



## Original Research

# Dosimetric analysis of LAD dose in left-sided breast cancer radiotherapy with deep inspiratory breath hold

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## ABSTRACT

**Objectives:** To analyze the dose to the left anterior descending artery (LAD) in patients who have received radiotherapy for left breast cancer with Deep Inspiratory Breath Hold (DIBH) technique and compare it with other cardiac dosimetric parameters, as well as the accepted dose constraints.

**Materials and Methods:** 20 patients (10 prospective and 10 retrospective) were selected for this study. All patients underwent 2 non-contrast radiation planning CT scans of 2.5 mm thickness - one with DIBH and one with free breathing. Contouring was done using the Radiation Therapy Oncology Group (RTOG) guidelines. LAD was delineated and given a PRV of 3 mm and 5 mm. Dose-volume histograms (DVH) were used to obtain the data from the approved plans.

**Results:** The lung volume receiving 17 Gy in percentage, Dmean of the heart, LAD Dmean and Dmax, and the Dmean and Dmax received by 3 mm and 5 mm PRVs were both very well achieved when compared to the dose constraints given by the DBCG HYPO trial. The study found a higher correlation between the mean heart dose and the 5 mm PRV dose ( $R^2 = 0.81$  and  $0.71$  respectively for the mean and max dose) than the 3 mm PRV, and a positive correlation between the heart dose and LAD making it a useful structure for predicting acute cardiac events.

**Conclusion:** The study of 20 patients found that DIBH is effective to minimize cardiac dose and potentially cardiac toxicity, with heart and LAD doses being comparable or lower compared to other studies. The LAD doses recorded were significantly less than those in non-DIBH studies, demonstrating the feasibility of routine contouring and recording LAD dose in left-sided breast radiation patients. Further research is needed to determine the dosimetry and clinical consequences of the Dmean and Dmax of the 5mm PRV to the LAD.

**Keywords:** Left anterior descending coronary artery, Deep inspiratory breath hold, Left-sided breast cancer, Radiotherapy

## INTRODUCTION

Radiation therapy (RT) is an integral part in the treatment of breast cancer, and nearly 75% of the patients post breast conservation surgery and 29.5% of patients post-mastectomy will require radiotherapy as a part of their treatment.<sup>[1]</sup> It eliminates subclinical disease following surgical excision of the overtly visible tumor. Radiation also lowers local recurrence rates and improves breast cancer-specific survival and overall survival by 20% in patients with early stage breast cancer who have undergone breast-conserving surgery, as well as in node-positive patients who have had a mastectomy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed

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conclusively that radiotherapy lowered the chances of any recurrence by half and the breast cancer–related mortality by about one-sixth, cementing its role as an integral part of early and locally advanced diseases.<sup>[2]</sup>

Radiotherapy planning for breast cancer is usually done using tangential beams to avoid direct entry of radiation beams into the lungs and heart. The technique of planning has evolved from 2D planning to 3DCRT, and to Forward Planned Intensity Modulated Radiotherapy (IMRT), which is currently the standard of care. The addition of subfields aids in achieving better dose homogeneity while protecting the vital organs at risk, namely, heart for left-sided breast cancers and lungs. Minimizing the radiation dose received by the heart has been a key component of radiation dose planning, especially in left-sided breast cancer cases. This is especially important as patients often receive anthracyclines or trastuzumab as a part of treatment – both of which are known to be cardiotoxic.<sup>[3]</sup> Hypertension and diabetes can further this risk and is common amongst our population. Darby *et al.* showed that there is a 7.4% increment in risk of ischemic heart disease per gray of radiation to the heart and the effects were seen between 5 and 30 years.<sup>[4]</sup>

Traditionally, mean heart dose has been used to calculate dose constraints for heart; however, it has been found that the dose received by the left anterior descending (LAD) artery correlated with adverse cardiac events.<sup>[5]</sup> This warrants prospective contouring and planning to limit the dose received by the LAD.

