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Original Article

A Prospective Study to Compare the Intensity-Modulated Radiation Therapy Planning by Flattening Filter Versus Flattening Filter free Beam in Carcinoma Larynx

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ABSTRACT

Aim: The application of Flattening Filter Free (FFF) mode of a linear accelerator may be utilized in management of carcinoma larynx. The study aimed to compare the dosimetric analysis, toxicities of patients treated as well as response rate among them with Flattening Filter (FF) and FFF beam for Carcinoma Larynx.

Material and Methods: This study was conducted as prospective observational study on 60 cases of carcinoma larynx at our institute during study period of 2 years. Patients were randomly treated by either FF beam (30 patients) or FFF beam (30 patients) and dosimetric parameters for both plans were assessed along with response and toxicities at 0, 3, and 6 months.

Results: Two groups were comparable with respect to baseline variables and tumor characteristics ($p>0.05$). We found dose of radiation to parotid gland, spinal cord, and oral cavity to be significantly higher in FF treatment group as compared to FFF treatment group ($p<0.05$). Complete response to therapy was significantly better in FFF beam therapy as compared to FF beam therapy ($p<0.05$). Parotid toxicities were significantly higher in FF group at 6 months and toxicities for oral cavity and larynx were found significantly higher in FF group at 3 as well as 6 months ($p<0.05$).

Conclusions: IMRT is one of the common treatment modalities used in management of patients with carcinoma larynx. FFF beam is as effective as FF beam therapy in delivering the dose of radiation to the target tissue, with minimum radiation leakage to the adjacent normal tissues thereby reducing the risk of toxicities of organ at risks (parotid and oral cavity) and inducing better clinical response. The most beneficial character of FFF beam plan is clinically desirable and physically acceptable treatment plan at lower dose for target coverage and reduction of peripheral dose around target without compromising the quality of beam.

Key Words: *Toxicities, Laryngeal Cancer, Flattening Filter, Flattening Filter Free, Intensity-modulated Radiation Therapy*

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INTRODUCTION

According to Global Cancer Observatory (GLOBOCAN) 2020, laryngeal cancer represents 1% of all the cancers worldwide attributing to mortality in 1% cases [1]. The age standardized rate of Carcinoma Larynx in male and female is documented to be 3.6 and 0.5 respectively according to GLOBOCAN 2020 data [1]. In India, Cancer larynx represents 11th most common cancer and cause of death as per GLOBOCAN 2020 data, attributing to 2.6% new cases and 2.5% deaths [2]. The treatment of carcinoma larynx vary depending upon the anatomical site and stage of laryngeal cancer [1]. The intensity-modulated radiation therapy (IMRT) is most commonly used modality for radiation therapy and it has been considered as successful mode of radiation therapy when done with the help of computed tomography (CT) as a tool in planning of treatment [3].

The treatment planning system and modern linear accelerator (LINAC) of IMRT have resulted in increased use of IMRT globally [4]. The drawback associated with IMRT is that it has higher monitoring units (MU) as compared to Three Dimensional Conformal Radiation Therapy (3DCRT) leading to higher leakage of the radiation dose from the head of gantry and thus delivering higher dose to the normal tissues as well as to the whole body [5, 6]. This leakage of radiation dose is associated with increased risk of induction of secondary tumor. Thus, it is essential to reduce the unnecessary leakage and scattering of radiation dose from gantry head along with shortening the duration of IMRT [7]. To overcome this issue, flattening filter removal have been suggested by few authors [8].

The technique of flattening filter was initially introduced to provide the flat doses at certain depth. However, modern LINAC systems of IMRT eliminates the need of flattening filter. One of the major characteristic of FFF beam is its forward peaked dose profile, along with increased dose rate at the targeted site, reduced dose distribution at organ at risk, reduced uncertainty in dose calculation, and reduced contamination of neutron of high energy beams (>15MV) as compared to filter flattening technique [9-11]. Thus FFF application in clinical practice is thought to be associated with reduced treatment time and reduced risk of secondary cancer due to radiation [12, 13]. The application of FFF mode of a linear accelerator may be utilized in management of carcinoma larynx so as to reduce the risk of secondary cancers. With the above background, this study was conducted to compare the different dosimetric parameters, toxicities of patients treated as well as response rate among them with FF and FFF beam for Carcinoma Larynx.

