Original paper

Predictors of cardiac and lung dose sparing in DIBH for left breast treatment

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ABSTRACT

This retrospective study of left breast radiation therapy (RT) investigates the correlation between anatomical parameters and dose to heart or/and left lung in deep inspiration breath-hold (DIBH) compared to free-breathing (FB) technique. Anatomical parameters of sixty-seven patients, treated with a step-and-shoot technique to 50 Gy or 50.4 Gy were included. They consisted of the cardiac contact distances in axial (CCD_{ax}) and parasagittal (CCD_{ps}) planes, and the lateral heart-to-chest distance (HCD). Correlation analysis was performed to identify predictors for heart and lung dose sparing. Paired t-test and linear regression were used for data analysis with significance level of $p = 0.05$. All dose metrics for heart and lung were significantly reduced with DIBH, however 21% of patients analyzed had less than 1.0 Gy mean heart dose reduction. Both $FB-CCD_{ps}$ distance and FB-HCD correlated with FB mean heart dose and mean DIBH heart dose reduction. The strongest correlation was observed for the ratio of $FB-CCD_{ps}$ and FB-HCD with heart dose sparing. A $FB-CCD_{ps}$ and FB-HCD model was developed to predict DIBH induced mean heart dose reduction, with 1.04 Gy per unit of $FB-CCD_{ps}$/FB-HCD. Variation between predicted and actual mean heart dose reduction ranged from −0.6 Gy to 0.6 Gy. In this study, $FB-CCD_{ps}$ and FB-HCD distance served as predictors for heart dose reduction with DIBH equally, with $FB-CCD_{ps}$/FB-HCD as a stronger predictor. These parameters and the prediction model could be further investigated for use as a tool to better select patients who will benefit from DIBH.

1. Introduction

Radiation therapy (RT) is an effective and well-established adjuvant treatment to provide local tumor control while enabling breast-conservation in women with early-stage breast cancer [1]. However, cardiac toxicity following breast cancer RT is a concern for patients with left-sided breast cancer due to anatomical proximity of the heart to the tumor target volume. Clinical studies show that when compared to patients treated with surgery alone, cardiac death occurred 1.7 times more in patients receiving adjuvant whole breast RT [2]. Darby et al. demonstrated that mean heart dose is proportional to the risk of ischemic heart disease, suggesting that the rate of major coronary events increases linearly with mean dose to the heart at the rate of 7.4% per Gy [3].

Besides heart toxicity, radiation related lung toxicity is also a concern in left-sided breast RT. Grantzau et al. conducted a large case-control study (n = 23,627) of the incidence of secondary primary lung cancer among early breast cancer patients who received post-operative

RT including those patients who also received adjuvant therapy or chemotherapy [4]. Their study indicated that the excess relative risk of lung cancer increased linearly by 8.5% per Gy in patients diagnosed with a second primary lung cancer, five or more years after breast cancer treatment.

Various techniques have been used to reduce dose to the heart and the left lung for breast cancer patients, including prone positioning [5], proton therapy [6], deep inspiration breath-hold (DIBH) [7], intensity modulated RT [8], and accelerated partial breast irradiation [9]. The most common of these techniques is DIBH and there is consensus that DIBH is an effective motion management technique to spare heart and lung dose in left breast cancer RT [7,10,11]. Reduction of the relative volume of irradiated ipsilateral lung has also been reported in DIBH RT [7]. During deep inspiration, lung expansion and diaphragmatic movements displace the heart laterally, posteriorly and inferiorly, increasing the distance between the chest wall and the heart, thus reducing the volume of the heart that receives a high dose.

DIBH adds major complexity and time to the simulation, planning

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and RT delivery process, and prolongs the daily treatment delivery time. In addition, not every patient with left breast cancer is a suitable candidate for DIBH. In a substantial proportion of patients, comparative dosimetry demonstrates insufficient dose reduction from DIBH to warrant the radiation course to be given in daily deep breath hold [12–15]. However, the utility of DIBH in terms of heart dose reduction has been challenging to predict in the individual patient. While the heart-sparing gains achieved by DIBH are likely related to the anatomical relationship between the heart, chest wall and breast, solid predictive metrics have been inconsistent [12,16–18].