Deep Inspiratory Breath Hold (DIBH) is the most widely used technique to reduce cardiac doses, as it allows and aids physical separation of the chest wall or the overlying breast tissue from the heart. Significant reduction in cardiac doses due to DIBH have been shown by various studies.<sup>[6–8]</sup> Uncertainties in doses to a structure such as LAD exist due to cardiac motion which needs to be accounted for. Planning organ at risk volume (PRV) is a convenient method to account for motion of such small structures.

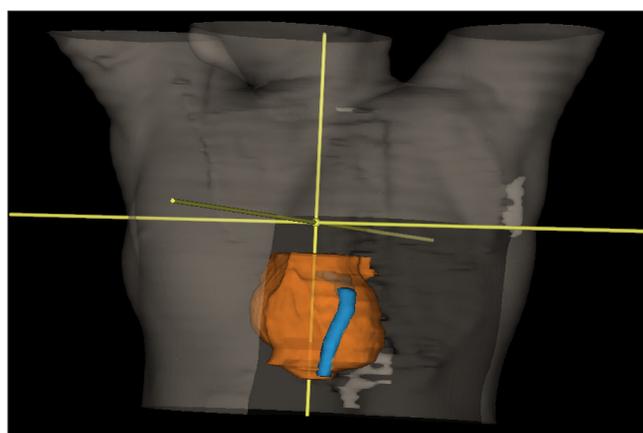
This study analyzes the dose of the LAD in patients who have received radiotherapy for left-sided breast cancer with DIBH technique and compares it with other cardiac dosimetric parameters of the patients, as well as the accepted dose constraints.

## MATERIALS AND METHODS

Twenty cases (10 prospective and 10 retrospective) were selected for this study from a single institute. The median age of the cohort was 49 years. Only cases who received radiotherapy using the UK START-B regimen,<sup>[9]</sup> that is, 40 Gy in 15 fractions and planned using forward IMRT after breast conservation surgery (BCS) or mastectomy were selected.

Eighteen patients who had undergone BCS received a boost to a dose of 12.5 Gy in five fractions using mini-tangents. Cases where the LAD was not visualized despite changing the exposure were excluded. All patients underwent two non-contrast radiation planning CT scans of 2.5 mm thickness – one with DIBH and one with free breathing on a GE Discovery CT 590 RT with RGSC. The optimal settings were found to be 120 kV and 340 mA. After patient coaching and assessment of the patient's breathing pattern, the amplitude of breath-hold was captured by an infrared sensor camera and corresponded to the DIBH CT taken simultaneously. The free-breathing scan was taken subsequently.

The RT Oncology Group breast cancer atlas was referred to define the clinical target volume (CTV). All ipsilateral breast tissue, except the muscles underneath and the overlying skin, was included in the CTV. The posterior boundary of the CTV in a chest wall radiation case stopped at the anterior pleural surface, which included the ribs and intercostal muscles. Internal mammary chain or axilla is not included routinely for node positive patients in our practice. With revisions made to the medial, lateral, inferior, and superior boundaries, the planning target volume (PTV) margin was 3 mm. The organs at risk that were marked included both lungs, the heart, LAD with a 3 mm and 5 mm PRV, the spinal cord with a 3 mm PRV, and esophagus. The LAD was contoured from its origin near the left coronary artery continuing below the right pulmonary vessel, and coursing along the anterior interventricular groove till the cardiac apex [Figure 1]. In three cases, a stent in situ aided the contouring. Planning was done with forward IMRT on the Eclipse™ planning system version 16.1 by Varian Medical Systems, with subfields added to achieve better dose distribution [Figure 2]. The volume receiving 97% of the dose was planned to be > 95% of the PTV for every plan. Dose constraints were set based on the Danish breast cancer group (DBCG) HYPO trial.<sup>[10]</sup>



**Figure 1:** Three millimeter Left anterior descending artery (LAD) Planning Organ-at-risk volume (PRV) and heart contour.

Dose-volume histograms (DVH) were used to obtain data from the approved plans. The parameters derived from the DVH were as follows – volume of the lung receiving 17 Gy in percentage, mean dose of the heart, volume of the heart receiving 17 Gy and 35 Gy, mean and max doses received by the LAD, and the mean and max doses received by the 3 mm and 5 mm PRV given to the LAD. The data were then tabulated for statistical analysis. All patients were treated with Varian Truebeam™ STx with daily kVCBCT image guidance and 6D couch correction.

