

## Intensity Modulated Radiotherapy (IMRT) Versus 3D Conformal Radiotherapy (3dcrt) In Early Stage Breast Cancer

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**Abstract: Background:** Breast cancer is the most common female cancer in the US and the second most common cause of cancer death in women. Approximately 268,670 new cases of invasive breast cancer and an estimated death toll of 41,400 women in 2018. Management of invasive breast cancer should be based on the clinical extent and pathologic characteristics of the tumor, in addition to the age of the patient, menopausal status, some biologic prognostic factors, and the preference and psychological profile of the individual patient, optimally in a multidisciplinary setting. Surgical, medical, and radiation oncology remain the primary therapeutic disciplines in the management of breast cancer. **Objective:** The aim of our work was to compare two radiotherapy techniques in breast cancer female patients underwent BCS. The first was 3DCRT and second was IMRT. **Subjective:** The study included 50 randomly selected patients with early stage left breast cancer who underwent BCS were planned and calculated with 6 MV photon beam on treatment planning system. CT studies of selected patients transferred to the treatment planning system. **Results:** the dose homogeneity within PTV was significantly better with IMRT than with 3DCRT plans. It achieved significant lung sparing compared to 3DCRT plans. It achieved significant heart and LAD sparing compared to 3DCRT plans. As regard to contralateral breast mean dose in 3DCRT plans, it showed a significant reduction of CB dose compared to IMRT plans. As regard to contralateral lung mean dose in 3DCRT plans, it showed a significant reduction of contralateral lung dose compared to IMRT plans. As regard to early skin toxicity in IMRT plans, it showed a significant reduction in skin toxicity with better cosmesis compared to 3DCRT plans. As regard to DFS and OS showed no statistically significant difference in IMRT plan compared to 3DCRT plans.

[Aliaa Mohamed Gamal Elden Mohamed, Rasha Abd Elghany Khedr, Hanan Shawky Mahmoud, Yasser Mostafa Al-Kerm and Ashraf Fathy Barakat. **Intensity Modulated Radiotherapy (IMRT) Versus 3D Conformal Radiotherapy (3dcrt) In Early Stage Breast Cancer.** *Cancer Biology* 2019;9(3):78-91]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 10. doi:[10.7537/marscbj090319.10](https://doi.org/10.7537/marscbj090319.10).

**Keywords:** Intensity Modulated Radiotherapy (IMRT); Versus 3D Conformal Radiotherapy (3dcrt); Early Stage Breast Cancer

### 1. Introduction:

Breast cancer is the most common female cancer in the US and the second most common cause of cancer death in women. Approximately 268,670 new cases of invasive breast cancer and an estimated death toll of 41,400 women in 2018 (Siegel et al., 2018).

In Egypt breast is the commonest site of cancer in women accounting about (32.0%) of cancer among women, age-standardized incidence rate per 100,000 was 48.8. By 2050, a 3-fold increase in incident cancer relative to 2013 was estimated, based upon data of incidence rates of cancer in Egypt in 2008-2011 Egypt National Cancer registry Program (NCRP2014) (Ibrahim et al., 2014).

In a population based cancer registries in Gharbyia, Egypt, breast cancer was the most frequent cancer among Egyptian females. Breast cancer represented 17.5% of all incident cancer, accounting for 35.7% of all newly diagnosed female cancers. The crude incidence rate for females was 33.1/100,000 female population (Ibrahim et al., 2007).

Radiotherapy plays an important role in the treatment of early-stage breast cancer, following breast conservative surgery that is due to decrease the risk of locoregional recurrence (Wang, 2013). This report updates previous analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of individual patient data from the randomized trials of radiotherapy after breast-conserving surgery (EBCTCG, 2011).

Although the beneficial effect of postoperative radiotherapy for breast cancer is well documented, some serious treatment-related morbidity of post lumpectomy RT are recorded (Ragaz and Ariel, 2012).

One of this serious morbidity is the increased risk of cardiac disease because of inclusion of part of the heart in the irradiated volume. Irradiation of the heart is associated with an elevated risk of long-term cardiac mortality. The pathophysiology and clinical manifestations of radiation-induced heart disease, including accelerated coronary disease, a common site

of atherosclerosis causing myocardial infarction (**Leung et al., 2016; Ring and Parton, 2016**).

Radiation pneumonitis following radiation therapy for breast cancer is one of late complications, and that it is more likely to occur in patients treated with 3-field conventional technique (**Heide et al., 2010**).

The risk of Lymphoedema, brachial plexopathy, impaired shoulder mobility, contralateral breast cancer and second non breast malignancies and the effect of radiotherapy on cosmetic outcome of breast is particularly high with conventional techniques (**Veronesi et al, 2017; Liyi et al., 2018**).

Three-dimensional conformal external beam radiotherapy requires virtual simulation and combines multiple RT fields to deliver a specific dose of radiotherapy to the tumor bed region while sparing the majority of normal surrounding tissue and solid organs and reduce some of the above mentioned side effects of radiotherapy (**Berrang et al., 2011**).

Intensity modulated radiotherapy (IMRT) uses a linear accelerator to deliver focused small beams of radiation that follow the exact contours of a tumor or target volume. Higher radiation doses can be used because of its better sparing to surrounding tissue, possibly resulting in more effective treatment. Computer imaging is used to evaluate the tumor throughout the course of treatment, permitting the most precise dose and treatment changes based on the changing tumor characteristics (**Plataniotis, 2010; Smith et al., 2010**).

#### **Aim of the Work:**

The aim of this study is to compare the dosimetric distribution of three dimensional conformal radiation therapy (3D-CRT) and Intensity modulated radiation therapy (IMRT) for early stage breast cancer patients who underwent breast conservative surgery regarding toxicity and doses delivered to target volume and organs at risk.

#### **Patients and Methods:**

This is a prospective study including 50 female patients with early left breast cancer from Clinical Oncology and Nuclear Medicine Departments, faculty of medicine, Tanta University and Alexandria University from June 2015 to June 2017. This study compared two groups of patients.

**Group I:** included 25 patients received their adjuvant radiotherapy using IMRT technique.

**Group II:** included 25 patients who received adjuvant radiotherapy using 3D-CRT technique.

Patients were followed during and after radiotherapy.

