Flattening Filter-Free Volumetric-Modulated Arc Radiotherapy for Left-Sided Whole-Breast, Partial-Breast, and Postmastectomy Irradiations

Rui Zhang^{1,2}, Yibo Xie¹, Chloe DiTusa¹, Raymond Ohler³, David Heins⁴, Daniel Bourgeois^{2,5}, Beibei Guo⁶

Departments of ¹Physics and Astronomy, ³Biological Sciences and ⁶Experimental Statistics, Louisiana State University, Baton Rouge, LA, USA, ²Department of Radiation Oncology, Mary Bird Perkins Cancer Center, Baton Rouge, LA, USA, ⁴Department of Radiation Oncology, CTSI Physics Services, Springfield, MO, USA, ⁵Department of Radiation Oncology, Slidell Memorial Regional Cancer Center, Slidell, LA, USA

Abstract

Purpose: Unflattened photon beams exhibit many benefits over traditional flattened beams for radiotherapy (RT), but comprehensive evaluations of dosimetric results and beam-on time using flattening filter-free (FFF) beams for all types of breast irradiations are still lacking. The purpose of this study was to investigate if FFF RT can maintain equal or better dose coverage than standard flattened-beam RT while reducing doses to organs at risk (OARs) and beam-on time for various types of breast cancer irradiations. **Methods and Materials:** FFF volumetric-modulated arc therapy (FFF-VMAT) and standard VMAT (STD-VMAT) treatment plans were created for 15 whole-breast irradiation (WBI) patients with 50 Gy/25 fractions, 13 partial-breast irradiation (PBI) patients with 38.5 Gy/10 fractions, and 9 postmastectomy irradiation (PMI) patients with 50 Gy/25 fractions. Planning target volume (PTV) coverage and dose to OARs were evaluated. **Results:** Both techniques produced clinically acceptable plans for all three types of irradiations. For WBI, FFF-VMAT plans exhibited similar PTV and OARs evaluation metrics as STD-VMAT. For PBI, FFF-VMAT plans showed significantly lower mean and maximum doses for ipsilateral and contralateral lungs, contralateral breast, and heart. For PMI, FFF-VMAT plans showed significantly lower mean dose and V_5 for contralateral breast but significantly higher D_{mean} , D_{30} for heart. FFF-VMAT techniques significantly higher D_{mean} , N_{30} for heart. FFF-VMAT techniques significantly reduced beam-on time than STD-VMAT for all cases. **Conclusion:** This work has shown that FFF beams are most beneficial for small-field irradiation such as PBI, and breast cancer patients could potentially benefit from the shortened beam-on time.

Keywords: Breast cancer, flattening filter-free, partial-breast irradiation, postmastectomy irradiation, volumetric-modulated arc therapy, whole-breast irradiation

Received on: 29-11-2021	Review completed on: 23-03-2022	Accepted on: 09-04-2022	Published on: 05-08-2022		

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among American women, and there are about 3.8 million breast cancer survivors in the United States.^[1] Radiotherapy (RT) has been coupled with surgery and chemotherapy as the standard of care for breast cancer patients and depending on the stage of disease, the patient can receive either breast-conserving irradiation, including whole-breast irradiation (WBI) and partial-breast irradiation (PBI), or postmastectomy irradiation (PMI), and flattened radiation beams have been used for breast RT in most clinics.

There has been an increasing interest in using flattening filter-free (FFF) beams for RT^[2-5] because unflattened photon

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Quick Response Code:	Website: www.jmp.org.in				
	DOI: 10.4103/jmp.jmp_146_21				

beams exhibit many benefits over traditional flattened beams, including reduced beam penumbra, head scatter, and out-of-field dose.^[6] Another benefit of FFF beams is the increased delivery efficiency due to the increased dose rate,^[5] which can potentially reduce the delivery time of treatments but is dependent on physical machine constraints, such as multileaf collimator (MLC) speed and gantry rotation speed.

> Address for correspondence: Dr. Rui Zhang, Department of Physics and Astronomy, Louisiana State University, Baton Rouge, Los Angeles, USA. E-mail: rzhang@lsu.edu

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How to cite this article: Zhang R, Xie Y, DiTusa C, Ohler R, Heins D, Bourgeois D, *et al.* Flattening filter-free volumetric-modulated arc radiotherapy for left-sided whole-breast, partial-breast, and postmastectomy irradiations. J Med Phys 2022;47:166-72.

