ORIGINAL ARTICLE

Relationship between the Patients' Setup Errors with Dosimetric and Radiobiologic Parameters in Whole Breast Radiotherapy

Zahra Alijani [1], Kourosh Ebrahimnejad Gorji [2], Ali Shabestani Monfared [3*], Abbas Rahimi Alisaraee [4], Ali Esmaeeli [5], Fatemeh Niksirat [2]

[1] *Student Research Committee, Babol University of Medical Sciences, Babol, Iran*

[2] *Department of Medical Physics Radiobiology and Radiation Protection, School of Medicine, Babol University of Medical Sciences, Babol, Iran*

[3] *Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran*

[4] *Department of Radiotherapy, Guilan University of Medical Sciences, Rasht, Iran*

[5] *Department of Physics, Islamic Azad University, Rasht, Iran*

*Corresponding Author: Ali Shabestani Monfared
Email: monfared1345@gmail.com

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Abstract

Purpose: This study aimed to investigate the effect of the patients' setup errors on dosimetric and radiobiologic parameters for left-sided Whole-Breast Irradiation (WBI) in three different radiotherapy techniques, including Intensity-Modulated Radiation Therapy (IMRT), Field-In-Field (FIF), and Conventional Wedge (CW).

Materials and Methods: Computed Tomography (CT) images of 10 female patients with early-stage left-sided breast cancer were used to simulate different radiotherapy techniques (IMRT, FIF, and CW). The dosimetric parameters; Conformity Index (CI), Homogeneity Index (HI), the dose received by at least 95% ($D_{95\%}$) of Planning Tumor Volume (PTV), the volume of lung and heart that respectively received at least 20% ($V_{20\%}$) and 40% ($V_{40\%}$) of the prescribed dose, as well as, the radiobiologic parameters, including Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) were assessed for setup errors in patients. The setup errors were assessed by shifting the isocenters and gantry angles of the treatment plans.

Results: The $D_{95\%}$ of the PTV for an isocenter misplacement plan in the posterior direction decreased by 66.99 (IMRT), 71.86 (CW), and 68.25% (FIF). The TCP of the PTV was reduced by 26.66, 39.16, and 36.97% for IMRT, CW, and FIF techniques, respectively. Increasing gantry angle by a ±10 degree caused a 43%, 41%, and 41% decrease in the $D_{95\%}$ of IMRT, FIF, and CW techniques, respectively. The TCP values decreased about 18% in all three techniques with a ±10 degree gantry angle shift; however, the NTCP values of the heart and lungs increased for all three methods. The CI and HI values had significantly more changes with increasing setup errors in the IMRT than in the two techniques.

Conclusion: The radiobiologic parameters in IMRT were less sensitive to setup errors compared to FIF and CW techniques. The radiobiological parameters can help estimate the setup errors along with physical parameters during breast radiotherapy.

Keywords: Whole Breast Radiotherapy; Setup Errors; Intensity-Modulated Radiation Therapy; Field-In-Field; Radiobiological Parameters.

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1. Introduction

Breast cancer is one of the most common cancers that cause death worldwide, accounting for approximately 15.2%-30% of all new cancer cases among women [1]. Following breast-conserving surgery, the Whole-Breast Irradiation (WBI) technique is a routine treatment for early-stage breast cancer providing long-term survival [2].

WBI generally performs with conformal three-Dimensional (3D) techniques, including two opposed tangential beams with wedge compensators. The main disadvantage of this technique is the formation of hot regions with doses greater than 110% of the prescribed dose within the breast [3-6]. Field-In-Field (FIF) technique with a more uniform dose distribution can be used instead of conformal techniques [6]. The FIF is a simple form of direct Intensity-Modulated Radiation Therapy (IMRT) that uses multiple fields and subfields to achieve a relatively uniform dose distribution inside the breast [7]. This technique could improve dose homogeneity and reduce hot and cold regions in Planning Target Volume (PTV), especially in WBI, compared to conventional methods [8]. However, with the FIF technique, the organs (such as the heart and lungs) radiation toxicities remain challenging, defining that this technique may not be appropriate for patients with particular anatomical conformations [9]. IMRT generates non-uniform spatial intensity distributions to achieve highly conformal dose distributions and decrease doses to Organs At Risk (OARs) [10, 11]. In addition, this technique can improve dosimetric and clinical outcomes such as lower incidence of acute toxicity, subacute complications, and undesirable inessential changes [12, 13]; consequently, IMRT can be a favored modality for WBI.

