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Original Article

Oncology Section

Radiation Pneumonitis After Conventional Radiotherapy For Breast Cancer: A Prospective Study

JENIFER JEBA[1], RAJESH ISIAH[2], J SUBHASHINI[3], SELVAMANI BACKIANATHAN[4], BALAMUGESH THANGAKUNAM[5], DEVASAGAYAM J CHRISTOPHER[6]

ABSTRACT

Background: Loco-regional radiotherapy is an important treatment modality in breast cancer and radiation pneumonitis (RP) is one of the early toxicities.

Aim: To study the occurrence, correlation of RP with patient and radiotherapy related factors and the effects on pulmonary function following conventional radiotherapy in breast cancer.

Settings and Design: Prospective study, from a tertiary hospital in a developing country.

Materials and Methods: Prospective analysis of clinical symptoms, pulmonary function and radiologic changes was done prior to and 12 weeks after adjuvant radiotherapy (n=46). Statistical analysis was done using SPSS version 10 software.

Results: Radiological and clinical RP was seen in 45.65% (n=21) and 19.56% (n=9) respectively. RP was significantly higher with age >50 years (OR 4.4), chest wall irradiation with electrons, (electrons 83.3% vs cobalt^{60} 32.4%, p=0.02) and supraclavicular field treatment with 6 MV photons (p= 0.011). There was significant relationship between Inferior Lung Distance (ILD) and RP (p=0.013). The fall in Total Lung Capacity (TLC) was significantly more in those with RP (p=0.02).

Conclusion: Clinical RP occurs in almost one-fifth of breast cancer patients treated with conventional radiotherapy. Chest wall irradiation with electrons, supraclavicular field irradiation with 6 MV photons, higher ILD and age >50 years was associated with increased RP. The pulmonary function parameter most affected was TLC. The factors associated with increased RP should be considered when adjuvant radiotherapy is planned to minimize its likelihood and intervene appropriately.

Keywords: Adjuvant radiotherapy, Pulmonary function, Radiology

INTRODUCTION

Adjuvant loco-regional radiotherapy is an important component in breast cancer treatment as it reduces loco-regional recurrence and improves overall survival [1]. It is crucial to minimize radiotherapy related complications, as most breast cancer patients have long survival. In planning radiotherapy for breast cancer, lung is a major organ at risk, because of the risk of radiation pneumonitis (RP) and radiation fibrosis. RP is an early inflammatory reaction that occurs four to twelve weeks after completion of thoracic irradiation, while radiation fibrosis is observed beyond six months [2]. The reported frequency of RP in breast cancer ranges from 1-80%. This wide range of incidence across studies 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 [3-14]. A recent meta-analysis on the incidence of early lung toxicity with 3-dimentional conformal irradiation for breast cancer identified ten different studies and reported the overall incidence of clinical and radiological RP as 14% and 42% respectively [15]. Several risk factors for RP following radiotherapy for breast cancer have been studied and a diversity of factors including age, BMI, irradiated lung volume, radiation dose, central lung distance (CLD), pre-radiotherapy functional level and concurrent chemotherapy have been identified. [3,6,12,16-19] Marks et al., did not show any association between the presence or absence of radiotherapy induced pulmonary symptoms and the frequency of radiotherapy induced radiographic changes (p=0.53) [20]. Hernberg et al., reported clinical signs of suspected pneumonitis in 29% with radiologic changes on computed tomography in as high as 68%, with these changes most frequent three months after radiotherapy [13].

There are numerous studies on the changes in pulmonary function post radiotherapy for breast cancer. In general, the studies have shown reduction in most pulmonary function parameters including Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV1), Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Diffusing Capacity for Carbon Monoxide (DLCO) within the first six months [6,8,21]. Conventional radiotherapy is often the most easily available and financially viable technique in most developing countries. There is scarcity of published data from developing countries on radiation induced pulmonary toxicity. This study was conducted in a tertiary care teaching hospital in India, to assess the incidence of RP in patients who received adjuvant conventional radiotherapy for breast cancer and to evaluate the relation between pulmonary function changes, and various patient and radiotherapy treatment related factors.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board/ ethics committee and all enrolled patients gave their written informed consent. Patients with histology proven breast cancer who received adjuvant conventional radiotherapy were prospectively enrolled between November 2003 and July 2005 (n=46). Systemic treatment was provided as per the institutional protocol. Patients who received prior radiotherapy to the chest wall or mediastinum and those with metastatic disease were excluded. 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. PFT parameters measured were; spirometry, Lung volumes (multi-breath Helium dilution method), transfer factor (DLCO) and Krogh's constant (DLCO/VA). The Jaeger Master screen PFT machine was utilized for these measurements.

