RESEARCH ARTICLE

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An Analysis of Predictors of Cardiac Sparing using Deep Inspiratory Breath Hold for Left Sided Breast Cancer Patients

Abhinav Dewan[1]*, Lalit Kumar[2], Kundan Singh Chufal[1], Manindra Bhushan[3], Irfan Ahmad[4], Soumitra Barik[5], Preetha Umesh[4], Swarupa Mitra[6], Krati Mehrotra[7]

Abstract

Objective: To analyse the dosimetric benefit achieved with Deep inspiratory breath hold (DIBH) for left sided breast irradiation and to identify the factors impacting it. **Methods:** Between 1st January'2023 to 31st December' 2023, 100 consecutive patients with left sided breast cancer receiving adjuvant radiotherapy and fulfilling the inclusion/exclusion criteria were enrolled in a prospective study conducted at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. Two radiotherapy plans (DIBH/Free breathing (FB)) were generated and evaluated for each patient. Plans were evaluated using dose-volume histogram (DVH). Anatomical and treatment parameters predicting cardiac sparing were generated. **Result:** DIBH led to improvement in dosimetry for lung and cardiac structures for all group of patients. Breathhold technique showed a significant increase in the circumference of the chest, separation and heart height. An approximately 45% increase in ipsilateral lung volume was seen with DIBH. It led to a reduction in the heart volume by 17.67%. After placement of the tangential fields, a decrease in maximum heart distance (MHD) and heart volume in treatment field (HVIF) was seen in the DIBH phase. **Conclusion:** DIBH appears to be a useful tool for limiting cardiac and pulmonary dose in all the patients with left sided breast cancer, potentially reducing long-term complications.

Keywords: DIBH- Left breast irradiation- Cardiac sparing- MHD- HVIF

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Introduction

Radiotherapy forms an essential component of multimodality management in breast cancer and has shown improved overall survival and local control [1-5]. However, this improvement in breast cancer survival is mitigated by an increase in cardiovascular morbidity and mortality that is sustained even after 15 years especially for left breast/chest wall irradiation. Incidence of ischemic heart disease tends to linearly increase with mean heart dose. Darby et al. [6] predicted a 7.4% increase in rate of coronary events for every 1 Gy increase in mean heart dose. Cardiac-morbidity may occur due to varying factors including the volume of heart within radiation portals, dose fractionation, dose to ventricles and left anterior descending artery (LAD) and use of cardiotoxic agents [7-8]. As of now, there is no threshold radiotherapy dose for late cardiac morbidity and every effort should thus be made to reduce the heart dose.

Advanced radiotherapy techniques aimed at decreasing cardiac exposure have been developed including 3-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), prone position treatment and more recently DIBH technique [9]. Various planning studies have shown promising results in reducing cardiac dose without compromising target volume coverage with DIBH when compared to FB. DIBH requires the patient to take a deep breath during simulation and aims to ensure an adequate and steady reproducibility for each fraction. DIBH tends to increase the lung volume and move the heart away from the target, thereby resulting in cardiac sparing [10-12]. Despite published evidence, data on factors impacting the dosimetry with DIBH are rare. We hereby aim to analyse the dosimetric benefit achieved with DIBH for left sided breast irradiation and to identify the factors impacting it.

*[1]Department of Radiation Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India. [2]Division of Medical Physics, Max Saket, Delhi, India. [3]Medical Physics Division, Department of Radiation Oncology, Rajiv Gandhi Cancer Institute, Research Centre, Sec-5, Rohini, Delhi, India. [4]Department of Radiotherapy, Rajiv Gandhi Cancer and Research Centre, Delhi, India. [5]Department of Radiation Oncology, Bagchi Sri Shankara Cancer Centre and Research Institute, Bhubaneswar, India. [6]Department of Radiation Oncology, Fortis Memorial Hospital, Gurgaon, Haryana, India. [7]Department of Dermatology, Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi, India. *For Correspondence: abhinavdewan25@gmail.com*

Materials and Methods

Between 1st January'2023 to 31st December' 2023, 100 consecutive patients with left sided breast cancer receiving adjuvant radiotherapy and fulfilling the inclusion/exclusion criteria were enrolled in a prospective study conducted at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. Inclusion criteria included – 1) Histologically proven breast cancer, 2) Patients undergoing breast conservative surgery (BCS) or modified radical mastectomy (MRM), 3) Axillary lymphnodes dissection or sentinel biopsy performed, 4) Negative microscopic margins, 5) Age between 18 and 70 years, 6) Karnofsky performance status ≥70%, 7) Written consent taken. Those patients who 1) Refused participation in the study, 2) Were unable to cooperate for DIBH training, 3) Patients with history of active cardiac/lung disease and 4) Previous history of irradiation were excluded from the present study. Institutional review board approval was obtained for the study.

Treatment Protocol

All patients with left sided breast cancer underwent surgery (BCS/MRM) with pathologic evaluation [13]. Systemic therapy was administered in a neoadjuvant or adjuvant setting based on clinical stage and pathological features. Adjuvant radiotherapy was delivered within 4 weeks of surgery and/or chemotherapy.

