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Original Article

TWO DIMENSIONAL VERSUS 3-DIMENSIONAL RADIATION THERAPY IN THE MANAGEMENT OF OPERABLE LEFT BREAST CANCER

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ABSTRACT

Background: Postoperative radiotherapy in the management of breast cancer was proven to be effective in reducing local recurrence. The aim of this work was to compare between 2 dimensional (2D) and 3 dimensional conformal radiotherapy (3D-CRT) considering dose homogeneity inside the target volume(s) and doses received by the surrounding risk structures. Clinical outcome including tumor control, survival and toxicity of both techniques were also prospectively compared.

Patients and Methods: Sixty female patients with left breast cancer following mastectomy or breast conservative surgery were included and each one had a 2D and 3D conformal planning. Both techniques were compared (physical study) for target volume coverage, dose homogeneity and doses received by the risk organs. For treatment (clinical study), only one technique was randomly applied. Patients were divided into group A including 30 patients who received treatment based on 2D planning and group B including 30 patients who received 3D-CRT.

Results: The physical study revealed no significant difference between both techniques in coverage or dose homogeneity inside the left breast (or chest wall) or supraclavicular lymph nodes (SCLN). However, 3D-CRT demonstrated a better coverage inside the internal mammary nodes (IMN). Another significant result was sparing the left lung from receiving a dose of 20 Gy or more (V20Gy) in favor of the 3D conformal plan. The estimated excess relative risk of right breast cancer was less in 3D-CRT (1.68 ± 0.815 %) compared to 2D (2 ± 0.66 %), but the difference was not statistically significant. Clinically, at a median follow up period of 29.5 months, there was no significant difference between both arms in the loco-regional recurrence, survival, or toxicity. However, a statistically significant less reduction of cardiac ejection fraction (EF) measured by isotopic scanning was noticed with 3D-CRT (5.127 ± 4.8839% for 2D versus 2.363 ± 4.7562% for 3D, P = 0.013).

Conclusion: 3D-CRT spared the left lung from receiving higher radiation dose during the post-operative radiotherapy with significant less reduction of cardiac EF. 3D-CRT should be offered for patients who are going to receive IMN irradiation for better coverage of the target volume.

Key Words: Left breast cancer, conformal radiotherapy.

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INTRODUCTION

Breast cancer is the most common malignancy in women, about 212,920 new cases of breast cancer were diagnosed in United States in the year 2006 which constituted approximately 31% of all new cancers in women[1]. Post- operative adjuvant radiotherapy is used as an integral part of the primary treatment of breast cancer and over 70% of women receive radiotherapy as an integral part of their primary treatment[2]. The rationale for post-operative radiation therapy (PORT) was to reduce local recurrence and furthermore, there were reports of a breast cancer cause-specific survival advantage for radiotherapy[3,4].

Standard tangential breast radiotherapy does not only treat portions of the chest wall, but also exposes lung and heart tissue to radiation. Studies of radiation toxicity showed that the effects on normal tissues can constitute a significant clinical problem and increased cardiac mortality in particular may offset any potential survival benefit of treatment[5,6]. The Oxford overview of radiotherapy trials in the year 2000 confirmed that standard mortality ratio for heart disease was 1.62 times higher for irradiated patients than for the non-irradiated patients[7].

The introduction of computerized tomography (CT) scanning and the availability of sophisticated 3-dimensional planning methods renewed interest in the technical aspects of breast cancer treatments, but this was mainly towards improving dose distributions within the breast itself[8]. The use of computed tomography in tangential breast irradiation provides a detailed picture of the dose distributions throughout the breast volume and surrounding normal tissue. Three-dimensional treatment planning allows dose escalation to the target volume without significantly increasing the dose received by surrounding normal tissue[9].

The full scale computed tomography scan with a true three-dimensional dose algorithm is more accurate than the three-slice model[10]. CT scanning-based 3D treatment in patients irradiated to the intact left breast has demonstrated a 50% reduction of the average excess cardiac mortality risk[11].

