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Evaluation of Doses to Organ at Risk with Deep Inspiratory Breath Hold Compared to Free Breathing in Left Sided Breast Cancer and Assessment of Patient Related Anatomical Factors

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Abstract

Introduction: With the improvement in prognosis for patients with breast cancer, reducing long-term toxicity from treatment has become increasingly important. Left breast Radiotherapy (RT usually results in higher dose delivery to the heart and lungs, which are treated as Organs at Risk (OAR. Heart irradiation increases the risk of radiation induced heart disease and major coronary artery disease in long term survivors.

Material and methods: After obtaining informed consent, 50 patients were enrolled in the study between October 2020 and February 2021. Two scans were performed on each patient, one in Free Breathing (FB) and one using Deep Inspiratory Breath Hold technique (DIBH). Contouring of target volume and Organ at Risk (OAR) were performed on both scans. Dose Volume Histograms (DVH) was generated for both scans for plan evaluation. Dose parameters were calculated and compared to assess doses to heart and lungs. In addition, anatomical parameters including Maximum Heart Distance (MHD), Haller Index (HI), Central Long Distance (CLD), chest wall separation (CWS), Heart Chest Distance (HCD), Lung Volume Difference (LVD), and Cardiac Contact Distance (CCD) in axial and parasagittal planes were also studied for impact on doses to heart and lung.

Results: The reduction in mean doses using DIBH was statistically significant for both heart and lung. Overall, the mean heart dose in FB was 5.60 ± 2.20 and in DIBH it is 2.50 ± 1.24 leading to a difference of 3.4 Gy.

About 17 patients (34% failed to attain a difference of ≥2 Gy with DIBH scans. This difference was persistent and significant in V_{10}, V_{30}, V_{35} of heart. Similarly, mean left lung dose reduction of 4.89 Gy was seen from 9.42 ± 2.80 in FB to 4.53 ± 2.20 using DIBH scan with statistically significant (p value=<0.05. Overall, V_{20} V_5 and V_{10} of both lungs showed no statistical difference in either group (FB and DIBH, respectively. On contrary to this, the impact of DIBH dose reduction was more pronounced in V_{20} and V_{30} of left lung and less marked in V_5 and V_{10}. The mean differences in different anatomical parameters between FB and DIBH scan were significant for all stated parameters except chest wall separation (FB=20.35 cm, DIBH=20.55 cm, p-value=0.68. The moderate correlation between the anatomical parameters and mean heart dose reduction was statically significant for CLD (r=-0.36, p- value 0.01, MHD (r=-0.40, p-value=0.007, HCD (r=0.50, p-value=0.001, CCDps (r=-0.43, p-value=0.002 while the rest of the parameters including CCDax, LVD, CWS and Haller index showed weak correlation with outcome variable. The Multivariate regression analysis concluded HCD (β=2.02 (CI=1.14-2.89),p-value=0.001)and CLD (β-1.499 (CI=-2.448-0.549),p-value=0.003 two variables that independently predict mean heart dose reduction for patients undergoing DIBH based left sided breast radiotherapy.

Conclusion: DIBH is a sublime technique and it is cost effective if used in suitable cohorts of patients. To improve selection criteria, HCD and CLD can be used as suitable anatomical predictors for reduction in mean doses to organs at risk.

Keywords: DIBH (Deep Inspiratory Breath Hold) • Radiotherapy • Organs at risk • Cardiac Contact Distance (CCD)