There were some studies that evaluated FFF beams for WBI and PMI, but conclusions from these studies are contradictory: for WBI, some studies reported that FFF and flattened beams will produce comparable WBI plans,^[5,7,8] while the other studies reported that FFF beams induced compromised target coverage for WBI using tangential dynamic and step-and-shoot IMRT,^[9] or improved WBI plan quality;^[10] for PMI, some studies showed that FFF beams better spared contralateral breast, contralateral lung and liver but did not reduce heart dose,^[11] while the other PMI study reported that significant dosimetric benefits for all organs at risk (OARs) using FFF beams.^[12] So far, comprehensive evaluations of dosimetric results and beam-on time using FFF beams for all three types of breast irradiations are still lacking.

This study was conducted to determine if 6 MV FFF volumetric-modulated arc therapy (FFF-VMAT) can maintain equal or better dose coverage than standard VMAT (STD-VMAT) for WBI, PBI, and PMI patients while significantly reducing doses to OARs and beam-on time.

MATERIALS AND METHODS

Patient selection

Fifteen left-sided postlumpectomy patients in our clinic were retrospectively selected for WBI planning, 13 left-sided postlumpectomy patients who met PBI criteria^[13] were retrospectively selected for PBI planning, and 9 left-sided postmastectomy patients were retrospectively selected for PMI planning. Computed tomography (CT) scans were acquired, and all patients were scanned in the supine position with the free-breathing CT data sets. The PMI patients had a 1-cm thick Superflab bolus (Radiation Products Design, Inc., Albertville, MN) placed on the surface of the ipsilateral chest wall for the purpose of dose buildup. The evaluation planning target volumes (PTVs_EVAL) for PMI, WBI, and PBI patients were contoured by the same radiation oncologist and by following the RTOG Atlas.[13] PTV EVAL for WBI was defined as the ipsilateral breast with 7 mm expansion, limited anteriorly to exclude the part outside the patient body and the first 5 mm of tissue under the skin, and posteriorly no deeper to the anterior surface of the ribs. PTV EVAL for PBI was defined as the excision cavity with 25 mm expansion, limited anteriorly to exclude the part outside the patient body and the first 5 mm of tissue under the skin and the part beyond the posterior extent of breast tissue. PTV EVAL for PMI included the left chest wall, left supraclavicular and axillary area and internal mammary chain area, excluded the Superflab bolus. Lungs, whole heart, contralateral breast, esophagus, trachea, spinal cord, and skin were contoured as the OARs.

Characteristics of flattening filter-free beams in our clinic

Figure 1 compares the normalized measured percentage depth dose data for the flattened and unflattened 6 megavoltage (MV) beam from an Elekta Versa HDTM (Elekta, Crawley, UK) linear accelerator (linac) in our clinic. The two beams are very similar with only slight differences in the buildup region, depth of maximum dose (d_{\max}) , and <5% difference in the low dose tail of the curve. The d_{\max} is 1.67 cm for the flattened beam and is 1.78 cm for the FFF beam. The 1.1 mm difference is in agreement with other institutions.^[4]

Figure 2 shows the normalized dose profiles for the flattened and unflattened 6 MV beam from the same machine in our clinic. It shows the forward peak and the flattened peak of the FFF and flattened beams, respectively, and shows a reduction in out-of-field dose for the FFF beam

Treatment planning and beam-on time evaluations

All treatment plans were created with 6 MV beam energy in a commercial treatment planning system (Pinnacle v9.8, Philips Medical Systems, Fitchburg, WI) using SmartArc optimization algorithm. All PMI and WBI plans had a prescribed dose of 50 Gy in 25 fractions, and PBI plans had a prescribed dose of 38.5 Gy in 10 fractions. 0° couch angle and maximum dose rate were used for all plans: STD-VMAT used 600 Monitor Units (MU)/min, while FFF-VMAT used 1200 MU/min. All plans utilized two partial arcs due to the complexity of the cases and the close proximity of the treatment target to lungs, heart, and contralateral breast, and collimator angle was set to 15° and 75° for the two arcs, respectively.

