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ORIGINAL ARTICLE

Physical and Radiobiological Dosimetric Comparison of Volumetric Arc Treatment Plans with or without Flattening Filter in Synchronous Bilateral Breast Cancer

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OBJECTIVE

This study aimed to evaluate the dosimetric and radiobiological differences between 6MV flattened filter (FF) and flattening filter-free (FFF) using the volumetric modulated arc (VMAT) technique for synchronous bilateral breast cancer (SBBC).

METHODS

Three SBBC patients underwent radiotherapy with 6X_FF beams using VMAT treatment plans, delivering a dose of 50 Gy in 25 fractions. Retrospectively, plans with five partial arc 6X_FFF beams using VMAT treatment plans were generated, maintaining identical parameters. The evaluation included a comparison of dosimetric planning indices, target coverage, and OAR (organ at risk) sparing, as well as NTCP (normal tissue complication probability) radiobiological parameters of OARs.

RESULTS

There was no significant difference observed in the Conformity Index (CI), Homogeneity Index (HI), and V95% in planning target volume (PTV) in both treatment plans. The mean NTCP values of the Poisson-LQ model for pulmonary pneumonitis and cardiac mortality were 2.47% and 0.19%, respectively, in 6X_FF treatment plans. In comparison, the corresponding NTCP values for pulmonary pneumonitis and cardiac mortality in the 6X_FFF plans were 2.16% and 0.18%, respectively. Statistical analysis using the NTCP model (Poisson-LQ and Lyman-Kutcher-Berman) revealed similar outcomes between 6X_FF and 6X_FFF VMAT plans across the assessed endpoints for the heart and lungs.

CONCLUSION

6X_FFF photon beams offer a treatment plan for SBBC patients that maintains similar target coverage while improving the preservation of organs and minimizing the biological effects, as compared to 6X_FF VMAT plans.

Keywords: Flattened filter-free; normal tissue complication probability; synchronous bilateral breast cancer; volumetric modulated arc therapy.

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INTRODUCTION

According to the Global Cancer Observatory (GLOBOCAN) 2022, breast cancer is the prevailing form of cancer among women globally.[1] Despite advances in the modalities of management, it remains the leading cause of cancer-related death in women.[2]

Synchronous bilateral breast cancer (SBBC) is defined as two malignant tumors identified within 6 months, one in each breast.[3–5] This unusual disease affects 1–3.5% of all breast cancer (BC) patients.[6] However, it has not yet been proven that SBBC has a worse prognosis than unilateral breast cancer. Some studies found that synchronous bilaterality was not an independent predictive risk factor in multivariate analysis compared with unilateral breast cancer.[5,7] SBBC occurs more frequently in younger patients and presents unique challenges, especially in radiation treatment planning. The treatment planning and dose delivery of SBBC are significantly more difficult and time-consuming than unilateral breast cancer radiation treatment planning due to the large radiation field, the complex anatomy, and the difficulty in achieving organ sparing, especially for the heart and lungs.[7]

Three-dimensional conformal radiotherapy (3DCRT) tangent field configuration is a common treatment approach for SBBC.[8,9] However, this may be associated with lesser organ sparing and lead to field overlaps.[10] To overcome these difficulties and preserve normal tissues, especially in complicated situations such as SBBC, advanced treatment planning including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) have been developed.[11–14]

Improvements in technology have significantly enhanced the efficiency of radiation therapy planning and delivery. RapidArc is a method that uses volumetric modulated arc treatment (VMAT) to generate modulated radiation beams by adjusting three parameters at once: the multileaf collimator (MLC) field aperture, dose rate, and gantry rotation speed. The main goal of VMAT treatment is to provide highly conformal radiation distributions while optimizing treatment and minimizing dose to the organs at risk (OARs), thereby improving treatment outcomes.[15] Studies by Popescu et al.,[16] Zhang et al.,[17] and Zhao et al.[18] have shown that VMAT treatment techniques are suitable for unilateral breast cancer and reduce the dose to the ipsilateral lung, heart, and contralateral breast/lung compared to IMRT.

Advances in radiation technology have also been made with the Varian TrueBeam linear accelerator. This cutting-edge technology offers both flattened and flattening filter-free (FFF) beams, with the FFF beams providing advantages such as lower scatter, higher dose rates, and improved beam-on time (BOT) for better treatment outcomes.[19,20] However, the lack of research on the effectiveness of FFF radiation in SBBC treatment highlights the need for further research in this area. The purpose of this study is to evaluate the dosimetric parameters, including radiobiological assessment (NTCP for lungs and heart), in treatment plans with 6X_FF and 6X_FFF beams.

MATERIALS AND METHODS

Patient Selection

A retrospective analysis was conducted on three patients treated for SBBC from November 2021 to January 2023 in the Department of Radiation Oncology, State Cancer Institute, IGIMS, Patna, Bihar. Each patient underwent a modified radical mastectomy, chemotherapy, and adjuvant external radiotherapy.

The characteristics of the three SBBC patients are presented in Table 1.

