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Dosimetric and Radiobiological Impact of Flattening Filter-Free Beam and Dose Calculation Algorithm Using RapidArc Plans for Cervical Cancer Treatment

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Abstract

Purpose: The aim of this study is to quantify the potential benefits of a flattening filter-free (FFF) beam and implement a dose-computation algorithm for cervical radiotherapy through dosimetric and radiobiological analyses using RapidArc.

Methods: Thirty-three patients were enrolled, and four RapidArc plans were created for each patient using a dual-arc flattening filter and 6-MV FFF photon beams for the two calculation algorithms. Homogeneity index (HI), conformity index (CI), target coverage, monitor units (MUs), and organ-at-risk (OAR) dosimetric characteristics were compared between the plans. Radiobiological characteristics and normal tissue complication probability (NTCP) scores were computed for the OAR using different biological models.

Results: No significant differences were observed in the $D_{max,}$ $D_{98\%}$, and CI in the planning target volume (PTV). Both computations estimated a significant difference in $V_{95\%}$, $D_{2\%}$, and HI for the PTV. Furthermore, the FFF beam showed a significant increase in the MUs and a significant reduction in $V_{30\%}$ for the femoral heads. The NTCP score showed a significant increase in the late effects on the bladder, rectum, and bowel with FFF beams.

Conclusion: The current study recommends FFF beams for better conformity, comparable dose coverage for the target, and OAR sparing invariable to the dose computation algorithm. The difference in the NTCP score for OAR was minimal with the FFF beam.

KEYWORDS
flattening filter-free, flattening filter, anisotropic analytical algorithm, Acuros XB, dosimetric evaluation, cervical cancer

1 | INTRODUCTION

Cervical cancer is the second most common gynecological malignancy and the fourth most common malignancy in women worldwide. In India, cervical cancer is the third most common malignancy in both sexes, and the second most common malignancy in females after breast cancer. Developing and underdeveloped regions are the most affected by this type of cancer. According to the GLOBOCAN2020 report, almost 70% of the global burden falls on developing countries.[1]

External radiotherapy is used to achieve an optimal balance between maximizing the doses for the tumor and minimizing the risk of side effects and long-term complications of organs at risk

(OAR) during cervical cancer treatment.[2] Therefore, external radiotherapy is accepted worldwide as the standard of care for cervical cancer management. Technological advances in radiation therapy, such as intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT), can modulate fluence maps using a multi-leaf collimator (MLC) to deliver highly conformal doses to the target volume with significant sparing of nearby normal tissues.[3]

Flattening filter-free (FFF) irradiation has recently been adopted in standard linear accelerators (LINAC) with large field sizes. It delivers radiation doses with high dose rates and efficiency.[4–6] The most significant advantage of FFF irradiation in IMRT is its high dose rate. Without a flattening filter (FF) in the beam path, FFF irradiation offers the opportunity to lower the out-of-field dose. Because the unflattened photon beam does not pass through the FF, the scattering and leakage radiation are lower than those of the flattened beam. In addition, FFF irradiation reduces delivery times in stereotactic treatments and lowers the secondary cancer risk in peripheral organs, which has been confirmed by many researchers.[7,8]

With these advantages of FFF beams, many researchers have studied the dosimetry of FFF and FF beams for various sites and showed a reduction in the mean dose to normal tissue, sparing normal tissue and OAR without compromising the target coverage.[9] Modern photon dose calculation algorithms are classified based on the complexity of the scattering model for photon and electron transport computations principally in a heterogeneous medium, and the calculation time. In cervical radiotherapy, the precision of the dose computation algorithm may be altered owing to heterogeneities around the target volume.

For photon beams, two dose computation algorithms are available in the Eclipse (Varian Medical System, USA) treatment planning system (TPS): the anisotropic analytical algorithm (AAA) and the Acuros XB (AXB) algorithm. Furthermore, the use of the FFF beam and these two computation algorithms for cervical carcinoma radiotherapy remains unexplored.

Physical quantities such as the dose and the dose-volume (DV) parameters are usually used for IMRT fluence optimization and plan evaluation in clinical settings. Biological parameters have a more direct correlation with treatment outcomes than the DV parameters. The American Association of Physicists in Medicine Task Group Report No. 166 provides detailed guidelines on the use of biological-based optimization and the advantages of biological models over DV evaluation criteria for different planning systems.[10]

Radiobiological analysis of a treatment plan is an essential adjunct to dosimetric evaluation in determining the overall quality of the treatment plan and the complication rate of OAR due to radiotherapy. In particular, when FFF beams are used, further radiobiological investigations are required because of their non-trivial time structure. Previous studies demonstrated that radiobiological analyses supported VMAT as a better choice because of its superior tumor control probability (TCP) and lower normal tissue complication probability (NTCP) in lungs and heart than IMRT and other modalities.[11]

Therefore, evaluation of the radiobiological parameters of a treatment plan using dosimetric parameters is a comprehensive and rational approach. Hence, the present study aims to quantify the potential benefits of the FFF beam and dose computation algorithms (AXB and AAA) on cervical radiotherapy using the RapidArc technique compared with the FF beam.

The present study investigated dosimetric parameters in terms of target coverage, OAR sparing capability, and various physical dosimetric indices, as well as radiobiological parameters for OAR.

2 | MATERIALS AND METHODS

2.1 | Patient selection

A cohort of 33 subjects with clinically proven locally advanced cervical cancer was retrospectively selected for this study, and patient treatment outcomes were not included. Patients diagnosed with carcinomas were graded according to the International Federation of Gynaecology and Obstetrics (FIGO) 2018 classification.

