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Research Article

# A Prospective Study of Dose Comparison between Deep Inspiratory Breath Hold (DIBH) Technique *vs.* Free Breathing (FB) Technique in Reducing Cardiac Dose in Left Sided Post Mastectomy Breast Cancer Patients Treated With Radiotherapy

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## ABSTRACT

Cardiac mortality and morbidity during breast cancer treatment can be caused by both radiotherapy and chemotherapy. As chemotherapy cannot be omitted due its proven overall survival benefit, newer radiotherapy techniques like DIBH with Real-time Position Monitoring (RPM), have been devised to minimise dose to the heart without compromising target coverage. Very sparse prospective data look into the benefit of DIBH in chest wall radiotherapy.

**Aim:** To determine dosimetrically whether DIBH reduces the cardiac (heart and left anterior descending [LAD] artery) and ipsilateral lung doses compared to FB, in patients receiving radiotherapy to left side chestwall with 3D-CRT technique and to quantify it.

**Material and methods:** 25 consecutive left sided postmastectomy breast cancer patients with minimum breath hold duration more than 15 seconds were selected. 2 plans were made for each patient using 3D-CRT technique with a dose of 40Gy in 15 fractions- first in FB (control) and the second in DIBH with RPM system. Dose volume histograms (DVH) for each patient were generated, recorded and analysed.

**Results:** The target coverage parameters (PTV) were found to be comparable in both plans. DIBH significantly reduced ($p<0.001$) the mean heart dose by 28.19% (from 5.18Gy to 3.72Gy), mean LAD dose from 25.94Gy to 16.99Gy (ie 34.50%), Maximum Heart Distance (MHD) from 2.17 cm to 1.22 cm (i.e. by 43.54%) and all heart parameters analysed. DIBH also reduced left lung V20Gy and mean lung dose and combined mean lung doses. **Conclusion:** With appropriate patient selection and adequate training, DIBH is an acceptable technique in reducing both cardiac and lung doses in left sided post mastectomy patients receiving radiotherapy without compromising target coverage. This could result in fewer radiotherapy-related complications even when using hypofractionated radiation doses. However, long terms follow up and studies with larger sample size are warranted in the future to consolidate the significance obtained in our study.

**Keywords:** Breast cancer, Post-Mastectomy radiotherapy, Deep inspiratory breath hold technique, Respiratory motion management and gating, Late effects of radiation treatment, Cardiac sparing, Cardiac mortality and morbidity

## ABBREVIATIONS

3D-CRT: 3D Conformal RT; ABC: Active Breathing Control; BCS: Breast Conserving Surgery; CW: Chest Wall; CTV: Clinical Target Volume; CT: Computerized Tomography; DBCG: Danish Breast Cancer Cooperative Group; DIBH: Deep Inspiration Breath Hold; DVH: Dose Volume Histograms; EBCTCG: Early Breast Trialists Collaborative Group; ECOG: Eastern Cooperative Oncology Group; FB: Free Breathing; IMC: Internal Mammary Chain; IMRT: Intensity Modulated Radiation Therapy; LAD: Left Anterior Descending Artery; MHD: Maximum Heart Distance; MLD: Mean Lung Dose; MRM: Modified Radical Mastectomy; OAR: Organs At Risk; PS:

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Performance Status; PTV: Planning Target Volume; PORT: Post-Operative Radiotherapy; PMRT: Post-Mastectomy Radiotherapy; RHHD: Radiation Related Heart Disease; RTOG: Radiation Therapy Oncology Group; RPM: Real Time Position Monitoring; RT: Radiation Therapy; SCF: Supraclavicular Fossa; TPS: Treatment Planning System; TLV: Total Lung Volume; WBI: Whole Breast Irradiation.

## HIGHLIGHTS

- Breast cancer is the most common cancer in terms of incidence and mortality in the world.
- Cardiac mortality and morbidity during breast cancer treatment can be caused by both radiotherapy and chemotherapy.
- Chemotherapy cannot be omitted due to its proven overall survival benefit.
- Newer radiotherapy techniques like DIBH with Real time Position Monitoring (RPM), have been devised to minimise dose to the heart.
- With appropriate patient selection and adequate training, DIBH is an acceptable technique in reducing both cardiac and lung doses in left sided post mastectomy patients receiving radiotherapy without compromising target coverage.
- This could result in fewer radiotherapy-related complications even when using hypofractionated radiation doses.

## INTRODUCTION

Breast cancer is the most common cancer in terms of incidence and mortality in the world [1]. Breast cancer management warrants multidisciplinary/multimodality treatment is a combination of surgery, chemotherapy, hormone therapy, biological therapy, and Radiation Therapy (RT) depending on the stage, molecular and genetic nature of the disease.

