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Original article

Uncomplicated Tumour Control Probability (UTCP) in post-operative radiotherapy of left breast cancer- three dimensional conformal versus Intensity Modulated Radiation Therapy (IMRT)

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Purpose: To compare calculated tumour control probability (TCP) of the target(s) and normal tissue complication probability (NTCP) for Organs At Risk (OAR); lungs, heart, and contralateral breast using 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) in patients with operable left breast cancer. Uncomplicated Tumour Control Probability (UTCP) was accordingly calculated.
Patients and Methods: Sixty female patients with operable left breast cancer either post mastectomy or breast conservative surgery (BCS) underwent 3D-CRT and IMRT planning. Target coverage and target dose distribution as well as doses received by OAR (lungs, heart) were evaluated in both techniques. The TCP for target volumes, the NTCP for late excess cardiac mortality and radiation pneumonitis using Burman model. UTCP for each target was also calculated by subtracting the sum of NTCPs for OAR from TCP of the each target
Conclusion: UTCP was significantly better in the IMRT arm in both left breast & chest wall targets either IMC was included in the target or not .

Key words: intensity-modulated radiation therapy (IMRT), left breast cancer, tumour control probability (TCP), normal tissue complication
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Original article

INTRODUCTION

Over the past five decades, radiotherapy (RT) has become an integral part of the combined modality management of breast cancer. Although its effect on local control has been long demonstrated, only recently adjuvant RT has been shown to have a significant effect on breast cancer mortality and overall survival (OS)[1]. Earlier reports of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed a reduction in breast cancer mortality associated with adjuvant radiation therapy that was offset by increases in non-breast cancer-related mortality. Of note, higher radiation doses were delivered to the heart and lungs in the older studies included in the meta analysis than are delivered with modern techniques, probably resulting in greater toxicity to these critical structures and accounting for at least some of the non–breast cancer mortality offsetting the benefits of radiation therapy[2,3].

In its landmark 2005 publication, which included greater follow-up of patients from earlier trials as well as analysis of data from patients enrolled on trials initiated through 1995, the EBCTCG has now documented a clear overall survival advantage due to the use of post mastectomy RT in node-positive patients. Among 8340 women treated with mastectomy and axillary clearance for node-positive disease and enrolled in trials of PMRT (generally to the chest wall and regional lymph nodes), the five-year local recurrence risk was reduced from 22.8% to 5.8%, with 15-year breast cancer mortality risks of 54.7% vs. 60.1% (reduction 5.4%, P =0.0002) and overall mortality reduction of 4.4% (64.2% vs. 59.8%, P =0.0009)[4].

Currently, breast cancer radiotherapy has gradually shifted towards computed tomography (CT)-guided treatment planning. This enabled the application of new techniques such as three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT)[5,6]. With these techniques, dose escalation to the target volume without significantly increasing the dose received by surrounding normal tissue could be achieved however, an accurate delineation of the target volume is critical because its size and shape directly affects the amount of normal tissue irradiated[7].

The main goal of IMRT in the treatment of breast cancer is the delivery of a much more homogeneous and/or conformal treatment plan to the patient[8]. Typically, dose inhomogeneities are observed with tangents at the entrance and exit points of the beams, in the nipple, and in the superior and inferior portions of the breast. These areas of over dosage can and will produce unnecessary acute and chronic toxicities in many patients[9].

Late cardiac damage following RT appears to result from injury to vascular endothelial cells, leading to tissue necrosis, capillary rupture, and/or micro thrombi[10]. Damage to the microvasculature then leads to myocardial ischemia and fibrosis[11]. As the clinical importance of late excess cardiac mortality becomes better recognized and the cardiac effects of RT have assumed a greater role in treatment plan evaluation. There is strong empirical evidence showing a correlation between cardiac irradiation and late excess cardiac mortality[12]. The most common pulmonary toxicity associated with RT was pneumonitis. Radiation-associated pneumonitis was a complication of loco-regional irradiation for breast carcinoma seen in 1-20% of cases[13,14]. The overall risk of pneumonitis following radiotherapy increased with increasing volume in the tangent fields or with addition of supraclavicular, axillary apex, and internal mammary fields to treat the regional lymph nodes[15].