Radiotherapy: Patients were treated with radiotherapy to the whole breast or chest wall, with or without nodal regions depending on the

stage of the disease. Patients were positioned on the simulation couch in supine position with arm abducted (90 degrees or greater) and head turned to the contralateral side in a stable and reproducible manner using a breast board. The breast board was used to ensure that the sternum was parallel to the couch top.

Opposed tangential fields or direct electron fields were employed for treatment of the chest wall. When opposed tangential fields technique was used, the lung volume treated was limited by keeping the perpendicular distance at the centre from the posterior tangential field edge to the posterior part of the anterior chest wall (CLD) between 2 and 3 cm. The caudal margin was chosen to include the entire chest wall. The cephalad margin was placed so that the beam clears the arm and also so that the lung volume within the matching anterior supraclavicular field is minimized. When electrons were used for chest wall irradiation an anterior field was used and electron energy was chosen appropriate to the thickness of the chest wall, based on the simulator check film or a planning CT scan when that was done.

The supraclavicular nodes were treated with an anterior field, usually at a 10-15 degree gantry rotation, to reduce the dose to the oesophagus and spinal cord. The field was simulated with the cephalic border to include the entire supraclavicular fossa, the caudal border just below the level of the abducted arm, medial margin at the patient's midline and lateral margin at the junction of medial two third and lateral one third of the clavicle. All patients were treated with conventional fractionation at 2 Gy per fraction to a total dose of 46-50 Gy/ single fraction per day/5 days a week over 41/2 to 5 weeks.

The internal mammary chain field was placed one centimetre across the midline and 5 cm to the ipsilateral side. The length of this field extended from the second intercostal space to the xiphoid process. The axillary nodes were included in the same field as the supraclavicular nodes. To optimize the dose distribution of the axilla, a small posterior axillary field was added, and the dose was calculated to the mid plane based on the thickness of the axilla.

Simulation film measurements were taken as a surrogate for irradiated lung volume; CLD the perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall at the center, maximum lung distance (MLD) the maximum perpendicular distance from the posterior tangential field edge to the posterior part of the anterior chest wall, superior lung distance (SLD) and inferior lung distance (ILD) the distance of lung in the central portion of the superior and inferior halves of the lateral tangential fields respectively and its average (ALD).

Assessment: The primary outcome studied was the occurrence of RP. Other outcomes included correlation between the occurrence of RP and various patient and treatment related factors and the changes in the pulmonary function tests.

Enrolled patients were evaluated with clinical assessment (symptoms of cough, dyspnoea or fever), chest radiograph and PFTs 12 weeks post radiotherapy. Radiological RP was diagnosed if chest radiograph showed radiographic changes suggestive of RP (presence of consolidation, ground glass opacification, linear or dense opacities, volume loss). Clinical RP was diagnosed if patients presented with cough, dyspnoea or fever and had radiological features suggestive of RP. Those who were symptomatic with RP were treated with corticosteroids. Patients were followed up for clinical symptoms upto 6 months.

STATISTICAL ANALYSIS

Results were expressed as mean ± Standard Deviation. All variables were tested for normal distribution by the Kolmogorov Smirnov test. Independent sample t-test was used to analyse means of continuous variables in patients with and without RP. Chi-Square test was done for comparison of categorical variables in patients with and without RP. Pearson correlation coefficient was used to establish correlations between changes in pulmonary function parameters and various simulation film measurements. A p-value of <0.05 was considered significant. Data was analysed using SPSS version 10 software.

RESULTS

Radiological and clinical RP

Forty-six female breast cancer patients who received adjuvant radiotherapy were prospectively enrolled. The mean age was 46 years (23- 64 years). Right and left sided breast cancer was seen in 52.2% and 47.8% respectively. All patients had adjuvant radiotherapy to the chest wall except one who received whole breast radiotherapy and boost to tumour bed following breast conservation surgery.