Radiation therapy plays a very critical role in the management of localized breast cancer. Post-operative Whole Breast Irradiation (WBI) is indicated for all patients after Breast Conserving Surgery (BCS) and Post-Mastectomy Radiotherapy (PMRT) after Modified Radical Mastectomy (MRM) if risk factors are present. Post-Operative Radiotherapy (PORT) not only reduced loco-regional recurrences by two-third but may also increase long term survival rates [2,3]. RT aims at delivering a prescribed dose of radiation (approximately 50Gy/biological equivalents) to either the whole breast/chest wall and regional lymph nodal regions as indicated. However, this has to be done by maintaining a balance between the tumor control probability and normal tissue complication probability at that dose (i.e., Therapeutic index) [4]. This is of utmost importance as most breast cancer patients become long-survivors and special care should be taken to ensure that these therapeutic interventions should not endanger the patient's general health and well-being [5]. However, it's a challenge to avoid irradiating/reducing dose to the surrounding normal tissues owing to is close proximity to the radiation treatment fields. This difficulty is compounded in left sided breast cancer patients in whom the heart, its major vessels and ipsilateral lung tend to be co-irradiated due to its close proximity to the anterior chest wall [6]. Hence the occurrence of late effects with significant health consequences like brachial plexopathy, radiation pneumonitis, cardiac morbidity and second malignancy [7]. Many recent studies have derived that mortality from heart disease is increased among women with left-sided breast tumours treated with adjuvant RT when compared to women with right-sided tumours [8-13]. The Early Breast Trialists Collaborative Group (EBCTCG) analysis concluded that radiation induced heart disease increased by 3% for every 1Gy increase in mean heart dose [12]. According to the retrospective study from Norway, relative risk of major coronary events increased linearly with mean dose to the heart by 7.4% per Gy. Also there does not appear to be a minimum dose threshold below which there is no risk of cardiac events [13]. Hence any dose to heart is significant. In the heart, dose to Left Anterior Descending (LAD) artery is the most studied probably because of 3 reasons-radiosensitive nature of LAD, its location i.e., closest major coronary vessel to tangential breast fields and because it is a common site of atherosclerosis causing myocardial infarction. The etiology of the excess cardiac mortality seen years after irradiation is not yet fully understood. In his retrospective analysis in those patients who developed cardiac symptoms, Correa et al. found a higher percentage of stress test abnormalities in patients who received left rather than right sided radiotherapy. Also majority of the abnormalities were in the LAD artery territory (70%) [14]. Radiation doses to heart is further increased in situations where the surgical scar is extending medially and where treatment of the Internal Mammary Chain (IMC) is warranted in right sided breast cancer patients [15].

Numerous techniques that minimize the dose to the heart without compromising target coverage have been devised [16]. These include use of sophisticated RT techniques like 3D based planning, intensity modulation and volumetric arc therapy. In addition, use of respiratory management strategies like Deep Inspiration Breath Hold (DIBH) are also being used to reduce cardiac dose in breast cancer RT. The DIBH technique is based upon the observation that during inspiration, the flattening of the diaphragm and expansion of the lungs pulls the heart away from the chest wall. During both simulation and treatment, the patient takes a deep breath and then holds it for a period of time during which radiation is administered. This allows for a decrease in radiation dose to the heart [17]. Currently, there are two very commonly used techniques for DIBH, voluntary DIBH (vDIBH) and moderate DIBH with Active Breathing Control (ABC) devices [18]. One example of vDIBH is the video-based Real-time Position Management (RPM) respiratory gating system marketed by Varian Medical Systems. DIBH has been associated with significant improvements in both mean heart doses and mean LAD doses. DIBH reduced the mean heart doses by 25-67% and mean LAD doses by 20-73% when compared to Free Breathing (FB) in the same patients [18]. Additionally, real world retrospective data from a large analysis of both community and academic centres also demonstrated that patients treated with DIBH had an average lower heart doses than those treated with free breathing [19]. But these studies have numerous drawbacks/lacunae like recent studies conducted have been analysed retrospectively, the sparse use of hypofractionated radiation doses, incompletely reported doses received by both LAD and the heart and that only few trials have included patients in whom both WBI and Chest Wall (CW) irradiation were indicated. Thus, the advantage of DIBH over FB have not equally studied in all stages of breast cancer. Thus, many gaps are still present in literature that can be and needs to be explored. The aim of this study is to dosimetrically evaluate the effect of Deep Inspiration Breath Hold (DIBH) technique in reducing cardiac (heart and LAD) and lung doses in left sided breast cancer patients treated with 3D-CRT technique, in comparison to *vs.* Free breathing (FB) technique through a prospective study.

## MATERIALS AND METHODS

### Pre-treatment evaluation, inclusion criteria and patient education

Study was conducted from November 2019 to November 2021 after obtaining Institutional ethical and scientific committee approval. 25 consecutive left sided breast cancer patients in whom radiation was indicated after primary modality of treatment (post MRM) and who satisfied inclusion criteria were enrolled in the study after obtaining consent. Inclusion criteria included women of age ≤ 70 years with good Performance Status (PS) i.e., Eastern Cooperative Oncology Group performance score, ECOG PS 0-1 who had undergone mastectomy in whom adjuvant radiotherapy was indicated and had no previous history of radiation treatment to the thorax or any cardiac and lung disease.

All the patients were given a brief introduction and explanation regarding the potential benefits of the procedure. Before Computerized Tomography (CT) simulation, all the patients underwent a 20-30 minutes long training session to enhance patient compliance and to determine individual Deep Inspiration Breath Hold duration. Verbal instructions were given during the training process to motivate the patients to achieve a constant breathing pattern. Patient practices breath holding at deep inspiration until they reach a steady and reproducible breathing pattern. Patients with comfortable breath hold duration of 20 ± 5 seconds were considered eligible to undergo treatment with DIBH.

## Simulation, treatment planning

All patients were treated in supine position with both arms above head, using a breast board with an inclination of 15°-30°. Radio-opaque wires were used to locate the visible surgical scar, the midline, the mid-axillary line and the superior and inferior field borders to assist in target definition while contouring. 2 thermoplastic masks were made-one with the patient in free breathing and the second with the patient in deep inspiration (Figure 1).

