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**Original article**

# Institutional Validation of Posterior Margin Delineation For Conformal Radiotherapy of Breast Cancer Regarding Set-Up Errors Nemrock Experience

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Original article

**Background and Aim of the Work:** The benefit of post-operative loco-regional radiotherapy for high risk breast cancer patients in combination with systemic chemotherapy has been well established over the past two decades however radiation toxicity on normal tissues still constitute a significant clinical problem. Standard tangential breast radiotherapy does not only treat portions of the chest wall, but also exposes lung and heart tissue to radiation The aim of this work is to evaluate set-up error at our department (NEMROCK) in 3-D conformal radiotherapy of the post-operative irradiation of breast cancer in the anterior-posterior direction and compare this error to the added margin beyond pectoral fascia using the middle of the rib or rib/pleural interface deep margin method.
**Methodology:** The maximum & minimum vertical distances between the pectoral fascia and the middle of the rib were measured on CT cuts for 30 patients and compared to the set-up error in the Maximum Lung Distance (MLD) after 2 weeks of irradiation by comparing Electronic portal images (EPI) to the Digitally Reconstructed Radiograph (DRR).
**Results:** The set-up error ranged from 2 to 6 mm with a mean value of 3.99 +/- 2.99 mm. The maximum vertical distances between the pectoral fascia and the middle of the rib ranged from 1.83 cm. to 4.02 cm. with a mean value of 2.8695 +/- 3.033 cm. The minimum vertical distances between the pectoral fascia and the middle of the rib ranged from 13 mm. to 14.3 mm and a mean of 13.26 +/- 0. 0026 mm.
**Conclusion:** The use of the middle of the rib or rib/pleural interface as a deep margin may be an over estimation of the truly required margin. The use of 5-7 mm. margins beyond the pectoral fascia (or according to each institute set-up error) is more reasonable.

**Key words:** brest cancer conformal, radiotherapy, set-up errors
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## INTRODUCTION

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[1].

The introduction of Computerized Tomography (CT) scanning and the availability of sophisticated 3-dimensional (3D) planning methods renewed interest in the technical aspects of breast cancer treatments, but this was mainly towards improving dose distributions within the breast itself[2,3,4,5,6].

Studies of radiation toxicity in the treatment of breast cancer 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[7,8,9]. The risk of radiation pneumonitis appeared to be related to the volume of lung irradiated[10,11].

In a study conducted by Kahán *et al.* which included 119 patients with breast cancer treated with conformal radiotherapy Radiogenic lung sequelae were assessed prospectively by means of clinical signs, radiologic abnormalities, and the mean density change of the irradiated lung on CT. Significant positive associations were detected between the development of lung abnormalities 3 months or 1 year after the radiotherapy and the age of the patient, the ipsilateral mean lung dose (MLD), the radiation dose to 25% of the ipsilateral lung (D(25%)) and the volume of the ipsilateral lung receiving 20 Gy (V(20 Gy)). The irradiation of the axillary and supraclavicular lymph nodes favored the development of pneumonitis but not that of fibrosis. No relation was found between the pre-radiotherapy plasma Tumor Growth Factor-beta (TGF-beta) level and the presence of radiogenic lung damage. At both time points, MLD was strongly related to age. Significant positive associations were demonstrated between the risks of pneumonitis or fibrosis and the age of the patient, MLD, D(25%), and V(20 Gy). A synergistic effect of MLD, D(25%), and V(20 Gy) with age in patients older than 59 years was suggested[12].

The technique of 3D conformal radiotherapy in post-operative irradiation of breast cancer involves many steps.

One of the most important steps is the delineation of Clinical Target Volume (CTV), a process that showed some variation in the literature specially in the deep (internal) border Which was defined for intact breast by the middle of the rib[13], by rib/pleural interface[14] or the pectoral fascia. The last method was described by Kiricuta *et al*. in his text and he advised an additional 5 mm. deeper to accommodate for set-up error to delineate the Planning Target Volume (PTV) but no margin to be added for the un-avoidable respiratory motion posterior as it will necessitates much lung volume inclusion in the treated volume[15]. The deep (internal) border for chest wall CTV was defined by rib/pleural interface[13] or in the same way as described by Kiricuta for intact breast. The Radiation Therapy Oncology Group (RTOG) used Posterior Rib-pleural interface. (Includes Pectoralis muscles, chestwall muscles, ribs) for the chest wall CTV delineation but for delineation of posterior margin in cases of intact breast they excluded pectoralis muscles,chest wall muscles and ribs[16].