The aim of the current prospective study was to compare between 2D and 3D-CRT considering dose homogeneity inside the target volume(s) and doses received by the surrounding risk structures. Clinical outcome including tumor control, survival and toxicity of both techniques were also prospectively compared.

PATIENTS AND METHODS

The current prospective randomized study was carried out on 60 female patients with left breast cancer following mastectomy or breast conservative surgery (BCS) treated at Kasr El–Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period between November 2004 and May 2008.

The inclusion criteria included:

1. Age 18-70 years.
2. Performance status (PS) ≤ 2 according to World Health Organization (WHO).
3. Pathologically confirmed diagnosis.
4. Pre-irradiation anthracycline-based combination chemotherapy on adjuvant or neo- adjuvant basis.
5. Indications for post-operative radiation therapy (T2 > 3cm, T3 and T4 Tumors. SCLN irradiation if > 4 involved axillary lymph nodes or inadequate axillary dissection. IMN irradiation in medial half and retro-areolar tumors or more than >10 involved axillary lymph nodes).

The exclusion Criteria included:

1. Positive pregnancy test.
2. Thin flat chest wall (better to be treated with electron beam).
3. Any contraindication to chest wall irradiation such as severe collagen vascular disease and previous chest irradiation.
4. History of other malignancy or severe co-morbid disease.
5. Any evidence of distant metastases.

Eligible patients were assessed by:

1. Careful history-taking.
2. Complete physical examination including local examination.
3. Laboratory work-up including: Blood picture, kidney function tests, liver function tests, CA15-3, serum free T3, free T4, TSH and serum B-HCG pregnancy test if suspected pregnancy.
4. Baseline chest radiograph and pulmonary function tests.
5. Baseline echocardiography and Technetium MIBI-Heart scan.

Each patient had both a 2D and 3D approved conformal planning. Both techniques were compared (physical study) for target volume coverage, dose homogeneity and doses received by the risk organs. For treatment (clinical study), only one technique was randomly applied (closed envelope method). Patients were divided into group A including 30 patients who received treatment based on 2D planning and group B including 30 patients who received 3D-CRT. Clinical outcome including tumor control, survival and toxicity of both techniques were also prospectively compared.

PLANNING PROCEDURES

CT scanning was carried out for all cases every 0.5 cm. from the chin to costophrenic angles in the treatment position and transferred to the treatment planning system (XiO). Delineation was carried out according to NEMROCK protocol (Figure1). Every case was planned by 2 and 3 dimensional plans. The left chest wall (or breast) was treated using 2 isocentric tangential beams with inclusion of IMN inside the tang. SCLN were irradiated using separate beam with proper angulation away from spinal cord.