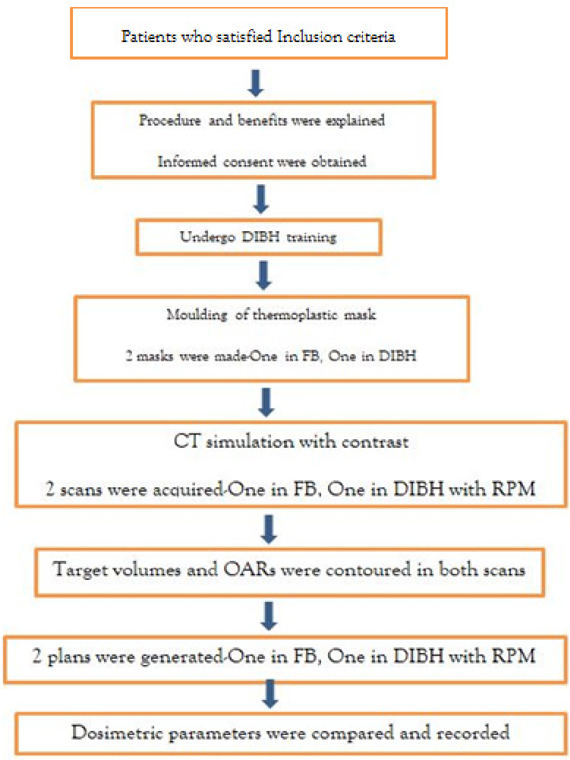


**Figure 1:** DIBH training and procedure.

Varian RPM device was used for assisting DIBH. An infrared reflective marker (RPM Box) was placed on the patient's abdominal surface, midway between the xiphoid process and the umbilicus to monitor the respiratory motion i.e., in proximity to the target chestwall, but outside the area to be covered by the radiation treatment fields. Its position was marked on the patients skin so that it could be reproduced every day during the treatment. The anteroposterior motion of the marker due to chest wall movement was detected by a camera. The patients were asked to breathe freely and then inhale and hold their breath at a comfortable level, just below their maximum inspiration capacity, for at least 15 seconds. This cycle was repeated two or three times in succession. The respiratory signal was recorded with the Varian RPM system. Once a comfortable deep inspiration level was found, lower and upper thresholds were placed on the respiratory signal to define the gating window. The width of the gating window was chosen such that the allowed amplitude of the residual RPM box motion was 0.5 cm.

After acquiring a steady breathing pattern, two sets of CT images with intravenous contrast were acquired for each patient with a slice thickness of 3mm. First scan was acquired in DIBH with RPM system which was used for actual treatment. This was followed by a second scan in Free Breathing (FB) which was used for comparative dosimetric analysis. CT data was acquired superiorly from the chin extending inferiorly 7-10 cm below the breast tissue. These CT images were then transferred online to the Eclipse TM (Varian Medical Systems, Palo Alto, CA, USA) Treatment Planning System (TPS). For consistency, contouring and treatment planning were done by the same physician and physicist respectively. Radiologist help was sought to confirm the delineated volumes. Both the target volumes i.e., Clinical Target Volume (CTV) and Planning Target Volume (PTV) chest wall and Organs at Risk (OARs) like heart, Left Anterior Descending (LAD) artery, both lungs, normal breast and spinal cord were delineated on both the scans. Contouring of the target volumes and organs at risk was performed in accordance with the guidelines published by the Radiation Therapy Oncology Group (RTOG) and the Danish Breast Cancer Cooperative Group (DBCG). CTV included the entire chest wall as bordered by the clavicular head cranially, 20 mm inferiorly to the palpable contralateral normal breast fold caudally, the mid-sternal line medially, and the mid-axillary line laterally [20,21]. The PTV was generated using a 5 mm margin from CTV, limited to the midline, and shrunk 3 mm from the skin. The ipsilateral lung was contoured using an automatic contouring tool. The heart was contoured in accordance with RTOG 1106 organs at risk atlases. Along with the pericardial sac, the superior aspect began at the level of the inferior aspect of the pulmonary artery passing the midline and extending inferiorly to the apex of the heart. The LAD coronary artery was delineated in the anterior inter-ventricular groove from its initiation down to the apex of the heart [22].

The prescription dose was 40Gy in 15 fractions at 2.67Gy per fraction. Two opposing 6 MV tangential conformal fields with multileaf collimator and wedges were used. Mono-isocentric technique was used to treat both CW and Supraclavicular Fossa (SCF). An example of a plan generated for comparison of DIBH and FB is seen in Figure 2. Dose-Volume Histograms (DVH) were generated for all delineated structures. A minimum of 95% of the target volume was to be covered by the 95% isodose line (V95% ≥ 95%). Hotspots should not exceed 110% and preferably not 107%. The field-in-field technique and wedges was used to avoid hotspots exceeding 110%. The dose to normal organs were kept as low as possible without compromising the target volume dose.

## Dose-volume parameters

Dose-volume histograms were extracted and compared for each of the DIBH and FB plans as seen in Figure 3.