Therefore, in clinical practice this predictive information is not available until after the patient has been subjected to two CT simulation scans, one in free-breathing and a second in DIBH, and comparative dosimetry in both free-breathing and DIBH has been computed [12]. Added procedure time, radiation exposure to contralateral lung and breast from the 2nd CT, dosimetry time and patient anxiety regarding the uncertain necessity of DIBH, could be prevented by a robust *a priori* predictor of the gains in heart dose achieved by DIBH in the individual patient. Such a capability would provide an important decision aid to help balance the known trade-offs of DIBH with the potential benefits for informed decision making and patient triage [12,16].

The purpose of this study was to develop and evaluate practical and easily clinically applicable anatomical parameters that predict DIBH-induced benefits over the free-breathing (FB) technique in terms of cardiac and lung dose sparing for left-sided breast radiation. Specifically, we investigated candidate parameters by correlating anatomical parameters with dosimetric data with the goal of developing a linear model to predict DIBH induced heart dose reduction.

2. Materials and methods

2.1. Patient population

A retrospective review study, approved by the institutional review board (IRB), was performed to quantitatively assess 67 consecutive women with left-sided breast cancer. All patients were treated with adjuvant whole breast RT at our institution between 2014 and 2017 using a Calypso Surface Beacon Transponder (Varian Medical Systems, Palo Alto, CA) guided DIBH technique [19]. All treatment plans included two parallel opposed step-and-shoot tangential fields. The prescription for the whole breast RT was either 50 Gy (2 Gy/fraction) or 50.4 Gy (1.8 Gy/fraction). Most patients also received a 10–14 Gy boost to the lumpectomy cavity. Boost dose was not considered in the current study. Fifty-seven of the patients were randomly selected for correlation analysis and model derivation and the remaining ten patients were used to test the model. Table 1 summarizes patient and treatment characteristics.

2.2. Simulation and treatment – FB and DIBH

All patients received computer tomography (CT) (GE Lightspeed 16, GE HealthCare) scans in the supine position lying on an inclined breast board. Before simulation, the patients underwent audio coaching and were asked to perform successive inhalation breath holds at about 80% of the maximum inhalation capacity for approximately 20 s. An anteroposterior sternum marker (BB) was placed and marked at the CT origin surrogate position during FB and its longitudinal displacement between FB CT and DIBH CT determined the DIBH mark location [20]. This longitudinal displacement of the BBs was recorded. The Varian Real-time Position Management (RPM) Respiratory Gating System (Varian Medical Systems, Palo Alto, CA) was utilized to monitor the patient breath hold status during DIBH CT simulation. Additional lateral marks, in the same axial plane as the BB on the sternum were used for visual monitoring and as reference for consecutive treatment on the linear accelerator (LINAC). During simulation, the RPM reflective block was placed on the patient as close to the Xyphoid process as possible.

Table 1
Patient, tumor and treatment characteristics (n = 67).

Category	Distribution	
Median Age (Range)	54	(32–78)
T category		
T1a	4	
T1b	7	
T1c	25	
T2	18	
T3	2	
Tis	11	
Nodal category		
N0	38	
N1	11	
N1a	10	
Nx	8	
Grade		
1	11	
2	20	
3	36	
Histology		
DCIS	15	
IDC	45	
ILC	7	
Surgery		
Lumpectomy	65	
None	2	
Total Dose/Dose per Fraction		
50/2	55	
50.4/1.8	12	
Systemic Therapy		
Chemotherapy	20	
Tamoxifen	2	
Trastuzimab	2	

Following standard clinical DIBH practice [21], patients underwent a FB CT scan immediately followed by a DIBH CT scan. For the DIBH CT scan the patient was instructed to hold their breath at the level when the lasers coincided with the sternal (primary) and lateral (secondary) DIBH mark. This was monitored with RPM and visually observed through in-room cameras (Pelco Corp., CA).

2.3. Contouring and treatment planning

Both the FB and DIBH CT image sets were transferred to the Monaco Treatment Planning System (TPS) (Elekta Inc., Stockholm, Sweden). Clinical target volume was contoured based on the Radiation Therapy Oncology Group breast atlas (www.rtog.org). The cardiac volumes were contoured based on NSABP B-39 protocol [22]. Lung volumes were generated with the EZ Sketch tool of the TPS. The whole breast treatment volume was defined by external radiopaque wires placed at the infraclavicular, midsternal, inframammary and mid-axillary borders by attending physicians during CT simulation.