Regional nodal irradiation (RNI) was delivered in case of >3 positive axillary lymphnodes. For 1–3 positive axillary nodes, supraclavicular region was irradiated. All patients undergoing BCS underwent sequential lumpectomy cavity boost if any of the following features were present - 1) Age <50 years, 2) Grade 3 and 3) Margin positive with no further surgery feasible.

Radiotherapy Planning

Patients were immobilized in supine position using vacloc with arms abducted above head. Radio-opaque wires were used to delineate surgical scars and mark tangential fields. All patients were instructed regarding the breath hold procedure using Varian Real time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA). RPM was used to observe the breathing pattern and achieve a stable lung volume during DIBH. A perspex box with infrared marker was used as an external surrogate and was tracked using an infrared camera. This marker was placed on the abdomen at a midpoint between xiphisternum and umbilicus. Patient was asked to take a deep breath and hold it for 20-30 seconds. Breathhold amplitude was analysed and threshold adjusted to ensure maximal movement of 5mm. Patients were counselled and made to practice breath-hold for 2 consecutive days. Those patients who were not able to do breathhold for >20 seconds were excluded from the study and underwent a free breathing scan only. As the patient got accustomed to the procedure, planning CT scans (with IV contrast) of 2 mm slice thickness were acquired in both FB and DIBH phase from the mid-neck to 5 cm caudal to breast tissue using Siemens Somatom CT simulator. DIBH images were attained with patient in maximum comfortable inspiratory phase. DICOM (Digital Imaging and Communications in Medicine) images were transferred to Eclipse Treatment Planning System (version 11.0 Varian Medical Systems, Palo Alto, California, USA). Target volumes and organ at risk (OARs) were contoured on both FB and DIBH scans.

Clinical target volume (CTV) for breast/chest wall, lumpectomy cavity and nodal regions were contoured as per Radiation Therapy Oncology Group (RTOG) contouring guidelines [14]. To account for set-up errors, a 5 mm margin was uniformly extended around CTV to define a planning target volume (PTV). OARs including heart, LAD, ventricles, lung, opposite breast, oesophagus and spinal cord were contoured as per the published atlas [15].

Forward IMRT radiotherapy plans were generated on FB and DIBH image sets using the Eclipse Treatment Planning System using an isotropic analytical algorithm (AAA) for photons. Monoisocentric technique using opposing non-divergent tangential fields along with single anterior supraclavicular field was used. Treatment optimization was achieved using field-in-field technique and field weightage in order to generate homogeneity. Gantry angles were identified to ensure adequate target coverage, while avoiding excess irradiation of OARs.

Radiotherapy was delivered using either conventional (50Gy/25#) or hypo-fractionation (42.5Gy/16#) depending upon patients' stage and physician choice. In general, low risk patients not candidates for systemic therapy received hypofractionated radiotherapy. High risk patients receiving systemic therapy and who were candidates for regional nodal irradiation (RNI) received conventional fractionation [16]. Electron boost to lumpectomy cavity (12Gy/4#) was planned if indicated. Treatment was delivered using DIBH plan on Varian Rapid Arc linear accelerator. Dose constraints were used as per the quantitative analysis of normal tissue effect in clinic (QUANTEC) data [17]. Dose constraints acceptable for radiotherapy planning were as follows - Heart mean dose <4Gy, ventricle mean dose <5Gy, LAD mean dose <10Gy, ipsilateral lung V20Gy ≤35%, cord max dose <45Gy, contralateral lung and breast mean dose ≤5Gy as per institutional protocol.

Dosimetric Evaluation

In the present study, two plans (DIBH/FB) were generated and evaluated for each patient. Plans were quantitatively evaluated using DVH. For target volume (PTV), D95%, D98% and D2% (dose received by 95%, 98%, and 2% volume), respectively, were reported. Additionally, V95% and V107% (the volume receiving at least 95% or 107% of prescribed dose) were also calculated. Acceptable parameters for target volume coverage included D90%>100%, V95% ≥95% and V107% ≤15% [16]. For OARs, the following parameters were reported and compared between the two plans – mean dose to heart, volume of heart receiving 5Gy, 10Gy, 20Gy, 25Gy, 30 Gy, mean dose to LAD, ventricles, lungs and opposite breast.

Anatomical Parameters

Planning CT scan of each patient was used to analyse anatomical parameters and compared between DIBH and FB datasets. These parameters included heart and lung volume, height of the heart (HH), chest-wall heart contact length (HCWL), circumference of chest (CC), chest depth and body mass index (BMI). HH was described as the difference between the superior and inferior contour of the heart. Maximal contact distance between the heart and chest wall was defined as HCWL. Thickness of the chest at the level of maximal chest separation was termed chest depth. Percentage change in lung volume with DIBH when compared to FB was defined as breathhold volume (BHV) [16].