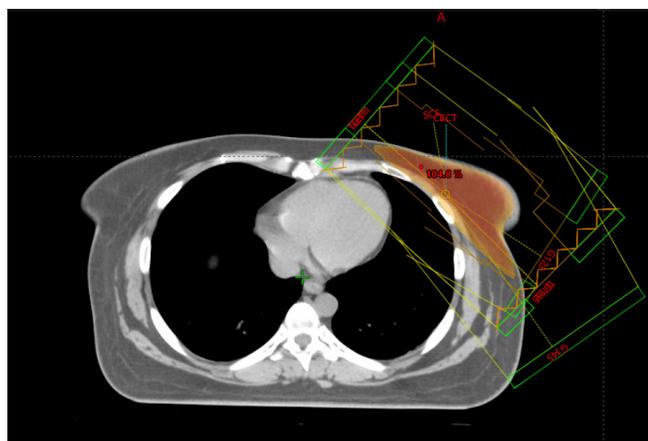


Figure 2: External beam planning.

### Statistical Analysis

Each data set was tested for normal distribution using the Kolmogorov–Smirnov Test. Correlation between various parameters was done using the Pearson’s correlation coefficient. The comparison of our data with the existing guidelines was done using the unpaired *t*-test. The statistical tests were done using JASP 0.17.3. We compared the doses from our study with those reported from other similar studies.

### RESULTS

There were 18 patients with BCS and 2 patients who had undergone mastectomy. Thirteen patients were node positive and received radiation to the supraclavicular fossa, while seven patients were node negative. The doses achieved in our cohort of patients are listed in Table 1.

When compared to the dose constraints given by the DBCG HYPO trial, the volume of the heart receiving 17 Gy and 35 Gy, and the volume of the left lung receiving 17 Gy were very well achieved. The Dmax of the LAD was comparable to the expected value. We found that the dose received by the 5 mm (mean and max) PRV had a higher correlation with the mean heart dose than the 3 mm PRV ( $R^2 = 0.81$  and  $0.71$ , respectively, for the mean and max dose) [Figures 3, 4, and 5]. There was a positive correlation between the mean dose of

Table 1: Doses achieved in our study.

Constraints	Mean observed value
Vol of Left Lung receiving 17 Gy	14.289 ± 4.688 (%)
Vol of Heart receiving 17 Gy	1.4759%
Vol of Heart receiving 35 Gy	0.4565%
Mean dose Heart	1.784 Gy ± 1.15 Gy
Mean dose LAD	6.079 Gy ± 5.709 Gy
Max dose LAD	18.4835 Gy ± 14.047 Gy
Mean dose PRV 3 mm	6.046 Gy ± 5.149 Gy
Max dose PRV 3 mm	24.602 Gy ± 13.232 Gy
Mean dose PRV 5 mm	6.1535 Gy ± 4.9546 Gy
Max dose PRV 5 mm	28.1565 Gy ± 12.419 Gy

Gy: Gray; PRV: Planning organ-at-risk volume; LAD: Left anterior descending artery.