For dose assessment, the FB CT images were rigidly co-registered with the DIBH CT to match the breast and chest wall within the treatment fields. The contours of the heart and left lung on the FB CT were mapped onto the DIBH CT (Fig. 1). All contours were evaluated by a physician for accuracy and completeness. After contouring and registration were completed, the DIBH CT image set was transferred to the XiO or Monaco TPS (Elekta Inc., Stockholm, Sweden) for planning. All breast plans consisted of two tangentially opposed isocentrically positioned beams using a forward planned step-and-shoot technique, with 6 MV, 10 MV, 18 MV beams or a mixture of energies to achieve dose homogeneity. The treatment beams from the DIBH plans were transferred to the FB CT images for comparison planning. The FB breast plans were modified by adjusting isocenter position, beam angle and
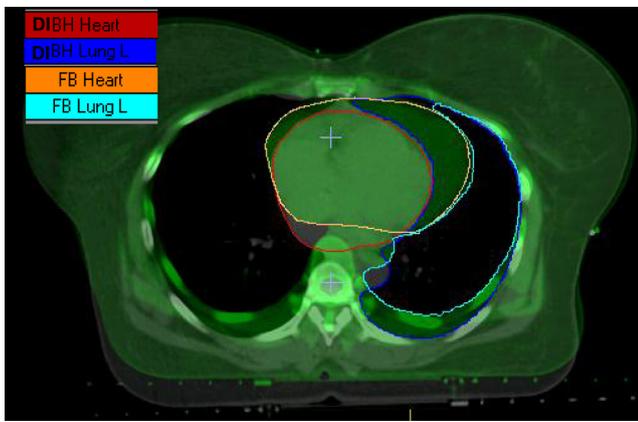
Fig. 1. Registration and fusion of FB (green, secondary) and DIBH (gray, primary) CT images. Contours of heart and left lung of FB were mapped on DIBH CT Image. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

monitor unit (MU), to achieve the same breast coverage as their corresponding DIBH plans (Fig. 2). Dosimetric values (mean dose, and dose-volume histograms (DVH) – V_3, V_5, V_{10}, and V_{20}) of the heart and left lung were recorded.

2.4. Cardiac contact distance and lateral heart-to-chest distance

The cardiac contact distance (CCD) is an anatomical parameter as illustrated in Fig. 3. For this work, we measured the CCD in both the axial (CCD_{ax}) and parasagittal (CCD_{ps}) planes in FB CT based on the method reported by Hiatt et al [23]. In the axial plane, the CCD_{ax} is defined as the shortest linear distance between the medial point of contact of the cardiac silhouette with the chest wall to the lateral point of contact with chest wall at the level of the top of the right hemidiaphragm. In a parasagittal plane, CCD_{ps} is determined as the linear distance of direct contact by the heart with the chest wall, measured at the midpoint of the left hemithorax as identified in the transverse and coronal plane. The lateral heart-to-chest distance (HCD) is defined at the same axial slice as CCD_{ax}, and it is the distance between the most lateral point of the heart and the chest wall.

2.5. Statistical analysis

DVHs were extracted and compared for each of the DIBH and FB plans. For both the heart and the left lung, the mean dose (D_{mean}) and V_5, V_{10} and V_{20} were measured and compared. Paired t-test (null hypothesis of zero difference in means) and linear regression were calculated using statistical computing language R (version 3.3; R Foundation for Statistical Computing, Vienna, Austria) [24], with statistical significance defined at the $p = 0.05$ level. The mean heart dose reduction linear prediction model was developed based on the method described by Wilkinson & Rogers [25]. In addition to the testing set, we

also performed cross validation using random subsampling [26] to reduce potential influence of biases in the data.

3. Results

3.1. Dosimetric comparison

As expected, DIBH significantly reduced dose to the heart and the left lung compared to FB ($P < 0.001$), and the DIBH-induced reduction of heart and lung doses was highly variable within patient cohort, as illustrated by the range, mean values and standard deviations (SD) of dose metrics for the heart and left lung in Table 2. The mean heart dose was 3.7 ± 1.4 Gy in FB compared to 1.7 ± 0.5 Gy in DIBH, which is a reduction by $2.0 (\pm 1.2)$ Gy on average. However, in 12 patients (21%) the mean heart dose reduction achieved by DIBH was less than 1.0 Gy. The average mean dose to the left lung was 7.5 ± 2.4 Gy for DIBH and 8.9 ± 3.6 Gy for FB. In 29 patients (50.9%), the V_{20} value of the heart was 0% when using the DIBH technique compared with an average of 4.0% when using FB. Among those 29 patients, 13 had a V_{10} value of 0% with DIBH. Twenty-six patients (45.6%) had less than 1.0 Gy mean dose reduction in the left lung and 5 patients (8.8%) received higher mean dose to the left lung (0.2–1.3 Gy) in DIBH compared to FB.