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Introduction

Breast cancer is the most frequently occurring cancer in women and it's the second leading cause of cancer death among females [1]. According to GLOBOCAN statistics, the annual incidence is 24% and almost 15% of annual deaths are attributed to breast cancer [2]. For more than two decades, the use of postoperative radiation alone in treatment of breast cancer has proven to be beneficial in terms of both loco regional control and overall survival [3-7]. However, with increasing advancements in therapeutic approaches including systemic chemotherapy, hormonal agents and targeted therapies there is a relative decline in breast cancer specific mortality [8]. Hence, survivors are likely to live long enough to experience long term toxicities of radical treatment especially radiation induce complications to heart and lung [9-10]. Traditionally, breast tangential fields resulted in mean heart dose (D mean) of 0.9-14 Gy in left sided tumors in contrast to 0.4-6 Gy in those having right sided tumors. These doses correlates well with development of coronary artery events and ischemic heart disease [11]. This effect is augmented by additional insult to lung tissue which will hinder patient's reserve to combat with cardiovascular stress in distant future and also lead to the development of secondary lung cancer. Historically, the lung doses received were in a range of 9-18 Gy. The risk increases in a linear manner at a rate of 7.4% for each Gray increase in heart dose and that of 11% for each gray increase in mean lung dose [12]. The absolute risk of developing lung cancer in 30 years following radiotherapy to breast receiving a Mean Lung Dose (MLD) of 5 Gy is 0.3% in nonsmokers and approximately 4% in smokers [13]. Recently, with the benefits of regional nodal irradiation coming into consideration, the heart and lung doses can increase up to 17-20 Gy and 25-30 Gy, respectively, further undermining the long term survival advantage gained by radiation [14-18]. The risk is further complicated by other contributing factors like previous history of cardiovascular disorders, interstitial lung diseases, use of anthracyclines and trastuzumab leading to substantial increase in incidence of cardiopulmonary events [19-20].

Foreseen facts, various techniques like treatment in prone position, use of conformal and intensity modulated therapy etc. have been investigated to reduce doses to these critical structures when planning breast radiotherapy. Among these techniques, Deep Inspiratory Breath Hold (DIBH) is the most novel mean of maximizing distance between heart and chest wall, thus reducing doses to heart and lung. During deep inspiration heart moves post inferiorly thereby decreasing the portion of heart receiving high radiation doses especially its apex that contains the Left Anterior Descending Artery (LAD). Theoretically, LAD is an end artery and dose to this portion contributes majorly in developing late cardiac events. Paradoxically the absolute volume of lung in irradiated field increases during deep inspiration but owing to the change in density and lesser attenuation of air, the relative lung volume decreases and thus so the mean lung doses. Nissen et al. reported a reduction in mean heart dose from 5.2 to 2.7 Gy and minor significant reduction in V_{20} Gy of lung. Marianne, et al. in a decrease in cardiac mortality and expected decrease in incidence of lung cancer.

Despite the significance of DIBH, the most critical factor is the correct identification of patients who can gain maximum benefit from such treatment. Due to wide anatomical variation among patients in shape of chest wall breast contours and heart size, not all get profited from such costly treatments. In a developing country like Pakistan where only access to standard treatment comes as a privilege, there should be meticulous criteria to select patients for whom DIBH can have lasting benefits. To implement and execute such specialized treatment necessitates the need of highly trained staff and sparing of extensive treatment delivery time in a busy radiotherapy department. This study highlights the dosimetric benefits of DIBH by evaluating difference in heart and lung doses attained by planning treatment on both Free Breathing CT (FB-CT) and Deep Inspiratory Breath Hold CT scans (DIBH-CT). Additionally, different anatomical parameters to achieve maximal dosimetric advantages from DIBH are discussed. Furthermore, patient related factors like age and BMI are mentioned to objectively set criteria to clinically determine patients that are best suitable for such costly treatment. Other than these a tumor specific parameter, that is the location of tumor in breast quadrant and its relation to the chest wall can be of significant impact in choosing patients appropriate to undergo this technique.

