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Radiobiological comparison of 3D conformal and intensity modulated radiation therapy in the treatment of left-sided breast cancer

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ABSTRACT

Background: The current study aimed to compare the tumor control probability (TCP) and normal tissue complication probability (NTCP) of three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) for left-sided breast cancer using radiobiological models. ***Methods:*** This study was conducted on 30 patients with left-sided breast cancer, who were planned for 3D-CRT and 6-9 fields IMRT treatments using the PROWESS treatment planning system. The planning target volume (PTV) dose of 50 Gy was administered for the 3D-CRT and IMRT plans, respectively. The Niemierko's equivalent uniform dose (EUD) model was utilized for the estimation of tumor control probability (TCP) and normal tissue complication probability (NTCP). ***Results:*** According to the results, the mean TCP values for 3D-CRT, 6-fields IMRT, and 9-fields IMRT plans were 99.07 ±0.07, 99.24 ±0.05 and 99.28 ±0.04, respectively, showing no statistically significant difference. The NTCPs of the lung and heart were considerably lower in the IMRT plans, compared to those in the 3D-CRT plans. ***Conclusions:*** From the radiobiological point of view, our results indicated that 3D-CRT produces a lower NTCP for ipsilateral lung. In contrast, for TCP calculations, there was a higher gain with IMRT plans compared to 3D-CRT plans.

Keywords: *Radiobiological evaluation, left-sided breast cancer, three dimensional conformal and intensity-modulated radiation therapy.*

INTRODUCTION

The most adopted radiation therapy treatment in breast cancer patients consists of Intensity Modulation Radiation Therapy (IMRT) and 3D conformal radiation therapy (3D-CRT), which have improved outcomes of treatment [1]. Despite the advanced treatment techniques applied in breast cancer radiotherapy, radiation-induced complications of the heart and toxicities of the respiratory system are relatively common. Radiation pneumonitis and pericarditis are recognized to be two potentially serious side effects of breast cancer radiotherapy, the risk of which may be reduced by the choice of appropriate radiotherapy technique [2, 3]. To deal with these issues, both dosimetric and radiobiological factors may enable us to distinguish between the different plans in radiotherapy. Hence, it is required to consider both radiobiological evaluation tools and dose distribution data to estimate biological modeling and evaluate the efficiency of different RT techniques. Tumor control probability (TCP) and normal tissue complications probability (NTCP) are two useful factors that determine the radiobiological efficiency of RT methods [4, 5]. The goal of radiotherapy in breast cancer is to

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offer a treatment plan that results in the minimum NTCP and maximum TCP [6]. Different biological models have been developed and tentatively used to obtain TCP and NTCP from the 3D dose distribution to find how can gain more effective treatments with lower delayed effect on the patient. For instance, the concept of EUD is applied to measure the biological effectiveness of radiotherapy methods using two equations. The EUD-based mathematical model is derived from a mechanistic formulation using a linear-quadratic cell survival model [7]. It has been proved that the appropriate radiobiological models give a large step to accept or deny a radiotherapy treatment planning [6]. To date, several studies have reported that IMRT results in a preferred dose distribution compared to 3D-CRT for the RT of breast cancer [8, 9]. However, there have been conflicting studies on the performance of IMRT and 3D-CRT, and it is unclear which of these techniques is superior [10, 11]. Moreover, many of these studies only have considered the dosimetry aspect and neglected its radiobiological aspects. Hence, in the current study, we used the EUD radiobiological model for TCP/NTCP calculations to investigate the radiobiological differences between 3D-CRT and IMRT plans for left-sided breast cancer. Moreover, some dosimetric parameters are compared in order to evaluate the delivered doses to OARs and dose homogeneity within the target volume for these techniques.

MATERIALS AND METHODS

Patients

This retrospective study was conducted on 30 patients with left-sided breast cancer without involving supraclavicular and axillary lymph nodes (with the nodal stage of N0) [12]. All patients underwent a computed tomography scan (CT scan) with a thickness of 3 mm using MDCT-64 (Siemens, SENSATION). Patients were positioned supine on a breast board with the left arm up. All CT images were transferred to the Prowess Panther V5.5 treatment planning system.