Of the 46 enrolled, the incidence of radiological RP was 45.65% (21 patients) and clinical RP in 19.56% (9 patients). Of those who were symptomatic, only 5 patients who had severe cough and dyspnoea were treated with corticosteroids. The mean time of onset of symptoms was 89 ± 37.02 days (35-149 days) post radiotherapy. The commonest symptom was cough in 77.7% (7/9 patients). Other symptoms were dyspnoea in 33.3% (3/9 patients) and both in 22.2% (2/9 patients). The commonest site of RP on chest radiograph was the upper zone, 85.7% (18/21 patients).

The various patient and treatment related factors that could contribute to RP were grouped and studied [Table/Fig-1]. The median age of patients with RP was 45 years. The mean age of those with RP was 46.9±10.71 years and was not significantly different from those who did not develop RP 45.56±8.11 years (p=0.631). The risk of RP was more with age>50 years (p=0.02) than <50 years. RP developed in 68.75% of patients in the > 50 years age group as compared to 33.3% in those at or below 50 years of age. The odds ratio with age >50 years to develop RP was 4.4. The incidence of RP was not significantly different with right or left sided breast cancer (p=0.246).

n=46	RP present n (%)	RP absent n (%)	p-value
Age			
Mean age in years	46.9	45.56	0.63
<50 years	10 (33.3)	20 (66.7)	
>50 years	11(68.7)	5 (31.3)	0.02
Laterality			
Right	9 (37.5)	15 (62.5)	0.24
Left	12 (54.5)	10 (45.5)	
Supraclavicular field RT			
$Cobalt^{60}$	11 (33.3)	22 (66.7)	0.011
6 MV photons	5 (100)	0 (0)	
6 MV photons and 9 MeV electrons	4 (66.7)	2 (33.3)	
RT to axilla			
Yes	9 (52.9)	8 (47.1)	0.44
No	12 (41.4)	17 (58.6)	
Chest wall RT			
$Cobalt^{60}$	11 (32.4)	23 (67.6)	0.02
Electrons	10 (83.3)	2 (16.7)	

[Table/Fig-1]: Association of RP with different patient and treatment related factors

Radiotherapy treatment related factors: Supraclavicular region was treated in 44 patients of which 33 (75%) had treatment with $cobalt^{60}$, five (11.4%) with six MV photons, and 6 (13.6%) with a combination of 6 MV photons and 9 MeV electrons. The incidence of

RP was significantly higher with use of 6 MV photons only (p=0.011). All five patients treated with 6 MV photons developed RP, while RP in those who were treated with cobalt^{60} and a combination of 6 MV photons and 9 MeV electrons was 33% and 67% respectively. There was no significant difference in the occurrence of RP between those who had axillary irradiation and those who did not (36.9% vs 63.1%, p=0.44). Chest wall irradiation was done with cobalt60 in 34 patients (73.9%) and with electrons in 12 (26.1%). The incidence of RP was significantly high with electrons (83.3% vs 32.4%, p= 0.02). Fourteen patients (30.4%) received IMC boost. The incidence of RP was higher in those who received IMC boost, 57.1% vs 40.6% in those who did not, but was not statistically significant (p=0.301).

The mean ILD in those with and without RP were 2.16 cm and 1.63 cm respectively. The difference between the mean ILD among those with and without RP was statistically significant (p=0.013). The differences in the mean MLD, CLD, SLD, ALD between the two groups was not statistically significant [Table/Fig-2].

The baseline FVC, FEV1, FEV1/FVC, TLC, DLCO and DLCO/VA were not significantly different between those with and without RP. There was a significant fall in the mean FEV1, mean FVC and mean TLC at 12 weeks, as compared to the baseline (p<0.001). Those who did not develop RP had a lesser fall in pulmonary function parameters. Those with RP had a mean fall in FEV1 and FVC by 9% and TLC fall by 14%. The fall in TLC between the two groups was however statistically significant (p=0.02) [Table/Fig-3]. The fall in DLCO correlated with MLD (r=0.349, p=0.022). The fall in TLC correlated with ILD, (r = 0.379, p=0.01), CLD(r =0.343, p=0.02) and with ALD (r =0.341, p=0.02).

