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ORIGINAL ARTICLE

Evaluation of Flattening Filter-Free RapidArc and Intensity-Modulated Radiation Therapy Techniques for Postoperative Cervical Cancer Treatment

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OBJECTIVE

To study the dosimetric characteristics and treatment plan complexity of Intensity-Modulated Radiotherapy (IMRT) and RapidArc (RA) techniques for Flattening Filter (FF) and Flattening Filter-Free (FFF) beams in the treatment of cervical cancer.

METHODS

A cohort comprising twenty post-operative cervical cancer patients was selected for this study. Four distinct sets of treatment plans were generated utilizing both RA and IMRT techniques employing FFF and FF beams. The dosimetric parameters were subjected to a comprehensive comparison, encompassing considerations such as the coverage of the Planning Target Volume (PTV), Conformity Index, Homogeneity Index, Heterogeneity Index, Gradient Index, Organ at Risk doses, and Peripheral doses.

RESULTS

The dose-volume parameters exhibited a significant difference in V_{95} between RA_FF and FFF plans. However, V_{98} demonstrated a higher percentage of coverage with FF beams for both IMRT and RA planning techniques ($p<0.01$). IMRT and RA plans resulted in a percentage reduction in V_{45} for the bladder and rectum with the FFF beam. Furthermore, the FFF beam showed a significant increase in MUs and a significant reduction in $V_{30\%}$ for the femoral head for both IMRT and RA plans. No difference was observed in normal tissue sparing with the FFF beam for both techniques.

CONCLUSION

Dosimetrically, FF and FFF beam plans exhibit comparable target coverage and OAR sparing for postoperative cervical carcinoma using both IMRT and RA techniques. However, in terms of plan quality, RA_FFF plans demonstrate a superior coverage index, conformity, and better sparing of normal tissue compared to IMRT_FFF, except for homogeneity.

Keywords: Cervical cancer; flattening filter free (FFF); IMRT; radiotherapy; rapidarc (RA).

INTRODUCTION

Cervical cancer is one of the most prevalent malignant tumors in women. Globally, it stands as the fourth leading cause of cancer-related deaths in women.[1] A considerable majority of cases occur in lower and middle-income countries, primarily due to the absence of widespread implementation of population-

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based cancer screening initiatives and human papillomavirus (HPV) vaccination.[2] In the initial stages, cervical cancer is commonly treated with surgical intervention, while radiotherapy and chemotherapy take precedence in intermediate and advanced stages. Concurrent chemoradiotherapy is globally recommended as the primary treatment approach for patients with International Federation of Gynecology and Obstetrics (FIGO) IB-IVA cancer when opting for definitive radiotherapy (RT). Radiotherapy is the preferred strategy for definitive and postoperative management of cervical and endometrial cancer.[3]

Traditional radiotherapy methods, such as the four-field box approach and front-to-back penetrating irradiation, have been widely used. However, they are associated with significant adverse effects on the gastrointestinal, urinary, and hematopoietic systems. In contrast, three-dimensional conformal radiation therapy (3DCRT) has more advantages than conventional therapy. It tailors the radiation beam according to the primary target, resulting in more precise target coverage while adhering to organ-at-risk constraints. Intensity-Modulated Radiotherapy (IMRT) and Volumetric-Modulated Arc Therapy (VMAT) are two contemporary approaches to delivering precise radiation doses to tumors, minimizing exposure to surrounding healthy tissues.[4] Intensity-modulated radiotherapy is effective in preserving surrounding normal tissues and organs together and provides a high dose to the target. The major disadvantage of IMRT is that it consumes longer treatment time and uses many fixed beam angles and monitor units (MU).[5]

Further, with technological advancement, intensity-modulated radiation therapy with image-guided treatment delivery (IG-IMRT) has been commonly employed due to its low acute toxicity profile, that is, acute grade II gastrointestinal (GI) toxicity of 60% with intensity-modulated radiation therapy (IMRT) versus 91% with 3DCRT.[6,7] On the contrary, treatment planning with the Rapid Arc (RA) (Varian Medical Systems, Palo Alto, CA) technique, which usually employs using one or more arcs by changing dose rate, multi-leaf collimator location, and gantry speed, integrates to decrease the number of MU and shortens treatment time compared to IMRT, resulting in maximal dosage to target from all angles while preserving normal tissues.[8]

VMAT and IMRT planning with FF beam is associated with certain drawbacks, such as prolonged delivery time, reduced treatment dose rate, decreased photon intensity, and increased treatment dose scattering. Therefore, flattening filter-free (FFF) beams were intended to decrease the long delivery treatment time since removing the flattening filter raises the dose rate by a factor of two to four.[9] A reduction of the treatment time reduces the probability of intrafraction motion of the target and organs at risk, which has been demonstrated to be not negligible for the treatment of prostate cancer.[10] Moreover, FFF beams differ significantly from traditional photon beams in several ways. In addition to having a distinct photon energy spectrum and varied head-scatter characteristics, they also have a different beam profile and a higher dose rate. As a result, FFF beams have unique beam characteristics such as a sharper penumbra, less head scatter, lower out-of-field dosage, and dosimeter response such as higher ion recombination.

Few studies have been conducted on the dosimetric effects of the FFF beam on RapidArc planning for cervical cancer. At the same time, faster treatments could have a clinical impact on cervical cancer patients in terms of comfort on the treatment table, immobility, and minimization of internal organ status changes, such as bladder or rectum filling changes over time, as well as the reduction of intra-fractional patient motion.[11–13]

Moreover, the previous studies were driven by the anticipation that variations in nominal energy and penumbra of Flattening Filter-Free (FFF) beams might affect the dosimetric outcomes for this particular deep-seated treatment site. Changes in secondary build-up could potentially influence target coverage and the sparing of organs at risk (OAR). Hence, the objective of this study is to identify the optimal treatment modality for post-hysterectomy cervical cancer treatment. This involves a comprehensive analysis and comparison of plan quality, utilizing a flattening filter-free beam in conjunction with Intensity Modulated Radiation Therapy (IMRT) and RapidArc (RA) procedures, assessed through various dosimetric indices.