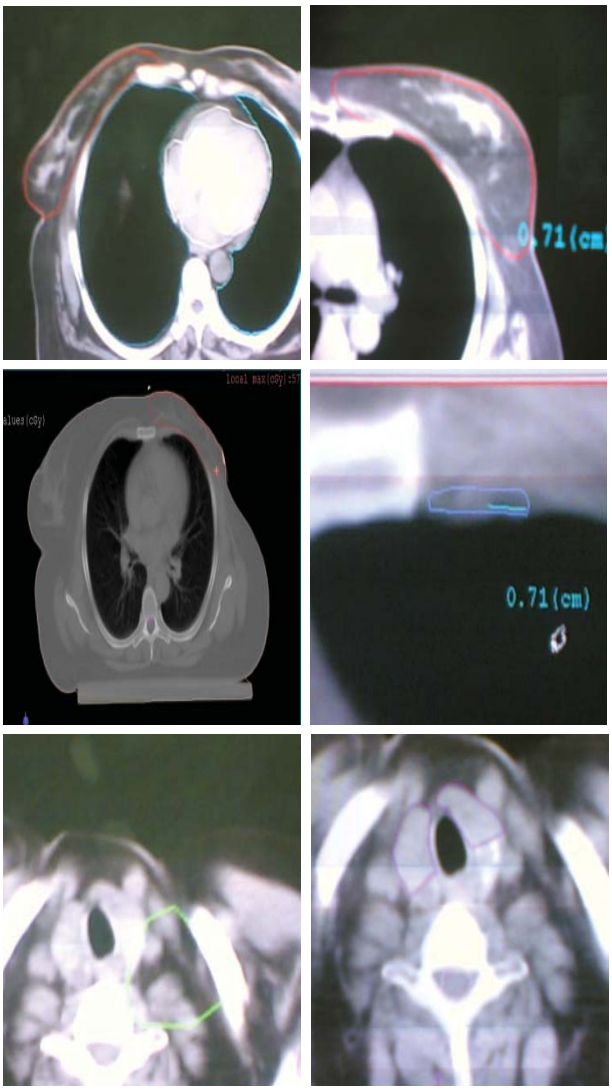

Figure 1: Delineation of target volumes according to NEMROCK protocol.

Plans were approved by both the physician and the physicist based on the following:

The 2D Plan:

Homogeneity of dose distribution inside the target volume(s) was considered acceptable if no area of 2cm2 or more received +/-7% of the prescribed dose (5040cGy/28ttt/2 3/5 weeks)[12].

The central lung and heart distances were not allowed to exceed 3 and 2 cm, respectively even on the expense of target coverage.

The 3D Plan:

Homogeneity of dose distribution inside the target volume(s) was considered acceptable if the part of the planning target volume (PTV) receiving a dose between 95 and 107% of the prescribed dose of 5040 cGy in 28 fractions of 1.8 Gy was at least 80 %[13].

The volume of the lung that received at least 20Gy (V 20 Gy) was not allowed to exceed 31 % as grade II pneumonitis can be kept at maximum of 8%[14].

The volume of the heart that received at least 40Gy (V 40 Gy) was not allowed to exceed 30 %.

Both plans were compared considering:

Different volumes receiving different doses to assess dose homogeneity. Coverage of PTVs and toxic dose to risk organs.

Normal tissue complication probability (NTCP) for both lungs and heart according to Burman model. (incorporated in the planning computer system "XIO")[15].

Tumor control probability (TCP) for target volumes according to Nahurn and Tait model[16].

The estimated excess relative risk of right breast cancer incidence (EERRRBCI): Was estimated from the breast curve which plotted dose against the excess relative risk of cancer incidence for 3 solid tumors (breast, bladder and stomach)[17].

The radiation induced toxicity was assessed according to the Radiation Therapy Oncology Group (RTOG) criteria. The cosmetic outcome for the patients treated with the 2D technique was compared with that for those treated with the 3D-CRT in the conservative surgery group using Gray score[18].

After the end of the course of radiation therapy, patients received tamoxifen if their tumors were ER and/or PR positive with switching to an aromatase inhibitor after 2-3 years in post-menopausal patients. All patients were put under follow up every 3 months for history taking, general and local examination in addition to repeating all pre-treatment investigations every 6 months.

Statistical considerations: Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows[19].

RESULTS

The current prospective randomized study was conducted on 60 female patients with left breast cancer at NEMROCK during the period between November 2004 and May 2008. All patients were planned by both 2D and 3D conformal techniques with only one of the two plans was chosen for treatment based on blind randomization. Therefore, patients were divided into group A including 30 patients who received treatment based on 2D planning and group B including 30 patients who received 3D-CRT.

The follow up period ranged from 6 months to 41 months with a median follow up of 29.5 months. Both groups were balanced in their clinico-pathological features except for the age which was significantly lower in group B than group A (mean 45.1 ± 8.079 years Vs 52 ± 7.151 years, P.value = 0.001) and the tumor grade where G III tumors were more common in group B (6 patients) versus no patient in group A (Table 1).