Measurements (mean ± SD in cm)	RP		p-value
	Yes	No	
MLD	2.63 ±0.76	2.57±0.52	0.754
SLD	2.08 ±0.76	2.11±0.53	0.864
ILD	2.16±0.71	1.63±0.64	0.01
ALD	2.12±0.63	1.87+0.5	0.156
CLD	2.38±0.73	2.12±0.58	0.203

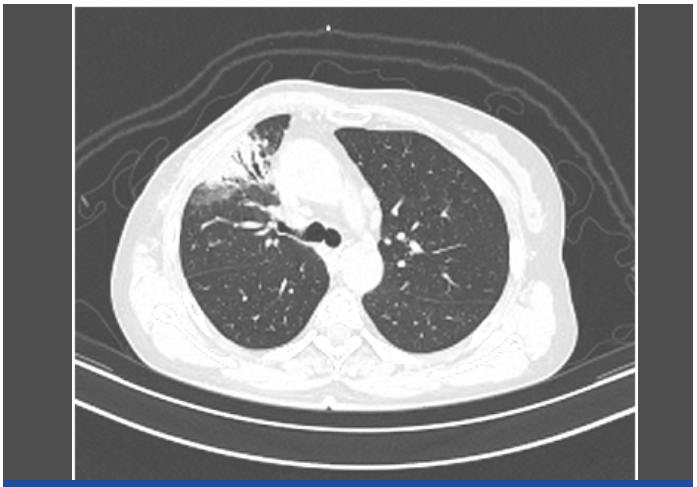
[Table/Fig-2]: Simulator film measurements in patients with and without RP RP=radiation pneumonitis, SD=standard deviation, MLD=maximum lung distance, SLD=superior lung distance, ILD=inferior lung distance, ALD=average lung distance, CLD=central lung distance

Pulmonary function parameters	Mean± SD		p-value	Percentage difference from baseline		p value
	Baseline	3 months		RP Yes	RP No	
FEV1	1.97±0.39 (L)	1.82±0.38 (L)	<0.001	9.5	6.3	0.239
FVC	2.34 ±0.45 (L)	2.16±0.43 (L)	<0.001	9.1	6.03	0.355
TLC	3.90±0.62 (L)	3.50±0.72 L)	<0.001	14.5	6.3	0.02
DLCO	5.33±1.79 mmol/min/ kPa	6.16±8.58 mmol/min/ kPa	0.515	-2.3	-37.6	0.42
DLCO/VA	1.83±0.55 mmol/min/ kPa/L	1.76±0.35 mmol/min/ kPa/L	0.315	1.64	0.13	0.805

[Table/Fig-3]: Changes in pulmonary function parameters after radiotherapy SD=standard deviation, RP=radiation pneumonitis, FEV1= Forced Expiratory Volume in first second, FVC= Forced Vital Capacity, TLC= Total Lung Capacity, DLCO= transfer factor, DLCO/VA= Krogh's constant

DISCUSSION

Conventional radiotherapy is often the preferred modality due to the lower treatment cost, in many developing countries. This is one of the larger studies from this sub-continent that prospectively studied the incidence of RP followed by adjuvant conventional radiotherapy for breast cancer. Radiological RP was found in 45.65% [Table/Fig-4] and clinical RP in 19.56%. Clinical symptoms were transient and only five patients needed treatment with corticosteroids. Another prospective study from this sub-continent (n=20) reported radiological RP in 15%, and fibrosis in 5% [8]. The incidence of radiological RP and clinical RP according to McDonald et al., was 27-40% and 0-10% respectively [22]. 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 [23,24]. The incidence of radiological and clinical RP in this study is similar to most reported studies [Table/Fig-5]. Mild and moderate RP can be missed if patients are not assessed and screened specifically for RP. Since this study was conducted prospectively it represents a more accurate estimation of RP. Retrospective data can lead to an underestimation of the problem.