In breast radiotherapy, deviations from the planned dose distribution can be related to several reasons, including patient positioning errors, patient rotation, breast positioning errors, and breast deformation [14, 15]. These deviations lead to under or overdosage in tumors and normal tissues, and increasing radiation side effects. Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) are the most common parameters that have been proposed for assessing radiobiological effects [16, 17]. These parameters can be used to analyze and compare the dose distributions obtained from different radiotherapy treatment plans.

In a study by Lee *et al.* [18], the setup errors of WBI were assessed at different radiotherapy techniques, including FIF and Conventional Wedge (CW), in terms of their dosimetric characteristics as well as TCP and NTCP parameters. In another study, Park *et al.* [19] evaluated the difference of actual dose distribution to normal tissues from planned dose distribution according to the extent of setup errors (deep inspiration breath holding or a free-breathing technique) in breast radiotherapy using the FIF technique. Chopra *et al.* [20] assessed the intrafraction breast movement and the effect of respiratory training on respiratory indices in accelerated partial breast radiotherapy (electron boost). The current study aimed to evaluate the changes in dosimetric and radiobiologic parameters (TCP and NTCP) using various techniques, including IMRT, FIF, and CW, due to patients' setup errors in WBI. To the best of our knowledge, although several studies investigated the effects of setup errors in the dose uncertainty of breast radiotherapy using FIF/CW/IMRT techniques, no investigations assessed/compared these three techniques by shifting the isocenters and gantry angles of the treatment plans.

2. Materials and Methods

2.1. Patients

This retrospective study was performed following the relevant ethical guidelines and regulations, and the national ethics committee approved the methods of this study. Ten female patients with a mean age of 54.6 ± 9 years (42-75 years) having early-stage left-sided breast cancer (lumpectomy) undergoing WBI therapy were investigated.

2.2. CT Scan

The patients' images were performed using a Computed Tomography (CT) simulator (Siemens Somatom Plus16; Siemens Healthineers, Munich, Germany) in a standard supine position. All patients were immobilized during CT acquisition, and their arms were elevated above the head. A free-breathing CT scan for each patient was obtained using the spiral acquisition technique (pitch = 1, kVp = 120, and mAs = 250) with a 3-mm slice thickness and 512 × 512 matrix size.

2.3.Treatment Planning

Tangential fields (2-field) were designed with three techniques (CW, FIF, and IMRT) for WBI using RayPlanTM (RaySearch Company, Sweden) treatment planning system. The prescription dose was 50 Gy in 25 fractions. The patients were treated by a 10-MV photon beam from an Elekta Presice® linear accelerator (Elekta Ltd, Crawley, UK). The algorithm used for dose calculations was collapsed cone convolution.

Clinical Target Volumes (CTVs) and the PTVs of the tumor, as well as OARs, including ipsilateral breast, ipsilateral lungs, and heart were delineated following International Commission of Radiation Units (ICRU) reports 50 and 62 [21]. The whole breast was considered as CTV. The CTV with a 5 mm margin except the anterior part was considered as PTV that must cover 97% of the prescription dose. IMRT plans were designed by defining the constraints depicted in Table 1 [22-24].

2.4. Setup Errors

Different isocenter and gantry angle displacements were assumed and performed in treatment planning software to evaluate setup errors. For each plan, the isocenter was shifted 0.5 cm to right-left (x), along with superior-inferior (y), anterior-posterior (z), and anterior-posterior and right direction (xyz) [25]. A sample of the isocenter shift and its effect on the dose distribution to the superior-inferior (y) direction in the IMRT technique is shown in Figure 1. In addition, the gantry angle was moved 2.5°–10° clockwise and counterclockwise with 2.5° steps in each tangential field.