Planning Parameters

In addition, tangential fields with half-beam block were placed to cover the target volume while minimizing irradiation of excess OARs for both FB and DIBH treatment plans. This was used to devise few planning parameters for each patient. These parameters included maximal lung orthogonal distance (LOD), maximum heart distance (MHD), heart volume in treatment field (HVIF) and heart chest-wall distance (HCWD) (Figure 1(a-c)).

MHD was defined as the maximal distance between the edge of the field and the border of heart. HCWD was the distance between the chest wall and the apex of heart (maximal heart point). Volume of heart encompassed by 50% isodose line was defined as HVIF. LOD was defined as the distance between the lung-chest wall interface and the edge of the field at the level of maximum chest separation [16].

Treatment Modification

DIBH technique depends upon the fact that the breath-hold position remains same during the whole treatment as was used in radiotherapy planning. In case of variation in patient's respiratory pattern or change in RPM monitored threshold amplitude of >5mm, the radiotherapy beam was automatically terminated and thresholds had to be adjusted accordingly.

Statistical Analysis

Data were reported as mean +/- standard deviation or as %. Dosimetric comparison was carried between the FB and DIBH plans. All statistical analysis was performed by the standard methods using SPSS computer software (Version 23, SPSS Inc, Chicago, IL, USA). Paired t-test and Wilcoxon signed-rank test were used for comparison of the continuous data. Strength of correlation between the various anatomical and dosimetric parameters was analysed using the Pearson or Spearman correlation coefficient. A $p<0.05$ was considered statistically significant. Further, linear regression analysis was applied to determine whether the characteristics independently predicted for cardiac sparing.

Results

Patient and Disease characteristics (Table 1)

Between 1st January' 2023–31st December'2023, 100 consecutive patients with left sided breast cancer undergoing radiotherapy and fulfilling the inclusion and exclusion criteria were enrolled in the present study. Out of these 100 patients, 53 underwent radiotherapy after BCS, while 47 underwent MRM. Mean age of patient cohort was 46.30±9.26years (Range, 27-66 years). Majority of the patients (75%) received RNI (Supraclavicular/Axillary level III irradiation).

Anatomical and Radiotherapy Treatment Planning Parameters

DIBH led to chest wall expansion, thereby resulting in constriction of heart volume and moving it away from anterior chest wall and away from the tangential radiotherapy beams. Differences in anatomical and treatment planning features are summarized in Table 2.

Significant changes in anatomical parameters of patient cohort were observed in the planning scans. Breathhold technique showed a significant increase in the circumference of the chest, separation and heart height. An approximately 45% increase in ipsilateral lung volume was seen with DIBH. It led to a reduction in the heart volume by 17.67%. After placement of the tangential fields, a decrease in MHD and HVIF was seen in the DIBH phase. In addition, it led to an increase in LOD and HCWD parameters.

Dosimetric Evaluation

Dosimetric parameters were evaluated for lung and cardiac structures including heart, ventricles and left anterior descending artery. DIBH led to improvement in

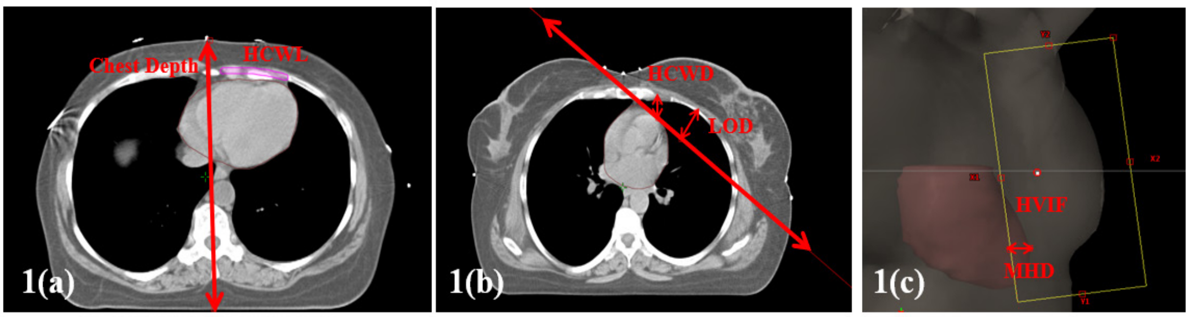

Figure 1. Anatomical and Planning Parameters during DIBH and FB planning (a). Heart-chest wall length (HCWL) and chest depth, (b) heart-chest wall distance (HCWD) and lung orthogonal distance (LOD), and(c) Maximum heart depth (MHD) and heart volume in field (HVIF).

