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A Prospective Study for Comparison of Dosimetric Analysis, Radiation Induced Toxicities and Response in Flattening Filter Versus Flattening Filter Free Beam in Oral Cavity Cancers

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ABSTRACT

Aim: This study aimed to compare the response, dosimetric parameters and toxicities of IMRT with Flattening Filter(FF) photon beam and Flattening Filter Free(FFF)photon beam in Oral Cavity cancers.

Material and Methods-This study was conducted as prospective observational study on total of 60 cases of oral cavity cancerat our institute during study period of 2 years. All 60 participants were randomly assigned into either of the two treatment group IMRT-FF and IMRT-FFF.Patients were followed and assessment of dosimetric parameters, response and toxicities grading was done.

Results- Two groups were comparable with respect to baseline variables and tumor characteristics and treatment ($p>0.05$). Mean number of fractions, as well as dose to brainstem, spinal cord and parotid were significantly higher in FF group as compared to FFF group ($p<0.05$). The response rate following radiation was found to be significantly better in FFF group as compared to FF group ($p<0.05$). Skin toxicities were significantly higher in FFF group at 3 months ($p<0.05$) whereas parotid as well as oral cavity were significantly higher in FF group at 3 and 6 months ($p<0.05$).

Conclusions-Intensity Modulated Radiation Therapy (IMRT) is common modality used for management of oral cavity cancer. FF photon beam and FFF photon beam, both modalities were compared in this study and we found that removal of flattening filter helps in equivalent delivery of dose of radiation to target tissue, with reduced scattering and leakage of radiation dose to adjacent normal tissues thereby reducing the risk of toxicities of organ at risks.

Key Words: *Intensity-modulated Radiation Therapy, Flattening Filter, Flattening Filter Free,Oral Cavity Cancer, Lip carcinoma*

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INTRODUCTION:

Carcinoma of oral cavity is one of the most common cancers documented across the globe.[1] It includes the cancer of lips, anterior two third of tongue, hard palate, retromolartrigone, buccal mucosa, gingiva and floor of mouth.[2] According to Global Cancer Observatory(GLOBOCAN) 2020, carcinoma of lip and oral cavity attribute to 2% of the new cancer cases with a proportional mortality rate of 1.8%.[3] As per GLOBOCAN 2020, lip and oral cavity cancers rank second among all the cancers with incidence rate of 10.3% in both the gender, and incidence of lip cancer is reported to be about 16.2% cases in males and 4.6% in females.[4]

The management of tumor depend upon the site, size and age of the patient. For early oral cancer, surgery and radiation therapy either alone or in combination are used.[5] Primary radiotherapy with or without chemotherapy may be the treatment of choice for locally advanced tumors if bone is not involved.[5] For radiation therapy, Intensity modulated radiation therapy (IMRT) is preferred.[6] Though IMRT has various advantages, one of the major drawback is higher leakage of radiation dose from the gantry head due to high monitoring units which results in leaking of radiation to the normal tissues, increasing the risk of second tumor induction.[7,8] It is therefore important to reduce the duration of dose delivery time and scattering of radiation dose from the head of gantry.[9] IMRT was done with flattening filter technique, which was initially introduced to provide flat doses of radiation at certain desired depth. To reduce the scattering from gantry head and for higher dose rate, removal of flattening filter is recommended.[9,10]

The modern linear accelerator (LINAC) systems utilize FFF method for delivering the higher dose of radiation at target side with reduced scattering of radiation dose to normal tissue. Based upon this modern linear accelerator (LINAC) systems, recent literature is mainly aimed at exploring the role of FFF photon beam in various cancers.[11,12] The FFF technique allow the delivery of forward peaked dose profile, thus delivering the higher dose of radiation at target site and reduced scattering of dose, reduced dose delivery at organ at risk, beam hardening and also neutron fluence for high energy of x-ray used in linac.[12,13]

The literature exploring the application of FFF mode of a LINAC in patients with oral caners especially in Indian scenario is scarce. This study was therefore conducted to compare the response, dosimetric analysis and toxicities of IMRT with FF and FFF beam in Oral Cavity cancers.

