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Dosimetric comparison of conventional and field-in-field techniques in early-stage breast cancer radiotherapy

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ABSTRACT

Background: Breast conserving surgery followed by adjuvant whole breast radiotherapy is the accepted treatment in early-stage breast cancer. Due to breast irregularities, it is difficult to achieve homogenous dose distribution with conventional techniques. Currently, it is possible to use varied breast irradiation techniques such as field-in-field (FIF) that is claimed to produce more homogenous distribution of doses within the target volumes while sparing the organs at risk, leading to a better treatment outcome. The present study aimed to compare the conventional and the FIF techniques dosimetrically. ***Materials and Methods:*** Twenty patients with early-stage breast cancer underwent computed tomography. Two different treatment plans were created for each patient: the wedge-based (conventional) plan and the FIF plan. Dosimetric parameters and monitor units were compared with paired sample t-test. ***Results:*** FIF technique obtained significantly lower dose homogeneity index, lower maximum doses and higher median doses in PTV (P<0.05). Similarly, the conformity index, and mean doses were higher in the FIF technique but the differences were not significant (P>0.05). In ipsilateral lungs, FIF significantly reduced the maximum and mean doses (P<0.05), and showed a tendency to reduce V20 (P>0.05). In patients with left-sided breast cancer, minimum and maximum doses and V40 of heart were significantly decreased in FIF plans (P<0.05). Doses to the contralateral lungs did not differ significantly. ***Conclusion:*** These results along with significantly less monitor units required for therapy in FIF suggest that this technique may be more advantageous during breast irradiation.

Keywords: *field-in-field, 3D conformal radiotherapy, wedge, breast irradiation, OAR dose.*

INTRODUCTION

Breast cancer is the most common malignancy in women in North America, Europe, Oceania, Latin America and the Caribbean, Africa, and most of Asia [1]. It is also one of the most frequent cancers in Iranian women [2]. External radiotherapy (RT) of the intact breast is an essential step following breast-conserving surgery (BCS) in the treatment of early-stage breast cancer. Many clinical trials comparing mastectomy with BCS followed by postoperative RT have shown similar results with these treatment procedures in women with early-stage breast cancer [3, 4].Currently, BCS followed by adjuvant whole breast RT is accepted as the standard treatment in women with early-stage breast cancer. It improves local control of the tumor as well as the post-treatment patient survival rate [5, 6].

However, the therapeutic results might be affected by the toxicity caused by irradiation.

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Some of the side-effects include breast pain, tiredness and fatigue, cardiotoxicity, rib fracture, and a shortened life-expectancy [7]. Therefore, it is important to deliver an accurate dose to the planning target volume (PTV). Since normal breast irregularities are exacerbated by breast tissue loss after BCS, it is difficult to achieve homogenous dose distribution in the breast tissue using conventional techniques. Dose changes of up to 15-27% of the irradiated volume have been reported in some studies [8].

With advances in RT techniques and equipment, it is possible to use alternative breast irradiation techniques and apply more homogenous dose distribution in the target volume while sparing the organs at risks (OARs), such as the lungs and the heart, resulting in a better treatment outcome. Recently, conventional hard wedges have been used to improve dose homogeneity and treatment efficiency. In wedge-based RT, although homogeneous dose distribution in the central axis of the target is achievable, occurring hot spot regions far from the axis is inevitable. These regions have been shown to receive elevated doses and are the main causes of reducing therapeutic results and the mentioned side-effects [9]. Following this, dynamic wedges were introduced. Newer breast irradiation approaches including intensity-modulated RT (IMRT), volumetric modulated arc therapy, intraoperative RT are now available. Using new computer-based treatment planning systems (TPS), dose distribution within the target as well as the doses of OARs can be easily analyzed. Highly conformal modalities in whole breast RT (WBRT) are required to achieve two fundamental goals: better dose distribution in the PTV and lower doses of the OARs [10].

