Changes in Pulmonary Function and Development of Clinical Radiation Pneumonitis in Breast Cancer Patients following Post Mastectomy Radiation Therapy

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Abstract: Background: Lung is the main organ at risk for radiation induced injury while treating breast cancers with Post Mastectomy Radiotherapy (PMRT). Restrictive lung changes are usually seen in spirometry which tends to normalize by 1 year. Central Lung Distance (CLD) is shown to correlate well with the percentage of ipsilateral lung volume irradiated.

Aims and Objectives: Spirometric changes following Radiation Therapy (RT) to chest wall in breast cancer patients using conventional fractionation and its correlation with acute radiation pneumonitis.

Materials and Methodology: Thirty Breast cancer patients who received RT to chest wall +/- supraclavicular fossa and axilla, following Modified Radical Mastectomy (MRM) and neoadjuvant or adjuvant chemotherapy using tangential beams with Co60 teletherapy to a dose of 50 Gray in conventional fractionation were included and followed up till 6 months post RT. Baseline chest X-ray and spirometry done pre-RT were compared with those taken at 1, 3 and 6 months after completion of RT. Patients were evaluated at each visit for signs and symptoms of radiation pneumonitis, when present were graded as per Radiation Therapy Oncology Group (RTOG) criteria.

Results: There was a significant fall in Forced Vital Capacity (FVC) by the end of 3 months (p value <0.01) which improved by 6 months without any active intervention in 95% of the patients. Mean baseline FVC was 83% which decreased to 70% by the end of 3 months and 79% at 6 months. Forced Expiratory Volume in first second (FEV1) and FEV1/FVC did not show any significant change compared to baseline. Spirometric changes correlated with reversible restrictive lung changes. One out of 30 patients developed symptomatic acute radiation pneumonitis (5%) of grade 3 severity who had moderate restrictive lung disease.

Conclusion: Significant decrease in FVC of the lungs is present following PMRT in carcinoma of breast patients in the initial 3 months which tends to normalize by 6 months. 5% of the patients develop symptomatic acute lung toxicity which can be further reduced by minimizing the irradiated lung volume.

Keywords: Breast cancer, Adjuvant radiotherapy, Radiation pneumonitis, Spirometry, CLD.

INTRODUCTION

Breast Cancer (BC) is the most common cancer in women worldwide with favourable survival rates with appropriatetreatment [1]. Adjuvant Radiotherapy plays an important part in the multidisciplinary approach for management of BC, as it reduces loco-regional recurrence and improves overall survival [2].

Lung is an important dose-limiting organ at risk for radiation induced injury. Hence, optimal RT planning to minimize its exposure is crucial to reduce toxicity [3]. RT induced lung injury is mediated by reactive oxygen species causing Radiation Pneumonitis (RP). It is characterized by diffuse alveolar damage leading to the loss of type I pneumocytes and alveolar edema in

acute phase (i.e. within 3months post RT); and pulmonary fibrosis in long-standing cases (>6months) [4-6].

Patients present in acute phase, usually between 4 and 12 weeks following completion of RT, with dry cough, dyspnoea, low-grade fever and pleuritic chest pain [5]. Symptomatic pneumonitis occurs approximately in 5-15% of patients irradiated for BC [7].

Radiological changes which include consolidation, ground glass opacification, linear or dense opacities, volume loss are usually confined to the lung tissue within the radiation portal [8]. Spirometric parameters including Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV1), Total Lung Capacity (TLC) have been consistently shown to fall within the first six months but tend to normalize by 1 year. FEV1/FVC is usually within normal limits or slightly decreased, signifying the restrictive type of lung disease [9]. Several risk factors for RP like age and

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pre-radiotherapy functional level of the patient, irradiated lung volume, radiation dose, Central Lung Distance (CLD), and use pneumotoxic of chemotherapy have been identified [10-12].

In patients treated with tangential fields to chest wall, CLD was shown to correlate well with the percentage of ipsilateral lung volume irradiated and hence European Organization for Research and Treatment of Cancer (EORTC) and European Society of Mastology (EUSOMA) states that the CLD should be kept within 3 cm to limit the predicted risk of RP to around 20.7% [13]. Although Radiation induced Pneumonitis may not increase the risk of death, it has a negative impact on quality of life, and breast carcinoma patients with compromised pulmonary functional reserve may have relatively inferior long-term treatment outcomes [14].

There is a limited data between the relevance of reduction in the spirometric parameters and its correlation with clinical symptoms. . In the present study we are quantifying the changes in spirometric parameters due to RT over 6 months of follow-up and its relationship with CLD.