2.5. Dosimetric Parameters

The quality of the treatment plans was analyzed using dosimetric parameters, including the mean dose of PTV, the dose received by at least 95% of PTV volume ($D_{95\%}$), the volume of lung, and heart that respectively received at least 20% ($V_{20\%}$) and 40% ($V_{40\%}$) of the prescribed dose. Furthermore, the Homogeneity Index (HI) and Conformity Index (CI) were calculated for the PTV. Equations 1 [26] and 2 [27] are related to HI and CI indices, respectively.

$$HI = \frac{(D_{2\%} - D_{98\%})}{(prescription\ dose)} \quad (1)$$

Where $D_{98\%}$ and $D_{2\%}$ represent the dose delivered to at least 98% and 2% of the PTV volume, respectively.

$$CI = \frac{V_{RI}}{TV} \quad (2)$$

V_{RI} is the volume received prescribed dose and TV is the target volume.

Table 1. Dosimetric parameters of IMRT technique. D_{max}: Maximum dose, D_{min}: Minimum dose, D_{mean}: Mean dose

D_{max} to PTV	D_{max} to 99.5% of PTV	D_{min} to 2% of PTV	D_{mean} of ipsilateral lung	Dose received by at least 20% of ipsilateral lung	Dose received by 10% of heart	Dose received by 5% of heart	D_{mean} of heart
< 53 Gy	< 48.5 Gy	< 51 Gy	< 20 Gy	<10 Gy	<15 Gy	<25Gy	<4 Gy

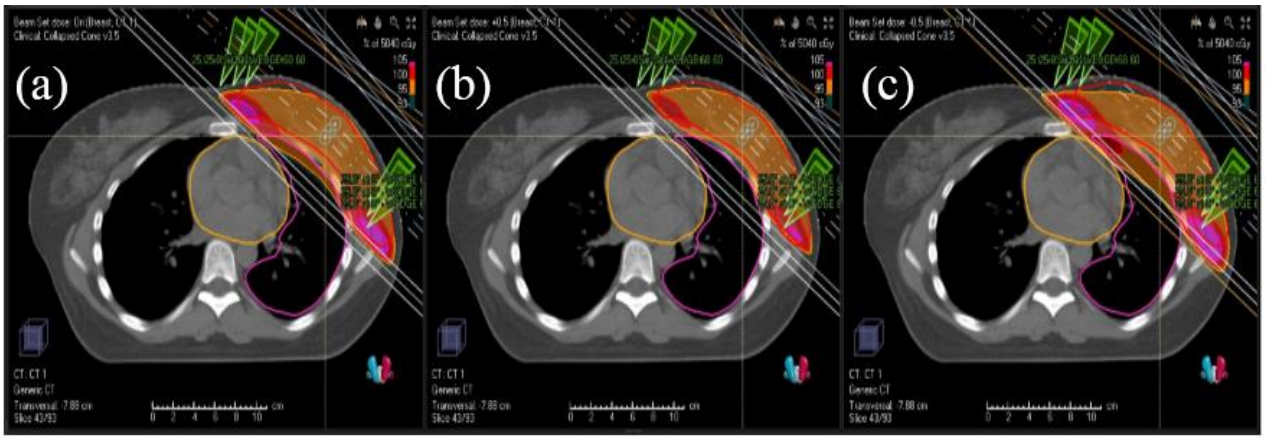

Figure 1. The effect of the isocenter shift to superior-inferior (y) direction in the dose distribution using the IMRT technique. (a) Origin, (b) +0.5 cm, and (c) -0.5 cm

2.6. Radiobiological Evaluation

TCP and NTCP parameters were used for radiobiological evaluations [28-30]. These parameters represent the risk of complications for OARs and tumor control probability which are calculated based on the dose distribution and radiobiologic parameters of the structure. The radiobiologic parameters were obtained from the data reported in previous studies [31-33], which are presented in Table 2.