For WBI, the beam isocenter was placed at the middle of the PTV_EVAL in the superior-inferior direction and lateral direction, and at the interface of breast tissue and chest wall in the anterior-posterior direction. The first arc was planned to be delivered counterclockwise with starting and stopping gantry angles determined by the fiducial markers placed on the skin, and the second arc was planned to be delivered clockwise over the same range of gantry angle.

For PBI, the beam isocenter was placed at the center of the PTV_EVAL. The first arc start was planned to be delivered counterclockwise with starting angle around 180° and stopping angles around 60°, and the second arc was planned to be delivered clockwise.

For PMI, the beam isocenter was placed at the middle of the PTV_EVAL in the superior-inferior direction and lateral direction, and in the lung in the anterior-posterior direction due to the past pointing.^[14] The first arc was planned to be delivered counterclockwise with starting angles between 170° and 180° and stopping angles between 304° and 320°, and the second arc was planned to be delivered clockwise.

The same optimization objectives were used for standard and FFF-VMAT plans. The treatment plans were considered clinically acceptable when the following criteria were met: for all PMI, WBI, and PBI patients, the volume of the PTV receiving at least 95% of the prescribed dose is \geq 95%; for PMI and WBI patients, the volume of lungs receiving at least 20 Gy is <20%,^[15] and the volume of heart receiving 22.5 Gy is <20%;^[16] for PBI patients, the volume of heart receiving 2 Gy is <40% and the volume of lungs receiving 11.5 Gy is <15%.^[13] After plan objectives were achieved through optimization, dose-volume metrics were calculated for target volume, lungs, heart, and



Figure 1: Normalized percent depth dose data for 6 MV flattened and FFF photon beams from one of the linacs in our clinic. MV: Megavoltage, FFF: Flattening filter-free

contralateral breast. Homogeneity index (HI)^[17] and conformity index^[18] were calculated for the target coverage.

The beam-on time was measured for the two arcs in one treatment fraction for each plan using a stopwatch. All plans were delivered through an Elekta Versa HD[™] linear accelerator (Elekta, Crawley, UK) with Agility MLCs. In addition, the total number of MU was obtained from the TPS for each plan.

The paired *t*-test was used to determine the statistical significance of the differences. All statistical analyses were conducted with R software (version 3.2.3. The R Foundation, Vienna, Austria), and the differences were considered statistically significant when P < 0.05.

RESULTS

The dose distributions for representative patients are shown in Figure 3. Figure 4a shows the cumulative dose-volume histograms (DVHs) for a typical WBI patient, and the two techniques are quite comparable. Figure 4b shows the DVHs for a typical PBI patient, and FFF-VMAT plan shows improved PTV coverage and better OARs sparing compared to STD-VMAT. Figure 4c shows the DVHs for a typical PMI patient. With similar PTV coverage, FFF-VMAT shows decreases in the high-dose region for the contralateral breast compared to STD-VMAT at the cost of increases in high dose for both the lungs and heart.

The total number of MUs, PTV and OARs evaluation metrics are summarized in Table 1. All treatment plans met the plan acceptance criteria and were deemed clinically acceptable by the radiation oncologist. All FFF-VMAT plans use significantly more MUs than STD-VMAT. For the WBI patient cohort, overall FFF-VMAT plans exhibit similar PTV and OARs evaluation metrics as STD-VMAT except for the significantly lower D_{mean} and HI for PTV, significantly lower V_1 for the contralateral breast, significantly higher D_{max} for the ipsilateral



Figure 2: Normalized dose profile for flattened and FFF 6 MV photon beams from one of the linacs in our clinic. MV: Megavoltage, FFF: Flattening filter-free

lung, and the significantly higher D_{max} for the heart. For the PBI patient cohort, FFF-VMAT plans show significantly lower D_{mean} and D_{max} for both ipsilateral and contralateral lungs and the contralateral breast, significantly lower V_1 and V_5 for the ipsilateral lung, significantly lower V_1 , D_{mean} , and D_{max} for the heart, compared to STD-VMAT. For the PMI patient cohort, FFF-VMAT plans show similar target coverage as STD-VMAT, significantly lower D_{mean} , D_{max} , and V_5 for the ipsilateral breast, significantly higher D_{mean} , D_{max} , and V_{20} for the ipsilateral lung, and significantly higher D_{mean} , $V_{22.5}$ and V_{30} for the heart.