#### **Inclusion criteria**

1. Age  $\geq$  18 years.
2. Female patients.

3. Left sided breast cancer.
4. Pathologically confirmed breast cancer with negative surgical margin.
5. Appropriate stage for protocol entry: pathological stage pT1 or pT2, pN0 or pN1 without distant metastases M0. According to AJCC-TNM 2010 version.
6. Performance status  $\leq$  1 score according to (ECOG) "European cooperative oncology group".
7. Patient underwent breast conservative surgery.
8. Patient must provide study specific informed consent prior to study entry.

#### **Exclusion criteria**

1. Male patients.
2. Right sided breast cancer.
3. Pathologically confirmed positive surgical margin after breast conservative surgery.
4. Patients underwent modified radical mastectomy.
5. Patients had previous radiotherapy to chest wall or breast.
6. Patients have contraindication to radiotherapy such as pregnancy, active systemic lupus erythematosus and other connective tissue diseases.
7. Non-epithelial breast malignancies such as sarcoma or lymphoma.
8. Sever and active co-morbidity and uncontrolled medical.

#### Pre-radiotherapy work up

All patients were subjected to the following work up after treated with (BCS):

#### **Radiotherapy technique**

#### **Treatment planning procedures**

##### **I. Immobilization and simulation:**

Computed Tomography (CT) studies of 50 randomly selected patients with early stage left breast cancer who underwent breast conservative surgery were planned and calculated on treatment planning system.

All cuts were then transferred to the treatment planning system.

##### **II. Delineation of target volumes and OARs:**

The target volumes including clinical target volume (CTV) and planning target volume (PTV) were defined and outlined according to RTOG breast cancer atlas for radiation therapy planning. OARs including both lungs, heart, lateral anterior descending artery (LAD), contralateral breast (CB), spinal cord and thyroid gland were also outlined.

##### **1. Outer body contour**

Outer body contour was delineated using auto-contouring tool.

##### **2. Breast target volumes**

##### **Breast clinical target volume (CTV):**

Consists of and takes into account the clinical borders placed at the time of CT simulation, the apparent glandular and fatty breast tissue visualized by CT, consensus definitions of anatomical borders from the RTOG breast cancer atlas, and included the lumpectomy CTV. The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly the pectoralis muscles and serratus anterior muscles were excluded from breast CTV.

#### **Breast planning target volume (PTV):**

Consists of the breast CTV generated above plus a 4-5mm 3D expansion (excluding heart and not to cross midline). This is the structure used for beam aperture generation.

#### **3-Supraclavicular lymph nodes**

This region was defined as the region around the supraclavicular vessels extending from the spinal process posteriorly to bisect the clavicle along its whole length antero-laterally & the sternomastoid muscle medially.

#### **4-Lumpectomy target volumes:**

##### **Lumpectomy:**

Represented the surgical cavity from the breast conserving surgery. Contouring used all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips. Patients without a clearly identifiable excision cavity were not eligible for protocol participation.

##### **Lumpectomy clinical target volume (CTV):**

The lumpectomy CTV consisted of the contoured lumpectomy plus a 1cm 3D.

##### **Lumpectomy planning target volume (PTV):**

The boost planning target volume (B-PTV) was accordingly generated by adding a further margin of 5mm to the previously defined CTV (Patel et al., 2014).

#### **International commission on radiation Units & Measurements**

##### **(ICRU) 50:**

“Prescribing, recording, and reporting Photon Beam Therapy”

#### **5. Contouring of organs at risk:**

The aim was to define the following risk organs to the planning system on all CT cuts as follow:

**1. Heart:** defined as all visible myocardium (excluding pericardium) from the apex to the right atrium. The pulmonary trunk, root of ascending aorta & superior vena cava were excluded. This was contoured on all cases.

**2. Lateral anterior descending artery (LAD):** Defined from where they branched at the left or right main coronary artery to the caudal edge of the endocardial surface of the left ventricle.

**3. Ipsilateral and contralateral Lung:** this might be contoured with auto segmentation with

manual verification.

**4. Spinal cord:** the spinal canal is delineated as the true spinal cord, not the spinal canal.

**5. Contralateral breast:** Included contralateral breast as defined by clinical markers and the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas.

In general the borders were:

- Posterior border: At the anterior surface of the pectoralis, serratus anterior muscles excluding chest wall, ribs, bony thorax and lung/heart.

- Medial border: The sternal - costal junction.

- Lateral border: Varies based on the size of the breast but typically was at the mid - axillary line and excluded the ipsilateral latissimusdorsi muscle.

- Cranial border: Similar to that of the ipsilateral breast CTV.

- Caudal border: inframamary fold and similar to that of the ipsilateral breast CTV.

- Anterior border: Skin minus 5 mm to minimize inaccuracy dose calculation at the skin surface.

**6. Thyroid gland:** delineated manually according to its C.T anatomy, the left and right lobes of the thyroid. All thyroid tissue should be contoured.

### **III. Planning**

#### **Group I IMRT technique**

Plans were created using step-and-shoot IMRT technique.

#### **IV. Plan acceptance**

3DCRT and IMRT plans for all 50 patients were compared using dose distribution, DVHs for PTV, lung, heart, CB and the maximum body dose. PTV dose coverage, was assessed using dose to 95% of the volume ( $D_{95\%}$ ) and the maximum point dose of the PTV ( $D_{max\%}$ ) according to (Sonali et al., 2014).

Dose homogeneity was assessed using homogeneity index HI (calculated as max dose /min dose).

#### **Breast PTV evaluation**

- Per protocol: At least 95% of the breast PTV evaluation received at least 95% (47.5Gy) of the whole breast prescribed dose of 50Gy.

- Per protocol: No more than 30% of the breast PTV evaluation exceeded 100% of the boost prescribed dose of 60 Gy.

- Dose homogeneity index (HI) and conformity index (CI) were calculated according to definition proposed by the International Commission on Radiation Units and Measurements (ICRU) Report 83. HI was defined as the difference between the near-maximum and near-minimum dose normalized to the median dose.

$HI = \frac{D2-D98}{Dp}$  where D2 and D98 are the dose received by 2% and 98% volume of PTV; and Dp is the prescribed dose. CI was defined as the ratio of volume of tissue receiving at least 95% of the prescribed dose divided by the volume of the PTV. The closer the CI to one, the more conformal is the plan.

#### **Lumpectomy PTV evaluation:**

- Per protocol: At least 95% of the lumpectomy PTV evaluation received at least 95% (at least 57Gy) of the boost prescribed dose of 60 Gy.
- Variation Accepted: At least 90% of the lumpectomy PTV evaluation received at least 90% (54Gy) of the boost prescribed dose of 60 Gy.
- Per protocol: No more than 5% of the lumpectomy PTV evaluation exceeded 110% (66 Gy) of the boost prescribed dose of 60 Gy. Variation Accepted: no more than 10% of the lumpectomy PTV. Evaluation exceeded 110% (will not exceed 66Gy) of the boost prescribed dose of 60 Gy.