3.2. Correlation between FB-CCD, FB-HCD and OAR dose sparing

The measured $FB-CCD_{ax}$, $FB-CCD_{ps}$ and FB-HCD were highly variable. The $FB-CCD_{ax}$ distance ranged from 0.4 to 11.1 cm, the $FB-CCD_{ps}$ distance ranged from 0 to 6.6 cm, and the FB-HCD distance ranged from 1.4 to 4.3 cm. The $FB-CCD_{ps}$ distance showed a positive linear correlation with the FB mean heart dose ($r = 0.63$; $p < 10^{-7}$) and DIBH-induced mean heart dose reduction ($r = 0.73$; $p < 10^{-10}$) (Fig. 4a and c). Every cm increase of $FB-CCD_{ps}$ resulted in 0.58 Gy increase in mean heart dose reduction.

The FB-HCD demonstrated a negative linear correlation with the FB mean heart dose ($r = -0.65$; $p < 10^{-7}$) as well as mean heart dose reduction by DIBH ($r = -0.71$; $p < 10^{-10}$) (Fig. 4b and d). The shorter the FB-HCD, the higher the mean heart dose reduction was, with a gradient of 1.17 Gy/cm. Neither $FB-CCD_{ps}$ nor FB-HCD showed a correlation with DIBH mean heart dose (Fig. 4c and Fig. 4d, dashed line). The correlation between $FB-CCD_{ps}$ and FB-HCD was weak (Fig. 5a), suggesting that no interdependence was present. The combination of FB-CCD and FB-HCD increased the prediction. The ratio of $FB-CCD_{ps}$ to FB-HCD was highly predictive of DIBH-induced mean heart dose reduction ($r = 0.80$; $p < 10^{-10}$) (Fig. 5b).

3.3. Correlation between lung volume and OAR dose sparing

There was weak correlation between FB lung volume and mean lung dose reduction (Fig. 6a, $r = 0.33$; $p = 0.012$); as well as weak correlation between lung volume change (DIBH lung volume – FB lung volume) and mean DIBH heart dose (Fig. 6b, $r = 0.44$; $p = 0.0006$). No correlations greater than 0.26 (corresponding to $p = 0.05$ for N = 57)
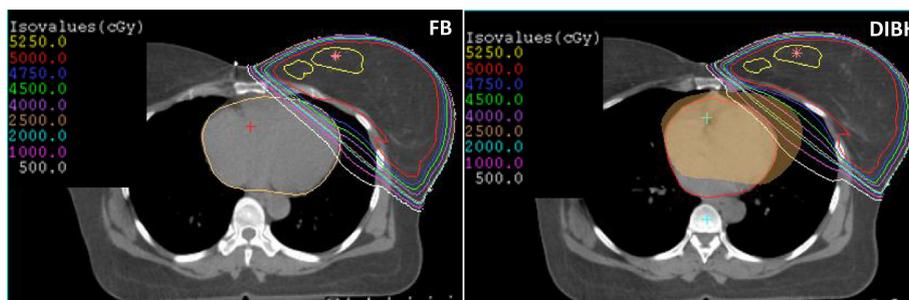
Fig. 2. Isodose distribution of the same plan calculated in FB CT (left panel) and DIBH CT (right panel) images.
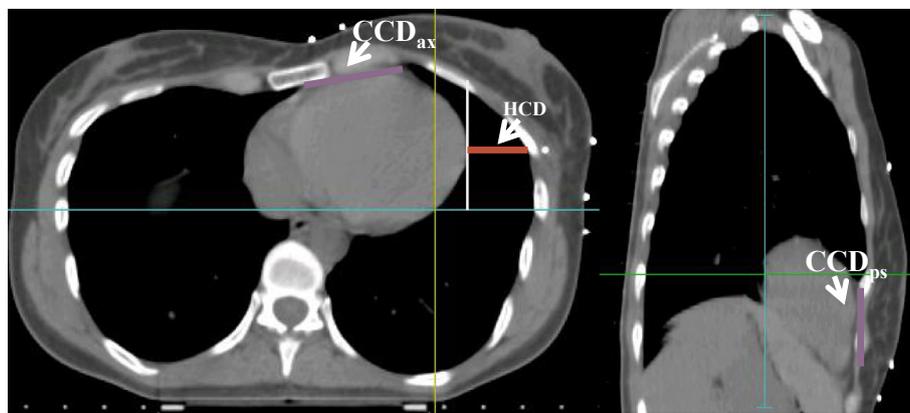
Fig. 3. Cardiac Contact Distance (CCD) as previously described [23] and lateral heart-to-chest distance (HCD) in FB CT scan. Please refer to Materials and Methods section for detailed description.

