A Study on Impact of Radiotherapy on Functional and Radiological Changes on Irradiated Lung in Breast cancer Patients

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Abstract:

Introduction : The invention of therapeutic use of radiation in various carcinomatous lesions lead to injuries of adjacent normal tissues, especially radiation induced fibrosis after administration of radiotherapy in patients of carcinoma breast. **Objectives :** The present study aims to find out prevalence of radiation induced fibrosis and evaluate impact of radiation therapy on functional and radiological parameters of pulmonary tissues in patients of carcinoma breast using spirometry and HR CT scan. **Method :** A total of 38 patients of carcinoma breast were evaluated with subsequent follow-up visits after administration of radiotherapy to assess changes in physiological function, type of radiological reaction etc. **Results :** The prevalence of radiation induced fibrosis in carcinoma breast patients was 13.16% with majority (80%) of cases with apical lateral involvement of lung tissue. Moreover, frequency of radiation induced fibrosis is directly proportional to mean lung dose and percent irradiated lung volume.

Key Words : Breat Cancer, Irradiation, Lung, Radiotherapy

Introduction :

Carcinoma breast has been ranked number one cancer among Indian women with age incidence and mortality rate as high as 25.8 and 12.7 per 1 lakh women. Better awareness and availability of modern diagnosis and treatment facilities would cause a favorable clinical picture in the country. [1]

Radiotherapy is believed to reduce mortality and improve life expectancy of carcinoma breast patients. Studies on meta-analysis revealed that there was little effect of radiotherapy on early deaths, but for later deaths, analysis observed reduced annual mortality rates from carcinoma breast. [2]

The success of radiotherapy hinges on delivering radiation selectively to the sites of malignancy while sparing the adjacent normal tissues. Although radiotherapies are carefully planned to include the smallest possible amount of healthy tissue, some normal tissues surrounding malignancy are irradiated, which result in symptomatic injury. [3] For example, the lungs are particularly radiosensitive and are susceptible to radiation pneumonitis and fibrosis. [4] Therefore, the total dose that can be safely be delivered to patients with tumors in the thoracic cavity has to be limited because of risk of these complications.

In community medicine perspective, it is essential to know effect of radiation on adjacent tissues especially highly sensitive tissues like lungs in patients of carcinoma breast. Dose and duration of radiotherapy in carcinoma breast patients are predictors of structural and functional damage to pulmonary tissues in form of radiation pneumonitis and pulmonary fibrosis and knowledge of it can be useful in prevention of such conditions.

In this study, we tried to evaluate lung injury in the patients requiring post-mastectomy radiation therapy (PMRT). Routinely in PMRT underlying lung gets involved. We quantified the changes in lung physiology using pulmonary function tests and

anatomical changes using radiologic investigations (Chest X ray and HRCT Imaging).

Aims and Objectives :

1. To determine the changes in lung functions (detected by spirometry) 0-12 months after treatment for breast cancer with radiotherapy alone or radiotherapy in combination with chemotherapy.
2. To determine the pre and post radiation (0-12 months) anatomical changes in the lungs (detected radiologically)
3. To determine safe dose-response relationship between radiotherapy dosage and lung function.

Method:

It was a prospective observational study including all patients aged 18 years or more having ductal carcinoma in situ or stage I to III invasive carcinoma, who require adjuvant radiation therapy using 3D CT technique to the breast or chest wall (2-field radiotherapy [2FRT]) with or without supraclavicular/post-axillary boost (4-field radio-therapy [4FRT]), to 50.4 Gy in 28 fraction lung DVH parameters (V10, V20, V30, V40).

Baseline investigations were carried out and relevant data collected before administration of radiation therapy (visit 0). Then, these patients were followed-up at 3, 6, 9 and 12 months after completion of radiation therapy.

We excluded patients suffering from bronchial asthma, or other lung diseases like active tuberculosis, lung cancer, cystic fibrosis, lung resection, presence of lung infiltrates or metastasis before initiation of radiation therapy.

We included all patients diagnosed with Carcinoma breast attending OPD between January 2007 to December 2009 at TB and Chest Department, P.S. Medical College, Karamsad, Gujarat, and found 44 cases eligible for our study. Of these, 6 patients were excluded (2 having incomplete treatment, one shifted to another district, and 3 lost to follow-up as they were NRIs). So, we have 38 patients remaining in our study.

Spirometry was done at baseline and 3, 6, 9 and 12 months after radiotherapy using Cosmed Pony FX Spirometer. FEV1, FVC and FEV1/FVC ratio were measured. Parameters were expressed in percentage of the predicted normal values (adjusted for age, sex, height & weight) as well as in absolute values.[5] PEFR was measured using pulmopeak peak flow meter and was expressed in L/min.