Contouring

The clinical target volume (CTV) was contoured by a radiation oncologist and according to the recommendation of International Commission on Radiation Units & Measurements (ICRU) report 83. The breast CTV included all breast parenchyma. The planning target volume (PTV) was generated by the addition of a margin of 5 mm in all directions to the CTV but was cropped 5 mm away from the skin. The overlap volume with lung tissues was also removed. The planning organ at risk volume (PRV) contours of all the involved OARs, including contralateral breast, entire heart, contralateral Lung, and ipsilateral lung, were plotted by the radiation oncologist.

Planning

3D-CRT

For each patient, three different plans were created using the two-treatment technique. Beams-eye-view (BEV) was used for selecting the optimal beam parameters. The 3D-CRT plan utilized tangential beams with wedges. The optimal wedge angle was 15. Additional same beams were used in some circumstances to allow for improved dose distribution by incorporating a mix of 6 MV and 15 MV. MLCs were configured to protect OARs. The dose distribution was normalized at the isocenter. The angles of gantry were optimized to decrease the beam divergence along the dorsal beam edge to decline irradiation of normal tissues with a standard hinge angle of 185-190 for the full coverage of PTV.

The goal of the optimization is to obtain a homogeneous dose, between 95 and 107% of the prescribed dose of 50 Gy in the PTV, while keeping the dose of the lungs and heart at the lowest amount.

IMRT

A team comprised of one radiation oncologist and one medical physicist generated the IMRT plans to avoid the variation of IMRT plan quality caused by the operator's experience and skill. Two IMRT plans were made for each patient; 6-field IMRT (IMRT-6F) and 9-field IMRT

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(IMRT-9F), with the same beam orientations, respectively. All beam energies were 6 MV and shaped with MLCs with 41 pairs of leaves. Fixed gantry step-and-shoot IMRT was applied for beam delivery. The isocenter was placed at the geometrical center of the PTV.

Initially, IMRT beams were equally spaced through the 210-sector angle in the axial plane. Owning to the different breast anatomies, various gantry angles were used in patients. Then, based on the radiation therapy oncology group-1005 (RTOG-1005), the volume-dose limits were determined for the target and OARs (table 1) and finally optimized for the best dose distribution by the treatment planning system. The prescription dose was 50 Gy in 25 fractions.

Table 1. Clinical dose-volume constraints for IMRT planning.

Target or OARs	Dose Constraints
PTV	V47.5 Gy ≥ 95%
	V55 Gy ≤ 2%
Ipsilateral Lung	V10 Gy ≤ 30%
	V20 Gy ≤ 20%
	V30 Gy ≤ 10%
Heart	V10 Gy ≤ 20%
	V20 Gy ≤ 15%
	V30 Gy ≤ 20%

Comparison of plans

To evaluate the plans, DVHs were generated for the PTV and all the OARs. Homogeneity index (HI), conformity index (CI), PTV average dose, ipsilateral lung average dose, and V20Gy were used for evaluating the left lung while heart average dose and V30Gy were used for heart. Conformity and homogeneity indexes were calculated according to equations 1 and 2, respectively.

$$CI = \frac{V_{47.5\,Gy}}{V_{PTV}} \quad (1)$$

$$HI = \frac{(D_{2\%} - D_{98\%})}{D_{50\%}} \quad (2)$$

Where; V47.5Gy represents the volume receiving 47.5Gy and D2%, D50%, and D98% denote the doses of 2%, 50%, and 98% volume of the target volume, respectively.

