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RESEARCH ARTICLE

Volumetric Estimation of Lung Dose and Its Association with Pneumonitis Following Radiotherapy in Breast Cancer Patients

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Abstract

Introduction: Lung is a major organ at risk during Post Mastectomy RadioTherapy (PMRT), because of the risk of Radiation Pneumonitis (RP). In countries like India 2D RT is widely used due to limited access to advanced technologies. We estimated the lung dose volumetrically in breast cancer patients treated with 2D tangential techniques, the incidence of acute RP and its association with lung dose. **Methodology:** Retrospective study of patients who underwent PMRT was done. The images with structure sets of cases planned using 2D technique were transferred to TPS and 3 D plans were generated. CLD, MLD, LL were measured from the 2D plan in the CT simulator. LDmean and V20 were measured from from DVH, in the TPS. Correlation between V20 and LDmean was done with CLD, MLD and LL. The incidence of radiation pneumonitis and its association with lung dose also was studied. **Result:** Total 50 patients were analyzed of which 3 patients had radiation pneumonitis. The mean CLD was 2.28 cm ± 0.54cm, MLD was 2.32 ± 0.6cm and LL was 12.52 ±2cm. V20 for two fields (MT+LT) was 17.04 ± 5.6 Gy and for three field (MT,LT and SCF) was 28.75 ± 8.6 Gy. Positive correlation was found between for V20 & LDmean and CLD, MLD & LL ($p<0.05$) 6% of patients developed Radiation pneumonitis but did not have association with V20 or MLD. **Conclusion:** Radiation pneumonitis is major concern after chest wall irradiation and the incidence is expected to be high with conventional technique where the volume is not accurately measured. It is still an option in countries like India with resource constraints by planning cautiously with the indicators of irradiated lung, like CLD and MLD within limits thus minimizing the incidence of radiation induced lung injury.

Keywords: Tangential technique- postmastectomy- Radiation pneumonitis

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Introduction

Breast cancer is the commonest cancer and the commonest cause of cancer mortality in women across the globe as well as in India [1]. Radiation therapy has a key role in the treatment of breast cancer. Many randomized trials have shown significant benefit with postmastectomy radiation therapy(PMRT) in patients with higher stage disease [2, 3]. It is crucial to minimize radiotherapy related complications, as most breast cancer patients have long term survival. In planning radiotherapy for breast cancer, lung is a major organ at risk, because of the risk of radiation pneumonitis (RP). The incidence and severity of it depends upon various factors like total dose and fractionation, RT technique, the amount of lung included in the field [4-6]. Conformal Radiotherapy, Breathhold techniques and respiratory gating reduces the lung dose and thus reduces the incidents of lung toxicities especially in patients for

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whom internal mammary region also has to be irradiated. Despite the advances in radiation techniques in the past decade, novel technology has decreased access in Low Middle Income Countries (LMIC) like India. Here the, radiation therapy with conventional technique is highly prevalent and inexpensive option. Advanced techniques and linac-based therapy may be reserved for selective cases [7, 8].

In our study we aimed to estimate the lung dose volumetrically and its association with acute radiation pneumonitis in breast cancer patients treated at our centre with 2D tangential techniques. The main objectives of the study was to measure the Lung Length (LL), Central Lung Distance (CLD), Maximum Lung Distance (MLD) and Mean Lung Dose (LD_{Mean}) from the 2D plans of breast cancer patients irradiated with 2D conventional tangential pair technique and compare it with the volume of lung receiving 20 Gy and to find out the incidence of acute radiation pneumonitis in these patients and its association with lung dose.

Materials and Methods

A retrospective study on breast cancer patients treated at our centre after mastectomy with conventional 2D radiation therapy from January 2016 and June 2017 was done after getting approval from the Institutional Review Board (IRB_ . Patients who underwent t breast conservation surgery (BCS), those who received prior radiotherapy to the chest wall or mediastinum or bilateral chest wall radiotherapy, and those with metastatic disease were excluded. Eligible patients received systemic treatment with chemotherapy with four cycles of Adriamycin 50 mg/m^2 and cyclophosphamide 600 mg /m^2 followed by 12 cycles of weekly paclitaxel 75 m/m^2 or 4- 6 cycles of Docetaxel 75 mg/m^2 and cyclophosphamide 600 mg /m^2. Targeted therapy with Trastuzumab was offered for patients with Her2 neu positive disease. All hormone receptor positive patients received hormone therapy with Aromatase inhibitors or Tamoxifen.