MATERIALS AND METHODS

Patient Selection

Twenty consecutive patients with histologically proven locally advanced cervical cancer were retrospectively included in this planning study. The carcinoma cases were graded according to the FIGO 2018 classification. The sample size for our study was determined through a power analysis, referencing Deng et al.[14]'s study. Deng et al.[14] reported a power of 100% with D_2 values (conformal radiotherapy (CRT) =650.8±48.9, IMRT =4907.0±47.9, VMAT =4962.2±22.5). Pairwise statistical differences were observed (CRT vs. IMRT, p<0.001; CRT vs. VMAT, p<0.001; IMRT vs. VMAT,

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p=0.002), with alpha (α=0.05) values obtained from the same study involving 15 patients. Therefore, we conducted a power analysis, determining a sample size of 20 patients to enhance the robustness of our study.

Simulation

The simulation was performed using CT-Sim (64 slices, Philips Ingenuity) in a supine position. Standard bladder protocol was maintained for all patients during simulation and treatment. A contrast-enhanced computed tomography (CECT) simulation was acquired from L2 to mid-thigh with a slice thickness of 3.0 mm for all planning CT images.

Contouring and Prescription of Target Volumes

The Clinical Target Volume (CTV) and Organs at Risk (OARs) of each patient were contoured by an experienced oncologist. The corresponding planning target volume (PTV) was generated by symmetrically expanding 7.0 mm from CTV. The OARs included the rectum, bladder, femur heads, and bowel in this study. In addition, to improve the target dose conformity, the assistance organ Body-PTV (B-P) was defined as the body volume in the CT data set minus the PTV, leaving a 0.3 cm gap. Furthermore, B-P was used in all RapidArc and IMRT optimization to standardize the optimized constraints. The prescribed dose to the target was 45 Gy in 25 fractions.

Treatment Planning

All the RapidArc and IMRT plans were generated using the Eclipse (v15.6 Varian Medical Systems, Palo Alto, CA, USA) treatment planning system. RapidArc plans were created using the dual arc (181–179 were set in the clockwise direction, and 179–181 were set in the counterclockwise direction), and IMRT plan seven fixed angles (51°, 102°, 151°, 202°, 251°, 302°, and 351°) were used with jaw tracking using FF, and FFF 6MV beam and Photon optimizer (PO) (Version 15.6.06, Varian Medical System) was selected for inverse optimization by physical and biological objectives. Hence, the physical constraints as Upper, Lower, and Mean objectives were used to limit the dose level in a defined portion of the structure volume, define a minimum dose level that a particular target volume should receive, and define the mean dose that should not be exceeded for the structure. In addition, the biological objective mainly used for OARs was Upper gEUD, where the parameter "a" can vary from +0.1 to +40. Each set of plan doses was calculated using the Anisotropic Analytical Algorithm (AAA) (Version 15.6.06, Varian Medical System) with a 2.5 mm dose grid resolution. Hence, the current study generated four plans (RA_FF, RA_FFF, IMRT_FF, and IMRT_FFF) for each patient. The Varian TrueBeam accelerator equipped with 120 leaves Millennium multi-leaf collimator (M120, MLC) was used to develop all RA and IMRT plans with a maximum dose rate of 600 MU/min and 1400 MU/min for FF and FFF photon beams, respectively.

Dosimetric Evaluation

The requirement of a conformal and homogeneous dose to the tumor is achieved in our case with no overdose or underdose. So, the quality of treatment plans is assured. IMRT and RA plans were quantitatively evaluated using dose-volume histogram (DVH) curve analysis. Various dosimetric metrics were evaluated using cumulative dose-volume histogram (DVH). Isodose distribution and dose-volume metrics were evaluated for the PTV volume received by 95% and 98% of the prescribed (V_{95}, V_{98}), near max ($D_{2\%}$), near min ($D_{98\%}$), Maximum Dose (D_{max}), Minimum Dose (D_{min}), Mean Dose (D_{mean}), D_{20}, D_{50}, D_{80} and V_{107}(cc).

Plan Evaluation Indices

The Homogeneity Index (HI) used in this study is the ratio of maximum dose (D_{max}) to prescription dose (PD). It is defined as the ratio of the maximum dose delivered to the target volume to the prescribed dose as per the RTOG protocol. If the value of HI is closer to 1, it indicates better homogeneity.[15]

Target volume coverage (C) is the ratio of D_{min} to PD. The plan is acceptable if TV covers 90% of the prescription isodose.[16]

The Conformity Index (CI) provides a reliable method for quantifying the degree of conformity based on isodose surfaces and volumes. It was calculated using the formula as reported in the RTOG 90–05 protocol. It is defined as the prescription isodose volume (PIV) that completely envelops the target volume (TV).[17]

The Gradient Index (GI) measures the shallowness or steepness of dose fall-off in tumor volume. GI is defined as the volume of PD to the 50% isodose volume of PD. A lower GI ratio indicates greater dose fall-off and better plan conformity.[18]

Akpati et al.[19] proposed a unified dosimetry index (UDI) that integrates contributions from all four above dosimetric components. It is considered an efficient tool for defining an ideal plan, with a value of one for an ideal treatment plan.

$$UDI = Coverage\ (C) \times CI \times HI \times GI$$

The Dose Heterogeneity Index (DHI) is computed to find the dose homogeneity inside the target volume. This index is defined as follows:[20]

Table 1 Dose-volume parameters for planning target volume using intensity modulated radiation therapy technique for FF and FFF beam

	IMRT_FF		IMRT_FFF		Difference	p
	Mean	SD	Mean	SD		
D_{max}	48.85	0.56	48.70	0.68	0.29	0.14
D_{min}	39.77	0.69	39.72	0.63	0.12	0.57
D_{mean}	45.44	0.20	45.34	0.24	0.23	0.08
D_{20}	45.85	0.26	45.83	0.30	0.06	0.32
D_{50}	45.37	0.22	45.32	0.23	0.11	**0.02**
D_{80}	44.95	0.21	44.89	0.15	0.14	**0.03**
D_{98}	44.15	0.18	44.09	0.21	0.13	0.30
D_{2}	46.67	0.35	46.69	0.40	-0.04	0.73
V_{107}(cc)	0.45	0.67	0.44	0.63	0.45	0.99
V_{95}(cc)	1113.15	87.01	1112.90	87.10	0.02	**0.03**
V_{90}(cc)	1114.54	86.42	1114.48	86.48	0.00	0.35
V_{50}(cc)	1114.56	86.40	1114.51	86.45	0.00	0.33
V_{25}(cc)	1114.56	86.40	1114.51	86.45	0.00	0.33
V_{95}(cc) (Body)	1316.71	121.69	1323.37	127.61	-0.51	0.09
MU	1524.00	135.72	2257	175.32	32.46	**<0.001**

FF: Flattening filter; FFF: Flattening filter-free; IMRT: Intensity-Modulated Radiotherapy; SD: Standard deviation; D_{max}: Maximum dose; D_{min}: Minimum dose; D_{mean}: Mean dose; MU: Monitor units. Vx is the volume receiving x% of the prescribed dose; Dx% is dose received by x% of volume

$$DHI=\left(\frac{D_{20\%}-D_{80\%}}{D}\right)\times 100$$

D_{20} and D_{80} represent the dose covering 20% and 80% of the target volume, respectively, and D is the prescription dose. According to the definitions of D_{20} and D_{80}, D_{20} is always greater than or equal to D_{80}. Therefore, a lower index reflects a smaller difference between the doses covering 20% and 80% of the target volume and indicates better dose homogeneity.