2.2 | Simulation

Simulations were performed using CT-Sim (64 slices, Philips Ingenuity) with the patients in the supine position and immobilized using a 6-clamp pelvic thermoplastic mask (Macro Medics®, Netherlands). The standard bladder protocol was maintained for all patients during the simulation and treatment. A contrast-enhanced computed tomography (CECT) simulation was performed from L2 to the mid-thigh with a slice thickness of 3.0 mm for all planning CT images.

2.3 | Contouring and prescription of target volumes

An experienced oncologist contoured the clinical target volume (CTV) and OAR for each patient. The corresponding planning target volume (PTV) was generated by symmetrically expanding 7.0 mm from CTV.

The OAR included the rectum, bladder, femoral head, and bowel. In addition, to improve the target dose conformity, the assistance organ body-PTV (B-P) was defined as the body volume in the CT dataset excluding the PTV and leaving a 0.3 cm gap. Furthermore, B-P was used in all RapidArc optimizations to standardize the optimized constraints. The prescribed target dose was 50 Gy delivered in 25 fractions.

2.4 | Treatment planning

Two sets of RapidArc with dual-arc plans were performed with jaw tracking using 6-MV FF and FFF beams. All RapidArc plans were generated using the Eclipse treatment planning system (v15.6; Varian Medical Systems, Palo Alto, CA, USA). A photon optimizer (PO; Version 15.6.06, Varian Medical Systems) was selected for inverse optimization based on physical and biological objectives. Hence, the physical constraints of the upper, lower, and mean objectives were used to limit the dose level in a defined portion of the structure volume, to define

the minimum dose level that a particular target volume should receive, and to define the mean dose that should not be exceeded for the structure, respectively. In addition, the biological objective mainly used for OAR was Upper gEUD, where the parameter "a" could vary from +0.1 to +40.

Subsequently, each set of planned doses was calculated using the AAA (Version 15.6.06, Varian Medical System) and the AXB in dose to medium (Version 15.6.06) algorithm, respectively with a 2.5-mm dose grid resolution. Hence, this study generated four plans (AAA, AAA_F, AXB, and AXB_F) for each patient. A Varian TrueBeam accelerator equipped with 120 leaves Millennium multi-leaf collimator (M120, MLC) was used to develop all RapidArc plans with a maximum dose rate of 600 MU/min and 1400 MU/min for the FF and FFF photon beams, respectively. According to the calculation algorithm, all the FFF plans were denoted as AAA_F and AXB_F.

2.5 | Dosimetric evaluation

The cumulative dose-volume histogram (DVH), isodose distribution, and dose-volume statistics were evaluated to assimilate the plan. PTV coverage was evaluated for the volume receiving 95% of the prescribed dose ($V_{95\%}$). The maximum dose, near maximum ($D_{2\%}$), near minimum ($D_{98\%}$), and mean dose to the PTV were also evaluated. The homogeneity index (HI), recommended by ICRU Report No. 83, and the conformity index (CI), proposed by Paddick et al.,[12] for the PTV were evaluated using Eqs. (1) and (2), respectively. Furthermore, the monitor units of all plans were evaluated.

$$\mathbf{HI} = \frac{\mathbf{D_{2\%}} - \mathbf{D_{98\%}}}{\mathbf{D_{50\%}}}, \tag{1}$$

and

$$\mathbf{CI_{Paddick}} = \frac{(\mathbf{TV_{PIV}})^2}{(\mathbf{TV} * \mathbf{PIV})}, \tag{2}$$

where D_2(%), D_{98}(%), and D_{50}(%) are the prescribed isodoses. A smaller HI indicates a more homogeneous target dose. In Eq. (2)TV is the target volume; TV_{PIV} is the target volume enclosed by the prescribed isodose volume, and PIV is the prescribed isodose volume. Hence, the ideal value of the CI is 1.

The OAR dose was compared using the following parameters: for the bladder and rectum, dosimetric parameters were analyzed using volume doses received by 30%, 40%, and 45% of the organ volume (V_{30}, V_{40}, and V_{45}), mean dose (D_{mean}) and near maximum dose (D_{2cc}). Dosimetric parameters V_{30} (%) and D_{2cc} were assessed in the femoral heads. Dose volumes V_{40} and V_{45} (volumes in cc with 40 and 45 Gy, respectively) were used to analyze the bowel.

2.6 | Biological evaluation

The Eclipse Biological Plan Evaluation plug-in was used to compute the NTCP.[13] Biological evaluation was performed on the OAR, bladder, rectum, femoral head, and bowel. The NTCP based on the Poisson model of each OAR with parameters and endpoints listed in Table 1 was assessed. Refer to Supplementary Table for the details of NTCP Models.

2.7 | Statistical analysis

Data were compiled and the means and standard deviations of different parameters were calculated using statistical methods. A two-tailed paired *t*-test was conducted to investigate whether there was a significant difference in the dose computation and biological evaluation. The threshold for statistical significance was set at $p<0.05$, and all analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA).

3 | RESULTS

3.1 | Dosimetric evaluation of PTV

RapidArc plans were generated using the FF and FFF of a 6-MV photon beam for both dose computation algorithms. The mean volume of PTV was 1628.9±208.3 cm^3 (range: 1213.0–2040.5 cm^3). The mean bladder and rectum volumes were 167.90±92.12 cm^3 (range: 50.6–433.3 cm^3) and 53.81±15.27 cm^3 (range: 19.8–99.10 cm^3), respectively.

The average anterior-posterior and right-left separation of the patient body was 21.33±2.3 cm (range: 16.3–23.9 cm) and 34.66±2.37 cm (range: 30.35–39.6 cm), respectively. The average PTV length was 22.08±1.25 cm (range: 20.43–24.76 cm).