Table 1. Patient and Disease Characteristics

Patient and Disease Characteristics	n (%)
Age (Mean ± SD)	46.30 +/- 9.26 years (Range, 27-66 years)
BMI (kg/m2)	26.73 +/- 2.81 kg/m^2
Quadrant (UIQ:UOQ:LIQ:LOQ:Multiple)	16(16%):39(39%):9(9%):12(12%):24(24%)
Pathological Tumor staging	
(pTis:pT0:T1:T2:T3)	3(3%):5(5%):27(27%):49(49%):16(16%)
Pathological Nodal Staging	
(pNx:pN0:pN1:N2:N3)	1(1%):38(38%):38(38%):14(14%):9(9%)
Surgery (MRM: BCS)	47(47%):53(53%)
Chemotherapy (No Chemo: Neoadjuvant:	
Adjuvant:Perioperative)	15(15%):14(14%):66(66%):5(5%)
Dose Fractionation Schedule	
(Conventional Fractionation: Hypofractionation)	25(25%):75(75%)

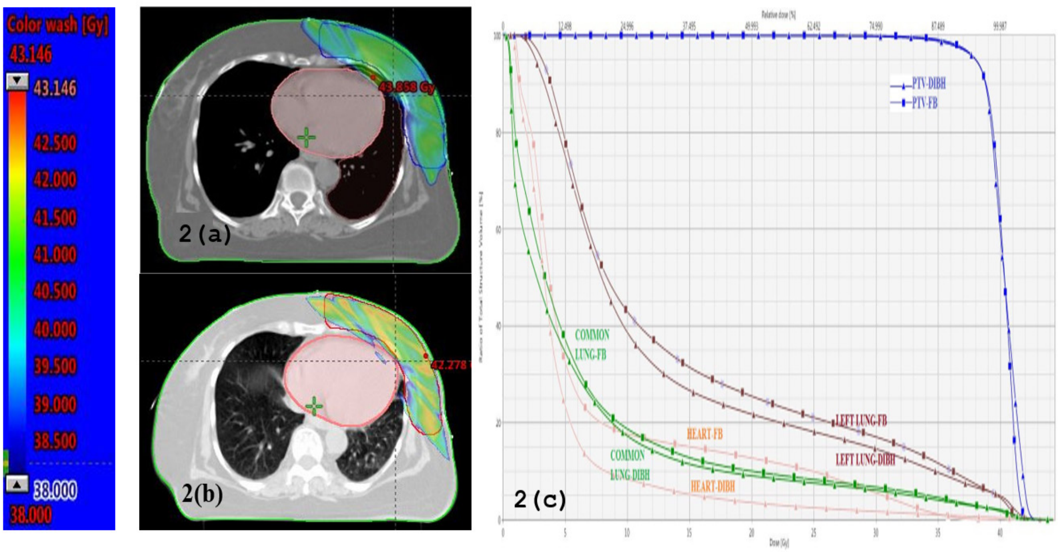

Figure 2. a, b, c: Comparison of Dose Volume Histogram (DVH) between DIBH and FB Plan for Left Sided Breast Cancer Irradiation

dosimetry for lung and cardiac structures for all group of patients (Table 3, Figure 2). A trend towards higher cardiac doses was seen in MRM patients for breathhold plans. Minimal dosimetric impact of DIBH was seen on the target volume (p>0.05).

Table 2. Comparison of Anatomical and Radiotherapy Treatment Parameters between Deep Inspiratory Breath Hold and Free Breathing Scans

	DIBH (Mean±SD)	FB (Mean±SD)	p-value
Anatomical Parameters			
Height of Heart (HH) (cm)	8.27 ± 0.88	7.66 ± 0.64	<0.001
Heart volume (cc)	428.13 ± 81.31	492.87 ± 68.21	<0.001
Common Lung Volume (cc)	3386.56 ± 545	1926.81 ± 347.01	<0.001
Chest depth (cm)	22.24 ± 1.93	20.67 ± 1.81	<0.001
HCWL (Chest wall Heart contact length) (cm)	4.63 ± 0.88	6.35 ± 0.85	<0.001
Chest circumference (cm)	202.89 ± 3.35	189.23 ± 3.07	0.434
Radiotherapy Treatment Parameters			
MHD (cm)	0.67 ± 0.30	1.18 ± 0.26	<0.001
HVIF (Heart volume in Treatment field)	8.88 ± 16.07	27.57 ± 24.31	<0.001
HCWD (Heart chest-wall distance)	1.08 ± 0.14	0.70 ± 0.13	<0.001
LOD (Lung orthogonal distance)	2.29 ± 0.29	1.85 ± 0.22	<0.001

Table 3. Dosimetric Comparison between Radiotherapy Planning in Deep Inspiratory Breath Hold and Free Breathing Phases