Table 2. Radiobiologic parameters used for calculating the TCP of left breast cancer and NTCP of lung and heart

Radiobiologic parameters		a	γ_{50}	TCD_{50}	TD_{50}	α/β
Tumor	**Breast**	-7.2	2	45.75	-	10
Organs	**Heart**	3	3	-	50	1.8-2
	Lung	1	2	-	24.5	1.8-2

Standard Equivalent Dose (SED) was calculated based on Equation 3 [34]:

$$SEDi = nd_i \frac{(1+\frac{d_i}{\alpha/\beta})}{(1+\frac{d_f}{\alpha/\beta})} \quad (3)$$

Where n, d_i, and d_f are the total number of a fraction, dose on i-th each voxel per fraction, and reference dose per fraction (2Gy), respectively. The ratio α/β is one of the tissue radiobiologic parameters.

TCP and NTCP were calculated using Equations 4 [35] and 5 [36]:

$$TCP(\{D\}) = \prod_{i=1}^{R}[TCP_i(\{SED_i\})]^{v_i} = \prod_{i=1}^{R}[\frac{1}{1+\left(\frac{TCD_{50}}{SED_i}\right)^{4\gamma_{50}}}]^{v_i},\ \sum_{i=1}^{R} v_i = 1 \quad (4)$$

$$\text{NTCP}(\{D\}) = \prod_{i=1}^{R}[NTCP_i(\{SED_i\})]^{v_i} = 1 - \prod_{i=1}^{R}[1-\frac{1}{1+\left(\frac{TD(v_{eff})_{50}^{i}}{SED_i}\right)^{4\gamma_{50}}}]^{v_i},\ \sum_{i=1}^{R} v_i = 1 \quad (5)$$

In these models, Tumor Control Dose 50% (TCD_{50}) is the dose that results in a tumor control probability of 50%, and TD $(v_{eff})_{50}$ is the tolerance dose of the organ that yields a 50% subsequent complication probability. The parameter γ_{50} describes the normalized gradient of the tumor-response curve at 50%. The above methods were conducted using an in-house code based on the MATLAB software package (v.R2018a, Math Works, Natick, MA).

2.7. Statistical Analysis

All statistical analyses were performed using SPSS software (V18, SPSS Inc., Chicago, USA). Kolmogorov-Smirnov (K-S) test was used to evaluate the parameters data distributions. The comparison of the dosimetric and radiobiologic parameters obtained from various radiotherapy techniques at different setup errors was performed using the Mann-Whitney test and Kruskal-Wallis test. The statistical significance level was assumed to be $P < 0.05$.

3. Results

3.1. Dosimetric Findings

Figure 2a shows the changes in $D_{95\%}$ values (averaged of all 10 patients) due to isocenter misplacement in various directions obtained from the assessed WBI techniques. Differences between the original plans and the plans with isocenter misplacement were significant in all directions in the IMRT technique ($P < 0.001$). Isocenter misplacements also significantly affected $D_{95\%}$ for CW and FIF plans in most directions; however, applying the setup errors in several directions (-x, -y, and -z) had no significant changes. These changes were greater in xyz direction, in a way that, the maximum difference was about 66.99%, 71.86%, and 68.25% for IMRT, CW, and FIF techniques, respectively.

The effectiveness of isocenter misplacement (isocenter error) at different directions on the OARs dosimetric parameters are shown in Figures 2b (for the lung) and c (for the heart). The dosimetric parameters of the lungs and heart were higher in the plans having isocenter misplacement compared to the original plans in all of the techniques (IMRT, CW, and FIF). The maximum changes in lung $V_{20\%}$ values were 79.61%, 14.49%, and 7.61% for IMRT, CW, and FIF techniques, respectively, observed between the original plan and isocenter misplacement in -xyz direction. The effect of this misplacement was greater in dosimetric parameters of IMRT plans compared to FIF and CW techniques.