The low Gradient Index (LGI) and High-Gradient Index (HGI) were calculated using the formula below. Low and high gradient indices were calculated using the following formula:

Low Gradient Index (LGI)=$V_{25\%}$ PID / $V_{50\%}$ PID

High Gradient Index (HGI)=$V_{50\%}$ PID/$V_{90\%}$ PID

$V_{25\%}$, $V_{50\%}$, and $V_{90\%}$ were volumes receiving 25%, 50%, and 90% of the prescription isodose dose (PID), respectively.

The OAR dose was compared using the following parameters: For the bladder and rectum, dosimetric parameters were analyzed using volume dose received by 30%, 40%, and 45% of the organ volume (V_{30}, V_{40}, V_{45}) mean Dose (D_{mean}) and near maximum dose (D_{2cc}). The dosimetric parameters V_{30}(%) and D_{2cc} were assessed in the femoral heads. V_{40} and V_{45} (volume in cc receiving 40 and 45 Gy) dose volumes were used to analyse the bowel. Additionally, the study considered parameters such as the body–PTV mean dose, low dose volumes (V_1, V_2, V_3, V_4, and V_5), intermediate-dose volumes (V_{10}, V_{20}, V_{30} and V_{40}), and monitor units (MU).

Statistical Analysis

The dosimetric difference between IMRT and RA plans was analyzed using the Statistical Package for the Social Sciences (version 23; IBM Corp., Armonk, NY, USA) in terms of the mean, standard deviation, and P-values. The independent paired t-test with a confidence interval limit of 95% was performed to assess the dosimetric endpoints for the target and OARs. P-values of less than 0.05 were used to denote statistical significance.

RESULTS

The mean volume of PTV, bladder, rectum, bowel, RTFH, and LTFH of all 20 patients were 1103.28±89.72 cm^3, 163.57±78.04 cm^3, 62.14±26.44 cm^3, 1962.88±781.43 cm^3, 97.26±10.70 cm^3, and 97.01±12.63 cm^3 [mean± standard deviation (SD)].

Clinically acceptable treatment plans were created using the RA and IMRT techniques for all patients. Qualitative and quantitative analyses were performed on dose distribution created for RA and IMRT plans. The data were derived from cumulative DVH data for each treatment plan.

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Table 2 Dose-volume parameters for planning target volume using RapidArc technique for FF and FFF beam

	RA_FF		RA_FFF		Difference	p
	Mean	SD	Mean	SD		
D_{max}	48.85	0.46	49.23	0.49	-0.78	**0.00**
D_{min}	40.44	1.73	40.20	1.64	0.59	0.12
D_{mean}	45.85	0.15	45.87	0.13	-0.05	0.25
D_{20}	46.33	0.19	46.43	0.16	-0.20	**0.00**
D_{50}	45.88	0.15	45.91	0.12	-0.06	0.18
D_{80}	45.43	0.13	45.39	0.11	0.08	0.19
D_{98}	44.23	0.09	44.08	0.17	0.35	**0.00**
D_{2}	47.06	0.24	47.24	0.24	-0.39	**0.00**
V_{107}(cc)	0.47	0.61	0.48	0.35	-2.25	0.94
V_{95}(cc)	1117.18	88.93	1115.71	87.82	0.13	0.76
V_{90}(cc)	1118.09	89.02	1118.05	89.02	0.00	**0.03**
V_{50}(cc)	1118.13	89.02	1118.63	89.46	-0.04	0.33
V_{25}(cc)	1118.13	89.02	1118.13	89.02	0.00	0.50
V_{95}(cc) (Body)	1320.17	133.58	1320.17	122.73	0.00	1.00
MU	593.37	64.31	677.97	81.78	12.16	**<0.001**

FF: Flattening filter; FFF: Flattening filter-free; RA: RapidArc; SD: Standard deviation; D_{max}: Maximum dose; D_{min}: Minimum dose; D_{mean}: Mean dose; MU: Monitor units

Table 3 Plan quality indices for planning target volume using IMRT and RapidArc technique for FF and FFF beam

	IMRT_FF		IMRT_FFF		Diff.	p	RA_FF		RA_FFF		Diff.	p
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
CI * 100	99.87	0.19	99.85	0.19	0.02	0.03	99.93	1.82	99.79	0.20	0.14	0.72
DHI = D_{20}-D_{80}/D *100	2.01	0.31	2.09	0.40	-4.27	0.22	2.02	0.26	2.31	0.24	-14.26	**0.00**

IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free; Diff.: Difference; SD: Standard deviation; CI: conformity index; DHI: Dose Heterogeneity index

Table 4 Dose-volume parameters for organs at risk using IMRT and RapidArc technique for FF and FFF beam

	IMRT_FF		IMRT_FFF		p	RA_FF		RA_FFF		p
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Bowel										
V_{40}	281.00	104.73	287.70	106.52	**0.01**	276.55	108.51	281.84	109.72	0.19
V_{45}	142.72	72.45	134.95	78.55	**0.03**	154.53	66.89	146.42	66.11	0.09
RTFH										
V_{30}	5.39	3.00	4.93	2.90	**0.00**	7.51	3.24	7.12	3.20	**0.00**
D_{2cc}	33.69	3.68	33.59	4.01	0.54	36.48	3.39	35.76	2.49	0.28
LTFH										
V_{30}	4.39	2.47	4.29	2.62	**0.00**	6.89	3.66	5.80	3.17	**0.01**
D_{2cc}	32.95	3.15	32.93	3.45	0.90	35.60	3.19	34.75	2.70	0.10

IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free; SD: Standard deviation; RTFH: Right femoral head; LTFH: Left femoral head

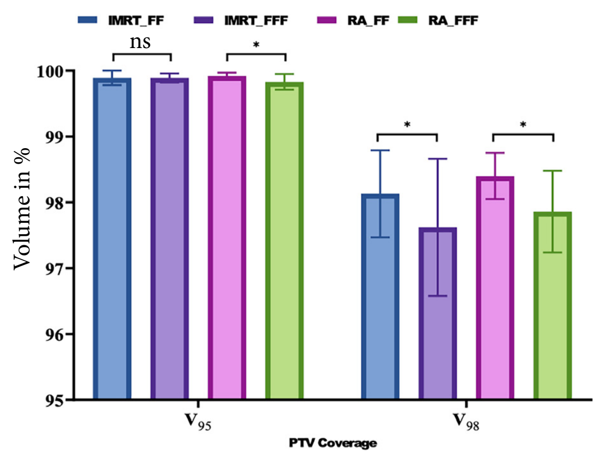

Fig. 1. Variation of PTV coverage for V_{95} and V_{98} dose-volume metrices with IMRT and RapidArc technique for FF and FFF beam.
*: Signifies p≤0.05. PTV: Planning Target Volume; IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

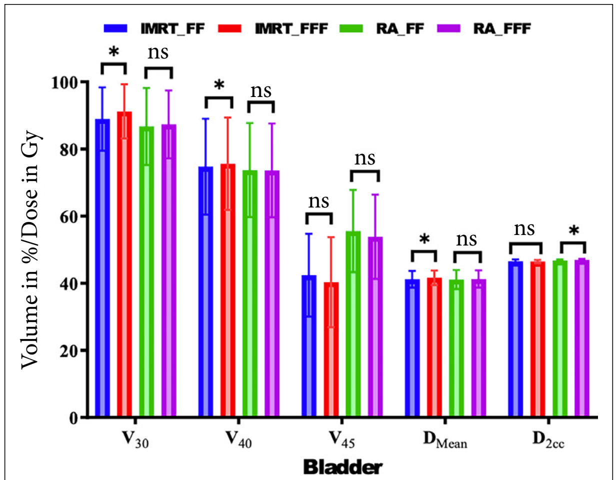

Fig. 2. Variation of different dose volume parameters (V_{30}, V_{40}, V_{45}, D_{mean}, D_{2cc}) for Bladder with IMRT and RapidArc technique for FF and FFF beam.
*: Signifies p≤0.05. IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

Table 1, Table 2, Table 3, and Table 4 summarize the planning target volume and OAR dose of IMRT and RA plans of FF and FFF beam plans.

Figures 1-4 represent the comparison between IMRT and RA plans for FF and FFF in terms of PTV coverage, bladder and rectum DVH parameters, and various plan quality indices.

Figure 5 represents the dose fall-off in the log-log plot between Dose (1 Gy to 40 Gy) in the BODY-PTV region for RA and IMRT plans for the FF and FFF techniques.

Figures 6, 7 show the isodose distribution in transverse, coronal, and sagittal planes for one patient planned with IMRT and RA techniques with FF and FFF beams. In the figures, 'ns' denotes non-significant (p>0.05), while '*' signifies p≤0.05.

The DVH comparison between IMRT and RA plans for FF and FFF plans is shown in Figures 8, 9.

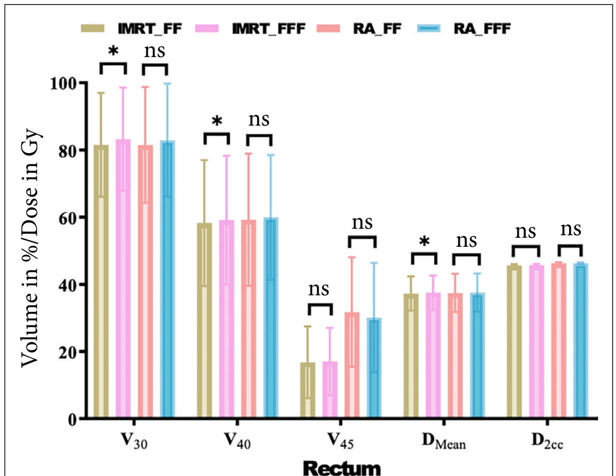

Fig. 3. Variation of different dose volume parameters (V_{30}, V_{40}, V_{45}, D_{mean}, D_{2cc}) for Rectum with IMRT and RapidArc technique for FF and FFF beam.
*: Signifies p≤0.05. IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

PTV Dose Distributions and Evaluations

As depicted in Figures 6, 7 of isodose distribution and Figures 8, 9 of DVH, no difference in V_{95} dose distribution was observed between IMRT FF and FFF plans. In contrast, a significant difference was observed between RA_FF and FFF plans, depicted in Figure 1. Moreover, V_{98} showed a higher percentage of dose distribution in plans with FF beams for both IMRT and RA planning techniques, with a significant difference observed between them (p<0.01).

Furthermore, there was a significant reduction in D_{50} observed in IMRT_FFF plans. Conversely, an increase in D_{50} was observed (p=0.18) with RA_FFF. Additionally, IMRT_FFF plans showed a decrease in D_{max} (p=0.14), whereas RA_FFF plans demonstrated a significant increase in D_{max} inside the PTV volume.

Plan Quality Indices

IMRT_FF and IMRT_FFF plans showed a homogeneous plan with a 6 MV photon beam, but a significant difference in homogeneity was observed with RA_FFF plans. Furthermore, there was a significant