Table 2
Dosimetric parameters (n = 57).

		Heart						Left Lung			
		D_{mean} (Gy)	V_3 (%)	V_5 (%)	V_{10} (%)	V_{20} (%)	V_{25} (%)	D_{mean} (Gy)	V_5 (%)	V_{10} (%)	V_{20} (%)
FB	Mean	3.7	21.0	10.2	5.9	4.0	3.5	8.9	31.8	22.7	16.2
	SD	1.4	7.2	4.4	3.7	3.0	2.8	3.6	10.9	9.4	8.0
DIBH	Mean	1.7	8.1	1.9	0.4	0.0	0.0	7.5	27.4	18.8	13.0
	SD	0.5	3.9	1.3	0.4	0.1	0.0	2.4	7.7	6.3	5.1
FB-DIBH (Δ)	Mean	2.0	13.0	8.4	5.6	3.9	3.5	1.4	4.4	3.8	3.2
	SD	1.2	4.9	3.7	3.4	3.0	2.8	1.5	4.1	3.8	3.5
P value (FB vs. DIBH)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

were found among lung volume and other predictors, FB-CCD$_{ps}$ and FB-HCD (data not shown).

3.4. Prediction model for DIBH induced mean heart dose reduction

A linear prediction fitting model was generated based on the data of 57 patients to predict the mean heart dose reduction (Δ mean heart dose) by DIBH. Model fitting produced intercept and slope of 0.69 ± 0.16 and 1.04 ± 0.11 Gy respectively with residual standard error of 0.75 on 55 degrees of freedom.

$$\Delta \text{ mean heart dose(Gy)} = 0.69 + 1.04 * (FB-CCD_{ps}/FB-HCD) \quad (1)$$

The random subsample cross validation on the 57 point datasets produced a root mean square error of differences between predicted and actual test samples of 0.10 Gy indicating stability of the model in this dataset. Ten cases withheld from model estimation were used to test the accuracy of the linear prediction model. The FB-CCD$_{ps}$ and FB-HCD values were obtained and actual mean heart dose reduction by DIBH was calculated. Predicted mean heart dose reduction was derived from the model. The data is presented in Table 3. The difference between the true and predicted heart dose deduction ranged from −0.6 to 0.6 Gy with a mean of 0.04 and standard deviation of 0.41 Gy.

4. Discussion

The results of our study demonstrate that the free-breathing cardiac contact distances in the parasagittal plane (FB-CCD$_{ps}$) and the free-breathing lateral heart-to-chest distance (FB-HCD) are two anatomical predictors for estimating the DIBH-induced reduction in mean heart dose in breast cancer patients. These clinically applicable parameters can be easily obtained within minutes, just after the acquisition of the CT imaging during CT simulation and without the need to obtain a second CT in DIBH and dosimetry planning, to determine the benefit of

DIBH in individual patients. Our findings can thus be translated readily into the clinical routine and care of patients with left breast cancer. FB-CCD$_{ps}$ and FB-HCD can be employed in the clinical decision making regarding the relative dosimetric benefits of the more complex DIBH treatment technique in individual patients. Such simple, low-cost and readily clinically applicable tools are becoming increasingly important to streamline clinical workflows, utilization of resources for an ever-increasing number of patients in an ever more economically-challenged health care environment. If patients, who do not derive substantial heart dose reduction from DIBH can be identified early in the planning process, additional imaging (DIBH CT) and ensuing radiation exposure to the lungs and contralateral breast, procedure time, dosimetry time, daily treatment time, health care expense, and ultimately patient anxiety regarding the DIBH process can be reduced.

Interestingly, when the analysis was reversed by extracting the anatomical parameters (CCD$_{ps}$, CCD$_{ax}$ and HCD) from the DIBH CT images, no correlation with mean heart dose reduction was identified (data not shown). Thus, it is essential to acquire a FB CT to measure the anatomical parameters (FB-CCD$_{ps}$ and FB-HCD) before deciding whether a DIBH CT is needed.

