

## ORIGINAL RESEARCH

# STUDY OF EARLY RADIATION PNEUMONITIS IN CARCINOMA BREAST AND LUNG TREATED WITH RADIOTHERAPY

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## ABSTRACT

**Introduction:** Radiation induced Pulmonary toxicity is common after radiation therapy (RT) to the thorax. Breast Cancer is one of the commonest cancers requiring chest wall irradiation. The quantification of lung tissue response to irradiation is important in designing treatments for maximum tumor control.

**Objective:** To study the impact of lung volume irradiated on early pneumonitis in patients undergoing RT for breast cancer.

**Method:** The Study was conducted as per ICH GCP guidelines and with Ethics Committee approval. This is prospective study of 26 patients with breast cancer treated with radiotherapy to the chest wall. Computerized tomography (CT) simulation was part of treatment planning. The volume of lung irradiated was calculated by using both CLD (Central Lung Distance) method and summation of area technique. Chest x-ray and spirometric tests were done first as a baseline procedure and later at one month and at 3 months after completion of radiotherapy.

**Results:** The incidence of acute radiation pneumonitis in carcinoma breast is 3.9%. With conventional technique of treatment planning for carcinoma breast, percentage of lung volume irradiated in majority of cases (16/26) was within 11% and CLD proved to be best predictor of it. The total dose of 45-50 Gy with conventional fractionation and dose/Fr of 180-200 cGy is safer.

**Conclusion:** The spirometry is helpful in assessing the radiation damage of lung. The CLD method of calculation of PIV (Percentage of Irradiated Lung Volume) is recommended.

**Keywords:** Radiation pneumonitis, acute radiation reactions, radiotherapy, breast cancer

## INTRODUCTION

Breast cancer is one of the commonest malignancies, encountered in women all over the world and is a leading cause of cancer death in females. Around 1% of all breast cancers occur in men.

In India, it is the second most frequent site of female carcinoma in Bangalore, Madras, Delhi, Bhopal and Barshi cancer registries and the most common site in Bombay.

Radiation induced pneumonopathy may occur as an "inflammatory reaction". Pneumonopathy might be a better term because this is not an infective process but occurring after completion of radiation or chemotherapy treatment. Symptomatic pneumonitis occurs approximately in 5-15% of patients irradiated for breast and lung carcinoma.<sup>1,2</sup> Radiation induced lung injury occurs in two phases: an early phase, radiation pneumonitis, developing 1-6 months after irradiation which can be followed by late phase, radiation fibrosis, which occurs after 6 months.<sup>3</sup> In 1921, Groover et al described one of the earliest reports of radiation damage of the lung.<sup>4</sup> In 1922, Tyler and Blackman described clinical and

radiological changes in the lungs and pleura, which they attributed to previous irradiation.<sup>5</sup> Hines confirmed their assumption when he presented the results of two autopsies of irradiated patients that showed pathological fibrosis of the lung. In the following years, clinical symptoms, functional changes, radiographical and histological findings were described in more detail.<sup>6</sup>

The early radiation pneumonitis incidence is firmly established at 5% for 820 ccy, 50% for 930 ccy and 80% for 1100 ccy following a single high dose rate exposure.<sup>7</sup> With fractionated radiotherapy, the average lung dose of 24.7 cy in 15 daily fractions would give 5% incidence of pulmonary damage, whereas 43.5 ccy in 15 daily fractions would produce early pulmonary damage in 95% of patients receiving such dose.<sup>8</sup> The pulmonary function test (PFT) shows the functional changes of radiation induced lung injury and are usually accompanied by a decrease of lung volumes in all compartments.<sup>3</sup>

The technical developmental like 3 dimensional (3D) imaging in planning, ability to plan 3-DCRT (3-D Conformal Radiotherapy), IMRT (Intensity Modulated Ra-

diotherapy), use of radioprotector like Amifostin, and angiotensin type 2 receptor blocker are some of the advents in minimizing this complication of radiation pneumonitis.

## OBJECTIVE

The objective was to study the impact of lung volume irradiated on early pneumonitis in patients undergoing RT for cancer breast.

## MATERIAL AND METHODS

A prospective clinical study consisting of 26 patients with Carcinoma of breast receiving radiation therapy to the chest wall was undertaken investigating the actual occurrence of early radiation pneumonitis and the association of volume of irradiation, radiation dose, fractionations and the other influencing factors (co morbid conditions) in the development of early radiation pneumonitis. Patients with diagnosis of histopathologically proven, carcinoma breast and carcinoma lung receiving radiotherapy (RT) on Telecobalt machine were included in the study. These patients received either post mastectomy Chest wall radiotherapy or Breast conservative radiotherapy. Patients with poor performance status i.e., KPS < 70% & those who have received previous chemotherapy with drugs like bleomycin and mitomycin were excluded from the study.