Material and Methods:

The present study was conducted as prospective observational study on total of 60 cases of oral cavity cancer reporting at our institute during the study period of 2 years i.e. from 1st December 2020 to 30th November 2022. Histopathologically confirmed cases of oral cavity cancer belonging to age range of 18 to 70 years with Karnofsky Performing Scale (KPS) of more than 70 were included whereas patients with oral cavity cancer not willing to participate in the study were excluded.

After obtaining ethical clearance from Institutional ethics committee of the institute, with Ethics Committee Registration No. ECR/1055/Inst/MP/2018 and approval dated 26/08/2021,all the patients fulfilling inclusion criteria were enrolled and written consent was obtained. Detailed history regarding sociodemographic factors and clinical variables was obtained and documented in proforma. Histopathology Report (HPR) proven cases of carcinoma oral cavity were evaluated for radiation (IMRT) and 60 eligible patients were treated by either FF beam (30 patients) or FFF beam (30 patients) on the basis of clinical judgement of treating consultant patient. After simulation on CT simulator, the data was transferred to treatment planning system, the ECLIPSE. The delineation of tumor and organ at risk (OAR) was performed and IMRT treatment plans were generated using FF photon beam and FFF photon beam. The different dosimetric parameters for OARs were assessed and compared. Thereafter response assessment was done according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria] and toxicities grading was done by Radiation Therapy Oncology Group (RTOG) criteria. All the patients were followed up at 0 month (at the initiation of treatment), 3 months and 6 months and response rate and toxicity if any were assessed.

Statistical analysis:

Data was compiled using MsExcel and analysed with the help of IBM SPSS software 20 (SPSS, Illinois, Chicago). Continuous variables were expressed as mean and standard deviation whereas categorical variables were expressed as frequency and proportion. Continuous variables between two groups were compared using independent t test whereas categorical variables were compared using Chi square test. P value of less than 0.05 was considered statistically significant.

Results:

The present study was conducted on a total of 60 cases of oral cavity cancer presenting at our study centre and based upon the radiation planning beam, patients were categorized into two groups (i) FF beam and (ii) FFF beam.

Mean age of patients belonging to FF group was 47.73±10.4 years whereas mean age of patients in FFF group was 46.37±9.96 years. Two groups were comparable with respect to baseline variables (p>0.05). None of the patients in both the groups had family history of cancer (p>0.05) [Table1].

Table 1- Distribution of baseline variables between two groups

Baseline variables		Flattening filter beam (n=30)		Flattening filter free beam (n=30)		P value
		N	%	n	%	
Age (years)	≤40	9	30.0	10	33.3	0.84
	41-50	8	26.7	9	30.0	
	51-60	9	30.0	6	20.0	
	>60	4	13.3	5	16.7	
Sex	Male	26	86.7	25	83.3	0.72
	Female	4	13.3	5	16.7	
Religion	Hindu	27	90.0	28	93.3	0.64
	Muslim	3	10.0	2	6.7	
Residence	Rural	18	60.0	15	50.0	0.44
	Urban	12	40.0	15	50.0	
Addiction	None	1	3.3	1	3.3	0.335
	Tobacco	19	63.3	14	46.7	

	Tobacco and alcohol	3	10.0	4	13.3	
	Tobacco and smoking	6	20.0	5	16.7	
	Tobacco, smoking & alcohol	1	3.3	6	20.0	
KPS	70	21	70.0	24	80.0	0.37
	80	9	30.0	6	20.0	

Abbreviations: KPS- Karnofsky Performing Scale; IMRT- Intensity Modulated Radiotherapy; FFF- flattening filter free; FF- flattening filter

Most common site of oral cavity cancer was buccal mucosa in 70% and 60% cases of FF and FFF group respectively. Majority of cases of FF group had stage IV A cancer (30%) whereas 43.3% cases belonging to FFF group had stage III cancer. Histopathology was suggestive of well differentiated squamous cell carcinoma in 73.3% cases in FF group and 66.7% cases in FFF group. Two groups were comparable with respect to tumor characteristics and treatment ($p>0.05$) [Table 2].