The average beam-on time for the three patient cohorts is listed in Table 2. All FFF-VMAT plans demonstrate significantly shorter beam-on time (on average 12% less time for WBI, 18% less for PBI, and 15% less for PMI) compared to STD-VMAT plans.

DISCUSSION

We compared FFF-VMAT and STD-VMAT for all types of breast cancer irradiations in this study. The results show that FFF-VMAT can maintain equal or better dose coverage and significantly reduce beam-on time compared with STD-VMAT in all cases. FFF beams can reduce dose to all OARs for small-field irradiation like PBI, whereas cannot significantly improve dose distributions for most OARs for large-field irradiation such as WBI or PMI.

For WBI, Wang *et al.*^[7] showed that FFF hybrid intensity-modulated RT (IMRT) plans can achieve similar plan quality as the clinically approved forward planning plans for WBI with breath-hold; Spruijt *et al.*^[5] reported that IMRT, hybrid IMRT, electronic tissue compensator, and multiple static field plans using flattened and FFF beams are dosimetrically comparable, and beam delivery times were on average 31% less for FFF plans; Koivumaki *et al.*^[9] reported a significant



Figure 3: Axial view of isodose distribution for STD-VMAT (first row) and FFF-VMAT plans (second row) for a typical (a) WBI patient, (b) PBI patient, and (c) PMI patient. The red color wash represents the PTV. STD-VMAT: Standard volumetric modulated arc therapy, FFF-VMAT: Flattening filter-free volumetric modulated arc therapy, WBI: Whole breast irradiation, PBI: Partial breast irradiation, PMI: Postmastectomy irradiation, PTV: Planning target volume



Figure 4: DVHs for STD-VMAT and FFF-VMAT for typical (a) WBI patient, (b) PBI patient and (c) PMI patient. STD-VMAT: Standard volumetric modulated arc therapy, DVHs: Dose volume histograms, FFF-VMAT: Flattening filter-free volumetric modulated arc therapy, WBI: Whole breast irradiation, PBI: Partial breast irradiation, PMI: Postmastectomy irradiation

reduction of beam-on time (18%–39%) when using FFF beams with tangential arc VMAT and tangential IMRT, but target coverage was compromised with FFF IMRT while no

reduction of coverage with FFF VMAT; Wisnoskie *et al.*^[8] showed that FFF beams with electronic tissue compensation planning technique can generate comparable breath-hold WBI

Table 1: Monitor units, planning target volume and organs at risk evaluation metrics (mean±standard
deviation) for whole-breast irradiation, partial-breast irradiation, and postmastectomy irradiation patients using
standard-volumetric-modulated arc therapy and flattening filter-free-volumetric modulated arc therapy