Materials and Methods

After approval by the hospital ethics committee for clinical research between October 2020 till February 2021, fifty women with left sided breast cancer who underwent either breast conservation surgery or mastectomy and were planned for adjuvant radiotherapy to the whole breast or chest wall with or without nodal irradiation (+/ tumor bed boost) were enrolled in the study. After obtaining written informed consent patients obtained coaching for inspiration breath hold for at least 20 seconds, patients unable to do so were excluded from the study. During CT acquisition patients were immobilized in supine position using inclined breast board with ipsilateral arm abducted above head and scan was obtained with 3 mm slice thickness. Patient's breath hold status during DIBH scan acquisition was monitored thru Varian Respiratory Gating System (Varian Medical Systems, Palo Alto, CA) was utilized to monitor the patient breath hold status during DIBH CT simulation by placing the RGS reflective block at Xiphoid sternum. Patients underwent a FB CT scan immediately followed by a DIBH CT scan both the FB and DIBH CT image sets were transferred to the Eclipse Treatment Planning System (TPS). Target volumes and organs at risk were contoured on both data sets individually. In breast conservation, Clinical Target Volume (CTV) was defined as the breast tissue visualized on CT down to deep fascia excluding muscles and rib cage and 5 mm margin below skin. In case of chest wall CTV included skin flaps down to deep fascia excluding muscles and rib cage in both cases 10 mm margin was created all around to make PTV. This margin is cropped 5 mm inside of skin in breast and along the skin in case of chest wall. In case of chest wall, alternate day bolus is used as part of institutional protocol. The SCF fossa was contoured using RTOG consensus guidelines from caudal edge of cricoid cartilage to junction of brachiocephalic/axillary veins. In case of cavity boost, the entire cavity was outlines including the surgical clips as CTV-B and 1 cm margin all around to make it PTV.

The ipsilateral lung, contralateral breast and heart along the entire pericardial sac extending from root of aorta or pulmonary trunk to the apex was contoured as organs at risk on both CT data sets. For each patient, Three-dimensional CT-based plans on FB and DIBH scans using the Eclipse treatment planning system (ver. 15.6; Varian, Palo Alto, CA, USA) were generated using tangential, forward IMRT planning. Each plan was prescribed 40 Gy in 15 fractions to the PTV and 10 Gy in 5 five fractions to boost if required while ensuring that PTV coverage was kept between 90% and 110% of the prescription. To achieve prescription goal, each plan was optimized with respect to tangential field angles, weights, and dynamic wedges with 6 MV, 10 MV, 15 MV beams or a mixture of energies to achieve dose homogeneity. Supraclavicular and axillary nodes were covered by a single anterior, or opposed anterior posterior fields based on the depth of volume. Dose volume histograms were reviewed and parameters for target volume and organs at risk were recorded for both the plans. Patient data collection was based on dosimetric and anatomical factors as shown in Figure 1.

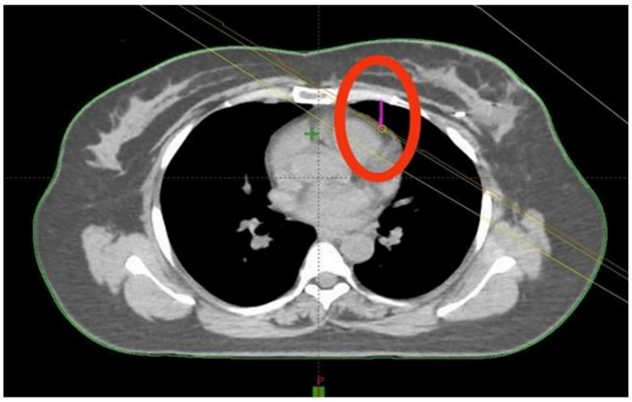

Figure 1. Central Lung Distance (CLD) perpendicular distance from the posterior edge of the field border to the anterior chest wall (lung interior). This is calculated in FB scan.

In addition to these the analysis was conducted on parameters like age and BMI. These parameters were chosen in accordance to the retrospective studies suggesting potential predictive factors in selecting patients eligible for DIBH scans in different populations.

Statistical analysis

All dosimetric parameters were inferred using Dose Volume Histograms (DVH) of Free Breathing (FB) plans and Deep Inspiratory Breath Hold (DIBH) plans. For dosimetric variables, differences in mean heart and lung dose both in FB and DIBH were analyzed using paired t-test for normally distributed data. The normality assumption was fulfilled by using Shapiro Wilk test. In addition to mean doses, dose to 95% of CTV, dose to 95% of PTV, V_5, V_{10} and V_{30} of heart and V_{20} and V_{30} of lung were also calculated and compared. The values for these parameters were deduced from DVH (Dose Volume Histograms) of FB and DIBH scans. As data was compared between two time points in same subject the condition of correlated data remained consistent throughout the study. The geometric variables were also measured in both scans. In addition to these patient related parameters age and BMI were also compared. The correlation, univariate and multivariate analysis using multiple linear regression techniques were done using these variables to predict their effect on reduction in heart and lung doses. The statistical significance was defined at p-value ≤ 0.05 and with a confidence interval of 95%.