METHODOLOGY

After the approval of Institutional ethics committee and informed written consent by the patients, 32histology proven breast cancer patients who received adjuvant RT with conventional fractionation were prospectively enrolled into the study. All patients had Karnofsky Performance Status (KPS) > 70, had undergone total mastectomy (simple or modified radical) with or without axillary lymph node dissection. Systemic treatment was allowed as per the institutional protocol. Exclusion criteria for the study were prior RT to the thorax, patients with metastatic disease or preexisting lung pathology.

All patients received RT dose of 50Gy in 2Gy per faction, 5fractions /week under Telecobalt. Two tangential beams were used with a breast cone or wedges for the chest wall and single Anterior-Posterior (AP) field for the Supraclavicular Fossa (SCF)(please use the full terminology along with abbreviation while using for the first time). All patients underwent Computerized Tomography (CT) simulation and CLD, defined as the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the centre of the field, was documented. Baseline chest X-ray and spirometry (best out of 3 attempts) were done prior to the start of RT and compared with those taken at 1, 3 and 6 months after completion of RT. Patients were evaluated in each visit for signs and symptoms of RP, when present was graded as per Radiation Therapy Oncology Group (RTOG) criteria.

Statistical Analysis

One-way ANOVA test and t-test were used to compare the means of independent samples of various spirometric parameters at different follow-up periods and between different groups respectively. P value of less than 0.05 was taken as significant. Pearson Correlation was used to establish the relationship between CLD and volume of lung irradiated with 0 to +1 taken as positive correlation. Statistical Package for the Social Sciences (SPSS®- Registered product of IBM) software trial version no. 19 was used for analysis of all the data.

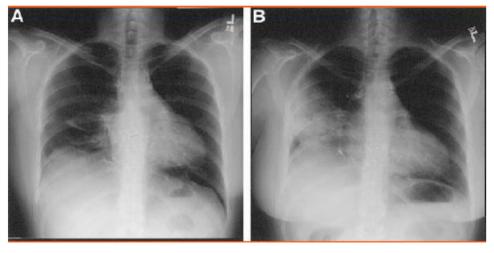


Figure 1: Chest radiographs showing features of RP [15].

Patients Irradiated site Age Stage Surgery Chemotherapy Enrolled-32 Stage II -16 MRM+ALND CW+Axilla+SCF-22 FAC-14 Mean 51Y -28 CW+SCF-5 P+AC-14 Evaluable-30 Range-32-70Y Stage III-11 Simple Mastectomy-2 CW ONLY-3 NONE-2

Table 1: Patient and Treatment Characteristics (F-(5Flurouracil, A-Adriamycin, C-Cyclophosphamide, P-Paclitaxel) (MRM- Modified Radical Mastectomy, ALND- Axillary Lymphnode Dissection, CW- Chest Wall)

RESULTS

Patients who met all the inclusion criteria and gave informed written consent were analysed. Out of 32 patients, two patients were excluded from the study as one of them was unable to be followed-up after RT and the other one developed metastasis to the liver.

Central Lung Distance

Mean CLD was observed to be 2.05cm with a strong positive correlation with ipsilateral lung irradiated (mean=115.62cc, Pearson Correlation=0.89). Relationship with right and left sided BC is summarized it the Table 2.

Table 2: Laterality and Corresponding CLD and Volume of Lung Irradiated

| | Right | Left |
|--------------------------------|------------|-----------|
| Percentage | 55% (n=21) | 45% (n=9) |
| CLD (p = 0.22) | 1.92 cm | 2.06 cm |
| Mean volume of lung (p = 0.07) | 121.75 cc | 108.11 cc |

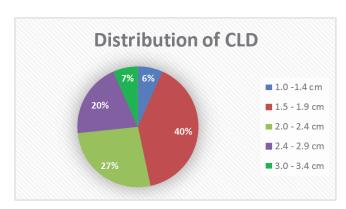


Figure 2: Pie chart showing percentage distribution of CLD.

Chest X Ray

Normal study was observed before starting RT in all patients except for one who had fibrocavitatory lesions in the right apical region which was not in the field of RT. At 1month post RT, 13% (n=4) patients had mild

hazy opacity in the area irradiated which resolved by 3 months in 2 patients, progressed to dense fibrosis in one patient by 6 months and persisted without any change in another patient.

Spirometry

Mean baseline values of FVC%, FEV1%, FEV1/FVC and PEF% were observed to be 84.96%, 80.79%, 81.74% and 74.45% respectively. There was a significant fall of 12.23.1% (p=0.0001) and 10.47% (p=0.011) in the FVC% and FEV1% measured at 1 month respectively. But the fall in FEV1/FVC and PEF% was not statistically significant.