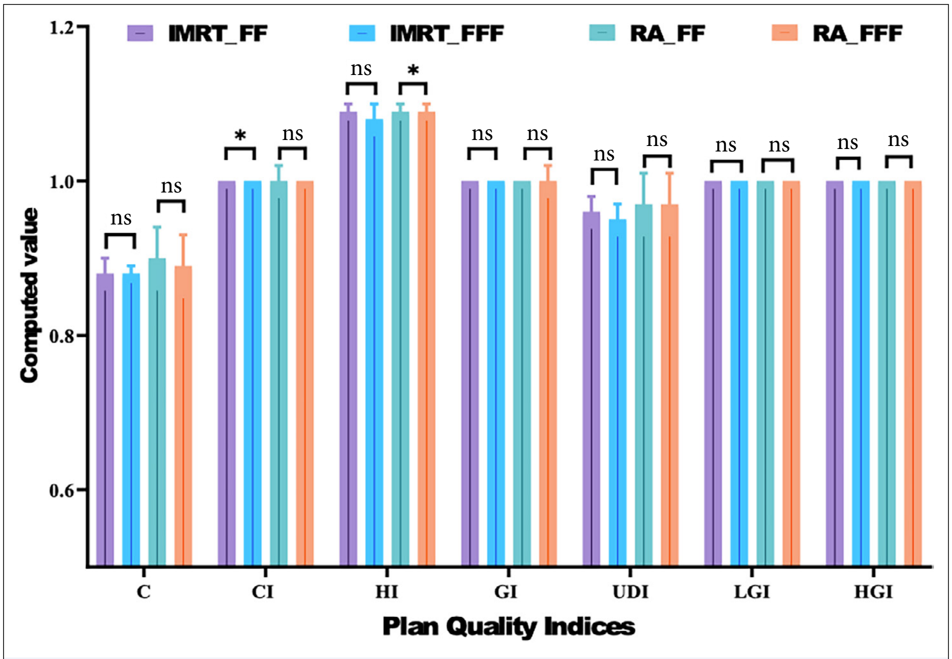

Fig. 4. Variation of different plan quality indices (C, CI, HI, GI, UDI, LGI and HGI) with IMRT and RapidArc technique for FF and FFF beam.

*: Signifies p≤0.05. C: Coverage index; CI: Conformity index; HI: Homogeneity index; GI: Gradient index; UDI: Unified dosimetry index; LGI: Low gradient index; HGI: High gradient index; IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

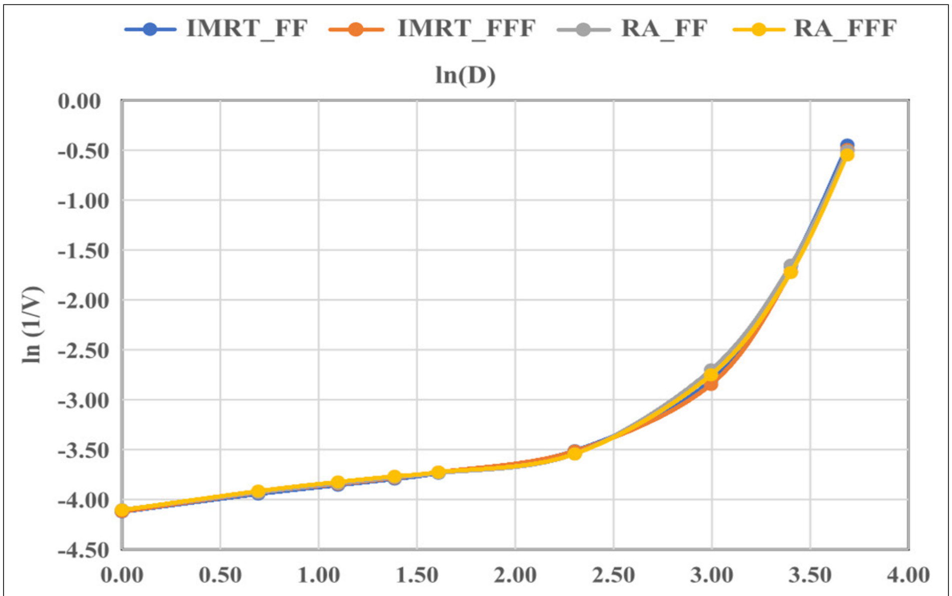

Fig. 5. The dose fall-off beyond the target region depicted in a log-log plot between Dose and Volume(1/V) shows the variation of low dose volume parameter for IMRT and RapidArc technique with FF and FFF beam.

IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

difference of 14.26% (p<0.01) in DHI with RA_FFF plans, whereas with IMRT_FFF, the difference was only 4.27%, which was insignificant. A highly conformal plan was found with RA_FF and RA_FFF

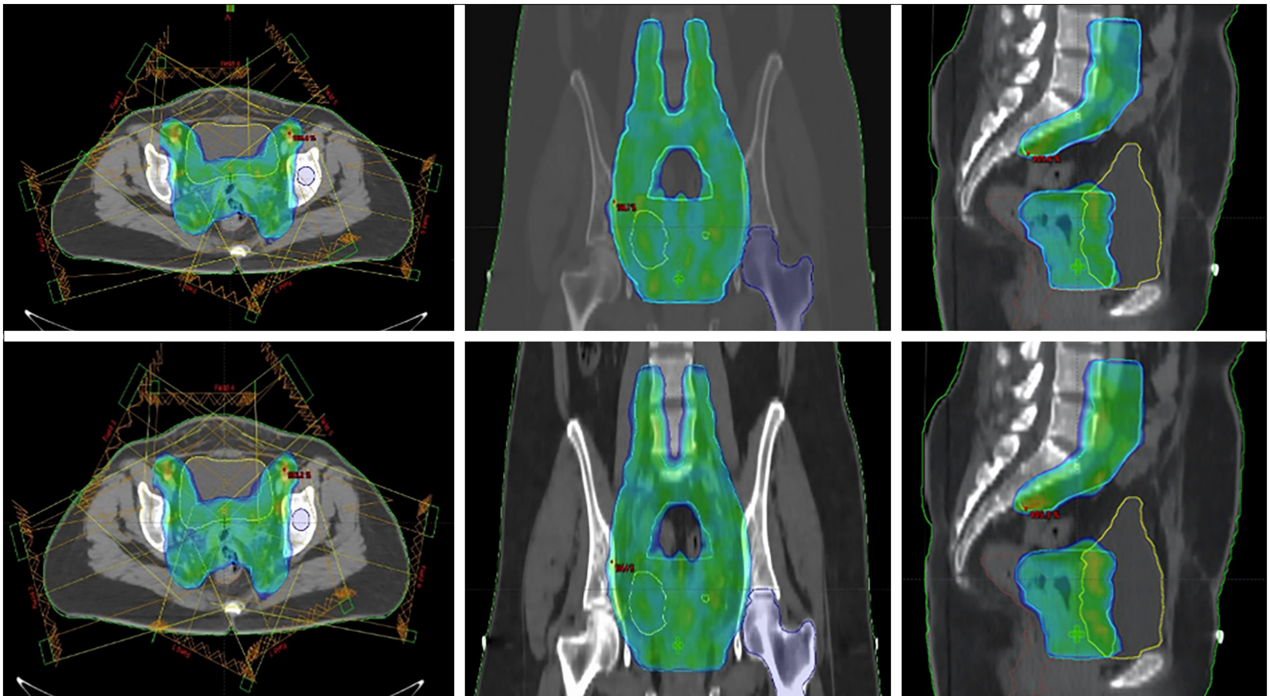

Fig. 6. Comparison of 95% prescription dose colour wash of a IMRT plan for FF (upper row) and FFF (lower row) 6MV beam in axial, coronal and sagittal views.
IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