For radiotherapy planning, the patient was positioned on a breast board inclined with appropriate wedge angle and ipsilateral arm abducted and kept ≥ 90˚, and head turned to the contralateral side. Reference points were marked by placing fiducials on the chest wall, in the midline and laterally on either side of the chest wall. CT scan without contrast was done on CT simulator (GE: Optima). with 5 mm slices thickness and RT planning was done using medial and lateral tangential fields to the chest wall with or without regional nodal regions. Axilla was included in the SCF field for patients with positive axillary lymph nodes with extranodal extension or incompletely dissected axilla. Field borders were placed as per the standard recommendations and marking was done on the patient's skin. Patients were treated with radiotherapy 40 Gy in 15 fractions to the chest wall, with or without nodal regions depending on the stage of the disease.

For the study, after 2D planning the images of treatment plans, with marker points at the corners and central axis of the field, were transferred from the CT simulator to the contouring workstation (MIM 6.8.6) for delineation of target volume and lungs. The target volumes were contoured with the marker points at the corners of the field as surrogates and the images were transferred to the treatment planning system (TPS), Eclipse, Varian, Version 13.3. 3D Plans were generated in TPS with the same beam parameters like field size, inter field distance, gantry angle and collimator angle. The Mean Lung Dose (LDmean) and Volume of lung receiving 20 Gy (V20) were obtained from the DVH of the 3D plans. Central Lung Distance (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 and Lung Length (LL) defined as the length of lung measured at the posterior edge of the tangential field, which extends through the diaphragm for right sided breast irradiation and through the shadow of the heart for the left sided breast irradiation was measured from the VT simulator after virtual simulation. The demographic and clinical details and details of treatment and toxicity were collected from the case records.

Statistical Analysis

Basic descriptive statistical methods mean, median and percentages were used to express the demographic, clinical and treatment details and indicators of irradiated ung volume. Karl Pearson correlation method is used to find out the correlation between CLD, MLD and LL with V20 and the LD_{mean}. The data sets were analyzed using the exploratory data analysis (EDA) method.

Results

Fifty female breast cancer patients who received adjuvant radiotherapy were studied. The mean age was 52 years (33-75 years). 22% (n-11) had hypertension and one patient had chronic obstructive pulmonary disease. 64% (n- 32) of patients were having stage III disease. 86% of patients received chemotherapy with a combination of AC and paclitaxel. One patient did not receive chemotherapy as she was not willing. 96% (n-48) patients were treated with MT, LT and SCF and two patients with MT and LT fields alone (Table 1).

The correlation between V20 and CLD, MLD & LL was analysed for all patients treated with tangential fields Mean CLD was 2.5 cm (1.2 cm to 3.54 cm). Majority (72%, n-36/50) had CLD ≤2.5cm. Of the patients with CLD >2.5 cm 71.4% (10/14) had V20 more than 20%. Mean MLD was 2.3 cm (Range: 1.27 to 3.61 cm) Mean LL was 12. 5 cm (Range:8.09-16.9 cm) Both MLD and LL also showed a positive correlation with V20 (r-0.705 and 0.433; p,0.05) respectively. The details of patients with V20 and indicators of irradiated lung volume (CLD, MLD & LL) are given in Table 2.

Though all indicators of irradiate lung volume had correlation with V20 for MT and LT fields, LL did not have correlation for 3 fields (MT, LT & SCF).