CT Simulation and Contouring

The patients were positioned in a supine position with their arms raised above their heads using a breast board and a thermoplastic mask to immobilize them. CT scans were taken with a slice thickness of 2.5 mm using a Revolution EVO scanner from GE Healthcare while the patients were free-breathing.

The CT images in DICOM format were imported into the Eclipse treatment planning system (version 16.1, Varian Medical Systems, USA) for detailed analysis and contouring. Contouring of all targets and OAR structures was performed by a single radiation oncologist according to ESTRO[21] and RTOG (Radiation Therapy Oncology Group contouring atlas group) recommendations.[22] Planning target volume (PTV) margins given to the chest wall clinical target volume (CTV) were 10 mm in anterior, lateral, and supero-inferior directions, with only 5 mm in posterior and medial directions. The CTV supraclavicular fossa (SCF) was given a 5 mm margin symmetrically. The organs at risk (OARs) contoured included the left and right lungs, heart, left anterior descending (LAD) artery, esophagus, thyroid, and spinal cord.

Treatment Planning

All treatment plans were created on Eclipse TPS (Varian Medical Systems, Palo Alto, CA, USA), version 16.1,

Table 1 Patients characteristics of the three SBBC cases

	Case-1	Case-2	Case-3
Age (years)/sex	45/Female	58/Female	43/Female
Pathological stage (TNM)			
Right breast	cT4b N1 M0	pT3 N2a M0	ypT2 N0 M0
Left breast	cT2 N0 M0	cT4b N3 M0	ypT2 N0 M0
ER/PR status	Negative/Negative	Negative/Negative	Positive/Negative
HER-2/neu status	Positive	Positive	Negative

SBBC: Synchronous bilateral breast cancer; TNM: Tumour, node and metastasis; ER: Estrogen receptor; PR: Progesterone receptor; HER-2/neu: Human epidermal growth factor receptor-2

using the Anisotropic Analytical Algorithm (AAA) for dose calculation. To ensure consistency in dose, dose limits, and inverse optimization parameters of the TrueBeam linear accelerator with the Millennium 120 multileaf collimator (MLC), the Photon Optimization (PO) algorithm was employed to optimize the 6X_FF and 6X_FFF plans. The prescribed dose for all patients was 50 Gy in 25 fractions, with each fraction delivering 2 Gy over a period of five weeks.

Retrospectively, VMAT plans were designed for all selected patients with 6X_FF and 6X_FFF beams at a dose rate of 600 MU/min and 1400 MU/min. A total of six treatment plans were used for three patients in this study. For plan creation, each plan was created using two isocenters with a total of ten coplanar partial arcs evenly divided, with five arcs at each isocenter, as shown in Figure 1.

For the right-sided target volume, five partial arcs of 50°–319°, 279°–195°, 195°–279°, 29°–195°, and 319°–55° with collimator angles of 345°, 17°, 10°, 350°, and 5° were used. For the left-sided target volume, 310°–41°, 81°–160°, 331°–160°, 160°–81°, and 41°–310° with collimator angles of 17°, 343°, 80°, 357°, and 3° were used to design both types of competing treatment plans, respectively.

To ensure fairness, the VMAT treatment plan using 6X_FFF was created with the same planning and optimization parameters as the VMAT plan using a 6X_FF photon beam. The dose was adjusted to ensure that 95% of the PTV received the prescribed amount while keeping the PTV below 107% of the prescribed dose.

During the optimization of the treatment plan, these constraints were applied to the OARs: heart mean dose ≤6 Gy, V30 ≤12%, V5 ≤20%; mean dose of both lungs ≤15 Gy, V5Gy ≤65%, V10Gy ≤40%, V20Gy ≤30%, V30Gy ≤15%; mean LAD ≤25 Gy, esophagus mean dose <20 Gy, and the maximum spinal cord dose ≤45 Gy.

Treatment Plan Evaluation

Cumulative dose-volume histograms (DVHs) were used to evaluate the dosimetric parameters for each