Results

Patient characteristics

Patient and treatment characteristics of 50 left sided breast cancer patients collected on Data set of 100 CT scans were analyzed (Figure 2).

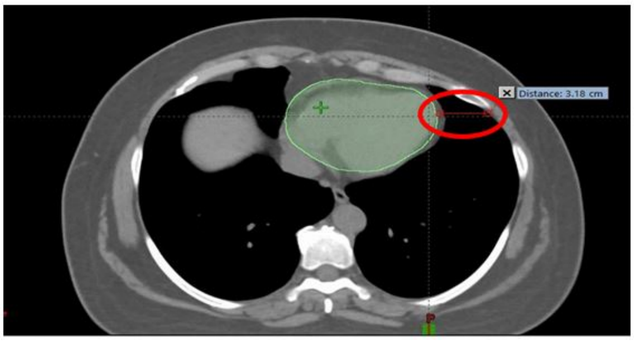

Figure 2. Heart Chest Distance (HCD) the distance between chest wall and maximum heart point measured on the axial plane.

Mean age of the patients was 47 (31-63), with mean Body Mass Index (BMI) of 28.6 (19.2-37.2). The mean breath-hold volume was 1.1 L and mean duration of breath-hold was 15 seconds. Of 50 patients, 34 (68%) patients received radiotherapy after Breast Conservation Surgery (BCT) and 16 (32%) after mastectomy. In addition, 35 (70%) patients received Regional Nodal Irradiation (RNI) (supraclavicular or/and axilla but not internal mammary nodes).

Doses to target volumes

Treatment plans were clinically acceptable with comparable dose coverage of target volume among both the groups. PTV D 90% for DIBH and FB was 39.31 Gy (38-41.60) and 39.9 Gy (38.14-43.17) respectively while CTV D 95% DIBH and FB was 41.31 Gy (31.79-99.40) and 40.41 Gy (32.02-43.09) respectively.

Dosimetry comparison of doses to organ at risk: There was significant reduction in both cardiac and lung doses in DIBH scan across all the subgroups irrespective of type of surgery or location of tumor. Overall, the mean heart dose in FB was 5.60 ± 2.20 Gy and in DIBH was 2.50 ± 1.24 Gy leading to a difference of 3.10 ± 0.35 Gy. 17 patients (34%) failed to attain a difference of ≥ 2 Gy with DIBH scans. In remainder, an average difference of 5.27 ± 1.45 was achieved with variability in reduction of 3.5 Gy to 9.60 Gy. The mean of heart volume receiving 5% of dose in FB group was 17.11 ± 6.70 and in DIBH was 7.80 ± 4.40. There is a statistically significant difference in both groups with a remarkable mean difference of 9.32. This difference was persistent and significant in V_{10}, V_{30} V_{35} of heart. Similarly, mean left lung dose reduction of 4.89 ± 0.50 Gy was seen from 9.42 ± 2.80 in FB to 4.53 ± 2.20 using DIBH scan. This difference was also statistically significant with a p value of <0.05. Overall, V_{20} V_5 and V_{10} of both lungs showed no statistical difference in both groups (FB and DIBH), respectively. On contrary to this, the impact of DIBH dose reduction was more pronounced in V_{20} and V_{30} of left lung and less marked in V_5 and V_{10} (Figure 3).