Fall in FVC% was statistically significant even at 3 months when compared to baseline with mean fall of 9.34% (p=0.01) signifying delayed recovery of restrictive lung injury. In contrast, the fall in FEV1% became statistically non-significant at 3 months as compared to baseline (7.82%, p=0.076) due to reversible airway obstruction. Values at 6 months were similar to baseline. This is summarized in Table 3.

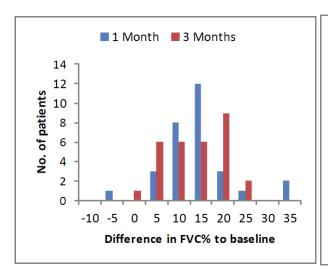
We further compared the Spirometric changes in patients with CLD less than 2cm (mean=1.65cm) with those of more than 2cm (mean=2.55cm). The results are summarized in Table 4.

Influence of Chemotherapeutic agents on Spirometric Parameters

The baseline FVC%, FEV1% and FEV1/FVC were comparable in patients who received taxanes + AC (n=11) or FAC (n=8), pre or post RT. On follow up, there was no statistical difference between the 2 groups. On the contrary, baseline mean PEF% was lower in the group who received FAC (66.7%) as compared to taxanes (80%). Subsequently a significant fall was noted at 1 month and 3 months (p=0.007). Tamoxifen was started post-RT depending on the hormone receptor status in 10 patients and there was no significant difference in spirometric parameters between the 2 groups.

Table 3: Variation in Mean Spirometric Parameters and Corresponding p Values with Respect to the Baseline

| | Baseline | 1 month | p value | 3 months | p value | 6months | p value |
|----------|----------|---------|---------|----------|---------|---------|---------|
| FVC% | 84.96 | 72.73 | 0.0001 | 73.62 | 0.001 | 80.83 | 0.55 |
| FEV% | 80.79 | 70.32 | 0.01 | 72.97 | 0.07 | 81.41 | 0.9 |
| FEV1/FVC | 81.73 | 78.69 | 0.1 | 80.53 | 0.7 | 78.34 | 0.24 |
| PEF% | 74.45 | 65.06 | 0.1 | 69.53 | 0.6 | 73.11 | 0.35 |



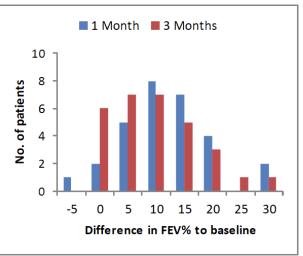


Figure 3: Histogram showing change in FVC% and FEV% at 1 and 3 months.

Table 4: Comparison of FVC% and FEV1% between Patients with CLD <2cm and >2cm

| | Ва | seline | P value | P value 1 month | | P value | 3 months | | P value |
|-------|-------|--------|---------|-----------------|-------|---------|----------|-------|---------|
| | <2 cm | >2cm | | <2 cm | >2cm | | <2 cm | >2cm | |
| FVC% | 87.6 | 81.375 | 0.06 | 75.75 | 69.84 | 0.1 | 77.23 | 72.48 | 0.07 |
| FEV1% | 81 | 79.13 | 0.8 | 79.72 | 71.16 | 0.07 | 74.71 | 73 | 0.77 |

Table 5: Follow Up and Toxicity Grading

| Actue toxicity | At the end of RT | At 1 month | At 3 months |
|---------------------------|------------------|------------|-------------|
| Pneumonitis | None | 1(3.3%) | None |
| Skin (grade II-III) | 7(23.3%) | 1(3.3%) | None |
| Pharyngitis and oesophage | 5(16.7%) | None | None |
| Laryngitis and trachitis | 1(3.3%) | None | None |

Clinical Assessment

One (5%) patient developed grade 3 RP after 1 month of RT with spirometry showing severe restrictive features and chest X ray showed diffuse haziness in the irradiated area. She required inhalational and oral steroids and symptoms subsided by 3rd month follow up.

DISCUSSION

Conventional RT using Co60 teletherapy is the most commonly employed technique in the developing countries. Hence minimizing various toxicities due to RT in such long-term survivors takes prime importance to improve the quality of life and reduce morbidity.