Electronic portal images (EPI) is a useful tool to verify setup reproducibility in loco regional radiotherapy (LRRT) for breast cancer. In a small pilot study evaluating the use electronic portal imaging (EPI) during treatment to determine intra- and inter-fraction motion in 20 patients undergoing breast radiotherapy and to correlate the magnitude of motion with patient specific parameters, the lung involvement varied by 1.1 +/- 0.2 mm and 1.8 +/- 0.6 mm intra- and inter-fraction, respectively. This indicates that the effect of breathing motion on the amount of radiated lung was not of major concern in the patients studied. Of other patient's specific parameters such as body weight, breast separation, field size and location of the target, only increasing age was significantly correlated with larger inter-fraction motion[17].

## AIM OF WORK

The aim of this study was to evaluate set-up error at our department in3-D conformal radiotherapy of the post-operative irradiation of breast cancer in the anterior-posterior direction and compare this error to the added margin beyond pectoral fascia using the middle of the rib or rib/pleural interface deep margin method. We hypothesized that both methods having larger margin than that is required to accommodate for set-up error and respiratory motion especially in the upper cuts. According to our hypothesis, much volume of the lung may be involved using both methods and using the method described by Kiricuta may be more appropriate especially that you can individualize the added margin according to each center set-up error.

## METHODOLOGY

Thirty patients with breast cancer were recruited in this study at Kasr El-Aini Center of Clinical Oncology & Nuclear Medicine(NEMROCK) during the period between January 2012 to June 2012.The eligible patients met the following Inclusion Criteria:

1. Female sex.
2. Left sided breast cancer.
3. Pathologically proven carcinoma following modified radical mastectomy or breast conservative surgery.
4. Age 18-70 years.
5. WHO performance status of 2 or better.
6. Need for post-operative radiation therapy(which was given 2 weeks following adjuvant chemotherapy ):-

A. Chest wall when at least one of the following indications was present:
- T2 Tumors more than 4 in maximum dimension.
- T3 & T4 Tumors.
- Pathologically involved axillary lymph nodes

B. Whole breast in all cases after breast conservative therapy with tumor bed boost in all cases.

**Exclusion Criteria:**
1. Positive pregnancy test.
2. Thin flat chest wall (better to be treated with electron beam).
3. Contraindication to chest wall irradiation e.g: severe collagen vascular disease & previous chest irradiation.
4. History of other malignancy or severe co-morbid disease.
5. Evidence of distant metastases (evident by negative bone scan , abdominal Ultrasound & chest radiograph).

All patients underwent history taking, general & local examination. Planning was performed as the following:

**CT Scanning:**
Patient was put on Planning C.T table in the treatment position comfortable, flat, supine, on chest board with both hands grasping the middle column of the chest board. The angle of the chest board was chosen so that the patient can pass easily through C.T pore & the sternum was made flat & parallel to table as much as possible. LASER beam was used to define the reference point " marked with radio-opaque marks" preferred to be over xiphoid process with tattooing LASER intersection points & an arbitrary superior point in the saggital LASER line for reproducibility of the centralized position". Multiple C.T cuts were taken every 5 mm. from the chin to upper abdomen. All cuts were transferred to treatment planning system (ECLIPSE version 11).

**Delineation of volumes:**
Heart was defined as all visible myocardium (excluding pericardium) from the apex to Rt. Atrium.

The pulmonary trunk, root of ascending aorta & superior vena cava were excluded. It is delineated using manual contouring. Lungs were delineated using auto-contouring tool. Chest wall "in mastectomy" was extended from a maximum of 1cm. medial to ipsilateral sternal edge medially to just beyond the mid-axillary line in presumed breast tail laterally & anterior axillary line in the remaining presumed breast tissue (radio-opaque wire marks helped in this step). It is drawn from the sterno-clavicular joint above to 1cm. below the level of the contralateral breast fold downwards. Breast "in conservative surgery" was delineated as all visible breast parenchyma as seen on C.T slices were included with 7mm. more extension of the lateral & medial margins , while posterior margin was extended to bisect the middle of the rib along its whole length. It was drawn from the sterno-clavicular joint above to 1cm. below the level of the breast fold downwards. The maximum (on the upper C.T cut) and minimum vertical distances between the pectoral fascia and the middle of the rib were measured and registered for all patients after delineation for post- operative irradiation of breast cancer using RTOG guidelines as shown in Figure (1).

**Planning:**

The breast or chest wall was treated isocentrically using 2 tangential beams with selective multi-leaf blocking to protect risk structures "heart & lungs". IMLNs, if indicated were included in the tangential beams.

