International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 9; Issue 04 (B); April 2020; Page No.21877-21884
DOI: http://dx.doi.org/10.24327/ijcar.2020.21884.4307

Research Article

A PROSPECTIVE STUDY TO EVALUATE RADIATION PNEUMONITIS IN BREAST CANCER PATIENTS AFTER ADJUVANT CONFORMAL RADIOTHERAPY

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A R T I C L E I N F O

Article History:
Received 10th January, 2020
Received in revised form 2nd February, 2020
Accepted 26th March, 2020
Published online 28th April, 2020

Key words:

Radiation Pneumonitis, Pulmonary Function Test, Central Lung Distance, Radiotherapy

A B S T R A C T

Aim– To study the incidence of radiation pneumonitis (RP) and its association with irradiated lung volumes and various patient and treatment related factors after adjuvant radiotherapy in breast cancer patients.

Material and method- A hospital based prospective quantitative follow up study. Total 80 breast cancer patients who received adjuvant conformal radiation were registered. Clinical assessment including screening for respiratory symptoms, chest radiograph and pulmonary function tests (PFTs) were done at baseline and 12 weeks after the completion of radiotherapy. RP was assessed both clinically using RTOG acute radiation morbidity scoring criteria as well as radiologically using radiological grading scale of radiation induced pneumonitis. Measurement of irradiated lung volume parameters (e.g. central lung distance) were done on simulator film.

Results-Total 76 patients were evaluated for occurrence of RPup to minimum of 12 weeks (1 patient expires and 3 patients not reported for subsequent follow-up). Radiological and clinical RP was seen in 45% (n=34) and 21% (n=16) respectively. Occurrence of RP was significantly higher with age >50 years (p-value 0.025) and higher irradiated lung volume parameters (>3cm).There was no significant difference noticed with other patient and treatment related factors. All pulmonary function parameters including FEV1, FVC, FEV1 ratio and FEF 25-75 were significantly reduced ($p<0.001$) after 12 weeks of radiotherapy completion except PEF which was reduced non-significantly ($p=0.140$). FEV1 ratio and FEF 25-75 were significantly reduced in those with RP than without RP group ($p<0.001$).

Conclusion- Age>50 years and higher irradiated lung volume (>3cm) were associated with increased RP. So, the factors associated with increased RP should be considered for selection of better radiotherapy plan which may subsequently reduce the chances of radiation pneumonitis and helps in maintaining good quality of life in breast cancer survivors.

INTRODUCTION

Breast cancer is the most commonly reported malignancy in women worldwide as well as in India. It is the fifth leading cause of all cancer related mortality (6.6%) after lung (18.4%), colorectal (9%), stomach (8.2%) and liver (8.2%). In 2018, breast cancer was accounting for almost 1 in 4 cancer cases among women (24.2%) and it also remains the leading cause of cancer related deaths (15%) in women. Breast cancer is at highest position in Indian women population with reported incidence rate of 27.7% and mortality rate of 12.2% in 2018. [1,2]In present scenario management of breast cancer is a multidisciplinary approach and in general, treatments of breast cancer consist of surgery as major modality, and adjuvant treatments including chemotherapy, radiotherapy, hormonal and targeted therapy, depending upon the stage.

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Adjuvant loco-regional radiotherapy is an essential component of treatment for the locoregional control and increases the survival after Breast Conservation Surgery (BCS) and is a part of management for a large percentage of post-mastectomy (MRM) patients.[3]

Radiotherapy is associated with some optimal toxicities, which are acceptable because the benefit gained by adjuvant radiotherapy generally overweight's these toxicities.[3]The recent past there are drastic changes in the advancement of technology pertaining to delivery of radiation. Modern radiation techniques have developed to get better dosimetric results in treatment of breast cancer such as intensity-modulated radiotherapy (IMRT) and volumetric-arc modulated radiotherapy (VMAT) which can improve radiation conformity and homogeneity.[4]With these advances, patients have good long term outcomes, hence acute and long term side effects assume great importance in patient's quality of life. In spite of technological advances in breast cancer treatment, it is not

possible to deliver radiation to the target site efficiently without exposure of surrounding normal critical structures which is responsible for radiation induced toxicities.[5]

Radiation pneumonitis (RP) is one among the acute adverse event after completion of radiotherapy, as in radiotherapy planning for breast cancer; lung is a major organ at risk. RP is an early inflammatory reaction that occurs four to twelve weeks after completion of thoracic irradiation. In long term, it may develop into radiation fibrosis.[6] The reported frequency of clinical and radiological RP were ranges from 0-29% and 1-80% respectively.[7-15] This wide range of incidence is due to variations in simulation techniques, treatment schedules, treatment portals, total dose, use of photons/ electrons, and use of various grading systems and end points. Several risk factors have been studied for RP including age, irradiated lung volume, radiation dose, central lung distance (CLD), pre-radiotherapy functional level and concurrent chemotherapy.[16] There is scarcity of published data from developing countries on radiation pneumonitis in breast cancer patients. The wide range in the incidence of clinical and radiological RP is likely due to variations in radiation planning technique and the method of measuring RP. Mild and moderate RP can be missed if patients are not assessed and screened, this can lead to an underestimation of the problem, mandating the need to carry out prospective studies focussing specifically on RP.This study prospectively addressed the incidence of RP and the association between various patient related factors, radiotherapy treatment related factors and changes in pulmonary functions after conventionally fractionated conformal adjuvant radiotherapy in breast cancer patients in a tertiary care center.

