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Intensity Modulated Radiotherapy Using Multiple in Fields Compared to Wedged Fields in Breast Irradiation: Clinical Impact on Early Skin Reaction and Organs at Risk Doses

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Abstract

Objective: To measure the impact of multiple fields in filed (MFIF) technique on dose homogeneity, doses to organs at risk (OARs) and acute skin toxicity in comparison to physical wedged (PW) tangential technique.

Methods: The study population consisted of 75 patients who had breast-conserving surgery and whole-breast radiation using MFIF. These patients were matched one-to-one to a control group of 75 patients treated with PW tangents, following ethical board approval and signing informed consents. Acute skin reaction was graded by CTCAE 3.0 scoring and multiple regression analysis of covariates was performed.

Results: CTCAE grade2 acute skin reaction occurred in 61.3% PW vs. 32% MFIF while grade 3 was encountered in 24% PW vs. 10.7% MFIF patients (P<0.01). Multiple regression analysis confirmed the excessive skin reaction to the related radiation therapy technique (P=0.0002) and whole breast PTV (P<0.001). Homogeneity index within PTV was significantly improved in MFIF plans (0.84 ± 0.7) compared with PW (0.94 ± 0.15) with a (P<0.01). There was also a significant reduction, in lung V20 from 14.3% ± 1.1 to 10.6 % ± 1.4 (P<0.01), heart V30 from 7% ± 5.8 to 6% ± 4.9 (p<0.001). Contralateral breast volume receiving dose more than 2 Gy was also reduced 2.3% ± 0.5 PW to 1.2% ± 0.2 MFIF (P<0.01).

Conclusion: The MFIF technique significantly improved PTV dose homogeneity index, while significantly reduced the incidence of grade 2/3 acute skin reaction and doses to OARs when compared to PW tangential fields in whole breast radiotherapy.

Keywords: Intensity modulated radiation; Multiple in fields whole breast irradiation

Introduction

The three-dimensional analysis of tangential parallel-opposed pair technique used for whole breast irradiation (WBI) demonstrated large dose inhomogeneity inside the target volume resulting in hot spots with increased risk of adverse effects and inferior cosmetic outcome [1-3]. Moreover, achieving acceptable dose homogeneity across the whole breast volume is difficult because of the continuous change in breast shape across multiple planes [4]. Various techniques have been tested in an attempt to improve the dose distribution in the PTV as physical wedged tangential (PW) systems and intensity modulation techniques [5-10].

The use of 3D treatment planning and intensity modulation with static multileaf collimator (sMLC) technique for tangential whole breast RT was found to be an efficient and reliable method for achieving a uniform dose throughout the whole breast. Strict dose–volume constraints can be readily achieved in most patients, resulting in both improved coverage of breast tissue, as well as a potential reduction in acute and chronic toxicities [4-6]. Moreover, several studies have reported improvement in the dose homogeneity with better sparing of OARs, when inverse planning intensity modulation radiation (IMRT) techniques were applied [11-15]. Additionally, moist desquamations were reported in 31% of patients treated with inverse IMRT versus 48% of patients treated with conventional wedged tangents [13]. However, the workload for planning and delivering inverse IMRT is significant compared to conventional PW, with an increase in rad-on time leading to higher bone marrow exposure to scattered doses [13,14]. The rationale of using MFIF was based on its improved performance compared with the conventional physical wedge (PW) and dynamic wedge systems [15]. Additionally, MFIF using beam's eye view (BEV) isodose-contouring and equalization of the maximum dose achieved the best reduction of high-dose volumes, without clear dosimetric advantage of other methods of intensity modulation including inverse IMRT over it [10].

The purpose of the study is to measure the impact of multiple fields in filed (MFIF) technique on dose homogeneity, doses to organs at risk (OARs) and acute skin toxicity in comparison to physical wedged (PW) tangential technique.