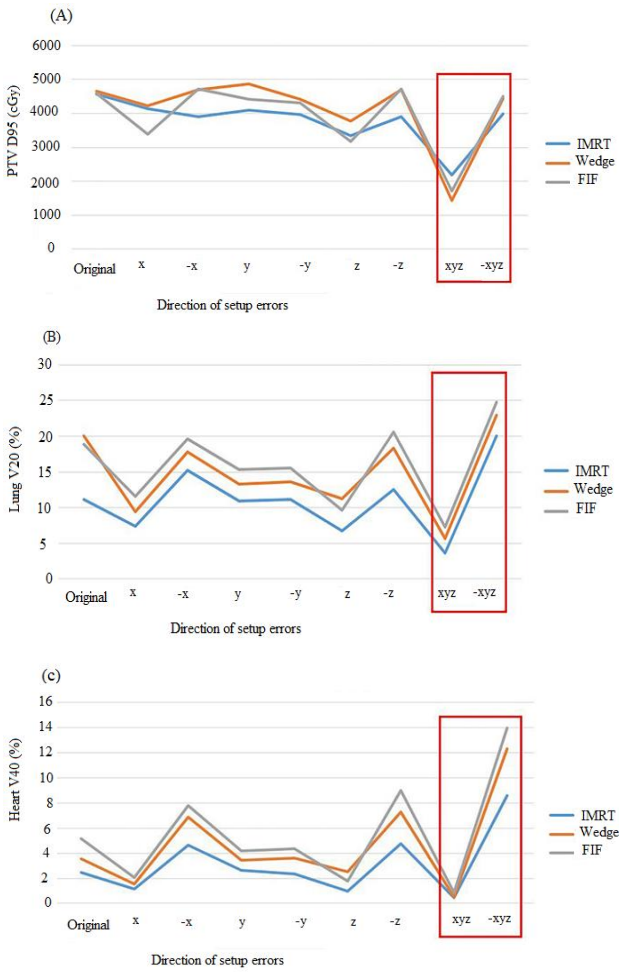

Figure 2. The physical results of the isocenter shifts in various directions: A) $D_{95\%}$ of the PTV, B) V_{20Gy} of ipsilateral lung, and C) $V_{40\ Gy}$ of the heart

Figure 3 shows the effect of gantry angle shifts in two directions on $D_{95\%}$ of the PTV. This figure illustrates that $D_{95\%}$ decreased significantly in all treatment techniques with gantry angle misplacement ($P < 0.001$). The influence of gantry misplacements in ±10 degrees was greater in the IMRT technique (43%) compared to FIF (41%) and CW (41%) techniques. The delivered dose to lungs in the plans with gantry angle misplacements was lower in all directions for the IMRT technique (14.49%); however, the gantry shift toward the -10 degree had a higher effect for FIF (7.96%) and CW (11.95%) (Table 3). Gantry misplacement in a counterclockwise direction showed an increase in the heart dose for all the treatment techniques. The maximum dose increase for the heart was about 59.43%, 93.75%, and 76.46% in IMRT, CW, and FIF techniques, respectively, for the plan with -10 degree gantry misplacement.

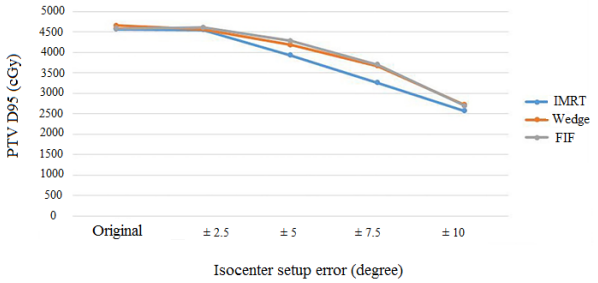

Figure 3. The physical results of the gantry angle shifts on $D_{95\%}$ of the PTV in the two directions for IMRT, field in field and conventional wedge techniques

Table 3. The effect of gantry angle shifts on the normal tissues (heart and lung) dosimetric parameters for IMRT, field in field, and conformal techniques