MATERIAL AND METHODS

The present study was conducted as prospective observational study on total of 60 cases of cancer larynx reporting to Department of Radiation Oncology, Govt. Medical College of Central India and associated hospital during the study period of 2 years i.e. from 1st December 2020 to 30th November 2022. Histopathologically confirmed 60 cases of Carcinoma Larynx belonging to age range of 18 to 70 years with Karnofsky Performing Scale (KPS) of more than 70 were included whereas patients not giving consent 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. Detailed sociodemographic and clinical history was obtained from them, following which they were subjected to detailed clinical examination and findings were entered in proforma. Further, laboratory workup was done in each case. Histopathology Report (HPR) proven cases of carcinoma larynx were evaluated for radiation (IMRT) and60 eligible patients were randomly treated by either FF photon beam technique (30 patients) or FFF photon beam technique (30 patients). 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 [14] 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 Ms Excel and analysed with the help of IBM SPSS software version 20 (IBM Corp. 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 with carcinoma larynx fulfilling inclusion criteria who were allocated in two groups The mean age of patients belonging to FF photon beam group and FFF photon beam group was 53.03±9.088 years and 59.27±9.667 years respectively. Two groups were comparable with respect to baseline variables (p>0.05). Family history of cancer was present in none of the cases irrespective of the group (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)	≤50	13	43.3	5	16.7	0.08
	51-60	11	36.7	10	33.3	
	61-70	5	16.7	11	36.7	
	71-80	1	3.3	4	13.3	
Sex	Male	26	86.7	27	90.0	0.69
	Female	4	13.3	3	10.0	
Religion	Hindu	28	93.3	21	70.0	0.06
	Muslim	2	6.7	8	26.7	
	Sikh	0	0	1	3.3	
Residence	Rural	22	73.3	19	63.3	0.41
	Urban	8	26.7	11	36.7	
Addiction	Smoking	6	20	7	23.3	0.53
	Smoking and Alcohol	0	0	2	6.7	
	Tobacco	12	40.0	11	36.7	
	Tobacco and Alcohol	1	3.3	1	3.3	
	Tobacco and smoking	4	13.3	4	13.3	
	Tobacco, Smoking	7	23.3	5	16.7	

	& Alcohol					
KPS	70	23	76.7	24	80.0	0.75
	80	7	23.3	6	20.0	

Abbreviations: KPS- Karnofsky Performing Scale; FFF- flattening filter free; FF- flattening filter

Most common site of cancer was vocal cords (50% in FF group and 46.7% in FFF group). Majority of cancer patients had stage IV A cancer in both the groups (53.3% in FF and 70% in FFF group). Histopathology revealed well differentiated squamous cell carcinoma in 66.7% cases in FF group and 53.3% cases in FFF group. Majority of patients were managed with External beam radiotherapy and concomitant chemotherapy in both the groups. We observed no significant difference in tumor characteristics and treatment between the groups (p>0.05) [Table 2].

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

Tumor characteristics & treatment			Flattening filter beam (n=30)		Flattening filter free beam (n=30)		P value
			n	%	n	%	
Site	Epiglottis		4	13.3	4	13.3	0.12
	Aryepiglottic fold	Right	7	23.3	8	26.7	
		Left	4	13.3	2	6.7	
	Arytenoid	Left	0	0	2	6.7	
	Vocal Cord	Right	7	23.3	8	26.7	
		Left	8	26.7	6	20.0	
Stage	I		2	6.7	1	3.3	0.70
	II		4	13.3	2	6.7	
	III		3	10.0	3	10.0	
	IVA		16	53.3	21	70.0	
	IVB		5	16.7	3	10.0	
HPR	WDSCC		20	66.7	16	53.3	0.57
	MDSCC		5	16.7	7	23.3	
	PDSCC		5	16.7	7	23.3	
Treatment	EBRT		1	3.3	1	3.3	0.44
	EBRT+CCT		24	80.0	20	66.7	
	NACT+EBRT+CCT		5	16.7	7	23.3	
	SURGERY+EBRT+CCT		0	0	2	6.7	

Abbreviations: MDSCC-Moderately Differentiated Squamous Cell Carcinoma, PDSCC- poorly differentiated Squamous Cell Carcinoma, WDSCC- Well Differentiated Squamous Cell Carcinoma. CT- Chemotherapy. EBRT- External Beam Radiation Therapy. CCT- Concurrent Chemotherapy. NACT- Neoadjuvant Chemotherapy

We found maximum and mean dose of radiation to parotid gland and oral cavity to be significantly higher in FF group as compared to FFF group (p<0.05). However, mean, maximum as well as minimum dose of radiation to spinal cord was significantly higher in FF 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)		T test	P value
		Mean	SD	Mean	SD		
Total dose		65.80	1.095	65.70	1.208	0.34	0.74
Parotid gland	Max	63.01	2.34	59.96	4.65	**3.21**	**0.002**
	Min	3.09	1.80	2.93	0.90	0.43	0.67
	Mean	25.53	3.21	23.72	1.83	**2.69**	**0.009**
Spinal cord	Max	45.66	4.26	42.47	2.99	**3.36**	**0.001**
	Min	1.56	1.07	0.84	0.49	**3.35**	**0.001**
	Mean	27.97	4.32	23.25	2.57	**5.14**	**0.001**
Oral cavity	Max	64.14	2.71	62.80	2.42	**2.02**	**0.048**
	Min	13.46	2.30	13.40	1.85	0.124	0.90
	Mean	35.64	6.00	21.30	1.47	**12.7**	**0.001**

In present study, complete response to therapy was significantly better in FFF beam therapy as compared to FF whereas the disease was progressive in significantly higher proportion of cases in FF group (p<0.05) [Figure 1].