	WBI			PBI			PMI		
	STD	FFF	p value	STD	FFF	p value	STD	FFF	p value
MU/fx	487±68	624±84	< 0.001*	657±80	737±80	< 0.001*	468±34	649±61	< 0.001*
PTV									
D _{mean} (Gy)	50.1±0.4	49.8±0.5	< 0.001*	38.2±0.4	38.2±0.5	0.346	49.3±0.3	49.3±0.4	0.838
D _{max} (Gy)	54.9±1.3	54.3±1.4	0.051	40.5 ± 0.4	41.2±0.8	0.001*	53.3±0.7	53.2±1.1	0.724
V ₁₀₇ % (%)	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	$0.0{\pm}0.1$	$0.0{\pm}0.1$	1.000
CI	$0.8{\pm}0.0$	$0.8{\pm}0.1$	0.635	$0.64{\pm}0.14$	0.62 ± 0.14	0.314	$0.7{\pm}0.1$	$0.7{\pm}0.0$	0.071
HI	$0.1{\pm}0.0$	$0.1{\pm}0.0$	0.012*	$0.2{\pm}0.2$	$0.1{\pm}0.0$	0.489	$0.1{\pm}0.0$	$0.1{\pm}0.0$	0.751
Ipsilateral lung									
D _{mean} (Gy)	$7.9{\pm}1.1$	$7.8 {\pm} 0.5$	0.851	$1.0{\pm}0.5$	0.6±0.2	0.004*	15.9±0.9	17.3±1.5	0.011*
D _{max} (Gy)	45.4±2.8	47.7±3.5	0.034*	14.0±6.5	11.2±6.6	0.01*	49.0±2.0	51.0±1.7	0.025*
V ₁ (%)	95.5±5.5	94.9±6.7	0.279	32.1±12.0	17.4±8.3	< 0.001*	100 ± 0.0	100 ± 0.0	0.356
V ₅ (%)	38.9±9.3	42.5±7.9	0.441	2.4±3.0	0.6±0.7	0.026*	85.4±7.7	87.1±6.6	0.589
V ₁₀ (%)	23.7±3.6	22.1±7.5	0.661	0.3±0.7	0.1±0.2	0.26	54.0±5.2	57.8±4.4	0.138
V_{20}^{10} (%)	12.5±2.5	10.6±4.5	0.227	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	29.1±2.2	31.8±3.5	0.011*
CL lung									
D _{mean} (Gy)	4.2±1.5	4.0±1.2	0.634	0.3±0.2	0.1 ± 0.04	0.02*	3.0±0.6	3.3±0.9	0.078
D _{max} (Gy)	27.6±11.7	26.6±12.9	0.4	1.5 ± 0.6	$1.1{\pm}0.8$	0.02*	21.5±4.7	22.6±3.6	0.395
V ₁ (%)	88.1±12.8	93.7±5.6	0.106	1.5±1.1	0.3±0.6	0.34	97.3±3.7	97.9±2.7	0.659
V ₅ (%)	29.7±17.2	27.4±16.2	0.651	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	12.5±7.1	16.3±11.2	0.124
V ₁₀ (%)	6.3 ± 6.5	5.3 ± 3.9	0.691	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	$1.4{\pm}1.2$	1.8 ± 1.9	0.545
V ₂₀ (%)	0.5 ± 0.8	$0.4{\pm}0.6$	0.089	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	$0.0{\pm}0.0$	$0.0{\pm}0.0$	0.637
Heart									
D _{mean} (Gy)	7.0±1.4	6.6 ± 1.1	0.387	0.8 ± 0.3	$0.4{\pm}0.7$	< 0.001*	9.0±1.5	9.9±2.0	0.017*
D _{max} (Gy)	38.3±4.6	40.6±4.3	0.048*	4.0±2.2	2.3±1.2	0.009*	41.7±4.9	44.6±3.2	1.000
V ₁ (%)	$100.0{\pm}0.1$	$100.0{\pm}0.0$	0.334	24.7±14.4	5.3±4.8	< 0.001*	100.0 ± 0.0	100.0 ± 0.0	1.000
V ₅ (%)	49.9±18.2	46.7±17.4	0.315	0.8±0.5	$0.0{\pm}0.0$	0.175	65.3±13.2	70.4±14.0	0.197
V ₁₀ (%)	17.6 ± 8.0	15.7±5.3	0.397	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	23.8±6.0	27.6±9.5	1.000
$V_{225}(\%)$	3.4±2.6	3.5±2.3	0.946	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	8.8±3.5	10.4±3.7	0.003*
V ₃₀ (%)	1.3±1.5	1.6±1.6	0.329	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	4.5±2.9	5.9±2.8	0.007*
CL breast									
D _{mean} (Gy)	1.6±0.2	$1.4{\pm}0.2$	0.321	0.2 ± 0.08	$0.14{\pm}0.07$	0.008*	3.8±1.1	3.2±0.8	0.025*
D _{max} (Gy)	10.1±2.8	11.2±7.3	0.439	1.1±0.3	0.8±0.3	0.043*	26.1±8.6	24.2±7.5	1.000
V ₁ (%)	76.9±12.6	68.3±13.2	0.011*	0.2±0.3	$0.0{\pm}0.1$	0.086	95.0±8.8	92.0±10.8	0.080
V ₅ (%)	0.5 ± 0.5	0.5 ± 0.7	0.642	$0.0{\pm}0.0$	$0.0{\pm}0.0$	-	22.6±12.4	15.4±8.5	0.032*

*Indicates statistical significance (P<0.05); - Indicates statistical test is not feasible. D_{max}: Depth of maximum dose, WBI: Whole breast irradiation, PBI: Partial breast irradiation, PMI: Postmastectomy irradiation, FFF: Flattening filter-free, STD: Standard, MU: Monitor units, PTV: Planning target volume, CL: Contralateral, HI: Homogeneity index