A comprehensive analysis was performed for the PTV and OAR to analyze dosimetric and radiobiological variations. The dosimetric parameters for the PTV coverage generated by the RapidArc plan using FF and FFF of 6 MV are summarized in Table 2. The FFF beam delivered a slightly higher mean dose and maximum dose (D_{max} and $D_{2\%}$) to the PTV than the FF beam for both algorithms. The differences in the $V_{95\%}$ and $D_{98\%}$ indices for the PTV were smaller; however, the difference was greater for the AXB algorithm. Furthermore, a significant difference was observed in the $V_{95\%}$ ($p<0.001$).

A comparison of the isodose distribution between the RapidArc plans using FF and FFF with a 6-MV beam for the AAA and AXB algorithms for the same patient along the axial, coronal, and sagittal planes is shown in Figures 1 **and** 2. DVH from RapidArc plans using FF and FFF with a 6 MV beam for the AAA and AXB algorithms is shown in Figures 3 **and** 4.

A significant increase in MUs was observed in all FFF beam plans, with differences of 13.9% (AAA vs. AAA_F, $p<0.001$) and 17.06% (AXB vs. AXB_F, $p<0.001$). There was no difference in homogeneity between the FF and FFF plans, despite the algorithms, but the results were statistically significant, $p = 0.004$ (AAA vs. AAA_F) and $p<0.001$ (AXB vs. AXB_F). The conformity index of the FFF plans was better than that of the FF with a difference of 3.06% and 1.02%, but they were not statistically significant ($p = 0.107$; AAA vs. AAA_F) and $p = 0.399$(AXB vs. AXB_F), respectively.

TABLE 1 NTCP based on Poisson model of each OAR with parameters and endpoints.

Organ	Model	End Point Toxicity
Bladder	NTCP Poisson-LQ	Contracture
	NTCP LKB	Late effects, grade ≥3
Rectum	NTCP Poisson-LQ	Necrosis/Stenosis
	NTCP LKB model	Late rectal bleeding, grade ≥2
		Late effects, grade≥3
Femoral heads	NTCP Poisson-LQ	Necrosis
Bowel	NTCP Poisson-LQ	Obstruction/Perforation

Abbreviations: OAR: organ at Risk; NTCP: normal tissue complication probability; LKB - Lyman–Kutcher–Burman; LQ: linear quadratic

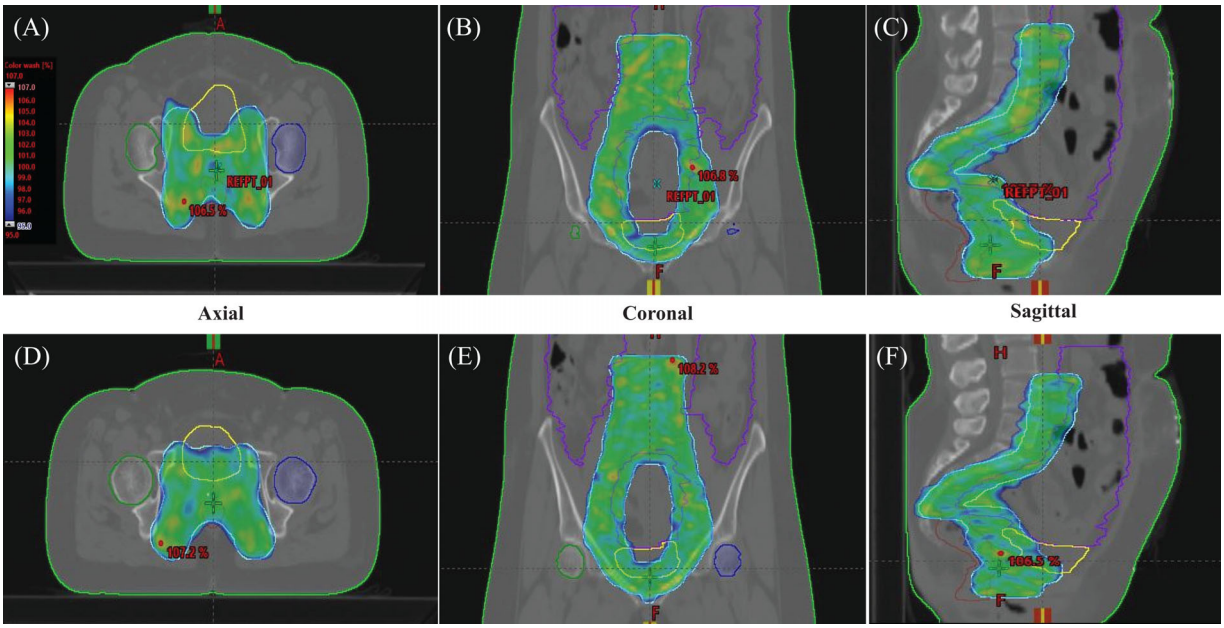

FIGURE 1 Comparison of 95% prescription dose colourwash of a RapidArc plan for FF (upper row) and FFF(lower row) 6 MV beam with AAA in axial, coronal and sagittal views.

3.2 | Dosimetric evaluation of OAR

For the bladder, there was an increase in the mean dose (D_{mean}) and dose volumes V_{30}, V_{45} and D_{2cc} with the FFF beam and AAA compared to the FF beam, but this was not statistically significant, except for D_{2cc}(p = 0.029). A slight (0.21%) decrease in V_{40} was observed; however, it was not significant (p = 0.498). In contrast, with the FFF beam and AXB, the mean dose (D_{mean}) and dose volumes ($V_{30,}$ V_{40} and $_{V45)}$ decreased compared to the FF beam, but the difference was not statistically significant, except for D_{2cc}, which increased by 0.66% (p<0.001).

