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Impact of Flattening Filter Free Photon Beam on Rapidarc Radiotherapy for Gynaecological Malignancies: A Comparative Study

Lalit Kumar[1, 2], Vimal Kishore[3], Manindra Bhushan[2], Girigesh Yadav[2], Abhinav Dewan[2], Pawan Kumar[2], Gourav Kumar[2], Rahul Lal Chowdhary[2]

1. Department of Applied Science and Humanities, Dr. A.P.J Abdul Kalam Technical University, Lucknow, India
2. Medical Physics Division and Radiation Oncology Department, Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India
3. Department of Applied Science and Humanities, Bundelkhand Institute of Engineering and Technology, Jhansi, India

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ABSTRACT

Introduction: To compare the dosimetric outcomes of 6 and 10 MV flattening filter free beam (FFFB) energies in gynaecological malignancies RapidArc (RA) planning.

Material and Methods: The RA plans were generated for a cohort of 20 patients using 6 and 10 MV FFFBs. The plans aimed to deliver a dose of 50.4Gy in 28 fractions to planning target volume (PTV); moreover, planning objectives were kept as low as reasonably achievable for organs at risk (OARs). Dosimetric analysis was performed in terms of PTV coverage, conformity index (CI), homogeneity index (HI), dose to OAR's, integral dose to normal tissue (NTID), and total number of monitor units (MU's).

Results: According to the results, volumes of PTV receiving prescription dose and CI values were 95.03±0.10% and 95.02±0.18%, as well as 1.018±0.028 and 1.024±0.027, respectively. Moreover, HI values were estimated at 1.063±0.008 and 1.068±0.010. Additionally, the corresponding values of mean NTID and MUs were 280.3±42.5 and 267.9±39.1 (liter-Gy), as well as 610.3±30.3 and 630.6±39.7 for FFFB using 6 and 10 MV, respectively. The 6 and 10 MV FFFBs were statistically similar in terms of mean dose to bladder, rectum and both femoral heads, while comparison yielded significant difference ($P<0.05$) in terms of HI, CI, MUs and NTID.

Conclusion: The FFFB of 6MV was found superior, compared to 10MV, for RA planning in case of gynaecological malignancies. Moreover, it offers better HI and CI values, as well as fewer numbers of MUs (3.33%). In addition, it delivers more NTID (4.42%) for similar target coverage and OAR's sparing.

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Introduction

Gynaecologic malignancies are the most common cancer sites reported with high morbidity and mortality rates in India [1]. The Indian National Cancer Registry Program reports indicate that around 50-60% of all cancer burden among women is primarily related to four sites, namely cervix uteri, breast, corpus uteri, and ovaries [2]. Radiotherapy (RT) is commonly used in the management of gynaecological malignancies.

Medical linear accelerators (linac) are used to deliver radiation therapy to cancer. With the recent advancements in technology, modern linacs are capable of delivering filtered beams (FB) as well as flattening filter-free beams (FFFB). Halcyon (Varian Medical System, USA) and Helical TomoTherapy (Accuray Incorporated, Sunnyvale, CA, USA) are two examples of ring-gantry based linac with FFF photon beams. Moreover, TrueBeam-STx (Varian Medical System, USA), Versa HD (Elekta, Stockholm, Sweden), and Artiste (Siemens Medical System, Germany) are few examples of standard C-arm linacs available in RT departments, which generate FB and FFFB.

Furthermore, Cyberknife (Accuray Incorporated, Sunnyvale, CA, USA) is a robotically-mounted linac with FFFB beam. The flattening filter (FF) is made of high Z materials, which is conical in shape. The FF is mainly situated between the primary collimator and the monitor chamber in linac head to flatten the forward peaking bremsstrahlung spectrum of megavoltage photon beams. Moreover, the FF makes the photon dose distribution uniform at reference depth; however, its presence reduces the photon beam dose rate acting as a major source of head scattered photons, which subsequently leads to the variation of in-air output with field size and exchange effect of secondary collimators [3].

*Corresponding Author:Tel: +91-47022646;Fax: +91-11-27051037; E-mail: lalitk48@gmail.com

The removal of FF from the beam path makes the filter-free photon beams widely known as flattening filter-free (FFF) beams. The FFFB has many distinct advantages over FB, including higher dose rate, cone-like profile, softer beam quality [4], increased superficial dose, and reduced out of field dose[5,6].High dose rate delivery reduces the treatment time. Subsequently, it tends to minimize the inter-fraction motion and enhance the patient's comfort. There are various studies investigating the dosimetric properties of FFFB [7-10].Some studies have also investigated the clinical properties of FFFB for different case scenarios, such as breast cancer [11], lung cancer [12],and other clinical sites [13-15].