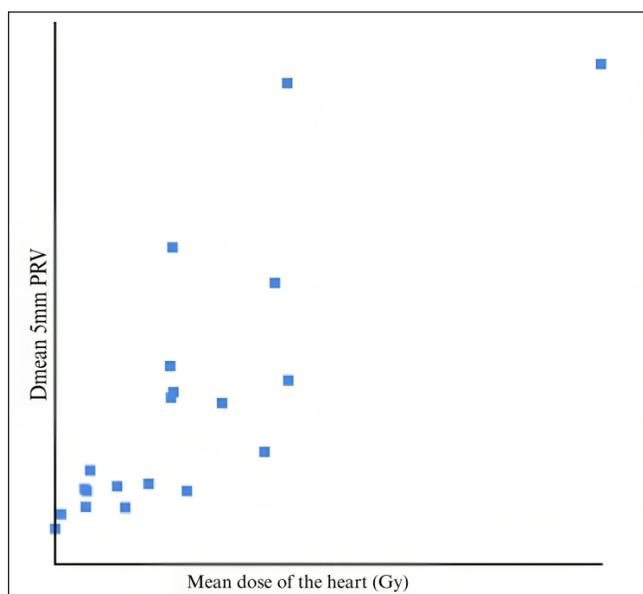
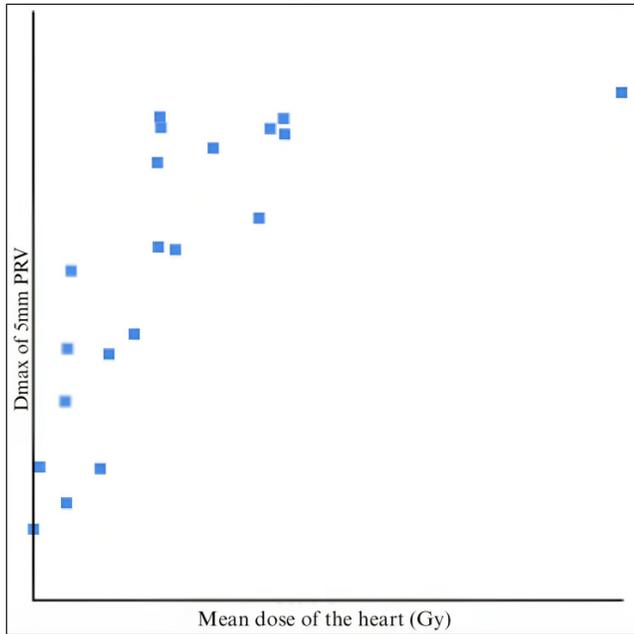


Figure 3: Mean dose of the heart vs. Dmean of 5 mm PRV. As this is a graph of correlation between the PRV and the mean dose, with each point representing a patient/value.

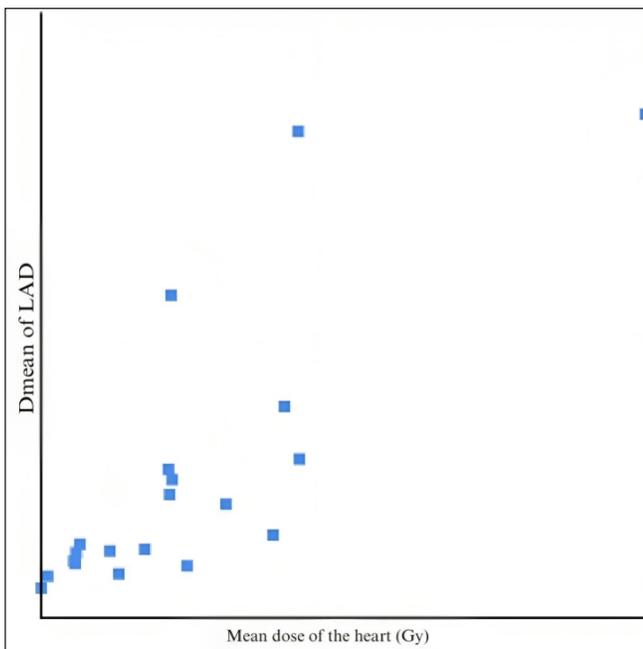
the heart and LAD ( $R^2 = 0.786$ ), which can be used as a more accurate structure to predict acute cardiac events.

### DISCUSSION

Radiotherapy has been proven to be a vital tool in the arsenal of oncologists to treat breast cancers in the postoperative setting. Yang and Ho have summarized the role of RT in breast cancers. After the surgical excision of the overtly obvious tumor, radiation treatment plays a crucial part in the care of breast cancer by curing the subclinical illness. In patients with early stage breast cancer following breast-conserving surgery as well as in node-positive patients who have had a mastectomy, radiation decreases local recurrence rates and improves breast cancer-specific survival.<sup>[11]</sup> The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) studied



**Figure 4:** Mean dose of the heart vs. Dmax of 5 mm PRV. PRV: Planning Organ at Risk Volume.



**Figure 5:** Mean dose of the heart vs. Dmean of LAD. LAD: Left Anterior Descending Artery.

the effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death and reported that breast cancer death rates are reduced by roughly a sixth, and the rate of disease recurrence is cut in half in the preserved breast after radiation. While the proportional benefits had little variation between different groups of women, the absolute benefit varied significantly between

different patient characteristics.<sup>[2]</sup> The benefit of RT was confirmed by other trials as well.<sup>[12-16]</sup> The current guidelines by National Comprehensive Cancer Network (NCCN) state that RT must be given in all cases who have undergone BCS, and in mastectomies with large tumors or node-positive cases.