The field-in-field (FIF) technique, also known as forward IMRT, uses multiple fields and subfields to achieve homogenous dose distribution in the PTV while reducing the OAR doses through shielding the critical structures in breast RT. It is claimed that this technique can provide more conformal dose coverage in the PTV and lower doses of the OARs, without any additional workload compared to three-dimensional conformal RT (3D-CRT) [11, 12].

In our department, FIF and conventional wedge-based RT are the most commonly used techniques in breast irradiation. A number of studies have previously compared these two techniques, each of which selected a number of indices as criteria for running the study. The present study was designed with 20 patients for precisely dosimetric comparison of these two important techniques in breast irradiation. Also in the present study all the important indices used in previous articles are used together to compare techniques. These criteria are some conformity indices to analyze the OAR and the PTV doses. RT machine monitor units (MUs) for these two approaches were also compared.

MATERIALS AND METHODS

Twenty patients with early-stage breast cancer (11 left-sided and 9 right-sided) were enrolled in this retrospective study. The patients' characteristics are listed in table 1. All patients had undergone breast-conserving surgery before being introduced to the radiotherapy department. Only patients with early-stage breast cancer without any lymph node involvement or distant metastasis were included in this study, i.e. patients with stage 0 (Tis, N0, M0), stage I (T1, N0, M0), and IIA (T2, N0, M0) who were confirmed through pathological tests. All patients with lymph node involvement or distant metastasis were excluded. The ability to raise the arms and to maintain this position during daily treatment was another criterion for participation in this study.

Table 1. Patients' characteristics

	Mean Value ± SD*	Range
Age (years)	48 ± 8.2	41- 60
Weight (kg)	73 ± 13.6	51- 95
BMI	28.5 ± 5	21- 38
Left Side Lesion	11 (55%)	-
Right Side Lesion	9 (45%)	-
Stage 0	4 (20%)	-
Stage I	12 (60%)	-
Stage IIA	4 (20%)	-

SD: standard deviation; BMI: body mass index. *Statistically significant

All patients underwent computed tomography (CT) with a16-slice Neusoft CT simulator (Neusoft Corporation, China). In the course of CT imaging, patients were positioned in the same manner as the treatment room position during irradiation (supine position with hands up, using a breast board to maintain the position). The entire breast and thorax of each patient were scanned with a 2/5 mm slice thickness in free-breathing mode. The CT datasets were then transferred to the DOSI soft Isogray (DOSIsoft, Paris, France) treatment planning system (TPS) via digital imaging and communication in medicine connection system (DICOM).

The clinical target volumes (CTVs) and the PTVs of the tumors as well as the contours of the OARs (including the heart and lungs) were delineated by the same oncologist in line with the International Commission of Radiation Units and Measurements (ICRU; reports 50 and 62) guidelines. Skin contours were automatically delineated with TPS. All the remaining breast tissue after the surgery process was considered as the CTV. The PTVs were created with a 5 mm extension of the CTVs except the anterior part. Subsequently, wedge-based (conventional) and FIF treatment plans were designed by the same medical physicist for each patient.

In the conventional plan, two opposing fields conformal to the breast were designed to entirely cover the PTV. To reduce inhomogenous doses within the PTV, hard wedges on the medial and the lateral sides were used. Severe breast surface irregularities which can cause inhomogeneity were normally observed in the PTV. Therefore, to achieve the most uniform and homogeneous dose distribution within the target volume, wedge angles were manipulated through trial and error process. The gantry angles were determined using the Beam's-eye-view ability of TPS by placing the healthy OARs out of the irradiated field as much as possible (figure 1). A copy of the wedge-based plan was defined by removing the wedges to carry out primary computation on the FIF plan with two equally weighted, open, and tangential fields with the same gantry angle as that used in the conventional technique. Dose distribution and hot/cold spot regions were determined using TPS. Two or three subfields were then added up to improve the dose homogeneity in the PTVs while reducing the OAR doses. Finally, the main field and the linked subfields were merged into one portal (figure2).

