111.10	109.6-111.7	
5	PTV Volume in % at D95	FIF	94.14±3.92	96.08	86.90-99.28	0.0001
		WF	84.82±9.33	85.65	67.60-97.40	

IV. DISCUSSION:

HNC is the second most common malignancy in India and is the most common malignancy in Indian men as stated in GLOBOCAN 2020.

Most commonly used addiction among the patients enrolled in this study was found to be smokeless tobacco (SLT) in various forms. While smoked tobacco and alcohol are the major causative factors for HNC worldwide, smokeless tobacco and betel nut are etiological agents responsible for it in the Indian population. Tobacco has been consumed in various forms like guthka, beedi and mishri. In this study, addiction with smokeless tobacco was seen most frequently in both the groups where tobacco chewing alone was more in FIF arm and Mishri abuse was seen more commonly in WF arm. This study also revealed significant use of tobacco by the patients in combination with mishri, guthka or alcohol abuse. The P value calculated was 0.33 for addiction between the two arms and was not significant statistically. Similar results with higher rates of addiction with smokeless tobacco in various forms were also observed in a study by **Jain V.S et al** in 2015 where addiction with SLT alone was recorded as 44.95% and in combination with alcohol it was recorded as 27.52%. [13]

In this study, it was observed that most of the patients belonged to locally advanced stages (Stage III and IV) accounting for 71% of the total cases. It was comparable to a study by **Rajjyoti et al**, where 83.8% HNC patients presented with locally advanced stage (stage III and stage IV combined) at the time of diagnosis. Also in a study by **VS Jain et al** in 2017, 69% patients reported were in advanced Stages III and IV of the disease which was again similar to the current study.[14,15]

The clinical parameters of acute and late toxicities did not witness any statistically significant difference amongst the two groups of FIF and WF in the current study.

Dosimetric analysis was done by generating two plans on the same PTV after selecting 20 patients (10 patients from each FIF and WF group) randomly from the total patients that were enrolled in this study.

In this study, The Mean ± SD of Homogeneity Index (HI) for FIF was calculated as 0.16±0.05 and the same for WF, it was calculated as 0.20±0.06. Median value calculated for FIF group was 0.14 with a range of (0.11-0.31) and the same for WF was calculated as 0.19 with a range of (0.14-0.34). The P value of HI was 0.011 which is statistically significant indicating FIF had a better homogenous dose distribution for a given PTV.

The Mean ± SD of Conformity Index (CI)for FIF was calculated as 1.01±0.04 and the same for WF, it was calculated as 1.12±0.13. The Median value for CI in this study for FIF was 0.99 with a range of (0.96-1.09) and for WF was 1.08 with a range of (0.97-1.40). The P value for CI was calculated as 0.002 which is statistically significant inferring that for the given PTV, use of MLCs in FIF provides a better conformity.

The value of Mean ± SD for Dmean in our study for FIF was 101.14±1.06 and the same for WF was 99.32±1.97. The Median value for Dmean in FIF was calculated as 101.10 with a range of (99.5-103.5) and the same for WF was 99.15 with a range of (96.3-102.7). The P value calculated was 0.0003 which is statistically significant indicating a higher mean dose to the PTV when treated with FIF as compared to WF technique.

The value of Mean ± SD for Dmax in this study for FIF was 109.74±0.92 and the same for WF was 110.84±0.67. The Median value for Dmax in FIF was 109.55 with a range of (108.4-111.6) and the same for WF was 111.10 with a range of (109.6-111.7). The P value for Dmax was calculated as 0.0001 which is statistically significant favouring FIF. For an ideal plan PTV, no more than a minimum diameter of 15mm of PTV should receive ≥107% (maximum dose) of the prescribed dose [as per ICRU 50] to prevent hotspot and severe radiation toxicities to the surrounding normal tissues.

In this study, PTV Volume in % at D95 was calculated for both FIF and WF. For FIF, the value of Mean ± SD was calculated as 94.14±3.92 and the same for WF was calculated as 84.82±9.33. The Median value of 96.08 with a range of (86.90-99.28) for FIF and for WF the Median value of 85.65 with a range of (67.60-97.40) was calculated. The P value was 0.0001, which is statistically significant indicating that PTV volume receiving 95% of prescribed dose is more with FIF technique.