If supraclavicular lymph nodes were irradiated; half beam blocked supraclavicular field was used with suitable gantry angle rotation away from the cord with posterio-superior blocking in the tangential portals to decrease overlap in the junctional area.

Digitally reconstructed radiographs (DRRs) were generated for the two tangential portals, supraclavicular portal & for 2 simulation portals using gantry angles of 0 & 90 degrees for easy anatomical Judgment.Plans then were approved by both physician & physicist based on the following:-

**Simulation:**

The aim of this step was to localize treatment portals isocenter (s) on patient surface using its/their definition in relation to the C.T reference point from the treatment planning system data, by means of distances in X ,Y & Z directions. The same position used in C.T scanning was reproduced using tattoo points for LASER localization of the reference point so that simulator isocenter (the intersection between gantry rotation axis & collimator rotation axis) was the reference point. The table was moved in the X, Y & Z directions as planning system described the isocenter of treatment portal in relation to the reference point. So that the simulator isocenter became the treatment portal isocenter. The isocenter of the treatment portal was verified by comparing simulator images with the corresponding DRRs, which should be identical. This step was also repeated for supraclavicular portal isocenter. The isocenter (s) of the treatment portals was/were more verified by checking the resultant source skin distance (SSD) of the treatment portals which were the same reported SSD by the treatment planning system . The LASER lines defining the isocenter (s) of the treatment portals were drawn on patient skin with tattooing beams entrance points. This step was done for both the 2D & the 3D arms.

**First Session:**

First session was given 2 weeks following chemotherapy. The patient was put on the treatment table in the same position used in scanning & simulation using LASER lines drawn on patient surface in the step of simulation. The treatment machine was ordered to open treatment portals transferred from the treatment planning system. The entrance points for the treatment portal were those tattoed on patient surface during simulation & the SSDs were the same. Electronic portal images (EPIs) were taken using I-view Electronic portal image device (EPID) of ELEKTA (I-view) & matched to DRRs. Differences of more than 5 mm. were not accepted.

**Weekly check:**

Toxicity was reported (according to RTOG criteria) & managed. New portal images (Figure 7) were matched to DRR. Difference of more than 5mm. were not accepted. & in this situation patients were re-simulated. The maximum vertical set-up error was reported i.e: the maximum difference in the MLD from that in DRR during weekly checks (Figure 2).

Statistical comparison of the set-up error & the previously mentioned vertical distances was carried out.

**Statistical Analysis:**

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. 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.

## RESULTS

**Patients Characteristics:**

Clinico-pathological features and body measures of the studied patients are listed in Table (1)

Set-up error in relation to differences in delineation methods (Table 2).

1. The set-up error for the thirty patients were assessed after 2 weeks of radiotherapy using E.P.I and the difference in the MLD from that in DRR ranged from 2 to 6 mm and a mean value of 3.99 +/- 2.99 mm.
2. The maximum vertical distances between the pectoral fascia and the middle of the rib ranged from 1.83 cm. to 4.02 cm. and a mean value of 2.8695 +/- 3.033 cm.
3. The minimum vertical distances between the pectoral fascia and the middle of the rib ranged from 13 mm. to 14.3 mm and a mean of 13.26 +/- 0. 0026 mm.

**Figure 1:** Measurement of the vertical distance between pectoral fascia and middle of the rib in the uppermost lung cut.