Methods

In this retrospective study which was approved by the ethical committee in our institute, the study population consisted of 75 consecutive patients who had breast-conserving surgery and whole-breast radiation using MFIF between May 2009 – December 2011. These patients were individually matched (one-to-one) to a control group of 75 patients treated with PW tangents during the same period. The PW (control) subjects were selected to broadly match the distribution of age groups, clinical stage, whole breast PTV volumes, hormones and chemotherapy of the MFIF (study) group. Binary logisitic regression was run using radiation field technique the PW (control) and the MFIF (study) as a binary dependent variable to calculate the probability predictive value which was used to match (control and study groups).

All patients signed informed consent before radiation. We excluded patients treated with implanted prosthesis, postoperative wound infection, and previous radiation to the same breast, connective tissue disorder or diabetes from both groups.

We opted to evaluate effectiveness of MFIF technique over PW in whole breast irradiation by comparing treatment dosmetric parameters and acute skin reactions.

We also opted to assess the impact of both (MFIF & PW) techniques on skin dose. Surface doses were measured in ten patients in each treatment group (MFIF & PW) using Lithium fluoride TLD chips (TLD-100 (Saint-Gobain Crystals & Detectors, Newbury, OH) with dimensions of $3.0 \times 3.0 \times 0.9$ mm^3. Four evenly spaced TLD chips were placed on the surface of each breast along the positive and the negative x-axis relative to the central axis of the beam. Measurements on both breasts were taken at equal intervals starting from 3 cm from the geometric edge, closest to the penumbra region of the beam. Their evaluation was carried out in a PCL3 TL reader of the FIMEL Company (Fontenay Aux Roses, France). TLDs were consistently annealed at 400°C for 1 h and 100°C for 2 h prior to irradiation and 100°C for 10 min after irradiation for pre-readout annealing.

Treatment Planning

All patients were scanned using Computed Tomography (CT). The breast CTV with 0.7 cm margin to PTV were outlined on each CT simulation image of 5 mm thickness each using Eclipse version 8.6 (TPS). Additionally, regional lymph nodes and organs at risk including both lungs, heart and spinal cord were also contoured for treatment planning and dose volume histogram (DVHs) generation. Finally the CTV boost was created to include the tumour bed and any seroma and a 1.5-2 cm margin in all directions to create PTV boost, editing 2-3 mm from the skin and lung surfaces.

A reference point was created as recommended by ICRU 50 convention as a point on central axis midway on a perpendicular line between the breast apex and the posterior field edge on designing medial and lateral tangential fields [16].

For generating MFIF plans, beam`s eye view (BEV) isodose-contouring and equalization of the maximum dose was applied. A dose distribution without any beam modifier was first created. The dose distribution based on open beam fields had been evaluated to lower maximum doses >107% within the PTV and to eliminate the hot spot volumes. Maximum target dose is defined as the highest dose in the target area provided this dose covers a minimum area of 2 cm^2. While hotspots are defined as an area outside the target that receives a higher dose than the specified target dose. It is considered clinically meaningful only if it covers an area of at least 2 cm^2 [17]. Using the isodose display features of the planning system for the >107% isodoses, multileaf collimator (MLC) segments were used to design blocking subfields (segments) to improve the dose homogeneity within the PTV. Main fields and subfields were merged in one portal, including several MLC segments for sequential irradiation. For patients treated using PW medial and lateral wedged tangential beams were used and the applied angles ranged from 15 to 30 degrees. Photon beam of 6 and 18 MV photon beam (Varian 2300 CD multimodality with 120-leaf Millennium) were used depending on patient separation.

A correction for lung inhomogeneity was made for all patients. The maximum, mean, and minimum dose values of PTV of MFIF and PW treated patients were compared using their DVHs. We also analysed the DVHs of ipsilateral lung, heart and contralateral breast for each patient. Moreover, we compared the total average monitor units (MUs) of MFIF to PW treated patients. The homogeneity index (HI) for each plan was calculated using the following formula and the mean values were compared.

Homogeneity index (HI) = (Dose Max - Dose Min) / Dose Mean in PTV

The significance of HI is that a lesser value of HI indicates greater 3D dose homogeneity in the planned target volume (PTV) [18].

Volumes over 20 Gy in the ipsilateral lung, 40 Gy in the heart and 2 Gy in the contralateral breast were used to establish the extent of the high dose received by the OARs.