Halcyon and TomoTherapy radiotherapy system utilizes FFF beam for the management of all types of cancer treatment, whereas C-arm linacs utilize FFFB predominantly for Stereotactic Radio Surgery and Radio Therapy. The present study aimed to investigate the capability of FFFB using C-arm linac to develop clinically acceptable treatment plans for gynaecological malignancies using the RapidArc (RA) technique. In addition, this study analyzed the dosimetric footprints of FFF photon beam energies on RA technique for gynaecological malignancies.

Regarding the filtered energy spectrum, the evidence indicated no significant precedents in terms of target coverage, organ-at-risk (OARs) sparing, and different physical indices for high energy beam over low energy beam [16].The FFFB has softer beam spectrum, compared to FFB. Therefore, the present study aimed to quantify the dosimetric differences between dose-volume parameters of 6 and 10 MV FFFBs in terms of target coverage, OARs sparing, and different physical indices.

Materials and Methods

This retrospective study included 20 patients with the mean age of ≥50 years and stage II to IIIB who received radiotherapy with Intensity-Modulated Radiotherapy (IMRT) and RapidArc (RA). With respect to the radiotherapy planning, computed tomography (CT) simulation was performed with patient immobilized in the supine position using ALL-IN-ONE board (AIO, Orfit Industry Nv, Belgium), thermoplastic Orfitcast (Orfit Industry Nv, Belgium), and knee rest. Moreover, a Somatom Sensation Open CT scanner, a 64-slice CT scanner (Siemens Medical System, Germany), was used to perform a CT scan with a 3.0 mm slice thickness. Target volume and OARs delineation were performed on CT images by a radiation oncologist as per Radiation Therapy Oncology Group recommendations. The planning target volume (PTV) was defined with a 5mm additional margin to the clinical target volume (CTV). The CTV includes cervix, uterus, adnexa, upper half of the vagina, and pelvic lymph nodes. The OARs, such as bladder, rectum, bowel, and bilateral femoral heads were delineated on CT images.

The RA plans were generated for each patient using the Eclipse Treatment Planning System (TPS) (version 11.0) (Varian Medical Systems, Palo Alto, CA, USA). Eclipse TPS uses progressive resolution optimizer algorithm as an optimization algorithm for treatment planning and anisotropic analytical algorithm for final dose calculation. A grid resolution of 2.5 mm was used for RA dose calculation. The planning was performed using a double arc including a clockwise (CW) arc along with a gantry angle of 179-181 degree and a counter-clockwise (CCW) arc with a gantry angle of 181-179 degree. The collimator was rotated to 10-30 degrees opposite for both arcs to minimize the inter-leaf leakage.

Plans were generated for each patient using 6 and 10 megavolts (MV) photon energies of FFFB produced by True Beam (TB)-STx linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The TB-STx was equipped with 60 pairs of a high-definition multi-leaf collimator (HD-MLC) (inner 32 pairs of 2.5 mm; outer 28 pairs of 5.0 mm) resolution at isocenter.

The RA planning was performed to deliver a prescription dose of 50.4 Gray (Gy) in 28 fractions to the PTV, and as low as reasonably achievable principle was used as a planning objective for OARs. The dosimetric analysis was done in terms of PTV coverage, conformity index (CI), homogeneity index (HI), dose to OAR's, integral dose to normal tissue (NTID), and the total number of monitor units (MUs).

Dosimetric Analysis

The dosimetric parameters and cumulative dose-volume histogram (DVH) were calculated and compared for the PTV and OARs.

The following dose metrics were calculated for PTV and OARs.

PTV: D_{mean} (mean dose), $V_{93\%}$ (volume receiving 93% prescription dose), $V_{95\%}$, $V_{98\%}$, $V_{100\%}$, $V_{107\%}$

Bladder: D_{mean}, V_{50Gy} (volume receiving 50Gy dose)

Rectum: D_{mean}, V_{50Gy}

Femoral Heads: D_{mean}, V_{40Gy}

Bowel: D_{mean}, V_{40Gy}

Normal tissues (Body-PTV): $D_{1\%}$ (Dose to 1% volume of normal tissues), $D_{2\%}$, V_{2Gy}, V_{5Gy}

Moreover, the dose values of CI, HI, and NTID were calculated using the following formula:

Conformity Index: Volume include 95% isodose/Volume of PTV [17].