Exposure to radiation dose has been documented as a key risk factor in the development of various heart diseases. Darby *et al.* concluded that the probability of developing ischemic heart disease increased by 7.4% for every gray of radiation received by the heart. The effects were seen from as early as 5 years post breast radiotherapy till three decades post RT as well.<sup>[4]</sup> There, however, was no apparent threshold with respect to the dose that was detected. According to the Surveillance, Epidemiology and End Results database (SEER), radiation treatment for left-sided breast cancer prior to 1990 was associated with a higher relative mortality, particularly in younger patients and those who also had chemotherapy like anthracyclines or trastuzumab.<sup>[17]</sup> The pathophysiology of radiation-related cardiotoxicity is micro- and macroangiopathy in the coronary arteries, which may lead to myocardial fibrosis and coronary artery disease.<sup>[18]</sup>

The UK START trial B results indicate that a radiation treatment plan that delivers 40 Gy in 15 fractions appears to have local-regional tumor recurrence and late adverse effect rates that are comparable to the conventional treatment fractionation of 50 Gy in 25 fractions.<sup>[9]</sup> Piroth *et al.* have described the possible mechanisms of cardiotoxicity by radiotherapy and have also stated the DEGRO breast cancer expert panel recommendations for dose constraints that are listed in Tables 2 and 3, respectively.<sup>[19]</sup>

The Danish Breast Cancer Group (DBCG) HYPO Trial compared hypofractionated with standard fractionated radiotherapy in early breast cancers and DCIS. The trial found that the 9-year locoregional recurrence risk was low, and both arms were comparable in terms of toxicity. In addition, the study provided stricter guidelines for dose constraints for the Organs at risk (OARs) that are enlisted in Table 4.<sup>[5]</sup>

Yeung *et al.* showed that when patients received breast or chest wall radiation with regional nodal irradiation, including internal mammary chain nodes, DIBH permitted a higher decrease in mean heart and LAD doses than when patients received whole breast radiotherapy (WBRT) without breath hold.<sup>[6]</sup> Wennstig *et al.* was one of the first to deduce that the LAD was a surrogate indicator of cardiac events. Radiation exposures to the LAD in women receiving conventional 3DCRT for breast cancer between 1992 and 2012 remained high and were linked to a higher need for coronary intervention in the middle of the LAD.<sup>[20]</sup> The results of the trial by Zureick *et al.* showed that any cardiac event, whether significant cardiac event or mild, was related with higher LAD

**Table 2:** Mechanisms of cardiotoxicity.

Pathophysiological findings	<ol style="list-style-type: none"> <li>1. RT leads to inflammation, oxidative effects, cytokine activity, and endothelial damage, and leads to an accelerated atherosclerotic process.</li> <li>2. Radiation dosages of less than 2 Gy can cause arteriosclerosis because they cause inflammation in endothelial cells, which are susceptible to radiation.</li> </ol>
Angiographic findings	<ol style="list-style-type: none"> <li>1. There was an increase in clinically significant coronary artery stenoses in the predefined hotspot areas in patients who underwent left-sided WBI/chest wall RT compared to patients who did not receive RT in these areas.</li> <li>2. A four- to seven-fold risk increase was seen in significant stenosis for the mid and distal LAD in radiation hotspot areas.</li> <li>3. The median dose to the damaged vs. undamaged coronary segments was 30.3 vs. 26.3 Gy in mediastinal Hodgkin's lymphoma cases that received RT.</li> </ol>
Functional imaging	<ol style="list-style-type: none"> <li>1. New perfusion defects were detected in 27, 29, 38, and 42% of patients after 6, 12, 18, and 24 months, respectively.</li> <li>2. Perfusion defects were seen in 10–20% of patients if the left ventricle was included in the radiation portals, as opposed to 50%–60% if &lt;5% versus ≥5% of the left ventricle was included.</li> </ol>
Strain rate imaging	<ol style="list-style-type: none"> <li>1. A strain and strain-rate reduction could be seen post RT.</li> <li>2. A considerable reduction in strain, indicated as a reduction in systolic myocardial deformation, could be seen in the apical segments receiving &gt;3 Gy vs. 3 Gy.</li> </ol>
Serum biomarkers	<ol style="list-style-type: none"> <li>1. Cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) or troponin (TnI) increase after left-sided breast RT.</li> <li>2. Patients with higher high-sensitivity cardiac troponin T (hscTnT) had a higher mean LAD dose and a higher V15, V20, and V30 for the LAD.</li> </ol>