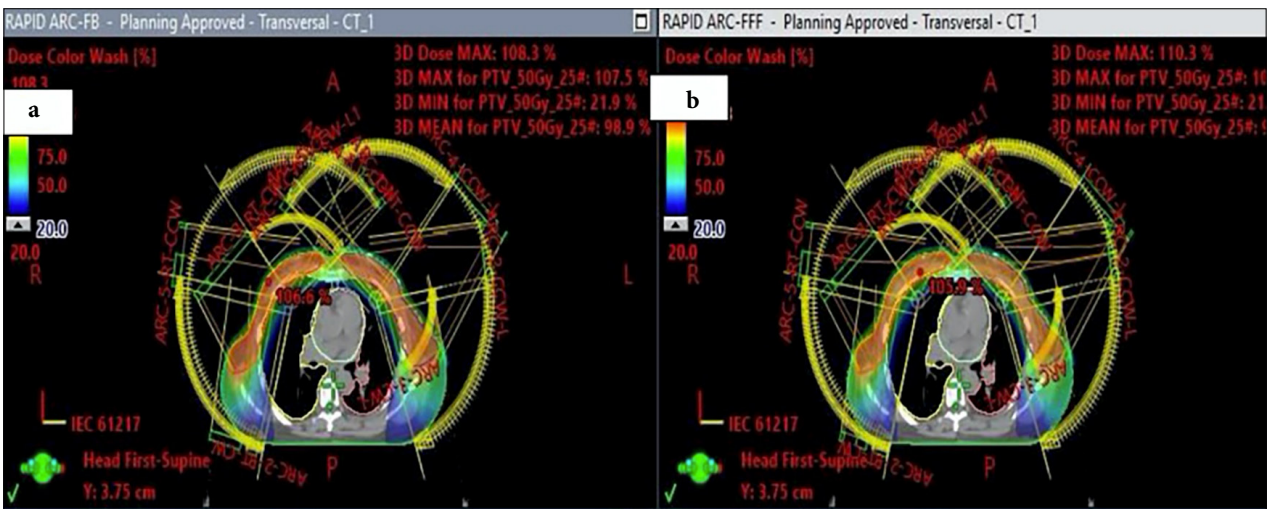

Fig. 1. The isodose distribution of (a) 6X_FF VMAT and (6) 6X_FFF VMAT plans of SBBC.
VMAT: Volumetric modulated arc; SBBC: Synchronous bilateral breast cancer.

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plan. Key metrics were examined for PTV, including mean dose (D_{mean}), V105%, V107%, D98%, and V95% (percentage of volume receiving at least 95% of the required dose). Target coverage was reported as V95% of PTV. HI was calculated using the following equation:

HI=(D2% – D98%)/D50%

Where D2%, D98%, and D50% denote the doses corresponding to 2%, 98%, and 50% of the PTV volume, respectively.[23]

CI was calculated based on the reference dose of the prescription dose to PTV using the following equation:

CI=Vref/TV

Where Vref denotes the total volume of all areas surrounded by the reference isodose (reference isodose = 95%) on the body, and TV denotes the physical volume of the PTV. A CI of 1 corresponds to an ideal conformation. A CI greater than 1 indicates that the irradiated volume is larger than the target volume and includes healthy tissue. If the CI is less than 1, the target volume is only partially irradiated.[24]

Radiobiological Assessment

In the Eclipse treatment planning system, two models—Poisson LQ and Lyman-Kutcher-Berman—are used for radiobiological assessment of NTCP values for lungs and heart. The NTCP from DVH data of the Lyman-Kutcher-Berman model was used to calculate the NTCP for radiation-induced pneumonitis, grade ≥ 2, in the lungs (D50=30.80 Gy, α/β=3, n=0.99, and m=0.37[25]); symptomatic pneumonitis ≤ 6 months in lungs (D50=21 Gy, α/β=3, n=1.02, and m=0.26), and symptomatic fibrosis > 6 months in the lungs (D50=25 Gy, α/β=3, n=0.15, and m=0.85[26]). The Poisson-LQ model was used to calculate the NTCP for radiation-induced mortality in the heart (D50=52.4 Gy, seriality (s)=1.0, α/β=3, and γ=1.3[27]) and NTCP for radiation-induced pneumonitis (D50=34.00 Gy, s=0.06, α/β=3, and γ=0.9[25]).

For OARs, the lungs, heart, LAD, esophagus, thyroid, and spinal cord were subjected to mean and maximum dose analysis, along with a set of appropriate Vx (Gy) values. Furthermore, the treatment parameters, including the monitor units (MU) and beam-on time (BOT), for each treatment plan were documented for evaluation purposes. BOT, defined as the radiation delivery time, excluded patient positioning and imaging procedures.

Statistical Analysis

The collected data were entered into Microsoft Excel and analyzed using SPSS 26.0 software. Continuous variables were expressed as mean and standard deviation (SD). A non-parametric test, Mann-Whitney U test, was computed to compare two groups (6MV_FF RapidArc and 6MV_FFF RapidArc). A p-value less than 0.05 was considered statistically significant.

RESULTS

To compare the 6X_FF and 6X_FFF VMAT treatment plans, the dosimetric characteristics and OAR dose were evaluated, along with the radiobiological evaluation of the NTCP value of the OARs analysis using the DVH. All patients' means and standard deviations for each assessment parameter were provided.

Figures 1a and 1b show the color wash isodose line distributions from the maximum PTV dose to the 20% line for the 6X_FF VMAT plan and the 6X_FFF VMAT plan, respectively. Dose-volume histograms (DVH) for target volumes and OARs in both plans are shown in Figure 2.

Dosimetric Parameters Related to PTV

Table 2 shows the comprehensive assessment of the dosimetric properties of PTV along with the corresponding p-values. When both techniques were compared, no significant difference was found in the maximum dose, mean dose, D98%, and V107% within the two PTVs (p>0.05).

The left and right PTV mean of the volume receiving 105% of the prescribed dose (V105%) in the 6X_FF VMAT plan was 10.1 cc, 3.31% higher than the 3.05%, 1.50% in the 6X_FFF VMAT plan. Additionally, there was a statistically insignificant variation in the homogeneity index (HI) values for both PTVs (p>0.05).