Homogeneity Index: $D_{5\%}$/ $D_{95\%}$[17].

Where $D_{5\%}$ and $D_{95\%}$ are the doses to 5% and 95% volumes of the PTV, respectively.

The value of CI and HI close to 1 indicates better conformal and homogenous dose distribution to the PTV.

Integral dose to normal tissues: Mean dose * volume of normal tissues outside PTV [18].

Patient-Specific Dosimetry Analysis

Patient-specific dosimetry was performed using ArcCHECK phantom along with ion-chamber (IC) CC-13S (IBA Dosimetry, Germany) and Dose1 electrometer

(IBA Dosimetry, Germany). Dose fluence map and point-dose measurement were acquired simultaneously. Ion-chamber measurements were corrected for temperature and pressure variations. An SNC software (version 6.2) (Sun Nuclear Corporation, Melbourne, Florida) used for the distance to agreement (DTA) and gamma analysis. A criterion of 3mm DTA and 3% dose difference with a threshold value of 10% was used for DTA and gamma analysis for all RA plans. A tolerance of ± 5% was considered as an acceptable IC measured doses, compared to TPS calculated dose [19].

Statistical analysis

The data were analysed in SPSS software (version 20.0) (Armonk, NY: IBM corp.) manufactured by International business machine corporation (IBM corp.). A p-value less than 0.05 was considered statistically significant.

Results

The dosimetric parameters for RA plans using FFFBs of 6 and 10 MV photon energies were analysed in this study. The dose distribution in all plans satisfied the clinical requirements. Dose-volume parameters calculated by cumulative DVH for PTV and OARs are listed in tables 1 and 2. There was no significant difference (P>0.05) between the two FFFB photon energies in terms of PTV coverage and OARs sparing. However, significant differences were observed between both photon energies regarding the mean dose to PTV and bowel, volumes of the bladder, and rectum receiving 50Gy dose with a p-value less than 0.05. Figure 1 illustrates the results of a comparison between the RA plans of 6 FFFB and 10 FFFB in terms of isodose distribution and DVH.

Table 1.Dosimetric parameters for planning target volume for RA plans using 6 MV and 10MV FFFBs

Parameters	6MV FFFB	10MV FFFB	P-value
	Mean±SD	Mean±SD	
Mean (Gy)	52.26±0.33	52.43± 0.39	0.001
$V_{93\%}$ (%)	99.84±0.15	99.79±0.22	0.071
$V_{95\%}$ (%)	99.63±0.23	99.57±0.30	0.057
$V_{98\%}$ (%)	98.30±0.46	98.19±0.40	0.065
$V_{100\%}$ (%)	95.03±0.10	95.02±0.18	0.904
$V_{107\%}$ (%)	3.91±7.37	7.23±11.13	0.007
Homogeneity Index	1.063±0.008	1.068±0.010	0.000
Conformity Index	1.018±0.028	1.024±0.027	0.034
Monitor Units	610.3±30.3	630.6±39.7	0.017
Normal Tissue Integral Dose (liter-Gy)	280.3±42.5	267.9±39.1	0.000

Table 2.Dosimetric parameters for organ at risk of RA plans using 6 MV and 10MV FFFBs

Structure	6FFF	10FFF	
	Mean±SD	Mean±SD	P-value
Bladder			
Mean(Gy)	41.55±1.42	41.46±1.31	0.509
V_{50Gy} (%)	35.26±4.72	36.06±4.71	0.010
Rectum			
Mean	41.37±2.10	41.53±2.25	0.200
V_{50Gy} (%)	25.95±7.49	28.03±7.35	0.002
Bowel			
Mean	17.58±4.32	17.08±4.27	0.000
V_{40Gy} (%)	6.44±4.44	6.15±4.55	0.299
Lt. Femur			
Mean	20.93±4.14	20.33 ±3.63	0.072
V_{40Gy}(%)	8.72±6.77	8.42±5.69	0.471
Rt. Femur			
Mean	20.56±3.97	20.47±4.36	0.610
V_{40Gy} (%)	9.08±6.34	9.33±7.11	0.427
Body-PTV			
$D_{1\%}$	48.15±1.22	48.53±0.97	0.146
$D_{2\%}$	45.10±1.73	45.34±1.67	0.371
V_{2Gy}(%)	64.62±7.14	62.02±7.06	0.000
V_{5Gy}(%)	53.26±6.37	52.91±6.31	0.002