For the rectum, there was an increase in the mean dose (D_{mean}) and in dose volumes, V_{40}, V_{45} and D_{2cc} with the FFF beam and AAA compared to the FF beam, but this was not statistically significant except for D_{mean}(p = 0.004). However, a significant decrease of 0.6% was observed in V_{30}(p = 0.004). In contrast, with the FFF beam and AXB, the mean dose (D_{mean}), dose volumes (V_{30} and V_{45}), and D_{2cc} were increased compared with the FF beam, but were not statistically significant, except for D_{2cc}(p = 0.020). However, the slight decrease in the dose volume observed in V_{45} was not statistically significant(p = 0.084). No significant difference was observed in the dose to the bowel, but in all planes, there was a slight increase in the dose volume with FFF beam plans, except for AXB_F for V_{45}.

A significant reduction was observed in both femoral heads in V_{30} using the FFF beam for the right by 7.83% (p = 0.019) and 4.75% (p = 0.020) and for the left by 1.53% (p<0.001) and 2.49% (p = 0.025) with AAA and AXB, respectively. Although D_{2cc} was also reduced, the difference was not statistically significant.

3.3 | Biological evaluation of OAR

Radiobiological evaluation of the OAR parameters was performed for all plans using Eclipse biological evaluation; the results are

TABLE 2 Comparison of PTV Parameters, Monitor Units, and OARs between 6MV_FF and 6MV_FFF RapidArc Plan.

Parameter		AAA Mean ±SD	AAA_F	Difference in %	*p*–value AAA vs. AAA_F	AXB Mean ±SD	AXB_F	Difference in %	*p*–value AXB vs. AXB_F
PTV	D_{min} (Gy)	45.04±2.06	45.04±1.76	0.00	0.320	45.64±2.01	45.95±2.16	-1.66	**0.009**
	D_{max} (Gy)	54.44±0.68	54.69±0.43	-0.46	0.112	55.45±0.49	55.50±0.43	-0.09	0.338
	D_{mean} (Gy)	50.79±0.39	50.88±0.15	-0.18	0.176	50.90±0.14	50.92±0.16	-0.04	**0.016**
	V_{95} (%)	97.56±0.96	97.27±1.05	0.30	<**0.001**	97.79±0.79	97.57±1.05	0.22	<**0.001**
	$D_{98\%}$ (Gy)	47.70±0.40	47.65±0.38	0.10	0.389	47.83±0.36	47.62±0.38	0.44	0.251
	$D_{2\%}$ (Gy)	52.58±0.49	52.96±0.88	-0.72	**0.030**	52.86±0.21	53.02±0.31	-0.30	<**0.001**
	MU	511.68±47.04	582.79±60.69	-13.90	<**0.001**	522.64±52.27	611.80±71.36	-17.06	<**0.001**
	HI	0.11±0.01	0.11±0.02	0.00	**0.004**	0.11±0.02	0.11±0.01	0.00	<**0.001**
	CI	0.98±0.01	1.01±0.13	-3.06	0.107	0.98±0.01	0.99±0.09	-1.02	0.399
Blac	V_{30} (%)	81.22±6.98	81.40±6.44	-0.22	0.198	81.16±6.73	81.03±4.66	0.16	0.369
	V_{40} (%)	57.15±5.28	57.03±5.22	0.21	0.498	56.82±5.29	56.76±5.27	0.11	0.712
	V_{45} (%)	39.79±5.91	39.81±6.06	-0.05	0.981	39.68±6.03	39.42±5.83	0.66	0.166
	D_{mean}(Gy)	42.89±2.62	42.92±2.48	-0.21	0.451	42.99±2.69	42.93±2.51	0.14	0.877
	D_{2cc}	49.88±0.61	50.09±0.31	-0.42	**0.029**	49.94±0.29	50.27±0.37	-0.66	<**0.001**
Rectum	V_{30} (%)	81.74±6.83	81.25±5.96	0.60	**0.035**	84.64±4.36	84.74±4.13	-0.12	0.251
	V_{40} (%)	58.03±5.47	60.06±4.92	-3.50	0.569	58.56±6.26	58.92±6.02	-0.61	0.250
	V_{45} (%)	39.80±4.80	40.70±5.62	-2.26	0.159	40.36±5.60	40.30±5.60	0.15	0.084
	D_{mean}(Gy)	43.36±3.05	43.44±2.90	-0.18	**0.004**	43.25±2.94	43.33±2.86	-0.18	**0.010**
	D_{2cc} (Gy)	49.44±0.58	49.67±0.45	-0.47	0.251	49.54±0.41	49.69±0.51	-0.30	**0.020**
Bow	V_{40} (cc)	337.58±94.85	346.77±40.16	-2.72	0.182	370.01±93.74	379.10±102.49	-2.46	0.446
	V_{45} (cc)	246.99±88.91	249.13±86.56	-0.87	0.473	249.74±87.64	248.86±87.61	0.35	0.850
RTFH	V_{30} (%)	14.69±4.16	13.54±4.54	7.83	**0.019**	13.06±4.95	12.44±4.72	4.75	**0.020**
	D_{2cc} (Gy)	42.29±2.66	41.76±3.50	1.25	0.265	41.41±3.76	41.15±3.88	0.63	0.358
LTFI	V_{30} (%)	11.77±4.26	11.59±4.17	1.53	<**0.001**	10.43±3.77	10.17±4.42	2.49	**0.025**
	D_{2cc} (Gy)	41.08±3.77	40.92±3.70	0.39	0.465	40.44±4.03	40.40±4.06	0.10	0.910

Abbreviations: PTV: planning target volume; D_{max}: maximum dose; D_{min}: minimum dose; D_{mean}: mean dose; MU: monitor units; HI: homogeneity index; CI: conformity index; SD: standard deviation; FF: flattening filter; FFF: flattening filter-free; AAA: analytical anisotropic algorithm; AXB: acuros XB; Vx is the volume receiving x% of the prescribed dose; Dx% is dose received by x% of volume; RTFH: right femoral head; LTFH: left femoral head; AAA_F: planned using FFF beam; AXB_F: planned using FFF beam.