Moreover, the conformity index showed a statistically significant increase in the 6X_FF VMAT (0.984 ± 0.008) when compared to the 6X_FFF VMAT (0.955 ± 0.036) in the right-sided PTV (p=0.050).

Total MUs and BOT were collected and analyzed. The VMAT plans utilizing 6X_FFF had a higher requirement for MUs and demonstrated a statistically significant decrease in BOT compared to the 6X_FF VMAT plan, with a p-value of 0.050.

Dosimetric Parameters Related to OARs

Table 3 provides a statistical analysis comparing dosimetric parameters for OARs between the two treatment plans.

Left Lung Dose Analysis

When comparing the mean lung dose (D_{mean}), V5Gy, V10Gy, V20Gy, and V30Gy (14.70 Gy, 68%, 40.99%,

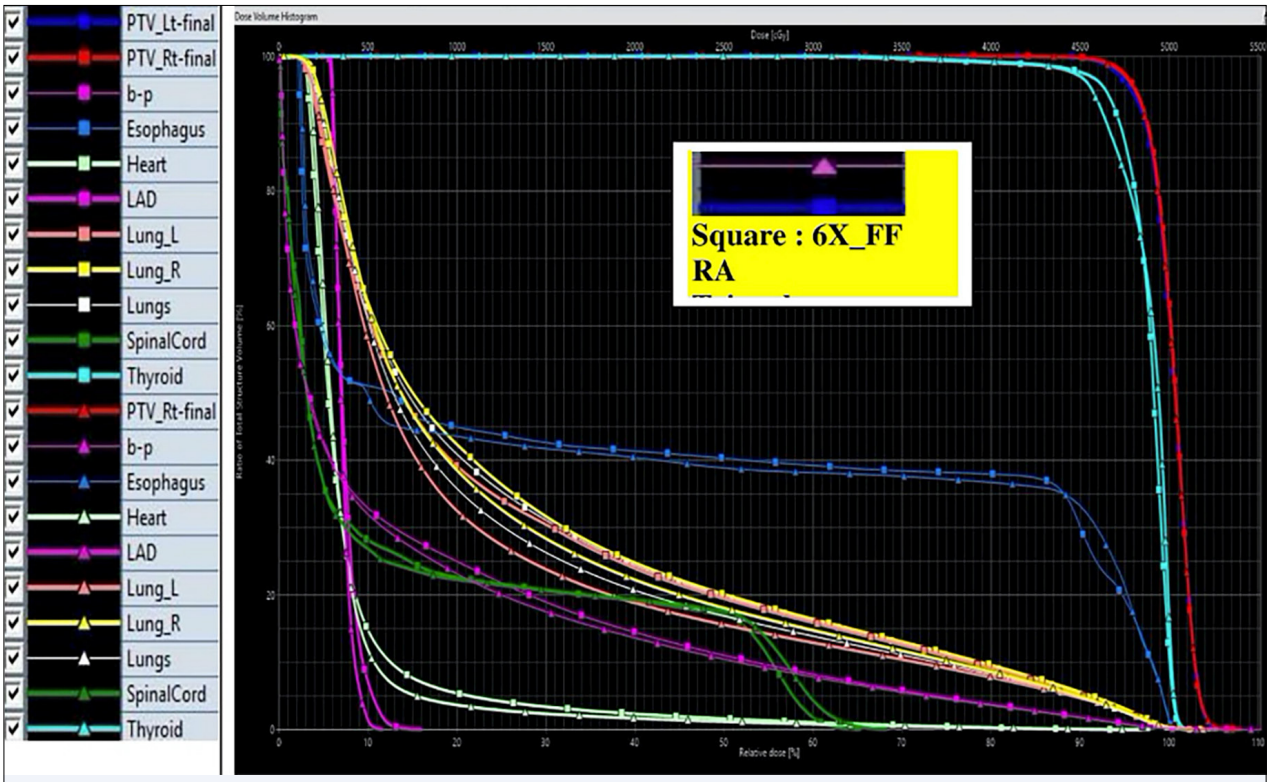

Fig. 2. The dose volume histogram showing both the target volumes and OAR of both techniques.
OAR: Organ-at-risk.

26.03%, and 18.5%) in the 6X_FF VMAT plan with the 6X_FFF VMAT plan, no statistically significant difference was found. The value was lower (13.98 Gy, 66.9%, 38.13%, 23.47%, and 17.07%) compared to the 6X_FF VMAT plan ($p>0.05$).

Right Lung Dose Analysis

The analysis for the right lung revealed a similar result. A statistically insignificant difference was found in the D_{mean}, V5Gy, V10Gy, V20Gy, and V30Gy in the 6X_FF VMAT plan (14.98 Gy, 66.1%, 42.7%, 27.47%, and 19.63%) compared to the 6X_FFF VMAT plan (14.63 Gy, 65.93%, 40.43%, 25.97%, and 18.57%) ($p>0.05$).

