



Prospective Study to Evaluate the Dosimetric Profile of Organ at Risk in Two-Field and Three-Field Left Breast Irradiation by Three-Dimensional Conformal Radiotherapy

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OBJECTIVE

In this study, we analyzed dose to organ at risk in the left breast cancer patients, in terms of dose volume histogram (DVH), with the quantitative analysis of normal tissue effects in the clinic dose constraints and calculate potential toxicity in terms of normal tissue complication probability (NTCP).

METHODS

This study included 60 post-operated left breast cancer patients who received chest wall/breast irradiation by three-dimensional conformal radiotherapy (RT). The patients had received a total dose of 40Gy in 15 fractions to whole breast/chest wall (two fields) and dose to supraclavicular fossa (three fields). We compared the DVH for heart, lung, and spinal cord in both fields.

RESULTS

Mean dose for lung was 17.49Gy and for heart 12.31Gy, and spinal cord maximum dose was 0.78Gy. The average lung NTCP for RP was 3.11%. The risk of RP was significantly greater in three-field radiation as compared to two field for lung ($p < 0.05$). We observed the statistically significant correlation of MHD and NTCP ($p < 0.00001$ and $p = 0.000402$). The correlation of central lung distance (CLD) was observed to be significant with three fields, that is, as the CLD increased risk of organ damage to lungs increased ($p = 0.00022$). The correlation of CLD and MHD with DVH was observed to be statistically significant ($p < 0.001$).

CONCLUSION

This study results are useful to reanalyze the previous 2D-based clinical reports about breast RT complications as a view point of the NTCP. Further studies are needed for the actual clinical data of complications with this DVH analysis.

Keywords: Breast cancer; cardiac toxicity; normal tissue complication probability; radiation pneumonitis; three-dimensional conformal radiotherapy.

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INTRODUCTION

Breast cancer is the second most common malignancy in the world. In India, breast cancer is the most common cancer diagnosed, with 200,000 (14.8%) of the total cancer cases according to the Indian Council of Medical Research.[1] Whole breast radiotherapy (RT) after lumpectomy and chest wall post mastectomy RT (PMRT) both have shown improved locoregional control and definite survival benefit.[2,3]

There have been concerns regarding an increase in cardiac mortality, especially in patients who had been treated with RT for the left-sided breast cancer.[4–6] This latent manifestation of cardiovascular disease is of great importance, since the survival rate for breast cancer patients is improving and breast cancer patients have remarkable life expectancy after completing treatment.[7–10]

As recommended by normal tissue complication probability (NTCP) models for cardiac mortality, it should be considered that NTCP value more than 5% could jeopardize the beneficial effect on survival of RT.[11] The NTCP of cardiac mortality increased with maximal heart distance (MHD), and the NTCP of radiation-induced pneumonitis (RP) increased with central lung distance (CLD).[12]

Thus, the purpose of this study is the dosimetric analysis of organs at risk (OAR) in the left breast cancer patients, in terms of dose volume histogram (DVH) to analyze adherence of plan with the quantitative analysis of normal tissue effects in the clinic (QUANTEC) dose constraints and calculate potential toxicity in terms of NTCP.

MATERIALS AND METHODS

Study Design

This prospective analytical study was initiated and followed by approval from the Institutional Ethical Committee. A written informed consent has been obtained from every patient enrolled in this study. From January 2018 to March 2019, a total of 60 post-operated (breast conservation surgery or mastectomy) patients of histopathologically proven left breast carcinoma who received chest wall/breast irradiation by three-dimensional conformal RT (3D-CRT) technique at a RT Center of Central India were enrolled in this study. The patients included in the study had stage I to III breast cancer, underwent post modified radical mastectomy or post breast conservation surgery, were between 18 and 70 years of age, had Karnofsky Performance Score

more than 70, had received a total dose of 40 Gy in 15 fractions to whole breast/chest wall, and those who received 40 Gy in 15 fractions to supraclavicular fossa (SCF) or 10–12 Gy electron beam boost to tumor cavity. The patients who were excluded from the study were <18 or more than 70 years of age, had metastatic disease (stage IV), and had received irradiation by use of accelerated partial breast irradiation, interstitial implants, intraoperative RT or intensity modulated RT, and those with uncontrolled cardiovascular or renal medical conditions.