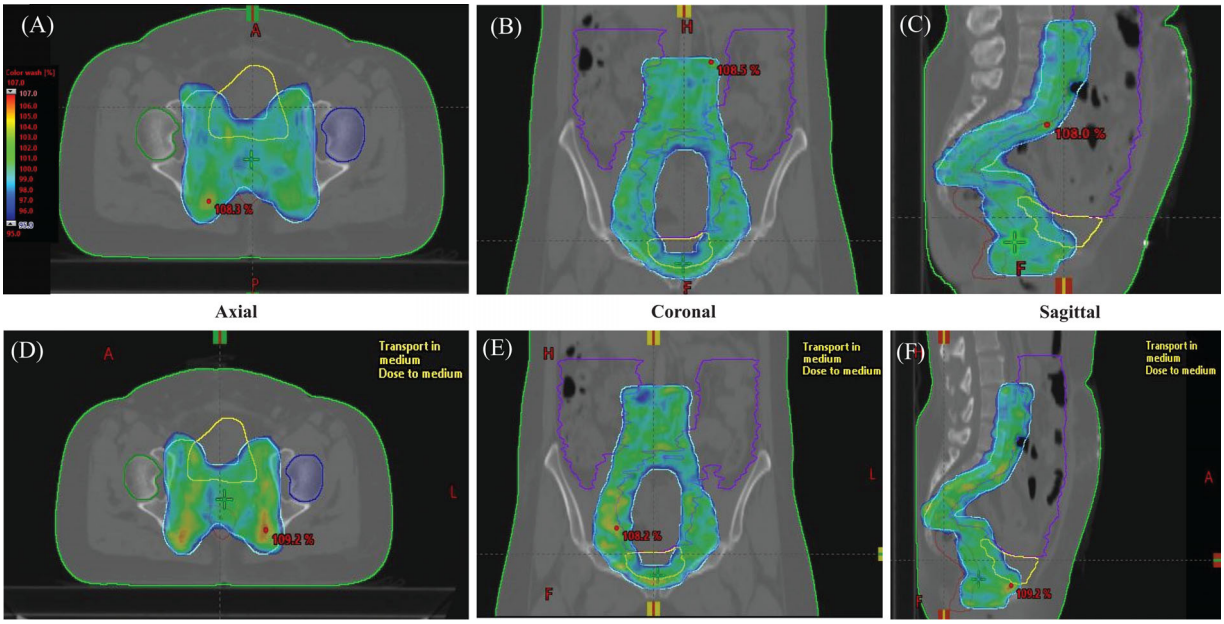

FIGURE 2 Comparison of 95% prescription dose colourwash of a RapidArc plan using FF (upper row) and FFF(lower row) 6 MV beam with AXB in axial, coronal and sagittal views.

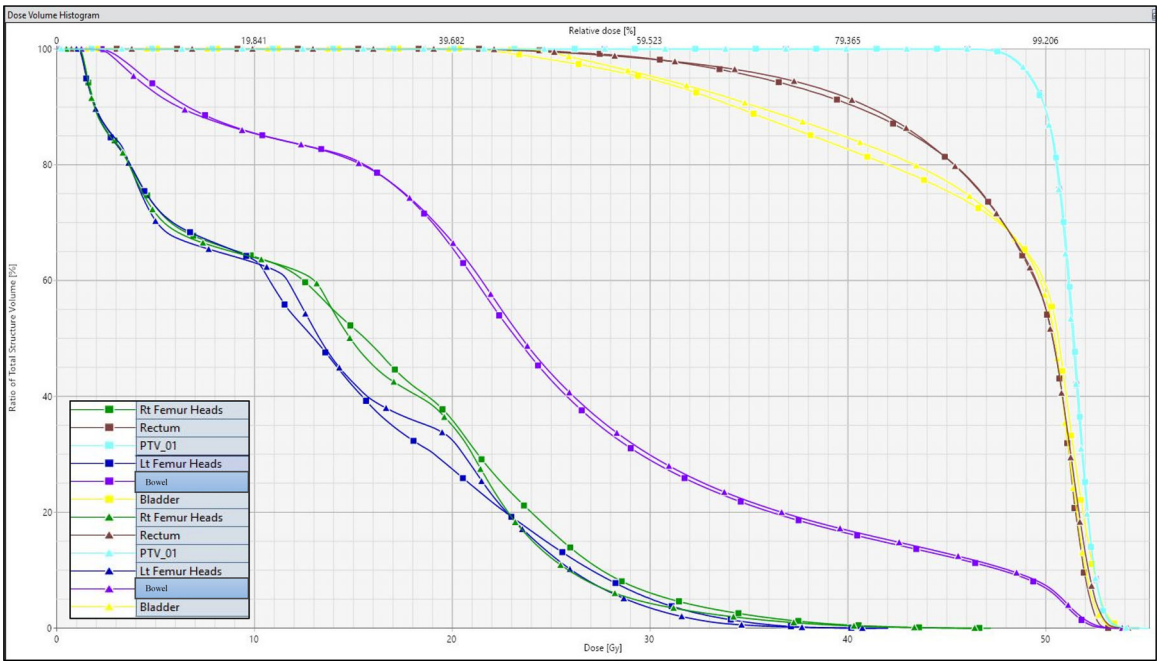

FIGURE 3 DVH comparison for target (PTV) and OARs(Bladder, Rectum, Bowel, Femur Heads) for a RapidArc plan using FF(square) and FFF(triangle) 6 MV beam with AAA.

summarized in Table 3. The NTCP score showed that the late effects grade≥3 increased for bladder in FFF beam plans and were statistically significant with $p = 0.033$ and $p = 0.009$ for AAA and AXB, respectively.