Treatment verification and quality assurance

Quality assurance was performed using 2 D array system. It is COMPASS software with the IMRT Matrix which is the most advanced solution for fast, accurate and reliable digital IMRT verification.

Radiotherapy Dose Prescription

Whole breast ± nodal areas radiotherapy was delivered as 50 Gy in 25 fractions over 5 weeks. A breast boost of 10 Gy in 5 daily fractions was delivered to all patients using a direct electron beam. The depth of the target boost volume, should be encompassed by the 90 per cent isodose. Electrons of 9–15 MeV may be required but exit doses to the heart should be avoided. For larger volumes, small tangential photon beams 6MV were devised.

Clinical Assessments of the Breast

Archived original datasets of each patient actually applied treatment plan (MFIF and PW) were reviewed by the radiation oncologist and the medical physicist conducting the study. The grade of acute skin reaction and its location in the breast were retrieved from recorded weekly patient assessment during the 5 to 6 weeks of RT and at weeks 1,2,4, and 6 after treatment by treating physician. Acute skin reactions were scored according to the radiation oncologists' records applying the CTCAE 3.0 scoring system [19]. We also observed the isodose distribution for MFIF and PW treated patients and recorded the location of high dose regions (maximum target doses and hot spots) as shown on the isodose distribution. The location for moist desquamation was also recorded to see if it matches the high dose regions.

Statistical analysis

All statistical analysis was performed using the SPSS software (version 13).

Baseline data were compared using the student t-test, Pearson χ^2 test for heterogeneity and trend the Fisher Exact test was used. The dosimetry data were summarized using means and standard deviations and comparisons were made using the independent sample t-test. Moreover, 95% confidence intervals (CI were quoted with all P-values. Linear regression was performed to assess the relationship between acute skin reaction and radiation therapy technique (PW and MFIF, maximum dose with in the PTV and whole breast PTV volume). Sample size was calculated using published tables for ± 5% precision Levels, where (CI) is 95% and maximum degree of variability is P=0.05.

Results

On comparing demographic characteristics and treatment parameters of MFIF treated patients to those treated with PW, no statistical significant was observed as summarized in Table 1. The median age was 48 years (range 28–68). The mean volume for the whole breast PTV was 1778.2 cc (range 380–3560 cc). There was no statistically significant difference between breast volumes in the two groups (P=0.103). In MFIF 1 to 4 static fields were planned within the two main tangential fields to achieve adequate dose distribution. Beam weights assigned to these segmented fields were between 5% and 7% of the total isocentric weight of the open beams. While in the PW, the wedge angles used were either 15º or 30º.There was a significant reduction in the total MUs delivered to medial and lateral tangential fields in the MFIF 122.3 ± 16 and 121.6 ± 18 MUs when compared with the PW 167 ± 31 and 159.9 ± 26 MUs (P<0.01).

	Multiple field in field (Study group)	Physical Wedge (Control group)	P Value
	N= 75	N=75	
Age groups			
>25- <35	5 (6.7%)	5 (6.7%)	0.065
>35-<45	24 (32%)	29 (38.7%)	
>45-<55	36 (48%)	23 (30.7%)	
>55-<65	5 (6.7%)	15 (20%)	
>65-<75	5 (6.7%)	3 (4%)	
TNM Stage			
Stage I	43 (57.3%)	32 (42.7%)	
Stage IIA	28 (37.3%)	38 (50.7%)	
Stage IIB	2 (2.7%)	3 (4%)	0.344
Stage IIIA	2 (2.7%)	2 (2.7%)	
Chemotherapy			
No Chemotherapy	4 (5.3%)	0 (0%)	
AC X 4 Cycle	40 (53.3%)	50 (66.7%)	0.211
ACX4 Cycles + Taxotere x4 Cycles	22 (29.3%)	16 (21.3%)	
FEC X 6Cycles	2 (2.7%)	2 (2.7%)	
TC x 6 cycles	0 (0%)	1 (1.3%)	
ACX4 Cycles + Herceptin Taxotere x4 Cycles	7 (9.3%)	6 (8%)	
Hormones			0.152
No Hormones	20 (26.3%)	14 (18.7%)	
Tamoxifen	47 (62.7%)	45 (60%)	
Letrozole	8 (10.7%)	16 (21.3%)	
Mean Whole Breast PTV Volume ± SD	1778.2 cc ± 838	1705.4 cc ± 889	0.103

Table 1: Patient and treatment characteristics of multiple fields in field (MFIF) study group and the physical wedge (PW) control group.