MATERIALS AND METHODS

It was a hospital based quantitative prospective follow-up study which was conducted in year 2018-2019 in a tertiary care center of north- west India. After approval of institutional Review Board/ Ethical committee, histopathological proven breast cancer patients who required adjuvant radiotherapy after surgical resection (either BCS or MRM) and ready to give informed written consent, were included in this study. Sample size was 80 breast cancer patients which calculated at 95% confidence interval, alpha error of 0.05 assuming 45% radiation pneumonitis among breast cancer patients following conventionally fractionated conformal radiotherapy with inclusion of 15% attrition.[16]Patients with any pre-existing lung pathology or with history of prior radiation therapy to thorax were excluded from study population.

All eligible patients were evaluated for institutional recommended treatment options and underwent surgical resection of breast malignancy either by mastectomy or breast conservative surgery (BCS) along with axillary lymph node dissection. All eligible patients were received chemotherapy by either neoadjuvant or adjuvant manner which was anthracycline followed by taxane based. Thereafter all eligible patients were counseled for available options of local radiotherapy. Patients who were agree to receive radiotherapy at linear accelerator by 3D-CRT technique, were considered for study protocol and evaluated accordingly.

Evaluation of pulmonary functional parameters- Pulmonary function tests (PFTs) parameters of the patients were measured using a precision portable spirometer (Model- Vitalograph 6800 Pneumotrac). Pulmonary function parameters were measured in terms of forced expiratory volume in first second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF) and forced expiratory flow at 25-75% (FEF 25-75). Ratio of FEV1 and FVC (FEV1 ratio) is one among the important pulmonary function indices and it also called Tiffeneau- pinelli index. All of these pulmonary function tests were done for all 80 patients at baseline and for 76 patients after 3 months of completion of radiotherapy. Since 4 patients had not completed follow up PFTs, therefore they were excluded of this study.

Radiation Technique- A total of 80 histologically confirmed unilateral invasive breast cancer patients without distant metastasis at diagnosis that had undergone mastectomy or breast conservative surgery (BCS) and were candidates for adjuvant radiation therapy to the chest wall (with or without nodal irradiation) were included. All patients were planned for adjuvant radiotherapy to the chest wall. In addition, patients were also planned for RT to supraclavicular fossa when there was histopathological evidence of axillary node metastases, when there was an inadequate lymph node dissection (less than 10 nodes examined pathologically) and when neoadjuvant chemotherapy was administered prior to definitive surgery. All patients were treated on Seimens Oncor Expression dual energy Linear Accelerator by 3-dimensional conformal radiotherapy (3DCRT) technique in supine position with arm abducted and head turned to the contralateral side using a breast board ensuring sternum is parallel to the couch top. All patients were immobilized while free breathing using a thermoplastic mould in supine position with both arms extended above their head, abducted and externally rotated. Scar sites were marked using lead markers. Patients underwent CT simulation in the same position without IV contrast. Target volumes were contoured according to the RTOG breast cancer atlas guidelines depending on the stage of the disease. All patients were treated by 40 Gy in 15 fractions with 2.67 Gy per fraction per day for 5 days a week over 3 weeks. Electron boost to the chest wall was given with 9 Gy in 3 fractions to all eligible patients. The most widely accepted technique for whole-breast irradiation is with medial and lateral opposed tangential field technique, in which the entire breast and chest wall, with a small portion of lung, is included in the irradiated volume. Nodal basins received either radiotherapy through an anterior field with gantry angled 10– 15 degrees to avoid the spinal cord and esophagus. The dose was calculated at a depth of mostly 3 cm (varied from 2–5 cm). The posterior axillary boost if required was completed using a posterior approach and the dose was calculated at mid plane. The treatment was planned with a goal of 100% volume of PTV to be covered by 95% isodose line. Dose homogeneity was optimized using wedges and 'field-in-field' technique using multi leaf collimators. Data collected included the volume of PTV receiving at least 95% and 90% of prescribed dose (V95 and V90) and also dose delivered to 90% of the volume of PTV (D90%) from the dose volume histogram. The treatment plan was accepted if ≤ 10% of the heart volume and ≤ 25% of the ipsilateral lung volume received 25 Gy.

Assessment of Irradiated Lung Volumes- Simulation film measurements was serve as a surrogate for irradiated lung volume: CLD (Central Lung Distance)- the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center, MLD

(Maximum Lung Distance) - the maximum perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall, SLD (Superior Lung Distance) and ILD (Inferior Lung Distance)- the distance of lung in the central portion of the superior and inferior halves of the lateral tangential fields respectively and its average (ALD).(Image 1and 2)

Assessment of Radiation Pneumonitis- RP was assessed clinically by usingCox *et al*.,[17] RTOG Acute Radiation Morbidity Scoring criteria and radiologically by using Radiological Grading Scale of Radiation Induced Pneumonitis by Koulouliaset *al*.[18] Clinical assessment (symptoms of cough, dyspnoea or fever), chest radiograph/ HRCT thorax and Pulmonary Function Test (PFT) were done at baseline and 12 weeks post RT for each patient. Patients were followed up for a minimum of 6 months.