Our study showed, for the first time, the utility of combining FB-CCD$_{ps}$ and FB-HCD. This combination exploited the independent metrics of the heart's proximity to the anterior chest wall and the separation of the heart from the lateral chest wall, to increase the predictive accuracy. Various factors have been examined to determine potential predictors for cardiac dose in left sided breast RT and results have been inconsistent. The maximum heart distance (MHD), described in a study of 50 patients by Taylor et al. [17] and defined as the maximum distance between the anterior cardiac contour and the posterior tangential field edges in CT images, showed a strong correlation with both the mean heart dose and biological equivalent dose. However, in another study by Borger et al. [18], MHD derived from the snapshot of the 2D simulator films, did not prove predictive of heart
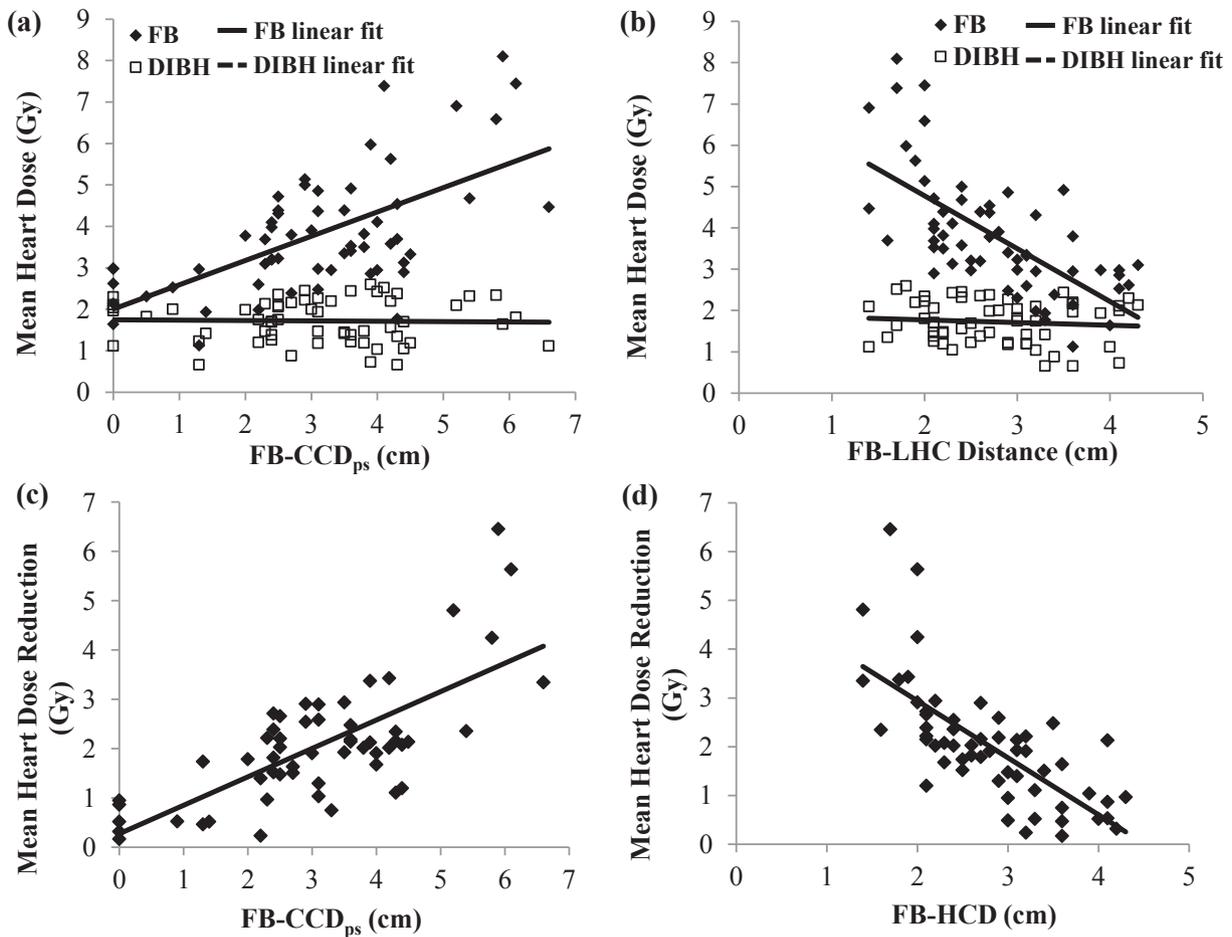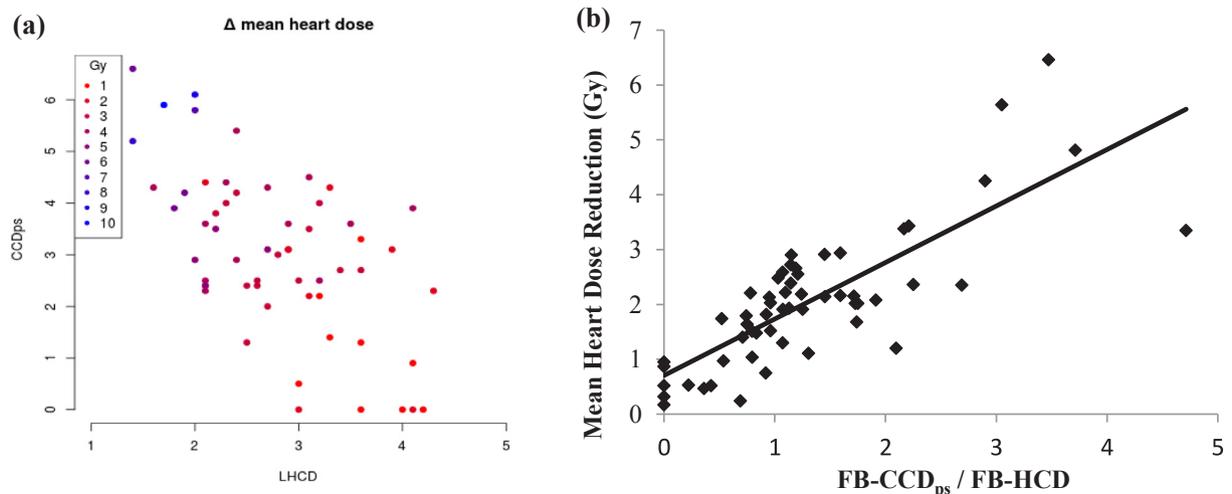
Fig. 4. Correlation between CCDps and mean FB and DIBH heart dose (**a**, r = 0.63 for FB; p < 10^−7); HCD and mean FB and DIBH heart dose (**b**, r = −0.65 for FB; p < 10^−7); CCD$_{ps}$ and mean heart dose reduction (**c**, r = 0.73; p < 10^−10); HCD and mean heart dose reduction (**d**, r = −0.71; p < 10^−10).