Comparison of dosimetric parameters as (breast separation, beam energies used in both tangent and boost fields) did not illustrate significant difference between the MFIF and the PW groups as summarized in Table 2. Moreover, there was no statistically significant difference in the dose delivered to 95% of the breast PTV between MFIF compared to PW (98% vs 99%) of prescribed dose respectively (P value = 0.6).

	Multiple Fields in Fields (study group) N=75	Physical wedge (control group) N=75	P Value
Breast separation in the central axis			
≥23 Cm	15(20%)	18(24%)	
≥21-<23 Cm	16(21.3%)	11(14.7%)	0.099
<21	44(58.7%)	16(61.3%)	
Tangent Beam Energy			
Mixed 6 & 18 MV photons	21(28%)	24(32%)	
18 MV	46(61.3%)	45(60%)	0.45
6 MV	8(10.7%)	6(8%)	
Boost Energy			
Electron (9-15 MEV)	60(80%)	58(77.3%)	0.150
Mini-Tangent photon	15(20%)	17(22.7%)	

Table 2: Comparison of dosimetric parameters between MFIF and PW patients.

The maximum target dose covering the PTV was significantly reduced in MFIF plans 107 ± 1.5 compared to 109 ± 2.5 in PW plans with a (95% CI for difference of 1.1-2.5) and a (P<0.01)(Figure 1 and 2). Moreover, there was also a significant reduction in the hot spot values in the MFIF when compared to PW field plans 108% ± 1.5 vs 110% ± 2.9 with a (P=0.008). Additionally, the mean PTV dose was reduced from 101.1% ± 0.9 in PW plans to 100.3% ± 0.8 in MFIF (P<0.0001) showing better dose distribution coverage in the PTV with MFIF plan. Consequently, significantly greater 3D dose homogeneity in the PTV was confirmed by the lesser value of HI for MFIF plans 0.84 ± 0.7 compared to PW plans 0.94 ± 0.15 with (95%CI of difference of 0.92-0.125) and (P<0.01).

With regards to the impact of MFIF and PW techniques on skin surface dose , measured by TLD, it was observed that skin doses with both techniques were less than the daily prescribed therapeutic dose of 200cGy . MFIF delivered slightly higher mean doses on the surface of the treated breasts than PW (129.5 cGy vs 123.4 cGy respectively). On the other hand, mean surface doses to the contralateral breast were higher with PW (13.7 cGy) compared to MFIF (11.4cGy) treated patients as shown in Table 3.
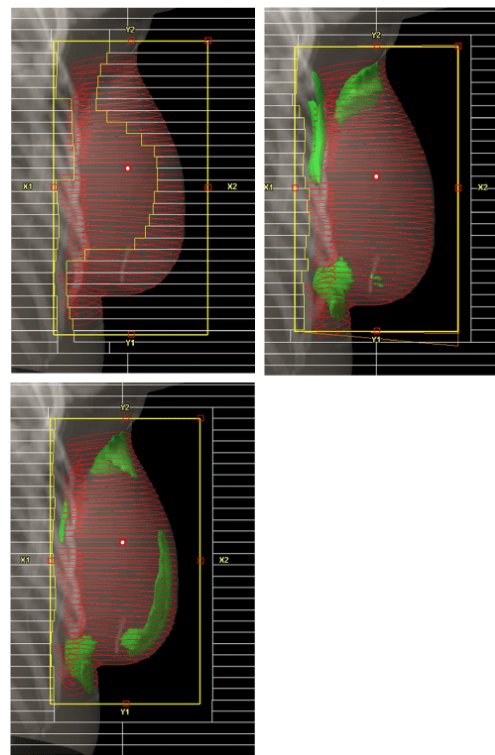