RT: Radiation therapy; WBI: Whole breast irradiation; Gy: Gray; LAD: Left anterior descending artery.

**Table 3:** DEGRO dose constraints.

Structure	Constraints
Dmean Heart	<2.5 Gy
DmeanLV	<3 Gy
V5LV	<17%
V23LV	<5%
DmeanLAD	<10 Gy
V30LAD	<2%
V40LAD	<1%

DEGRO: German Society of Radiation Oncology; LV: Left ventricle; LAD: Left anterior descending artery.

**Table 4:** DBCG HYPO dose constraints.

CTVp	
V95%	≥95%
V105%–V107%	≤2%
V107%–V110%	<2cm <sup>3</sup>
Dmax	≤110%
Lung	
V17 Gy	≤25%
Heart	
V17 Gy	≤10%
V35 Gy	≤5%
LADCA	
Dmax	≤17 Gy

DBCG: Danish Breast Cancer Cancer Group; LAD: Left anterior descending artery; Gy: Gray; PRV: Planning organ-at-risk volume. CTVp: Clinical Target Volume of the primary tumor; LADCA: Left Anterior Descending Coronary Artery.

Dmean, LAD Dmax, and heart Dmean values. A threshold LAD Dmean EQD2 of 2.8 Gy was identified.<sup>[5]</sup> Duma *et al.* suggested that the dose to the LAD or the Dmean to the left ventricle were not surrogate parameters for the Dmean heart in every case. Hence, a heart Dmean is non-specific and contouring of the different heart substructures is needed to ascertain late toxicities.<sup>[21]</sup> Data from lung radiotherapy have also found that mean heart dose (MHD) does not correlate with major adverse cardiovascular events (MACE) and LAD is a better surrogate marker V15 Gy.<sup>[22]</sup> Jacob *et al.*, illustrated that MHD is insufficient to reliably predict each patient's dosage to the LV and coronary arteries, especially the LAD, and that distribution of doses to individual cardiac substructures may be necessary to accurately study radiation-induced cardiotoxicity. The proportion of the variance in the Dmean of the substructure that was predictable from MHD was moderate to low, especially LAD.<sup>[23]</sup> Sakyanun *et al.* showed that radiation doses to the LAD area, heart, and lungs are significantly decreased when the DIBH method is used to treat left breast cancer. The study also proved a positive correlation of the mean heart dose with the breast size in cubic centimeter and the maximum heart distance measured in centimeter.<sup>[8]</sup>

Delineation of LAD can be problematic, compounded by its physiological motion. Studies have suggested a 1 cm margin to account for this.<sup>[24]</sup> In our study, we chose to make two PRVs, 3 mm and 5 mm, to account for this motion.<sup>[25–27]</sup> Knöchelmann *et al.* showed a positive linear correlation