disease. The discrepancy between the two studies may be related to the variable definition of MHD. It may also be attributable to organ motion and overestimation of heart volume as the 2D derived MHD. In addition, MHD is not a pure anatomical parameter and depends on the arrangement of the tangential field. Therefore, the full planning and tangent field placement process have to be carried out in order to obtain MHD. Similarly, the parameter heart volume in field (HVIF) described by Register et al. [16] identified as a prominent predictor of mean heart

dose reduction by DIBH. This parameter again required tangent fields to be placed for an assessment and prediction of heart sparing. In contrast, our combined FB-CCD$_{ps}$ and FB-HCD leverages both 3D anatomy while reducing the 3D CT-based information to 2 plain numbers in a basic formula that can be readily applied based on a simple chest CT without the needs of tangent field placement.

Our results for FB-CCD$_{ps}$ (Fig. 4a) are consistent and confirm the findings by Rochet et al. [12], who suggest that longer FB-CCD$_{ps}$

Fig. 5. Correlation between FB-CCD$_{ps}$ and FB-HCD for mean heart dose reduction (**a**); FB-CCD$_{ps}$/FB-HCD and mean heart dose reduction (**b**, r = 0.80; p < 10^−10).
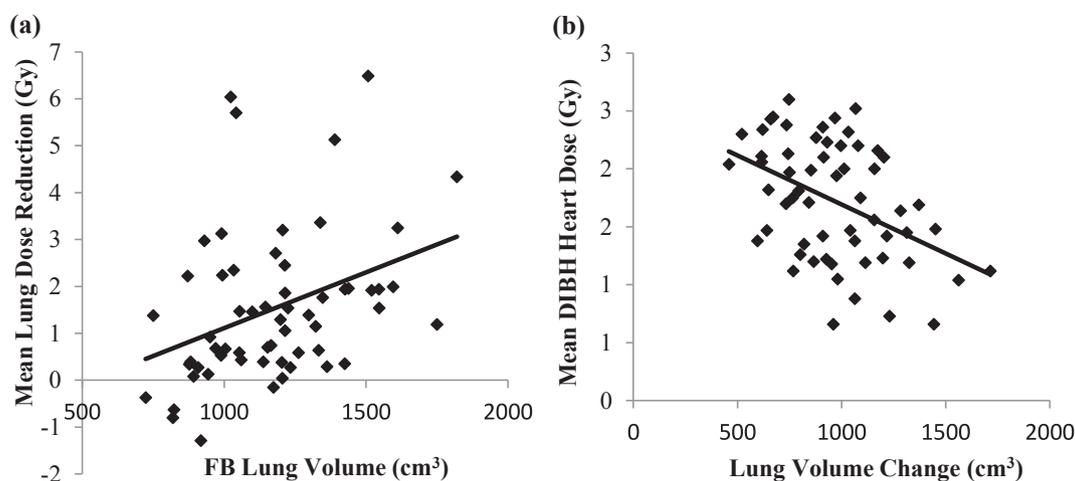
Fig. 6. Correlation between FB lung volume and mean lung dose reduction (**a**, r = 0.33; p = 0.012); Lung volume change by DIBH and mean DIBH heart dose (**b**, r = −0.44; p = 0.0006).