Table 1. Demographic and Treatment Details of Patients Treated with Postmastectomy RT at Malabar Cancer Centre from 2016-2017

		Number (%)	
Age		Median 52 yrs (33- 75 years)	
Comorbidities	DM	11	(22)
	HT	7	(14)
	COPD	1	(2)
	CAD	-	0
	Multiple	3	(6)
Stage	II	18	(36)
	III	32	(64)
Chemotherapy	AC+Paclitaxel	43	(86)
	TC	6	(12)
Radiation Therapy	MT+LT	2	(4)
	MT+LT+SCF+/-AXILLA	48	(96)

A-Adramycin; C- Cycophosphamide; T- Docetaxel; MT- Medial Tangent; LT- Lateral Tangent; SCF – Supraclavicular Fossa

Table 2. Correlation between CLD, MLD and LL and V20 /LDmeanfor Tangential Fields in Patients with Breast Cancer Treated with Postmastectomy 2DRT from 2016 to 2017

	V20			
	≤ 20 %	21 – 30 %	>30%	(%)
CLD_{mean} (cm) r-0.686, p,0.05				
≤2.5	32	3	1	36 (72)
>2.5	4	9	1	14 (28)
Total	36 (72%)	12 (24%)	2 (4%)	50 (100)
MLD				
≤ 2.3	24	1	1	26 (52)
≥ 2.3	12 (50%)	11 (45.8%)	1 (4.1%)	24 (48)
Total	36 (72%)	12 (24%)	2 (4%)	50 (100)
LL_{mean}				
≤12.5	23	2	0/25	25 (50)
≥12.6	13	10	2	25 (50)
Total	36 (72%)	12 (24%)	2 (4%)	50 (100)

CLD, Central Lung Distance; MaxLD, Maximum Lung Distance; LL, Lung Length

CLD and MLD had a positive correlation with mean lung dose. The Mean of LD mean was 9 Gy and 18 Gy respectively for 2 fields (MT/LT) and 3 fields (MT/LT & SCF) fields. Mean lung dose and V20 for 2 fields and 3 fields were compared. A statistically significant difference increase in lung dose was seen with MT, LT and SCF fields (Table 3).

Three patients (6%) had radiation pneumonitis for whom CLD were 2.3 cm, 3.3 cm and 2 cm and V20 were 33.3%, 20% and 40% mean lung dose for these patients were 10.43, 19.26 and 15.97 gy respectively but did show any positive correlation. Patients, who had CLD 3.3 cm and V20, 20%, did not receive RT to SCF

Discussion

Radiation therapy with conventional tangential techniques is the traditional method of treating patients with breast cancers and its association with pneumonitis is well established. The main limitation with this 2D technique is that, during treatment planning, the volume of lung receiving radiation cannot be quantified and CLD and MLD are used as indicators of irradiated lung volume.

In our cohort majority of the patients were having

Table 3. Correlation between V20 and MLD for 2 and 3 Field Treatment in Patients with Breast Cancer Treated with Postmastectomy 2DRT from 2016 to 2017

	MT, LT	MT, LT, SCF	Correlation (pvalue)
V20 (mean)	17 +/-5.6 Gy	34.6 +/- 8.7 Gy	r- 0.77 (p, 0.05)
Mean LD (mean)	10.2 Gy+/-2.6	18.7 Gy +/-3.8	r- 0.731 (p, 0.05)

locally advanced disease as shown in many other studies from India requiring multimodality treatment [9, 10]. We analysed patients who received postmastectomy radiation therapy to chest wall and SCF,. Internal mammary chain was not included at the time of treatment

In our country still there are many centres which do not have facility for conformal radiotherapy. Though evidences show that conformal therapy reduces dose to the underlying critical organs. Study by Ayata et al has shown that IMRT to chestwall significantly improved the dose distribution and limited the dose to lung and heart [11]. Similarly Lind et al analysed the pulmonary complications using various techniques of RT and concluded that 3DCRT is helpful than 2D RT in reducing the dose to the lung [12]. But we have limitations for the same due to various logistic and resource constrains and large patient load.