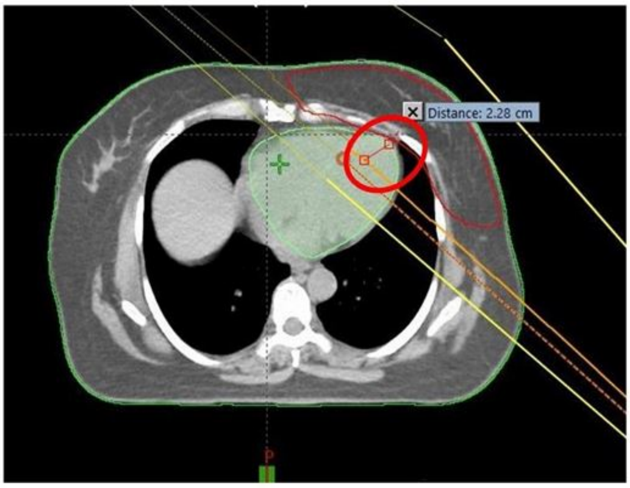

Figure 3. Maximum Heart Distance (MHD) measured on the CT slice with the thickest section of heart contained within the field and is defined as the distance between the anterior cardiac contour crossing over the posterior edge of the tangential fields.

Anatomical parameters

The mean difference in different anatomical parameters between FB and DIBH scan with percent difference in their values is stated in Figure 4.

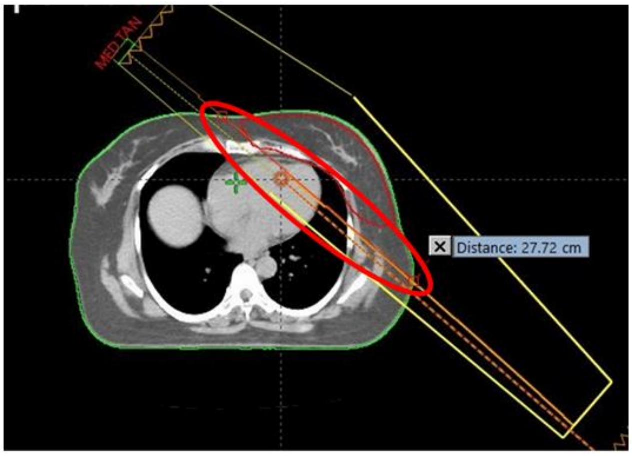

Figure 4. Chest Wall Separation (CWS) measurement between the most posterior field edges of the beam from the medial and lateral tangents of the non-diverging beam pair, measured at the center of the field on the cranio-caudal axis.

Most of these had statistically significant differences in the mean values between the two scans, however further analysis for interpretation of regression and correlation the values from FB data set was included except for lung volume difference (Figure 5).

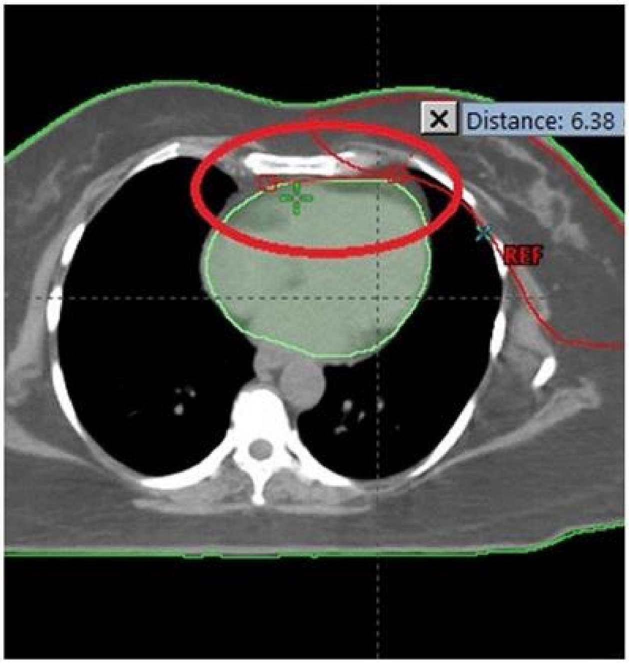

Figure 5. Cardiac Contact Distance (CCD) axial distance measured as the shortest linear distance from the points of contact of the cardiac sihouette with the chest wall, at the level of the dome of the right diaphragm, in the axial plane of the CT scan.