A similar mean NTCP without a significant value was observed for the rectum for necrosis/stenosis in all the plans. The NTCP score for late rectal bleeding grade≥2 was significantly higher with the FFF beam plans with $p = 0.043$ and $p = 0.022$ for AAA and AXB, respectively. The NTCP score for late effects grade≥3 was increased for FFF with AAA plans, but they were not statistically significant ($p = 0.844$); however, for FFF with AXB, the values were significant ($p<0.001$).

Although the NTCP score for the bowel showed an increase for FFF with AAA plans, it was insignificant ($p = 0.760$). However, a significant increase in the NTCP score was observed for FFF with AXB plans for

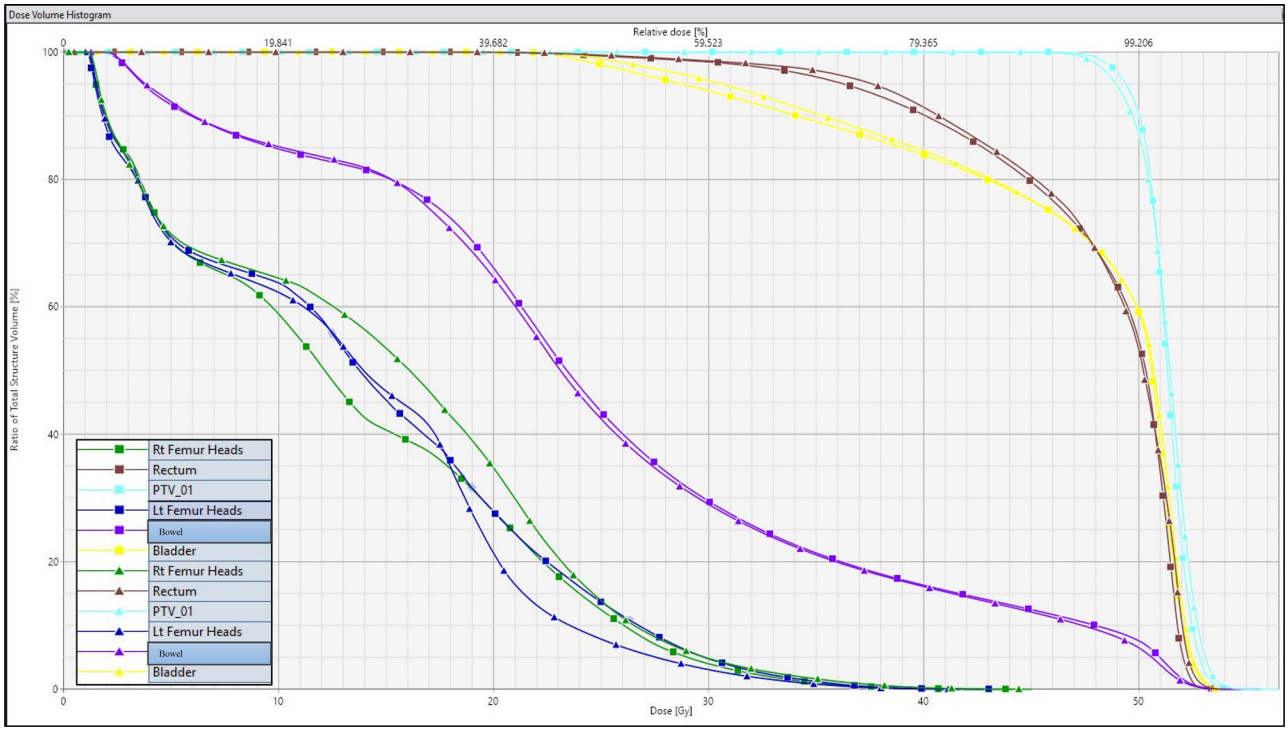

FIGURE 4 DVH comparison for target (PTV) and OARs(Bladder, Rectum, Bowel, and Femur Heads) for a RapidArc plan using FF(square) and FFF(triangle) 6 MV beam with AXB.

bowel ($p = 0.008$). No NTCP score was found for the femoral heads using the current model and proposed endpoint.

4 | DISCUSSION

Arc therapy plans are crucial in the definitive and adjuvant treatment of cervical carcinoma and have demonstrated successful limitation of radiation-induced complications compared with three-dimensional conformal radiotherapy (3DCRT). A recent study by Takakusagi et al. on moderately hypofractionated VMAT with FFF beams for localized prostate cancer found no significant differences in DVH parameters for the target volume and in all parameters for the bladder and rectum.[16] Furthermore, IMRT with a FFF beam can achieve dosimetrically and clinically acceptable plans, as reported by Tamilarasu et al.[14] In a similar study, Kumar et al. performed a feasibility study on RapidArc plans using FFF beam, which yielded similar target coverage and a significant increase in the target mean dose for cervical cancer.[15]

Zhang et al. dosimetrically evaluated patients with cervical cancer after hysterectomy and found similar targets and OAR sparing using VMAT with FFF beams.[17] In the current study, no significant differences were found in D_{max}, $D_{98\%}$, and CI between the FF and FFF beams with AAA and AXB plans; D_{min} and D_{mean} exhibited statistically significant differences. In a similar study, Bell et al. found that the combination of a high dose rate and mARC resulted in a decrease in treatment time and out-of-field dose for prostate cancer.[18]

Furthermore, we applied jaw tracking for all plans. Mani et al. also studied the impact of jaw tracking with RapidArc plans, which reduced the low-dose volume and the maximum and mean dose.[19] The jaw tracking effect in Rapid Arc plans keeps only the jaws as close as possible to the MLC aperture during dose delivery and leaf transmission, and leakage.