Table 2- Distribution of tumor characteristics and treatment between two treatment groups

Tumor characteristics			Flattening filter beam (n=30)		Flattening filter free beam (n=30)		P value
			n	%	n	%	
Site	Buccal mucosa	Right	10	33.3	5	16.7	0.53
		Left	11	36.7	13	43.3	
	Lateral border of tongue	Right	5	16.7	9	30	
		Left	4	13.3	3	10.0	
Stage	I		4	13.3	3	10.0	0.07
	II		4	13.3	6	20.0	
	III		6	20.0	13	43.3	
	IVA		9	30.0	8	26.7	
	IVB		5	16.7	0	0	
	IVC		2	6.7	0	0	
HPR	WDKSCC		22	73.3	20	66.7	0.58
	MDKSCC		7	23.3	7	23.3	
	PDKSCC		1	3.3	3	10.0	
Treatment	CT+EBRT		1	3.3	0	0	0.36
	EBRT+CCT		4	13.3	6	20.0	
	NACT+EBRT+CCT		2	6.7	1	3.3	
	NACT+EBRT+CCT+CT		1	3.3	0	0	
	NACT+SURGERY+EBRT		2	6.7	0	0	
	NACT+SURGERY+EBRT+CCT		0	0	2	6.7	
	SURGERY+EBRT		19	63.3	20	66.7	
	SURGERY+EBRT+CCT		0	0	1	3.3	
	SURGERY+EBRT+CCT+CT		1	3.3	0	0	

Abbreviations: MDKSCC-Moderately Differentiated Keratinising Squamous Cell Carcinoma, PDKSCC- poorly differentiated KeratinisingSquamous Cell Carcinoma, WDKSCC- Well Differentiated Keratinising Squamous Cell Carcinoma. CT- Chemotherapy. EBRT- External Beam Radiation Therapy. CCT- Concurrent Chemotherapy. NACT- Neoadjuvant Chemotherapy HPR- Histopathology Report.

The mean, maximum as well as minimum dose to brainstem and parotid were significantly higher in FF group as compared to FFF group ($p<0.05$). Minimum and mean dose delivery to spinal cord was documented to be significantly higher in FF group as compared to FFF group ($p<0.05$) [Table 3].

Table 3- Comparison of dosimetric parameters between two groups

Dose in Gray		Flattening filter beam (n=30)		Flattening filter free beam (n=30)		P value
		Mean	SD	Mean	SD	
Total dose		62.93	3.39	61.73	2.72	0.14
Brainstem	Max	40.28	4.36	37.24	5.36	**0.02**
	Min	15.37	5.54	4.33	3.09	**0.001**
	Mean	21.51	4.69	17.65	5.51	**0.005**
Parotid	Max	49.45	13.03	19.76	3.51	**0.001**
	Min	7.08	2.85	3.28	3.35	**0.001**
	Mean	19.80	3.51	11.17	1.71	**0.001**
Spinal cord	Max	40.40	4.39	40.22	7.71	0.91
	Min	1.04	0.67	0.59	0.36	**0.002**
	Mean	21.37	4.50	17.03	8.64	**0.02**

The response rate following radiation was found to be significantly better in FFF group as compared to FF group ($p<0.05$) [Figure 1]