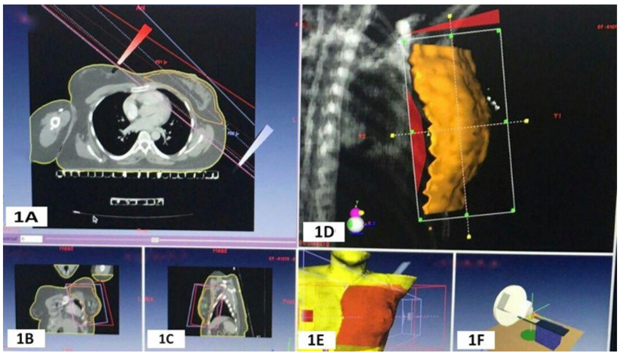

Figure 1. Image of Isogray TPS software on computer, shows conventional breast radiotherapy plan using hard wedges in 3 different CT scan sections (**1A** axial, **1B** coronal, and **1C** sagittal), Beam's eye view (BEV) of tangential field in digitally reconstructed radiography (DRR) (**1D**), treatment fields on the patient's body surface in schematic view (**1E**) and a schematic view of the patient position in the treatment room (**1F**).

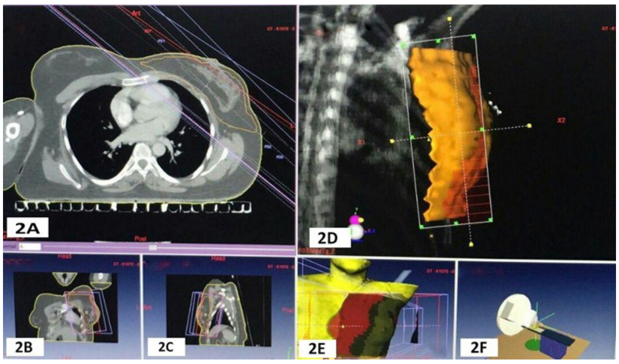

Figure 2. Image of Isogray TPS software on computer, shows Field-in-field breast radiotherapy plan using MLCs in 3 different CT scan sections (**1A** axial, **1B** coronal, and **1C** sagittal), Beam's eye view (BEV) of tangential field in digitally reconstructed radiography (DRR) (**1D**), treatment fields on the patient's body surface in schematic view (**1E**) and a schematic view of the patient position in the treatment room (**1F**).

The daily treatment dose for each patient was 2 Gy/fraction with 25 fractions overall with the aim of determining the best dose distribution while reducing the doses of the OARs in each

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plan. The reference point was freely shifted through the PTV. All plans were calculated with a point kernel (collapsed cone) algorithm, using the DOSIsoft Isogray TPS.

All plans were designed by the same medical physicist, after consultation with another physicist in difficult cases. The plans were checked and verified by an experienced oncologist.

Dose volume histograms (DVHs) were calculated for the PTVs, the heart, the ipsilateral lungs, and the contralateral lungs for each treatment plan in all patients (heart DVHs were considered only in left-sided breast cancer cases).

Dose homogeneity index (DHI) was employed to evaluate dose homogeneity in the PTVs. This index can be used to compare dose tolerance within the PTVs between conventional and the FIF techniques. The numerical value of DHI was calculated with the equation (1) [13]:

$$DHI = \frac{D2 - D98}{Prescription\ dose} \qquad (1)$$

In equation (1), D98 refers to the dose received by 98% of the PTV on the cumulative DVH, indicating that 98% of the target volume received this dose or a higher dose. Therefore, D98 is considered the ''minimum dose.'' D2 is the dose received by 2% of the PTV on the cumulative DVH, indicating that only 2% of the target volume received this dose or a higher dose. Therefore, D2 is considered the ''maximum dose.'' Lower DHI values denote more uniform dose distribution within the target volume [14].

Another index used in this study was the PTV dose improvement (PDI) or the percentage of the PTV receiving 97%-103% of the prescribed PTV dose. This index was used to evaluate improvement in the PTV dose coverage when wedges or subfields were compared to open fields without beam modifiers. Higher PDI values demonstrated better improvement in the PTV dose coverage.