Patient positioning and fixation

Patients were positioned in the supine position, on an angled board such that the sternum was horizontal with the ipsilateral arm abducted to 90°. The patient must remain in identical position for computed tomography (CT) simulation and subsequent treatment. Patients were immobilized using thermoplastic mold. Care must be taken at data acquisition to adapt all the supporting devices to the individual patient's size and shape to maximize comfort, and so aid reproducibility for subsequent treatment.

Clinical landmarks

The target was defined to consist of the chest wall/breast and SCF. The chest wall/breast borders consisted of the medial border at or 1 cm over the patient's midline, the lateral border at 2–3 cm beyond all palpable breast tissue to the mid axillary line, the superior border at the sternal angle, and the inferior border at 2 cm below the contra lateral inframammary fold. SCF borders are delineated as the superior border at thyrocricoid groove, the inferior border matched with upper border of tangential field, the medial border at or 1 cm across midline extending upward following medial border of sternocleidomastoid muscle to thyrocricoid groove, and the lateral border at insertion of deltoid.

Data transfer methods and algorithm

Three-dimensional CT imaging scans multiple slices with slice thickness 5 mm were obtained with the patient in the treatment position that was used throughout treatment. A reference point was defined and marked on the customized thermoplastic mold used for patient immobilization.

CT cuts were transferred in the digital imaging and communications in medicine (DICOM) format images and viewed using treatment planning system (TPS) Eclipse version 15.6 (Varian Medical Systems, Palo Alto, CA, USA). The Anisotropic Analytical Algo-

rithm version 15.6 (Varian Medical Systems, Palo Alto, CA, USA) was used for dose calculation in TPS. High-energy 6MV photon beams were used in planning and all data of approved plans were digitally transferred to Varian Clinac 2300 CD linear accelerator (M/s Varian Medical Systems, Palo Alto, CA, USA).

Target volume delineation

The Radiation Therapy Oncology Group breast cancer atlas was used to define the planning target volume. The heart was defined as all visible myocardium, the apex, the right auricle, atrium, and infundibulum of the ventricle. The pulmonary trunk, the root of the ascending aorta, and superior vena cava were excluded from the study. The ipsilateral lung volume was contoured, with the exclusion of the hilum, trachea, pulmonary vessels, and aortic branches. The spinal cord was contoured according to the bony limits of the spinal canal.

Dose prescription

The prescription dose and fractionation were 40Gy in 15 fractions, five fractions/week and 40Gy in 15 fractions to SCF for PMRT, and 40Gy in 15 fractions followed by 12.5Gy in five fractions electron beam boost to lumpectomy tumor cavity. The dose constraints for the treated volumes were a minimum of 90% and a maximum of 110% of the prescribed dose.

RT technique

The RT was performed using the two-field standard tangential technique (n=25) or three-field technique (n=35). All of the patients treated with the two-field technique had undergone lumpectomy. PMRT was done with three-field technique.

Doses calculations and adjustments in beams weight, wedges, blocks, and beam orientations were made as desired in an interactive fashion. Beam orientations were selected and beams were 3D-shaped using multi leaf collimators based on the projection of the structures of interest as seen with beam's-eye view. Setup instructions including field size, gantry, collimator, and table position were provided to facilitate the implementation of treatment beams at the physical simulator and treatment machine.

Plan evaluation

The sparing of OAR (lung, heart, and spinal cord) was evaluated by comparing their mean doses, lung V_{10Gy} (volume of lung receiving more than 10Gy), lung V_{20Gy} , lung V_{30Gy} , heart V_{25Gy} (volume of heart receiving more than $_{25Gy}$), and maximum dose to spinal cord.