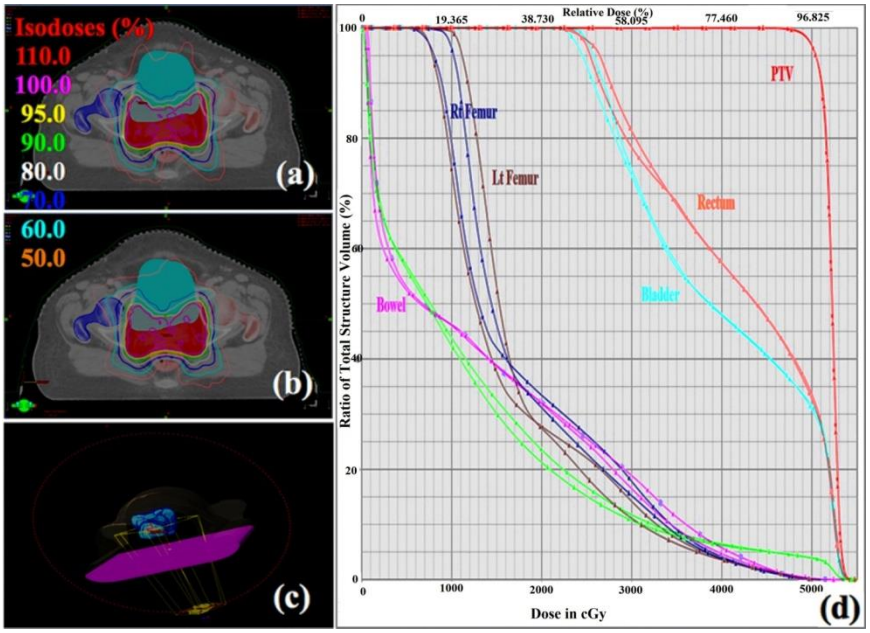
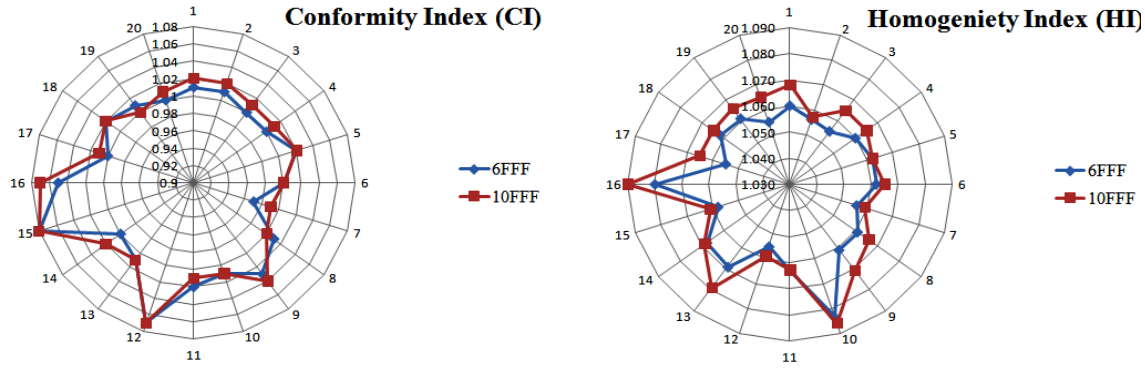


Figure1. Isodose distribution for RA plans using (a) 6 MV FFF, (b) 10 MV FFFB, (c) double arc beam arrangement for RA planning, and (d) DVH comparison between both photon energies.



(a) (b)

Figure 2.Comparison between 6 MV FFF and 10 FFFB RA plans in terms of (a) Conformity Index and (b) Homogeneity Index for an individual patient.

The volume values of PTV receiving prescription dose for FFFBs of 6 and 10 MV photon energies were 95.03±0.10% and 95.02±0.18%, respectively; moreover, the corresponding HI values were estimated at 1.063±0.008 and 1.068±0.010, and the CI values were determined at 1.018±0.028 and 1.024±0.027. In the same line, the NTID and MUs values were 280.3±42.5 and 267.9±39.1 (liter-Gy), as well as 610.3±30.3 and 630.6±39.7,respectively.