Table 2: The average beam-on time (min) per fraction for standard-volumetric-modulated arc therapy and flattening filter-free-volumetric-modulated arc therapy plans

	WBI			PBI			PMI		
	STD-VMA	T FFF-VMAT	<i>p</i> value	STD-VMAT	FFF-VMAT	p value	STD-VMAT	FFF-VMAT	p value
Beam-on time (min)	2.6±0.2	2.3±0.1	< 0.001*	1.8 ± 0.1	1.5 ± 0.1	< 0.001*	$2.0{\pm}0.0$	$1.7{\pm}0.0$	< 0.001*
*Indicates statistical	significance	(<i>n</i> <0.05). WBI:	Whole-breast	irradiation. F	PBI: Partial-breast	irradiation	PMI Postmas	tectomy irradiati	on VMAT.

*Indicates statistical significance (p<0.05). WBI: Whole-breast irradiation, PBI: Partial-breast irradiation, PMI: Postmastectomy irradiation, VMAT: Volumetric-modulated arc therapy, FFF: Flattening filter-free, STD: Standard

plans as flattened beams, and FFF beams can significantly reduce contralateral breast maximum dose and beam-on time (22%–42%); Thomas *et al.*^[19] compared FFF beams with standard beams for various cancer sites, including breast, for which they planned with tangential forward IMRT, and they

reported comparable plan quality and improved treatment efficiency; Maier *et al.*^[10] reported that FFF VMAT and FFF tangential arc VMAT could significantly improve plan quality and reduce delivery time in simultaneous integrated boost (SIB) irradiation of right-sided breast cancer than

flattened plans, but FFF IMRT plans were inferior to flattened plans. Our study is generally consistent with these previous studies as we found comparable plan quality using FFF and flattened beams, and we confirmed FFF beams can significantly reduce beam-on time. The different target (right-sided and SIB) used in Maier *et al.*^[10] could be the reason for the improved plan quality when FFF beams were used.

For PMI, Lai et al.^[11] showed modified VMAT using FFF beams provided superior dosimetric results than modified VMAT using flattened beams with respect to contralateral breast, contralateral lung, and liver doses Subramaniam et al.^[12] showed that RapidArc plans using FFF beams were superior to conventional RapidArc plans with respect to contralateral breast, heart, and lung doses. In our study, we found FFF-VMAT significantly reduced contralateral breast dose but did not reduce heart dose compared to STD-VMAT, which is consistent with Lai et al.,[11] and slightly increased dose to lungs. Lai et al.[11] also showed that FFF-VMAT did not reduce ipsilateral lung dose. The distant organ doses were reduced using FFF beams since FFF beams are characterized by reduced out-of-field dose due to lower head leakage at off-axis locations.^[3,6] On the other hand, since the isocenter of VMAT plans was located outside the PTV (under chest wall and within the ipsilateral lung) for PMI, leakage through MLCs near the FFF beam axis may be higher than flattened beam due to the peaked FFF beam profile. This explains the increased mean organ doses near PTV. It is possible Subramaniam et al.[12] used a different definition of PMI target and a different planning goal, i.e., they planned to cover 100% of the PTV with 90% prescribed dose, while both Lai et al.[11] and our study aimed for 95% of the PTV received 95% prescribed dose. This could be the reason we did not observe the significant dosimetric benefits for all OARs using FFF beams as Subramaniam et al. did.

For PBI, Thomas et al.[19] compared FFF beams with standard beams for IMRT and VMAT, and they reported comparable plan quality and improved treatment efficiency. Because they did not provide dosimetric data for their plans, it is not feasible to compare their results with ours; one abstract^[20] that compared FFF beams and flattened beams for prone accelerated PBI, and it reported FFF beams provided dosimetrically equivalent target coverage and similar OAR doses compared to flattened beams. However, they did not provide details of their prescribed dose or planning technique, so it is difficult to compare their findings with ours. Among all three types of breast cancer irradiations, we found that FFF beams provided the largest benefit for PBI and significantly reduced doses to all OARs. This is consistent with the previous report^[21] from the American Association of Physicists in Medicine Therapy Emerging Technology Assessment Work Group that recommended FFF beams are advantageous for small-field treatments.