Calculation of the NTCP

Using the dose calculation data, we derived the DVH curves of each OAR. For each patient and structure, a cumulative DVH was exported from Eclipse with a bin size of at most 5 cGy and imported into third party program R studio. Here, NTCP calculations explained below were performed using DVH metrics vignette.[13,14]

From these DVH curves, we performed the NTCP calculations for each NTCP model, the Lyman-Kutcher-Burman (LKB) model for radiation-induced pneumonitis, and pericarditis. The equivalent uniform dose (EUD) method was used for reducing the DVH curves to a single dose. The Relative Seriality (RS) model was used for calculation of the NTCP for late cardiac mortality. The LKB NTCP and RS models used in this study are briefly described below.[15–18]

LKB NTCP model:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\theta}^t e^{-\frac{x^2}{2}} dx$$

$$t = \frac{EUD - TD50}{m \cdot TD50}$$

$$EUD_{LKB} = \left(\sum_i D_i^n \cdot \frac{V_i}{V_{tot}} \right)^{\frac{1}{n}}$$

Where TD50 is the 50% tolerance dose at 5 years; EUD is the EUD; n and m are tissue-specific parameters; D_i is the dose element, and V_i is the volume element. The parameters for complication of radiation-induced pneumonitis are TD50=24.5, n=0.87.

RS model for late cardiac mortality:

$$NTCP_{heart} = \left\{ 1 - \prod_{i=1}^n [1 - P(D_i)^s]^{\Delta v_i} \right\}^{\frac{1}{s}}$$

$$P(D_i) = 2^{-\exp\{\gamma(1 - \frac{D_i}{D_{50}})\}}$$

Where $D_{50}=TD50$ (=52.3Gy); s is the RS factor (=1), and γ is the maximum relative slope (=1.28).

The CLD is defined as the perpendicular distance from the posterior edge of the tangential field to the posterior part of the anterior chest wall in the middle of the field. Maximum Heart Distance (MHD) is the maximum distance of the heart contour to the posterior field border measured in the beam's eye view of the medial tangential fields.

Before calculation, DVH data were converted to the dose biologically effective to 2 Gy per fraction irradiation, using linear-quadratic model (α/β was equal to 3 Gy for both lung and heart). For the left lung, clinical

pneumonitis of grade greater than 2 was used as endpoint in NTCP calculation. In the case of heart, NTCP calculation endpoint was excessive cardiac mortality in the irradiated patients with the left-sided breast cancer. The RS model coefficients used for lung and heart NTCP calculation in this study were obtained from data analysis of patients with breast cancer by Gagliardi et al.[11] In each plan, we calculated the NTCP of RP and cardiac toxicity as described above. We evaluated the change in NTCP values of RP between 3 cm and 4 cm of the CLD. For evaluating the change in NTCP by the MHD, we also measured the MHD in every treatment plan.

Statistical Analysis

Data were compiled using Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 20.0 (SPSS Inc, Chicago, IL, USA). The mean and standard deviation of quantitative variables was calculated. The mean between two groups was compared using independent t-test. Quantitative discrete variables were compared using the Chi-square test. The correlation coefficient was estimated to assess the relationship between CLD and MHD with NTCP. $P < 0.05$ was considered statistically significant and $p < 0.01$ was considered highly significant.

RESULTS

This prospective analytical study included 60 breast cancer patients who have received RT using the two-field standard tangential technique or three-field technique (Table 1).

The present study attempted to evaluate dose-volume histogram of heart, lung, and spinal cord in 3D-CRT, to analyze adherence of plan with QUANTEC dose constraints. Mean dose for lung was 17.49 Gy, and V_{20Gy} was 39.88%. Mean dose for heart was 12.31 Gy and spinal cord maximum dose was 0.78 Gy. However, the test of significance observed no statistical difference in the mean dose for heart, lung, and spinal cord among patient receiving two-field or three-field radiation therapy ($p > 0.05$) (Table 2).