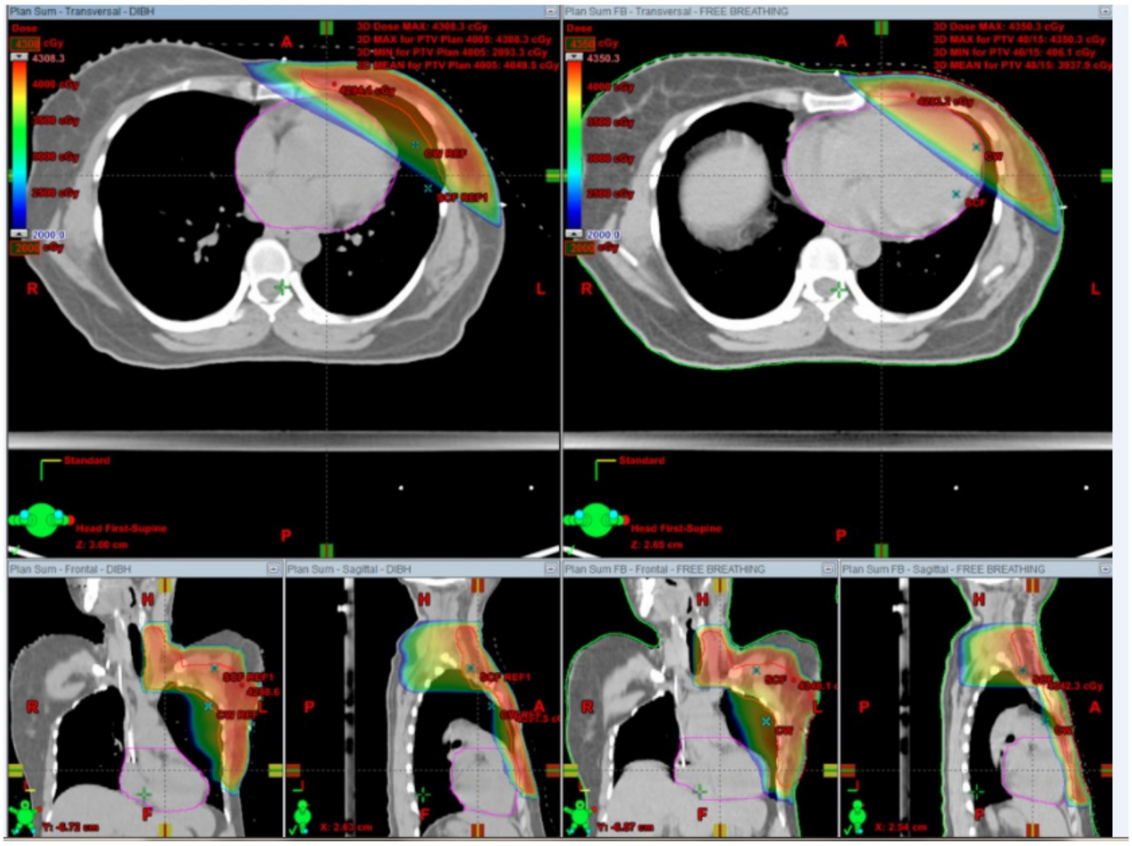

**Figure 2:** Treatment plan in DIBH *vs*. FB.

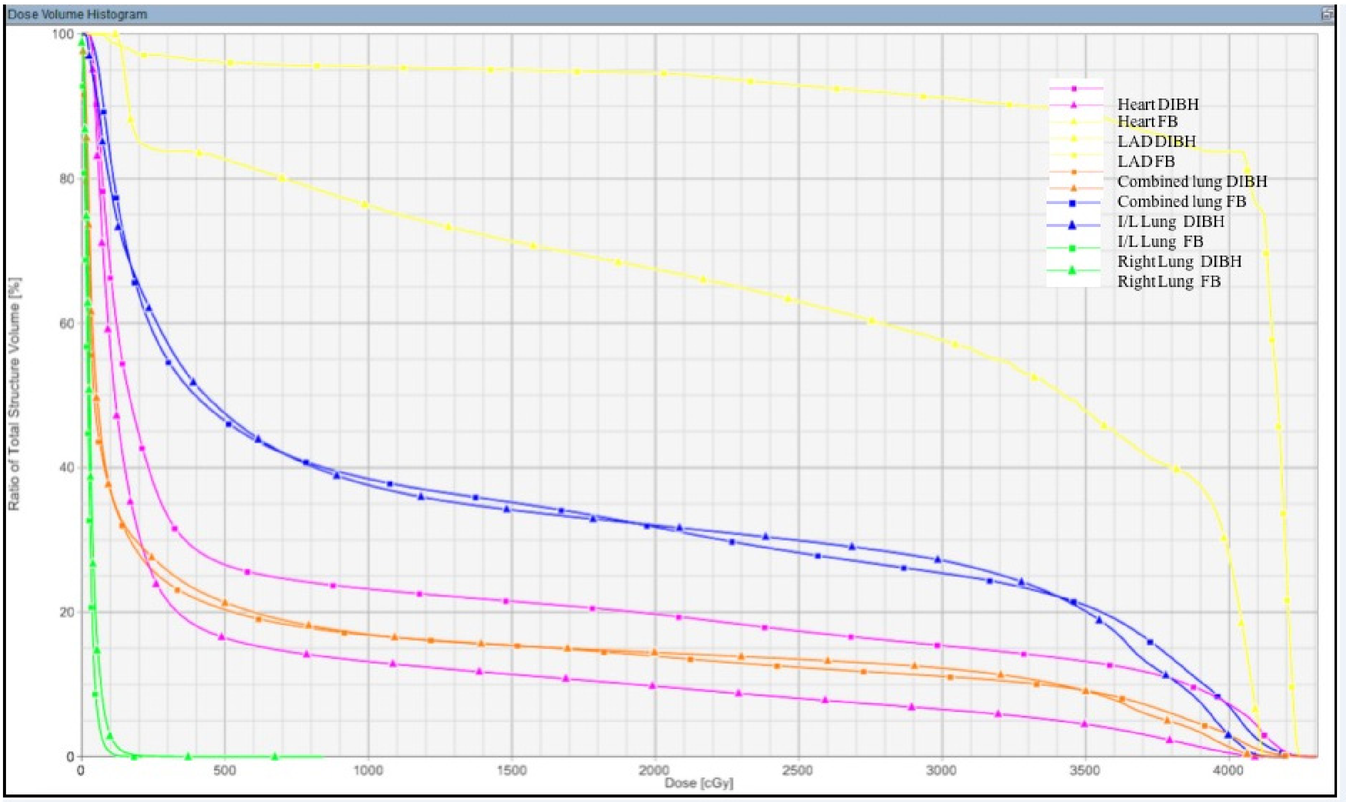


**Figure 3:** DVH in FB *vs*. DIBH **Note:** ( ) Heart DIBH, ( ) Heart FB, ( ) LADDIBH, ( ) LADFB, ( ) Combined lung DIBH, ( ) Combined lung FB, ( ) I/L Lung DBIH, ( ) I/L Lung FB, ( ) Right Lung DBIH, ( ) Right Lung FB.

- Heart-Mean dose (D mean), maximum dose (D max), Percentage volumes that received doses ≥ 5Gy (V5), 10Gy (V10), 15Gy (V15), 20Gy (V20), 25Gy (V25), 30Gy (V30). The dose parameters that will be recorded for LAD were D mean and D max.
- Left lung-D mean, D max percentage volumes that received doses ≥ 5Gy (V5), 10Gy (V10), 15Gy (V15), 20Gy (V20), 25Gy (V25), 30Gy (V30) were recorded.
- Combined lungs-Mean Lung Dose (MLD), V20 and Total Lung Volume (TLV) was also recorded for both lungs.
- For PTV coverage, D mean, D max, V90 (Volume that received 90% of dose) and V95 (Volume that received 95% of dose) was recorded.