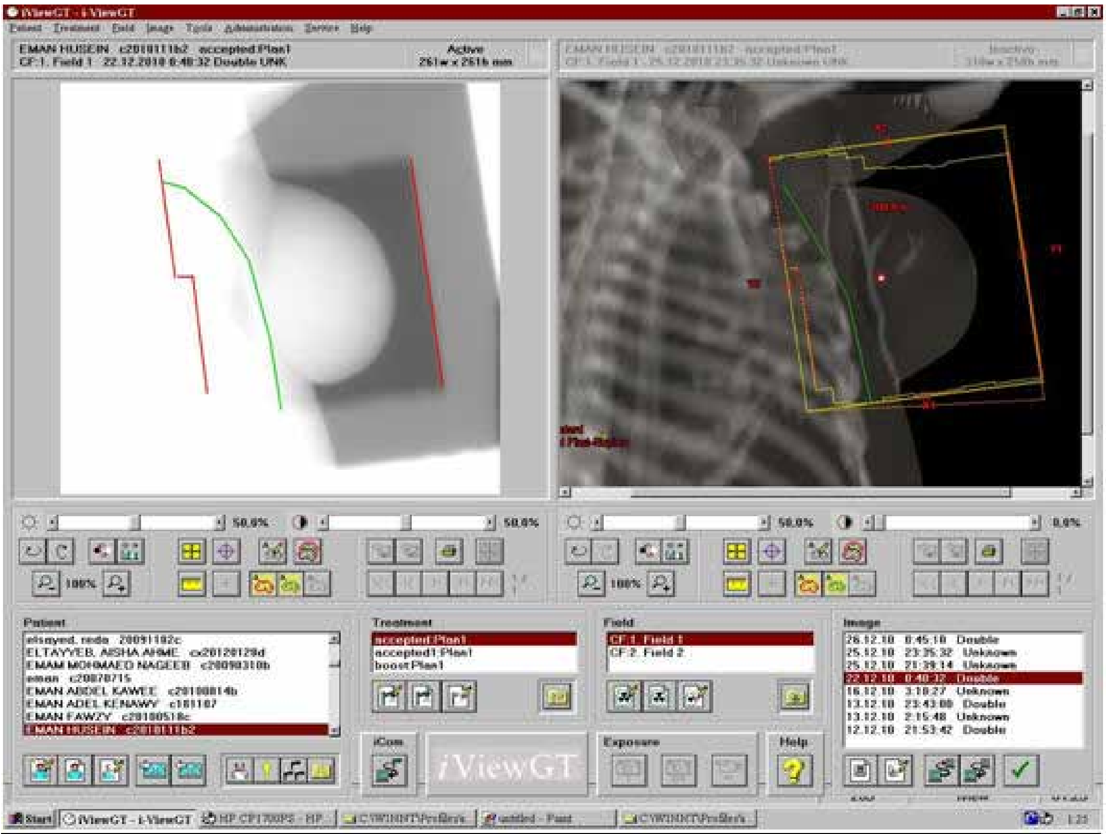

**Figure 2:** Comparison of Electronic Portal Image (EPI)to the left with Digitally Reconstructed Radiograph (DRR) to the right.

**Table 1.** Clinico-pathological features and body measures of the studied patients(30 patients).

| | |
|---|---|
| Age(years)-(mean+/- SD)<br>-range | 52+/-7.15<br>40-65 |
| WHO Performance status: - 0<br>-1<br>-2 | 18(60%)<br>12(40%)<br>0(0%) |
| Menopausal status: Pre*<br>Post | 13(43.3%)<br>17(56.7%) |
| Pathology:-IDC | 30(100%) |
| Grade - II<br>-III | 30(100%)<br>0(0%) |
| Intraductal Componant. no<br>≤ 20 %<br>> 20 % | 27(90%)<br>2(6.7%)<br>1(3.3%) |
| Quadrant –UOQ<br>- IQs & Retroareolar<br>- LOQ | 21(70%)<br>4(13.3%)<br>5(16.7%) |
| T -1& 2<br>-3 & 4 | 22(73.3%)<br>8(26.6%) |
| -No. of +ve nodes: -0<br>-1-3<br>-≥4 | 9(30%)<br>17(56.7%)<br>4(13.3%) |
| ER -positive<br>- negative<br>- not assessed | 22(73.3%)<br>7(23.3%)<br>1(3.3%) |
| PR - positive<br>- negative<br>- not assessed | 22(73.3%)<br>7(23.3%)<br>1(3.3%) |
| HER2u -positive<br>-negative<br>- not assessed | 9(30 %)<br>20(66.6%)<br>1(3.3%) |
| Weight(kg)-range<br>-mean +/-SD<br>-median | 61-105<br>84.9 +/-12.1<br>85 |
| Height(cm.)-mean | 169.27 +/-8.9 |
| SA($m^2$) -mean | 1.89 +/-0.12 |
| Tangential separation(cm.) | 25.33 +/-2.91 |
| Surgery : -MRM<br>-BCS | 6 (20 %)<br>24 (80%) |

SA:-Surface Area , MRM:-Modified Radical Mastectomy,BCS:- Breast Conservative Surgery, SD:- Standard Deviation , IDC:-Invasive Duct Carcinoma
T:- Tumor , N :-Nodal status
ER:-Estrogen Receptor , PR:-Progestron Receptor, HER2u:-C-erb 2receptor
DM:-Dibetus Melitus , HTN:-Hypertension, BA :-Bronchial Asthma
UOQ:- Upper Outer Quadrant , IQs:- Inner Quadrants
LOQ:-Lower Outer Quadrant, WHO: - World Health Organization
* peri –menopausal patients with less than 2 years cessation of menstruation were added to pre –menopausal.