In the present study, the average lung NTCP for radiation pneumonitis was 3.11%. The risk of radiation pneumonitis was observed to be significantly greater in three-field radiation technique as compared to two fields for lung ($p < 0.05$). Hence, late cardiac mortality probability for heart did not vary significantly between two-field and three-field technique, but average heart NTCP was 2.42%, as shown in Table 3.

Table 1 Patient demographics and treatment characteristics of 60 included left side breast cancer patients

Characteristic	n
Age	
<50 years	33
>50 years	27
Residence	
Rural	26
Urban	34
Religion	
Hindu	48
Muslim	12
Others	0
Tumor subtypes	
HR+, Her2-	11
HR+, Her2+	11
HR-, Her2-	12
HR-, Her2+	26
Tumor grade	
Grade I	14
Grade II	36
Grade III	10
Tumor stage	
IIB 25	
IIIA 14	
IIIB 11	
IIIC 10	
Karnofsky performance status	
70	2
80	21
90	25
NA	12
Neoadjuvant chemotherapy	11
Chemotherapy regimen	
FEC*	11
AC fb T (4+4)†	28
EC fb T (4+4)‡	17
CAF§	4
Trastuzumab	15
Hormonal therapy	
Letrozole	11
Anastrozole	3
Tamoxifen	10
Menopausal Status	
Premenopausal	16
Postmenopausal	44

*: Six cycles of 5-fluorouracil, epirubicin, and cyclophosphamide; †: Four cycles of Adriamycin and cyclophosphamide followed by four cycles of paclitaxel; ‡: Four cycles of epirubicin and cyclophosphamide followed by four cycles of paclitaxel; §: Six cycles of cyclophosphamide, Adriamycin, and 5-fluorouracil. HR: Hormonal receptor; NA: Not available

The NTCP in the ipsilateral lung revealed a significant difference as the CLD increased from 3 cm to 4 cm ($p = 0.0012$), as shown in Table 4. The NTCP in

Table 2 Dose distribution to organs at risk (Lung, Heart, and Spinal Cord)

Organ at risk	Dose constraint	Quantec value	2 field	3 field	p
Lung	$V_{30\%}$ (%)	–	35.99±2.49	34.88±7.43	0.66
	$V_{20\%}$ (%)	≤30	41.15±9.56	39.60±7.84	0.57
	$V_{10\%}$ (%)	–	47.97±11.14	44.55±8.28	0.25
	Mean dose (Gy)	13–20	17.84±4.11	17.42±3.87	0.75
Heart	$V_{25\%}$ (%)	<10	25.40±6.02	28.06±9.87	0.39
	Mean dose (Gy)	26	12.34±2.78	12.33±2.98	0.93
Spinal cord	Max dose	–	0.50±0.14	0.85±1.22	0.36

*: Percentage of ipsilateral lung volume receiving dose of 30Gy; †: Percentage of ipsilateral lung volume receiving dose of 20Gy; ‡: Percentage of ipsilateral lung volume receiving dose of 10Gy; §: Percentage of heart volume receiving dose of 25Gy. Gy: Gray

Table 3 Normal tissue complication probability (NTCP) for radiation pneumonitis and late cardiac mortality

Organ NTCP%	Two-field (Average±SD)	Three-field (Average±SD)	p
Lung NTCP% for radiation pneumonitis	0.40±0.18	3.72±1.63	0.001
Heart NTCP% for late cardiac mortality	2.31±0.13	2.88±1.56	0.27

the heart did not reveal a significant difference as the MHD increased from 2 cm to 3 cm ($p=0.05$) (Table 5).

The present study observed the statistically significant correlation of MHD and NTCP, that is, as the MHD increased, the NTCP also increased in both two-field and three-field radiation therapy ($p<0.00001$ and $p=0.000402$), as depicted in Figure 1. The correlation of CLD was observed to be significant with three-field radiations, that is, as the CLD increased risk of organ damage to lungs increased ($p=0.00022$), as depicted in Figure 2.