### Treatment delivery

Though 2 plans were generated i.e., 1 with DIBH and 1 with FB, all patients were treated in plans generated with DIBH technique. 3D conformal RT (3D-CRT) technique was used to deliver treatment.

### Statistical analysis

Data was coded and recorded in MS Excel spreadsheet program. SPSS v23 was used for data analysis. Descriptive statistics is elaborated in the form of means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Group comparisons were made using independent sample t-test for continuously distributed data, and chi-squared test for categorical data. The mean change in the quantitative variables at different follow up periods were assessed by paired t-test/one-way repeated measures ANOVA. Values achieved in FB plans were considered standard for calculation of standard deviation. The change in the proportion of categorical variables were assessed by McNemar Chi-square test. P value <0.05 was considered statistically significant.

## RESULTS

Between December 2019 to November 2021, a total of 25 patients with 50 CT scans who underwent tangential field radiotherapy for left sided breast cancer with DIBH technique, were eligible for this study as shown in Table 1. Median age was 47.6 years with a range extending from 28 years to 69 years. 12 out of 25 women (48%) analysed had Stage III A disease while only 1 woman had Stage I disease. Indication for Adjuvant RT in Stage I was inadequate axillary dissection with other risk factors like young age, high grade and triple negativity. Mean breath hold duration was 19.84 ± 3.84 seconds with a range extending from 15 second to 30 seconds.

**Table 1:** Patient characteristics.

| Patient characteristics | |
|---|---|
| **Characteristics** | **n (%)** |
| Median age | 47.6 years ( Range 28-69years) |
| Menopausal status | |
| Premenopausal | 11 (44%) |
| Perimenopausal | 04 (14%) |
| Postmenopausal | 10 (40%) |
| Prior fertility treatment | 3 (12%) |
| Family history | 4 (16%) |
| AJCC Staging | |
| Stage I | 01 (4%) |
| Stage IIA | 04 (16%) |
| Stage IIB | 08 (32%) |
| Stage IIIA | 12 (48%) |
| Surgery | |
| MRM+ALND | 25 (100%) |
| Hormone Status | |
| ER/PR | 17 (68%) |
| HER 2 neu | 04 (16%) |
| Chemotherapy | 23 (92%) |
| Mean Breath Holding Duration (seconds) | 19.82 seconds |

Dosimetric analysis was done with the help of DVH generated for FB and DIBH plans for each patient. The dose volume parameters for the Heart, LAD, left lung, both lungs and PTV were compared and recorded using the thus generated DVH as shown in Tables 2-5. DIBH significantly reduced mean heart doses in comparison with FB. All cardiac volume parameters analysed showed a significant reduction with DIBH as tabulated in Table 2.

The relative reduction in average mean heart dose (D mean) with DIBH technique was 1.46Gy or 28.19% i.e., to more than one-fourth (from 5.18Gy (with FB) to 3.72Gy (with DIBH) (p value <0.001)). The mean of maximum heart dose (Dmax) was reduced from 38.63Gy with FB to 37.73Gy with DIBH (corresponding to a 2.3% reduction of maximum heart dose). However, this reduction was not statistically significant (p=0.381).

LAD artery is the closest major coronary vessel to tangential breast fields. Because of its small volume, delineating and evaluating the dose to LAD is a difficult task and depends on the physician's expertise. This is further aggravated by setbacks like washout of contrast before acquiring both sets of CT images, presence of motion artefacts and improper slice thickness. Very few studies in the literature have dealt with doses to the LAD and no standard protocols are present for the estimation of LAD doses nor have limiting factors or tolerances been defined. LAD doses in FB and DIBH plans were evaluated by tabulating the Dmean and Dmax doses as shown in Table 3. Mean of LAD dose was reduced from 25.94Gy (in FB) to 16.99Gy (in DIBH) with a significant pvalue<0.001. This corresponds to a relative reduction of 8.95Gy or 34.50% in the mean LAD doses with DIBH technique. The mean maximum LAD (Dmax) was reduced from 39.86Gy with FB to 38.39Gy with DIBH which was statistically significant (p=0.003). This corresponds to a 3.69% reduction of maximum LAD dose with the use of DIBH technique.

The Maximal Heart Distance (MHD) is the width of heart in the tangent fields at its maximal level as shown in Figure 4 [23]. Smaller Maximum Heart Distance (MHD) was observed in DIBH scan when compared to FB scans. The mean MHD in FB and DIBH scans were 2.168 cm and 1.224 cm respectively. The maximum heart distance was thus reduced to almost half (43.54%) in DIBH technique, with a significant p value <0.001. There was a significant reduction in the ipsilateral mean lung doses (Dmean) and other lung volume parameters with DIBH technique when compare to FB technique as shown in Table 4. Even combined lung parameters like V20Gy and Mean Lung Dose (MLD) was significantly reduced as tabulated in

Table 5. CT scans using DIBH showed a significant larger Total Lung Volume (TLV). The TLV was 2011.01 cc in FB scan and 3123.38 cc in DIBH scan. The mean increase in the Total Lung Volume was 55.31% (p<0.001).

In PTV, Dmean, Dmax and V95% ie% volume of PTV receiving more than 95% of prescribed dose was analyzed. There was no significant difference in the Breast PTV target dose coverage parameters in both the plan in terms of Dmean, Dmax. But V95% values were significantly better with DIBH plans.

