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Original Article



# A Prospective Study to Compare Intensity-modulated Radiation Therapy Planned by Flattening Filter Free and Flattening filter Beam in Patients of Carcinoma Cervix

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## ABSTRACT

**Background**: Modern linear accelerator (LINACs) is capable of delivering flattening filter (FF) and flattening filter free (FFF) photon beams as well. FFF and FF photon beam based LINACs have their own advantage and disadvantage and the choice between them ultimately depends on specific need of patientstumour site and treatment planning techniques.

**Aim**: This study aimed to compare the quality of intensity-modulated radiation therapy (IMRT) treatment plan for cervical cancer with and without a FF photon beam in terms of dosimetric analysis, toxicities, and response.

**Materials and Methods**: This study was conducted as prospective analytical study in Department of Radiation oncology at tertiary care centre on 60 patients with cervical cancer. Participants were divided into two groups according to treatment plan i.e. IMRT-FF and IMRT-FFF and were compared for tumour characteristics, dose volume histogram, toxicities, and response to treatment.

**Results**: The patients of two groups were comparable with respect to baseline variables and tumour characteristics and treatment ($p>0.05$). Significantly higher proportions of cases in FFF group had complete response ($p<0.05$). Mean total dose, urinary bladder maximum dose, bowel minimum and maximum dose as well as rectum maximum dose were significantly higher in FFF group ($p<0.05$) as compared to FF group. Minimum rectum dose was significantly higher in FF group ($p<0.05$). Hematuria was observed in significantly higher proportions of patients of FF group and itching was observed in higher proportions of cases in FFF group at 3 months ($p<0.05$) after completion of radiotherapy.

**Conclusion**: The FFF photon beams in comparison to the FF photon beam provide a clinically desirable and physically acceptable treatment plan at lower dose for target coverage. FFF photon beam in comparison to FF photon beam provides better organ at risk (OAR) sparing by less scattered dose and runs treatment process smoothly. Overall treatment time is less for FFF Beam than FF beam.

**Key Words**: *Intensity-modulated radiation therapy, Flattening filter free, flattening filter, Toxicities, Organs at risk*

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## INTRODUCTION:

Cervix cancer is the eighth most common gynecological malignancy found in women worldwide. Developing countries are mostly affected by this type of cancer disease. According to the GLOBOCAN-2020 report, more than 70% of global burden falls in developing countries.[1] Nearly 20%–25% of the cervical cancer related death globally occurs in India. In India, the age- standardized rate of cervical cancer varies from 4.9 to 23.7 per lakh population. [2,3] India reflects a similar picture as cancer cervix is the second most common cancer in women in India with high prevalence in rural areas.

External radiotherapy is accepted as a standard of care for the management of cervix cancer worldwide. Purpose of external radiotherapy for cervix cancer is to achieve an optimal balance between maximum doses to tumour and minimize the risk of side effects and long term complications to organ at risk (OARs).[4] IMRT technique is the treatment of choice for gynaecologic cancer due to adequate target volume (TV) coverage and increased OAR's sparing as compared to three dimensional conformal radiotherapy (3DCRT).[5] Historically, flattened beam was used to generate the clinically acceptable doses inTV and for reducing doses to OAR's by 3DCRT or advanced technique such as IMRT or volumetric modulated arc therapy (VMAT). In recent years, utilization of advanced technique increased due to creation of conformal plans.[6]

Modern LINACs are capable of delivering filtered beam and flattening filter free photon beams as well. Introduction of FFF Beam in radiotherapy has enhanced the treatment delivery as the removal of a flattening filter from the path of beam causes more efficient photon production and increased dose rate substantially at treatment level. In this technique, flatten beam is modified by fluence modification algorithm to generate required dose distribution, thereby invalidating need for flatten beam. Therefore, flattening filter becomes unnecessary in advanced technique. Increased dose rate results in shorter treatment time, which reduces intrafraction motion and enhances patient's treatment comfort. In addition, the FFF Beam offers other dosimetric advantages such as reduced scatter, reduced leakage and reduced out of field scatter doses.[7,8] This reduction in out of field doses may lead to minimizing the risk of radiation induced secondary malignancies.[9] Several studies have been published about the properties of FFF beams from different Medical electron linear accelerators based on dosimetric measurements and Monte Carlo measurement as well.[10,11] A few investigators have also reported the feasibility of FFF beams for IMRT treatment planning.[12,13]

As FFF beam delivery may lead to higher treatment efficiency in conjunction with arc-based delivery configuration like Rapid Arc (RA) radiotherapy delivery. So, we compared clinically acceptable RA plans with FFF photon beam and FF Beam for their potential benefits to cervix cancer patients. This study aimed to compare the quality of intensity-modulated radiation therapy (IMRT) treatment plan for cervical cancer with and without a flattening filter photon beam in terms of dosimetric analysis, toxicities and Response. At present no similar study has been done or reported earlier.