Diagnosis of Radiation Pneumonitis- Radiation pneumonitis is usually a diagnosis of exclusion. The differentials could be disease progression, concomitant infection, and exacerbation of chronic obstructive pulmonary disease, reactivation of latent tuberculosis or radiation pneumonitis. Presence of cough with or without sputum, dyspnoea, chest discomfort, high grade fever and myalgia may be pointers toward an infective pathology. A complete blood count, throat swab, sputum culture/ sensitivity and chest x ray may be warranted based on the clinical assessment. High- resolution computed tomography (HRCT) was used in the diagnosis and grading of radiation pneumonitis. It may show ground glass opacities, consolidation, fibrosis, atelectacticcicatrisation, pulmonary volume loss or pleural thickening.[9]

Treatment of Radiation Pneumonitis-Steroids form the mainstay of treatment of radiation pneumonitis. Once infection and disease progression are ruled out, the patient should receive oral prednisolone 1 mg/kg (max- 60 mg) for a period of two weeks followed by slow tapering over weeks. Abrupt stopping can lead to worsening of symptoms.[19]

Statistical Analysis

Qualitative data were expressed in percentage or proportions and quantitative data were expressed in mean ± SD. The significance of proportions was inferred by Chi- square test and significance of difference in means was inferred by Paired and Unpaired T – test as and when required. Statistical analysis was done by using SPSS version 26 software. For significance p value <0.05 was considered as significant.

OBSERVATIONS AND RESULTS

Total eighty histopathologically proven breast cancer patients who received adjuvant radiotherapy and fulfill the inclusion and exclusion criteria were prospectively enrolled and further evaluated for occurrence of radiation pneumonitis and its relations with patient and treatment related factors. Demographic and histological parameters of study population were demonstrated in Table 1. Among the registered patients for study majority (98.75%) were female population. The mean age was 48.2 years with range of 20 to 71 years.

Induction chemotherapy was required in 25 patients because they were presented in locally advanced stage and it was not possible to achieve adequate clear margin with upfront resection in these patients, rest all were treated with afferent surgical resection followed by adjuvant chemotherapy except for one patient who was not the candidate for adjuvant chemotherapy and she received only adjuvant radiotherapy.Most of the patients were reported in advanced stage so they underwent MRM (68 patients, 85%) either afferent or post neoadjuvant chemotherapy followed by adjuvant radiotherapy to the chest wall and only 12 patients (15%) received whole breast radiotherapy following breast conservation surgery (BCS). By administration of induction chemotherapy, 3 patients were converted to the BCS category in which initial required surgical resection was MRM. One among these 3 patients was of stage IIIA at presentation. All enrolled patients were treated with chest wall irradiation by bilateral opposed tangential fields and electron boost to the scar site were given in eligible 36 patents. 52 patients required additional anterior field to treat the supraclavicular fossa. Additional boost to axilla with separate posterior field was required only in 7 patients. All enrolled patients received complete prescribed treatment and tolerated well with minimal treatment related toxicities like dermatitis.

After completion of radiotherapy treatment all patients were actively searched for occurrence of radiation pneumonitis after 4 and 12 weeks and maximum for upto 6 months. Among the total registered patients 1 patient expired after 15 days of completion of radiotherapy (due to non-malignant cause) and 3 patients were lost subsequent follow-up, so total 76 patients were evaluated for occurrence of RP up to minimum of 12 weeks.

Reported incidence of clinical RP was 21% (16 patients)and radiological RP was 44.7% (34 patients). Clinically 12 (75%) patients had only complain of mild dry cough (grade 1) which was relieved spontaneously after sometime without any medications, and only 4 patients (25%) were required some medications (anti-tussive or cough suppressants) to relieved the symptoms and they responded well with them (grade 2). No any patients had history of any symptoms which was not responding to primary medications. So, there was no any patient of grade 3 or 4 clinical radiation pneumonitis in our study. Radiologically 32 patients (94%) were of grade 1 and grade 2 (21 and 11 patients respectively) and only 2 patients shown the signs of grade 3 radiation pneumonitis. For total grading of Radiation Pneumonitis, higher grade was taken among the clinical symptoms and radiological pulmonary changes. Among the 76 patients, 34 (44.7%) patients were assigned under radiation pneumonitis. Among these 34 patients, 20 (58.8%) were of grade 1, 12 (35.3%) were of grade 2 and only 2 patients (5.9%) were of grade 3 radiation pneumonitis. While not a single patient was reported with grade 4 and 5 of RP.(Image 3) Possible patient and treatment related factors which may contribute in the development of RP were elaborated in Table-2. The median age of patient with and without RP was 51 and 46 years respectively. The mean age ofthose with RP was 51.3±10.6 years and was significantly different from those who did not develop RP 45.5±10.5 years (p=0.020).The risk ofdeveloping RP was more in patients with age of ≥50 years(p=0.025) than <50 years. RP developed in 57.14% of patients in the ≥ 50 years age group as compared to 34.1% in those below 50 years of age. The mean age was 51.7 year for the patients who were clinically symptomatic for RP.RP was demonstrated in 42.4% of cases in right sided breast cancer patients and 46.5% of left sided breast cancer patients. The incidence of RP was more in left sided disease but not significantly different with right sided breast cancer

(p=0.817). However, in clinical RP group 12 out of 16 (75%) were of left sided breast cancer patients.

