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Original Article

Pulmonary Toxicity in Patients with Carcinoma Breast Treated With Post-operative Chest Wall Irradiation

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ABSTRACT

Background: Radiation plays a very important role in the multimodality treatment of breast cancer. As overall survival increases, the long-term toxicity due to radiation also increases. This study intends to evaluate the incidence and assess pulmonary toxicities in patients undergoing post-operative radiation with conventional radiotherapy techniques.

Materials and Methods: Patients with invasive breast cancer who have completed surgery and chemotherapy were selected and given radiation to the chest wall and regional lymph nodes, when indicated, using a conventional simulator and Co-60 Tele Cobalt Therapy machine to a dose of 50 Gy in 25 fractions and boost radiation for Breast Conservation Surgery patients. These patients were followed up at 3 and 6 months following radiation with the help of chest X-ray, Contrast-Enhanced Computed Tomography. Thorax if indicated, and pulmonary function tests. Clinical symptoms were recorded.

Results: The incidence of symptomatic radiation pneumonitis is low in our study population. This study showed a significant decrease in Forced Expiratory Volume in 1 s following radiation. This reduction was associated with central lung distance (CLD) and locoregional lymph node irradiation.

Conclusion: The CLD is the main factor affecting radiation toxicity. The majority of patients show some reduction in pulmonary function even though symptomatic radiation toxicity is rare.

Key words: Breast cancer, Chest wall radiation, Co^{60} teletherapy, Central lung distance, Pulmonary toxicity

INTRODUCTION

Breast cancer is the most common type of cancer seen among females in Kerala. The management of breast cancer consists of the integration of surgery, chemotherapy, radiotherapy, hormonal therapy, and biological therapy. Each mode of treatment is tailored according to the stage and characteristics of the particular patient's disease.

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Radiotherapy plays an important role in the multimodality treatment of breast cancer.[1] It is given to prevent local recurrence and also helps in palliation. Radiation treatment is given after breast conservation surgery (BCS) and in patients undergoing Modified Radical Mastectomy (MRM), if there are certain adverse features.[1,2] It is delivered to the breast, chest wall, and regional lymph nodes in the curative setting. Since breast cancer patients may survive for years, the toxicity of a particular treatment manifests as long as the patient survives. Radiation therapy (RT) is not without consequences. It causes short-term and long-term toxicities. Since the radiation portal partly passes through the underlying lung, there is a chance that it may manifest as short-term and long-term pulmonary damage.

This study tried to assess the incidence and factors associated with pulmonary toxicity and quantitatively and

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qualitatively measure it with pulmonary function tests (PFT), chest X-ray, and contrast-enhanced computed tomography.

Aims and Objectives

The aim of the study was to study the pulmonary toxicity following post-operative RT using conventional radiotherapy techniques in patients with carcinoma breast and to evaluate the incidence of radiation pneumonitis (RP) in this study population. This study also aimed to assess radiation toxicity with PFT quantitatively.

MATERIALS AND METHODS

This hospital-based prospective study was conducted in the Department of Radiotherapy, Government Medical College Hospital, Kozhikode, Kerala. The study population consisted of 40 female patients registered from July 2013 to December 2013 with histological diagnosis of carcinoma breast who were candidates for post-operative RT and were willing to undergo follow-up according to the study guidelines with informed consent. Those patients with ages between 18 and 65 years, Stage 1–3, with Eastern Cooperative Oncology Group performance status ≤2 and with no history of the previous pulmonary disease were included in the study. The study was conducted after obtaining ethical clearance from the ethical committee. Patients were enrolled after obtaining written informed consent. Privacy and confidentiality were maintained.

At the time of recruitment, the following data were collected: Name, age, address, socioeconomic status, menopausal status, hematological and biochemical parameters, previous comorbidities, site of the primary tumor, stage at diagnosis, histopathological report, details of surgery performed, chemotherapy taken, and whether hormonal agents were being used.

Radiotherapy was planned and administered after obtaining informed consent. All patients were asked to undergo a PFT to get a baseline value.

Radiation was scheduled to begin within 3 weeks after chemotherapy. A dose of 50 Gy in 25 fractions was planned using gamma rays from a Cobalt 60 machine using medial and lateral tangential fields. Patients were treated in the supine position with the ipsilateral arm abducted, externally rotated, and placed above the head. The tangential field borders were determined clinically and marked by radio-opaque wires. The medial border was 1 cm from the mid-line or the medial end of the mastectomy scar. The superior border was at the caudal border of the clavicular head. The inferior border was 1 cm below the inframammary fold, and the lateral border was at the mid-axillary line. The supraclavicular fossa was treated separately if indicated. Boost doses of 10 Gy in 5 fractions were given to patients who had undergone BCS. During the simulation, the central lung distance (CLD) values for each patient were recorded.