**Materials and Methods:**

The present study was conducted as a prospective analytical study in Department of Radiation oncology, Government Medical College of Central India and associated Hospitals, on a total of 60 patients with cervical cancer during the study period of 18 monthsi.e.from1st December 2021 to 30th June 2022. All the cases belonging to 18 to 70 years with histopathologically proven Squamous Cell Carcinoma (SCC) confirmed case of cervical cancer with any stage and KarnofskyPerforming Scale (KPS) score in the range of 70 to 80 being managed with IMRT by flattening Filter free and Flattening Filter were included in our study. Patients not willing to participate in the study were excluded from the study. After obtaining ethical clearance from Institute's ethical Committee, all the cases fulfilling inclusion and exclusion criteria were recruited and data regarding sociodemographic factors, clinical history, tumour, its stage, presence of metastasis, etc. was obtained and entered in proforma. All 60 Participants were divide into two groups according to treatment plan i.e. IMRT-FF and IMRT-FFF. The patients in two groups were compared for baseline variables, tumour characteristics, dose volume histogram, toxicities & response to treatment. Patients were followed up at 0, 3, 6 months and response were evaluated according to RECIST criteria.[14]

**Statistical Analysis:**

Data was compiled in MS Excel and analyzedusing IBM SPSS software version 20 (IBM SPSS Illinois Chicago). Continuous data was expressed as mean standard deviation (SD) whereas continuous data was represented as frequency and percentage. Least significant difference for measuring intergroup variance of metric data was done by student's t-test, whereas non metric data was analysed by Fisher's exact test/chi square test. P value of less than 0.05 was considered as significant.

**Results:**

This study was conducted on 60 patients with cervix cancer and mean age of patients with cervix cancer was 51.27±9.63 years and 51.23±11.69 years in FF and FFF group respectively.Majority of the patients of both groups belonged to more than 40 years of age and were Hindu. The observed difference in baseline variables between two groups was statistically insignificant ($p>0.05$)[Table1].

The patients of two groups were comparable with respect to tumour characteristics and treatment ($p>0.05$)[Table2].

In present study, significantly higher proportions of cases in FFF group(96.7%) had complete response as compared to FF group (46.7%) ($p<0.05$)[Figure1].

In present study, mean total dose, urinary bladder maximum dose, bowel minimum and maximum dose as well as rectum maximum dose were significantly higher in FFF group ($p<0.05$) as compared to FF group. Minimum rectum dose was significantly higher in FF group ($p<0.05$) [Table 3].

At the time of presentation, no symptoms were present in any of the organ at risks, whereas hematuria was observed in significantly higher proportions of patients of FF group and itching was observed in higher proportions of cases in FFF group at 3 months (p<0.05) after completion of radiotherapy[Table4].

**Tables:**

Table 1: Comparison of baseline variables between the groups

| Baseline variables | | IMRT-FF (n=30) | | IMRT-FFF (n=30) | | P value |
|---|---|---|---|---|---|---|
| | | N | Percent | N | Percent | |
| Age (years) | <40 | 2 | 6.7 | 6 | 20.0 | 0.36 |
| | 41-50 | 14 | 46.7 | 9 | 30.0 | |
| | 51-60 | 10 | 33.3 | 10 | 33.3 | |
| | >60 | 4 | 13.3 | 5 | 16.7 | |
| Religion | Hindu | 27 | 90.0 | 30 | 100.0 | 0.78 |
| | Muslim | 3 | 10.0 | 0 | 0.0 | |
| Residence | Urban | 18 | 60.0 | 17 | 56.7 | 0.79 |
| | Rural | 12 | 40.0 | 13 | 43.3 | |
| Addiction | No | 24 | 48.0 | 26 | 86.7 | 0.55 |
| | Smoking | 1 | 3.3 | 0 | 0.0 | |
| | Tobacco | 5 | 16.7 | 4 | 13.3 | |
| KPS | 70 | 19 | 63.3 | 18 | 60.0 | 0.79 |
| | 80 | 11 | 36.7 | 12 | 40.0 | |