Supraclavicular fossa irradiation was indicated in 50 patients and it was treated with separate anterior field. Among these 50patients, 24 (48%) was developed RP in follow-up and 26 (52%) had not developed. Incidence of RP was not significant in this study with supraclavicular fossa treatment (p=0.474). However, in clinical RP group 75% cases (12 patients) were treated for supraclavicular fossa with additional anterior field. Additional axillary boost with separate posterior field was indicated in only 7 patients and among them 3 patients developed RP but this was also statistically non-significant (p=1.000).There was no significant difference in the occurrence of RP between those who had received boost with electrons to the chest wall and those who did not (48.5% vs 51.5%, p=0.645).Similar results were also obtained for the clinically symptomatic patients also with chest wall e- boost.

Mean of CLD in those with RP was 3.31 cm and 2.67 cm in those without RP and the difference was statistically significant (p<0.001). Similarly the mean values of MLD, ILD SLD and ALD were significantly higher in those RP demonstrated and the mean values for MLD were 3.46 and 3.04 cm (p<0.001), for ILD were 3.30 and 2.76 cm (p<0.001), for SLD were 2.52 and 2.11 cm (p=0.010) and for ALD were 2.91 and 2.44 cm (p=0.001) in those with and without RP respectively. For the patients with clinical symptoms of RP the mean values of CLD, MLD, ILD, SLD and ALD were 3.46 cm, 3.77 cm, 3.42 cm, 2.74 cm and 3.08 cm respectively. So, the chance of symptomatic RP was higher with larger irradiated lung volumes.(Table 3)

Table 4 is elaborating the changes in pulmonary function parameters after 12 weeks of completion of radiotherapy from baseline. Statistically significant fall was noticed in the mean values of FEV1, FVC,FEV1 ratio and FEF 25-75 after 12 weeks of radiotherapy (p<0.001), however mean value of PEF was also decreases but that was not statistically significant (p=0.140). When we compared these PFT values in both the groups of with and without RP, FEV1 was reduced 12.1% from baseline after RT in with RP group and 9.6% in without RP group. Reported percentage fall was significantly higher in FEV1 ratio (p=0.015) and FEF 25-75 (p<0.001) in patient those with RP than without RP group. In other parameters, it was not significant while comparing both above groups.

Table 1 Patients' Demographic and Treatment Characteristics

Sex	**Male**	**1 (1.25%)**
	Female	**79 (98.75%)**
Age (Median- 48.2 years)	≥ 50	43 (53.75%)
	<50	37 (46.25%)
Anatomical Site	Right	33 (41.25%)
	Left	47 (58.75%)
TNM stage (according AJCC 2017 staging System)	IA	3 (3.75%)
	IB	0 (0%)
	IIA	9 (11.25%)
	IIB	23 (28.75%)
	IIIA	26 (32.5%)
	IIIB	7 (8.75%)
	IIIC	6 (7.5%)
	Not Accessed	6 (7.5%)
Histology	Infiltrating Ductal Carcinoma	76 (95%)
	Infiltrating Lobular Carcinoma	1 (1.25%)
	Malignant Paget's disease	1 (1.25%)
	Malignant Phylloid	2 (2.5%)
Marker Status	ER Positive	48 (60%)
	PR Positive	42 (52.5%)
	Her 2 Neu Positive	10 (12.5%)

Table 2 Association of RP with different patient and treatment related factors

N=76	With RP (n=34)	Without RP (n=42)	P – value
Age			
Mean age in years± SD	51.3± 10.6	45.5± 10.5	**0.020**
<50	14	27	
≥50	20	15	**0.025**
Laterality			
Right	14	19	
Left	20	23	**0.817**
Supraclavicular field RT			
Yes	24	26	
No	10	16	**0.474**
Axilla Boost			
Yes	3	4	
No	31	38	**1.000**
Electron boost to chest wall			
Yes	17	18	
No	17	24	**0.645**

*RP- Radiation Pneumonitis, RT- Radiotherapy

Table 3 Simulator film measurements in patients with and without RP

Measurement (Mean ± SD in cm)	With RP	Without RP	*P*-value
CLD	3.31± 0.72	2.67± 0.62	<0.001
MLD	3.64± 0.71	3.04± 0.60	<0.001
ILD	3.30± 0.70	2.76± 0.63	<0.001
SLD	2.52± 0.70	2.11± 0.64	0.010
ALD	2.91± 0.64	2.44± 0.56	0.001

*RP- Radiation Pneumonitis, CLD- Central Lung Distance, MLD- Maximum Lung Distance, ILD- Inferior Lung Distance, SLD- Superior Lung Distance, ALD- Average Lung Distance