Moreover, the cumulative DVHs of both plans were extracted from the PROWESS treatment planning system. According to the equivalent uniform dose (EUD) model, for a dose of 1.8-2 Gy in each fraction, equivalent dose, TCP, and NTCP were calculated by equations 3-5, [13].

$$EUD = \left(\sum_{i=1}(V_i D_i^a)\right)^{\frac{1}{a}} \quad (3)$$

$$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (4)$$

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (5)$$

where "a" is a unit-less model parameter for each normal structure or tumor of interest, and v_i is a dimensionless value representing the *ith* partial volume receiving dose D_i (in Gy). In addition, TCD_{50} is the tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated, and γ50 is a unit-less model parameter that is specific to the tumor of interest and describes the slope of the dose-response curve. Finally, TD50 is the tolerance dose for a 50% complication rate at a specific time interval when the whole organ of interest is homogeneously irradiated. The radiobiological parameters used for Niemierko's model calculations are summarized in table 2.

Table 2. Biological parameters used to calculate Niemierko's model.

Tissue	a	Y50	TD50 (Gy)	TCD50 (Gy)
Breast	-7.2	2	-	28
Lung	1	2	24.5	-
Heart	3	3	50	-

Statistical analysis

Statistical analyses were performed using SPSS software (version 24.0; SPSS, Chicago, IL). The paired student's t-test was used for assessing the difference between the models. P-values less than 0.05 were considered statistically significant. Also, statistical analysis of the data was performed by calculating means, range, median, and standard deviations. The data were presented as the mean ± SD.

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RESULTS

Figure 1 presents Beam Eye View (BEV), plans, and the corresponding DVHs of 3D-CRT, IMRT-6-fields, and IMRT-9-fields for one representative patient.

Target volume

The results of mean dose, EUD, TCP, CI, and HI parameters for the 3D-CRT, IMRT-6-fields, and IMRT-9-fields plans are listed in Table 3. The average mean dose (Gy) for 3D-CRT, IMRT-6F, and IMRT-9F plans were 50.88±0.47, 51.93±0.36, and 52.14±0.31 for the target volume, respectively, indicating a statistically significant difference. Moreover, the EUD of the target was lower in the 3D-CRT plans compared to those in the IMRT plans (50.22 (0.47) versus 51.50 (0.48) and 51.81 (0.38)), which were significantly different (p-value =0.04). The mean TCP values for 3D-CRT, 6-fields IMRT plans, and 9-fields IMRT plans were 99.07 (0.07), 99.24 (0.05), and 99.28 (0.04), respectively. The HI for 3D-CRT, IMRT-6F, and IMRT-9F plans were 0.21±0.02, 0.17±0.01, and 0.15±0.02, respectively. As can be seen, there are statistically significant differences between these plans. Additionally, the CI for IMRT plans was higher compared with 3D-CRT plans (0.97 (0.01) and 0.96 (0.02) versus 0.93 (0.02)). Generally, by increasing the number of beams (3D-CRT to IMRT-6fields and IMRT-9fields), mean dose, EUD, TCP, and CI are increased as well, but HI is decreased.