Our study is the first study that compares dose distribution and beam-on time for FFF and standard beams for all types of breast irradiations, while the previous studies only considered WBI or PMI, or neglected time comparison. FFF-VMAT significantly lowered the contralateral breast dose for PMI, and significantly lowered all OAR doses for PBI. Clinically, these can be translated to patients' benefits: it has been reported one radiogenic second cancer occurred in every 200 breast cancer patients treated with RT,^[22] and the beneficial effect of RT was offset by an 18% increase in contralateral breast cancer, a 27% increase in heart disease death rate, and a 78% increase in lung cancer death rate.^[23] These breast cancer patients with an increased risk of radiogenic side effects could significantly benefit from FFF beams. Furthermore, FFF beams significantly reduce treatment times for breast cancer patients, which indicates FFF-VMAT plans could be advantageous for the patients who are unable to remain on the treatment couch for long periods due to discomfort and the patients who need reduced treatment time such as patients treated with breath hold or with hypofractionated prescriptions.

One limitation of our study is that we did not compare other techniques except for VMAT for flattened and FFF beams. However, among RT techniques, VMAT has been increasingly used and shows specific advantages,^[24-30] and it is expected that VMAT will eventually replace conventional IMRT due to its faster delivery, increased degrees of freedom for dose optimization, and improved dose conformity.^[31] Therefore, our study should be very valuable for breast cancer management.

CONCLUSIONS

By comparing FFF-VMAT and STD-VMAT for WBI, PBI, and PMI, we concluded that FFF-VMAT can maintain equal or better target coverage and significantly reduce beam-on time compared to STD-VMAT in all cases. FFF beams are most beneficial for small field irradiation like PBI in that they can significantly reduce OAR doses and can benefit breast cancer patients who need reduced treatment time.

Financial support and sponsorship

This work was supported by National Institutes of Health (grant no. K22CA204464), American Cancer Society (grant no. RSG-22-030-01-CTPS), Louisiana Board of Regents Proof-of-Concept/Prototyping Initiative Fund, Louisiana State University LIFT2 Fund, and Louisiana State University Faculty Research Grant.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- 1. American Cancer Society: Key Statistics for Breast Cancer. Available from: https://www.cancer.org/cancer/breast-cancer/about/howcommon-is-breast-cancer.html. [Last accessed on 2022 Feb 24].
- Vassiliev ON, Kry SF, Chang JY, Balter PA, Titt U, Mohan R. Stereotactic radiotherapy for lung cancer using a flattening filter free Clinac. J Appl Clin Med Phys 2009;10:14-21.
- Cashmore J, Ramtohul M, Ford D. Lowering whole-body radiation doses in pediatric intensity-modulated radiotherapy through the use of unflattened photon beams. Int J Radiat Oncol Biol Phys 2011;80:1220-7.