**Table 2:** Comparison of FB and DIBH-cardiac dose volume parameters.

| Comparison of cardiac dose volume parameters in FB *vs*. DIBH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | V5 (%) | V10 (%) | V15 (%) | V20 (%) | V25 (%) | V30 (%) | Dmean Gy | Dmax Gy |
| **FB** | **Mean** | 16.35 | 10.38 | 8.7 | 7.3 | 6.33 | 5.43 | 5.18 | 38.63 |
| | **STD** | 10.45 | 6.12 | 5.07 | 4.7 | 4.41 | 4.05 | 2.39 | 4.9 |
| **DIBH** | **Mean** | 13.1 | 6.94 | 5.41 | 4.24 | 3.4 | 2.77 | 3.72 | 37.73 |
| | **STD** | 9.59 | 5.22 | 4.61 | 4.22 | 3.86 | 3.52 | 1.57 | 4.83 |
| **p value** | | 0.006 | 0.002 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.381 |
| **% decrease with DIBH** | **Mean** | 17.74 | 33.14 | 37.82 | 41.92 | 46.29 | 48.99 | 28.19 | 2.33 |
| | **STD** | 8.23 | 14.71 | 9.07 | 10.21 | 12.47 | 13.09 | 34.31 | 1.43 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; STD-Standard Deviation; V5Gy-Volume of Heart receiving 5Gy; V15Gy-Volume of Heart receiving 15Gy; V25Gy-Volume of Heart receiving 25Gy; V35Gy-Volume of Heart receiving 35Gy; V40Gy-Volume of Heart receiving 40Gy; D mean-Mean Dose; D max-Maximum Dose.

**Table 3:** Comparison of FB and DIBH-LAD dose parameters.

| Comparison of LAD dose parameters in FB *vs*. DIBH | | | |
|---|---|---|---|
| | | Dmean | Dmax |
| | | Gy | Gy |
| **FB** | **Mean** | 25.94 | 39.86 |
| | **STD** | 8.17 | 1.78 |
| **DIBH** | **Mean** | 16.99 | 38.39 |
| | **STD** | 9.39 | 2.56 |
| **p value** | | <0.001 | 0.003 |
| **% decrease with DIBH** | **Mean** | 34.5 | 3.69 |
| | **STD** | 14.93 | 43.82 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; STD-Standard Deviation; D mean-Mean Dose; D max-Maximum Dose.

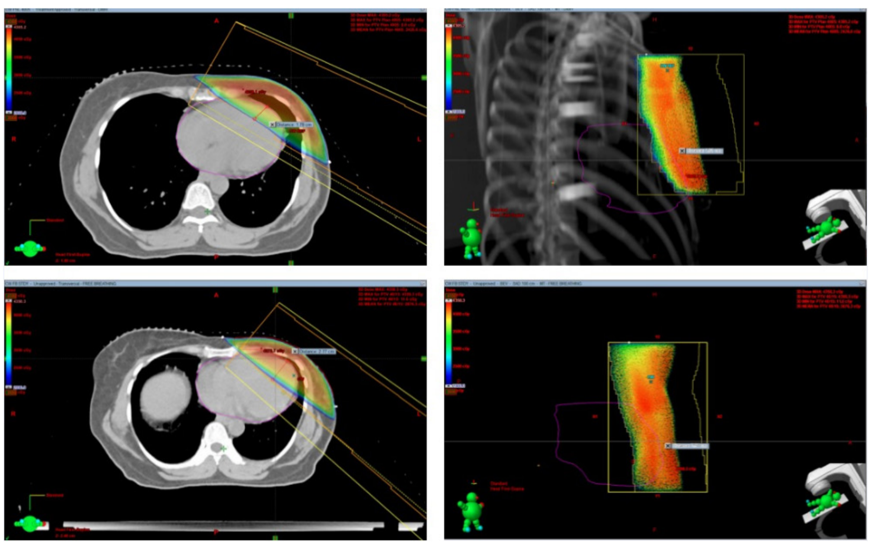

**Figure 4:** Calculating MHD in DIBH *vs*. FB in axial sections and in beams eye view (BEV).

**Table 4:** Comparison of FB and DIBH-lung dose volume parameters.

| Comparison of ipsilateral lung dose volume parameters in FB *vs*. DIBH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | V5 (%) | V10 (%) | V15 (%) | V20 (%) | V25 (%) | V30 (%) | Dmean | Dmax |
| FB | Mean | 44.51 | 30.56 | 25.74 | 22.81 | 20.02 | 17.31 | 10.77 | 41.1 |
| | STD | 10.47 | 7.51 | 6.64 | 6.51 | 6.77 | 6.69 | 2.45 | 1.12 |
| DIBH | Mean | 34.25 | 22.56 | 19.43 | 17.36 | 15.41 | 13.34 | 8.72 | 41.34 |
| | STD | 8.4 | 7.21 | 7.14 | 6.89 | 6.32 | 5.99 | 2.63 | 0.89 |
| p value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.219 |
| % decrease with DIBH | Mean | 23.05 | 26.18 | 24.51 | 23.89 | 23.03 | 22.94 | 19.03 | 0.59 |
| | STD | 19.77 | 3.99 | 7.53 | 5.84 | 6.65 | 10.46 | 7.35 | 20.54 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; STD-Standard Deviation; V'X'Gy-Volume of Left Lung receiving 'X'Gy; eg-V10Gy-Volume of Left Lung receiving 10Gy; D mean-Mean Dose; D max-Maximum Dose.

**Table 5:** Comparison of FB and DIBH-combined lung dose parameters.

| Comparison of combined lung dose volume parameters in FB *vs*. DIBH | | | | |
|---|---|---|---|---|
| | | V20Gy% | MLD Gy | TLV cc |
| FB | Mean | 10.47 | 5.424 | 2011.01 |
| | STD | 2.86 | 1.15 | 550.89 |
| DIBH | Mean | 8.19 | 4 | 3123.38 |
| | STD | 2.72 | 1.08 | 719.27 |
| p value | | <0.001 | <0.001 | <0.001 |
| % decrease with DIBH | Mean | 21.78 | 26.25 | 55.31 |
| | STD | 4.89 | 6.09 | 30.57 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; STD-Standard Deviation; MLD-Mean Lung Dose; V20Gy- Volume of Both lungs receiving 20Gy; TLV-Total Lung Volume.