Ethical Clearance :

The study was approved by institutional ethical committee of P.S. Medical College, Karamsad.

Prospective clinical evaluation of pulmonary fibrosis:

All patients were regularly checked at 3, 6, 9 and 12 months after completion of treatment. All the patients were then classified into 3 groups. (a) No reaction: no registered respiratory symptoms.(cough with /without dyspnea, fever), (b) Slight reaction: respiratory symptoms caused by radiotherapy but not treated with corticosteroids and (c) Sever reaction: same as 2 but treated with corticosteroids.

Prospective evaluation of chest radiograph :

X-ray chest was done at baseline and 3, 6, 9 and 12 months after radiotherapy and Cheat X-ray finding were divided into four grades viz., grade 1 – Linear streaks, grade 2 – Patchy consolidation, grade 3 – Confluent consolidation and grade 4 – Atelectasis. The untreated side was used as a control and also information from pre-treatment chest x-ray and CT chest were collected.

P**rospective evaluation of HRCT chest :**

High Resolution CT (HRCT) chest was done at baseline and 6 and 12 month following the radiotherapy. The lung density on the treated side was examined using the standard lung window. An increase in density was graded according to a CT –adapted modification of Arriagada's classification i.e., 0 = no change, 1 =low opacity in

Table 1 : Demographic characteristics of study participants (n=38)

Charact eristics	**N (%)**
Mean age in Years (Range)	50.13 (33-76)
Sex	
Male	2 (5.26)
Female	36 (94.74)
Site of involvement	
Right	23 (60.53)
Left	15 (39.47)
Chemotherapy Received	
Yes	37 (97.37)
No	1 (2.63)
Hormonal therapy Received	
Yes	29 (76.32)
No	9 (23.68)

Table 2 : Changes in pulmonary function in follow-up visits after radiotherapy

Parameters	**V0**	**V3**	**V6**	**V9**	**V12**
Average FVC	100.79	100.06	100.61	101.68	103.35
Average FEV 1	98.30	98.80	98.59	100.10	101.58
Average FEV 1/FVC ratio	104.21	104.95	103.88	104.49	104.67
Average PEFR	385.52	383.42	381.56	377.72	374.28

(FVC=forced vital capacity, FEV1=forced expiratory volume at 1 second, PEFR= peak expiratory flow rate)

linear streaks, 2 = moderate opacity and 3 = complete opacity.[6] The lung was also divided into three regions suggested by Arriagada. i.e. Apical-Lateral (A-L),Central-Perihilar (C-P) and Basal–Lateral(B-L).

Before starting of radiotherapy the average baseline FVC of the patients was 100.79%. Change in FVC after 3, 6, 9 and 12 months of completion of radiotherapy was - 0.73%, - 0.18%, + 0.89% and + 2.56% respectively. Before starting of radiotherapy the average baseline FEV1 of the patients was 98.30%. Change in FEV1 after 3, 6, 9 and 12 months of completion of radiotherapy was + 0.5%, + 0.29%, + 1.8% and + 3.28% respectively.

The average baseline FEV1/FVC ratio was 104.21. Change in FEV1/FVC ratio after 3, 6, 9 and 12 months of completion of radiotherapy was + 0.74, - 0.33, +

Table 3 : HRCT changes of lungs according to arriagada's classification

Arriagada's classification	V 0	V 2	V 4
No reaction	38	27	12
Slight reaction	0	5	2
Moderate reaction	0	0	0
Severe reaction	0	0	0

Table 4 : Radiation field and HRCT changes in patients diagnosed with radiation fibrosis (n=5)

Patient No.	Radiation field	Chest Region involved	Radiation
1	Chest wall +Axilla +SCL region	A – L , B –L	Slight
2	Chest wall +Axilla +SCL region	A – L	Slight
3	Chest wall +Axilla +SCL region	A – L	Slight
4	Chest wall +Axilla +SCL region	B – L	Slight
5	Chest wall +Axilla +SCL region	A – L	Slight

Table 5 : Relationship between radiation fibrosis and percentage irradiated lung volume (PIV)

Mean lung dose (Gy)	Total patients exposed N (%)	Total patients developing Radiation fibrosis N (%)
≤ 5	3 (7.9)	1(33.33)
5.1 – 10	8 (21.05)	0 (0.00)
10.1 – 15	19 (50.00)	3 (15.78)
15.1 – 20	8 (21.05)	1 (12.5)
Total	38 (100)	5 (13.16)