#### **Lung:**

Per protocol: No more than 15% of the ipsilateral lung exceeded 20 Gy. Variation Accepted: No more than 20% of the ipsilateral lung exceeded 16Gy.

#### **Heart:**

Per protocol: No more than 5% of the whole heart exceeded 16 Gy. Variation Accepted: No more than 5% of the whole heart exceeded 20 Gy.

#### **Contralateral breast:**

Per protocol: The maximum dose to contralateral breast didn't exceed 240 cGy and no more than 5% exceeded 144 cGy. Variation Accepted: The maximal dose to contralateral breast didn't exceed 384 cGy and no more than 5% exceeded 240 cGy.

#### **Beam-eye view (BEV):**

Beam-eye view revised for each plan to ensure proper coverage of the PTV with maximum sparing of the risk organs.

**Axial CT cuts:** Isodose lines on axial CT cuts were revised for ensuring dose homogeneity and adequate PTV coverage. Other parameters such as the central lung distance and heart distance, were also revised.

#### **V. Dose prescription and dose limitation to OARs (Figure 22, 23)**

A total dose of 50Gy was prescribed and normalized to the isocenter of PTV according to the (ICRU) reports 50, 62 recommendations and definition for normalization point. The ipsilateral lung tolerance dose was taken to be mean lung dose less than 30% of prescribed dose, volume receiving 20 Gy ( $V_{20Gy}$ ) less than 15% and volume receiving 30 Gy ( $V_{30Gy}$ ) less than 10%. The tolerance dose to the heart was taken to be  $V_{30Gy}$  less than 5%,  $V_{40Gy}$  less than 10%. As regard

CB aim was to keep mean dose to this volume as low as possible.

The previous tolerance doses for heart, lung and CB were based on Danish breast cancer cooperative group DBCG treatment planning objectives and French guidelines SFRO.

#### **VI. Follow up**

Patients had weekly follow up during radiotherapy treatment to determine tolerance and toxicity of the treatment, and manage complications.

#### **3. Results:**

##### **Patient characteristics Clinical features: (table 1)**

Including age, menopausal status, site of disease and medical problems as well as chemotherapy received.

This table shows that the mean age of the IMRT cases was ( $50.57 \pm 11.48$ ). The youngest case was 28 years old and the oldest one was 70 years old, while the age of 3DCRT patients was ( $51.2 \pm 10.8$ ).

The youngest case was 30 years old and the oldest one was 72 years old with no statistical significance difference (P value =0.711).

Premenopausal patients were more common (56%) than postmenopausal cases (11%) of the patients in IMRT group and in 3DCRT cases also premenopausal patients were more common (52%) than postmenopausal cases were (48%) with no statistically significant difference (P value =0.711).

In both groups the upper outer quadrant site is the most common, it was 76% in IMRT group and 72% in 3DCRT with no statistically significant difference (P value =0.415).

Most of the patients didn't have an important medical history (52% in IMRT cases) and (56% in 3DCRT cases) (P value=0.652).

More than half of the cases received chemotherapy in the form of anthracyclin based and taxanes based regimens (13 cases) in the IMRT group versus 14 cases in the 3DCRT with no statistically significant difference (P value =0.395).

##### **Pathological features: (Table 1)**

Including the pathological types, grade, percentage of intra-ductal component, tumor size, number of positive nodes, ER, PR and her2-neu and KI67.

In this study, most of the cases were invasive ductal carcinoma; 88% in group I and 84% in group II and also most of cases were grade II 60% in group I and 72% in group II, with no statistically significant difference (P value =0.711,0.56) respectively.

T2 was the most common in both groups; it was 64% in IMRT group and 68% in 3DCRT with no statistically significant difference (P value =0.452).

The mean size of tumor mass was ( $2.90 \pm 0.78$ ) in IMRT group while in 3DCRT was ( $3.1 \pm 0.81$ ) with no statistical significance difference (P value =0.385).

Most of the cases had less than 25% of intra-ductal component; they were 76% in group I and 80% in group II with no statistically significant difference (P value =0.389).

Fifteen patients (60%) were with negative nodal involvement in group I and in group II they were 14 patients (56%), also 20 of the patients (80%) were ER positive and 19 patients (76%) were PR positive in group I and 19 cases (76%) ER positive and 19 patients (76%) were PR positive in group II with no

statistically significant difference (P value =0.415, 0.674, 0.425) respectively.

Most of the cases were Her2-neu negative 84% in IMRT group, 76% in 3DCRT cases with no statistically significant difference (P value= 0.136).

Most of the cases in both groups were negative for ki67 {The Ki-67 proliferation index is define a high Ki-67 proliferation index if  $\geq 20\%$  positive cells to define "positive" (high risk). Thirteen patients in group I (52%) and 14 patients in group II (56%) with also no statistically significant difference (P value =0.521).

**Table (1): Distribution of the patients of the two studied groups according to the clinical data and the pathological tumor features.**

	Gp. I "IMRT" "n=25"		Gp. II "3DCRT" "n=25"		P
	No	%	No	%	
<b>Clinical Data</b>					
<b>Age</b>	50.57 $\pm$ 11.48		51.2 $\pm$ 10.8		0.711
<b>Menstrual status</b>					
Pre-menopausal	14	56.0	13	52.0	0.711
Post-menopausal	11	44.0	12	48.0	
<b>Site</b>					
UO	19	76.0	18	72.0	0.415
IO	2	8.0	2	8.0	
UI	3	12.0	2	8.0	
LI	1	4.0	3	12.0	
<b>Medical History</b>					
-ve	13	52.0	14	56.0	0.652
DM	5	20.0	3	12.0	
HTN	3	12.0	4	16.0	
Both	4	16.0	4	16.0	
<b>Chemotherapy</b>					
Anthracyclin based	8	32.0	8	32.0	0.395
Taxan based	5	20.0	6	24.0	
None	12	48.0	11	44.0	
<b>Pathological tumor features</b>					
<b>Pathological type</b>					
Invasive ductal	22	88.0	21	84.0	0.711
Invasive lobular	3	12.0	4	16.0	
<b>Tumor grade</b>					
Grade I	7	28.0	5	20.0	0.56
Grade II	15	60.0	18	72.0	
Grade III	3	12.0	2	8.0	
<b>T stage</b>					
T1	9	36.0	8	32.0	0.452
T2	16	64.0	17	68.0	
<b>Tumor size</b>	2.9 $\pm$ 0.78		3.1 $\pm$ 0.81		0.385
<b>Intra-ductal component</b>					
<25.0%	19	76.0	20	80.0	0.389
>25.0%	6	24.0	5	20.0	
<b>N classification</b>					
N0	15	60.0	14	56.0	0.415