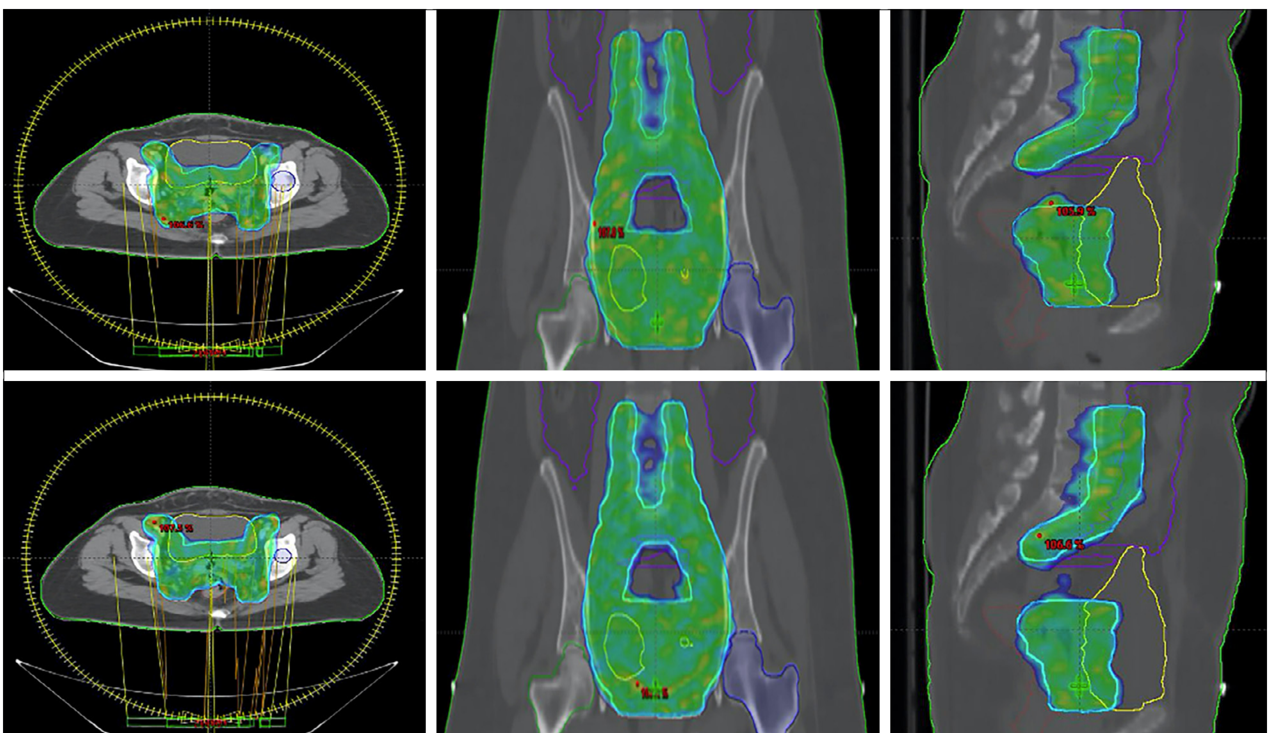

Fig. 7. Comparison of 95% prescription dose colour wash of a RapidArc plan for FF (upper row) and FFF (lower row) 6MV beam in axial, coronal and sagittal views.
FF: Flattening filter; FFF: Flattening filter-free.

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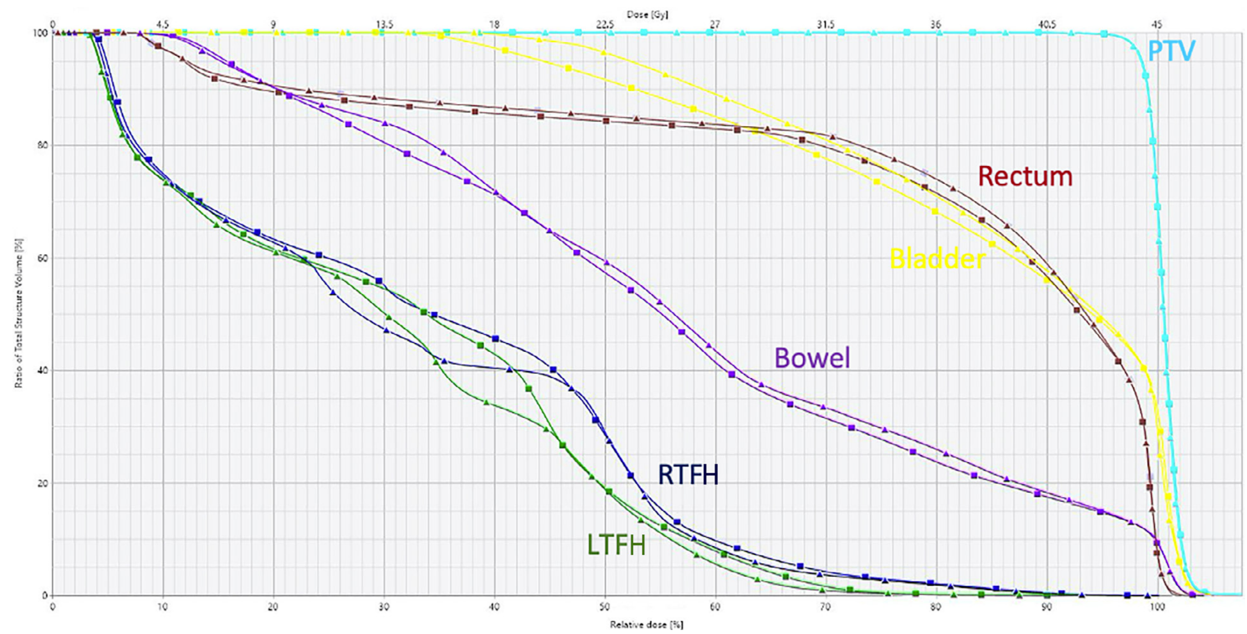