Dosimetric Parameters	DIBH	Free Breathing	p-value
Heart			
Mean	2.50±0.57	4.40±0.75	0
V5Gy	5.92±3.31	12.17±3.63	0
V10Gy	2.68±2.01	7.92±2.61	0
V20Gy	1.52±1.38	5.77±2.25	0.001
V25Gy	1.23±1.23	5.12±2.25	0.002
V30Gy	0.99±1.08	4.41±2.15	0.002
V40Gy	0.460±0.72	2.57±1.88	0
Ventricle			
Mean Left	3.32±1.89	6.68±1.89	0.243
Right	3.70±3.48	6.83±5.12	0
LAD			
Mean	8.89±5.14	21.14±8.49	0
V5Gy	44.69±26.27	70.01±26.85	0.007
V40Gy	4.11±7.99	25.45±22.18	0
Lung			
Mean Ipsilateral	10.58±3.72	11.71±4.12	0
Contralateral	0.71±0.73	0.77±0.73	0
Common	5.31±2.06	5.69±2.22	0
V5Gy Ipsilateral	43.60±19.35	45.02±19.55	0
Contralateral	0.39±1.72	0.28±1.19	0
Common	20.64±9.42	20.50±9.62	0
V13Gy Ipsilateral	23.41±8.54	25.84±9.61	0
V20Gy Ipsilateral	19.50±7.42	22.04±8.25	0
Common	9.15±3.60	10.05±4.16	0
PTV			
D98%	41.41±3.17	41.70±3.43	0.135
D95%	42.67±3.18	42.96±3.38	0.084
D50%	45.82±3.48	46.10±3.59	0.082
D2%	47.64±3.74	47.75±3.85	0.558
V107%	5.13±2.88	7.15±5.88	0.089
V95%	96.77±3.50	95.94±3.90	0.587
Monitor units	552.64±153.60	538.18±152.76	0.002

Correlations between OAR doses and Treatment Parameters (Tables 4, 5)

Correlation between the difference in OAR dosimetry and free breathing anatomical parameters is shown in Table 4. Difference in the mean heart dose correlated statistically with the free breathing chest depth and difference in lung volume. In addition, free breathing In-field heart volume (HVIF) showed a significant correlation with the difference in high-dose cardiac parameters (ΔV25Gy, ΔV30Gy, ΔV40Gy). ΔLAD mean dose correlated with free breathing MHD and difference in lung volume (ΔLV).

Correlation between free breathing anatomical and DIBH dosimetric parameters is shown in Table 4. Free breathing MHD and In-field heart volume (HVIF) showed a significant correlation with DIBH cardiac dosimetric variables. Inverse correlation between FB-HCWL and breathhold common lung (V20Gy and Mean) and

Table 4. Correlations between OAR dose and Change in Treatment Parameters

Parameters	ΔMHD	p-value	ΔHVIF	p-value	ΔHH	p-value	ΔChest Depth	p-value	ΔHCWD	p-value	ΔLOD	p-value	ΔHCWL	p-value
Heart														
ΔVol	0.307	0.002	0.059	0.562	-0.114	0.259	-0.153	0.128	0.02	0.843	-0.179	0.075	0.126	0.212
ΔMean	0.122	0.225	0.097	0.337	0.058	0.564	0.009	0.932	0.192	0.056	-0.069	0.495	-0.04	0.695
ΔV5	0.303	0.002	0.015	0.884	0.155	0.124	0.135	0.182	0.154	0.126	0.062	0.543	0.087	0.391
ΔV10	0.248	0.013	0.116	0.252	-0.002	0.982	0.109	0.282	0.17	0.09	0.079	0.434	0.081	0.422
ΔV20	0.333	0.001	0.224	0.025	-0.096	0.344	0.03	0.764	0.147	0.145	-0.017	0.866	0.059	0.562
ΔV25	0.313	0.002	0.242	0.015	-0.162	0.107	-0.033	0.745	0.091	0.367	-0.09	0.371	0.055	0.586
ΔV30	0.295	0.003	0.298	0.003	-0.149	0.138	-0.025	0.806	0.086	0.395	-0.09	0.373	0.092	0.361
ΔV40	-0.016	0.871	0.33	0.001	-0.188	0.061	-0.041	0.683	0.005	0.96	-0.033	0.742	0.011	0.912
LAD														
ΔMean	0.105	0.296	-0.052	0.606	-0.058	0.568	-0.128	0.205	0.12	0.233	-0.156	0.12	0.016	0.873
ΔMax	-0.107	0.288	-0.093	0.357	-0.122	0.228	0.065	0.518	0.143	0.154	-0.245	0.014	-0.065	0.519
ΔV5	-0.091	0.367	-0.213	0.034	-0.107	0.29	0.036	0.719	0.023	0.824	-0.209	0.037	-0.018	0.856
ΔV40	0.096	0.344	0.123	0.222	0.092	0.361	-0.222	0.026	0.093	0.356	-0.026	0.797	0.009	0.931
ΔLt. Ventricle Mean dose	0.051	0.616	0.155	0.123	-0.279	0.005	0.155	0.123	0.052	0.607	-0.111	0.27	-0.197	0.049
ΔRt. Ventricle Mean dose	0.092	0.361	0.515	<0.001	0.064	0.527	-0.016	0.872	0.004	0.971	-0.219	0.028	0.094	0.352