In the present study, correlation of CLD and MHD with dose-volume histogram was observed to be statistically significant ($p=0.001$). For the breast the slope of the V_{10Gy} , V_{20Gy} and V_{30Gy} were nearly constant, as illustrated in Figure 3.

The analysis for the heart DVH was reflected through the heart volume V_{25Gy} plotted versus MHD. The MHD was observed to be significantly correlated with dose-volume histogram ($p<0.001$), as depicted in Figure 4.

DISCUSSION

This study aimed to estimate the doses of irradiation to the OAR in 3D-CRT and also to evaluate if two-dimensional (2D) radiographic parameters such as CLD and MHD have a role in predicting the lung and heart volume at different dose levels.

RT has become the essential modality of treatment in post-operative cases of locally advanced breast can-

Table 4 Association of CLD (Central lung distance) with NTCP (Normal tissue complication probability)

Lung	CLD (Average±SD)		p
	3 cm	4 cm	
NTCP%	1.85±1.36	3.42±1.97	0.012

Table 5 Association of MHD (Maximum Heart distance) with NTCP (Normal tissue complication probability)

Heart	MHD (Average±SD)		p
	2 cm	3 cm	
NTCP%	1.31±0.61	2.58±1.78	0.05

cer.[19] The 3D-CRT has been replacing the 2D conventional planning techniques, but 2D techniques are still most common in the developing world. The main advantages of 3D-CRT are both the evaluation of target volume coverage as well as assessing the OAR doses that are essential in predicting the risk of radiation toxicities.[20]

QUANTEC suggested <20% chance of symptomatic pneumonitis with if <30% of lung received 20Gy ($V_{20} \leq 30\%$), whereas in the present study, V_{20Gy} was 39.88%. The mean dose in the present study was 17.49Gy. QUANTEC suggested 10% and 20% symptomatic pneumonitis at the mean dose of 13 Gy and 20 Gy, respectively.

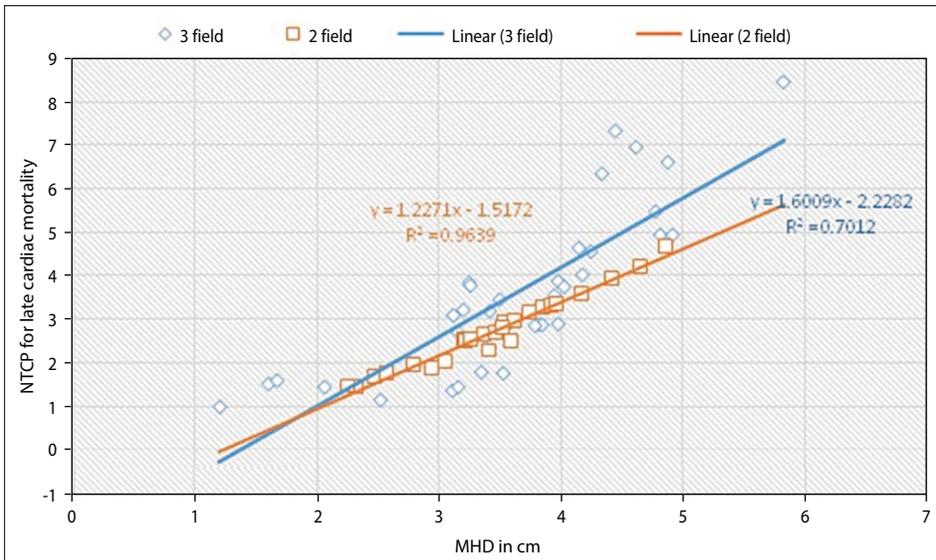


Fig. 1. Correlation of MHD with NTCP for late cardiac mortality.
 MHD: Maximum heart distance; NTCP: Normal tissue complication probability.