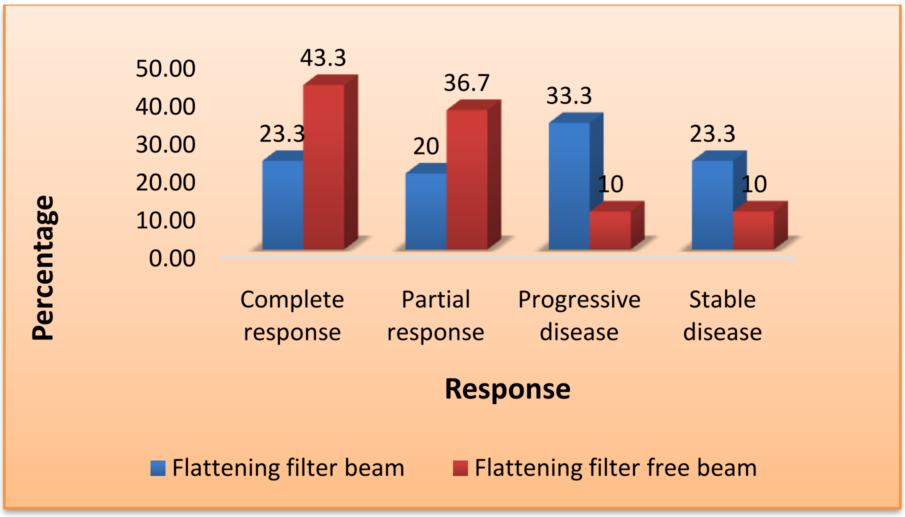

Figure 1: Comparison of response between the groups

In present study, toxicities were observed in none of the cases in both the groups at 0 months, whereas parotid toxicities were significantly higher in FF group as compared to FFF group at 6 months and oral cavity and larynx toxicities were significantly higher in FF group as compared to FFF group at 3 as well as 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	%	
Parotid	0 months	Nil	30	100.0	30	100.0	NA
	3 months	Grade 1	5	16.7	11	36.7	0.08
		Grade 2	25	83.3	19	63.3	
	6 months	Grade 1	4	13.3	16	53.3	**0.001**
		Grade 2	26	86.7	14	46.7	
Spinal cord	0 months	Nil	30	100.0	30	100.0	NA
	3 months	Nil	30	100.0	30	100.0	NA
	6 months	Nil	30	100.0	30	100.0	NA
Oral cavity	0 months	Nil	30	100.0	30	100.0	NA
	3 months	Grade 1	1	3.3	7	23.3	**0.007**
		Grade 2	17	56.7	21	70.0	
		Grade 3	10	33.3	2	6.7	
		Grade 4	2	6.7	0	0	
	6 months	Grade 1	2	6.7	16	53.3	**0.001**
		Grade 2	18	60.0	12	40.0	
		Grade 3	8	26.7	2	6.7	
		Grade 4	2	6.7	0	0	
Larynx	0 months	Nil	30	100.0	30	100.0	NA
	3 months	Grade 1	0	0	7	23.3	**0.001**
		Grade 2	6	20.0	21	70.0	
		Grade 3	22	73.3	2	6.7	
		Grade 4	2	6.7	0	0	
	6 months	Grade 1	2	6.7	12	40.0	**0.001**
		Grade 2	23	76.7	16	53.3	
		Grade 3	5	16.7	2	6.7	

DISCUSSION

According to GLOBOCAN 2020, laryngeal cancers are 11th most common cancer and cause of death, with incidence of 2.6% and contributing to 2.5% of all the cancer related deaths [2]. It is essential to determine the site and staging of cancers as they helps in deciding the treatment of the cancers. Treatment modalities include surgery, chemotherapy or radiotherapy, and in advanced cases, multimodality treatment is required [1]. The IMRT is a successful, effective and commonly used radiation modality in management of carcinoma larynx, which has treatment planning system and modern linear accelerator (linac) [3, 4]. Though IMRT is considered superior to 3DCRT, it is associated with higher leakage of radiation dose from the head of gantry due to presence of high monitoring units (MU) and the technique of flattening filter, thereby delivering higher dose to not only the target organ but to the normal tissues as well [5, 6], Recently, the role of FFF photon beam is being studied extensively, which helps in increased dose delivery at the targeted site and reduced dose leakage at organ at risk [9-13]. The present study was conducted on a total of 60 cases with carcinoma larynx presenting in Department of Radiation Oncology at out institute to compare the dosimetric parameters, toxicities, and response of IMRT with FF and FFF photon beam for Carcinoma Larynx. The performance status was assessed using KPS score and more than 75% cases had performance status of 70 whereas remaining patients had KPS score of 80.