Both Lungs Dose Analysis

Analyzing both lungs together, lower values were found in the 6X_FFF VMAT plan for D_{mean}, V5Gy, V10Gy, V20Gy, and V30Gy with 14.35 Gy, 66.33%, 39.4%, 25.37%, and 18.57% when compared to the 6X_FF VMAT plan (14.86 Gy, 66.9%, 42.13%, 26.87%, and 19.1%). These values are statistically not significant ($p>0.05$). Regarding the 6X_FF VMAT plan, the overall results were slightly better with the 6X_FFF VMAT plan.

Heart and LAD Dose Analysis

The mean cardiac doses were found to be approximately the same for each technique. The mean cardiac dose was 5.30 Gy and 5.31 Gy, respectively, for both planning techniques. The volume doses to the heart in V5Gy, V10Gy, V20Gy, and V30Gy in the 6X_FF VMAT plan (23.5%, 9.47%, 4.17%, and 1.74%) were slightly higher than in the 6X_FFF VMAT plan (22.8%, 9.63%, 4.47%, and 2.10%) ($p>0.05$). Likewise, the maximum and mean LAD doses for the 6X_FF VMAT plan were higher at 8.88 Gy and 5.58 Gy than at 7.12 Gy and 4.79 Gy, but there was no significant difference.

Spinal Cord, Thyroid, Esophagus Dose Analysis

The maximum doses in the esophagus, thyroid, and spinal cord were higher in the 6X_FF plan. Although the mean dose of the thyroid in the two plans was similar, there was no statistically significant difference.

Radiobiological Assessment of OARs

Table 4 shows the comparison of the normal tissue complication probability (NTCP) model (Poisson-LQ and Lyman-Kutcher-Berman) outcomes for 6X_FF and 6X_FFF VMAT plans across various OARs and endpoints. By utilizing the Poisson-linear quadratic (Poisson-LQ) model,

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Table 2 The dosimetric results for the clinical target volume (PTV) in 6X_FF VMAT& 6X_FFF VMAT plan

PTV parameter	Treatment plan		p
	6X_FF Rapid Arc (mean±SD)	6X_FFF Rapid Arc (mean±SD)	
PTV- left sided (LT)			
D_{max} (Gy)	54.2±0.668	54.1±0.060	0.275
D_{mean} (Gy)	50.3±0.162	50.2±0.173	0.127
D98%(%)	94.8±1.54	94.3±1.36	0.376
V95%(Gy)	97.2±1.46	97.23±1.45	0.513
V105%(CC)	10.1±8.06	3.05±2.59	0.275
V107%(CC)	0.563±0.501	0.073±0.0808	0.796
CI	0.978±0.0131	0.946±0.0306	0.127
HI	0.0985±0.0116	0.0964±0.0109	0.827
PTV- right sided (RT)			
D_{max} (Gy)	53.96±0.3720	53.42±0.599	0.513
D_{mean} (Gy)	50.35±0.119	50.19±0.056	0.513
D98%(%)	95.57±0.873	95±0.8	0.658
V95%(Gy)	98.47±0.873	97.97±0.850	0.658
V105%(CC)	3.31±2.55	1.50±0.462	0.275
V107%(CC)	0.11±0.1900	0.013±0.023	0.376
CI	0.984±0.008	0.955±0.036	0.050
HI	0.084±0.008	0.088±0.009	0.513
MU	1302.0±127	1720±293	0.127
BOT(seconds)	190±2.44	158.10±1.35	0.050

PTV: Planning target volume; VMAT: Volumetric modulated arc; SD: Standard deviation; D_{max}: Maximum dose; D_{mean}: Mean dose; D98%(%): Dose received by 98% of the volume; V95%: Volume that receives at least 95% of the prescribed dose; V105% &V107%: Volume receiving at least 105% & 107% of prescribed dose (in cc); CI: Conformity index; HI: Homogeneity index; MU: Monitor unit; BOT: Beam on time

we found that the mean mortality risk for the heart was similar between the two techniques, with a value of 0.19±0.18 for 6X_FF RapidArc and 0.18±0.17 for 6X_FFF RapidArc (p=0.658). Similarly, when assessing the risk of pneumonitis for the lungs, we observed comparable results, with values of 2.47±1.88 for 6X_FF RapidArc and 2.16±2.08 for 6X_FFF RapidArc (p=0.268).

Furthermore, the Lyman-Kutcher-Berman model analysis revealed no significant differences in the risk of grade ≥2 pneumonitis (5.76±2.44 for 6X_FF RapidArc and 5.25±2.80 for 6X_FFF RapidArc, p=0.275), symptomatic pneumonitis within six months (6.84±5.77 for 6X_FF RapidArc and 6.00±6.31 for 6X_FFF RapidArc, p=0.275), or symptomatic fibrosis after six months (65.25±4.25 for 6X_FF RapidArc and 64.43±4.30 for 6X_FFF RapidArc, p=0.275).