IMRT allows the possibility to reduce unnecessary heart and lung doses. One of the first clinical benefits for IMRT was in the treatment of concave structures, such as the chest wall, which wraps around the lung and the anterior portion of the heart. With IMRT, it is possible to reduce the volume of the lung irradiated to full doses by tangential fields, and in left-sided cases, the heart can also be partially spared[16]. Hurkmans *et al*., evaluated conformal tangential beam irradiation to the intact left breast with and without intensity modulation, instead of rectangular tangential treatment fields. The authors discovered that the use of conformal tangential fields decreases the Normal Tissue Control Probability (NTCP) for late cardiac toxicity on average by 30% compared to using rectangular tangential fields, while the tangential IMRT technique can further reduces this value by further 50%[17].

Furthermore, primary breast irradiation using tangential IMRT technique significantly reduces the dose to the contralateral breast compared to the conventional tangential techniques and the primary breast size significantly affects the scatter dose to the contralateral breast but not the ipsilateral lung or heart dose[18]. An important caveat of IMRT is that not all patients can receive this therapy option. Many patients are treated well with 3DCRT, and the benefits achieved using IMRT may be minimal or even non existent so, it is essential to select patients who would benefit from such technique[19].

The purpose of the current study is to compare target dose distribution, homogeneity and doses received by OAR (lungs, heart, and contralateral breast) using 3DCRT and IMRT planning in patients with operable left breast cancer. Calculated TCP for target volumes, NTCP for OAR, UTCP for each target and risk of second malignancy in the contralateral breast were also compared.

PATIENTS AND METHODS

Sixty female patients with operable left breast cancer following BCS or mastectomy were recruited in the current study at Kasr El–Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period between December 2008 and July 2010. Eligible patients underwent 3D-CRT and IMRT planning to intact left breast (or chest wall) and regional lymph nodes. Supraclavicular nodes were irradiated if 4 or more involved axillary lymph nodes or inadequate axillary dissection (< 10 nodes). Internal mammary nodes (IMN) were irradiated in medial half tumors > 5cm, more than 10 involved axillary lymph nodes or radiologically involved nodes. The planning process included the following:

A) Target delineation:

CT cuts were taken with the patient in deep breath hold every 5 mm from the chin to upper abdomen to obtain a good quality digital reconstructed radiograph (DRR). LASER was used to define a reference point using radio-opaque marks (preferred to be over xiphoid process) with tattooing of LASER intersection points All cuts were transferred to treatment planning system (XIO). Delineation of the planning target volume (PTV) was carried out according to following:

1. ***a. Left breast (BCS)***: The breast PTV included all visible breast parenchyma as seen on the CT slices extending from the anterior midline to the mid-axillary line, excluding 5 mm from the superficial skin surface to avoid artifact-driven results in the beamlet intensity distributions. The medial and/or lateral margins were reduced if the treatment volume included >2 cm lung or the cardiac apex encroached in the volume (without any influence on dosimetric evaluation). Superior and inferior margins were at the sternoclavicular joint and 1 cm below the inframammary fold (or overlapping breast tissue), respectively. Posterior margins extended to the deep fascia to include pectoralis major muscle and ribcage.

2. ***b. Chest wall (mastectomy)***: The chest wall borders were defined as follows: medially; the mid-sternum, laterally; the mid-axillary line, superiorly; the inferior aspect of the head of the clavicle, and inferiorly; 2 cm below the contralateral inframammary fold. The most superficial 0.5-cm section of the chest wall surface was not included in the target volume because of the known sensitivity of the dose calculation method to limitations in the build up region to avoid artifact-driven results in the beamlet intensity distributions.
3. ***c. Supraclavicular lymph nodes:*** The borders were defined as the region around Supraclavicular vessels extended from spinal process posteriorly to bisect the clavicle along its whole length and the sterno-mastoid muscle in its maximum anterolateral and medial extension respectively. The delineation was from the level of cricothyroid membrane downwards to the level of sterno-clavicular joint.
4. ***d. Internal mammary nodes:*** The IMC PTV was defined by an elliptical cylinder, with a major (lateral) and minor (anterior-posterior) axes of 30 and 20 mm, respectively, centered on the IMC vessels. It was delineated only in the first three intercostals spaces.
5. ***e. Organs at risk:*** Heart, lungs, contralateral breast and spinal cord were delineated according to their C.T anatomy.