Table 6 : Relationship between radiation fibrosis and mean lung dose

PIV (%)	No. of patients exposed N(%)	No. of patients developing Radiation fibrosis N (%)
< 5	2 (5.3)	0 (0.00)
5 – 9.9	8 (21.1)	1 (12.5)
10- 14.9	7 (18.4)	1 (14.28)
15- 19.9	20 (52.6)	3 (15.0)
≥ 20	1 (2.6)	0 (0.00)
Total	38 (100)	5 (13.16)

0.28 and + 0.46 respectively. The average baseline PEFR was 385.52 L/min. subsequently it was reduced 2.1 L/min, 3.96 L/min, 7.8 L/min and 11.14 L/min after 3, 6, 9 and 12 months of completion of radiotherapy respectively.

There is no any statistically significant reduction in pulmonary function after 12 months of completion of radiotherapy. (P value for FEV1 is 0.96, for FVC is 0.96, for FEV1/FVC ratio is 0.98 and for PEFR is 0.92.)

Prior to initiation of radiotherapy all the patients had normal HRCT (not showing any signs of fibrosis, infiltration or consolidation). On subsequent follow up, 5 patients identified as having radiation induced fibrosis. According to Arriagada's classification all 5 patients had slight radiological reaction.

In two patients, HRCT after six months of completion of radiotherapy showed few linear streaks in the apical region which was cleared on subsequent follow up at 12 months after radiotherapy which is suggestive of either allergic or infective in origin. These findings were not consistent with radiation induced lung damage.

Out of 5 patients with radiation fibrosis 3 patients had fibrotic reaction in apical region (A - L) consistent with the axillary and supraclavicular radiation field, whereas one patient had lesion in both A-L and B-L region. One patient had lesion only in B-L field.

The percentage of irradiated lung volume ranged from 3.2% to 20.05% with average PIV is 13.63% and median is 15.79%. Frequency of radiation induced fibrosis is increased with increase in PIV.

The Mean lung dose range from 2.9 to 20.0 Gy with average mean lung dose 11.76 Gy. Frequency of radiation fibrosis increases with increase in Mean Lung Dose. (Table No. 6)

Discussion :

Classic radiation pneumonitis is characterized by chronic cough, fever, and nonspecific infiltrates within the irradiated lung. It generally appears 4 to 9 months after completion of treatment. Its incidence is 1% to 2% after Whole breast irradiation. [7,8] In a study, 21% patients developed radiation induced symptoms.[9], Whereas as per another study, 14.6% patients developed radiation pneumonitis.[10] Our study reported prevalence of radiation induced pneumonitis as 13.16% which is at par with other studies.

There is no statistically significant change in pulmonary function parameters as assessed by spirometry like FEV1, FVC and FEV1/FVC ratio in follow-up visits after administration of radiotherapy. All the PFT parameters decreased at 6 to 12 months, but then recovered to almost their previous normal values. These findings correlated with a study having similar findings. [11] In a study, the median-matched vital capacity (VC), forced expiratory volume in one second (FEV1), and total lung capacity (TLC) were reduced 15%, 9%, and 7%, respectively, at the long-term follow-up ($p < 0.001$).[12]

Our study observed that most of the subjects (80%) had pulmonary abnormalities as grade-1 (slight radiological reaction showing few linear streaks in apical lung region as per HRCT findings. A study showed that at 3 months after RT, the pulmonary changes were classified at HRCT as follows: 91.8 % were Grade 0, 8.19 % Grade 1, and 0 % Grade 2. At 6 months, 86.98 % were Grade 0, 11.47 % Grade 1, and 1.6 % Grade 2. At 12 months, 88.52 % were Grade 0, 9.19 % Grade 1 and 3.27% Grade 2.[13]

A study concluded that radiological abnormalities detected on CT images and scored according to the CT adapted modification of Arriagada's classification system can be used as objective endpoints for RT-induced pulmonary complications in breast cancer.[14] Minimal HRCT findings were evident in half of the patients as per a study including small septal lines, linear and sub-pleural opacities and to a lesser extent, focal-ground glass opacification.[15]

Conclusion:

We observed 13.16% prevalence of radiation induced lung fibrosis (slight radiological reaction, as per Arriagada classification) in patients of Carcinoma breast who received radiotherapy, majority of them

(80%) having involvement of apical lateral region. There is no change in pulmonary function parameters like FVC, FEV1 and FEV1/FVC ratio except PEFR which decreases in subsequent follow-up visits after radiotherapy. We also observed that frequency of radiation induced fibrosis increases with increase in PIV and mean lung dose.

Declaration:

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Conflict of Interest: Nil

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