The correlation of anatomical parameters on heart and lung doses between both scans is summarized in Figure 5 to determine if any of these parameters independently predicted cardiac and lung sparing, univariable and multivariable regression analysis was conducted (Figure 6).

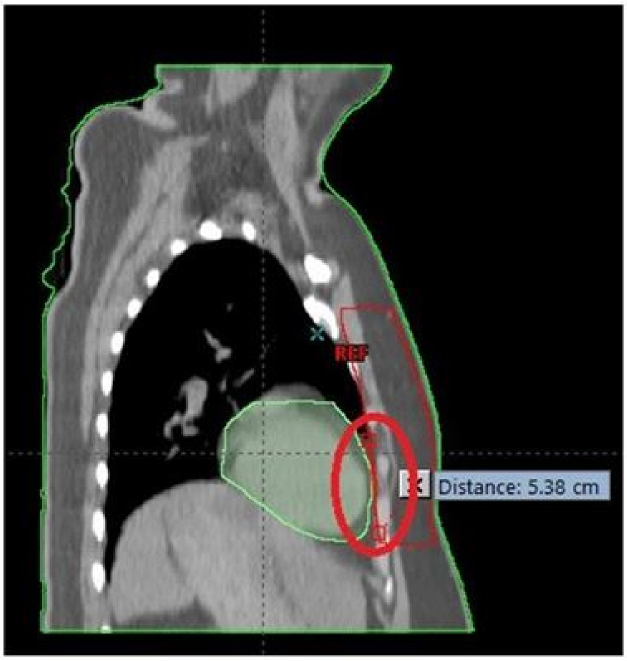

Figure 6. Cardiac Contact Distance (CCD) parasagital the linear distance of direct contact by the heart with the chest wall, measured in parasagittal plane.

Lung volume difference

With deep inspiration, the chest wall expands with an absolute increase in lung volume. This study demonstrated an increase in mean lung volume of 77% (1532 cc) between DIBH and FB scan (3511 cc *vs.* 1979 cc, p 0.01). This Lung volume difference showed marginal statistically significant difference weak positive correlation in reduction in mean heart doses (r=0.25, p-value=0.08). While weak negative correlation was seen in lung volume difference and reduction in mean lung dose with a statistical significant difference (r=-0.28, p-value 0.04).

Maximum heart distance

A mean difference in Maximum Heart Distance (MHD) between FB and DIBH was 21.11% (0.8 cm) suggesting that deep inspiration had decreased the portion of the heart inside the irradiated field. The MHD had a moderate negative correlation to reduction in mean heart dose. There was a significant association in predicting heart dose reduction in univariable model (β-0.54 (CI-0.96-0.12), p-value 0.01 but this has failed to maintain its significance in multivariate model as shown in Figure 6.

The CCD (ax) and CCD (ps)

These parameters were calculated both on FB and DIBH scans and the difference between CCD. Ax and CCD. PS measured on FB and DIBH were statistically significant. In this study the CCDps has moderate negative correlation with mean heart dose reduction as opposed to CCDax which had non-significant correlation. Both these parameters did not show any dependence in the regression models as shown in Figure 6.

The heart chest distance HCD: HCD has positive correlation, with greater distances achieving greater cardiac sparing (Figure 7).

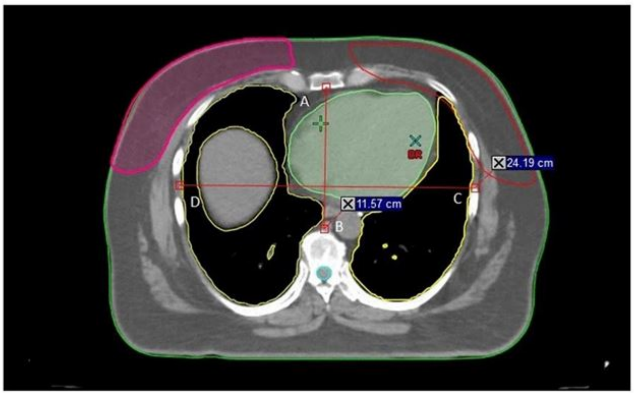

Figure 7. Haller Index (HI) ratio between transverse diameter of the chest and the shortest distance betwwen the sternum and vertebrae.