B) 3D-CRT planning:

The isocenter was positioned in the middle of the PTV. The partially wide tangential field (PWTF) plans were performed using standard forward planning

methods, the gantry angle was optimized in the beam's eye view (BEV) for a minimum lung area and beam divergence toward the lung was compensated by adjusting the gantry angle of the beams. The ipsilateral lung was spared using a multileaf collimator (MLC). The shape of the MLC was defined in the BEV with a distance of 10 mm to the PTV to compensate the penumbra in craniocaudal direction and toward the lung (Figure 1).

C) IMRT planning:

Seven coplaner equi-angular beams were used, Figure (2). The treatment planning system generated the beam intensity profiles with a bixel (or beam element) size of 5x5 mm^2, using step and shoot IMRT. Dose calculation was via pencil-beam method. Cost functions were selected and determined to satisfy the

plan goals regarding the target coverage and risk organs protection. All beam weights and intensity profiles were optimized using Helios inverse planning IMRT module. Optimization was performed by means of a steepest gradient search algorithm, then the segmentation process accomplished according to leaf motion calculator (LMC) algorithm. Dose constraints to PTV & organs at risk were estimated numerically. Online modifications could be attempted during optimization process to be able to get the best calculated fluence map and dose distribution. Then the segmentation process started to build the actual fluence for each beam according to leaf constrains of the treatment machine and the process accomplished via LMC algorithm. All plans were calculated at the XIO version 4.2 planning system (Figure 2).

D) Dose prescription:

All plans used 6 MV photons and the 100% isodose surface was prescribed to receive a total dose of 50Gy in 25 equal daily fractions for 5 weeks (2Gy/day). Aboost of 12Gy over 6 fractions to the tumor bed of intact breast was delivered.

E) Planning evaluation:

Dose–volume histograms (DVHs) were generated for all relevant structures in both techniques and PTV dose coverage and homogeneity were compared.

Physical parameters for PTV dose coverage and homogeneity and OAR radiation doses included:

1. Homogeneity of dose distribution inside the target volume(s) were considered acceptable if the PTV received a dose between 95% and 107% of the prescribed dose according to the ICRU 62 report.
2. Thevolumeofthelungthatreceivedatleast20Gy(V20 Gy) was not allowed to exceed 31 % as grade II pnemonitis can be kept at maximum of 8%.
3. The volume of the heart that received at least 40Gy (V40Gy) was not allowed to exceed 30%.
4. The NTCP for late pulmonary and cardiac toxicities were calculated according to Burman model incorporated in the planning computer system "XIO"[20].
5. The TCP model assumes an average α-value of 0.3Gy-1, a normal distributed population of α-values with standard deviation (SD) of 0.13 Gy-1, and α/β-ratio of 10 Gy and a clonogen density of 10^2 cm^{-3} [21,22].
6. UTCP for each target was also calculated by subtracting the sum of NTCPs for OAR from TCP of each target

Statistical analysis:

Data were statistically described in terms of range, mean, standard deviation, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using T.Test for paired samples. A probability value (*P* value) less

than 0.05 was considered statistically significant. All statistical calculations were done using computer package SPSS version 16 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

The current study was conducted at Kasr El–Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) and included 60 female patients with left breast cancer (30 patients post mastectomy and 30 patients post BCS). All patients underwent 3D-CRT and IMRT planning. IMC were included in the planning of 30 patients of the whole group.

(I) Coverage of the PTV and Homogeneity:

- Left breast PTV: In the 30 patients with BCS,V45Gy& D90% were all significantly better in the3D-CRT
- group while TCP showed no statistical significance between both groups as shown in Table (1).
- Chest wall PTV: In the 30 patients with mastectomy, V45Gy was significantly better in the3D-CRT group. TCP was as shown significantly better in the IMRT in Table (2).
- IMC PTV: In the 30 patients with IMC, only V45Gy & TCP were better in the IMRT than in 3D-CRT technique with a statistically significant difference. D90% difference did not reach statistical significance as shown in Table (3).