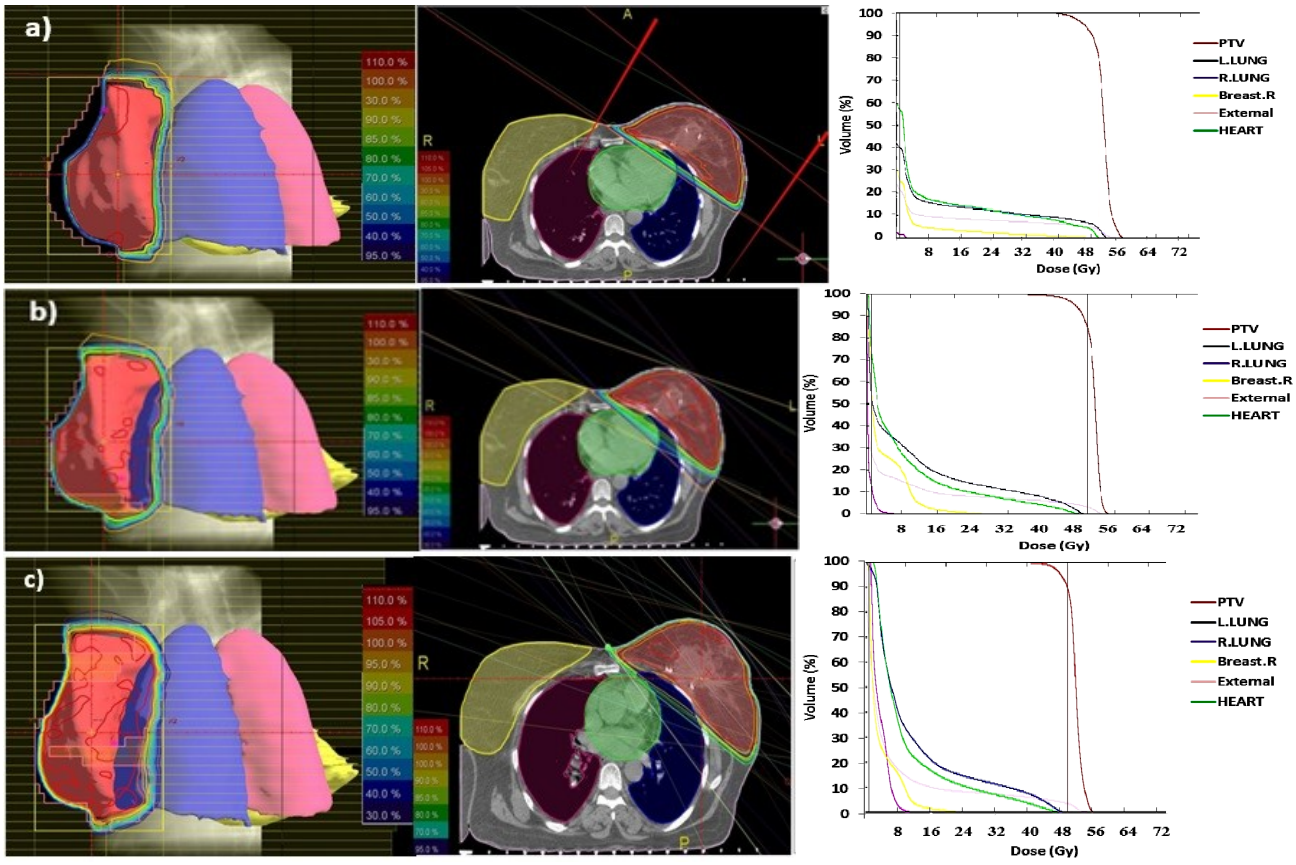

Figure 1. The Beam Eye View (BEV), plans, and the corresponding DVHs of **a)** 3D-CRT, **b)** IMRT-6-fields, and **c)** IMRT-9-fields.

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Table 3. Mean Dose, EUD, TCP, CI, and HI for the target volume in 3D-CRT, MRT-6F, and IMRT-9F.

Parameter	3D-CRT (SD)	IMRT-6F (SD)	IMRT-9F (SD)	p-value
Mean dose (Gy)	50.88 (0.47)	51.93 (0.36)	52.14 (0.31)	< 0.001
EUD (Gy)	50.22 (0.47)	51.50 (0.48)	51.81 (0.38)	0.04
TCP (%)	99.07 (0.07)	99.24 (0.05)	99.28 (0.04)	0.000
CI	0.93 (0.02)	0.96 (0.02)	0.97 (0.01)	< 0.001
HI	0.21 (0.02)	0.17 (0.01)	0.15 (0.02)	< 0.001

Organs at risk (OAR)