Similar dosimetric results were observed with a study by **Gurkha M. et. al**where FIF plans and WF plans were compared for early glottis carcinomas. In this study, better CTV coverage with better D95% was achieved for FIF plan even though here Dmax was slightly more for FIF plan. HI was found to be better with FIF technique providing a better homogeneity to the given CTV and hence assured that FIF can be an alternative for wedge field technique.[16]

Another study that supported the current study was carried out by **R. Prabhakar. et .al** in 2008, where two plans with FIF and WF technique were generated on the same PTV. Results showed that FIF is better than wedge planning in terms of maximum dose, D2, V>107% and CI for most of the sites and hence it is feasible to replace wedge filter with FIF in radiotherapy treatment planning.[17]

The goal of these techniques is to treat PTV with a homogeneous dose distribution, sparing the spinal cord, and other OARs in the treatment region. The above mentioned studies favour the use of FIF over WF which is similar to the results produced in our study.

Responses for all the patients enrolled in the study were assessed using RECIST v1.1.

At first follow up (3 months after treatment completion), both the groups recorded 100% Complete Response (CR) with 19 patients belonging to each FIF and WF group.

Response assessed at second follow up (6 months after treatment completion) showed that 86.8% of patients (16 from FIF and 17 from WF arm) had CR. A total of 13.13 patients had Progressive Disease (PD) where 10.5% had nodal recurrence and only 1 patient in FIF arm showed the evidence of distant metastasis.

At the third follow up (9 to 12 months after treatment completion), a total of 57.9% of patients had CR (12 patients in FIF group and 10 in WF group). 23.59 % of patients had PD with 3 patients in each group had nodal recurrence, 1 in each arm developed recurrence at the primary site and only 1 in FIF group progressed to distant metastasis.

Loss of follow up of 2 patients in FIF arm and 5 patients in WF arm was observed at the end of 12 months from the treatment completion.

All the patients in the study were also assessed for the response based on their stage at diagnosis. None of the patients belonged to Stage I. Disease recurrence and progression was common in advanced stages (Stage III and Stage IV which was recorded in the form of recurrence at primary and nodal or distant metastasis and none of these was seen with the early staged disease (Stage II). Out of 38 patients, a total of nine patients (23.63%), all belonging to locally advanced stage (Stage III, IV A and IV B) experienced disease progression out of which 8 patients showed loco-regional recurrence and only one patient showed evidence of distant

metastasis. A study by **NerinaDenaro.et al,** onFollow-up in Head and Neck Cancer stated that 50% to 60% of patients with locally advanced disease develop a loco-regional recurrence within 2 years and 20% to 30% develop distant metastases. [18]

In view of current COVID-19 pandemic, follow up amongst the patients in our study was very poor where 18.4% patients showed loss of follow up.

V. CONCLUSION:

HNC is an important health issue in India and worldwide as it is one of the most common types of cancer affecting a large population.It needs a multidisciplinary team management to ascertain the diagnosis, management of HNCs and for supportive care during and after the treatment. RT plays in the role in the treatment. 3DCRT with various techniques using beam modifying devices have been developed, of which Field in Field (FIF) using Multi Leaf Collimators (MLCs) and bilateral wedge field technique using Enhanced Dynamic Wedges (EDW) are the ones most widely used to distribute a homogenous dose to the target volume using conformal techniques.

No significant difference was observed amongst the two study groups of FIF and WF in terms of acute and late tissue toxicities.

Dosimetric analysis showed statistically significant results favouring FIF technique with respect to homogenous dose distribution, dose conformity, mean dose to the PTV, maximum dose which was less for FIF reflecting that hotspot can be better avoided with FIF technique. PTV volume in % at 95% dose was better with FIF when compared to WF technique indicating that PTV volume receiving 95% of prescribed dose is more with FIF technique.

Response assessment showed that most of the patients with locally advanced disease experienced disease progression.

The study helps us to establish that FIF is a better alternative to WF technique in terms of dose distribution to the PTV as well as normal tissue sparing.

Treating head and neck carcinomas possesses a great challenge even with the use of multimodality treatment approach. Other factors like poor hygiene and improper oral intake, presence of any comorbid condition and disease nature also affects the treatment outcome.

The current COVID -19 pandemic made it difficult for the patients to report for regular follow ups. As a result, patients could not undergo a timely assessment which in turn affected the overall treatment outcome.

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