**Table 5:** Comparison of our doses with similar studies.

Study	Free Breathing ± DIBH studied	Fractionation Schedule	Mean dose Heart in Gy (Free breathing/ DIBH)	Mean dose LAD in Gy (Free breathing/ DIBH)	Max dose LAD in Gy (Free breathing/ DIBH)	Mean dose PRV 5 mm in Gy (Free breathing/ DIBH)	Max dose PRV 5 mm in Gy (Free breathing/ DIBH)
Mendez <i>et al.</i> <sup>[31]</sup>	Free breathing	50 Gy/25#	2.3		≥28		
Poitevin-Chacón <i>et al.</i> <sup>[32]</sup>	Free breathing	50 Gy/25#	3.7	24.48	33.205		
Hayden <i>et al.</i> <sup>[27]</sup>	Free breathing + DIBH	50 Gy/25#	6.9/3.9			31.7/21.9	51.6/45.6
Gaál <i>et al.</i> <sup>[33]</sup>	Free breathing + DIBH	50 Gy/25#	3.16/1.38	13.05/4.55	39.81/18.92		
Gaál <i>et al.</i> <sup>[33]</sup>	Free breathing + DIBH	50 Gy/25#	4.87/2.13	18.95/7.47	47.03/31.86		
Sakyanun <i>et al.</i> <sup>[8]</sup>	Free breathing + DIBH	50 Gy/25#	19.84/11.48	5.38/2.95			
Naimi <i>et al.</i> <sup>[34]</sup>	Free breathing	40 Gy/15#	3.08	11.45	29.5		
Bartlett <i>et al.</i> <sup>[35]</sup>	Free breathing + DIBH	40 Gy/15#	0.66/0.44	7.8/2.9	36.8/21		
Berg <i>et al.</i> <sup>[36]</sup>	Free breathing + DIBH	40 Gy/15#	1.5/1.2		11.8/11		
Our study		40 Gy/15#	1.784	6.079	18.483	6.153	28.1565

DIBH: Deep Inspiratory Breath Hold; LAD: Left anterior descending artery; Gy: Gray; PRV: Planning organ-at-risk volume.

between LAD Dmean and MHD; however, the mean dose of the ipsilateral lung (MLD) was significantly higher in DIBH compared to free breathing scans. They also found that ipsilateral lung volumes receiving at least 5 Gy, 10 Gy, and 15 Gy (V5, V10, V15) were significantly higher in DIBH compared to nDIBH in both fractionation schemes.<sup>[28]</sup>

Garg and Kumar studied doses to the heart and LAD in left-sided post mastectomy radiotherapy planned with 3DCRT and inverse planning IMRT with 5–7 mostly tangential beams. They noted that 3DCRT technique had significantly lower doses to the heart and LAD than IMRT plans. They also found that doses to LAD were significantly higher than mean heart dose in both 3DCRT and IMRT plans.<sup>[29]</sup> In a dosimetric study by Ahmad *et al.*, 3DCRT, VMAT, and IMRT plans were compared for ultra-hypofractionated left-sided breast radiotherapy, without DIBH. Unsurprisingly, they found that although coverage and V25 OAR doses were better with VMAT, the low doses of V5 were of concern.<sup>[30]</sup>

The comparison of our data with a few similar studies is enlisted in Table 5.

## STRENGTHS

There are only a few studies that have studied the dosimetry of LAD using the UK START B hypofractionated dose regimen, more so using the DIBH technique. Only selected publications have studied the correlation of PRV-LAD and heart doses.

## LIMITATIONS

Our sample size is small, and an accurate comparison of our data to other studies could not be done due to variations in either the fractionation protocols or the planning techniques used. Cardiac toxicity is a long-term complication which requires a long follow-up and clinical correlation.

## CONCLUSION

In our cohort of 20 patients, the heart and LAD doses were either comparable or lower when compared to other similar studies of comparable dose fractionation protocols. The LAD doses that we have recorded are significantly less than those reported in the non-DIBH studies. This objectively demonstrates that DIBH is an effective technique to minimize cardiac toxicity. Though challenging in some cases, it is feasible to routinely contour and record LAD dose in patients receiving left-sided breast radiation. Dosimetry and clinical implications of the Dmean and Dmax of the 5 mm PRV to the LAD may be useful in the future, and it requires further research and clinical correlation.

## Ethical approval

Since this a dosimetric study and does not involve any active intervention on any patient, the IRB and IEC approval does not apply to this study.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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