The results of Mean Dose, EUD, NTCP, and V20Gy for ipsilateral lung are presented in table 4. The mean dose (Gy) of the ipsilateral lung for IMRT plans were considerably higher than 3D-CRT (p-value <0.001). According to the results, the average mean dose (Gy) for 3D-CRT, IMRT-6-fields, and IMRT-9-fields plans were 6.8 ±1.95, 9.28 ±1.31, and 10.30 ±1.73 for ipsilateral lung and 3.62 ±1.24, 6.36 ±1.50, and 8.35 ±2.05 for heart, respectively (tables 4 and 5). The average EUD values for 3D-CRT and 6-9 fields IMRT plans were 6.75 (1.94), 9.18 (1.37), and 10.26 (1.70), respectively. However, this difference was not statistically significant (p-value = 0.19). Furthermore, the comparison between these techniques showed that the NTCPs of the ipsilateral lung for 3D-CRT, 6-fields -IMRT, and 9-fields-IMRT plans were 0.02±0.01, 0.06±0.04, and 0.15±0.11, respectively. In other words, 2.48 Gy and 3.5 Gy reductions in mean dose result in 67% and 87% lower complications for 3D-CRT plans. There was no significant difference between these methods (p -value = 0.058). According to the results, the average V20 Gy values for 3D-CRT, IMRT-6F, and IMRT-9F plans were 12.69 ±3.88, 16.60 ±2.90, and 17.26 ±3.10, respectively. As can be seen, there is a statistically significant difference between them.

The NTCP and EUD were also calculated for the heart (Table 5). The results indicated that the NTCP of heart was almost zero for all plans. Moreover, for 3D-CRT, IMRT-6F, and IMRT-9F, the average EUD values were 13.51 ±4.25, 14.44 ±3.09, and 14.97 ±2.89, respectively. Generally, the difference between three methods in terms of NTCP and EUD of heart was not statistically significant and meaningful. Additionally, the average values of V30 Gy of the heart for IMRT-9F, IMRT-6F, and 3D-CRT plans were 36.67 (18.21), 35.52 (18.51), and 26.69 (12.96), respectively, indicating a statistically significant difference. As can be seen, despite the considerable amount of dosimetric differences between 3D-CRT and IMRT methods, no significant difference was found in the NTCP for the heart.

Table 4. Mean Dose, EUD, NTCP, and V20Gy for the ipsilateral lung in IMRT-6F and IMRT-9F.

Parameter	3D-CRT (SD)	IMRT-6F (SD)	IMRT-9F (SD)	p-value
Mean dose (Gy)	6.80 (1.95)	9.28 (1.31)	10.30 (1.73)	< 0.001
V20Gy (%)	12.69 (3.88)	16.60 (2.90)	17.26 (3.10)	0.029
EUD (Gy)	6.75 (1.94)	9.18 (1.37)	10.26 (1.70)	0.19
NTCP (%)	0.02 (0.01)	0.06 (0.04)	0.15 (0.11)	0.058

Table 5. Mean Dose, EUD, NTCP, and V30Gy for the heart in IMRT-6F and IMRT-9F.

Parameter	3D-CRT (SD)	IMRT-6F (SD)	IMRT-9F (SD)	p-value
Mean dose (Gy)	3.62 (1.24)	6.36 (1.50)	8.35 (2.05)	< 0.001
V30Gy (%)	26.69 (12.96)	35.52 (18.51)	36.67 (18.21)	0.004
EUD (Gy)	13.51 (4.25)	14.44 (3.09)	14.97 (2.89)	0.125
NTCP (%)	0.00	0.00	0.00	0.805