FF photon beam of IMRT increased the dose delivery at the target site, but the risk of radiation exposure to nearby normal tissues is also high. To overcome this issue, FFF photon beam have been recommended, and the major characteristic of FFF beam is its forward peaked dose profile. The advantage of FFF beam is increased dose delivery to the targeted site with reduced dose distribution at organ at risk, thereby reduced risk of secondary cancer due to radiation [12, 13]. In our study, though we observed no significant difference in total dose and number of fractions of radiation therapy in both the groups ($p<0.05$), the dose of radiation delivered to organs at risk, i.e. parotid gland, spinal cord and oral cavity were documented to be significantly higher in FF group as compared to FFF group suggesting FFF to be better modality in reducing radiation delivery to nearby normal tissues.

Our study findings were supported by the findings of Yan et al in which the authors suggested that among all cancer sites studied, the differences in FF and FFF beam are more important in head and neck cancers, with maximum reduction in mean dose of up to 2.82 Gy for laryngeal cancers could be achieved using FFF beam [8]. Our study findings were also in line with the findings of Dobbler et al, in which the authors found use of FFF beam to significantly reduce the dose to the organ at risks by 18% as compared to FF beam with target achievement in majority of cases for spinal cord (D1ccm < 45 Gy), for the parotids (D50% < 30 Gy); with almost similar delivery time [15]. In contrast to present study, Ogata et al documented FFF-VMAT could achieve the plan comparable to the quality of FF VMAT with similar homogeneity and conformity for PTVs between both the plans [16]. Sun et al compared the FF and FFF beam in esophageal cancers and reported that though the dose delivery to target organs were equivalent in two treatment plan groups, FFF beam was helpful in significantly decreasing peripheral dose to the normal tissues around the target tissue [17]. Kumar et al found comparable dose distributions to the target organs as well as peripheral tissues in two treatment arms with no significant difference in organ at risk doses [18].

Response was assessed in all the patients using RECIST criteria [17]. In our study, complete response was noted in significantly higher proportions of cases of FFF group (43.3%) whereas the disease was progressive or stable in significantly higher proportions of cases of FF group (33.3% and 23.3% respectively). To best of our knowledge, only limited studies have been done on dosimetric comparison of FF and FFF beam plans of IMRT, and none of them have shown the response rate. Though we noted dose delivery to target organs to be comparable in both the beam plans, the response rate was better in FFF treatment plan group as compared to FF group, which could be attributed to low radiation exposure to organ at risk, low adverse effects and better compliance and tolerability in FFF group.

We reported significantly higher grades of toxicities to parotid in higher proportions of patients of FF group as compared to FFF group at 6 months ($p<0.05$), whereas toxicities to oral cavity and larynx were documented to be of higher grade in FF group as compared to FFF groups at 3 months as well as at 6 months of follow up ($p<0.05$). However, toxicities at spinal cord were observed in none of the patients at any of the follow up in both the groups. This could be attributed to higher dose delivery at these tissues in FF group due to leakage of radiation dose from the head of gantry [5, 6].

Our study findings were concordant with the findings of Dobbler et al, in which peripheral doses could be significantly reduced by 18 % using FFF beam as compared to FF beam and thereby the risk of radiation leakage to organ at risk could be reduced thereby this technique is essential for reduction of second cancer induction [15]. Our study findings were contrasting to the findings of Ogata et al, in which authors observed no significant difference in OAR sparing (spinal cord, parotid, larynx) between the two treatment plans i.e. FF-VMAT and FFF-VMAT [16]. Similarly, Sun et al found FFF beam to be helpful in significantly decreasing peripheral dose to the normal tissues and hence reducing the risk of organ toxicities and secondary cancers [17]. In contrast Kumar et al found comparable dose distributions to the target organs as well as peripheral tissues, suggesting no difference in two treatment arms with respect to organ at risk doses and their toxicities [18].

The limitations of our study were its low sample size and short duration of follow up.

CONCLUSION

IMRT is one of the common treatment modality used in management of patients with carcinoma larynx. Flattening filter free beam is as effective as flattening filter beam therapy in delivering the dose of radiation to the target tissue, with minimum radiation leakage to the adjacent normal tissues thereby reducing the risk of toxicities of organ at risks (parotid and oral cavity) and inducing better clinical response.

Conflict of interest: None

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