PTV coverage hence V_{95}(%), was significantly higher with the FF beam plans, but the difference was very small, 0.3% and 0.22% for AAA (p=<0.001) and AXB(p=<0.001). The variation of V_{95}(%) with PTV volume is shown in Figure 5. Ding et al. studied the dosimetric characteristics of FFF beams in VMAT plans for rectal cancer and showed that the plans could achieve the clinical constraints.[20] There was an improvement in the near-min dose of the PTV; hence, $D_{2\%}$ was observed with FFF beams was 0.72% and 0.3% for AAA (p=0.03)and AXB (P=<0.0001), and they were statistically significant.

Raju et al. reported that the dose difference was small in the prostate; the dose computed by AAA had a higher maximum dose to the PTV than AXB by 1.01%, which agrees with our current study results that were obtained using the AXB algorithm for both FF and FFF beams.[20] In a similar study, Rana et al. used RapidArc plans to perform a planning study of prostate cancer patients in which the clinical dosimetric effects of AAA and AXB were compared, and results were in the range of −0.21–0.67% for the PTV-$D_{95\%}$.[22]

The FFF beam achieved the same homogeneity (HI) as the FF beam for both algorithms, and there was no difference in the average values of the FF and FFF plans; however, the value was statistically significant in both scenarios. For the FFF beam plans, there was a statistically significant improvement in the conformity index observed for both algorithms, with differences of 3.06% and 1.02% for AAA and AXB, respectively. Lalit et al. showed that 6 MV with an FFF beam produced

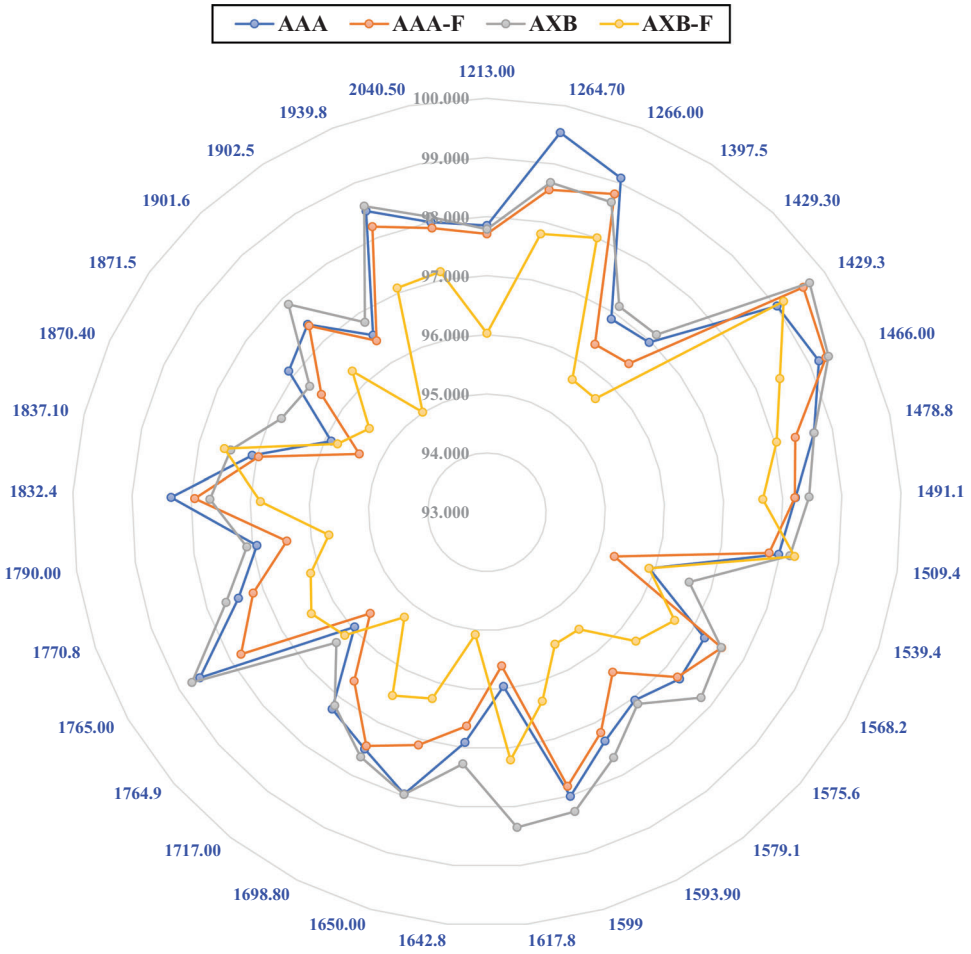

FIGURE 5 Variation of dose-volume parameter (V95%) with PTV volume for FF and FFF beam with AAA and AXB dose computation algorithm.

more conformal and homogeneous dose distributions in gynecological malignancies.[23]

For the bladder, there was an increase in the dose to V_{30}, V_{45}, D_{mean} and D_{2cc}, except for V_{40}, which was very small <0.5% and not statistically significant for the AAA. However, a significant increase was observed in D_{2cc} for both algorithms with FFF. In contrast, a reduction in the dose parameters (V_{30}, V_{40}, V_{45}, D_{mean}, and D_{2cc}) was observed with AXB_F; however, the difference was not statistically significant. A similar trend was observed in the rectum; there was an increase in the dose-volume parameters V_{30}, V_{40}, V_{45}, D_{mean}, and D_{2cc}.