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DISCUSSION

The use of IMRT to treat the whole breast cancer improves both dose homogeneity and target coverage, as well as to increase the dose to normal tissue compared with 3D-CRT. In the current study, dosimetric and radiobiological comparisons were made between 30 breast cancers of 3D-CRT and IMRT plans. Dosimetric parameters of various techniques using 3D-CRT and IMRT in the left breast cancer were evaluated in a large number of studies [1, 14, 15]. The present study made a further comparison using DVHs, TCP, and NTCP metrics for various RT techniques most commonly applied in breast cancer radiotherapy. From the dosimetric point of view, the IMRT plans were superior to the 3D-CRT in terms of PTV coverage. Based on the results of the present study, using IMRT significantly increases the mean dose in the target ($p<0.001$). In addition, HI and CI were significantly improved in IMRT plans compared with the 3D-CRT plans. In a study by Kim *et al.* [16], IMRT techniques were compared with 3D-CRT. In comparison to 3D-CRT, IMRT revealed a higher dose distribution in D_{mean} and V95% and also better CI and HI. They also suggested that the percentage of volume at high doses of V30Gy and V40Gy on lungs, heart, and liver was approximately 70% lower for IMRT than for 3D-CRT. In another study, Baycan *et al.* [14] showed that IMRT enables better dose homogeneity throughout the target and decrease dose to OARs compared with 3D-CRT in breast cancer radiotherapy following lumpectomy. Some other studies reported improved PTV coverage while significantly protecting the heart can be achieved using more optimal non-uniform beam orientations [17]. However, both IMRT and 3D-CRT provided almost similar results regarding the PTV coverage. In-depth analysis of dosimetric data reveals a significant difference in the quality of the target coverage and normal tissue dose. Pneumonitis and cardiovascular diseases are common side effects following the radiotherapy. NTCP models are important tools for calculating complication risks. Also, the volume of lung receiving 20 Gy (V20) has been found to predict the risk of symptomatic radiation pneumonitis in literature [18]. Hence, it is very important to minimize to reduce ipsilateral lung V20 Gy, and heart V30 Gy and also improve homogeneity and conformity for patients with left-sided breast cancer. Moreover, the clinically acceptable risk of radiation therapy depends on the risk-benefit ratio of individual patient condition. Rastogi *et al.* [18] compared 3D-CRT and IMRT treatment plans for post-mastectomy radiotherapy (PMRT) to the left chest wall. They concluded that 3D-CRT in comparison to IMRT significantly increased the V20 for lung ($p<0.001$). Based on the results of the present study, 3D-CRT plan reduced not only V20 for the ipsilateral lung but also V30 for the heart.

Several studies in the literature have compared the radiotherapy techniques biologically. Lee *et al.* [19], based on a biological model, calculated the secondary cancer risk of different organs after radiation treatment of breast cancer. The results indicated that 3D-CRT is associated with lower secondary radiation dose than IMRT, but dose homogeneity of IMRT was better than those of 3D-CRT. In other words, 3D-CRT resulted in lower radiation-induced cancer risk in breast radiation therapy than IMRT. In the study of Zhang *et al.*, the physically and biologically effective dose (BED) of the heart were compared using different methods [20]. They concluded that IMRT provided a higher target dose coverage and dose uniformity rather than 3D-CRT. Moreover, the dose of heart and cardiac NTCP decreased using IMRT plans. Mavroidis *et al.* [21] showed that PTV coverage was good for both IMRT and CRT techniques for breast cancer; however, sparing of heart and lung was slightly better for IMRT and the probability of complications of heart was reduced. Hurkmans *et al.* [22] reported that the NTCP values were smaller in conformal tangential fields compared to the rectangular fields, while a further reduction to 2.0% could be achieved with the IMRT technique. In the current study, we found that the TCP for 3D-CRT plans was lower than IMRT plans. There was a significant difference in the TCP to target among different RT methods. Although the NTCP difference of OARs was only found in ipsilateral

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lung, the value is the smallest with 3D-CRT. No remarkable difference of NTCP for ipsilateral lung was observed and the NTCP values of the heart were zero for all plans.

The major limitation of this study is the lack of any follow-up data or clinical complications incidence, which should be considered for evaluating the whole treatment aspects. In summary, our calculated NTCP was consistent with published data compared to IMRT and 3D-CRT. Due to uncertainties involved in model parameters, it recommended not considering the absolute values of the calculated NTCP with biological models in the clinical evaluation of the treatment plans. However, these values provide an invaluable tool for comparing the rival treatment plans.

CONCLUSION

This study examined the use of radiobiological models for comparing the 3D-CRT and IMRT plans of breast cancer. From the radiobiological point of view, our data presented higher NTCP for ipsilateral lung for IMRT plans compared to 3D-CRT plan. However, the TCP was lower for 3D-CRT. Also, HI and CI were improved in the IMRT plans compared with 3D-CRT plan.

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