Table 4 Changes in pulmonary function parameters after Radiotherapy

Pulmonary Function Parameters	Mean± SD		p-value	Mean ± SD of differences from baseline in PFTs (Percentage reduction)		p-value
	Baseline	After 3 months		With RP	Without RP	
FEV1 (L)	1.86± 0.44	1.67± 0.38	<0.001	0.21± 0.28 (12.1%)	0.19± 0.22 (9.6%)	0.728
FVC (L)	2.12± 0.47	2.03± 0.39	<0.001	0.07± 0.27 (3.5%)	0.11± 0.17 (5.4%)	0.434
FEV1 Ratio	0.88± 0.07	0.82± 0.09	<0.001	0.08± 0.08 (9.2%)	0.04± 0.06 (5.6%)	0.015
PEF (L/min)	253.41± 58.54	248.13± 56.10	0.140	4.71± 39.57 (1.9%)	6.24± 24.83 (2.4%)	0.838
FEF 25-75 (L/sec)	2.24± 0.62	2.09± 0.61	<0.001	0.28± 0.32 (12.2%)	0.06± 0.21 (2.6%)	<0.001

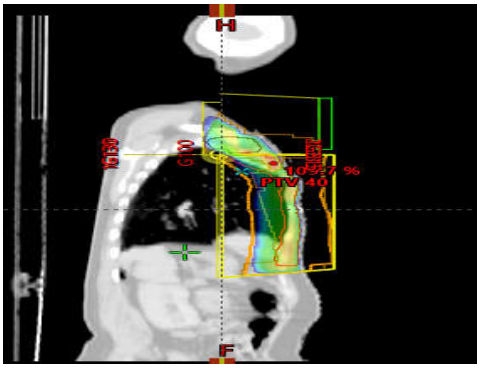


Image 1 Sagittal view of treatment plan showing chest wall and SCF field coverage and beam arrangement

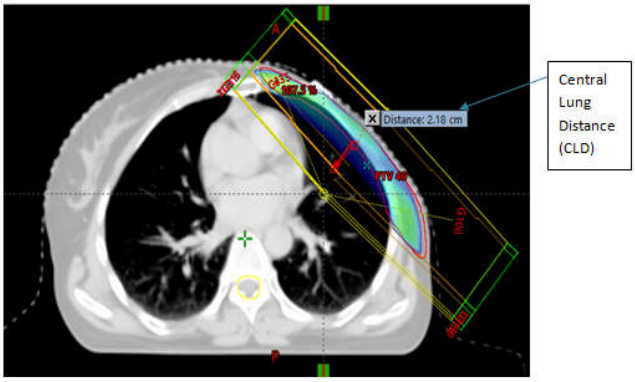
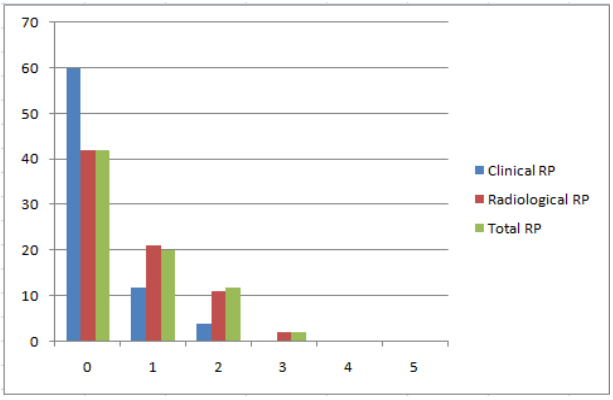


Image 2 Axial view of treatment plan showing CLD measurement



*In above graph grade of RP was plotted over x-axis and on y-axis number of patients

Image 3 Incidences of Radiation Pneumonitis (with grade)

DISCUSSION

RP is an early inflammatory reaction due to acute exudation in the alveolar space and migration of inflammatory cells after thoracic irradiation. Type II pneumocytes which produce surfactant are the cells associated with RP. The natural history of the radiation lung injury can be divided into 5 phases: immediate phase (hours to days); latent phase; acute exudative/ clinical RP phase (4–12 weeks post- RT); intermediate phase with resolution of exudate and deposition of fibroblast and the final phase when fibrosis is established (usually 6–12 months post-RT).[7]

Several cellular and molecular changes occur in a series when the lung tissue exposed to ionizing radiation. Pulmonary irradiation can produce a lot of reactive oxygen species and reactive nitrogen which causes oxidative damage of DNA, lipid, and protein. The resulting injury or apoptosis of alveolar epithelial cells and vascular endothelial cells then induce a series of inflammatory reactions and chemotaxis of monocytes, lymphocytes, and granulocytes, which gather at the site of tissue injury. So, when the lung tissue is exposed to an ionizing radiation, alveolar epithelial cells and vascular endothelial cells are damaged, and inflammatory mediators are released that causes dilatation and increased permeability of blood vessels which allows for efficient accumulation of blood exudate and inflammatory cells at the site of tissue injury.[15]

Most of the available literatures in this context were retrospective in nature which can lead to underestimation of this problem. In the Indian sub-continent thisis a prospective and one among the larger studies about the incidence of RP followed by adjuvant conventional radiotherapy for breast cancer and their correlation with various patient and treatment related factors which can lead to a more accurate estimation of this problem. In this study the incidence of clinical RP and radiological RP were 21% and 44.7% respectively, thatwere similar to the results of a prospective study of same sub-continent by Jeba*et al.*,[16] and also within the range of the most reported studies in which clinical and radiological RP were ranges from 0-29% and 1-80% respectively.[7-15]This reported wide range in the incidence of clinical and radiological RP is most likely due to variations in selected patient profile, radiation planning techniques and the method of its assessment.