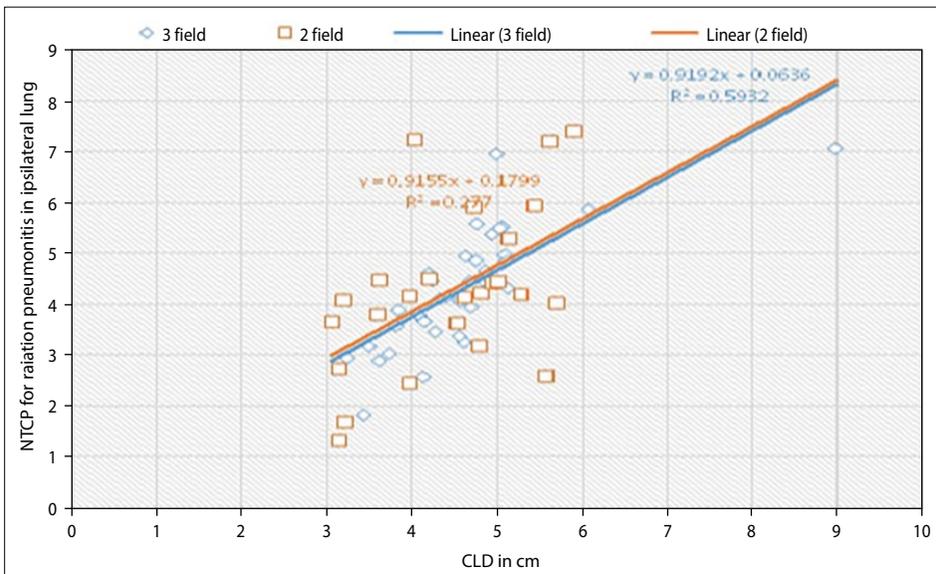
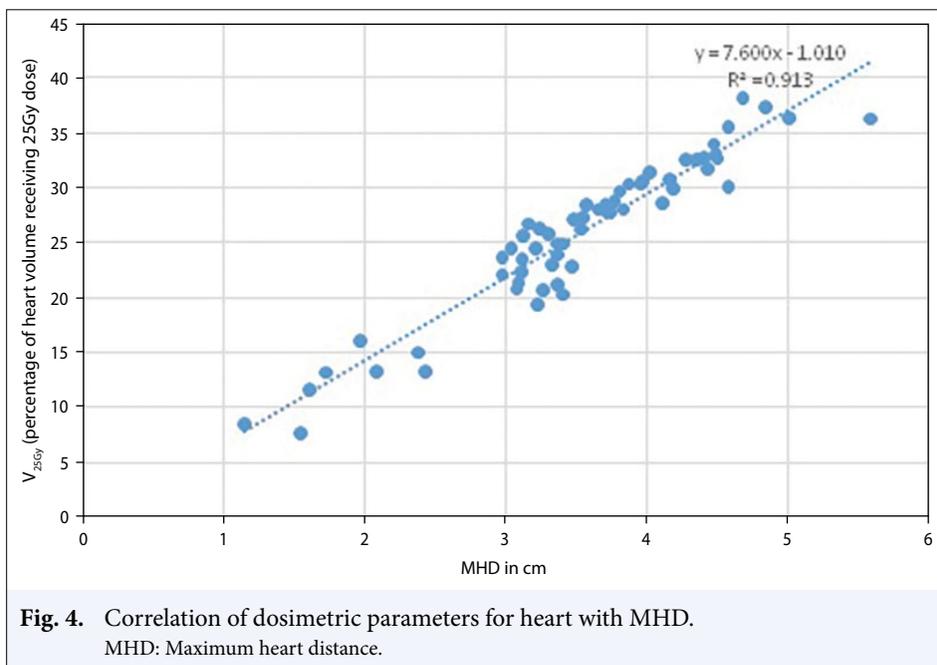
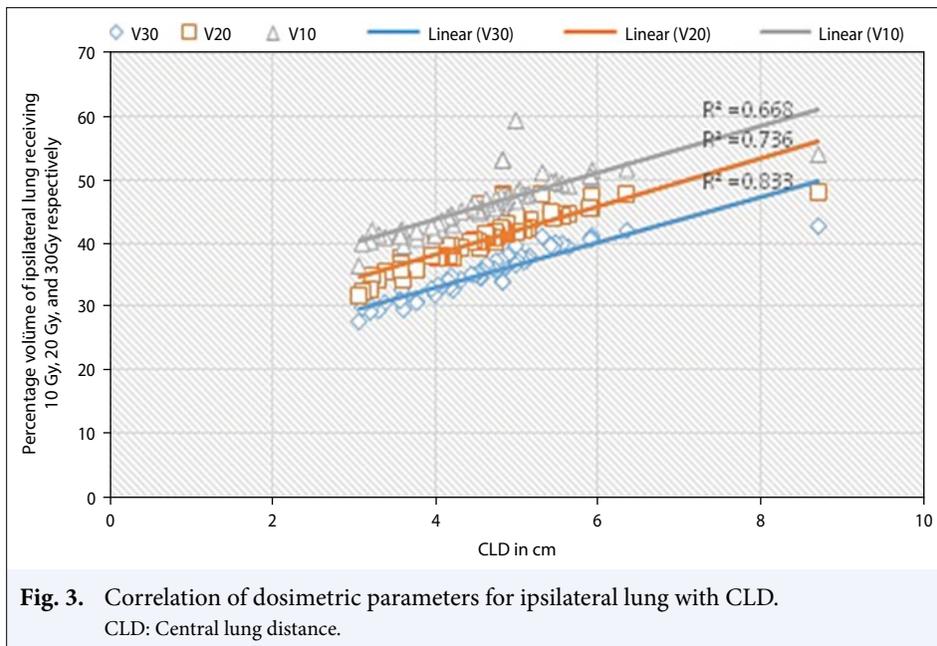