Figure 1: Beam`s eye view images. A: Open tangential field (left superior) showing Maximum target dose in green occupying large volume of breast PTV in red . B: Physical wedge (right superior) resulted in reduction in the Maximum target dose volume in breast PTV . C: Field in field (left inferior) resulted in almost complete disappearance of Maximum target dose from breast PTV.
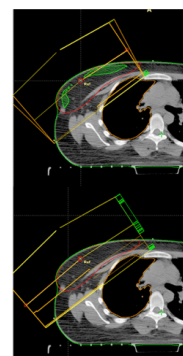

Figure 2: Showing axial CT simulation images. A: Physical wedge (superior) showing Maximum target dose in green occupying large volume of breast PTV in red. B: Field in field (inferior) resulted in complete disappearance of Maximum target dose from breast PTV.

10.6% ± 1.4 vs 14.3% ± 1.1 (P<0.01) and 6% ± 4.9 vs 7% ± 5.8 (P<0.001) respectively. Moreover, The PTV volume covered by more than 107% of the dose was reduced (5.2% ± 1 vs 8.4% ± 1.2 respectively, P<0.01) for MFIF compared to PW plans. More interestingly, the percent volume of the contralateral breast receiving

over 2 Gy was significantly reduced (1.2 ± 0.2 vs to 2.3 ± 0.5) in MFIF compared to PW plans respectively (P<0.01) (Table 4).

	MFIF Plan		PW Plan		P Value
	N= 10 patients		N= 10 patients		
	cGy	**(%)**	**cGy**	**(%)**	
Mean dose at surface treatment breast ± SD	129.5 ± 3.2	(64%)	123.4 ± 3.6	(61%)	0.638
Mean dose at surface contralateral breast ± SD	11.4 ± 1.1	(5.7%)	13.7 ± 1.5	(6.8%)	0.875

Table 3: Results of TLD readings; Therapeutic dose delivered for each plan was 200cGy. Numbers in parentheses are % of total dose delivered.

Taking into consideration organs at risk: lung V20, heart V30 in the MFIF group of patients were significantly reduced compared to the PW group of patients.

Using the IMRT verification system 2D Array, the Gamma Index was in the range from 99.78% to 99.98% and the average is 99.89%. More interestingly, the application of MFIF technique resulted in significant reduction in the incidence of acute skin reaction compared to PW. Grade 2 and 3 (moist desquamation) acute skin reaction were detected in 46 patients (61.3%) and 18 patients (24%) of patients treated using PW compared to 24 patients (32%) and only 8 patients (10.7%) of MFIF respectively (P<0.01). Additionally, grade 3 skin reaction (moist desquamation) was encountered in 16 patients (88.9%) of the group with whole breast PTV volume >2700 cc < 3700 treated

using PW plans compared to only 8 patients (53.3%) of the same breast PTV volume treated using multiple MFIF plans (P<0.01).

	Multiples Fields in Fields (Study group) Mean ±SD	PW (Control group) Mean ±SD	P Volume	95% CI
Over 107% in PTV	5.2 ± 1	8.4 ± 1.2	P<0.01	2.7-3.5
Over 20 Gy in ipsilateral lung	7.3 ± 0.35	7.5 ± 0.67	P=0.134	-0.27-0.31
Over 2 Gy in contralateral breast	1.2 ± 0.2	2.3 ± 0.5	P<0.01	0.96 -1.2
Over 40 Gy in heart	0.97 ± 0.9	1.1 ± 0.7	P=0.096	-0.6-0.45

Table 4: The percentage volumes of doses over 107% in PTV and the volumes over the constraint dose of OARs.

We also correlated the distribution of the hot spot locations receiving >100% of prescribed dose and maximum target dose within breast PTV to areas of moist desquamation. The breast area is the most common location for maximum target dose while the axillary area, inframammary fold, and sternal/parasternal areas are common location for hot spot foci outside breast PTV in both MFIF and PW treated patients as shown in Table 5. The majority of patients with moist desquamation over the breast or axillary areas had the high dose regions located at these two areas in both MFIF and PW treated patients. On the other hand, the occurrence of moistdesquamation at the inframammary fold or sternal areas are not so correlated with the high dose regions.