(II) Doses to Risk Organs:

1. ***Left lung:*** The parameters used to evaluate the radiation doses to the left lung were all significantly lower in IMRT than in 3D-CRT technique. These significant differences in radiation doses to left lung were maintained whether IMC was included or not in the planning volume as shown in Table (4, 5) & Figure (3).
2. ***Heart:*** The parameters used to evaluate the radiation doses to the heart (V40Gy, Dmean and NTCP) were better in IMRT than in 3D-CRT technique with a statistically significant differences (*P*.value <0.05). These significant differences in radiation doses to the heart were also maintained whether IMC was included or not in the planning as shown in Table (6, 7).

III) Uncomplicated Tumour Control Probability (UTCP):

UTCP was significantly better in the IMRT arm in both left breast & chest wall targets either IMC was included in the target or not as shown in Table (8)

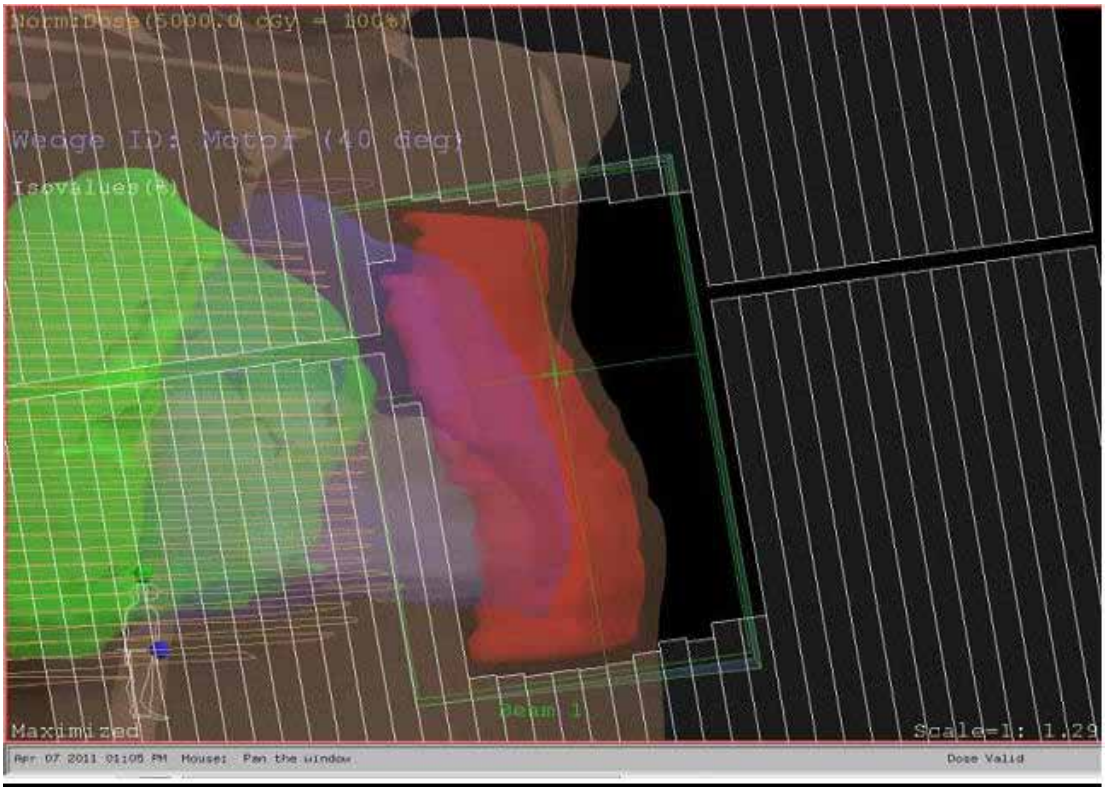

Figure1: 3D-CRT planning with two PWTF (BEV).