Technique	Organ		Original	Gantry angle shift							
				Clockwise				Counter-clockwise			
				+2.5	+5	+7.5	+10	-2.5	-5	-7.5	-10
IMRT	Heart $V_{40\%}$	Mean	2.44	2.28	2.13	2.02	2.01	2.67	2.99	3.41	3.89
		SD	0.46	0.38	0.38	0.46	0.42	0.61	0.41	0.78	0.58
	Lung $V_{20\%}$	Mean	11.18	11.08	11.13	11.31	11.74	11.45	11.83	12.27	12.8
		SD	2.56	2.42	2.55	2.55	2.1	1.7	2	2.44	1.78
Field-in-Field	Heart $V_{40\%}$	Mean	5.14	3.79	3.37	3.03	2.77	5.09	6.11	7.37	9.07
		SD	1.23	0.53	0.64	0.48	0.55	0.9	1.34	1.54	2.08
	Lung $V_{20\%}$	Mean	18.84	14.8	14.63	13.46	14.97	15.49	15.64	16.68	17.34
		SD	4.5	3.39	2.91	3.08	2.83	3.39	2.33	2.81	3.79
Conventional wedge	Heart $V_{40\%}$	Mean	3.52	3.2	2.87	2.74	2.67	3.61	4.8	5.63	6.82
		SD	0.66	0.7	0.48	0.49	0.64	0.61	0.81	0.78	1.36
	Lung $V_{20\%}$	Mean	13.39	13.22	13.41	13.71	14.17	13.66	13.92	14.43	14.99
		SD	1.99	2.63	1.86	2.73	2.11	2.17	2.63	2.58	2.08

HI and CI values for all techniques were better significantly for original plans compared to the plans with the gantry and isocenter misplacement. In general, the dosimetric results related to the gantry and isocenter misplacements obtained from the CW, FIF, and IMRT techniques, showed similar trends; however, the changes were greater in the IMRT technique.

3.2. Radiobiological Findings

The results showed that the biological effects depend on the misplacement directions (Table 4). The plan with isocenter misplacement had lower doses of the PTV compared to the original plans, and consequently, TCP values were lower in all the treatment techniques. Maximum differences were observed between the original and the -xyz isocenter misplacement plans which were equal to 26.66%, 39.14%, and 39.04%, respectively, for the IMRT, CW, and FIF plans. Higher organ dose values were related to the plans with isocenter misplacement in -xyz direction, in a way, the NTCP values for the OARs were higher in this direction for all the techniques. Changes in NTCP values regarding the isocenter misplacement were higher in FIF than in IMRT and CW techniques. In addition, TCP values of the plans with gantry angle shifts were lower compared to the original plans. In contrast, the NTCPs and OARs' doses were higher in the gantry shifted plans compared to the original plans.

4. Discussion

Since the hearts are considered sensitive organs, we selected the left breast cases to evaluate the setup error [37, 38]. Based on our results, significant changes occurred in the heart and lung doses due to setup errors. For example, maximum changes in $V_{40\%}$ of the heart for the IMRT technique was about 2% in the original plan, more than 8% in xyz direction. These findings have a good agreement with the other related previous investigations [39, 40].

In the present work, we only reported $D_{95\%}$ values for the PTV, due to the similar trends with the mean dose and $V_{95\%}$ of the PTV, which is also expressed in the previous studies [18, 41, 42]. Our findings demonstrated that the differences in $D_{95\%}$ values between the original and isocenter misplacement plans were higher along the xyz direction because the xyz direction can be affected by lung expansion and diaphragmatic movements [25, 43]. Prabhakar *et al.* [42] investigated the effect of setup error on the PTV and OARs in 12 patients (8 patients with right-sided and 4 left-sided breasts) using the CW radiotherapy technique. To simulate the setup error, the planning isocenter was shifted for 3 and 10 mm in 3 directions (x, y, z). They expressed that the isocentric shifts along the posterior direction significantly affected the dose to the heart, ipsilateral lung, contralateral lung, and contralateral breast, followed by the lateral direction. In addition, in agreement with the previous studies [39, 44, 45], the changes in the CI and HI values were significantly higher for the IMRT plans with isocenter misplacement in all cases.