A detailed history, clinical examination, routine baseline investigations including chest x-ray and spirometry tests was done. Treatment details were explained to the patient and their attendant and informed consent was obtained. Radiotherapy planning was done using CT simulation and x-ray simulation. Treatment was executed once the simulation data were transferred to treatment planning system and dosimetry was performed. During treatment period, patients underwent weekly haemogram and were reviewed periodically for reactions. Once the treatment was completed patients were examined for signs and symptoms of skin reaction as well as pulmonary reaction. Follow-up was done once in a month up to 6 months and once in 3 months thereafter.

Post mastectomy irradiation was delivered to the chest wall to a dose of 50 Gy in 25 fraction, 5 F/Wk at mid depth with tangential fields and 40-42 Gy in 20-21 fractions, 5 F/Wk to the supraclavicular/axillary fields at mid depth with single anterior portals and at the end, posterior axillary boost of 10 Gy/5F at mid depth was delivered. For breast conservative cases, Whole breast radiotherapy of 50 Gy/25F/5F/Wk was delivered with tangential portals with SAD technique.

Treatment set up Patient in treatment position (supine with arms abducted above the shoulder) was placed in CT simulation and radio-opaque markers were placed on the borders of the treatment fields for field localization. The serial axial sections were taken at 10 mm interval and area of lung included in each section in the treatment area was measured and total volume of lung

in the treated volume was measured by summation of all these areas both for supraclavicular and chest wall fields. In the tangential fields, the percentage of irradiated lung volume was calculated by using the relationship between CLD and PIV as described by Bornstein et al in the year 1990 using the formula  $(9.9 \times \text{CLD}) - 9$ . The grading of pulmonary toxicity was done by according to radiotherapy oncology group (RTOG) criteria.<sup>9</sup>

**Statistical Methods** The logistic regression has been carried to find the effect of Total volume Irradiation on PFT. The Chi-square is used to find the significance of occurrence of Pneumonitis in the different levels of volume of irradiation (SC & Axilla).

## RESULTS

Total 27 patients were included in this study, 26 patients were females and one patient was male. Among the females, 25 were treated for carcinoma breast and one patient treated for carcinoma lung. The lone male patient was treated for carcinoma breast. The study subjects were in the range of 29-73 yrs. The maximum numbers of patients were in the age group of 40-60 years. Bronchial asthma was seen in 1 patient as associated comorbid condition.



Fig 1: Tangential volume of lung



Fig 2: Central Lung Distance (CLD)

Among 25 women 6 cases were premenopausal ladies and 19 cases were postmenopausal. 12 patients were treated for the lesions in the left breast and 14 patients in the right breast. Histopathological analysis revealed 24 cases of IDC, (infiltrating ductal carcinoma); one each had invasive lobular carcinoma and Paget's disease.

**Radiotherapy field details:** 3 patients had chest wall irradiation only. 5 patients of breast conservation had whole breast radiotherapy with 4 patients also receiving regional nodal irradiation. 22 patients had concurrent regional nodal irradiation. Internal mammary field was given for 7 cases.

**Chemotherapy details:** 11 patients had received chemotherapy before radiotherapy and 7 after radiotherapy. The chemotherapy regimes received were 2 cases CMF regimes, 4 cases FAC and 12 patients the AC regimes. The time interval between chemotherapy & radiotherapy was 3-4 weeks either before or after the radiotherapy treatment.

**Hormone therapy:** 13 patients had hormone receptor study and depending on the investigation results, 7 cases were started on Hormone therapy after radiotherapy treatment.

**Investigation results:** One patient's chest x-ray showed homogenous opacity in the right apex region of lung, which was in the irradiated area confirming the pneumonitic changes. Rests of the patients chest x-ray were normal before and after treatment during follow up periods as per the protocol.

**Spirometry:** The best out of 3 performances was taken for the study. Their base line pulmonary function was measured on the day of starting RT and 1 month and 3 months post RT. The percentage of values of forced vital capacity (FVC), forced expiratory value (FEV), forced expiratory volume percentage (FEV%) and one peak expiratory flow (PEF) were take for comparison before RT and after RT. Results observed were: 16 patients out of 26 patients had decrease in percentage in values of FVC, FEV1, FEV1% and PEF on an average of 14.6%, 10.7%, 4.2% and 9% respectively. Haematological parameters were normal during RT and after RT and all patients were given supportive treatment during radiotherapy.

**The percentage of lung irradiated:** In this study for carcinoma of breast, the percentage of lung irradiated for tangential fields was measured using CLD. The CLD of 1-1.5cms, 2-2.5 cms and 3 – 3.5 cms, the percentages were in the range of 1-6% (7/26), 10-15% (16/26), 20-25% (3/26) respectively. The volume of lung irradiated was calculated by summation of area technique. The mean average of 16.82 cc for SC/axilla and for the chest wall was 8.02 cc. The lowest for S.C was 8.46 cc and highest was 32.94 cc. For chest wall lowest was 1.18 cc and highest was 18.57 cc.