Table 3
Mean heart dose deduction prediction model test (n = 10).

Patient	FB-CCD$_{ps}$ (cm)	FB-HCD (cm)	Δ mean heart dose (Gy)		
			Actual	Predicted	Difference
1	2.0	3.6	1.1	1.3	−0.2
2	1.9	3.2	1.1	1.3	−0.2
3	0.2	4.3	0.7	0.7	0.0
4	1.8	3.9	0.8	1.2	−0.4
5	4.5	1.8	3.9	3.3	0.6
6	3.6	1.9	3.2	2.7	0.5
7	3.3	2.6	2.5	2.0	0.5
8	2.4	2.7	1.0	1.6	−0.6
9	3.7	1.8	2.8	2.8	0.0
10	3.4	2.2	2.5	2.3	0.2

predicted higher cardiac dose, but FB-CCD$_{ax}$ showed no correlation with cardiac dose. To our knowledge, this study is the first to report the use of FB-HCD distance as a predictor for cardiac dose sparing during DIBH. Utilization of FB-HCD has the advantage of being defined only in the axial FB CT slice, enabling a rapid measurement after the FB CT scan.

The linear model developed in our study suggests that on average, every unit increase of FB-CCD$_{ps}$/FB-HCD leads to a 1.04 Gy heart dose reduction based on the linear relationship between FB-CCD$_{ps}$/FB-HCD and heart dose reduction (Fig. 5b). This suggests that a substantial proportion of patients (21% in our cohort) may derive a heart dose reduction of less than 1 Gy with DIBH over the FB plan. In our patients with an FB-CCD$_{ps}$/FB-HCD ratio of 0.5 or less, the average mean heart dose reduction was 0.58 Gy. While a true threshold, below which heart dose reduction would be judged ineffective, is difficult to define based on current data, our predictive model would allow to set a cut-off based on institutional preferences and the literature and ultimately the individual patient's preference, below which the complexity of the DIBH may not be deemed warranted.

Limitations. It should be noted that this work only included patients receiving whole breast treatment with two tangent step-and-shoot fields. Thus, our conclusions may not apply to post-mastectomy chest wall treatment, or cases including supraclavicular or IMC treatment fields [27,28], or treatment with complex delivery techniques, such as Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) [29,30]. Additionally, no practical recommendations have been reported, which describe the range of FB-HCD distance and FB-CCD$_{ps}$ for which the benefit of DIBH technique will outperform the additional efforts and costs associated with its use.

Another limitation is that only ten test cases were used to test the prediction model, though cross validation was used to reduce bias and linear model was built with 57 data points, the absolute error in prediction was approximately 20% on average in the test set. Ten was chosen because only a total of sixty-seven cases were approved in the IRB. Lastly, the baseline cardiac health for patients in the study group was not considered. The study by Simonetto et al. suggested that the DIBH technique would benefit the most for patients with a favorable tumor prognosis, high mean heart dose or high baseline ischemic heart disease [31]. The accuracy of FB-HCD distance and FB-CCD$_{ps}$ as predictors should be validated by further independent studies.

5. Conclusion

Our study demonstrates that our combined parameters of simply measured anatomical distances taken from FB CT scans can predict DIBH-induced mean heart dose reduction in breast cancer patients. Every unit increase in the FB-CCD$_{ps}$/FB-HCD ratio corresponds to an additional 1.04 Gy mean heart dose reduction achieved by DIBH. This easily implementable, and low-cost parameter is available with very little time commitment and early in the simulation process without the need for a CT in breath hold, treatment planning or dosimetry, and may aid the decision making for the use of DIBH in individual patients. Our results require validation with a larger independent cohort.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.09.240.

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