## DISCUSSION

The incorporation of a combined-modality treatment approach into the management of breast cancer has led to an improvement in both local control and overall survival. Due to significant doses received by OARs such as the heart and lungs while delivering radiotherapy to the thoracic region, especially the left side; there are higher probabilities of developing complications. This in turn lead to long-term morbidity and mortality with radiotherapy, which has become a concern [24]. Late cardiac morbidity is a serious concern for left sided breast cancer patients who receive tangential RT, especially in the younger age group. In the recent update of EBCTCG overview on the favourable and unfavourable effects of radiotherapy on the long-term survival of breast cancer patients, there is a clear evidence that Radiation related heart disease (RHHD) increases by 3% per Gy ($p<0.00001$). This data gives strong evidence that risk of RHHD is related to cardiac dose in irradiated breast cancer patients [2]. According to a study conducted by Darby et al. on major coronary events, it was found that rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy ($p<0.001$), with no apparent threshold. Correa et al in a retrospective review of cardiac morbidity in post irradiation patients of breast cancer had found out that coronary stenosis especially in the LAD was the most common cause of RRHD [14]. Techniques of radiotherapy have improved over the years in an attempt to decrease doses to OARs and thereby reduce the probability of complications. Intensity modulated radiation therapy (IMRT), tomotherapy and respiratory motion management have been tried in order to reduce the cardiac dose. DIBH has been associated with significant improvements in both mean heart doses and mean LAD doses, with respective decreases of 29-62% and 35-70% when comparing the same patients planned with FB [6,24-33]. But, many gaps are still present in literature that can be and needs to be explored.

Our study is an attempt to prospectively evaluate the efficacy of DIBH technique and its dosimetric benefits over FB technique, in cardiac (heart and LAD) and lung sparing in left sided breast cancer patients treated with 3D-CRT technique. 25 patients who satisfied the inclusion criteria and underwent MRM were included in the study. Dose volume histograms generated from the plans were used for recording dose-volume parameters for target volumes and OARs. These were recorded in the prepared performa and analysed. Our results were comparable to the most studies without any compromise in PTV coverage as shown in tables 6-8. Thus, in short, DIBH technique significantly reduces doses to not only the heart, and the LAD but also to ipsilateral and combined lung volume parameters even with hypofractionated radiation doses. Therefore, respiratory management with DIBH is a feasible, effective and a relatively easy method of cardiac dose sparing without compromising on target volume coverage that can be implemented in clinical practice for women who have undergone MRM. The results are also comparable to other novel techniques like IMRT which has been favoured as another alternative method in reducing cardiac doses. But IMRT has got other problems like high integral dose and low dose spill. The fact remains that DIBH plans are more complex for implementation in the clinical setup especially in high volume centres. Not only does it have a more complex setup warranting technical expertise and is more time consuming (in terms of total treatment time), but also requires a good patient cooperation. The main drawback of this study is that it being a dosimetric study, it was not possible to evaluate clinical endpoints in terms of cardiac morbidity and mortality. Long term follow-up of these patients and clinical correlation with cardiac dose volume parameters may shed some light on this matter and may serve as a guide for cardiac dose parameter in the future.

**Table 6:** Comparison of cardiac dose volume parameters obtained in our study with other published data.

| Comparison of cardiac dose volume parameters obtained in our study with other published data | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Patient | Area(s) treated | Dmean (Gy) | | V25Gy (%) | | V30Gy (%) | | V10Gy (%) | | V5Gy (%) | |
| | | | FB | DIBH | FB | DIBH | FB | DIBH | FB | DIBH | FB | DIBH |
| Vikstrom et al. 2011 | 17 | Breast | 3.7 | 1.7 | 2 | 0 | - | - | - | - | - | - |
| Hayden et al. 2012 | 30 | Breast+boost | 6.9 | 4 | - | - | 7.1 | 2.4 | - | - | - | - |
| Hjelstuen et al. 2012 | 17 | Breast+SCV+Axilla+IMC LN | 6.2 | 3.1 | 6.7 | 1.2 | - | - | - | - | - | - |
| Joo et al. 2015 | 32 | Breast/CW ± SCV+Axilla | 7.2 | 2.8 | - | - | 10.7 | 2 | 14.6 | 4 | - | - |
| Daruppu et al. 2017 | 19 | CW | 6.8 | 4.76 | 9.1 | 4.9 | 8.4 | 4.7 | 12.4 | 7.7 | 21.4 | 16 |
| Our study | 25 | CW+Axilla | 5.2 | 3.7 | 6.3 | 3.4 | 5.4 | 2.8 | 10.4 | 6.9 | 16.4 | 13 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; V'x'Gy-Volume of Heart receiving 'x'Gy; D mean-Mean Dose.

**Table 7:** Comparison of cardiac dose volume parameters obtained in our study with other published data.

| Comparison of cardiac dose volume parameters obtained in our study with other published data | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | Patient | Area(s) treated | LAD Dmean (Gy) | | LAD Dmax (Gy) | | MHD (cm) | |
| | | | FB | DIBH | FB | DIBH | FB | DIBH |
| Vikstrom et al. 2011 | 17 | Breast | 3.7 | 1.7 | 2 | 0 | - | - |
| Hayden et al. 2012 | 30 | Breast+boost | 6.9 | 4 | - | - | 7.1 | 2.4 |
| Hjelstuen et al. 2012 | 17 | Breast+SCV+Axilla+IMC LN | 6.2 | 3.1 | 6.7 | 1.2 | - | - |
| Joo et al. 2015 | 32 | Breast/CW ± SCV+Axilla | 7.2 | 2.8 | - | - | 10.7 | 2 |
| Daruppu et al. 2017 | 19 | CW | 0.8 | 4.76 | 9.1 | 4.9 | 8.4 | 4.7 |
| Our study | 25 | CW+Axilla | 0.2 | 3.7 | 0.3 | 3.4 | 5.4 | 2.8 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; LAD-Left anterior descending artery; D mean-Mean Dose; Dmax- Maximum dose; MHD-Maximal Heart Distance.