**Abbreviations:** KPS: karnofsky performing scale, IMRT-FF: Intensity-modulated radiotherapy, FF: flattening filter, FFF: flattening filter free

Table 2: Comparison of tumour characteristics & treatment between the groups

| Tumour characteristics & treatment | | IMRT-FF (n=30) | | IMRT-FFF (n=30) | | P value |
|---|---|---|---|---|---|---|
| | | N | Percent | N | Percent | |
| Stage | III | 12 | 40.0 | 15 | 50.0 | 0.44 |
| | IV | 18 | 60.0 | 15 | 50.0 | |
| HPR | SCC Grade1 | 22 | 73.3 | 21 | 70.0 | 0.54 |
| | SCC Grade2 | 6 | 20.0 | 4 | 13.3 | |
| | SCC Grade3 | 2 | 6.7 | 4 | 13.3 | |
| | NKSCC Grade1 | 0 | 0.0 | 1 | 3.3 | |
| Treatment | EBRT | 12 | 40.0 | 16 | 53.3 | 0.31 |
| | CCRT | 18 | 60.0 | 14 | 46.7 | |

**Abbreviations:** SCC: squamous cell carcinoma, NKSCC: non keratinizing squamous cell carcinoma, EBRT: external beam radiotherapy, CCRT:concurrent chemo radiotherapy

Table 3: Comparison of dosimetric analysis of organ at risk between two groups

| Dose( in Gray) | IMRT-FF (n=30) | | IMRT-FFF (n=30) | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Total dose | 49.44 | 3.58 | 52.76 | 4.36 | **0.002** |
| UB min | 28.71 | 7.56 | 25.82 | 9.25 | 0.19 |
| UB max | 51.73 | 4.12 | 55.41 | 4.22 | **0.001** |
| UB mean | 46.90 | 2.84 | 45.80 | 3.23 | 0.16 |
| Bowel min | 1.19 | 0.44 | 1.83 | 1.06 | **0.003** |
| Bowel max | 47.80 | 2.89 | 51.10 | 3.61 | **0.0002** |
| Bowel mean | 23.59 | 8.05 | 22.33 | 9.59 | 0.58 |
| Rectum min | 27.01 | 10.59 | 20.23 | 10.38 | **0.015** |
| Rectum max | 51.10 | 4.23 | 53.42 | 3.78 | **0.029** |
| Rectum mean | 45.44 | 4.94 | 44.04 | 4.18 | 0.24 |

**Abbreviations:** UB: urinary bladder

Table 4: Comparison of toxicities between the groups

| Toxicities observed in organ at risk during observation period | | | IMRT-FF (n=30) | | IMRT-FFF (n=30) | | P value |
|---|---|---|---|---|---|---|---|
| | | | N | Percent | N | Percent | |
| Cervix | 0 month | NC | 30 | 100 | 30 | 100 | 1.00 |
| | | Adhesion | 0 | 0.0 | 0 | 0.0 | |
| | 3month | NC | 15 | 50.0 | 19 | 63.3 | 0.3014 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Adhesion | 15 | 50.0 | 11 | 36.7 | |
| | 6 month | NC | 25 | 83.3 | 27 | 90.0 | |
| | | Adhesion | 5 | 16.7 | 3 | 10.0 | 0.4422 |
| Urinary bladder | 0 month | NC | 25 | 83.3 | 23 | 76.7 | 0.5221 |
| | | Burning Micturition | 5 | 16.7 | 7 | 23.3 | |
| | 3month | NC | 16 | 53.3 | 19 | 63.3 | 0.4360 |
| | | Burning Micturition | 14 | 46.7 | 11 | 36.7 | |
| | 6 month | NC | 20 | 66.7 | 27 | 90.0 | |
| | | Haematuria | 10 | 33.3 | 2 | 6.7 | **0.0250** |
| | | Urinary Incontinence | 0 | 0.0 | 1 | 3.3 | |
| Bowel | 0 month | NC | 20 | 66.7 | 21 | 70.0 | 0.5362 |
| | | Diarrhea | 10 | 33.3 | 8 | 26.7 | |
| | | Obstruction | 0 | 0.0 | 1 | 3.3 | |
| | 3month | NC | 18 | 60.0 | 22 | 73.3 | 0.143 |
| | | Diarrhea | 11 | 36.7 | 4 | 13.3 | |
| | | Obstruction | 1 | 3.3 | 4 | 13.3 | |
| | 6 month | NC | 19 | 63.3 | 22 | 73.3 | |
| | | Diarrhea | 5 | 16.7 | 3 | 10.0 | 0.6668 |
| | | Obstruction | 6 | 20.0 | 5 | 16.7 | |
| Rectum | 0 month | NC | 22 | 73.3 | 24 | 80.0 | 0.5449 |
| | | Itching | 8 | 26.7 | 6 | 20.0 | |
| | 3month | NC | 27 | 90.0 | 20 | 66.7 | **0.0296** |
| | | Itching | 3 | 10.0 | 10 | 33.3 | |
| | 6 month | NC | 30 | 100 | 30 | 100 | 1.000 |