Conformity index (CI) or the ratio volume confined by prescription isodose to the target volume was also analyzed [15]. Median PTV doses (D_{50}) were extracted and compared according to the ICRU recommendations (reports 50 and 62) [16]. Maximum, minimum, and mean PTV doses were also evaluated.

DVHs were determined for the ipsilateral lungs, the contralateral lungs, and the heart (in left-sided cases). Minimum (D_{min}), maximum (D_{max}), and median (D_{50}) doses for these tissues were measured and compared between the conventional and the FIF plans. The V40 of the heart (in left-sided breast irradiation) and the V20 of the ipsilateral lung were also compared.

The MUs needed for each plan were also evaluated. Planning complexity and the number of portals determined the MUs and the treatment time. This process might be challenging, especially in older patients, for whom maintaining the treatment position for a long period is intolerable.

All statistical analyses were performed using IBM SPSS software version 22. Normality of data distribution was evaluated by SPSS normality test (Kolmogorov – Smirnov test) and then, paired sample *t-test* was employed to compare the mean value of the mentioned indices. The significance level was set at $p < 0.05$.

RESULTS

Twenty patients with early-stage breast cancer (11 left-sided and 9 right-sided) were enrolled in the present study. The mean volumes and the standard deviations of the PTVs and the OARs are summarized in table 2.

Table 2. Volumes of planning target volume and organs at risk.

	Mean Volume (cm^3) ± SD	Maximum	Minimum
PTV	958.3 ± 444.3	1962.1	394.4
Ipsilateral Lung	1057.8 ± 237.4	1510	605.1
Contralateral Lung	1013.4 ± 202.4	1521.1	586.5
Heart	547.5 ± 98.6	784.5	481.6

SD: standard deviation; PTV: planning target volume.

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A comparison of dosimetric parameters for the PTVs between the conventional and the FIF techniques is presented in table 3. The FIF plan showed significantly lower DHI values (0.15 vs. 0.16, P=0.005), lower maximum doses (50.56 vs. 51.84 Gy, P=0.0001), greater volumes receiving 97% and 103% of the prescribed doses (P=0.0001 and 0.02, respectively), and higher median doses (46.86 vs. 46.26 Gy, P<0.0001) compared to conventional technique. The CI, the mean doses, and the volumes receiving 95% of the prescribed dose were also higher in the FIF technique, but the differences were not significant (P>0.05). PDI was equal in both groups.

Table 3. Comparison of dosimetric parameters for planning target volume.

	Wedge Plan (Mean ± SD)	FIF Plan (Mean ± SD)	p- value
DHI	0.16 ± 0.02	0.15 ± 0.03	0.005*
CI	0.94 ± 0.004	0.95 ± 0.01	0.08
PDI	0.57 ± 0.13	0.57± 0.18	0.12
Mean Dose (Gy)	46.57 ± 3.78	46.60 ± 3.88	0.4
Max Dose (Gy)	51.84 ± 4.30	50.56 ± 4.57	0.0001*
Min Dose (Gy)	26.18 ± 4.69	25.42 ± 4.28	0.04*
Median Dose (Gy)	46.26 ± 3.75	46.86 ± 3.88	< 0.0001*
D2 (Gy)	49.93 ± 4.14	49.16 ± 4.29	< 0.0001*
D98 (Gy)	42.26 ± 3.73	42.02 ± 3.75	0.03*
V95% (cm^3)	876.77 ± 363.3	878.41 ± 359.11	0.25
V97% (cm^3)	788.26 ± 319.55	825.73 ± 333.14	0.0001*
V103% (cm^3)	246.53 ± 158.96	305.40 ± 178.29	0.02*

SD: standard deviation; PDI: planning target volume dose improvement; DHI: dose homogeneity index; CI: conformity index; D2: dose received by 2% of the PTV on the cumulative dose volume histograms; D98:dose received by 98% of the PTV on the cumulative dose volume histograms. *statistically significant Vx%: volume of tissue receiving x percent of prescribed dose.