In present study reported clinical symptoms were transient and dry cough was most common (87.5%) and most of them regressed spontaneously within few days (grade 1) and only 4 patients (grade 2) needed treatment with anti-tussive or cough suppressant. Symptomatology of present study correlates with McDonald *et al.,*[10]which also reported non-productive cough as the commonest symptom in 88%, dyspnoea in 35%, but high incidence of fever in 53% of cases was encountered by them,which was not seen in this study. Lingos *et al.*,[11] elaborated that radiation pneumonitis was occurs 4–12 weeks after RT completion and can be clinically silent, although some patients may experience cough, dyspnea, fever, and chest discomfort.Lind *et al.,*[12] in a retrospective study with 710 patients also reported a similar median onset as 3 months (range 1 to 9 months). However, Wennberg*et al.,*[13] reported the median time to RP diagnosis as 5.5 weeks after radiotherapy. Moreover, Takatli*et al.*,[9]in a small prospective study (n=20) also found pulmonary function impairments after 6-16 weeks of radiotherapy with partial recovery by 52 weeks. The mean time for the onset of symptoms in present study was 72 days (21-105 days) after completion of radiotherapy which also correlates with majority of above-mentioned studies.

Age of the patient also significantly affected the occurrence of RP and in this study the incidence of RP was significantly more with age >50 years (p=0.025, OR 2.57), which was consistent with the results of many other studies on breast cancer patients.[10,13,16,20,21]In context to the median age of study population, Gagliardi *et al.*,[22] has been demonstrated that the lung doses were 26.9Gy for age >57 years and 40.6 Gy for age <57 years that gives 50% of normal tissue complication probability(NTCP). However, there were reports of Lind *et al.*[12] and Kubo *et al.*,[23] which did not show any statistically significant effect of age on RP.

This study also did not find an association between the laterality of breast cancer and incidence of RP (p = 0.817), which was also consistent with many other previous studies. [10,12,16,23]

Numerous studies have been demonstrated that addition of lymph nodal irradiation in addition to local therapy increases the irradiated lung volume and the radiation dose to the lung tissue, which leads to increased risk of RP also.[11-13,16,21,24]Kahan et al.,[20] also reported that risk of RP was increased 2.5 times and risk of radiogenic fibrosis was increased 2 times with irradiation of the axillary and the supraclavicular lymph node regions. In a meta-analysis by Gokula*et al.*,[7] also found a strong association between supraclavicular field irradiation and the incidence of RP. However, present study also shown an increase in incidence of RP in those who received an additional supraclavicular field

irradiation in comparison to those who did not, but this was not reached upto statistical significance (70.6% versus 61.9%, p=0.474). In this study additional boost to axillary lymph nodes required in very few cases (7 patients only) and among them 3 develops RP, which was not showing any association with RP (p=1.000).

Incidence of RP is higher with use of electrons for chest wall irradiation due to the enhanced scattering effect and altered dose distribution of electron beam by the presence of inhomogeneity in the path of the electron beam due to chest wall contour.[25] This present study also found a small increase in the incidence of RP with use of electrons for boost at chest wall, as compared to those who did not required boost (50% versus 42.8%), but this also did not reach upto statistical significance (p=0.645). However, Wennberg *et al.*,[13]demonstrated that there was increased risk of symptomatic RP with use of electron beam to treat the chest wall (p=0.046). So, it is important to select patients carefully for treatment with electron beam and pay attention in the selection of the right electron beam energy, compensate for the chest wall thickness inhomogeneity with use of bolus material and define all treatment portals in treatment planning system instead of using routine portals at simulation.

For prediction of the irradiated lung volume in conventional radiotherapy planning for breast cancer patients, central lung distance (CLD) is one of the various simulator film measurement parameters and it has been found useful one.[26]Bornstein *et al*.,[14]demonstrated that at the time of simulation, CLD was easy to measure and reproducible, and while using tangential fields for local therapy, it was the best predictor of irradiated ipsilateral lung volume.According to Hardman *et al*.,[27] prediction of irradiated lung volume for each mm of CLD were 0.6% and 0.5% for left and right lungs respectively. They predicted that about 6%, 16% and 26% of ipsilateral lung volume would be included in the tangential field portal with the CLD of 1.5, 2.5 and 3.5 cm respectively, with a mean prediction interval of 90% ± 7.1%.[14,27]In this series, Kubo *et al*.,[23] identified that a CLD >1.8 cm and short axis length of the radiation field were significant risk factors for RP with radiotherapy after breast-conserving surgery. Moreover, Lingos *et al*.,[11]also showed that only 1% incidence of RP with less than 3 cm CLD. However, Lind *et al*.,[12] did not find statistically significant association of CLD or ALD measurements with RP. Jeba*et al*.,[16]also found a non-significant (p=0.203) higher mean CLD in those with RP (2.38 cm) than those without RP (2.12cm) but they found that the difference in the mean ILD in above two groups was statistically significant (p= 0.013). In the present study while we comparing the various simulator film parameters of lung volume measurement in between the two groups of with and without RP, the mean values of all these parameters (including CLD, MLD, SLD, ILD and ALD) were found statistically significant.