Fig. 2. Correlation of CLD with NTCP for radiation pneumonitis in ipsilateral lung.
 CLD: Central lung distance; NTCP: Normal tissue complication probability.

Similarly, for heart mean dose given in the present study was 12.31 Gy, however, QUANTEC proposed 26 Gy, so it corresponds to QUANTEC constraint. Spinal cord maximum dose is 0.78 Gy which is way lower than QUANTEC constraint of 50 Gy for 0.2% myelopathy rate. However, test of significance observed no statistical difference in mean dose for heart, lung, and spinal cord among patient receiving two-field or three-field radiation therapy ($p > 0.05$). [11]

In the present study, the average lung NTCP for radiation pneumonitis was 3.11%. The risk of radiation pneumonitis was observed to be significantly greater in three-field radiation technique as compared to two fields for lung ($p < 0.05$). The rationale behind this effect is due to the presence of the anterior supraclavicular field, which elevates radiation dose in lung parenchyma that lies beneath the chest wall. The findings of our study are similar to the findings of study conducted by



Noh et al.[12] They documented the NTCP of radiation-induced pneumonitis to be 0.5% and it was higher in reverse hockey stick method followed by three fields and least in two fields (0.0%, 0.0%, 3.1%, $p < 0.001$). A study by Das et al.[21] also reported higher risk of RP in three fields as compared to two field. These results are consistent with our NTCP calculations, suggesting that the LKB NTCP model with a reference parameter set may be useful for predicting RP.