Age incidence 61% (16/26) were in the age group of 40-60 years.

**Table 1: Age Distribution in Carcinoma of breast patients**

Age groups (in years)	Number (%)
Thirty-Forty	6 (23.1)
Forty- Fifty	7 (26.9)
Fifty- Sixty	9 (34.6)
Sixty & Above	4 (15.4)
Mean Age in yrs	48.08 ± 10.22

**Table 2: Percentage distribution of volume irradiation in SC & Axilla**

Volume of Irradiation in SC & Axilla (cm <sup>3</sup> )	Number (%)
<10.00	3 (13)
10.00-25.00	18 (78)
>25.00	2 (8.7)

The proportion of volume of irradiation above >25.00 is 8.7% out of which the occurrence of pneumonitis is 50% which is near statistical significance with p=0.083.

**Table 3: Incidence of Radiation Pneumonitis**

Complications	Pneumonitis (%)
Follow up 1 (At the end one month)	Nil
Follow up 2 (At the end of 3 months)	1 (3.9%)

Symptomatic radiation pneumonitis occurred in 3.9% (1/26) of patients treated with locoregional irradiation.

## DISCUSSION

There has been a steady increase in rate of breast cancer cases since 1950, with a sharp rise in 1980s because of the increased use of mammography, as screening procedure.<sup>10</sup> The invasive (infiltrating) ductal carcinoma is the most common type of breast cancer, comprising more than 50% of all cases. The tubular, medullary, comedo, inflammatory, lobular and Paget's disease are other histopathological types.<sup>11</sup> Pauline et al (2004), in their study mentioned that symptomatic RP occurred in 4.1% of patients treated with locoregional radiotherapy as compared with 0.9% those treated with breast or chest wall irradiation only.<sup>12</sup> In our study group, symptomatic RP occurred in 3.9% (1/26) of patients treated with locoregional radiotherapy as compared with 0% for those treated with chest wall irradiation only (3/26), though we had only 3 cases. According to Jedidiah et al (2003), low performance status conditions of lung disease like COPD and bronchial asthma are factors for development of clinical radiation pneumonitis.<sup>13</sup>

In our study 12/26 patients were treated for left-sided lesion and 14/26 patients for right-sided lesion. There was no difference in results between these two groups of patients. Also, the results for 3 patients who received chest wall irradiation only after mastectomy were similar to those for the patients treated with locoregional irradiation. There was also no difference between the percen-

tage of lung irradiated between tangential fields as well as when additional internal mammary nodal (IMN) field was added.

Nattinger and associates in 1998, in their analysis of women aged 65-79 years showed that the frequency of breast conserving surgery ranged from 5 to 9% in East South Central States to 20% in the middle atlantic states. The use of BCS ranged from 38.5% in medical school affiliated hospitals to 9.6% in private hospital.<sup>11</sup> In our study of women aged 30 to 65 years, frequency of BCS is 19.2%.

Rothwell et al, showed a 16% incidence of RP in patients receiving PMRT to chest wall using a model dose of 40G in 15F over 3 weeks, which is equivalent to 46Gy/23F with conventional fractionation.<sup>1</sup> Roach et al (1995) in a multivariate analysis of 1900 cases, states that radiation fraction sizes of greater than 2.67 Gy were associated with an increased risk of RP.<sup>14</sup> In our study PMRT was delivered to the chest wall to a conventional dose of 50Gy in 25 Fr at mid depth with tangential fields and 40-42 Gy in 20-21 Fr; 5 Fr/wk to the axilla/supraclavicular fields at mid depth with single anterior portals at the end posterior axillary boost of 10 Gy/5 Fr at mid depth was delivered. The RP occurred in only one case (1/26) i.e. 3.9% and most of our patients, the CLD was in the range of 2-2.5 cms.

In a study by Lind et al (2002), the RP was an uncommon complication after either local or locoregional radiotherapy. Techniques employing tangential beams for the breast/chest wall  $\pm$  IMN and an SC field for regional nodal irradiation were associated with a higher incidence of RP (5.2%) compared to patients treated with only tangents (0.9%).<sup>15</sup> In our study with the conventional dose/fraction the incidence of radiation pneumonitis seen in patients treated with locoregional radiotherapy was (1/23) 4.3% compared to patients treated with only tangential (0%).