The change in HCD was significant in both groups (FB and DIBH) with a value increasing from 2.45 ± 0.79 to 3.63 ± 0.69 respectively leading to a significant reduction in both heart and lung doses. This factor independently predicted for cardiac sparing as shown in Figure 8 in both univariate and multivariate analysis.

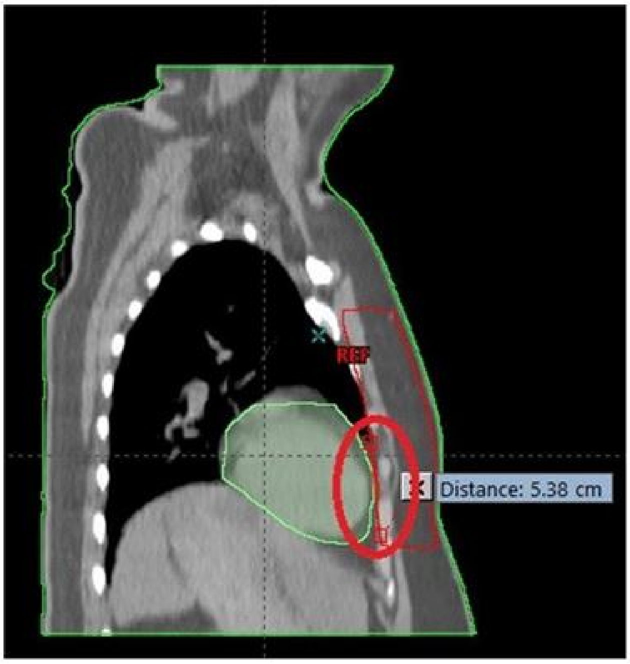

Figure 8. Cardiac Contact Distance (CCD) parasagittal the linear distance of direct contact by the heart with the chest wall, measured in parasagittal plane.

Chest wall separation

There was limited effect of DIBH on CWS. The average mean length in both the scans was 20.3 in FB and 20.5 in DIBH scans (p 0.68) showing no marked difference in the two measurements between the scans. Hence the correlation of CWS, positive with mean lung dose reduction and negative for reduction in mean heart dose, also failed to show any significance. The models were also consistent in not concluding any significance for these values.

Central lung distance

In multivariable model, there was a negative relationship between central lung distance and mean heart dose reduction (β=-1.499, (CI=-2.448-0.549), p-value 0.003) The significant difference in measuring this parameter between FB and DIBH scan was 12% (Figure 4) with moderate negative correlation between reduction in mean heart and lung doses as shown in Figure 5. This value has also predicted for reduction in mean heart dose in both uni and multivariate models.

Haller index

In this study haller index has not shown any statistical significant correlation in reducing mean heart dose. Similarly, the results of regression models were not significant in suggesting any relationship between this and predicting mean heart dose reduction using DIBH technique (β-0.55 (CI-2.89-1.78), p-value 0.63).

Age and BMI

In addition to these, age and BMI failed to predict the reduction in mean heart dose. Furthermore, all these anatomical parameters were also checked against reduction in mean lung dose in DIBH plan, the values are shown in Figure 6 and correlation and mean differences in respective.

Discussion

This study illustrated the impact of using DIBH scans in reduction in heart and lung doses in left sided breast radiotherapy. The results are consistent with previous studies reported in literature. This single institution based study focused on Asian population in resource constrained center. It marks the importance of selection criteria based on anatomical or patient related parameters to identify patients who will benefit from this cost-effective technique.

According to literature, Darby et al. and many others have reported mean heart dose from FB left side breast radiotherapy plans to be 4.9 Gy (range, 0.03 to 27.72) dictating an increase in cardiac morbidity of 5.7% with no risk factors to 9.6% with one risk factors between ages 40-80 years. Furthermore, a systemic review has suggested vast range of differences in mean heart doses reported in Asian population ranging from 7.9 Gy to 3.4 Gy with most of these quoting a reduction to 1.3 Gy using DIBH scans. These results are very much consistent in our study suggesting an average mean heart dose of 5 Gy from FB to 2.5 Gy in DIBH based radiotherapy. Contrary to reduction in heart doses no significant effect in reduction of V_5 V_{10} and V_{20} of both lungs were documented however, there was significant impact in reduction of mean lung dose of left side with marked decrease in ipsilateral lung V_{20} and V_{30} of DIBH plans.