Changes in radiobiologic parameter values, particularly the NTCP for the heart and lung, were investigated by isocenter and gantry-shifted plans in this study. Owing to the results, the shift of the gantry angle in a counterclockwise direction caused maximum

Table 4. The isocenter and gantry angle shift effects on the TCP and NTCP for IMRT, field in field, and conventional wedge techniques

Technique	Organ	(%)	Original	Isocenter shift				Gantry angle shift			
				+z	-z	+xyz	-xyz	+5	-5	+10	-10
IMRT	PTV	TCP	99.94	96	99.8	73.3	91.1	98.2	99.54	70.41	91.59
	Lung	NTCP	1.21E-06	2.71E-08	2.12E-04	5.03E-10	4.87E-03	3.7E-07	5.54E-06	3.1E-07	4.34E-05
	Heart	NTCP	0.004	0.001	0.211	0.0003	1.24	0.018	0.025	0.023	0.038
Field-in-Field	PTV	TCP	99.8	84.23	99.96	62.9	99.94	99.59	97.9	77.54	85.4
	Lung	NTCP	1.55E-05	4.17E-07	2.68E-03	1.20E-08	4.28E-02	3.66E-06	5.32E-05	2.12E-06	3.28E-04
	Heart	NTCP	0.117	0.03	0.627	0.008	1.7	0.151	0.092	0.271	0.11
Conventional wedge	PTV	TCP	99.96	97.4	99.96	60.82	99.77	94.27	99.87	54.76	89.55
	Lung	NTCP	3.65E-06	4.05E-06	7.89E-04	1.22E-09	2.99E-02	2.36E-06	1.58E-05	3.89E-06	1.00E-04
	Heart	NTCP	0.054	0.039	0.0362	0.003	1.62	0.083	0.049	0.166	0.064

changes in NTCP values. It was found that the changes in the heart dose and the heart NTCP values were greater than the ipsilateral lung in isocenter and gantry misplacement plans. The reason can be related to the small volume of the heart, which is partially positioned in the tangential field boundaries. In our study, the setup uncertainties had more effects on FIF compared to IMRT and CW techniques. Lee *et al.* [18] assessed the impact of the patient setup errors in WBI using two techniques, including CW and FIF. They reported that the biological effects of the isocenter shifts depended on the shift direction. In a way, the isocenter shifts plan with a posterior direction delivered lower doses to the PTV, causing decreased TCP value. On the other hand, isocenter shifts plan with a superior direction resulted in opposite flinging (the NTCP in the normal organs increased and the TCP in the tumor decreased). Notably, the shift direction (gantry angle; clockwise and counterclockwise) did not significantly affect the NTCPs of the normal organs. In addition, they have found that the FIF technique is more sensitive to setup errors compared to CW; however, dosimetric differences in the setup errors obtained from the FIF technique were relatively small.

The OARs' dosimetric and radiobiologic parameters had higher changes due to patients' setup errors in the FIF technique compared to IMRT and CW techniques. In plans with isocenter misplacements at xyz direction, the maximum change in NTCP values was found in CW and FIF for the heart and lung, respectively, which could be associated with the higher irradiations transmitted through these structures [46]. The changes in dosimetric parameters due to isocenter misplacement were lower for the IMRT technique compared to FIF and CW techniques. Generally, IMRT and FIF techniques are more desirable for WBI because of higher dose homogeneity as well as lower chronic and acute toxicities compared to the CW technique [23, 39]. In addition, IMRT treatment delivery time is not much longer than FIF (20 min vs. 15 min); however, its pre-treatment procedures, including organ contouring, inverse planning, and pre-treatment patient quality assurance are more time-consuming [44].

One of the main limitations of the current study is considering patients' motions only in xyz directions; however, patients have rotations along different axes, which could be a subject for further investigation. In addition, Volumetric Modulated Arc Therapy (VMAT), which is one of the main methods for breast treatment, could be selected for future study. Furthermore, more studies with more extensive patient data are required to check our results further.

5. Conclusion

The dosimetric and radiobiologic parameters are sensitive to setup errors in patients for WBI with different radiotherapy techniques. The radiobiologic parameters of the IMRT technique had the highest sensitivity to the patients' setup errors compared to the FIF and CW techniques. Evaluating the TCP and NTCP parameters can be an alternative method for estimating the effect of setup errors for breast radiotherapy.

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