We studied correlation between CLD, MaxLD and LL measured from 2D tangential plans and volume of ipsilateral lung receiving 20 Gy. A positive correlation was found between V5, V10 and V20 by Indra et al in their study on correlation of 2D parameters on lung and heart dose. In their study the median CLD for left and right lung were 1.86 ± 0.62cm and 1.59± 1.25cm [13]. In our patients the same was 2.28 ±0.54.for ipsilateral lung. Another study by Onal et al comparing 2 field and 4 field RT by 3DCRT, CLD and MLD were measured by conventional plan and found to have correlation with lung doses. Similarly Kong et al also in their study found that there is a linear correlation of CLD with ipsilateral LD mean V20,V30 and V40 [14, 15].

Study by Aznar et al showed that mean ipsilateral lung Dose was 9 Gy and it increased with addition of nodal regions. In our study the mean lung dose for MT and LT was 10.2 Gy 2.6 Gy) and it was 18.7 ± 3.8 Gy when SCF was added which is in concordance with various other studies which also have shown that with nodal irradiation ipsilateral mean lung dose and V20 is higher [16, 17].

V20 and Mean LD were significantly high for patients receiving treatment with MT, LT and SCF fields than those treated with MT and LT fields which warrants caution while adding nodal irradiation.

In our study, 6% of patients of the 50 patients studied show clinical radiation pneumonitis. Internal mammary chain was not included as a part of routine treatment, which may be one reason for the low incidence of radiation pneumonitis in our cohort. In the study by Jenifer et al showed that, 19.5% had clinical radiation pneumonitis. In their study cohort patients were treated with a combination of photons and electrons, photons alone on telecobalt machine, and with electrons alone. Of these patients treated with photons had statistically significant radiation pneumonitis. However in their study correlation with pneumonitis and CLD was not made out, but there was a correlation with inferior lung distance. The probable reason for the increased incidence of radiation pneumonitis may be the inclusion of internal mammary field for these patients [18].

Hande Bas Ayata et al, compared dose distribution and OAR doses in conventional tangential technique and IMRT and it showed that the percentage of mean V20 of ipsilateral lung that receive 20Gy were 14.36 ±6.93 with 3DCRT plans [11]. In our study, beam arrangements for treatment were simulated in treatment planning system and dose calculated.Ipsilateral Mean V20 for two fields (MT and LT) and three fields (MT,LT and SCF) were 17 ± 5.6 and 28.75 ± 8.6.

A prospective study by Jeba et al has shown radiological and clinical RP in 45.65% (n=21) and 19.56% (n=9) respectively which showed association with age, chest wall irradiation with electrons, and supraclavicular field treatment with 6 MV photons (p= 0.011) [18]. We also observed radiation pneumonitis in patients who received SCF irradiation. Study by W.wang et al has shown that MLDs are significantly associated with Radiation Pneumonitis [19]. But our patients who developed radiation pneumonitis did not show a significant correlation with any of the analysed parameters. Moreover one of the patient treated with MT, LT and SCF ,who developed radiation pneumonitis had CLD 2 cm, Mean LD was 16 Gy but V20 was 40%. The reason may be lesser lung volume in this patient. One of them had V20 20%

Three patients had radiation pneumonitis for whom CLD was 2.3 cm, 3.3 cm and 2 cm and V20 was 33.3%, 20% and 40% mean lung dose for these patients were 10.43, 19.26 and 15.97gy respectively but did show any positive correlation. Patients, who had CLD 3.3cm and V20, 20%, did not receive RT to SCF.

One of the major limitation of our study is its retrospective nature. Here the target volumes were drawn according to the fiducials on the CT simulation images and plans were generated. The target volume coverage was not analysed. Patient with mild respiratory symptoms were not evaluated with imaging to confirm radiation pneumonitis and hence there may be a bias in the count. Also in this the radiation pneumonitis is not confirmed by imaging.

In conclusion, Radiation treatment for breast cancers is traditionally being done with conventional tangential beams. The main concern with this is the dose received by the underlying structures like lung and heart. However careful planning which includes lung with a CLD of < 2.5 -3 cm is still an option in countries like India with resource constrains. The incidence of radiation induced lung injury can be minimized in this setting. Probably similar study conducted in a larger cohort may be needed to analyze the correlation of radiation pneumonitis with the lung dose. Also confirmation of pneumonitis by imaging in patients with mild symptoms may bring out better results.

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