DISCUSSION

Our study showed no statistical difference in the dosimetric parameters between both treatment planning methods. The use of FFF photon beams to implement SBBC treatment plans aims to increase the effectiveness and precision of radiation therapy. In this study, we found that the 6X_FFF treatment plan has similar PTV coverage, CI, and HI value as 6X_FF RapidArc, as depicted in Figures 1, 2, and Table 2. Previous publications[28,29] evaluated the dosimetric parameters of different methods based on 3DCRT, IMRT, and VMAT for SBBC patients. Table 5 shows that few studies have investigated the dosimetric parameters of VMAT for SBBC with 6X_FF and 6X_FFF. Our study differed from others in the use of five arcs instead of only two or three.

Techniques such as VMAT or IMRT promise a more even distribution of radiation doses across the lung volume, with dose limitations for V5, V10, and V15 correlating with the incidence of symptomatic radiation pneumonitis (RP)[30] and subsequent pulmonary fibrosis.[31] A V5 value of less than 65% is aimed to mitigate the risk of RP.

Based on previously published work,[32–34] to reduce the risk of severe pulmonary toxicity for bilateral

Table 3 The dosimetric parameters for organ-at-risk (OAR) in 6X_ FF VMAT& 6X_ FFF VMAT plan

OAR parameter	Treatment plan		p
	6X_FF VMAT (mean±SD)	6X_FFF VMAT (mean±SD)	
Left lung (LT)			
D_{mean} (Gy)	14.70±20.18	13.98±28.04	0.275
V5 (%)	68±10.75	66.9±12.05	0.827
V10 (%)	40.99±3.72	38.13±7.600	0.513
V20 (%)	26.03±3.10	23.47±5.49	0.275
V30 (%)	18.5±3.99	17.07±5.46	0.275
Right lung (RT)			
D_{mean} (Gy)	14.98±24.33	14.63±28.8	0.513
V5 (%)	66.1±5.48	65.93±8.70	0.827
V10 (%)	42.7±4.36	40.43±6.0	0.376
V20 (%)	27.47±4.79	25.97±6.18	0.275
V30 (%)	19.63±5.51	18.57±6.45	0.275
Both lung			
D_{mean} (Gy)	14.86±22.41	14.35±28.35	0.275
V5 (%)	66.9±7.71	66.33±10.11	0.513
V10 (%)	42.13±4.38	39.4±6.60	0.275
V20 (%)	26.87±4.10	25.37±6.72	0.513
V30(%)	19.1±4.85	18.27±6.70	0.275
Heart			
D_{mean} (Gy)	5.30±1.67	5.31±1.84	0.827
V5 (%)	23.5±10.2	22.8±12.1	0.827
V10 (%)	9.47±6.98	9.63±7.17	0.827
V20 (%)	4.17±4.08	4.47±4.04	0.658
V30 (%)	1.74±2.19	2.10±2.08	0.658
LAD			
D_{max} (Gy)	8.88±1.68	7.12±1.21	0.275
D_{mean} (Gy)	5.58±2.27	4.79±1.22	0.513
Thyroid			
D_{max} (Gy)	50.6±1.70	51.5±0.691	0.513
D_{mean} (Gy)	48.4±1.81	48.5±1.69	0.827
Esophagus			
D_{max} (Gy)	46.9±6.35	47.40±6.52	0.513
D_{mean} (Gy)	14.91±5.38	14.6±5.31	0.513
Spinal cord			
D_{max} (Gy)	29.5±3.18	30.3±3.60	0.513

VMAT: Volumetric modulated arc; SD: Standard deviation; D_{mean}: Mean dose; V5%, V10%, V20%, V30%: Volume receiving at least 5 Gy, 10Gy, 20Gy, 30Gy (percentage); LAD: Left anterior descending

breast radiation and locally advanced BC, the threshold value of the mean lung dose (MLD) is limited to below 12–15 Gy and V20Gy > 30% without sacrificing the necessary RT field coverage. A published study by Karlsen et al.[35] found that MLD was associated with an increased risk of radiation pneumonitis (RP) and radiation fibrosis (RF). Specifically, they found that the chance of RP increased by 12% for every 1 Gy increase in MLD.

In our present study, the reduction of MLD to both lungs from 4.42% lower in the FFF VMAT plan remained within acceptable thresholds. For the 6X_FFF VMAT plan, a reduction in both lung mean doses was found to be 3.8% compared to the 6X_FF VMAT plan.

In a previous published work,[35] it was found that for each percentage increase in V20, there was a 6% higher occurrence of RP. In our current research, we ob-

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Table 4 NTCP mean value in both VMAT plan with endpoints for Heart &Lungs

NTCP model	OAR structrure	Endpoints	6X_FF RA mean±SD	6X_FFF RA mean±SD	p
Poission-LQ	Heart	Mortality	0.19±0.18	0.18±0.17	0.658
	Lungs	Pneumonitis	2.47±1.88	2.16±2.08	0.268
Lyman-KutcherBerman	Lungs	Pneumonitis,Grade≥2	5.76±2.44	5.25±2.80	0.275
	Lungs	Symptomatic Pneumonitis ≤6 month	6.84±5.77	6.00±6.31	0.275
	Lungs	Symptomatic Fibrosis >6 month	65.25±4.25	64.43±4.30	0.275