NC – no complaints

**Figures:**

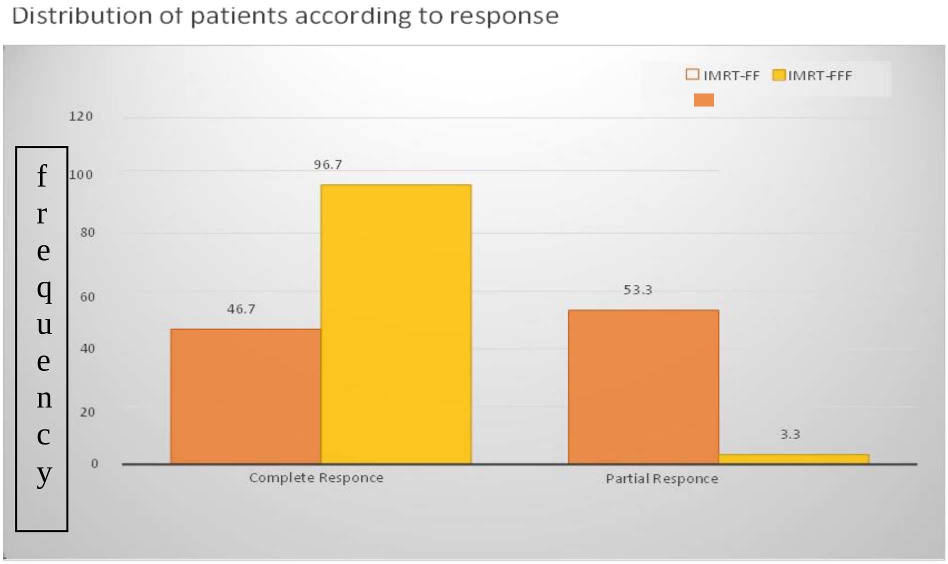


Figure 1: Comparison of response between the groups

**DISCUSSION:**

Cervix cancer is the fourth most common gynaecological malignancy found in women worldwide. Developing countries are mostly affected by this type of cancer disease. Although according to the GLOBOCAN2020 report, almost 70% of global burden falls in developing countries.[1,4] India reflects a similar picture as cancer cervix is the second most common cancer in women in India with high prevalence in rural areas.[15] Due to the inadequacy of population-based screening programs, lesser access to proper healthcare facilities in rural areas, lack of health education and awareness, especially among the high- risk groups, 70–80% cases of cervical cancer present in advanced stages (stage III and IV) in India.[15] Along with the local extent of disease, nodal status also greatly influences the treatment strategy and outcome. Probability of lymph node involvement increases as the clinical stage advances.

Since the first decade of the twenty-first century, the feasibility of IMRT is being explored in the treatment of cervical cancer with the hope of improved tumour control and lesser radiotherapy associated toxicity. In survey, 15% of IMRT users reported treating a gynaecology patient with this technique.[16] In external radiotherapy, the use of flattening filter-free (FFF) radiation beams obtained by removing the flattening filter (FF) in standard linear accelerators is rapidly increasing, and the benefits of clinical use are the issue of research. Advanced treatment techniques have increased the interest in the operation of linear accelerators in FFF mode. The differences of the beams with non-uniform dose distribution created by removing FF compared to the beams with uniform dose distribution used as a standard were examined. These differences were compared in the treatment plans of cervical patients who have different planning target volumes. The present study was conducted on 60 patients with cervical cancer. To assess dosimetric analysis, response and toxicities among patients treated with FF beam and FFF beam for cervical cancer.