Locations of high dose regions	Distribution of high dose regions				Moist desquamation occurred at the same area of the high dose region			
	Inside breast		Outside breast		MFIF (8)		PW (18)	
					Yes	No	Yes	No
	PTV Maximum target dose		Hot spot					
	MFIF	PW	MFIF	PW				
	(8)	(18)	(8)	(18)				
Axillary			2 4		2(100%)	0	4(100%)	0
Breast	3	8			2(65%)	1(33%)	6(75%) 2(25%)	
Inframammary fold	1	2	1 3		0	2(100%)	2(40%) 3(60%)	
Sternal / Parasternal			1 1		0	1(100%)	0 1(100%)	

Table 5: The distribution of the high dose regions and its relationship to areas of moist desquamation. Numbers in parentheses are number of patients who developed moist desquamation in MFIF and PW respectively.

Multiple regression analysis revealed that acute skin reaction in both groups was significantly related to radiation therapy technique (PW and MFIF) (P=.0002), maximum dose with in the PTV (P<0.01) medial tangential fields monitor unit.

(P=0.011) and whole breast PTV volume (P<0.01).

Discussion

An investigation into a range of published modulation methods of breast IMRT, including inverse-planning and different types of forward planning including plane compensation, beam`s eye view dose contouring, minimization of dose variation and equalization of maximum dose algorithms, was conducted. The majority of these methods improved dose uniformity over wedge-only plans especially for breast sizes of 500 cm$^3$ or greater. However, MFIF using beam`s eye view (BEV) isodose-contouring and equalization of the maximum dose achieved the best reduction of high-dose volumes, without clear dosimetric advantage of other methods of intensity modulation including inverse IMRT over it [10].

In the present study, we evaluated the impact of MFIF using beam`s eye view (BEV) isodose-contouring on various treatment dosimetric parameters, incidence of acute skin reaction and organs at risk doses compared to PW. There was a significant reduction in both the hot spot values and PTV volume covered by maximum target dose in the MFIF plans when compared to PW plans (107.6% vs 109.4%, P<0.01) and (6.4% vs 9.4%, P<0.001) respectively. Similarly, Guillian et al. concluded that there was a statistically significant improvement in both the absolute volume receiving >107% (Vol > 107) and the absolute volume receiving <95% (Vol < 95) of the prescribed dose in the forward (IMRT) group when compared to the PW group [20]. De la Torre et al. also reported that MFIF technique allowed for better dose uniformity and the elimination of hot spots [21]. The mean values of the homogeneity index (HI) were significantly improved in MFIF compared to PW plans (0.83 ± 0.7 vs 0.94 ± 0.1) (P<0.001) as the lesser value of HI in MFIF indicated a significantly greater 3D dose homogeneity in the PTV. More interestingly, Cem et al. concluded that Dose HI was significantly lower for the FIF (0.117 ± 0.021) than for the single wedge (0.131 ± 0.025, P=0.02) and double wedged plan (0.128 ± 0.025, P=0.04), respectively [22]. Concerning TLD measured skin surface dose, MFIF plans reduced contralteral breast surface dose compared to PW (11.4 cGy vs 13.7cGy respectively). Moreover, MFIF delivered none significantly higher mean doses on the surface of the treated breasts than PW (129.5 cGy vs 123.4 cGy respectively). Our results were consistent with de la Torre et al as they proved that MFIF reduced contralateral breast surface dose compared to PW [21]. More interestingly, the percent volume of the contralateral breast receiving over 2 Gy was significantly reduced (1.2 ± 0.2 vs to 2.3 ± 0.5) in MFIF compared to PW plans respectively (P<0.01). A siginifcant reduction in the contralateral breast doses per 2-Gy fraction from 7.3 cGy ± 2.1 cGy in wedged tangential (WT), to 4.7 cGy ± 1.9 cGy in planned forward segments (ST); p<0.01 was also reprted by Ludwig et al. in their dosimetric study [23]. With regards to other organs at risk : lung V20, heart V30 in MFIF treated patients were significantly reduced compared to PW treated patients 10.6% vs 14.3% (P<0.01) and 6%vs 7% (P<0.001) respectively. Ohashi et al. reported a significant reduction in lung V20 from 8.9% to 7.4% (p<0.01), and heart V30 from 15.9 ml to 7.6 ml (p<0.01) for PW when compared to MFIF [23].