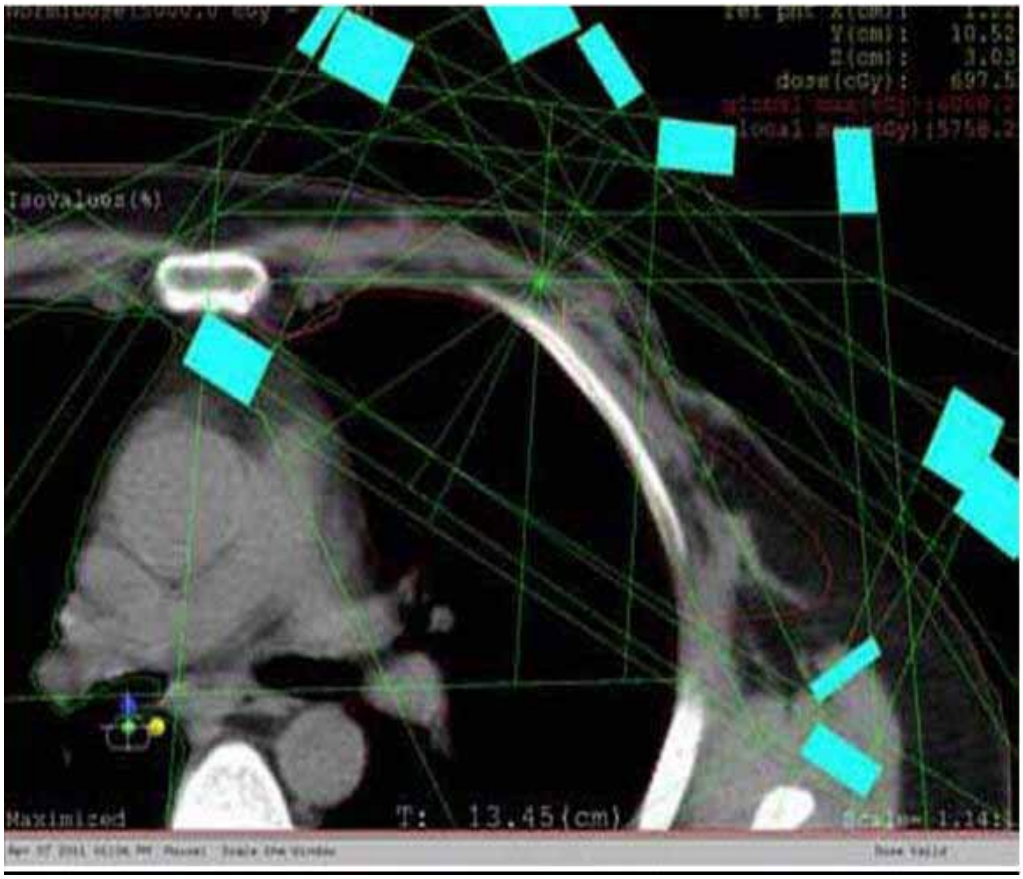

Figure 2: IMRT (Seven coplaner equi-angular beams).

a) CRT b) IMRT

Figure 3: dose distribution (colour wash).

Table 1: Target coverage of the breast PTV.

Parameter	3D-CRT (mean ± S.D)	IMRT (mean ± S.D)	*P.*Value
V45Gy	98.80 ± 7.89%	98.40 ± 6.67%	0.014
D90%	4780.83 ± 119.03 cGy	4883.73 ± 166.08 cGy	0.001
TCP	65.90 ± 7.10%	64.23 ± 4.80%	0.096

Table 2: Target coverage of the chest wall PTV.

Parameter	3D-CRT (mean ± S.D)	IMRT (mean ± S.D)	*P.*Value
V45Gy	98.96 ± 0.70%	98.43 ± 0.94%	0.002
D90%	4780.87 ± 85.68 cGy	4802.63 ± 127.37 cGy	0.398
TCP	68.34 ± 4.74%	66.24 ± 4.89%	0.006

Table 3: Target coverage of the IMC PTV.

Parameter	3D-CRT (mean ± S.D)	IMRT (mean ± S.D)	*P*-Value
V45Gy	95.97 ± 2.96%	97.73 ± 1.45%	0.001
D90%	4678.87 ± 209.65 cGy	4735.48 ± 114.29 cGy	0.059
TCP	67.83 ± 5.10%	71.23 ± 4.36%	0.0001

Table 4: Evaluation of left lung radiation doses (IMC included).