The physical study revealed no significant difference between both techniques in coverage or dose homogeneity (V45Gy, V40 Gy, D90%, Dmax., Dmin. and TCP) inside the left breast (or chest wall) or SCLN-PTV (13 patients). However, in the 15 patients treated with IMN irradiation, most parameters used to judge dose homogeneity and target coverage inside the IMN- PTV (V45Gy, V40 Gy, D90%, Dmin. and TCP) were significantly better in the 3D conformal plans than in the 2D plans. The only parameter that showed better but non significant difference was the Dmax (Table 2).

Another significant result was sparing the left lung from receiving a dose of 20 Gy or more (V20Gy) in favor of the 3D conformal plan. Table (3) As regards the doses received by the heart, none of the V40Gy, V50Gy, maximum heart dose (MHD) and NTCP parameters were significantly different between the 2D and 3D conformal plans. The D50% was significantly lower (better) in the 3D conformal plans.

In the 13 patients treated with the SCLN irradiation; toxic dose parameters to the spinal cord and the thyroid gland were not significantly different between the 2 techniques. The modal skin dose was not statistically different between the 3D conformal plans (37.9 ± 4.285Gy) and the 2D plans (37.85 ± 4.305Gy) with P.value. This was applied for patients with either mastectomy or breast conservative surgery. The estimated excess relative risk of right breast cancer was less in 3D-CRT (1.68 ± 0.815%) compared to 2D (2 ± 0.66 %), but the difference was not statistically significant.

Clinically, local recurrence had occurred in one patient (3.3%) in each group. There was no statistically significant difference between both groups in the number of patients developed distant metastases, 3 patients (10%) in group A versus 5 patients (16.7%) in group B (P.value = 0.706) Furthermore, one patient died in each group from extensive metastatic disease (lungs and liver). There was no statistically significant difference in the loco-regional recurrence-free survival (LRRFS) (Figure 2), disease-free survival (DFS) and overall survival (OS) between both groups.

Considering the radiation induced toxicity (according to RTOG toxicity criteria), there was no statistically significant difference between both groups. However, a statistically significant less reduction of cardiac EF measured by isotopic scanning was noticed with 3D-CRT (5.127 ± 4.8839% for 2D versus 2.363 ± 4.7562% for 3D, P = 0.013). (Figure 3) There was no significant difference in the cosmetic outcome for the patients with conservative surgery between both groups as measured by Gray score. The mean score was 6.93 ± 1.033 in group A versus 7.27± 0.961 in group B (P.value =1.0).

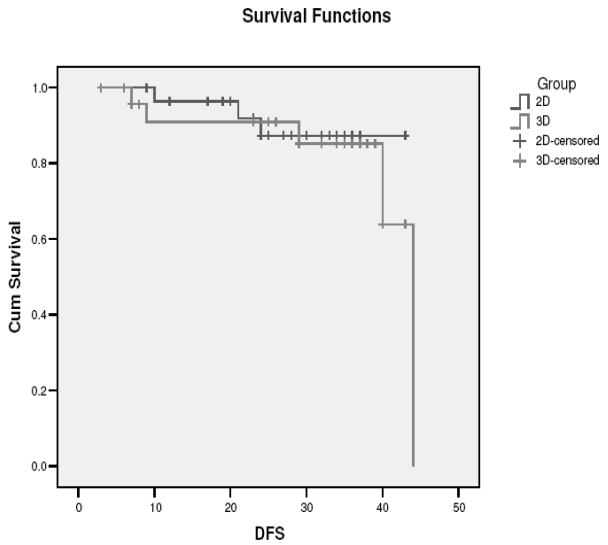

Figure 2: Loco-regional recurrence-free survival (LRRFS) for both groups. (P.value = 0.65)

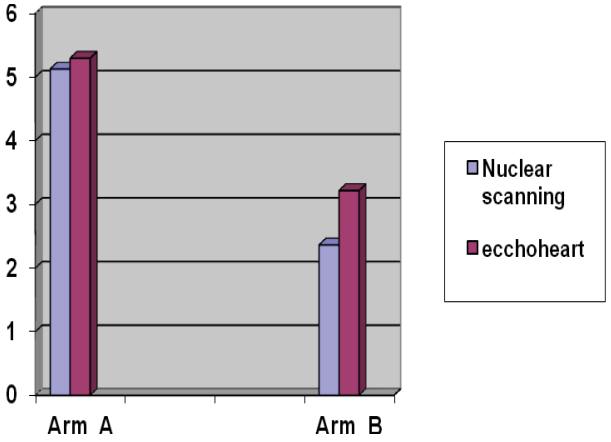

Figure 3: Percentage of the reduction of the ejection fraction (EF) in both groups.