**Table 8:** Comparison of lung dose volume parameters obtained in our study with other published data.

| Comparison of lung dose volume parameters obtained in our study with other published data | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Patient | Area(s) treated | I/L Dmean (Gy) | | I/L V20Gy (%) | | Combined V20Gy (%) | | TLV (cc) | |
| | | | FB | DIBH | FB | DIBH | FB | DIBH | FB | DIBH |
| Vikstrom et al. 2011 | 17 | Breast | 6.9 | 5.9 | 12.2 | 10 | - | - | - | - |
| Hayden et al. 2012 | 30 | Breast+boost | - | - | - | - | - | - | 1126 | 2054 |
| Hjelstuen et al. 2012 | 17 | Breast+SCV+Axilla+IMC LN | 21.7 | 16.4 | 44.5 | 33.7 | - | - | 2365 | 4676 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Joo et al. 2015 | 32 | Breast/CW ± SCV+Axilla | - | - | 18.9 | 16.7 | - | - | - | - |
| Daruppu et al. 2017 | 19 | CW | 3.6 | 12.3 | 11.6 | 10.7 | 15.5 | 10.7 | - | - |
| Our study | 25 | CW+Axilla | 0.8 | 8.7 | 2.8 | 17.4 | 10.5 | 8.9 | 2011 | 3123.4 |

**Note:** FB-Free Breathing; DIBH-Deep Inspiratory Breath Hold; I/L Dmean-Ipsilateral Mean Lung Dose; I/L V 20Gy-Volume of Ipsilateral lung receiving 20Gy; Combined V20Gy-Volume of Both lungs receiving 20Gy; TLV-Total Lung Volume.

## CONCLUSION

The following conclusions can be derived from the results of this dosimetric comparison:

1. DIBH technique has a huge impact on cardiac dose volume parameters. While DIBH significantly reduced the mean heart dose by 1.46Gy or 28.19% (from 5.18Gy to 3.72Gy; $p<0.001$), the mean LAD mean dose was reduced from 25.94Gy to 16.99Gy (ie by 8.95Gy, 34.50%). These reductions are likely to reduce long term cardiac morbidity and mortality.
2. Both ipsilateral lung and combined lung dose volume parameters were also significantly reduced by the use of DIBH technique. While ipsilateral lung mean dose was reduced from 10.77Gy to 8.72Gy (i.e., by 2.05Gy or 19%, $p<0.001$), combined lung mean doses were reduced from 5.424Gy to 4Gy with DIBH technique (i.e., by 1.42Gy or 26.15% or $p<0.001$).
3. These results were achieved with comparable PTV values.

Thus, with appropriate patient selection and adequate training, DIBH is an acceptable respiratory management technique in reducing both cardiac and lung doses in left breast cancer patients who have undergone MRM for whom adjuvant radiotherapy is indicated. In conclusion, DIBH should therefore be considered for all suitable patients, as this could result in fewer radiotherapy-related complications.

However, short term toxicity assessment and long term follow-up is required to analyse the clinical outcomes resulting from the reductions in heart and lung doses. Moreover, studies with larger sample size are warranted in the future to consolidate the significance obtained in our study.

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My family, parents, friends, colleagues and God who guides me.

## STATEMENTS AND DECLARATIONS

### Ethics approval

All procedures performed in this study were in accordance with the ethical standards of the Institutional and/or National research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was reviewed and approved by Institutional Ethics Committee of Yashoda Academy of Medical Education and Research (IEC-YAMER) affliated to the Yashoda group of hospitals (Reg No ECR/49/INST/AP/2013/RR-19) with refernce no CDT/16/2019. Since it is only a dosimetric comparison with no intervention in the actual treatment delivered/revealing of patient identity, no ethical issues were involved.

## CONSENT TO PARTICIPATE

Informed consent for radiation treatment was taken from all patients included in the study at the time of CT simulation.

## CONSENT TO PUBLISH

Not applicable

## CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

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## COMPETING INTEREST

The authors have no relevant financial or non-financial interests to disclose.

## AUTHOR CONTRIBUTION

All authors have played their respective significant roles in the completion of this study. Detailed role of each person has been outlined below.

1. Conception of design, preparation of study design and protocol, reviwing of contours from a radiological point of view, data analysis and tabulation, interpretation of data, preparation of first and subsequent drafts.
2. Conception of design, preparation of study design and protocol, ethical and scientific committee approval procedures, identification of patients suitable for the study, acquiring consent for study after explaining the study, contouring of CT data sets, reviewing plans and data collection, data analysis and tabulation, interpretation of data, preparation of first and subsequent drafts.
3. Preparation of study design and protocol, reviewing of contours, reviewing plans, rechecking data collected for data analysis and tabulation, correction of first and subsequent drafts.
4. Preparation of study design and protocol, identification of patients suitable for the study, acquistion of CT images for contouring and planning, development of good and acceptable plans with both techniques, inputs and clearing any 'planning' related queries/doubts, rechecking data collected for data analysis and tabulation, correction of first and subsequent drafts.
5. Preparation of study design and protocol, reviewing of contours, reviewing plans, rechecking data collected for data analysis and tabulation, correction of first and subsequent drafts.

Dev Ravishankar, Devika Sunil, Nalini Yadala, Arun Gandhi, Kirti Ranjan Mohanty all authors have read and approved the submitted version (and any substantially modified version that involves the author's contribution to the study). All authors have agreed to authorship and order of authorship for this manuscript. All authors have the appropriate permissions and rights to the reported data.

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings presented in the study are included in the article. Raw data that support the findings of this study are available from the corresponding author, upon reasonable request. Further inquiries can be directed to the corresponding author.

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