Trutwein et al. reported that these differences were minor, (less than 1% of the OAR volume in most cases) especially compared with the large standard deviation.[24] Therefore, their toxicity levels were similar. Chakir et al. found no significant difference in the FF and FFF plans for OAR with 6 and 10 MV photon beams.[25] Vassiliev et al. analyzed the beam characteristics of an accelerator with and without an FF and showed that as the FFF beam field dose decreased, the total scattering factor decreased with a change in the field, and the change decreased in the lateral dose curve with depth.[26] These characteristics are conducive to protecting normal tissues.

In the current study, the FFF beam required 13.9% and 17.06% more MUs than the FF beam to achieve dose uniformity within the target, which implies that MUs are required for a point in a segment far away from the central axis to achieve the same depth dose as the point in the center. However, this higher MU offset was compensated by a higher dose rate by a factor of 2.3, as reported by Xiao et al.[5] Hence, the FFF requires more modulation to reduce the higher beam intensity near the central axis, owing to the forward heterogeneous peak profile of the FFF beam. Furthermore, RapidArc plans with FFF reduce the treatment time and potentially improve tumor control. In addition, the dose rate increases with an FFF beam, thereby reducing the probability of patient motion and increasing comfort.[27]

Sayah et al. reported that switching from AAA to AXB had the most significant effect on high-density structures.[28] In the current study, dose reduction (V_{30} and D_{2cc}) was observed in the femoral heads with an FFF beam; however, only V_{30} was significant for both computation algorithms. Radiotherapy plans are generally designed and evaluated based on physical objectives; however, plan evaluations based on biological indicators are more relevant to clinical efficacy.[29] DVH data, reliable biological parameters, and various radiobiological models such as the Poisson and LKB models have been developed to calculate the probability of normal tissue complications to estimate the clinical efficacy of radiotherapy plans. However, the application of these models is hindered by inadequate fitting biological parameters.

TABLE 3 Comparison of NTCP score for OAR between 6MV_FF and 6MV_FFF RapidArc plan.

OAR	Model	Endpoint/Stage	NTCP Score		*p*–value	NTCP Score		*p*–value
			AAA	AAA_FFF	AAA vs AAA_F	AXB	AXB_FFF	AXB vs AXB_F
			Mean ±SD			Mean ±SD		
Bladder	NTCP LKB	Late effects, grade ≥3	2.22 ± 0.78	2.23 ±0.75	**0.033**	2.21±0.80	2.42±0.87	**0.009**
Rectum	NTCP Poisson-LQ	Necrosis/Stenosis	0.03 ±0.01	0.03±0.01	0.430	0.03±0.01	0.03±0.01	0.129
	NTCP LKB	Late rectal bleeding, grade≥ 2	2.57 ± 0.70	2.58 ±0.68	**0.043**	2.57±0.68	2.59±0.69	**0.022**
		Late effects, grade≥ 3	0.43 ±0.10	0.45 ±0.10	0.844	0.45±0.10	0.46±0.10	**<0.001**
Bowel	NTCP Poisson-LQ	Obstruction/ Perforation	1.24 ± 1.07	1.25 ±1.05	0.760	1.35±1.08	1.36±1.10	**0.008**

Abbreviations: OAR: organ at risk; NTCP: normal tissue complication probability; LKB: Lyman–Kutcher–Burman; LQ: linear quadratic; SD: standard deviation; FF: flattening filter; FFF: flattening filter-free; AAA: analytical anisotropic algorithm; AXB: acuros XB; AAA_F: planned using FFF beam; AXB_F: planned using FFF beam.

Yan et al. studied the biological differences between FF and FFF beams for the prostate and found that FFF beams resulted in lower or comparable NTCP values for the OAR.[30] In the current study, with the FFF beam, the NTCP score for OAR increased for the bladder. Furthermore, a significant increase was observed in the rectum and bowel when the AXB algorithm was used.

Dini et al. irradiated lung fibroblasts of a Chinese hamster and two patient-derived glioblastomas stem-like cell lines and they discovered the use of FFF beams at a high dose rate.[11] Nakano et al. studied radiobiological effects on non-small-cell lung cancer. They showed that photon beams with a high dose rate used for radiation therapy were suitable for cell survival, motility, and physical characteristics.[31]

The major limitation of the current study is its dependence on dosimetric and radiobiological data rather than clinical evidence. Further studies are required to determine the clinical outcomes of dose-volume parameters in these situations.

However, the current study thoroughly investigated the impact of the FFF beam and its potential dosimetric and radiobiological advantages in AAA and AXB computation algorithms for cervical cancer using the RapidArc technique. The accurate prediction of the NTCP in this study was dependent on the accuracy of the model and related parameters, which needs to be verified in future studies.

5 | CONCLUSION

The FFF beams yielded equivalent results in the target volume coverage with a homogeneous dose distribution and better conformity than the FF beam for both dose computation algorithms (AAA and AXB). In addition, the difference in mean dose-volume parameters for OAR was minimal, although a significant decrease was observed in the femoral heads. Furthermore, radiobiological analysis showed a significant increase in the NTCP score, even though the mean difference was minimal. In conclusion, a 6-MV flattening filter-free X-ray beam generates dosimetrically and clinically acceptable plans using the RapidArc technique.

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CONFLICT OF INTERESTS DECLARATION

The authors declare that they have read the article and have no competing interests.

ETHICS STATEMENT

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SUPPORTING INFORMATION

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