Table 5. Linear Regression Analysis

Variables	ΔHeart mean Parameter estimate (95%CI)	p-value	ΔHeart V5Gy Parameter estimate (95%CI)	p-value	ΔHeart V10Gy Parameter estimate (95%CI)	p-value	ΔHeart V20Gy Parameter estimate (95%CI)	p-value	ΔHeart V25Gy Parameter estimate (95%CI)	p-value
ΔMHD	0.311 (-0.337-0.958)	0.343	5.262 (2.090-8.433)	0.001	2.878 (0.410-5.347)	0.023	3.179 (1.229-5.128)	0.002	2.980 (1.033-4.927)	0.003
ΔHVIF	0.005 (-0.005-0.014)	0.339	-0.006 (-0.053-0.041)	0.803	0.013 (-0.024-0.050)	0.424	0.035 (0.006-0.064)	0.019	0.041 (0.012-0.070)	0.006
ΔHCWL	-0.067 (-0.233-0.100)	0.429	0.367 (-0.447-1.182)	0.373	0.225 (-0.049-0.859)	0.483	0.009 (-0.492-0.510)	0.973	-0.018 (-0.518-0.482)	0.943

Variables	ΔHeart V30Gy Parameter estimate (95%CI)	p-value	ΔHeart V40Gy Parameter estimate (95%CI)	p-value	ΔLAD mean Parameter estimate (95%CI)	p-value	ΔLAD max Parameter estimate (95%CI)	p-value	ΔLt. ventricle Mean Parameter estimate (95%CI)	p-value	ΔRt. Ventricle Mean Parameter estimate (95%CI)	p-value
ΔMHD	2.635 (0.820-4.451)	0.005	0.209 (-1.304-1.722)	0.785	1.898 (-5.485-9.280)	0.611	-9.846 (-24.441-4.750)	0.184	0.435 (-1.499-2.369)	0.656	2.053 (-0.500-4.607)	0.114
ΔHVIF	0.046 (0.018-0.073)	0.001	0.044 (0.021-0.066)	<0.001	-0.028 (-0.138-0.082)	0.617	-0.146 (-0.364-0.072)	0.187	0.028 (-0.001-0.057)	0.057	0.121 (0.083-0.159)	< 0.001
ΔHCWL	0.027 (-0.440-0.493)	0.909	-0.114 (-0.503-0.275)	0.561	0.283 (-1.613-20180)	0.767	0.362 (-3.389-4.112)	0.849	-0.478 (-0.975-0.019)	0.059	-0.374 (-1.031-0.282)	0.26

ipsilateral V20Gy was noted.

Linear regression analysis (Table 5) was applied to ascertain whether the characteristics could independently predict for sparing the heart, LAD and ventricles. All patients undergoing regional nodal irradiation showed a 6.98% and 8.21% unit increase in the mean heart and left ventricle dose, respectively. Every 1cm increase in lung orthogonal distance (LOD) in the FB scan led to a 13.84% relative decrease in heart V5Gy. DIBH led to a 9.78% unit decrease in heart V5Gy in all patients undergoing MRM.

In addition, regression models for cardiac dose parameters and absolute/relative difference in anatomical parameters were generated. A unit % decrease in HVIF with DIBH led to a 0.63% and 0.26% decrease in heart V25Gy and mean left ventricle dose, respectively. For every unit % decrease in MHD, a relative decrease of 0.29% V5Gy was noted with breathhold technique. All patients undergoing IMC irradiation showed a 9.62% unit increase in cardiac V10Gy value. Breathhold led to an increase in separation between cardiac apex and chest wall (HCWD) with a relative decrease in mean cardiac and left ventricular dose of 0.103% and 0.26% for every unit % increase in HCWD respectively.

Discussion

Our results are in line with previously published data demonstrating favourable alteration of patients' anatomy with DIBH that results in heart moving away from the chest wall and outside the tangential radiotherapy fields. It in turn permitted significant cardiac and lung sparing [6, 18]. In women with one or more established cardiac risk factors, both the baseline and the absolute increase in risk of radiation-induced ischemic heart disease was significantly higher [6]. This risk can further increase even with the smallest of radiotherapy doses. Various studies have noted variable mean heart dose-values; we however accept the fact that there is no safe upper limit for the same.

In the current study, the mean dose to heart in DIBH was 2.50Gy, which is lower than an average dose of 4.10Gy reported without breathing control in a systematic review. A significant variability in mean doses received by heart among other countries has been witnessed. This reflects the difference in the RT techniques, anatomical variations and difference in contouring techniques and guidelines [19]. Mean cardiac dose reduction between FB and DIBH ranged from 15.10% to 81.10% (Mean difference 59%). Nissen et al. documented a mean heart dose reduction of 48% compared to FB [20-21].