- Georg D, Knöös T, McClean B. Current status and future perspective of flattening filter free photon beams. Med Phys 2011;38:1280-93.
- Spruijt KH, Dahele M, Cuijpers JP, Jeulink M, Rietveld D, Slotman BJ, et al. Flattening filter free vs. flattened beams for breast irradiation. Int J Radiat Oncol Biol Phys 2013;85:506-13.
- Cashmore J. The characterization of unflattened photon beams from a 6 MV linear accelerator. Phys Med Biol 2008;53:1933-46.
- Wang Y, Vassil A, Tendulkar R, Bayouth J, Xia P. Feasibility of using nonflat photon beams for whole-breast irradiation with breath hold. J Appl Clin Med Phys 2014;15:4397.
- Wisnoskie SB, Liang X, Wahl AO, Bennion NR, Granatowicz AD, Zhou S, *et al.* Using flattening filter free beams in electronic tissue compensation whole breast irradiation with deep inspiration breath hold. J Appl Clin Med Phys 2020;21:280-7.
- Koivumäki T, Heikkilä J, Väänänen A, Koskela K, Sillanmäki S, Seppälä J. Flattening filter free technique in breath-hold treatments of left-sided breast cancer: The effect on beam-on time and dose distributions. Radiother Oncol 2016;118:194-8.
- Maier J, Knott B, Maerz M, Loeschel R, Koelbl O, Dobler B. Simultaneous integrated boost (SIB) radiation therapy of right sided breast cancer with and without flattening filter – A treatment planning study. Radiat Oncol 2016;11:111.
- Lai Y, Chen Y, Wu S, Shi L, Fu L, Ha H, *et al.* Modified volumetric modulated arc therapy in left sided breast cancer after radical mastectomy with flattening filter free versus flattened beams. Medicine (Baltimore) 2016;95:e3295.
- Subramaniam S, Thirumalaiswamy S, Srinivas C, Gandhi GA, Kathirvel M, Kumar KK, *et al.* Chest wall radiotherapy with volumetric modulated arcs and the potential role of flattening filter free photon beams. Strahlenther Onkol 2012;188:484-90.
- Vicini FA, Cecchini RS, White JR, Arthur DW, Julian TB, Rabinovitch RA, *et al.* Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for earlystage breast cancer: a randomised, phase 3, equivalence trial. Lancet. 2019;394(10215):2155-64.
- Khan FM. Treatment planning I: Isodose distributions. In: The Physics of Radiation Therapy. Ch. 11. Philadelphia, PA: LWW; 2003.
- Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70-6.
- Hardenbergh PH, Munley MT, Bentel GC, Kedem R, Borges-Neto S, Hollis D, *et al.* Cardiac perfusion changes in patients treated for breast cancer with radiation therapy and doxorubicin: Preliminary results. Int J Radiat Oncol Biol Phys 2001;49:1023-8.
- Wu Q, Mohan R, Morris M, Lauve A, Schmidt-Ullrich R. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas. I: Dosimetric results. Int J Radiat Oncol Biol Phys 2003;56:573-85.
- 18. van't Riet A, Mak AC, Moerland MA, Elders LH, van der Zee W.

A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: Application to the prostate. Int J Radiat Oncol Biol Phys 1997;37:731-6.

- Thomas EM, Popple RA, Prendergast BM, Clark GM, Dobelbower MC, Fiveash JB. Effects of flattening filter-free and volumetric-modulated arc therapy delivery on treatment efficiency. J Appl Clin Med Phys 2013;14:4328.
- Galavis P, Barbee D, Jozsef G. Dosimetric advantages of flattening free beams to prone accelerated partial breast irradiation. Med Phys 2016;43:3556.
- Xiao Y, Kry SF, Popple R, Yorke E, Papanikolaou N, Stathakis S, *et al.* Flattening filter-free accelerators: A report from the AAPM Therapy Emerging Technology Assessment Work Group. J Appl Clin Med Phys 2015;16:5219.
- 22. Grantzau T, Mellemkjær L, Overgaard J. Second primary cancers after adjuvant radiotherapy in early breast cancer patients: A national population based study under the Danish Breast Cancer Cooperative Group (DBCG). Radiother Oncol 2013;106:42-9.
- 23. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005;366:2087-106.
- Palma DA, Verbakel WF, Otto K, Senan S. New developments in arc radiation therapy: A review. Cancer Treat Rev 2010;36:393-9.
- 25. Popescu CC, Olivotto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R, *et al.* Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. Int J Radiat Oncol Biol Phys 2010;76:287-95.
- Qiu JJ, Chang Z, Wu QJ, Yoo S, Horton J, Yin FF. Impact of volumetric modulated arc therapy technique on treatment with partial breast irradiation. Int J Radiat Oncol Biol Phys 2010;78:288-96.
- Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: A review of current literature and clinical use in practice. Br J Radiol 2011;84:967-96.
- Nichols GP, Fontenot JD, Gibbons JP, Sanders ME. Evaluation of volumetric modulated arc therapy for postmastectomy treatment. Radiat Oncol 2014;9:66.
- Riou O, Fenoglietto P, Bourgier C, Lauche O, Boulbair F, Charissoux M, et al. Feasibility of accelerated partial breast irradiation with volumetric-modulated arc therapy in elderly and frail patients. Radiat Oncol 2015;10:209.
- Sapkaroski D, Osborne C, Knight KA. A review of stereotactic body radiotherapy – Is volumetric modulated arc therapy the answer? J Med Radiat Sci 2015;62:142-51.
- Popple RA, Balter PA, Orton CG. Point/Counterpoint. Because of the advantages of rotational techniques, conventional IMRT will soon become obsolete. Med Phys 2014;41:100601.