N1	10	40.0	11	44.0	
<b>ER</b>					
-ve	5	20.0	6	24.0	0.674
+ve	20	80.0	19	76.0	
<b>PR</b>					
-ve	6	24.0	6	24.0	0.425
+ve	19	76.0	19	76.0	
<b>HER 2</b>					
-ve	21	84.0	20	76.0	0.136
+ve	4	16.0	5	24.0	
<b>Ki67</b>					
< 20%	13	52.0	14	56.0	0.521
≥ 20%	12	48.0	11	44.0	

**Table (2): Comparison between the two studied groups regarding the body measures.**

	Gp. I "IMRT" "n=25"		Gp. II "3DCRT" "n=25"		P
<b>Tangential separation (cm)</b> Mean S.D.	24.2±6.85		23.2±7.02		0.1236
<b>Breast volume (cm<sup>3</sup>)</b> Mean S.D.	725.5±98.0		698.5±89.2		0.265
<b>Boost volume (cm<sup>3</sup>)</b> Mean S.D.	95.2±28.6		85.2±19.8		0.296
<b>Supra-calvicular lymph node volume (cm<sup>3</sup>)</b> Mean S.D.	60.0±11.9		62.5±10.6		0.621
<b>Heart volume (cm<sup>3</sup>)</b> Mean S.D.	485.0±42.3		475.2±39.8		.468
<b>Lung volume (cm<sup>3</sup>)</b> Mean S.D.	1097.1±264.2		1102.0±256.3		0.219
<b>Thyroid volume (cm<sup>3</sup>)</b> Mean S.D.	13.6±2.58		14.01±2.64		0.161
<b>BMI</b>					
Normal	12	48.0	13	52.0	0.201
Overweight	5	20.0	6	24.0	
Obese class I	4	16.0	5	20.0	
Obese class II	4	16.0	1	4.0	

This table shows 12 patients (48%) had normal body index.,5 cases (20%) were overweight and 8 Patients (32%) were obese in IMRT group while in 3DCRT group there were 13 patients (52%) had normal body index, 6 cases (24%) were overweight and 6 Patients (24%) were obese with no statistically significant difference (P value =0.201).

The mean tangential separation was (24.2 cm<sup>3</sup> ± 6.85) in IMRT group, while it is (23.2 cm<sup>3</sup> ± 7.02) in 3DCRT group, the difference between plans were not statistically significant (p=0.123).

Breast volume in IMRT cases was in range of (324 cm<sup>3</sup>- 1384) with a mean of (725.5 cm<sup>3</sup> ± 98) while breast volume in 3DCRT cases was in range of (320.0 cm<sup>3</sup>- 1310) with a mean of (698.5 cm<sup>3</sup> ± 98.2) with no statistically significant difference (p=0.265).

Boost volume in IMRT cases was in range of (52 cm<sup>3</sup>- 120) with a mean of (95.2 cm<sup>3</sup> ± 28.6) while boost volume in 3DCRT cases was in range of (50.0 cm<sup>3</sup>- 109) with a mean of (85.2 cm<sup>3</sup> ± 19.8) with no statistically significant difference (p=0.296).

There is no statistically significant difference also in supraclavicular lymph node volume (p=0.621) with mean volume (60.6cm<sup>3</sup> ± 11.9) and (62.5 cm<sup>3</sup> ± 10.6) in IMRT, 3DCRT respectively.

The mean lung volume was (1097 cm<sup>3</sup> ± 264.2) and (1102.0cm<sup>3</sup> ± 256.3) in IMRT and 3DCRT respectively with no statistically significant difference (p=0.219).

The mean heart volume was (485 cm<sup>3</sup> ± 42.3) and (475.2 cm<sup>3</sup> ± 39.8) in IMRT and 3DCRT respectively with no statistically significant difference (p=0.468).

The mean thyroid volume was ( $13.6 \text{ cm}^3 \pm 2.58$ ) in IMRT cases and ( $14.01 \text{ cm}^3 \pm 2.64$ ) in 3DCRT patients with also no statistically significant difference ( $p=0.161$ ).

### Result of dosimetric data:

#### Dosimetric data on target coverage:

Dosimetric data on coverage of the WBI CTV & SCLN-PTV tables (3)

This table shows that the values of the whole breast radiation were as follow, the maximum mean dose received ( $48.14 \pm 0.96$ ) for 3DCRT plans compared to ( $53.20 \pm 1.03$ ) for IMRT plans. The difference between both plans was statistically significant ( $p=0.044$ ) and the minimum mean dose was ( $43.33 \pm 0.89$ ) for 3DCRT plans compared to ( $45.80 \pm 0.92$ ) for IMRT plans. The difference between both plans was statistically significant ( $p=0.039$ ), 98.5% of the mean breast volume received 45Gy for

IMRT plans compared to 93.3% for 3DCRT plans with statistically significant difference ( $p=0.036$ ), and 98% of the mean breast volume received 47.5Gy for IMRT plans compared to 94.1% for 3DCRT plans with statistically significant difference ( $p=0.044$ ).

PTV  $D_{90\%}$  of the mean breast volume received a dose of ( $46.79 \pm 1.03$ ) for 3DCRT plans compared to ( $48.76 \pm 0.92$ ) for IMRT plans. The difference between plans were statistically significant ( $p=0.042$ ) and so PTV coverage was better in IMRT plan.

As dose homogeneity index ranged from 0.82-1.01 for 3DCRT plans compared to 0.34-1.32 for IMRT plans so the dose homogeneity within PTV was significantly better with IMRT than with 3DCRT plans ( $p=0.036$ ), while conformity index was ranged from 0.91-1.33 for 3DCRT plans compared to 0.89-1.2 for IMRT plans so the CI within PTV was significantly better with IMRT than with 3DCRT plans ( $p=0.047$ ).