Every patient was monitored at 3 months and 6 months following radiation with chest X-ray and PFT. A detailed history was taken and a clinical examination was done to assess pulmonary toxicity. High-resolution computed tomography was taken for those patients with doubtful chest x-ray findings. Clinical symptoms, X-ray findings, and forced expiratory volume in 1 s (FEV1) values were recorded.

Data were entered into Microsoft Excel and analysis was performed using the SPSS version 20.0 software and analyzed with the help of descriptive statistics such as mean, standard deviation (SD), percentage, and statistical tests such as Independent *t*-test, one-way ANOVA test, and Chi-square test applied appropriately.

RESULTS

Forty patients had participated in our study, with the mean age being 47.6 years. Twenty-two patients in our study presented with early disease (55%) and 18 patients with locally advanced disease (45%). Only four patients (10%) had undergone BCS, while 36 patients (90%) had undergone mastectomy (MRM). Thirty patients (75%) had received regional nodal radiation, while ten patients (25%) did not. Table 1 shows categorization of patients according to the CLD, with majority of patients in category 3 (17 patients).

In our study, we found a low incidence of symptomatic RP. There was no case of radiation fibrosis or radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP). We have only one patient with symptomatic RP. She was a 65-year-old lady with Stage III_B breast cancer. She received chest wall irradiation and regional lymph node radiation with a CLD of 2.8 cm. She had a 22.8% reduction in FEV1. She complained of dry cough and dyspnea on exertion, and her X-ray showed diffuse haziness, which any other disease could not explain. FEV1 values were recorded at baseline, that is, before chemotherapy or radiation and

Table 1: Patient categorization according to CLD

Category	CLD (cm)	Number of patients
1	≤1.5	2
2	1.6–2	9
3	2.1–2.5	17
4	2.5–3	12

at 3 months and 6 months after completion of RT. Our study population had a baseline mean FEV1 of 1.93 L. The mean FEV1 of our study population at 3 months after RT showed a significant decrease to 1.78 L. At 6 months, the mean FEV1 of our study population decreased to 1.67L ($P = -0.012$) [Table 2].

The mean FEV1 values progressively decreased after RT. Although we had only one patient with symptomatic RP, the FEV1 values showed a uniform decrease following RT. Even though the PFT values showed deterioration in most patients, clinically symptomatic RP is rare. The percentage decrease in FEV1 was compared with CLD.

There is a statistically significant relationship between the percentage decrease in FEV1 and CLD. $P = 0.23$ [Graph 1].

The mean percentage decrease in FEV1 was compared in the group receiving locoregional lymph node radiation and the group that did not receive nodal RT.

There is a decrease in pulmonary function in patients with locoregional RT, but the relation is not statistically significant. $P = 0.52$ [Graph 2].

DISCUSSION

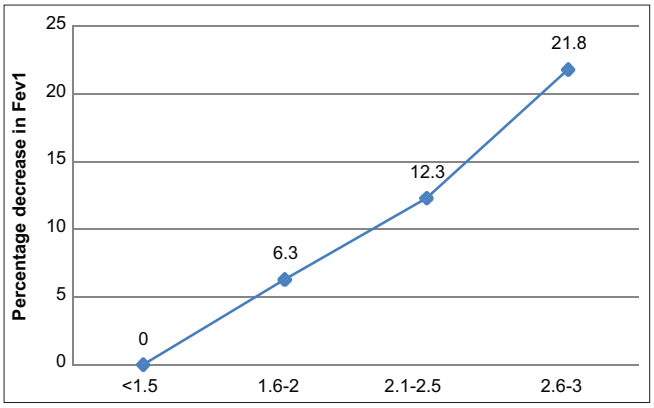
Pulmonary Function After RT

Fall in lung function parameters after radiotherapy for breast cancer is well described. Ooi *et al.* demonstrated that FEV1, Forced Vital Capacity (VC), VC, Total Lung Capacity, and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) progressively declined after radiotherapy and remained irreversible at 12 months ($P < 0.05$).[3] Tokatli *et al.* found a significant reduction in FEV1 and VC at 6, 16, and 52 weeks after radiotherapy compared with baseline.[4]

In our study, mean FEV1 reduced from 1.93 L (SD 0.288) at baseline to 1.67 L (SD 0.258) 6 months after RT.