**Table 2:** Set-up error in relation to differences in delineation methods.

| Mean +\- S.D | Range | |
|---|---|---|
| 3.99 +/- 2.99 mm. | 2-6 mm. | Set-up error |
| 28.695 +/- 30.33mm. | 18.3 mm. - 40.2 mm. | D.D.M (uppermost cut-maximum value) |
| 13.26 +/- 0. 0026 mm. | 13-14.3 mm. | D.D.M (mid-beam cut value) |

D.D.M = Difference in Delineation Method.
S.D = Standard Deviation.

## DISCUSSION

Standard opposed tangential fields with appropriate use of wedges to optimize dose homogeneity remain the most commonly employed method for delivery of chest wall or whole breast irradiation. A number of publications have explored the potential advantages of 3D conformal radiation therapy (3-D CRT) or intensity-modulated radiation therapy (IMRT) to treat patients with breast cancer. Theoretically, 3-D CRT involves a reduction in the volume of normal tissues receiving a high dose, with an increase in dose to the target volume that includes the tumor and a limited amount of normal tissue. Usually up to 2 to 3 cm of underlying lung is included in the tangential portals. The amount of lung included in the irradiated volume is greatly influenced by the portals used. Bornstein *et al.* determined the amount of lung irradiated in 40 patients with breast cancer using CT scans for treatment planning in the treatment position. Parameters measured from simulator films included the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center of the field (central lung distance [CLD]), the maximum perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall (maximum lung distance [MLD]), and the length of lung as measured at the posterior tangential field edge on the simulator film. The best predictor of the percentage of ipsilateral lung volume treated by the tangential fields was the CLD. A CLD of 1.5 cm predicted that approximately 6% of the ipsilateral lung would be included in the tangential field, a CLD of 2.5 cm, approximately 16%, and a CLD of 3.5 cm, approximately 26% of the ipsilateral lung[18].

In this study we hypothesized that the use of the middle of the rib or rib/pleural interface as a deep margin may be an over estimation of the truly required posterior margin having larger margin than that required to accommodate for set-up error especially in the upper cuts with the aim of using a more limited institute-individualized posterior margin and as previously mentioned and described by Kiricuta *et al*. no margin to be added for the un-avoidable respiratory motion posterior as it will necessitates much lung volume inclusion in the treated volume margin; hence reducing the normal lung tissue irradiated without compromising the target volume dose. Especially that the majority of the patient population presenting to our centre show thick chest walls. We reviewed and analyzed the planning CT of 30 patients with left-sided breast cancer planned for postoperative radiotherapy either to the chest wall or whole breast and the middle of the rib or rib/pleural interface were used as deep margins; set-up error for the thirty patients were assessed after 2 weeks of radiotherapy using E.P.I.The set-up error in the vertical direction varied from 2-6 mm. with a mean value of 3.99 +/- 2.99 mm. , while the vertical distance between pectoral fascia and the middle of the rib varied between 18.3 mm. - 40.2 mm. and 13-14.3 mm. with mean values of 28.695 +/- 30.33mm. and 13.26 +/- 0. 0026 mm. in the upper cut (thick pectoralis) and mid beam cut (thin pectoralis) respectively. To our knowledge, no previous study evaluated these measures and as shown the maximum vertical set-up error (6 mm.) was much less than the minimal vertical distance between pectoral fascia and the middle of the rib in the studied patients even in the mid beam cut (thin pectoralis) which showed a minimal value of 13 mm. which means that we can spare at least 7 mm. in the posterior delineation in the mid beam cut and at least 12.3 mm. in the upper cut (difference between minimal vertical distance between pectoral fascia of 18.3 mm. and the maximum vertical set-up error of 6 mm.). We believe that , the use of added institution evaluated set-up error to a posterior margin of pectoral fascia may spare good volume of lung and heart from receiving toxic radiation dose specially in the machines using motorized wedge technology as the direction of leafs motion is perpendicular to the wedge (i.e: leafs move cranio-caudal), as the leafs will be more easy covering lung tissue when removing deep part of the target volume more in the upper cuts, a hypothesis that need further research to prove.

## CONCLUSION

The use of the middle of the rib or rib/pleural interface as a deep margin may be an over estimation of the truly required margin. The use of 5-7 mm. margins beyond the pectoral fascia (or according to each institute set-up error) is more reasonable and may help to decrease the lung volume that is involved in the radiation field. Further study of the effect of the delineation method on planning outcome especially the effect on the lung volume that is involved in the radiation field is highly recommended.

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