NTCP: Normal tissue complication probability; VMAT: Volumetric modulated arc; OAR: Organ-at-risk; SD: Standard deviation

served a decrease of 16.73% in the V20 Gy of the 6X_FFF VMAT plan, while the 6X_FF VMAT plan decreased by 10.99%. Both reductions are within the acceptable limit. Concerning V10Gy, we observed a decrease of 6.5% in our 6X_FFF VMAT plan compared to the acceptable plan limit, as well as 7.57% according to Wu et al.[36]

In our present study, we found a reduction in lung volume at V30Gy of 4.44% in the 6X_FFF VMAT plan compared to the 6X_FF VMAT plan. Published work by Vogelius & Bentzen[37] observed that for every 1% increase in V30Gy, there was an incremental risk of 10% for RP.

As can be seen in Figure 3a, our current study reveals that the V5Gy in the 6X_FFF VMAT is 66.3% and 66.9% in the 6X_FF VMAT plan. These results are 2.9% higher in the 6X_FF VMAT plan and slightly higher than the acceptable limit of 2% in the 6X_FFF VMAT plan. As indicated in Table 5, the current V5Gy result is lower than that of earlier published work.

Not reported in other studies in the past, we conducted an NTCP assessment, which is not utilized directly in assessing radiotherapy plans at present, but it may be a crucial tool for comparing such plans and methods. NTCP analysis aids in discovering novel approaches to reduce complication rates caused by radiotherapy.[38] The NTCP values of OARs, including both lungs and heart, comparing the 6X_FF VMAT with 6X_FFF VMAT are shown in Table 4 and Figures 3a, 3b, and 3c. The 6X_FFF VMAT plans demonstrate a reduction in these parameters of 13.39% (pneumonitis), 10.18% (pneumonitis grade ≥2), 13.08% (symptomatic pneumonitis (≤6 months)), and 1.26% (symptomatic fibrosis >6 months) compared to the 6X_FF VMAT plans. Both radiotherapy techniques demonstrate statistically similar NTCP outcomes for the heart and lungs across the evaluated endpoints, based on the findings.

Darby et al.[39] reported in a population-based case-control study of major coronary events that they underestimated standard radiotherapy for unilateral breast cancer, reporting that a mean cardiac dose of

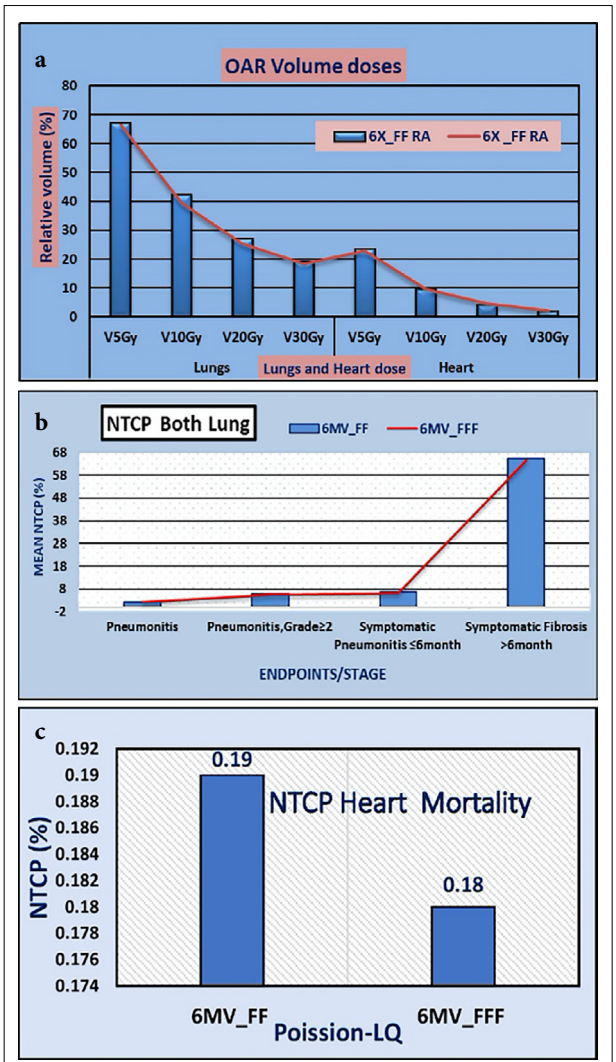

Fig. 3. (a) Volume doses of lungs and hearts between 6X_FF and 6X_FFF VMAT plan. (b) NTCP values for lungs in both model between 6X_FF and 6X_ FFF. (c) NTCP value for Poission-LQ model between 6X_FF and 6X_FFF.
OAR: Organ-at-risk; NTCP: Normal tissue complication probability; VMAT: Volumetric modulated arc.