[Table/Fig-4]: Typical HRCT of a patient with right sided RP and normal left lung

Author	Type of study	n	Radiological RP (%)	Clinical RP (%)
Lingos et al., [3]	Retrospective	1624	1	NA
Kim et al., [4]	Prospective	261	22.6	1.9
Price et al., [5]	Retrospective	770	NA	2.5
Tokatli et al.,[6]	Prospective	20	80	10
Lind et al., [7]	Prospective	475	11	NA
Chakraborty et al., [8]	Prospective	20	15	0
Kubo et al., [9]	Prospective	472	21	2.9
Wennberg et al., [10]	Prospective	121	NA	23
Lind et al., [11]	Retrospective	177	24	14
Hernberg et al., [13]	Prospective	34	68	29
Ooi et al., [14]	Prospective	30	80	63.3
Gokula et al., [15]	Meta-analysis		42	14
Bornstein et al., [16]	Prospective	40	NA	2
McDonald et al., [22]	Review		27 - 40	0 -10
Current study	Prospective	46	45	19

[Table/Fig-5]: Incidence of RP post radiotherapy in breast cancer

In this study, cough was the commonest symptom (77.7%), followed by exertional dyspnoea (33.3%) and none developed fever. McDonald et al., reported non-productive cough as the commonest symptom in 88%, dyspnoea in 35% and a high incidence of fever in 53% [22]. The mean time for the onset of symptoms was 89 ± 37.02 days (35-149 days) after radiotherapy. Lind et al., in a retrospective study also reported a similar median onset as 3 months [12]. Wennberg et al., reported the median time to RP diagnosis as 5.5 weeks after radiotherapy [10].

The incidence of RP was significantly more with age >50 years (p=0.022, OR 4.4). This finding is consistent with the results of many other studies on breast cancer patients [4,7,10,24-26]. With

the median age of the study population as a limit Gagliardi et al., has demonstrated that the lung dose that gives a complication probability (Normal Tissue Complication Probability) of 50% as 40.6 Gy for age <57 years and 26.9 Gy for age >57 years [25]. However, there are reports, which do not show statistically significant effect of age on RP [9,12]. As with many other studies, this study did not find an association between RP and laterality (p = 0.246) [9,12,13].

Lymph nodal irradiation increases the irradiated lung volume and the radiation dose to the lung. Numerous studies have demonstrated increased risk of RP with local and regional radiotherapy compared to that of local radiotherapy alone [3,4,7,10,12,14]. The present study also shows an increased incidence of RP in those who received axillary irradiation, but this did not reach statistical significance (52.9% vs 41.4%, p=0.44). RP was significantly higher with use of 6 MV photons for supraclavicular field treatment, all five who had such treatment developed RP (p = 0.011). Ooi et al., looked at serial high resolution computed tomography features of lung injury after 3-field radiotherapy for breast cancer and found a high incidence of lung injury and functional impairment with concurrent supraclavicular field irradiation [27]. Gokula et al., also in meta-analysis found a strong association between supraclavicular field irradiation and the incidence of RP (OR=5.07; 95% CI=1.95-13.22) [15]. Kahan et al., reports a 2.5 times higher risk of RP and a twofold risk of radiogenic fibrosis with irradiation of the axillary and the supraclavicular lymph node regions [24].

The present study found a significantly higher incidence of RP with use of electrons for chest wall irradiation, as compared to cobalt 60, 83.3% vs 32.4% (p=0.02). Wennberg et al., also identified use of electron beam treatment for the chest wall as a factor that increased risk of symptomatic RP (p=0.046) [10]. The presence of inhomogeneity in the path of the electron beam significantly alters the electron beam dose distribution and enhances the scattering effect, leading to difficulty in determination of dose distribution [28] and this could likely be the reason for the higher incidence of RP with use of electrons for chest wall irradiation. It is important to carefully select patients 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. There are no direct head on comparisons between photons and electrons in postmastectomy radiotherapy with regard to assessment of pulmonary toxicity. Photons have been found superior to electron in achieving better locoregional control and less skin telangiectasia [29].