**Table (3): Dosimetric data on coverage of the CTV (WBI)**

Dosimetric data parameter	Gp. I "IMRT" "n=25"	Gp. II "3DCRT" "n=25"	P
<b>CTV (WBI)</b>			
V45 Gy in %	98.5±0.98	93.3±1.2	0.036*
V47.5 Gy in %	98.0±0.22	94.1±0.68	0.044*
D90% in Gy	48.76±0.92	46.79±1.03	0.042*
D max. in Gy	53.20±1.03	48.14±0.96	0.044*
D min. in Gy	45.80±0.92	43.33±0.89	0.039*
Homogeneity Index	0.56±0.041	0.90±0.036	0.036*
Conformity Index	1.00±0.01	1.21±0.04	0.047*
<b>SCLN-PTV</b>			
V45 Gy in %	96.8±2.62	93.6±1.98	0.018*
V47.5 Gy in %	95.3±1.21	91.0±1.52	0.036*
D90% in Gy	48.39±0.88	46.41±0.92	0.028*
D max. in Gy	53.33±0.89	50.98±0.92	0.103
D min. in Gy	45.80±0.92	44.32±0.79	0.029*
Homogeneity Index	0.93±0.056	1.21±0.046	0.045*
Conformity Index	0.93±0.04	1.23±0.05	0.037*
<b>B-PTV</b>			
V54 Gy in %	99.1±0.32	97.2±0.22	0.048*
V57 Gy in %	99.1±0.16	96.1±0.23	0.049*
D90% in Gy	60.80±0.42	56.26±0.68	0.016*
D max. in Gy	62.93±0.78	60.13±0.69	0.026*
D min. in Gy	56.13±0.45	53.33±0.51	0.011*
Homogeneity Index	0.96±0.11	1.21±0.107	0.046*
Conformity Index	1.1±0.07	0.92±0.08	0.041*
<b>Contra-lateral breast</b>			
V5 Gy in %	2.68±0.82	1.1±0.82	0.022*
CB mean dose in Gy	2.13±0.93	1.09±0.71	0.017*
<b>Heart</b>			
V40 Gy in %	0.45±0.21	1.5±0.16	0.011*
V30 Gy in %	0.91±0.42	2.05±0.98	0.042*
D50% in Gy	1.33±0.50	2.31±0.61	0.041*

Mean heart dose in Gy	2.5±1.03	4.1±1.22	0.035*
<b>LAD</b>			
Mean dose in Gy	18.9±6.22	26.2±5.85	0.0025*
<b>Lung</b>			
Lung V20 Gy in %	15.6±2.6	17.2±2.5	0.045*
Mean lung distance in cm	1.82±0.42	2.68±0.51	0.044*
Mean lung dose in Gy	2.3±0.88	3.58±1.9	0.027*
<b>Contra lateral Lung</b>			
V5 Gy in %	3.2±0.9	2.1±0.6	0.031*
Mean lung dose in Gy	1.20±0.3	0.82±0.10	0.048*
<b>Thyroid</b>			
Mean dose in Gy	6.2±4.36	10.6±3.9	0.005*

**CTV:** clinical target volume, **WBI:** whole breast irradiation, **V45Gy:** volume that received 45Gy, **V47.5Gy:** volume that received 47.5Gy, **D90%:** dose received by 90% of the volume, **Dmax:** maximum dose, **Dmin:** minimum dose. **HI:** Homogeneity Index, **CI:** Conformity Index.

**SCLN:** supraclavicular lymph nodes, **PTV:** planning target volume, **V45Gy:** volume that received 45Gy, **V47.5Gy:** volume that received 47.5Gy, **D90%:** dose received by 90% of the volume, **Dmax:** maximum dose, **Dmin:** minimum dose, **HI:** Homogeneity Index, **CI:** Conformity Index.

This table shows that the values of the supraclavicular lymph nodes radiation were as follow, the maximum mean dose received (50.98±0.92) for 3DCRT plans compared to (53.33±0.89) for IMRT plans with no statistically significant difference (p value=0.103).

The minimum mean dose was (44.32±0.79) for 3DCRT plans compared to (45.80±0.92) for IMRT plans. The difference between both plans was statistically significant (p=0.029). (96.8%) of the mean SCLN volume received 45Gy for IMRT plans compared to (93.6%) for 3DCRT plans with statistically significant difference (p=0.018), and (95.3%) of the mean SCLN volume received 47.5Gy for IMRT plans compared to (91%) for 3DCRT plans with statistically significant difference (p=0.036).

PTV D<sub>90%</sub> of the mean supraclavicular LN volume received a dose of (48.39Gy) for 3DCRT plans compared to (46.41Gy) for IMRT plans. The difference between plans were statistically significant (p value=0.028) and so PTV coverage was better in IMRT plan.

As dose homogeneity index ranged from 0.90-1.33 for 3DCRT plans compared to 0.87-1.12 for IMRT plans so the dose homogeneity within PTV was significantly better with IMRT than with 3DCRT plans (p=0.045).

Conformity index was ranged from 0.91-1.36 for 3DCRT plans compared to 0.84-1.09 for IMRT plans so the CI within PTV was significantly also better with IMRT than with 3DCRT plans (p=0.037).

**B-PTV:** boost planning target volume, **V54Gy:** volume that received 54Gy, **V57Gy:** volume that received 57Gy, **D90%:** dose received by 90% of the volume, **Dmax:** maximum dose, **Dmin:** minimum dose, **HI:** Homogeneity Index, **CI:** Conformity Index.

This table shows that the values of the boost planning target volume radiation were as follow, the maximum mean dose received (60.13±0.69) for 3DCRT plans compared to (62.93±0.78) for IMRT plans. The difference between both plans was statistically significant (p=0.026) and the minimum mean dose was (53.33±0.51) for 3DCRT plans compared to (56.13±0.45) for IMRT plans. The difference between both plans was statistically significant (p=0.011).

The mean boost volume received 54Gy for IMRT plans was (99.1%) compared to (97.2%) for 3DCRT plans with statistically significant difference (p=0.048), and the mean boost volume received 57Gy for IMRT plans was (99.1%) compared to (96.1%) for 3DCRT plans with statistically significant difference (p=0.049).

PTV D<sub>90%</sub> of the mean boost volume received a dose of (56.26Gy) for 3DCRT plans compared to (60.80Gy) for IMRT plans. The difference between plans were statistically significant (p=0.016) and so PTV coverage was better in IMRT plan.

As dose homogeneity index ranged from 0.89-1.41 in 3DCRT plans compared to 0.80 -1.1 for IMRT plans so the dose homogeneity within PTV was statistically significant better with IMRT than with 3DCRT plans (p=0.046).