Organ related toxicities is a major concern during radiotherapy.Dosimetric analysis is important in determination of organ toxicities. Kole *et al*.[17] reported IMRT to be more effective in delivering target dose as well as reducing toxicity to adjacent organs as compared to other modality.AlsoIMRT is helpful in maintaining homogeneity.[17] Our study documented that mean total dose was higher in IMRT-FFF group (49.45±3.58) as compared to IMRT-FF (52.77±4.37) and statisticallysignificant ($p<0.05$) and insignificant respectively. UB min dose (28.71±7.57 & 25.82±9.25) and mean dose (46.9±2.84 & 45.81±3.23)were also higher in IMRT-FFF group respectively and were statistically insignificant ($P>0.05$). UB max dose was lowered in IMRT-FFF group (51.73±4.13 & 55.41±4.23) and statistically significant ($p<0.05$).In case of bowel min (1.19±0.44 &1.83±1.06) and max dose (47.8±2.89 and 51.1±3.61) were also lower IMRT-FF as compared to IMRT-FFF group and were statically significant in both groups ($P<0.05$) whereas mean bowel dose was higher in IMRT-FF group as compared to IMRT-FFF group (23.59±8.05 and 22.33±9.59) and were insignificant ($P<0.05$).

Similarly, no set minimum, maximum as well as mean dose pattern were observed in rectum dose. Min dose (27.01±10.59 and 20.24±10.39), and mean (45.44±4.95 and 44.04±4.19) rectum dosewerehigher in IMRT-FF as compared to IMRT-FFF whereas max Dose (51.1±4.24 and 53.42±3.78) was higher in IMRT-FFF group and statistically significant difference were observed in Min and max dose of rectum ($P<0.05$) whereas maximum dose was insignificant ($p>0.05$). Tamilarasu, *et al*[6] found mean dose to bladder, rectum, femur and bowel were not statistically significant difference between two plans. Our results are in contrast to those observed in other studies involving FFF beams for large and complex targets. Nicolini*et al*.[18] and Subramaniam *et al*.[19] reported that VMAT with FFF beam plans resulted in minor improvement in plan quality, thereby suggesting their applicability for large and complex targets. 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.[4] Kry*et al.* (confirmed that removal of flattening filter helps in reducing the out of field dose and thereby sparing the adjacent critical organs at risk, and hence reducing the long term risk of secondary cancer.[20] 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.[21]

In present study, majority i.e. 46.7% and 96.7% patients of IMRT- FF and IMRT-FFF group respectively had complete response whereas partial response observed as 53.3% and 3.3% in both group respectively. Test of significance showed statistically significant difference in response among two groups ($p<0.05$). Further, all the patients were follow-up till 6 months following radiotherapy and symptoms were assessed. Cervix, Urinary bladder, Bowel and Rectum symptoms were recorded for assessing the organ involvement. Our study observed that though the cervix symptoms, i.e. Adhesion, Obstruction, Diarrhea increased up to 3 month and decreased at 6 month following radiotherapy in both the groups as compared to baseline. No statistically significant differences were observed during any month of follow-up ($p>0.05$) after completion of radiotherapy by both procedure. Similarly no statistically significant differences were observed at presentation and after 3 month whereas statically significant difference was observed at follow-up of 6 month ($p<0.05$) for urinary bladder, bowel and rectum symptoms. The findings of present study were supported by findings. We not found any study to compare symptomatic findings in the previous study.

## CONCLUSION:

IMRT-FF and IMRT-FFF are standard photon beam used for management of patients with cervical cancers. The FFF photon beams in comparison to the FF photon beam provide a clinically desirable and physically acceptable treatment plan at lower dose for target coverage. FFF photon beam in comparison to FF Photon Beam provides better OAR sparing by less scattered dose and runs treatment process smoothly. Overall treatment time is less for FFF Beam than FF beam. Overall organ toxicities and symptoms among both modality are comparable but it is somewhat shifted to IMRT-FFF. Therefore, the IMRT-FFF photon beam can be used dosimetrically for cervical cancer treatment planning.

**Conflict of Interest:** None

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