Doses received by the OARs including the ipsilateral lung, the heart (in left-sided breast irradiation), and the contralateral lung are presented in table 4. In the ipsilateral lungs, the FIF technique reduced the maximum and the mean doses significantly (P<0.05) compared with the wedge-based technique and showed a tendency to reduce the V20 and the minimum doses (P>0.05). In patients with left-sided breast cancer, the minimum and the maximum doses to the heart were significantly decreased in the FIF plan (P<0.05). Moreover, theV40 of the heart was significantly decreased in the FIF technique. FIF also led to reduction of the mean dose to the heart, but the change was not significant (P>0.05). In the contralateral lungs, the values showed no significant differences (P>0.05).

Table 4. Doses to organs at risk.

	Wedge Plan (Mean ± SD)	FIF Plan (Mean ± SD)	p- value
Ipsilateral Lung			
Min Dose (Gy)	0.11 ± 015	0.10 ± 0.12	0.06
Max Dose (Gy)	48.09 ± 4.149	46.83 ± 4.09	< 0.0001*
Mean Dose (Gy)	7.97 ± 2.62	7.57 ± 2.31	0.02*
Lung V20 (%)	14.04 ± 4.8	13.88 ± 4.6	0.2
Heart (in left sided breast irradiation)			
Min Dose (Gy)	0.45 ± 0.17	0.42 ± 0.14	0.03*
Max Dose (Gy)	46.37 ± 3.38	44.54 ± 4.16	0.0002*
Mean Dose (Gy)	6.85 ± 1.84	6.51 ± 1.69	0.12
Heart V40 (%)	6.25 ± 2.9	5.38 ± 2.9	0.03*
Contralateral Lung			
Min Dose (Gy)	0	0	-
Max Dose (Gy)	2.45 ± 1.01	2.55 ± 1.06	0.08
Mean Dose (Gy)	0.17 ± 0.08	0.16 ± 0.08	0.13

SD: standard deviation

The mean number of MUs in the wedge-based and the FIF plans were 401.6 ± 57.17 and 270.6 ± 34.17, respectively. Compared with the conventional plans, the FIF plan reduced the number of MUs significantly (P<0.0001), leading to shorter treatment times.

DISCUSSION

The gold standard treatment for early-stage breast cancer is conservative surgery followed by RT [17,18]. RT can increase the patient's survival rate by 4.8% and reduce the chances of recurrent malignancy by 19.7% over 20 years [19]. However, despite the advantages of postoperative RT in breast cancer patients, it might lead to a number of complications. These late adverse effects are related to dose inhomogeneity that can be caused by several

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factors such as the irregular shape and large size of the breast (9,20-22). Various RT techniques including the wedge-based technique and the FIF technique have been developed to ensure homogenous dose distribution within the target volume and to spare healthy tissues near the tumor (23, 24). The conventional technique, wherein two opposing tangential fields with wedge filters are applied, commonly optimizes dose distribution. This technique is reported to provide excellent local control with rare long-term complications (17,18). However, one fundamental disadvantage of the conventional technique is that increasing the wedge angle leads to an increased scatter component from the wedge, administering nonessential doses to the patient (25-27). Moreover, increasing the wedge angle in a tangential field RT might increase the dose in the medial and the lateral beam entries. Therefore, inducing high dose regions caused by wedge filters is inevitable (28).

Many studies have indicated that dose distribution during WBRT can be improved using the FIF technique (28-33). In this technique, alternative subfields are added to the main field by employing a multi-leaf collimator (MLC) instead of wedge filters. The main fields and the relative subfields are subsequently merged together in one portal. In the FIF technique using MLC scatter doses administrated to the patient can be decreased compared to those in the conventional wedge-based techniques. The FIF technique reduces the number of MUs and the total treatment time. Additionally, some hotspot regions that persist in the conventional techniques and the additional time required for commissioning the wedge can be avoided (27).