Conformity index was ranged from 0.82-1.00 for 3DCRT plans compared to 0.91-1.3 for IMRT plans so the CI within PTV with statistically significant better with IMRT than with 3DCRT plans (p=0.041).

#### **Dosimetric data on organs at risk (OAR):**

The dose received by the contralateral breast was assessed using parameters of V5Gy and mean doses where values ≤2Gy were considered acceptable as shown (table 15).



The doses received by organ at risk were evaluated in both groups by several dosimetric parameters. The dose to the heart was evaluated by the V40 Gy, D50% and mean heart dose as shown in (table 16).

The lateral anterior descending artery (LAD) was assessed by means of the mean dose received in (table 17).

As regard to ipsilateral lung, its evaluation was based mainly on the V20Gy (considered acceptable below 20%) as well as the mean long distance (accepted below 2 cm) and the mean lung dose was also used as shown in (table 18).

The dose received by the contralateral lung was assessed using parameters of V5Gy and mean doses where values  $\leq 2.5$ Gy were considered acceptable as shown (table 19).

The thyroid gland was assessed by means of the mean dose received (table 20).

**V5 Gy:** volume received 5 Gy.

This table shows the dosimetric data of the contralateral breast. The percentage of the mean CLB volume received 5Gy was 2.68% in group I compared to 1.1% in group II which showed a statistically significant difference (p value= 0.022).

CB mean dose was (1.09Gy) for 3DCRT plans compared to (2.13Gy) for IMRT plans. 3DCRT plans showed a significant reduction compared to IMRT plans (p= 0.017).

**V40Gy:** volume received 40 Gy, **V30Gy:** volume received 30 Gy, **D50%:** dose received by 50% of the volume.

This table shows the dosimetric data of the heart. The volume of the heart receiving 40Gy was  $0.45 \pm 0.21$  percent in group I, compared to  $1.5 \pm 0.16$  percent in group II with statistically significant difference (P value=0.011).

The volume receiving 30Gy was ( $0.91 \pm 0.42$ ) in group I while it was ( $2.05 \pm 0.98$ ) in group II with

statistically significant difference (P value=0.042), fifty percent of the heart volume received mean dose of  $1.33 \pm 0.50$  in IMRT plan compared to  $2.31 \pm 0.61$  in 3DCRT with statistically significant difference (P value=0.041).

Mean heart dose received was  $2.5 \pm 1.03$  in IMRT plan compared to  $4.1 \pm 1.22$  in 3DCRT with statistically significant difference (P value=0.035). So IMRT plans achieved significant heart sparing compared to 3DCRT plans.

This table shows the mean LAD dose received was 18.9Gy in IMRT plans compared to 26.2Gy in 3DCRT plan with statistically significant difference (p value=0.0025).

This table shows the dosimetric data of the ipsilateral lung. V<sub>20Gy</sub> was 17.2% for 3DCRT plans compared to 15.6% for IMRT plans with statistically significant difference of (p= 0.045).

The mean lung dose was 2.3Gy in IMRT plans compared to 3.5Gy for 3DCRT plans with statistically significant difference (p= 0.027).

The mean long distance was 1.82cm in group I plans compared to 2.68cm in group II of 3DCRT with statistically significant difference (p=0.044).

So IMRT plans achieved significant ipsilateral lung sparing compared to 3DCRT plans.

This table shows the dosimetric data of the contralateral lung. V<sub>5Gy</sub> was 2.1% for 3DCRT plans compared to 3.2% for IMRT plans, with statistically significant difference (p= 0.031).

The mean lung dose received was 1.20Gy in IMRT plans compared to 0.82Gy for 3DCRT plans with statistically significant difference (p= 0.048).

The mean thyroid gland dose was 6.2Gy in IMRT plans compared to 10.6Gy in 3DCRT plan with statistically significant difference (p value=0.005).

**Result of acute toxicity effect:**

**Table (4): Acute toxicity of both study groups**

Early toxicity	Gp. I "IMRT" "n=25"		Gp. II "3DCRT" "n=25"		p
	No	%	No	%	
<b>Skin</b>					
Grade I	4	16.0	7	28.0	0.032*
Grade II	2	8.0	6	24.0	
Grade III	0	0.0	2	8.0	
<b>Lung</b>					
Grade I	0	0.0	1	4.0	-
Grade II	0	0.0	1	4.0	-
<b>Heart</b>					
Grade I	0	0.0	1	4.0	-
Grade II	0	0.0	0.0	0.0	-

Acute skin toxicity grade 1 according to the RTOG toxicity grading was developed in 4 patients of group I compared to 7 patients in group II. In group I 2 cases (8%) had grade 2 toxicity compared to 6 cases in group II (24%). Only two patients (8%) of group II developed grade 3 radiation dermatitis.

No one in group I developed lung toxicity while only 1 case had grade I lung toxicity (4%) in group II, and another one case had grade II lung toxicity diagnosed by X-ray.

No one in group I developed cardiac toxicity however only one case of group II 3DCRT patients had grade I heart toxicity two months after the end of radiotherapy according to RTOG toxicity grading.

#### Of late toxicity effect:

In this current study no one developed late toxicity in group I. One case (4%) was identified grade

1 skin toxicity and another case of grade 2 skin toxicity in the form of palpable in duration (fibrosis) of both the lumpectomy site and whole breast was found in patients treated with 3D-CRT.

One patient in group II 3DCRT developed grade 1 lung toxicity and another case developed grade 1 heart toxicity.

Table (6) shows that skin toxicity was significantly affected by high body mass index and obesity during the first week to the end of radiotherapy (P value=0.001).

This table shows also the skin toxicity was significantly affected by medical history of diabetes especially after the end of radiotherapy (P value =0.0036).

**Table (5): Late radiation toxicity in both studied groups**

Late toxicity	Gp. I "IMRT" "n=25"		Gp. II "3DCRT" "n=25"	
	No	%	No	%
<b>Skin fibrosis</b>				
Grade 1	0	0	1	4.0
Grade 2	0	0	1	4.0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
<b>Lung fibrosis</b>				
Grade 1	0	0	1	4.0
Grade 2	0	0	0	0
<b>Cardiomyopathy</b>				
Grade 1	0	0	1	4.0
Grade 2	0	0	0	0

**Table (6): Relation between demographic data and incidence of acute skin toxicity in both groups.**

	Gp. I "IMRT" "n=25"				Gp. II "3DCRT" "n=25"			
	Total	Skin toxicity "n=6"	No skin toxicity "n=19"	P value	Total	Skin toxicity "n=15"	No skin toxicity "n=10"	P value
<b>BMI</b>								
Normal	12	0	12	0.001*	13	3	10	0.001*
Overweight	5	0	5		6	6	0	
Obese class I	4	2	2		5	5	0	
Obese class II	4	4	0		1	1	0	
<b>Diabetic</b>								
Yes	9	5	4	0.0025*	7	7	0	0.0036*
No	16	1	15		18	8	10	

#### Survival analysis

The 3 year over all survival was 92% in the IMRT group versus 96% for the 3DCRT group. The difference between the groups was not significant with a p value of (p value-0.621).