- P. value = 0.013 for nuclear scanning and 0.051 for echoheart

Table 1: Clinico-pathological features of both groups.

Group	A 30 patients	B 30 patients	P.value
Age(years) -Mean+/- SD -Range	 52+/-7.15 40-65	 45.1+/-8.079 34-60	 0.001
Performance status: -0 -1 -2	18(60%) 12(40%) 0(0%)	18(60%) 12(40%) 0(0%)	1.0
Menopausal status: Pre Post	 13(43.3%) 17(56.7%)	 20(66.7%) 10(33.3%)	 0.119
Pathology: IDC	 30(100%)	 30(100%)	 1.0
Grade: -II -III	30(100%) 0(0%)	24(80%) 6(20%)	0.024
Intraductal Componant. no ≤ 25 % > 25 %	 27(90%) 2(6.7%) 1(3.3%)	 25(83.3%) 4(13.3%) 1(3.3%)	 0. 832
Quadrant: -UOQ -IQs & Retroareolar - LOQ	 21(70%) 4(13.3%) 5(16.7%)	 20(66.7%) 5(16.7%) 5(16.7%)	 0.934
T1 T2 T3 T4	4(13.3%) 20(66.6%) 3(10%) 3(10%)	5(16.7%) 18(60%) 3(10%) 4(13.3%)	0.754
No. of +ve nodes: -0 -1-3 -≥4	9(30%) 17(56.7%) 4(13.3%)	11(36.7%) 13(43.3%) 6(20%)	0.647
ER: -Positive -Negative -Not assessed	22(73.3%) 7(23.3%) 1(3.3%)	23(76.6%) 6(20%) 1(3.3%)	0.761
PR:- Positive - Negative - Not assessed	23(76.6%) 7(23.3%) 0(0%)	22(73.3%) 6(20%) 2(6.7%)	0.597
HER2 neu -Positive -Negative - Not assessed	4(13.3%) 8(26.7%) 18(60%)	3(10%) 9(30%) 18(60%)	0.904
Surgery: -BCS -MRM	15 (50%) 15 (50%)	15 (50%) 15 (50%)	1.0
follow up period (months): -Range -Median	 6-39 28.5	 6-41 31.5	 0.904

Table 2: Dose homogeneity and target coverage parameters inside the IMN-PTV for the 15 patients treated with IMN irradiation.

Parameter	2D (mean ± SD) (n =15)	3D-CRT (mean ± SD) (n =15)	P.value
V45Gy	76.47 ± 20.195%	89 ± 8.856%	0.036
V40 Gy	84.47 ± 21.280%	98.13 ± 1.727%	0.005
D90%	3947.73 ± 1178.14 cGy	4664.53 ± 365.24 cGy	0.019
Dmax.	4944.6 ± 806.724 cGy	5141.13 ± 460.18 cGy	0.436
Dmin.	3258.67 ± 1873.85 cGy	4499.13 ± 416.24cGy	0.036
TCP	59.85 ± 4.9 %	75.9 ± 1.9%	0.003

- V45Gy & V40 Gy : The percentage of the PTV volume received at least 45 and 40 Gy, respectively.
- D90% : The dose received by 90% of the PTV.
- Dmin.: The minimum dose received by 5% of the PTV.
- Dmax.: The maximum dose received by 5% of the PTV.
- TCP : Tumor control probability.

Table 3: Parameters used to evaluate left lung toxic dose.