In the present study, late cardiac mortality probability for heart did not vary significantly between two-field and three-field technique, but average heart NTCP was 2.42%. These findings were similar to the findings of study conducted by Noh et al.[12], in which they observed NTCP of cardiac mortality as 0.7%. NTCP of cardiac mortality was significantly higher in reverse hockey stick method with no difference in three fields and two fields (0.0%, 0.0%, 3.1%, $p < 0.001$) similar to finding of our study.[17]

Hurkmans et al.[22] reported NTCP values for excess cardiac mortality due to acute myocardial ischemia (MI) with minimum and maximum values of 0.1 and 7.5% (locoregional and tangential RT) and 0.0 and 6.1% (tangential technique). Another study reported an increased incidence of MI in case of the left side RT ($p=0.02$).[23]

The CLD is commonly used as a simple parameter to assess irradiated lung volume. We observed that as the CLD increased from 3 cm to 4 cm, risk of organ damage ipsilateral lung as revealed by NTCP increased ($p<0.01$). Furthermore, a statistically significant correlation of CLD and NTCP was established, as the CLD increased, the NTCP also increased ($p<0.001$) in three-field radiation therapy ($p<0.001$) but not in two-field technique. This finding is suggestive of the fact that chances of occurrence of pneumonitis in the three-field radiation technique are highly dependent on the CLD; probably, the supraclavicular field in the three-field method increases the irradiated lung volume. Noh et al.[12] also observed increased in NTCP of RP as the CLD increased.

The MHD is a radiographic parameter that helps to measure the irradiated heart volume for each patient. Hurkmans et al.,[22] in their study, used RS model for predicting NTCP of cardiac mortality and suggested a cardiac mortality curve equation based on MHD. Our study observed that as the MHD increased from 2 cm to 3 cm, the NTCP heart also increased ($p<0.01$). Furthermore, we observed that a statistically significant correlation of MHD and NTCP was established, which means that as the MHD increased, the NTCP also increased ($p<0.001$) both two-field and three-field radiation therapy ($p<0.001$). Similar to the findings of present study, Noh et al.[12] also observed increased in NTCP of radiation-induced cardiac mortality as the MHD increased.

In the present study, correlation of CLD with DVH was observed to be statistically significant. For the breast, the slope of the V_{10Gy} , V_{20Gy} , and V_{30Gy} was nearly constant. Das et al.[21] observed findings similar to our study and concluded that the correlation of treatment parameters (CLD) provides a direct link to the volume of the lung treated to a given dose. Another retrospective study by Teh et al.,[24] to correlate DVH with RP observed the occurrence of steroid requiring RP after 6 months and the overall incidence of RP was 1.1%. In contrast to our study, Minor et al.,[25] in their retrospective study of 353 patients, observed no correlation between CLD and pneumonitis.

In the present study, correlation of MHD with DVH was observed to be statistically significant. The analysis for the heart DVH was reflected through the heart

volume V_{25Gy} plotted versus MHD. The MHD was observed to be significantly correlated with DVH. Das et al.[21] study findings were similar to our study and suggested positive correlation of treatment parameters (MHD) with volume of heart treated to a given dose. Contrasting findings were observed by Borger et al.,[26] in which they assessed the risk of cardiovascular disease (CVD) after adjuvant radiation. They did not find any significant correlation between MHD and NTCP heart.

An accurate absolute NTCP model of excessive late cardiac mortality and RP requires accurate clinical data. However, several factors limit the accuracy of these models. These include a long latency period before clinical complications arise, the relatively low incidence of radiation-induced cardiac complications with newer RT techniques, and the relatively high prevalence of ischemic heart disease in the general population and the absence of good dosimetric and volumetric data in retrospective studies. Although the absolute NTCP values should be viewed with caution, they must be fitted to clinical outcome data and then are useful approximations of risk. This study is limited in that it does not consider many other risk factors of cardiovascular diseases, such as a history of hypertension, smoking, and use of combined cardiotoxic chemotherapy.

CONCLUSION

We did not analyze the actual clinical data of complications in this study; hence, it is difficult to apply our results directly to the clinic. However, our results are useful to reanalyze the previous 2D-based clinical reports about breast RT complications as a viewpoint of the NTCP.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Gandhi Medical College, Bhopal Ethics Committee (no: 3827-29/MC/IEC/2018, date: 30/01/2018).

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