The 3 year disease free survival in the IMRT group was 84%, (two patients had local recurrence and

another 2 patients had distant relapse) versus 80% in 3DCRT group (3 patients had local recurrence and 2 patients had distant relapse). The difference between the groups was not statistically significant (p value-0.621).

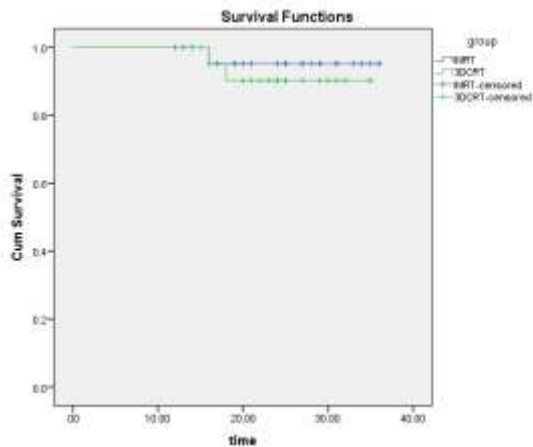


Fig. (1): Overall survival in both IMRT and 3DCRT groups.

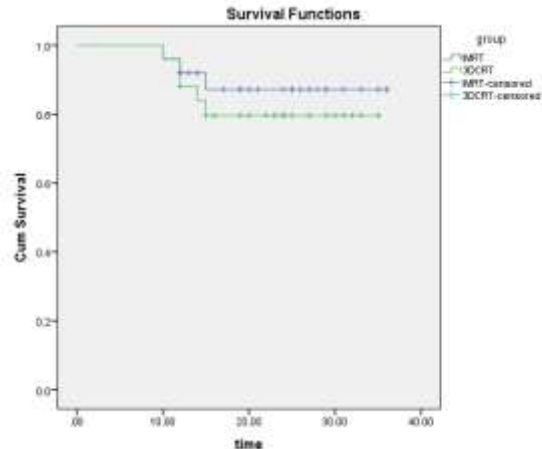


Fig. (2): Disease free survival in both IMRT and 3DCRT groups

#### 4. Discussion:

##### Target volume coverage

As regard target coverage current study revealed IMRT achieved adequate and comparable target coverage. IMRT resulted in significant higher maximum dose and significant in homogeneous dose within PTV compared to 3DCRT.

Compared results of current study with other authors;

**Fiorentino et al., 2017** compared 3DCRT and 4-fields IMRT treatment plans, in terms of target dose coverage, integral dose show significant target coverage of IMRT compared to 3DCRT which is consistent with current study results.

**Rastogi et al., 2018** in his study achieved statistically significant improvement in conformity index with IMRT compared to 3DCRT and this is consistent with current study results. However in contradiction to our results no significant difference was noted in homogeneity index in this study whereas our study showed significant difference in homogeneity index with IMRT compared to 3DCRT.

**Li et al., 2016** concluded that, IMRT improved neither the conformity index nor homogeneity index, in contrast to our study and this may be due to the difference in patient characteristics where they included patients with post mastectomy whereas we included patients who did breast conservative surgeries.

**Beckham et al., 2007** concluded that IMRT significantly improved not only Conformity index but also homogeneity index which is matching with current study results.

**Moorthy et al., 2012** in this study found good coverage in both whole breast PTV and boost PTV in

IMRT plan compared with 3DCRT plan which is consistent with current study results.

**Jin et al., 2013** studied twenty Chinese patients with left sided breast cancer were treated with conservative surgery followed by radiotherapy planned using five different radiotherapy techniques including conventional tangential wedge based fields and tangential inverse planning IMRT. Tangential IMRT plan improved the PTV dose homogeneity index by 0.02 and 0.03 when compared to conventional tangential wedge based plan. This is consistent with current study results.

##### OARs

##### Contralateral breast (CB)

As regard CB dose, current study revealed significant reduction of CB dose for 3DCRT mean dose was 1.09 Gy compared to 2.13 Gy for IMRT, ( $p=0.017$ ).

Compared the current study results with work of other authors.

**Rastogi et al., 2018** showed that the average CB mean dose was 2.8 Gy for IMRT and 1.7 in the 3DCRT which is consistent with our results which showed a mean CB dose of 1.09 Gy for tangential 3DCRT plans compared to 2.13 Gy for IMRT plans.

**Fong et al., 2009** showed that the mean dose to the CB was significantly reduced with the tangential IMRT plans 1.8 Gy compared to 2.3 Gy with wide tangential 3DCRT technique ( $p = 0.01$ ). This is not consistent our results (1.09Gy with tangential 3DCRT plans versus 2.13Gy for IMR T plans) ( $p < 0.001$ ).

##### Heart

As regard to heart dose our study showed that IMRT plan is better than 3DCRT plans (mean  $V_{30Gy}$  0.91% versus 2.05% and mean  $V_{40Gy}$  0.45% versus 1.5

% while mean heart dose 2.5Gy versus 4.1Gy for IMRT and 3DCRT plans respectively.

Compared the current study results with work of other authors.

**Jo et al., 2017** showed that heart  $V_{30Gy}$  was lower than with IMRT with 3DCRT (1.5% and 5.4% respectively) and also  $V_{40Gy}$  was lower than with IMRT than with 3DCRT (0% and 4% respectively) with significant difference (P value <0.001) which is matching with our current study results.

**Moorthy et al., 2012** study showed that  $V_{30Gy}$  was also lower with IMRT than with 3DCRT (2.7% and 3.9% respectively) and mean heart dose was lower than with IMRT than with 3DCRT (7Gy and 7.4Gy respectively) but without any significant difference which is contradiction in our current study results which is  $V_{30Gy}$  0.91% versus 2.05% with (P value 0.033) and mean hear dose 2.5Gy versus 4.1Gy with (P value 0.042) in IMRT and 3DCRT respectively.