Truong [3], in his review article in 2004, concluded that the incidence of symptomatic RP was 4% in patients who also received nodal with chest wall irradiation. Similar results were found in our study with symptomatic or clinical RP seen in 5% patients who received locoregional RT with extended supraclavicular field; the time of onset of symptoms was 5 weeks. This time of onset of symptoms was also similar to the patients studied by Wennberg et al. [15] in 2002. However in the present study, radiological asymptomatic RP was found in 15% (n=3) and 5% (n=1) at 1 month and 3 months post RT respectively. These early radiological changes represent diffuse alveolar damage with edema. All patients with radiological RP had received SC and axillary RT with single AP field. Kahan et al. [16] had concluded in their study that irradiation of axilla and SCF increased the risk of radiological fibrosis by 2.5 times.

Gagliardi et al., established that the lung doses with equivalent Normal Tissue Complication Probability (NTCP) of 50% to be 40.6 Gy in patients <57 years and 26.9 Gy in >57 years. Hence in this study we compared the incidence of RP and spirometric changes between the two groups of >50 years and <50 years. There was no significant difference in the baseline spirometry or the subsequent reduction in lung volumes post RT. Jeba et al. [12] also compared the patients of >50 years age group with that of <50 years and found significant difference in the incidence of RP with odds ratio of 4.4 for developing RP in patients aged >50 years. But the performance status of the patients is not mentioned in this study. As we included only patients with KPS>70 and had a smaller sample size, we cannot conclusively establish the influence of age on incidence of RP.

Chakraborty et al. [18] reported the mean reduction of various pulmonary function parameters as compared with the pre-radiation values to be 0-19%. Ooi et al. [19], also demonstrated progressive decline in FEV1%, FVC%, TLC%, and DLCO after radiotherapy which remained irreversible at 12 months (p<0.05). In our study, statistically significant mean fall of 11.1% (p=0.01) and 9.8% (p=0.011) in FVC% and FEV1% at 1 month which tended to normalize by 6 months as compared to baseline was observed. In comparison, reduction in the FEV1/FVC and PEF% (3.04% and 7.4%) was not significant. These results supports that the radiation induced lung injury is mainly restrictive type [4]. Similar results were reported by Krengli et al. [20], and Tokatli et al. [21].

The mean CLD in our study was 2.05 cm which was within permissible limits. Lingos *et al.* [22] concluded that the incidence of RP is <1% when CLD was kept less than 3cm. The present study also supports significant correlation between CLD and volume of ipsilateral lung irradiated with strong Pearson Correlation of 0.89. Based on linear regression model by Bornstein *et al.* [13] the percentage of ipsilateral lung irradiated would be 11.3% which is within acceptable limit.

In a study by Jeba *et al.* [12] the mean CLD in patients who developed symptomatic RP was 2.38 cm. Hence in this study we tried to investigate whether limiting the CLD to less than 2cm further reduced the incidence of RP and/or fall in lung volumes post RT as opposed to the standard 3cm limit that is usually recommended. We found significant difference in the mean volume of lung irradiated between the 2 groups with mean volume being 88.5cc in patients with CLD < 2cm, as compared to 161.14cc in patients with CLD > 2cm. But the difference in the reduction in various spirometric parameters was not significant as seen in Table 4. Hence stringent limitation of CLD to 2cm may not be necessary though further prospective studies with larger sample group are necessary.

Yu et al. [23] found no difference in the incidence of RP with various chemotherapy regimens when given sequentially (p=0.05). We did not observe any influence of chemotherapy over Spirometric parameters except for PEF% which was lower in patients receiving FAC regimen, probably reflecting selection bias as patients receiving FAC chemotherapy generally had a lower performance status and higher co-morbidities compared to patients receiving taxanes.

Careful clinical follow-up, focused on early detection of relevant symptoms and signs, would appear the most reliable measure for the early detection of radiation pneumonitis and subsequent fibrosis. According to Rothwell *et al.*, [15] developments of symptoms in the acute phase imply the possibility of permanent damage.

Our findings are in full agreement with previously published reports and we believe that, with conventional fractionation, the inclusion of a small portion of lung in the irradiated field is acceptable. However, as far as these observations can be generalized, one should strive to keep radiation field below the level of one-third of the total lung.

CONCLUSIONS

This study demonstrated a significant reduction in FVC% and FEV1% following RT in breast carcinoma patients in the initial 3 months which tends to normalize by 6 months. FEV1/FVC was maintained within normal limits, signifying the restrictive type of lung injury. 5% of the patients who received loco regional RT developed symptomatic acute lung toxicity which could be reduced by minimizing the irradiated lung volume. CLD correlated well with the volume of ipsilateral lung irradiated. Larger prospective studies to study the factors for minimizing the decrement in spirometric parameters and its correlation with clinical RP would be useful.

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