Due to technological advancement in radiotherapy planning and delivery system in present scenario more concern is giving to volumetric constraints of lung, but simulator film parameters is still considering as important part in this aspect. Lind *et al*.,[28] suggested thatno case of RP was found in patients who received doses of $\geq$20 Gy to<30% of the ipsilateral lung volume, that is V20<30.In a recent prospective trial Goldman et al.,[29] also demonstrated significant reduction in the rate of radiation pneumonitis and short-term changes of PFT by applying a dose constraint of $V_{20}\leq$30% to the lung tissue.Clinical data suggest that a total lung dose of more than 20 Gy given with conventional fractionation should be avoided if the unirradiated lung volume is not sufficient to guarantee essential breathing function.[30]

Numerous studies were published on the changes in pulmonary function post radiotherapy for breast cancer, which have shown progressive reduction in most of pulmonary function test (PFT) parameters within the first six months after completion of radiotherapy, and these changes were irreversible at 12 months.[8,9,24]Jeba*et al*.,[16] demonstrated significant fall in the mean FEV1, FVC and TLC, 12 weeks after radiotherapy compared to the baseline measurements in all patients ($P<$ 0.001). Ooi*et al.,*[24]and Chakraborty *et al.,*[8]also noticed progressive reduction in FEV1, FVC, TLC, and DLCO after radiotherapy and remained irreversible at 12 months ($P<$ 0.05). Whereas, Tokatli*et al.,*[9] found progressive significant reduction in FEV1, VC, FVC and DLCO with noted partial recovery in FVC and DLCO at 52 weeks after radiotherapy compared with baseline.However,Fragkandrea*et al.,*[31] reported no significant decrease in PFTs, and also no significant differences have been reported between mean values of FVC and FEV1 in before and three months after RT and also between before and six months after RT.In the present study we also noticed a significant fall in the mean values of FEV1, FVC, FEF1 ratio and FEF 25-75, from baseline measurements in all patients (p<0.001), 12 weeks after completion of radiotherapy. However, mean PEF value also reduced but that was not statistically significant (p=0.140).Reduction in various PFT parameters have been reported within 3- 4 months of radiotherapy completion and ranges from 3% to 22%. [10,24]In the present study we noticed a significant percentage mean fall in all PFT parameters. Percentage decline of FEV1 ratio and FEF 25-75 were significantly higher in patients those with RP, than those without RP. But in other parameters noted percentage reduction in this study was non significantly related in both groups. These above findings were in favor of restrictive pathology (pneumonitis) among the RP patients' group.

CONCLUSION

More than 50 years of the patient's age and higher irradiated lung volume as measured in simulator film (e.g.CLD>3cm) were associated with increased incidence of RP. So, these factors should be also considered as important parameters in radiotherapy planning for breast cancer patients. Selection of better radiotherapy plan with lower irradiated lung volume in simulator film (CLD < 3cm) may subsequently reduces the chances of radiation pneumonitis and helps to maintain a good quality of life in breast cancer survivors.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency

for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, Accessed 17/10/2017.
3. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 2.2019. National Comprehensive Cancer Network. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed on 1/10/2019.
4. Haciislamoglu, E., Colak, F., Canyilmaz, E., et al. The Choice of Multi-Beam IMRT for Whole Breast Radiotherapy in Early-Stage Right Breast Cancer. Springerplus, 2016; 5: 688.
5. Supakalin N, Pesee M, Thamronganantasakul K, Promsensa K, Supaadirek C, Krusun S; Comparision of Different Radiotherapy Planning Techniques for Breast Cancer after Breast Conserving Surgery. Asian Pac J Cancer Prev, 2018;19(10): 2929-2934.
6. McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127-35.
7. Gokula K, Earnest A, Wong LC. Meta-analysis of incidence of early lung toxicity in 3-dimensional conformal irradiation of breast carcinomas. Radiat Oncol 2013,8:268.
8. Chakraborty A, Sharma SC, Behera D, Negi PS. Effect of radiation on pulmonary functions in patients with breast cancer. Indian J Chest Dis and Allied Sci 1991;33:195-200.
9. Tokatli F, Kaya M, Kocak Z, Ture M, Mert S, Unlu E, et al. Sequential pulmonary effects of radiotherapy detected by functional and radiological end points in women with breast cancer. Clin Oncol (R Coll Radiol) 2005;17:39-46.
10. McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 1995;31:1187–203.
11. Lingos TI, Recht A, Vicini F, Abner A, Silver B, Harris JR. Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1991;21:355-60.
12. Lind PA, Marks LB, Hardenbergh PH, Clough R, Fan M, Hollis D, et al. Technical factors associated with radiation pneumonitis after local +/- regional radiation therapy for breast cancer. Int J Radiat Oncol Biol Phys 2002;52:137-43.
13. Wennberg B, Gagliardi G, Sundbom L, Svane G, Lind P. Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. Int J Radiat Oncol Biol Phys 2002,52:1196– 206.
14. Bornstein BA, Cheng CW, Rhodes LM, Rashid H, Stomper PC, Siddon RL, et al. Can simulation measurements be used to predict the irradiated lung volume in the tangential fields in patients treated for breast cancer? Int J Radiat Oncol Biol Phys 1990;18:181-7.
15. Huang Y, Zhang W, Yu F, Gao F. The cellular and molecular mechanism of radiation- induced lung injury. Medical Science Monitor, 2017; 23: 3446-345.
16. Jeba J, Isiah R, Subhshini J, Beckjanathan S, Thangakunam B, Christopher DJ. Radiation Pneumonitis After Conventional Radiotherapy For Breast Cancer: A Prospective Study. Journal of Clinical and Diagnostic Research 2015;9:XC01-5.
17. Cox JD, Stetz J, Pajak TF (1995). Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*, 31, 1341-6.
18. Kouloulias V, Zygogianni A, Efstathopoulos E, et al (2013). Suggestion for a new grading scale for radiation pneumonitis based on radiological findings of computerized tomography: Correlation with clinical and radiotherapeutic parameters in lung cancer patients. *Asian Pac J Cancer Prev*, 14, 2717-22.
19. Giridhar P, Mallick S, Rath GK, Julka PK; Radiation Induced Lung Injury: Prediction, Assessment and Management. Asian Pacific Journal of Cancer Prevention, 2015;16(7):2613-7.
20. Kahan Z, Csenki M, Varga Z, Szil E, Cserhati A, Balogh A, et al. The risk of early and late lung sequelae after conformal radiotherapy in breast cancer patients. Int J Radiat Oncol Biol Phys 2007;68:673–81.
21. Kim HJ, Jang WI, Kim TJ, Kim JH, Kim SW, Moon SH, et al. Radiation-induced pulmonary toxicity and related risk factors in breast cancer. J Breast Cancer. 2009;12:67-72.
22. Gagliardi G, Bjohle J, Lax I, Ottolenghi A, Eriksson F, Liedberg A, et al. Radiation pneumonitis after breast cancer irradiation: Analysis of the complication probability using the relative seriality model. Int J Radiat Oncol Biol Phys. 2000;46:373–81.
23. Kubo A, Osaki K, Kawanaka T, Furutani S, Ikushima H, Nishitani H. Risk factors for radiation pneumonitis caused by whole breast irradiation following breast-conserving surgery. J Med Invest 2009;56:99-110.
24. Ooi GC, Kwong DL, Ho JC, Lock DT, Chan FL, Lam WK, et al. Pulmonary sequelae of treatment for breast cancer: A prospective study. Int J Radiat Oncol Biol Phys 2001;50:411–419.
25. Khan FM, Gibbons JP. Khan's The Physics of Radiation Therapy. 5th ed. Philadelphia: Lippincott Williams and Wilkins Ltd; 2014. Chapter 14, Electron Beam Therapy; pp.280.
26. Neal AJ, Yarnold JR. Estimating the volume of lung irradiated during tangential breast irradiation using the central lung distance. Br J Radiol 1995;68:1004–8.
27. Hardman PD, Tweeddale PM, Kerr GR, Anderson ED, Rodger A. The effect on pulmonary function of local and loco regional irradiation for breast cancer. Radiother Oncol 1994;30:33-42.
28. Lind PA, Wennberg B, Gagliardi G, Fornander T. Pulmonary complications following different radiotherapy techniques for breast cancer, and the association to irradiated lung volume and dose. Breast Cancer Res Treat. 2001;68:199-210.
29. Goldman UB, Anderson M, Wennberg B, Lind P. Radiation pneumonitis and pulmonary function with lung dose–volume constraints in breast cancer irradiation. Journal of Radiotherapy in Practice. 2014; 13, 211–217.

30. Hermann T S J, Molls M. Radiation Pneumopathy. Experimental and clinical data. In: Dunst J, Sauer R H (eds). Late Sequelae in Oncology. Berlin, Heidelberg, New York, 1995: 135–140.
31. Fragkandrea I, Kouloulias V, Mavridis P, Zettos A, Betsou S, Georgolopoulou P, et al. Radiation induced pneumonitis following whole breast radiotherapy treatment in early breast cancer patients treated with breast conserving surgery: a single institution study. Hippokratia 2013;17:233.

How to cite this article:

Pawan Kumar *et al* (2020) 'A Prospective Study to Evaluate Radiation Pneumonitis in Breast Cancer Patients After Adjuvant Conformal Radiotherapy', *International Journal of Current Advanced Research,* 09(04), pp. 21877-21884.
DOI: http://dx.doi.org/10.24327/ijcar.2020. 21884.4307

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