Breathhold implementation is a cumbersome process creating various challenges for radiation oncology team including the resource constraints, simulation slots, coaching etc. Therefore, attempt was made identify the anatomical and planning parameters which can be used as indicators of cardiac sparing upfront. A meaningful correlation between the change in OAR dosimetry and FB anatomical parameters was seen (MHD and V10Gy/Mean LAD; Chest Depth and Mean Heart/Contra-lateral lung V5Gy/Ipsilateral lung average; HVIF and ΔV25/ΔV30/ΔV40) (Table 4). In addition, significant correlation between DIBH dosimetric variables and anatomical factors was noted (BMI and Heart ΔV5Gy; MHD and Heart ΔV10/ΔV20; HCWD and Contra-lateral lung ΔV5Gy/Ipsilateral Lung Average; HVIF and Heart ΔV25Gy/ΔV30Gy/ΔV40Gy). Register et al. [16] reported the correlation between dosimetric parameters and change in anatomical parameters. Alteration in HCWL between FB/DIBH significantly correlated with all cardiac dose parameters. Likewise, ΔHH correlated with measured cardiac and LAD dosimetric parameters. Mean MHD significantly correlated with majority of the cardiac parameters including mean ΔHeart dose. To summarize, Register et al. noted that changes in anatomical parameters had meaningful correlation with heart and LAD dosimetric parameters.

Subsequent regression analysis confirmed significance of chest separation, LOD, type of surgery, RNI, IMC inclusion, ΔHCW (Absolute/Relative), ΔLung volume (Absolute/Relative), ΔMHD (Absolute/Relative), ΔHH (Absolute/Relative) in predicting cardiac doses. MHD, chest separation, LOD, HCW and HH denote a complex interaction between the anatomical and radiotherapy treatment parameters exclusively for each patient due to breathhold. It tends to indirectly characterise the volume of heart exposed to radiation during radiotherapy treatment planning. Our study aims to document these easily quantifiable surrogates of cardiac sparing with DIBH for individual patients.

Historically, there is lack of published data with regards to identifying a subset of patients benefiting from DIBH. Significant dosimetric benefit with DIBH was noted for patients undergoing MRM. In addition to cardiac sparing, DIBH tends to decrease the lung volume exposed to radiation; thereby leading to decrease in overall lung dose. Published studies indicate constant cardiac sparing with breathhold; however, results seem variable as far as lung data is concerned. Our results showed a significant cardiac and pulmonary sparing with DIBH which was in line with observations made by Swanson et al. [10] and Register et al. [16]. In contrast, Shim et al. [12] noted a non-significant improvement in V20Gy and mean lung dose, which may be a result of a much smaller % increase in lung volume (approximately 45%) as compared to 79% (Change in common lung volume) observed in the present study.

Despite breathhold technique, some of the patients had minimal benefit as far as OAR dosimetry is concerned. This in turn can be attributed to favourable anatomy or sub-optimal respiration pattern of the individual patient. This fact highlights the need for identification of predictive factors and formulation of a model for documenting OAR sparing pre-treatment.

Most of the available literature focuses on cardiac and lung sparing; while few authors have tried to correlate between radiotherapy treatment planning and anatomical features with cardiac doses. Majority of the studies have focussed on MHD and HVIF. A strong linear correlation between the mean heart dose and HVIF was noted by Wang et al. [22] with an increment of 67cGy mean heart dose for every 10cm3 increase in HVIF volume. Hayden et al. [11] noted a strong correlation between heart V30Gy and MHD/HVIF. Few studies have attempted to analyse the individual factors predictive of benefit with DIBH and observed HVIF/MHD as an independent factor suggestive of cardiac sparing [16, 23]. Our results were keeping in line with the pre-existing data.

Tanna et al. [23] analysed 134 patients selected for DIBH using different selection approaches including - 1) For all patients with mean heart dose >3Gy, 2) MHD>1cm, 3) Using upfront selection criteria ie. Extensive tumor bed, inferior quadrant and all chest wall cases, 4) All left sided breast cancer cases. Tanna et al. recommended the upfront selection criteria for DIBH radiotherapy treatment. In addition, in cases where MHD was >1cm in FB scan, benefit of DIBH was seen. Breathhold was not recommended for all left sided breast cases as it may result in 'over-selection' of cases and put an extra burden on our resources. Therefore, it is practical to calculate MHD (Cut-off >1.1cm) and HVIF (Cut-off 27.5cc) on FB scans to select cases for DIBH.

Major limitations of our study included the dosimetric nature of the study and limited number of patients. London cancer guidelines [24] recommended cardiac dose interpretation to be done taking into consideration the underlying cardiac risk factor; however, this was not the case in our study. In addition, electron boost to lumpectomy cavity was delivered on a free breathing scan for all patients.

Benefits obtained with DIBH must be weighed against the complex nature of treatment, prolonged treatment time and more effort and expertise required for the treating technologist and patient. Most important factor for a successful breath-hold is patient's ability to comply with the breath-hold instructions, age, performance status and comorbidities.

To summarize, DIBH appears to be a useful tool for limiting cardiac and pulmonary dose in all the patients with left sided breast cancer, potentially reducing long-term complications. Ours is the first study from Northern India attempting to identify predictive factors for dosimetric benefit with DIBH. MHD and HVIF can be used as surrogates for reduction in cardiac dose parameters including heart, LAD and ventricles.