#### **Lateral anterior descending artery (LAD)**

As regard LAD dose, current study revealed significant reduction of LAD dose for IMRT mean dose was 18.9 Gy compared to 26.2Gy for 3DCRT, (p=0.0025).

Compared the current study results with work of other authors.

**Moorthy et al., 2012** study showed that maximum dose to LAD is 41.22Gy in 3DCRT group and 29.16Gy in IMRT group with statistically significant difference (P value 0.0046) which is consistent with the current study which is maximum dose was 47.7Gy (mean 26.2Gy) in 3DCRT group while in IMRT group the maximum dose was 36Gy (mean 18.9Gy) with statistically significant difference (P value 0.0025).

#### **Ipsilateral lung**

As regard lung sparing current study showed that tangential IMRT plans resulted better statistically significant in lung sparing in all dose volume parameters (DVPs) than tangential 3DCRT plans. Mean lung dose in Gy was 2.3Gy in IMRT patients versus 3.58Gy in 3DCRT,  $V_{20Gy}$  was 15.6% in IMRT plan versus 17.2% in 3DCRT plan.

Compared the results of current study with work of other authors.

**Mansouri et al., 2014, showed that tangential beam IMRT of the whole breast compared to 3DCRT reduces the ipsilateral lung dose-volume (V20Gy), The mean volume for V20Gy lung doses were 13% and 19% for the IMRT and 3DCRT planning respectively (P value: 0.48)** with no statistically difference which is not matching with our study  $V_{20Gy}$  was 15.6% versus 17.2% with (P value 0.045). This may be due to the difference in number of beams used.

**Jo et al., 2017** compared tangential beam IMRT plans with conventional tangential 3D plans for the adjuvant radiotherapy of the whole breast in 20 patients with early breast cancer. All IMRT plans showed a significant improvement of lung  $V_{30Gy}$  of 6.9% compared to 17 % with the conventional technique with statistically significant difference which is matching with our study.

#### **Contralateral lung**

As regard to contralateral lung dose in the current study, we found that 3DCRT plan is better than IMRT plans ( $V_{5Gy}$  3.2% versus 2.1% and mean dose 1.2Gy versus 0.8Gy) for IMRT and 3DCRT plans respectively.

Compared the current study results with work of other authors.

**Xie et al., 2014** compared the dosimetric characteristics of left-sided whole breast irradiation among 3-dimensional conformal radiotherapy (3DCRT), 4-field inverse-planned intensity-modulated radiotherapy (IP-IMRT) and hybrid IMRT technique.  $V_{5Gy}$  of contralateral lung was significantly larger for IP-IMRT 8% compared to 0.45% in 3DCRT plan which is consistent with the current study ( $V_{5Gy}$  2.1% versus 3.2%) for 3DCRT and IMRT plans respectively with significant difference (P value=0.031).

#### **Thyroid**

As regard thyroid dose, current study revealed significant reduction of thyroid dose for IMRT mean dose was 6.2Gy compared to 10.6Gy for 3DCRT, (p=0.005).

Compared the current study results with work of other authors.

**Kim et al., 2013** showed that the thyroid mean dose was 17.2Gy for IMRT and 26.7Gy in the 3DCRT which is consistent with our results which showed a mean thyroid dose of 10.6Gy for tangential 3DCRT plans compared to 6.2Gy for IMRT plans with statistically significant difference (P value 0.005).

#### **Toxicity**

As regard to acute skin toxicity in the current study (at 20 months follow up), we found that IMRT plan is better than 3DCRT plans, 76% with **excellent/good cosmetic** in IMRT group compared to 40% in 3DCRT group.

Compared the current study results with work of other authors.

Jagsi et al., 2010 the authors describe 78% of patients with excellent/good cosmetic results using an IMRT technique (at 2.5 years of median FU) which is consistent in our study cosmetic results.

Rastogi et al., 2018 study showed statistically significant difference in acute skin toxicity which is matching with our current study; 53.5% with grade 1 dermatitis in IMRT plan compared to 50% in 3DCRT while in our study 16% and 28% respectively, 20.9%

of IMRT patients with grade 2 skin toxicity versus 42.2% in 3DCRT while in our study 8% and 24% respectively.

Rastogi et al., 2018 showed no significant difference in acute lung toxicity grade 1 (radiation pneumonitis) 2 patients in IMRT plan versus 7 patients in 3DCRT while in our study was only 1 patient had grade 1 radiation pneumonitis in 3DCRT, that is may be due to our small sample study population.

#### Factors of influence on acute skin toxicity

Regarding all parameters of our study with potential influence on skin toxicity, we found significant correlations for only two patient related factors medical history of diabetes mellitus and high body mass index (BMI).

#### High body mass index

In our study patients with higher body mass index developed significantly more skin toxicity grade I and II compared to patients with normal body mass index during weeks of radiotherapy course in both 3DCRT and IMRT plans ( $p=0.001$ ).

A study from De Langhe and colleagues could show comparable results as high BMI ( $p<0.001$ ) during RT ( $p=0.029$ ) was associated with the development of G2 skin toxicity **De Langhe et al., 2014**. BMI was also confirmed as significant risk factors for the development of acute skin toxicity, in accordance with the majority of published reports (**Freedman et al., 2006; Goldsmith et al., 2011; Dorn et al., 2012**). BMI was previously found to be strongly correlated with breast volume and this explain the association between larger breast volumes, body mass index and toxicity which is thought to be due to dose inhomogeneity (**Dorn et al., 2012**).

#### Conclusion and Recommendations:

Our study demonstrates superior dose distribution of IMRT technique in early breast cancer over 3DCRT in terms of improvement of the coverage of all target volumes including whole breast PTV, supraclavicular LN PTV and boost PTV.

Using IMRT plan technique improves homogeneity and conformity indices in all target volumes.

IMRT technique significantly reduces dose to heart, lateral anterior descending coronary artery, ipsilateral lung and thyroid gland however using IMRT plan increases low dose region in the contralateral breast and contralateral lung.

IMRT plans shows significant reduction in early skin toxicity with better cosmesis compared to 3DCRT plans.

Small number of study population and short follow-up are the major limitations of the present

study for proper assessment of late radiation toxicity in both IMRT and 3DCRT plans.

Tangential IMRT should be an option especially in those patients with large breast volume and left sided breast cancer. Yet we should weight advantage versus disadvantage of using IMRT plan technique because of spread low dose volume in contralateral breast and contralateral lung on individual patient selection basis.

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