In conventional planning, various simulator film measurements have been used to predict the volume of lung in the radiation field of which CLD has been found to be a useful predictor. Bornstein et al., identified CLD as the best predictor of ipsilateral lung volume when using tangential fields. CLD was found to be highly predictive, reproducible and easy to measure at the time of simulation. 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 [16]. The CLD helps predict the irradiated lung volume; 0.6%/mm and 0.5%/mm for the left and right lungs respectively [21]. Lingos et al., showed that with CLD less than 3 cm, the incidence of RP is only 1% [3]. In the present study the mean CLD in those with RP was higher (2.38 cm) than those without RP (2.12cm). Though the mean CLD was higher, the difference in the mean CLD was not statistically significant. Very few patients (n=5) had CLD more than 3 cm, which probably explains why there was no significant effect of CLD on RP. Kubo et al., 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 [9]. Lind et al., did not find statistically significant association between CLD or ALD measurements and RP [12]. In the present study, only the difference in the mean ILD between those who had RP and did not have was statistically significant (p= 0.013). The risk of pulmonary morbidity with tangential breast irradiation is as low as one per thousand if the lung included in the treatment field is less than 2-2.5cm [30].

The present study found a significant fall in the mean FEV1, FVC and TLC, 12 weeks after radiotherapy compared to the baseline measurements in all patients (p<0.001). In those who developed RP, there was statistically significant difference in the fall in TLC compared to those who did not develop RP (p=0.02). Those who developed RP had a mean fall in FEV1 and FVC by 9% and TLC fall by 14% while those who did not develop RP had a lesser fall (6%) in these parameters [Table/Fig-3]. Fall in lung function parameters after radiotherapy for breast cancer is well described. Chakraborty et al., revealed a fall in the value of FVC, TLC, FEV1, DLCO and FRC, in the majority after radiotherapy, with only DLCO decline being statistically significant [8]. The mean reduction of each pulmonary function parameters as compared with the pre-radiation values ranged between 0-19%. Ooi et al., demonstrated that FEV1, FVC, TLC, and DLCO progressively declined after radiotherapy and remained irreversible at 12 months (p<0.05) [14]. Krengli et al., found significant reduction in lung function parameters (FEV1, FVC, TLC, maximal expiratory flow at 50% and 25% of vital capacity, and DLCO) at three months, with only partial recovery at nine months [31]. Tokatli et al., found significant reduction in FEV1 and VC at 6, 16 and 52 weeks after radiotherapy compared with baseline [6]. But FVC and DLCO were significantly reduced only at 6 and 16 weeks after radiotherapy compared with pre-radiotherapy values. The present study also found that the fall in DLCO correlated with MLD (r=0.349, p=0.022). The fall in TLC correlated with ILD, (r=0.379, p=0.01), CLD (r=0.343, p=0.02) and with ALD (r=0.341, p=0.02). This correlation has not been described in published literature.

CONCLUSION

This study demonstrated that the incidence of radiological RP was higher than clinical RP, with the likelihood of RP higher with age above 50 years, chest wall irradiation with electrons, supraclavicular field treatment with 6 MV photons and higher ILD. There was a universal fall in all pulmonary function parameters (except DLCO), with the fall in TLC being significantly more in those with RP. The factors associated with increased risk of RP should be considered when adjuvant radiotherapy is planned to minimize its likelihood and intervene appropriately. Though there are no definite guidelines, at least in women at increased risk for RP and those with pre-existing lung disease, planned for adjuvant radiotherapy, potential risks should be discussed and serial radiological imaging and pulmonary function test monitoring should be considered. Future studies to assess the impact of RP on the development of radiation fibrosis and serial pulmonary function would be useful.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Palliative Care Unit, Department of Radiotherapy, Christian Medical College and Hospital, Vellore, India.
2. Physician, Department of Radiotherapy, Christian Medical College and Hospital, Vellore, India.
3. Professor, Department of Radiotherapy, Christian Medical College and Hospital, Vellore, India.
4. Professor, Department of Radiotherapy, Christian Medical College and Hospital, Vellore, India.
5. Professor, Department of Pulmonary Medicine, Christian Medical College and Hospital, Vellore, India.
6. Professor, Department of Pulmonary Medicine, Christian Medical College and Hospital, Vellore, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Jenifer Jeba,
Associate Professor, Palliative Care Unit, Department of Radiotherapy, Christian Medical College and Hospital,
Vellore-632004 India.
E-mail : jenifermugesh@yahoo.com

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