Author Contribution Statement

Abhinav Dewan: Concept, manuscript writing, statistics, Review manuscript, data collection. Lalit Kumar: Concept, manuscript writing, Review manuscript . Kundan Chufal: Concept, statistics, Reviewed manuscript. Maninder Mishra: Review manuscript, concept, data collection. Irfan Ahmad: Manuscript review, Data analysis, statistics. Soumitra Barik: Data analysis, statistics, Manuscript review. Preetha Umesh: Data analysis, statistics. Swarupa Mitra: Manuscript review, data collection. Krati Mehrotra: Manuscript review, data collection

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None.

Conflict of Interest

None to declare.

References

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. Lancet. 2005;366 (9503):2087-106. https://doi.org/10.1016/S0140-6736(05)67887-7.
2. Early Breast Cancer Trialists' Collaborative Group; Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16. https://doi.org/10.1016/S0140-6736(11)61629-2.
3. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Post operative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997;337(14):949-55. https://doi.org/10.1056/NEJM199710023371401.
4. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999;353(9165):1641-8. https://doi.org/10.1016/S0140-6736(98)09201-0.
5. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116-26. https://doi.org/10.1093/jnci/djh297.
6. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98. https://doi.org/10.1056/NEJMoa1209825.
7. Marks LB, Yu X, Prosnitz RG, Zhou SM, Hardenbergh PH, Blazing M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys. 2005;63(1):214-23. https://doi.org/10.1016/j.ijrobp.2005.01.029.
8. Borger JH, Hooning MJ, Boersma LJ, Snijders-Keilholz A, Aleman BM, Lintzen E, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: The role of irradiated heart volume. Int J Radiat Oncol Biol Phys. 2007;69(4):1131-8. https://doi.org/10.1016/j.ijrobp.2007.04.042.
9. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst. 2005;97(6):419-24. https://doi.org/10.1093/jnci/dji067.
10. Swanson T, Grills IS, Ye H, Entwistle A, Teahan M, Letts N, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. Am J Clin Oncol. 2013;36(1):24-30. https://doi.org/10.1097/COC.0b013e31823fe481.
11. Hayden AJ, Rains M, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. J Med Imaging Radiat Oncol. 2012;56(4):464-72. https://doi.org/10.1111/j.1754-9485.2012.02405.x.
12. Shim JG, Kim JK, Park W, Seo JM, Hong CS, Song KW, et al. Dose-Volume Analysis of Lung and Heart according to Respiration in Breast Cancer Patients Treated with Breast Conserving Surgery. J Breast Cancer. 2012;15(1):105-10. https://doi.org/10.4048/jbc.2012.15.1.105.
13. American College of Radiology. Practice guideline for the breast conservation therapy in the management of invasive breast carcinoma. J Am Coll Surg. 2007;205(2):362-376. https://doi.org/10.1016/j.jamcollsurg.2007.02.057.
14. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6. https://doi.org/10.1016/0360-3016(95)00060-C.
15. Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2011;79(1):10-8. https://doi.org/10.1016/j.ijrobp.2009.10.058.
16. Register S, Takita C, Reis I, Zhao W, Amestoy W, Wright J. Deep inspiration breath-hold technique for left-sided breast cancer: An analysis of predictors for organ-at-risk sparing. Med Dosim. 2015;40(1):89-95. https://doi.org/10.1016/j.meddos.2014.10.005.
17. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S3-9. https://doi.org/10.1016/j.ijrobp.2009.09.040.
18. Tanna N, McLauchlan R, Karis S, Welgemoed C, Gujral DM, Cleator SJ. Assessment of Upfront Selection Criteria to Prioritise Patients for Breath-hold Left-sided Breast Radiotherapy. Clin Oncol (R Coll Radiol). 2017;29(6):356-361. https://doi.org/10.1016/j.clon.2017.01.004.
19. Taylor CW, Wang Z, Maculay E, Jagsi R, Duane F, Darby SC. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. Int J Radiat Oncol Biol Phys. 2015;93(4):845-53. https://doi.org/10.1016/j.ijrobp.2015.07.2292.
20. Ledsom D, Reilly AJ, Probst H. Assessment of deep inspiration breath hold (DIBH) amplitude and reduction in cardiac dose in left breast cancer patients. Radiography (Lond). 2018;24(2):98-103. https://doi.org/10.1016/j.radi.2017.11.005.
21. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol. 2013;106(1):28-32. https://doi.org/10.1016/j.radonc.2012.10.016.
22. Wang W, Purdie TG, Rahman M, Marshall A, Liu FF, Fyles A. Rapid automated treatment planning process to select breast cancer patients for active breathing control to achieve cardiac dose reduction. Int J Radiat Oncol Biol Phys. 2012;82(1):386-93. https://doi.org/10.1016/j.ijrobp.2010.09.026.
23. Taylor CW, McGale P, Povall JM, Thomas E, Kumar S, Dodwell D, et al. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice. Int J Radiat Oncol Biol Phys. 2009;73(4):1061-8. https://doi.org/10.1016/j.ijrobp.2008.05.066.
24. http://www.londoncanceralliance.nhs.uk/media/123021/lcacardiac-sparing-breast-radiotherapy-sop-march-2016.pdf.