Several studies have aimed to identify factors to devise criteria for patient selection that can identify patients that can make most from this technique. Many of these studies found that the main contributing factor is the volume of contoured heart which remains in the irradiating field. To analyze this, multiple parameters have been formulated in different studies. The results from our study demonstrated that FB-HCD and FB-CLD are two anatomical predictors for estimating the DIBH-induced reduction in mean heart dose in left sided breast radiotherapy plans. Although, these parameters did not have significant impact on mean left lung dose reduction. Register et al found that change in Heart Volume in Field (HVIF) to be an independent predictor without any anatomical parameter stating reduction in mean heart and lung doses.

Tanna, et al. suggested maximum heart depth MHD to be an independent predictor using DIBH scans for those having a cut off ≥ 1 cm heart tissue in field. There were multiple of the studies suggesting numerous other anatomical factors including cardiac contact distance, lung volume differences, and Haller index as significant predictors to select patients upfront that are most suited for DIBH plans. However due to variance, all these studies have failed to give consistent results. Our study has gathered various anatomical predictors from literature and employed the results in the clinical settings that will help in decision making for low-cost FB *vs.* DIBH scans in resource limiting departments. Upfront selection will also help in eliminating the need for performing two scans and can be obtained within minutes of CT acquisition.

The cohort used in this study has a clinical representation as it was comprised of both breast conservation surgery and post mastectomy patients and the results showed that mean heart and lung reduction was appreciated in both irrespective of the surgery offered. The heart mean dose was 3.0 Gy and 3.3 Gy in BCS and Mastectomy patients respectively with insignificant p-value 0.44. This again was in view with the proposed literature review.

With new data suggesting survival advantage, one of the crucial factors that contribute to the increase in mean dose to respective organs at risk is the consideration of regional nodal irradiation including the IMC and supraclavicular nodes. The results of this study included 58% of patients who had clinically node positive disease, 70% of these ended up having nodal irradiation. DIBH significantly decreased mean heart dose to <4 Gy. These results were in concordance with the Yeung et al. study that suggested <4 Gy dose to heart good enough to avoid long term cardiac complications. However, IMC irradiation was not offered to patients in this study group assuming that these patients will derive higher benefit from DIBH technique.

The caveat of this study is the sample size that might have limited the statistical significance of many anatomical predictors including Haller index, CCDps MHD and lung volume difference that already have established their role in selecting patients for DIBH from previous studies in literature. Another explanation could be the anatomical variation in Asian population that hinders these parameters as promising predictors for DIBH based radiotherapy. In addition to these none of these parameters have shown to reduce mean left lung dose reduction in multivariate analysis

The current study is a prospective analysis of dosimetric evaluation and identification of anatomical parameters unlike many in the literature that are retrospective in nature, this allows for more reliable and reproducible results in a clinical setting. Despite this, a larger sample size is required to render external and internal validity of the results of the underlying study.

Conclusion

Deep inspiratory breath hold is an effective method of reducing doses to organs at risk. However, in an economically challenged healthcare environment cost effectiveness can be a question. Hence, anatomical predictors like FB-HCD and FB-CLD can be used to identify patients who can derive maximum benefit from this technique.

Author Contribution

- **Data collection:** Samaha Nawaz, Aqueel Shahid, Raheel Mukhtar
- **Data analysis:** Tabinda Sadaf, Asma Rashid, Muhammad Abubakar
- **Manuscript writing**: Tabinda Sadaf, Asma Rashid, Samaha Nawaz, Amna Munawar
- **Concept:** Tabinda Sadaf, Asma Rashid

Conflict of Interest

Nothing to disclose.

Data Availability Statement for this Work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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