Table 5 Literature review summary on synchronous bilateral breast cancer (SBBC) with focus on lung and heart doses

Title of study	Author	Volume (Gy)	Heart		Both lungs		Total no. of arc and patients
			FF_VMAT	FFF_VMAT	FF_VMAT	FFF_VMAT	
Is synchronous bilateral breast irradiation using flattening filter-free beam-based volumetric-modulated arc therapy beneficial? A dosimetric study. (2020)	Nagaraj and Veluraja	D_{mean} (Gy)	11.80	12.24	10.44	10.22	2 Partial arc and Total 15 patients: 5 right-sided mastectomy, 6 left-sided mastectomy, 4 breast conservation surgery
		V20(%)	-	-	13.32	13.25	
		V10(%)	42.27	44.25	30.47	29.49	
		V5(%)	-	-	65.70	61.54	
Treatment planning with unflattened as compared to flattened beams for bilateral carcinoma of the breast.	Suresh Tamilarasu (2017)	D_{mean}	10.17	10.84	15.47	15.82	2 partial arcs and Five patients who had undergone bilateral mastectomy with axillary lymph node
		V20(%)	-	-	-	-	
		V10(%)	-	-	34.3	37.8	
		V5(%)	-	-	84	84.2	
Evaluation of optimal treatment planning for radiotherapy of synchronous bilateral breast cancer including regional lymph node irradiation.	Cho Y, et al. (2019)	D_{mean}	13.2 Gy	-	14.4Gy	-	15 patients, and two partial arcs
		V20(%)	-	-	27.5%	-	
		V10(%)	-	-	41.1%	-	
		V5(%)	-	-	67.9%	-	
Dosimetric comparison of postmastectomy radiotherapy plans for synchronous bilateral breast cancer, including regional lymph node irradiation	Wu X, Huang J, Lin X, et al. (2023)	D_{mean} (Gy)	6.19	-	15.02 (left) & 14.91(right)	-	3 partial arcs and Total 10 mastectomy patients
		V20(%)	-	-	28.43 (Lt.) and 27.47 (Rt.)	-	
		V10(%)	-	-	42.50 (Lt.) and 40.98 (Rt.)		
		V5	-	-	65.05 (Lt.) and 2.309 (Rt.)		
Present study		D_{mean} (Gy)	5.30	5.31	14.86	14.35	5 partial Arc each side and 3 patients MRM
		V20(%)	-	-	26.87	25.37	
		V10(%)	9.47	9.63	42.13	39.4	
		V5(%)	-	-	66.9	66.33	

VMAT: Volumetric modulated arc; MRM: Modified Radical Mastectomy

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3–4 Gy was an acceptable value and that the frequency of major coronary events increased linearly with a cardiac mean dose increase of 7.4% per 1 Gy. The study by Cho et al.[40] reported that a median cardiac dose of 5 Gy was acceptable for SBBC patients with 50 Gy in 25 fractions delivered to the PTV breast and is consistent with other cardiac toxicity studies. Similarly, according to Bergom et al.,[41] trials have found that a mean dose to the heart of 3–5 Gy is considered acceptable for treatment planning of breast cancer radiation therapy.

Our study results show the advantage of five partial arcs on each side with dual isocenters for SBBC patients, finding that the mean cardiac dose of about 5.31 Gy is only 0.19% higher in FFF plans compared to 6X_FF plans. This is lower than the findings of Wu et al.,[36] Nagaraj & Veluraja,[38] Tamilarasu et al.,[42] and Cho et al.,[40] as shown in Table 5. Fiorentino et al.[43] published a study of 50 Gy in 25 fractions of VMAT treatment administered to 16 women with SBBC. Their reported average cardiac D_{mean} was 8.3±3.3 Gy. Furthermore, our study results showed that V10Gy was 9.47% in the 6X_FF VMAT plan and 9.63% in the 6X_FFF plan, which was lower than the findings of Nagaraj & Veluraj.:[38] 77.59% in the 6X_FF VMAT plan and 78.23% in the 6X_FFF plan. Details of the study are shown in Table 5. In addition, the biological evaluation based on the NTCP value of the heart with cardiac mortality can be seen in Table 4, and Figure 3c shows that the NTCP value of the heart for 6X_FFF VMAT was 5.26% lower than that for the 6X_FF VMAT plan.

This research highlights the importance of tailoring strategies to specific situations due to the variability in dosimetric outcomes among different treatment methods. The potential use of 6X_FFF and DIBH radiation in clinical settings could potentially lower pulmonary and cardiac doses for patients undergoing treatment.

However, it is important to recognize the limitations of this study. Notably, the current study included only three patients.

CONCLUSION

For SBBC patients, the 6X_FFF photon beams provide a radiation treatment plan that is both dosimetrically acceptable and has an insignificant dose difference in target coverage compared to 6X_FF VMAT plans. In addition, patients treated with a 6X_FFF photon beam demonstrate improved OAR sparing, improving patients' quality of life by reducing the risk of lung and heart complications. Thus, the FFF photon beam can be used effectively for SBBC treatment planning.

Ethics Committee Approval: The study was approved by the Indira Gandhi Institute of Medical Sciences Ethics Committee (no: 1225/IEC/IGIMS/2023, date: 05/10/2023).

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