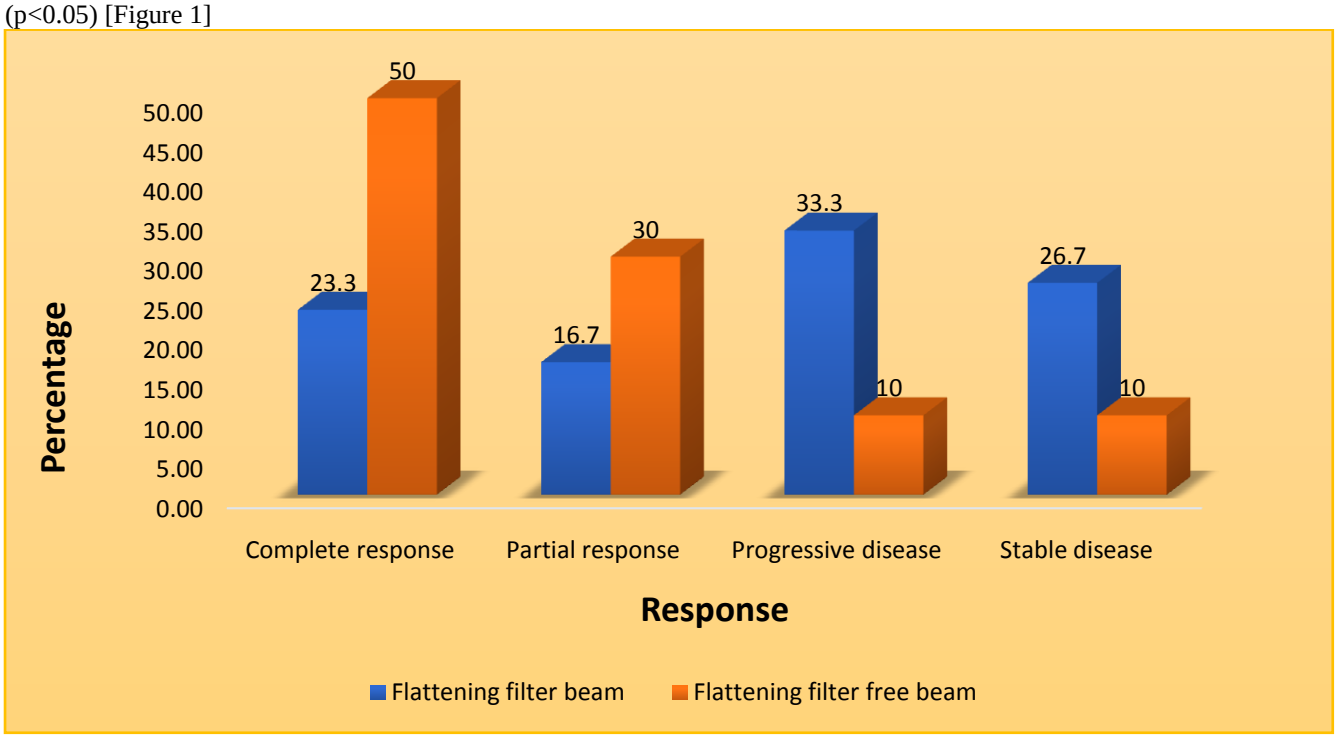

Figure 1: Comparison of response between the groups

In present study, toxicities were observed in none of the cases in both the groups at 0 months. The grade of skin toxicities were significantly higher in FFF group as compared to FF group at 3 months ($p<0.05$) whereas parotid as well as oral cavity were significantly higher in FF group as compared to FFF group at 3 and 6 months ($p<0.05$) [Table 4].

Table 4- Comparison of toxicities between two groups at different time interval

Toxicities			Flattening filter beam (n=30)		Flattening filter free beam (n=30)		P value
			n	%	n	%	
Skin	0 month	Nil	30	100	30	100	NA
	3 months	Grade1	10	33.3	4	13.3	**0.009**
		Grade2	18	60.0	13	43.3	
		Grade3	2	6.7	11	36.7	
		Grade4	0	0	2	6.7	
	6 months	Grade1	18	60.0	10	33.3	0.132
		Grade2	10	33.3	14	46.7	
		Grade3	2	6.7	4	13.3	
		Grade4	0	0	2	6.7	
Parotid	0 month	Nil	30	100	30	100	NA
	3 months	Grade1	7	23.3	20	66.7	**0.001**
		Grade2	23	76.7	10	33.3	
	6 months	Grade1	6	20.0	18	60.0	**0.002**
		Grade2	24	80.0	12	40.0	
Brainstem	0 month	Nil	30	100	30	100	NA
	3 months	Nil	30	100	30	100	NA
	6 months	Nil	30	100	30	100	NA
Oral cavity	0 month	Nil	30	100	30	100	NA
	3 months	Grade1	0	0	6	20.0	**0.001**
		Grade2	13	43.3	20	66.7	
		Grade3	17	56.7	4	13.3	
	6 months	Grade1	0	0	8	26.7	**0.008**
		Grade2	24	80.0	19	63.3	
		Grade3	6	20.0	3	10.0	

DISCUSSION:

Intensity modulated radiation therapy (IMRT) is preferred form of radiation therapy and it is equipped with treatment planning system and Modern linear accelerator (LINAC).[15] Though IMRT is preferred over 3DCRT, it is associated with leakage of radiation to the adjacent nearby tissues from the gantry head increasing the risk of secondarytumor induction.[7,8] This high leakage is attributed to flattening filter technique, which provide flat doses of radiation at certain desired depth.[9,10] However, FFF beam technique reduce the leakage and scattering of radiation and thereby reducing the risk of secondary tumors.[16] The disadvantage associated with FF beam technique can be countered by removal of flattening filter, which not only increase the dose delivery to the targeted site, it also reduced scattering of dose, reduce dose delivery to organ at risk, reduce the dose distribution to organ at risk, lead to beam hardening and neutron fluence for high energy of x-ray used in linac.[11,12] This study was conducted on a total of 60 cases of oral cavity cancer and were allocated into either of the two groups. Two groups were comparable for baseline variables and tumor characteristics ($p>0.05$). Though the present study observed no significant difference in total dose delivered to target organ between two groups ($p>0.05$), number of fractions were significantly higher in FF beam group as compared to FFF group ($p<0.05$). The dose of radiation delivered to organs at risk, i.e. brainstem, parotid gland and spinal cord were documented to be significantly higher in FF group as compared to FFF group. This findings suggests FFF filter helps in reducing the leakage of radiation to organ at risk and adjacent nearby normal tissues.

Our study findings were comparable with the findings of in which Dobbler et al found FFF beam plan to reduce the dose delivery to organ at risk by as high as 18% when compared to FF beam arm and the target dose achievement could be obtained in majority of patients with head and neck cancers with similar delivery time.[17] In a study of Yan et al, the

authors reported differences in FF and FFF beam to be important parameters in management of head and neck cancers, and the maximum reduction in mean dose could be achieved up to significant proportion to the organ at risk.[10]Tamilarasu et al also reported similar number of beams and their orientations for all plan with a significant difference in CI, HI and dose between FF and FFF group.[18] Similarly, Arslan et al found no significant difference in dose delivery to target tissue between two treatment arms but when critical organ doses were compared, the risk of dose delivery to organ at risks were significantly lower in FFF group as compared to FF group.[19]

The present study aimed to assess the response rate between the two treatment groups. The response was assessed using RECIST criteria.[14] We reported significantly better response in FFF group with complete response in 50% in FFF and 23.3% in FF group. However, disease was progressive/ stable in significantly higher proportions of cases of FF group (60% in FF group and 20% in FFF group) ($p<0.05$). None of the previous studies have assessed and compared the response rate between FF and FFF beam plans of IMRT, rather limited studies have been done for dosimetric comparison between FF and FFF beam plans. Though dose delivery to target organs in both the treatment were found to be comparable in our study, response rate was found to be better in FFF treatment plan group as compared to FF group. This could be attributed to low radiation leakage and reduce radiation delivery to organ at risk, lower risk of organ toxicities and associated adverse effects, thereby improving the compliance and tolerability in FFF group.

In present study, FFF beam therapy was associated with significantly higher grades of skin toxicities at 3 months whereas parotid and oral cavity toxicities were significantly higher in FF group at 3 as well as 6 months ($p<0.05$). Brainstem toxicities was observed in none of the patients irrespective of type of treatment group. These findings were supported by Tamilarasu et al where the authors reported significantly lower dose delivery to organ at risk in FFF group as compared to FF group, reducing the risk of toxicities to organ at risk.[18] Similar findings were documented by Dobbler et al, in which the authors suggested that using FFF beam therapy of IMRT, peripheral doses delivery to organ at risk could be significantly reduced by 18% as compared to FF beam and hence this may be associated with significant reduction in organ toxicities and reduction in risk of second cancer induction.[17]Kry et al also found removal of flattening filter to improve the dose delivery to target tissue with reduced radiation leakage to organ at risk, thereby sparing the adjacent critical organs at risk, and hence reducing the long term risk of secondary cancer.[20]

The study had certain limitations, first the sample size of the study was small and patients were followed up for only a short duration of time and hence long term toxicities could not be compared.

CONCLUSION:

Oral cavity cancers are one of the common cancers, the incidence of which is higher in elderly and males. Squamous cell carcinoma is the most common histopathological form of oral cavity cancer, with majority of cases presenting with locally advanced cancer. These patients often require multimodality management as majority of cases present in locally advanced stage. IMRT is common modality used for management of oral cavity cancer. Flattening filter beam and flattening filter free beam both the modalities were compared in this study and we found that removal of flattening filter helps in equivalent delivery of dose of radiation to the target tissue, with reduced scattering and leakage of radiation dose to the adjacent normal tissues thereby reducing the risk of toxicities of organ at risks.

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