The differences in HI, CI, MUs, and NTID values were found significant with a P-value less than 0.05. Figure 2 shows a comparison between 6 FFFB and 10 FFFB RA plans for individual patients in terms of CI and HI.

Regarding the bladder and rectum, there was no significant difference between both photon energies in terms of mean doses; however, a significant difference was found between both photon energies in terms of percentage volumes receiving a dose of 50 Gy. Similarly, both the femoral heads showed no significant differences between both photon energies in terms of mean dose and volume receiving doses of 40Gy.

In the patient-specific dosimetric analysis, IC measured dose were in agreement with the TPS calculations and was found within the prescribed tolerance. Figure 3 shows the percentage difference between IC measured dose and TPS calculations for 6 and 10 MV FFFB RA plans of the individual patient, respectively. Furthermore, the mean percentage dose differences were 2.1 (SD: 1.1) and1.1(SD: 1.8) for 6 and 10 MV FFFBs, respectively. It should be mentioned that they were within the prescribed tolerance.

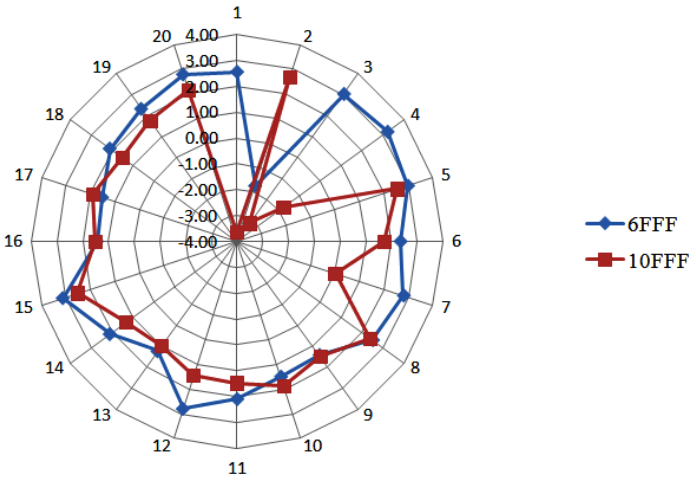


Figure 3. Percentage difference between 6 FFF and 10 FFFB RA plans regarding IC measured and TPS calculated dose for individual patient.

The origin of these difference lies in the degree of modulation and gradient created in planning for a particular plan, uncertainty in MLC position, inherent setup error, measuring devise error, and dose calculation algorithm. The mean DTA values were 97.2 (SD: 1.3) and 98.2 (SD: 1.1) for 6 and 10 MV FFFBs, respectively. Additionally, the mean gamma indices values were 99.1 (SD: 0.8) and 99.2 (SD: 0.6) for 6 and 10 MV FFFBs, respectively.

Discussion

The present study demonstrates the feasibility of using FFFB for gynaecological malignancies. Clinically acceptable plans were generated using FFFB of 6 and 10 MV photon energies with an Eclipse TPS. The dosimetric plans revealed no significant difference between FFF of 6 and 10 MV photon energies in terms of PTV coverage and OARs sparing. Kumar et al.[20] reported no significant differences between RA plans of FF and FFF photon beams of 6 MV and 10MV energies in terms of PTV and OARs in cervical cancer. Regarding the dose to OARs, there was no significant difference between RA plans of 6 and 10 MV FFFBs in terms of the mean dose to bladder, rectum, femoral heads, except for bowel (P=0.000)

The results of the patient-specific dosimetric analyses were in agreement with those obtained from TPS calculations and were found within the prescribed tolerance. The European True-Beam Council multi-institutional study concluded that the delivery of RA and IMRT plans was evenly precise based on the results of 224-patient-specific QA plans using FFF photon beams[21]. Homogeneous photon fluence across the irradiation field covering the target is indispensable for all radiotherapy treatment plans. In inverse planning, computer optimization bestows an ample degree of freedom to accurately deal with the non-uniform profile nature of FFF beam. Several authors reported comparable planning indices for FFF, compared to FF beam, depending upon the different disease sites and energies[22, 23]. The dosimetric data showed that 6 MV FFFB produced more conformal (P=0.051) and homogenous (P=0.005) dose distribution for gynaecological malignancies, compared to 10MV FFFB.