Parameter	3D-CRT (30 plans) (mean ± S.D)	IMRT (30 plans) (mean ± S.D)	*P.*Value
V20 Gy	28.67 ± 5.53%	17.21 ± 2.46%	0.001
V30 Gy	23.83 ± 5.80%	10.27 ± 2.01%	0.001
NTCP	3.710 ± 2.89%	0.96 ± 0.39%	0.001

Table 5: Evaluation of left lung radiation doses (IMC excluded).

Parameter	3D-CRT (30 plans) (mean ± S.D)	IMRT (30 plans) (mean ± S.D)	*P.*Value
V20 Gy	24.41 ±5.55%	16.24 ± 1.94%	0.001
V30 Gy	20.45 ± 5.99%	8.93 ± 1.45%	0.001
NTCP	2.610 ± 2.56%	0.712 ± 0.33%	0.001

Table 6: Evaluation of heart radiation doses (IMC included).

Parameter	3D-CRT (30 plans) (mean ± S.D)	IMRT (30 plans) (mean ± S.D)	*P*-Value
V40 Gy	9.68 ± 4.54%	0.86 ± 0.34%	0.001
Dmean	967.34 ± 277.94 cGy	1483.35 ± 302.94 cGy	0.001
NTCP	2.62 ± 1.05%	0.84 ± 0.27%	0.001

Table 7: Evaluation of heart radiation doses (IMC excluded).

Parameter	3D-CRT (30 plans) (mean ± S.D)	IMRT (30 plans) (mean ± S.D)	*P.*Value
V40 Gy	7.40 ± 5.28%	0.38 ± 0.79%	0.001
Dmean	721.28 ± 289.30 cGy	1336.90 ± 224.95 cGy	0.001
NTCP	1.83 ± 0.93%	0.57 ± 0.21%	0.001

Table 8: Uncomplicated Tumour Control Probability for left breast & chest wall (IMC included or not).

Target	%UTCP -3D-CRT (30plans) (mean ± S.D)	%UTCP –IMRT (30 plans) (mean ± S.D)	*P*-value
Left breast + IMC	59.57 ± 3.16	62.43 ± 4.14	0.001
Left breast (no IMC)	61.47 ± 3.61	62.948 ± 4.26	0.001
Chest wall + IMC	62.01 ± 0.8	64.24 ± 4.23	0.001
Chest wall (no IMC)	63.91 ± 1.25	64.958 ± 4.35	0.001

DISCUSSION

Comprehensive radiotherapy treatment of the breast cancer often involves treatment to the breast or chest wall and supraclavicular, infraclavicular, and internal mammary nodes, which increases the complexity of treatment planning owing to the convoluted target volume and the proximity of the heart and mediastinum[23,24]. IMRT has the potential to improve target volume coverage and to reduce inhomogeneities. Perhaps more importantly, IMRT also has the potential to significantly reduce doses delivered to the heart and lung and therefore promises to minimize the risk of complications from treatment[8]. This study was designed to compare the degree of target coverage and target dose distribution, comformality, normal tissue avoidance and doses received by OAR using 3DCRT and IMRT planning in patients with operable left breast cancer.

In the breast and chest wall PTV, D90% was better in the IMRT technique, implying better target dose coverage compared to the 3D-CRT technique. This result was more consistent with what was reported by Krueger *et al*., who attempted to develop an IMRT technique for post mastectomy RT that improved target coverage while sparing all appropriate normal tissues using an in-house optimization system. Priority was given to matching the heart doses achieved with partially wide tangent fields (PWTFs) while maintaining 50 Gy ± 5% to the chest wall, internal mammary, and supraclavicular nodes. Other normal tissue doses were then minimized. The results revealed that IMRT resulted in more uniform chest wall coverage than PWTFs. The average chest wall minimal dose was 43.7 ± 1.1 Gy for IMRT and 31.2 ± 16.5 Gy for PWTFs ($P = 0.04$)[25].

TCP is helpful in comparing the relative target coverage between different plans as it is a function of the volume and the magnitude of target underdosage. TCP values in the current revealed no difference between 3D-CRT and IMRT techniques (64.9% vs 63.7%). Cho *et al*., showed that the TCP for the IMRT was higher (73.7%) than the 3D- CRT (70.4%), but this was on the expense of increased NTCP of the heart[12].