Fig. 8. DVH comparison for target (PTV) and OARs (Bladder, Rectum, Bowel, Femur Heads) for a IMRT plan using FF (square) and FFF (triangle) 6MV beam.
PTV: Planning target volume; RTFH: Right femoral head; LTFH: Left femoral head; DVH: Dose-volume histogram; OARS: Organs at risk; IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

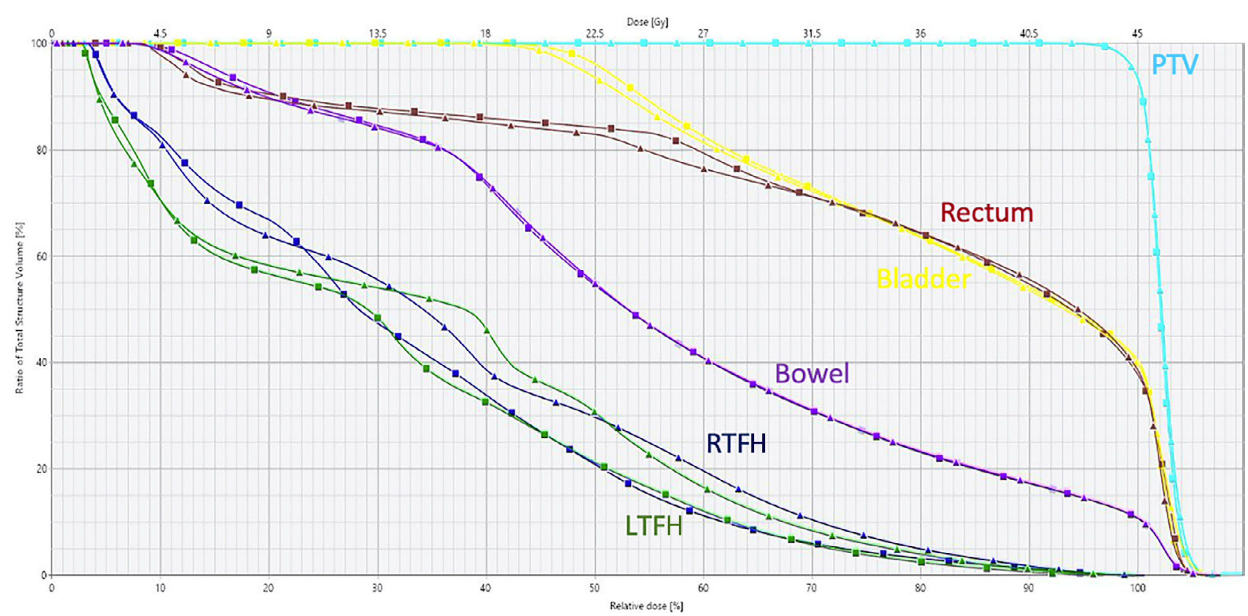

Fig. 9. DVH comparison for target (PTV) and OARs (Bladder, Rectum, Bowel, Femur Heads) for a RapidArc plan using FF (square) and FFF (triangle) 6MV beam.
PTV: Planning target volume; RTFH: Right femoral head; LTFH: Left femoral head; RA: RapidArc; DVH: Dose-volume histogram; OARS: Organs at risk; IMRT: Intensity-Modulated Radiotherapy; FF: Flattening filter; FFF: Flattening filter-free.

techniques. However, a significant difference was observed with IMRT plans for FF and FFF.

The evaluation of UDI, LGI, and HGI indices revealed a significant difference in UDI between IMRT and RA plans utilizing the FFF beam. However, all the plans achieved similar plan quality indices in their respective techniques. Additionally, no differences were observed in LGI and HGI indices among plans using the FFF beam, IMRT, and RA.

Dose Sparing of the OARs

Bladder: There was a significant increase in V_{30}, V_{40}, and Mean Dose (D_{mean}) observed with the IMRT_FFF beam; however, a reduction in V_{45} was found with IMRT_FFF ($p<0.05$). Furthermore, no significant difference was observed in the near-max dose (D_{2cc}). For RA_FFF, a decrease in V_{45} was found ($p=0.07$), and a significant increase in D_{2cc} was observed ($p<0.01$).

Rectum: A significant increase in V_{30}, V_{40}, and Mean Dose (D_{mean}) was found with IMRT_FFF plans. However, no difference was observed in V_{45} and D_{2cc}. Furthermore, no significant difference was found between RA_FF and RA_FFF plans; a decrease in V_{45} was found with RA_FFF plans.

A large percentage reduction in V_{45} was observed with IMRT plans compared to RA for both the bladder and rectum, as shown in Figures 2, 3.

Bowel: The RA_FFF plans showed a reduction in V_{40}, but no improvement was observed in V_{45}. On the contrary, there was a significant increase in V_{40} with the IMRT_FFF technique; however, a significant reduction was observed in V_{45}. Moreover, a similar scenario was observed with RA_FFF, but these differences are not statistically significant.

RTFH & LTFH: In both femoral heads, no significant differences were found between IMRT_FF and IMRT_FFF, except in V_{30} ($p<0.05$). However, a significant increase in femoral head dose was found with RA_FFF plans.

The total number of monitor units (MU) is important for assessing the low dose to normal tissue and treatment time. The present study observed a significant increase in monitor units with FFF beam plans for IMRT and RA techniques. Moreover, the percentage difference in the increase in MUs is less in RA (12.16%) plans compared to IMRT (32.46%) plans.

The quantitative analysis of Figure 5 showed that dose fall-off beyond the target region was similar for all the datasets. Furthermore, we have taken ln(D) vs. ln(1/V) to evaluate the rate of dose fall-off beyond PTV. The fall-off shows that for low dose volumes (V_1, V_2, V_3, V_4, and V_5), the change in dose fall-off is similar, which continues till V_{10}. However, a steep dose fall-off was observed with intermediate dose volumes (V_{20}, V_{30} and V_{40}), starting from V_{20}, which clearly shows a steeper dose gradient found with RA plans with FF compared to FFF for V_{20} and V_{30} ($p<0.01$).

DISCUSSION

In FFF beams, the softening of the photon energy spectra leads to the shift of the maximum dose to the surface, peak forward, and a smaller penumbra width, resulting in reduced dispersion from the unit head.[9,21] These characteristics have been very beneficial for the treatment of various tumors. Furthermore, in addition to inverse planning, computer optimization provides significant flexibility to effectively address FFF beams' non-uniform profile. The dosimetric advantages of FFF beams in the treatment of postoperative cervical cancer patients were investigated by comparing them directly with RA and IMRT techniques in the current study.