Our study confirmed a significant reduction in the incidence of grade2 acute skin reaction as it occurred in 32% in MFIF vs 61.3% in

PW (P<0.01). Similary, Harsolia et al. confirmed a significant reduction in acute grade 2 skin reaction with IMRT compared with wedges (41% vs 85% respectively, P<0.01). More intersringly, in the present study, acute grade 3 skin reaction (moist desquamation) was significantly reduced in MFIF compared to PW (10.7% vs 24% P<0.01), while Harsolia et al. reported only, a trend toward reduced acute grade 3 or greater dermatitis (6% vs. 1%, P= 0.09) in favor of IMRT vs PW [24,25]. A possible explanation of the reduced incidence of grade 3 dermatitis might be related to the better matching between MFIF and PW with no significant difference in breast volumes , beam energies or other parameters between the treatment groups based on binary logistic regression. On the other hand, Harisola et al. did not clarify how they matched patients in both treatment groups (IMRT vs PW) to avoid bias in their results. Moreover, they mentioned that patient in PW were treated using 2-D planning and there was a significant difference in number of patient treated with 6 MV beam in PW compared to IMRT who were mainly treated with mixed 6 and 18 MV beams. Additionally, the tumor bed boost was 10 Gy /5 fractions in our study compared to 16 Gy/8 fractions in Harsolia et al study. We also observed that the majority of patients with moist desquamation over the breast or axillary areas had the high dose regions located at these two areas in both MFIF and PW treated patients. Similarly, Sun et al., concluded a relation between the distribution of the hot spot locations and most areas of moist desquamation following whole breast irradiation [26].

Our study proved that clinical application of the MFIF using beam`s eye view (BEV) isodose-contouring and equalization of the maximum dose, achieved significant improved performance when compared to the effect of conventional PW technique. It significantly enhanced the dose homogeneity index, it reduced the maximum dose covering the PTV and the PTV volume covered by the maximum dose. Moreover it reduced doses to organs at risks (lung, heart, contralateral breast) and finally, reduced incidence of grade2 grade 3 acute skin.

There are several sentinel studies scrutinizing on the use of inverse IMRT to improve dose distributions with whole breast irradiation [25,27-30]. However, the increase in rad-on time in IMRT resulted in higher bone marrow exposure to scattered doses. Moreover, the significant cost and requirement of human resources demanded by the implementation of the most advanced IMRT should be considered meticulously [13,14]. On the contrary, the MFIF technique did not require a lot of resources for treatment planning and delivery [27]. Furthermore, the MFIF technique does not require a pretreatment QA procedure, which is essential for IMRT [10,27,28].

There were limitations to our study. First, our study was a retrospective analysis with limited number of patients, which potentially limits the generalizability of our results to results of prospective studies. Second, Comparing the MFIF treated patient one to one to a matched control group of patient treated using PW was subjected to the effect of confounding variables. Patients in the control (PW) group were individually matched to the MFIF patients based on age, breast size, TNM staging, chemotherapy regimen and hormonal treatment given.

Fortunately, with individual matching the problem of confounding variables was much reduced, although it was difficult to find an individually matched control. Moreover, the effect of confounding variables was further adjusted by using multivariate analysis. We are planning to extend the follow up duration of the whole study population to two years to further evaluate the impact of significantly

reduced acute skin reaction achieved by MFIF compared to PW on cosmetic outcome.

Conclusion

The MFIF technique significantly improved PTV dose homogeneity index, while significantly reduced the incidence of grade 2/3 acute skin reaction and doses to OARs when compared to PW tangential fields in whole breast radiotherapy.

Conflict of Interest Statement

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All authors declare that there was no conflict of interest on conducting this study. They also confirm that no financial support nor grants were given to conduct this study.

Ethics Standard

The study has been approved by our institutional ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent

All persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study all were omitted. Include the following: Informed consent was obtained from all patients for being included in the study.

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