Table 2: Comparison of FEV1

FEV1	Baseline	3 months	6 months
Mean	1.9378 L	1.7898 L	1.6785
Std. deviation	0.28803	0.24617	0.25892
Median	1.9000 L	1.7950 L	1.67
Mode	1.92 L	2.20 L	1.42



Graph 1: Mean percentage decrease in forced expiratory volume in 1 s compared to each category of central lung distance

Pulmonary Toxicity After Radiation

Radiation lung injury typically presents three distinct clinical stages, namely, RP, fibrosis, and BOOP.[5]

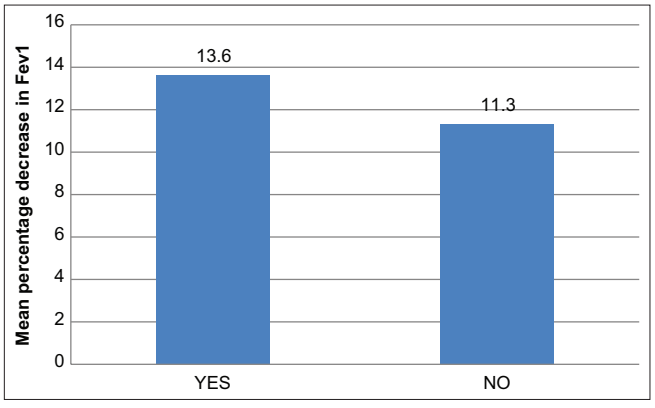
RP is an early inflammatory reaction that occurs 4–12 weeks after completion of thoracic irradiation, while radiation fibrosis is observed beyond 6 months.[6,7] Pulmonary fibrosis is a late injury that can take months to years to evolve and is characterized by progressive fibrosis of the alveolar septa and pleura.

Among pulmonary injuries following RT of the whole breast, the most clinically significant pulmonary disorder is RT-induced BOOP syndrome. It is characterized by infiltrating shadow expansion outside the RT field of the lung. Crestani described the following factors for diagnosing BOOP.[8]

- RT to the chest within past 12 months.
- General and or respiratory symptoms are lasting for more than 2 weeks.
- Radiographic lung infiltration outside the RT port.
- No evidence of a specific cause.

Incidence of Pulmonary Toxicity

The reported frequency of RP in breast cancer ranges from 1 to 80%. This wide range of incidence across studies is due to variations in simulation techniques, treatment



Graph 2: Relationship between locoregional lymph node irradiation and mean percentage decrease in forced expiratory volume in 1 s

schedules, treatment portals, total dose, use of photons or electrons, and the use of various grading systems and endpoints and types of tools to access it.[4-9] A recent meta-analysis on the incidence of early lung toxicity with three-dimensional conformal radiation for breast cancer identified ten different studies and reported the overall incidence of clinical and radiological RP as 14% and 42%, respectively.[10]

In our study, population of 40 patients, we had only one case of symptomatic RP. She had haziness in her chest X-ray and dyspnea on exertion, which developed 5 months after RT. She is a 65-year-old lady who took chest wall and locoregional lymph node irradiation with CLD of 2.6 (category 4). Our study showed a low incidence of RP, that is, 2.5%. We had no cases of BOOP syndrome.

Role of CLD

CLD is useful for assessing the amount of lung volume included in the radiation portal. CLD is directly proportional to the lung volume exposed to RT. Bornstein *et al*. identified CLD as the best predictor of ipsilateral lung volume when using tangential fields.[11] A CLD of 1.5 cm predicted that about 6% of the ipsilateral lung would be included in the tangential field, a CLD of 2.5 cm about 16%, and a CLD of 3.5 cm about 26% of the ipsilateral lung with a mean 90% prediction interval of ±7.1% of ipsilateral lung volume. The CLD helps predict the irradiated lung volume; 0.6%/mm and 0.5%/mm for the left and right lungs.

Our study showed a consistent decrease in pulmonary function as CLD increases. There is a statistically significant relationship between the percentage decrease in FEV1 and CLD.

Role of Locoregional Lymph Node Irradiation

Lymph nodal irradiation increases the irradiated lung volume and the radiation dose to the lung. Studies have demonstrated an increased risk of RP with local and regional radiotherapy compared to that of local radiotherapy alone.[12]

We assessed the percentage decrease in FEVI in those patients with lymph node RT and those without lymph node radiation. There is more reduction in FEV1 in the group in which lymph node radiation was given. This result was not significant statistically because we had only few patients who did not take RT to regional lymph nodes.

CONCLUSION

Even though we use conventional methods for simulation using conventional X-ray simulators and two-dimensional radiotherapy using Tele cobalt unit, the incidence of RP is low. However, we found out that there is a statistically significant decrease in FEV1 after radiotherapy. This study also showed that there is a decrease in FEV1 with the increase in CLD.

Further studies with more sample size, long duration of follow-up, and more variables with probable association with the number of lung injuries should be conducted in the future.

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