FFF beam plans showed similar target coverage and increased bladder, rectum, and femoral head protection with RA techniques compared to IMRT. Furthermore, RA plans achieved less MU than IMRT. The RA_FFF plans showed a higher maximum dose to PTV, as presented by D_{max} and D_2, compared with IMRT_FFF for better target coverage. Furthermore, with both techniques, a significant reduction in V_{98} was found with the FFF beam, as shown in Figure 3. Similar results were found by Manna et al.[11] using RA_FFF dose distribution. On the contrary, Tamilarasu et al.[12] showed no difference in dose distribution between FF and FFF with IMRT except D_{50} $D_{2\%}$, and no significant difference was found in $D_{98\%}$ and $D_{95\%}$ of the PTV. However, in the current study, a significant reduction in D_{50} was observed with IMRT_FFF plans. Conversely, an increase in D_{50} was observed ($p=0.18$) with RA_FFF. This referred to the fact that a fixed-field IMRT has a limited number of radiation beams, leading to the omission of some ideal beam angles; the RA technique utilizes all the available degrees of freedom during optimization. This approach contributes to the generation of an optimal dose distribution, resulting in improved treatment plans.

In the current study, we have used many plan quality indices to qualitatively analyze the treatment plans generated by the FFF beam compared to FF for IMRT and RA techniques. The results are compared to find out the effective treatment plan for the treatment of post-op cervical cancer patients. Our study showed that RA produces more conformal and homogeneous plans than IMRT. This was consistent with the report that more conformal and homogeneous plans using the RA technique for post-operative cervical cancer patients.[14]

However, there was no difference in the Gradient Index for RA and IMRT plans. With FFF, most of the quality indices showed non-significant variation, except CI with IMRT_FFF plans and HI with RA_FFF

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plans. In addition, a decrease in UDI value was observed with IMRT_FFF, as shown in Figure 4, although this is not statistically significant. Zhang et al.[22] showed that VMAT_FFF produces an inferior heterogeneity plan compared to VMAT_FF while keeping similar conformity in the modalities. Moreover, Treutwein et al.[23] found an inferior plan quality with IMRT_FFF in terms of both HI and CI compared to IMRT_FF. We quantified that the RA plans irradiated more dose to the left and right femoral heads compared to doses to the bladder, rectum, and small bowel in IMRT plans. However, the differences were not statistically significant. These differences indicated that the number of fields used for IMRT directly impacts the quality of the IMRT plan, as RA plans decreased the MU and delivery time reported in previous studies.[24,25]

For OAR, the doses are smaller for FF than for FFF; partly, this can be traced to a smaller part of the PTV receiving the minimum dose required by the objectives. FFF for both bladder and rectum showed a decrease in dose for V_{45}; however, this is not statistically significant. Furthermore, an increase in dose in dosimetric parameters (V_{30}, V_{40}) was found with the FFF beam for both the IMRT and RA techniques. However, these differences are small too, in most cases less than 1% of the volume of the OAR, especially in comparison to the large standard deviation. The previous study with IMRT and RA showed a minimal improvement in dose to OARs with the FFF beam.[23,26]

Further, after a hysterectomy, the small bowel falls into the pelvis where the uterus previously resided, further increasing the amount of small bowel irradiated to the prescription dose. Rates of grade 2 and higher acute gastrointestinal (GI) toxicity of 50–90% with conventional CRT have been reported in the literature. Acute GI symptoms typically involve varying degrees of diarrhea, cramping, and abdominal pain, which can negatively impact the quality of life during treatment.[14,27] For the bowel, using the FFF beam in both IMRT and RA demonstrates a reduction in dose for V_{45}, which is statistically significant. However, there is an observed increase in dose for V_{40} with IMRT_FFF and RA_FFF, although this increase is not statistically significant for RA_FFF. Therefore, our study consisted of the study done by Cozzi et al.[28] in which the authors stated that RA showed significant improvements in OAR and normal tissue sparing with uncompromised target coverage compared to IMRT.

Previous studies on the IMRT technique used a PRO optimizer to generate their FF and FFF beam plans.[12,24] Furthermore, sparing plans optimized with PO have higher MLC variability and monitor units for better organs at risk. In the current study, the IMRT and RA plans were generated using the PO optimizer and showed improved sparing of V_{45} for the bladder in Figure 3 and rectum in Figure 4 with the IMRT technique. Binny et al.[29] showed that IMAT treatment plans with the PO optimizer provide comparable planned dose conformity to target volume and improved OAR sparing compared with the PRO optimizer. Furthermore, studies showed that the PO optimizer generates more complex plans than PRO.[30]

There was a significant increase in MU observed with the FFF beam for IMRT (32.5%, $p<0.01$) and RA (12.2%, $p<0.01$) techniques. Though the delivery time of the FFF beam (Dose rate 1440 MU/min) is higher than FF (600 MU/min), the increase in MU is related to achieving uniform dose distribution with an inhomogeneous profile. This finding is in line with the results from previous studies.[31] Furthermore, RA allowed a significant reduction in MUs compared to IMRT, correlating with the risk of increased low-dose normal tissue irradiation, potentially elevating the risk of second malignancies. Therefore, the study of low-dose volume depending upon the treatment technique is essential for inverse planning, as various authors indicate.[32,33] As shown in Figure 5, the RA technique exhibited a decrease in the low-dose volume, with a rapid fall observed with the use of the FFF beam. Additionally, the combined effect of RA and the FFF beam, resulting in a reduction in treatment time, is advantageous in several aspects. It improves patient comfort during treatment, particularly those lying with custom-made masks. It reduces the risk of intra-fraction motion, minimizes organ displacement, and enables the accommodation of more patients for treatment under the same machine.

CONCLUSION

The advantage of FFF beam planning for post-cervical cancer patients was studied in light of advanced planning techniques with an updated planning platform and various plan indices. The FFF beam achieved a target and OAR dose distribution similar to the FF beam for patients with RA and IMRT plans. RA plans showed significant dosimetric advantages on target coverage and OAR sparing compared with IMRT in treating postoperative cervical cancer with an FFF beam. Additionally, the higher MU for the FFF IMRT plan can be offset by a high dose rate, providing the added benefit of reducing overall treatment time and the motion management of the target.

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