The current study also revealed that target dose coverage and dose homogeneity in IMC PTV were significantly better in IMRT than 3D-CRT except for the HI in which the difference did not reach the statistical significance. Furthermore, there was a significant difference in TCP between the 3D-CRT (67.8 %) and IMRT (71.2%) techniques. In the study conducted by Cho, *et al*., it was found that the IMRT technique had the best IMC coverage compared with 3D-conformal technique (86.8% vs 56.2%) and wide split tangent (3D-conformal) technique had a notable amount of overdosage in the IMC.

The parameters used to evaluate left lung radiation doses in the current study were significantly lower in IMRT than 3D-conformal technique. These significant differences were maintained whether IMC was included or not in the planning volume. Moreover, the NTCP for late radiation pneumonitis in 3D-CRT and IMRT techniques were 3.69% and 0.92%, respectively. In the subgroup of patients without IMC irradiated, the NTCP was 2.61% in 3D-CRT and 0.71% in IMRT technique. Similar results were also demonstrated by Krueger *et al*., with decreased left lung doses in IMRT compared to 3D-CRT technique though IMRT technique was quite different from our technique. They used 9 coplanar beams distributed around the chest wall to reduce the exit of the beams through the left lung and thereby reducing the mean dose but at the same time increasing the volume of normal tissue receiving low doses of radiation[26]. Fogliata *et al*., suggested that for the ipsilateral lung a mean dose lower than 15 Gy and/or a volume receiving more than 20 Gy lower than 22% were accepted for IMRT breast irradiation planning[27]. This was more or less consistent with the results obtained in our study (mean dose = 14.36.00 ± 1.93.29 Gy and V20 Gy = 17.210 ± 2.46% if IMC was included).

Similarly, the parameters used to evaluate the radiation doses to the heart were significantly lower in the IMRT technique. The benefit of IMRT technique was kept valid whether IMC irradiation was given or not. The NTCP for late cardiac toxicity was kept below 1% (< 0.75% with IMC and < 0.57% without IMC

irradiation). Remouchamps *et al.*, showed that the mean volume of heart receiving > 30 Gy (heart V30) was lower with the IMRT technique than with the deep tangent wedged technique (6.8% and 19.1%, respectively; $P < 0.004$). The introduction of moderate deep inspiration breath-holds to the deep tangent IMRT technique reduced the heart V30 by 81% to a mean of 3.1% ($P < 0.0004$)[28]. Our results were even better as the heart volume which received more than 30 Gy and was 5.8% with IMC, and 3.2% without IMC).

Olivotto and colleagues conducted a study to determine if multi-field, inverse-planned, IMRT improves conformity and reduces dose to the heart and lung without an excessive increase in healthy tissue dose when treating women with left-sided breast cancer with IMC in the target volume. DVHs were derived for IMRT and best standard plans (modified-wide tangents or direct internal mammary techniques). Conformity index, Homogeneity index and doses to normal tissues were compared. IMRT vs. standard plans (STD) improved mean values of CI (0.892 vs. 0.559), HI (0.97 vs. 0.73), V30-heart (0.45% vs. 6.59%) and V20-left lung (12.8% vs. 20.6%); P=0.001. Mean Healthy Tissue (whole body minus PTV) dose was 5.3Gy vs. 5.2Gy for IMRT vs. STD plans, (P_0.46). The maximum heart depth in the best standard plan can be used to select patients likely to benefit from conformal IMRT. By establishing a goal for heart dose improvement it is possible to calculate the proportion of patients with left-sided breast cancer who will require IMRT[29].

In spite of having non-significant results regarding TCP of the left breast and even better TCP for the chest wall in the CRT group, which may be owned to the little better homogeneity in IMRT specially this effect was more pronounced in the smaller volume (chest wall), UTCP showed better results in all cases due to the much better sparing of OAR.

CONCLUSION

IMRT planning improves target coverage and decreases irradiation of the OAR. UTCP was significantly better in the IMRT arm in both left breast & chest wall targets either IMC was included in the target or not .

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