Furthermore, the data revealed that 6 MV FFFB required significantly (P=0.017) fewer number of MUs (3.33%), compared to 10 MV FFFB for gynaecological malignancies. This can be attributed to the fact that 10 MV FFF has more forward peak and non-uniform beam profile, compared to 6 MV FFF. Vassiliev et al.[23] reported the increased number of MUs for 6 MV FFF, compared to 18 MV FFF beam used for prostate IMRT planning. The MUs may depend on the target size, location, and degree of modulation used during plan optimization for sparing the OARs. The present study revealed that 6 MV FFFB delivers significantly (P=0.000) higher NTID (4.42 %), compared to 10 MV FFFB. Low dose-volume analysis of normal tissues showed no significant (P>0.05) difference between 6 and 10 MV FFFBs regarding the dose to the different body volume of $D_{1\%}$ and $D_{2\%}$. The volume receiving 2Gy (V_{2Gy}) and 5Gy (V_{5Gy}) were found to be significantly reduced (P<0.05) for 10 MV FFFB, compared to 6 MV FFFB. This reduction in NTID, V_{2Gy}, and V_{5Gy} of normal tissues may result in the lower risk of radiation-induced secondary malignancy using 10 MV FFFB. Cashmore et al.[24] reported a reduction in unwanted and unnecessary scatter dose by up to 70% for IMRT using FFFB. Furthermore, Kargl et al.[25] reported a reduction of 52% and 65% for 6 and 10 MVs in the treatment of head leakage in case of prostate IMRT using FFFB.

However, the advantage of 10 MV FFFB beam can be outweighed due to the unavoidable presence of neutron flux associated with a higher energy (E>8MeV) photon beam [26]. Neutrons are mainly generated in linac through the interaction of high energy photon (E>8MeV) with the nuclei of high atomic number materials present in the linac head, patient body, and treatment room walls. The production of photo-neutrons depends on the different mechanisms, such as giant dipole resonance, quasi deuteron, and delta resonance [27]. However, Kry et al. [28] reported an approximately 20% reduction in neutron fluence per

monitor unit for FFFB, compared to FFB and concluded a 69% reduction in total neutron fluence for the entire course of prostate IMRT. This can be attributed to the fact that neutron fluence per monitor unit decreases with the removal of FF when the number of photons produced at the target to deliver a given dose at isocenter decreases with the removal of FF. Consequently, neutron fluence per MU decreases due to the reduction of photo-neutron interaction events occurring in linac head components and other contributing components [29].

The National Council on Radiation Protection and Measurements Report (No 79) states that neutrons are highly penetrating particles with high relative biological effectiveness in nature. However, the neutron has fewer contribution in total dose to patient as compared to scatter photon contribution. Owing to their radiation weighting factor of 20, neutrons may lead to significantly higher biological damage to normal tissue, compared to the X-rays [30]. Several studies reported the impact of different photon energy (filtered) on gynaecological malignancies using IMRT and VMAT techniques and reported the advantage of 6 MV photon beam over their counterpart higher energy photon beams [16,18,20]. Gynaecological malignancies are managed using the amalgam of external beam radiation therapy and brachytherapy (BT). In a certain scenario, BT boost may not be viable due to coexisting medical conditions, unfavourable anatomy, or patient denial to undergo the procedure. In such a scenario, a higher dose of external beam radiation using FFFB may be an alternative, which can deliver radiation without any additional discomfort to patients. Hass et al. [31] reported the stereotactic body radiotherapy boost to the patients with cervical cancer using FFFB generated from Cyberknife following the conventional fractionated RT. They concluded that no grade 3 or 4 bladder and rectal toxicities were observed after a median follow-up of 14 months.

The limitation of the current study included its reliance on the dosimetric data rather than any evidence based on post-treatment clinical outcomes. However, the present study carefully looked at the possible approximation of using FFF beam generated from conventional linacs for the treatment of gynaecological malignancies.

Conclusion

Based on the dosimetric comparison of RA plans generated using FFFB of 6and 10 MV photon energies, FFFB has shown the potential to generate clinically acceptable RA plans. The RA plans using 6 MV FFFB was to be found superior, compared to RA plans of 10MV FFFB for the treatment of gynaecological malignancies. Furthermore, 6 MV FFFB generated better homogenous and conformal dose distribution to the target volume and required a fewer number of MUs (2.8%) for similar target coverage and OARs sparing, compared to 10 MV FFFB.

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