Bornstein et al in 1990, gave a whole breast irradiation of 40-50 Gy in 4-5 weeks and boost to primary site and incidence of RP was less than 2%.<sup>14</sup> We have given whole breast radiotherapy of 50 Gy/25F in 5 weeks with boost to the primary site with interstitial brachytherapy and not seen either symptomatic or radiological RP in any cases. Lind et al, have reported a very low incidence of <1% of RP with local radiotherapy using fields with a mean population CLD of 1.7 cms.<sup>16</sup> Study found CLD to be the most useful predictor of percentage of ipsilateral lung volume encompassed by the tangential fields in the treatment of breast cancer and it was determined both by CT scan and on the simulator film and he found the median percentage of lung volume in the field to be 15.5% for a CLD of 2-2.5 cms, 23% for CLD of 2.6-3.0 cms and 24% for a CLD of a 3.1-3.5 cms.<sup>14</sup> We have measured CLD using Bornstein et al method and percentage of irradiated lung volume has been calculated and mean CLD of 2-2.5 cms is associated with complication of RP of 4.3% (n=1/23).

In our study the analysis of spirometric results was

done. 16 out of 26 patients, had decrease in percentage of values in the following compartments i.e. FVC, FEV1, FEV1% and PEF, on an average of 14.6%, 10.7%, 4.2% and 9% respectively. When this was compared with the CLD, all of them had CLD of more than 2 cms. Percentage of Chemotherapy induced pulmonary toxicity independently of radiotherapy, and hence combining these modalities may result in enhanced lung damage. Both the sequencing of chemotherapy and radiotherapy, radiotherapy treatment technique, and the drugs used may be important in determining this effect.<sup>17</sup> In the Joint Center for Radiotherapy (JCRT) experience, when a supraclavicular or full axillary field was treated in addition to breast tangential fields, the incidence of symptomatic radiation pneumonitis in patients treated with concurrent chemotherapy and irradiation was 9% (eight of 92), compared with 1% (three of 236). Higher incidences of symptomatic radiation pneumonitis have been reported in series in which a photon "hockey-stick" field was used to treat the internal mammary lymph nodes concurrently with chemotherapy.<sup>18</sup> In a series from the University of Pennsylvania<sup>19</sup>, there was only a 5% incidence (three of 63) of radiation pneumonitis among patients treated with concurrent cyclophosphamide and fluorouracil and PMRT. In another study, cyclophosphamide and doxorubicin administered immediately after a course of radiotherapy was associated with a much higher incidence of developing pulmonary fibrosis on chest x-ray, compared with receiving CMF<sup>20</sup>. In a study by Jacquine et al 1999 no changes in spirometric values after only radiotherapy for breast carcinoma, whereas addition of chemotherapy definitely had an impact that too if the time interval between radiotherapy and chemotherapy was less than 4 weeks<sup>21</sup>. In our study, among the 18 cases, 11 cases received chemotherapy 3 to 4 weeks before radiotherapy, out of which 8 cases showed decreased values in spirometry, who had AC based regimes and 7 received 3 to 4 weeks after radiotherapy, out of which 4 cases had anthracycline based regimes, 3 had CMF and all had PFT changes. Cassidy et al in 1975, in their study mentioned that effect of RP is potentiated by doxorubicin. In addition to the enhanced toxicity observed in skin, intestines and heart, the lung also appears to be very sensitive to this combination<sup>22</sup>. In our study (12/15) patients with PFT variations had received Adramycin based chemotherapy. be careful when using Adramycin and also interval between chemotherapy and radiotherapy should be more than 3-4 weeks. Mehmet KOC et al in 2002, observed that the development of lung fibrosis in patients treated with combination of tamoxifen and radiotherapy is significantly higher than the patients treated with radiotherapy only<sup>23</sup>. In our study, 13 patients had hormone receptor study and depending on investigation results, 7 cases were started on hormone therapy after radiotherapy treatment and hormone therapy did not have any impact on development of RP.

## CONCLUSION

Symptomatic radiation pneumonitis occurring in 3.9% of patients treated with locoregional radiotherapy is acceptable. In women aged > 55 years careful radiotherapy planning should be done to minimize the inclusion of lung as the lung function is already compromised in older age group. Karnofsky performance status (KPS) of >70 is associated with less incidence of radiation induced lung toxicity. Addition of internal mammary nodal field will not increase the percentage of lung volume irradiated. CLD is the best method of calculating the percentage of lung volume irradiated, so CT simulation is recommended for planning carcinoma breast, when percentage of lung volume irradiated is limited to 11%. With the present conventional technique of radiotherapy in carcinoma breast, the tangential  $\pm$  regional radiotherapy, dose specification of 45-50 Gy/4-5 weeks and observed spirometric values are within acceptable limits. CT scan is better for evaluation of RP changes compared to chest x-ray in lung fields closer to chest wall. When chemotherapy is added to radiotherapy one should be careful with Adramycin based regimes, as it can add to the radiation injury to the lung and also interval between radiotherapy and chemotherapy should be > 3-4 weeks. The use of radiation protector like Amifostine may be studied in reducing the radiation induced lung injury.

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