In a study conducted by Yavas *et al.* (2012), 20 consecutive patients with left-sided breast cancer undergoing BCS were enrolled. Two different treatment plans (FIF and conventional) were designed for each patient and the dosimetric parameters were measured. The FIF technique provided better dose distribution in the PTV and reduced the mean doses of the OARs. The MUs required for the treatment were also significantly reduced. Thus, it was concluded that the FIF technique was more effective in whole breast irradiation (34). Cem Onal *et al.* (2011) used dosimetric indices similar to those in the present study to compare the FIF and the wedge-based techniques in breast irradiation among 30 patients. Their results were consistent with the study performed by Yavas *et al.* (2012). Compared with the wedge beam technique, the FIF technique improved the DHI by 18% and reduced the required MUs by 22% (35).

Li-Min Sun *et al.* (2014) conducted a study and obtained contradicting results with the earlier mentioned studies. Two different FIF and wedge filter techniques were compared and three indices (homogeneity, conformity, and uniformity) along with doses of the OARs were measured. The results indicated that the wedge-based technique provides a significantly lower DHI and a significantly higher CI than the FIF technique. It was concluded that the FIF technique has no superior dosimetric advantage over the conventional technique in breast irradiation (36).

In the present study, the same indices as the ones used by Onal *et al.* (2011) and Sun *et al.* (2014) were employed. The results revealed that the FIF technique was more effective than the wedge-based technique in terms of DHI, CI, median dose (D50), maximum dose, doses of the OARs, and MUs. DHI was significantly reduced by 7.7%in the present study (0.167 and 0.154 for the conventional and FIF techniques, respectively and p=0.005). This finding was consistent with the previously mentioned studies except with the study by Sun *et al.* (2014). Lower DHI denotes lesser dose changes within the target volume. CI was higher in the FIF technique, but the difference was not statistically significant. The FIF technique also reduced the maximum dose and improved the D50, which was consistent with the previous studies.

PDI was employed to evaluate the improvement in the dose distribution in the treatment plans using physical wedges or the FIF technique compared to open field techniques without any beam modifiers. Lee *et al.* (*2008*) set dose levels corresponding to PDI indices of 97%-103% despite the fact that most of the previous studies used PDI indices between 95%-107%.The former was more rigorous and accurate, as shown in the present

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study. However, contrary to the findings of Lee *et al.* (*2008*), the present study observed no significant difference (similar to the results observed by Onal *et al.* (2011)).

The dose of the OARs is another criterion for choosing a better technique in RT. In agreement with the results of other studies, mean doses received by the ipsilateral lung was significantly reduced by 5% (p=0.02). The V20 of the ipsilateral lung and doses to the contralateral lung were also reduced in the FIF technique. However, the differences were not statistically significant. Moreover, compared with the conventional technique, the FIF technique significantly reduced the V40 of the heart by 14% (p=0.03). The maximum dose received by the heart (in left-sided irradiation) was also significantly decreased in the FIF technique by 4% (p=0.0002). The FIF technique declined the mean doses to the heart (in left-sided irradiation), but the difference was not statistically significant.

The MUs required for each technique were also dropped in the FIF plans by 33% (P<0.0001). Similar to the results of Yavas *et al.* (2012), Onal *et al.* (2011), and Sun *et al.* (2014) studies, the differences in the MUs between the two techniques were highly significant (P<0.0001). In fact, the MUs are reduced due to their adjustment between the subfields in the FIF technique. Treatment time can be saved due to the reduction of MUs and wedge-less treatment planning, as there was no need for the RT technicians to re-enter the treatment room after daily setup. Moreover, there was no pretreatment quality assurance procedure in the FIF technique, which was essential for IMRT. Due to these advantages, FIF is a simple, attainable, beneficial, and time-saving technique.

It is suggested that future investigations compare the FIF technique and the conventional RT in other cancers as well as in various types of TPS systems.

CONCLUSION

The FIF and the wedge-based techniques were dosimetrically and clinically assessed in the present study. Dosimetric results were clearly in favor of the FIF plan. The FIF technique using MLC achieved a more homogenous dose distribution throughout the target volume while it reduced doses to the surrounding healthy tissues. Considering these results and also the significantly less MUs required for therapy, the FIF technique seems to be more advantageous than the conventional technique during WBRT.

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