Parameter	2D (mean ± SD) (n =60)	3D-CRT (mean ± SD) (n =60)	P.value
V20Gy	20.18 ± 5.67%	18.22 ± 5.289%	0.031
V30Gy	16.25 ± 5.827%	14.52 ± 5.309%	0.056
D50%	189.13 ± 106.182cGy	149.13 ± 78.132 cGy	0.03
MLD	2.058 ± 0.5169cm.	1.809 ± 0.552cm.	0.306
NTCP	0.747 ± 0.5169%	0.5893 ± 1.58203%	0.014

- V20Gy : The percentage volume of the lt. lung received at least 20Gy.
- V30Gy : The percentage volume of the lt. lung received at least 30Gy.
- D50% :The dose received by 50% of the lt. lung volume.
- MLD : Maximum lung distance.
- NTCP : Normal tissue complication probability.

DISCUSSION

The current prospective randomized study was conducted on 60 female patients with left breast cancer following mastectomy or breast conservative surgery and anthracycline-based combination chemotherapy. The follow up period ranged from 6 - 41 months with a median follow up of 29.5 months.

Both groups were balanced in their clinico-pathological features except for the age which was significantly lower in group B than group A (mean 45.1 ± 8.079 years Vs 52 ± 7.151 years, P.value = 0.001) and the tumor grade where G III tumors were more common in group B (6 patients) versus no patient in group A. This imbalance noticed between both groups (age and grade) is not of great impact as the St., Gallen Consensus, 2005 (confirmed in 2007) considered age of less than 35 years and grade more than I as independent prognostic factors for node negative disease only. In the current study, only one patient was less than 35 years old (in Group B) with node positive status and no grade I tumors were reported in any of the patients.

The difference between 2D and 3D CRT in the coverage of the PTVs was almost insignificant for breast (in BCS), chest wall (in MRM) and SCLN. This difference was significant in the coverage of IMN in favor of 3D-CRT rather than 2D planning. This difference may be attributed to missing a part of IMN in the lower cuts during 2D planning. The same problem was noticed in the trial conducted by Diane et al.[20] The problem of good coverage can be solved by taking lower CT cuts.

A comparison among wide split tangent technique (adopted in the current study), intensity modulated radiation therapy (IMRT) and oblique electron therapy technique was carried out in a planning study by Cho et al.[21] involving 12 patients irradiated for left breast and IMN. The average NTCP for the heart and lung was comparable for both IMRT and oblique electron techniques (≤ 0.7%) while the wide split technique (conformal, non-intensity modulated) showed a higher average NTCP (› 2%)[21].

The calculated TCP for the left breast PTV was comparable to that obtained by John Cho B. et al.[21] as they obtained TCP for the left breast PTV of 70.4 +/- 2.2 % using conformal planning compared to 70.2 ± 2.3 % in the current study using conformal planning.(ref) The calculated cardiac NTCP was better in the current study than that given by Coen et al. as 75 % of our patients (45 patients) has no IMN irradiation[22].

The evaluation of the toxic does received by the risk organs revealed that the significant difference

between 2 D and 3D-CRT was seen mainly for the Lt. Lung. V20Gy is now considered as a good parameter to evaluate toxic dose to the lung and predicts complications as confirmed by Kahan et al.[12] and it was significantly better in the current study in favor of 3D-CRT[23]. Similarly, the same information was appicable for the NTCP. However, in view of the fact that the lung is a late reacting tissue, the impact of better V20Gy or NTCP values translated into better toxicity profiles was not expected to be seen during the relatively short follow up period.

On the other hand, the condition was a little bit different for the heart which is a late reacting tissue also, the significant improvement in D 50 % (for 3D-CRT) had a little but significant less reduction in the cardiac EF only detected by the isotopic scanning but not the echocardiography (borderline significance). This significance was small (less than 3%) and did not affect the outcome according to RTOG toxicity criteria.

CONCLUSION

3D-CRT spared the left lung from receiving higher radiation dose during the post-operative radiotherapy with significant less reduction of cardiac EF. 3D-CRT should be offered for patients who are going to receive IMN irradiation for better coverage of the target volume.

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