



Cardiac exposure in left-sided breast cancer patients undergoing deep inspiratory breath hold radiation therapy

Huijun Zhu^{1#}, Huiwen Sun^{2#}, Jiaming Zhang^{1#}, Yiting Xie¹, Jacek Jassem³, Pierfrancesco Franco^{4,5}, Weiliang Sun², Wenqi Liu¹, Haiying Yue¹

¹Department of Radiation Oncology, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China; ²Department of Oncology, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China; ³Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; ⁴Department of Translational Medicine (DIMET), University of Eastern Piedmont, Novara, Italy; ⁵Department of Radiation Oncology, 'Maggiore della Carità' University Hospital, Novara, Italy

Contributions: (I) Conception and design: H Yue, W Liu; (II) Administrative support: H Zhu, Y Xie; (III) Provision of study materials or patients: H Zhu, H Yue; (IV) Collection and assembly of data: H Sun, J Zhang; (V) Data analysis and interpretation: W Sun, H Zhu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Wenqi Liu, MD, PhD; Haiying Yue, MD, PhD. Department of Radiation Oncology, The Second Affiliated Hospital of Guangxi Medical University, 166 East University Road, Nanning 530007, China. Email: liuwenqigx@163.com; 614963036@qq.com.

Background: Left-sided breast cancer (BC) patients undergoing post-operative radiation therapy (PRT) may have higher risk of late cardiovascular toxicity, which may be reduced by heart-sparing RT techniques. This study evaluated dosimetric parameters of the deep inspiration breath hold (DIBH) compared to free breathing (FB) RT. We analysed factors impacting on doses to the heart and cardiac substructures and sought anatomic factors allowing patient selection for DIBH.

Methods: The study group included 67 left-sided BC patients who underwent RT after breast-conserving surgery or mastectomy. Patients treated with DIBH were trained to hold their breath. Computed tomography (CT) scans were performed in both FB and DIBH patients. Plans were generated using 3-dimensional (3D) conformal RT. The dosimetric variables were obtained from dose-volume histograms, and the anatomical variables were derived from the CT scans. The variables in the two groups were compared by *t*-test, the U test, and the chi-squared test. Correlation analysis was performed using Pearson's correlation coefficient. Receiver operating characteristic curves were used to analyze the efficacy of the predictors.

Results: Compared to the FB, DIBH allowed for a mean dose reduction to the heart, left anterior descending coronary artery (LAD), left ventricle (LV), and right ventricle (RV) by 30.0%, 38.7%, 39.3%, and 34.7%, respectively. DIBH markedly increased the heart height (HH), heart chest wall distance (HCWD), the mean distance between the ipsilateral lung and breast (DBIB), and decreased the heart-chest wall length (HCWL) ($P < 0.05$). The different value of HH, DBIB, HCWL, and HCWD between DIBH and FB were 1.31, 1.95, -0.67, and 0.22 cm, respectively (all $P < 0.05$). Δ HH was an independent predictor of the mean dose to the heart, LAD, LV, and RV, with the area under the curve values of 0.818, 0.725, 0.821, and 0.820, respectively.

Conclusions: DIBH significantly reduced the dose to the entire heart and its substructures in left-sided BC patients undergoing post-operative RT. Δ HH predicts the mean dose to the heart and its substructures. These results may inform patient selection for DIBH.

Keywords: Breast cancer (BC); radiotherapy; deep inspiration breath hold (DIBH); heart protection

Submitted Mar 01, 2023. Accepted for publication May 16, 2023. Published online May 29, 2023.

doi: 10.21037/gs-23-160

View this article at: <https://dx.doi.org/10.21037/gs-23-160>

Introduction

Post-operative radiation therapy (PRT) for breast cancer (BC) has been shown to considerably reduce the risk of locoregional recurrence and death (1-3). PRT includes the breast or chest wall, and in patients with high-risk features—additionally lymph node areas (4). Patients with operable BC carry a relatively good prognosis with 5-year overall survival (OS) in the range of 80–90% (5). Thus, late side effects from treatment may be highly relevant. One of the most common long-term health hazards of PRT is cardiovascular disease (CVD) (6). Notably, the dose administered to cardiac substructures is associated with cardiac events (6,7). In left-sided BC, a relevant dose can be received by the left ventricle (LV) and coronary arteries (8), given the close proximity of the heart to the target volume. Hence, left-sided BC patients are at higher risk of late-onset CVD (9). For example, in the study of Darby *et al.*, the risk of major coronary events increased linearly with the mean dose (D_{mean}) to the heart, at a rate of 7.4% per 1 Gy (10). Nilsson *et al.* demonstrated that the left anterior descending coronary artery (LAD) dose is strongly associated with the risk of high-grade coronary artery stenosis in left-sided BC patients (11). Alternatively, studies showed the mean heart dose and doses to cardiac substructures to be associated with elevated cardiac enzymes. Skyttä *et al.* found a positive correlation between D_{mean} to cardiac substructures and the cardiac troponin T serum level (12). The percentage volume of the LV receiving ≥ 2 Gy correlated significantly with NT-proBNP (13).

Techniques accounting for breathing movements, such

as deep inspiration breath hold (DIBH) and inspiration breath hold (IBH), minimize unnecessary lung and heart RT doses (14,15). During DIBH and IBH, the lungs are inflated, the respiratory motion is minimized, and the heart position changes, leading to a lower exposure than with free breathing (FB) (16). However, breath-holding techniques are associated with additional time, costs, and a high workload. It is, therefore, essential to identify patients who may mostly benefit from them.

This study aimed to retrospectively examine the plausibility, feasibility, and potential benefits of DIBH, and to identify anatomical variables identifying patients likely to benefit most from this procedure. For this purpose, we compared RT doses to normal tissues in left-sided BC patients irradiated using DIBH and FB, and investigated the association between several anatomic features and dose exposure to the heart. We present this article in accordance with the STARD reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gs-23-160/rc>)

Methods

Patients

We retrospectively analyzed the data including the parameters of CT planning scan images and Radiation plan for 67 left-sided BC consecutive patients from The Second Affiliated Hospital of Guangxi Medical University who received RT after breast-conserving surgery (BCS) or mastectomy. Due to the retrospective study design, informed consent was not required. The study was approved by The Second Affiliated Hospital of Guangxi Medical University Ethics Committee (approval No. 2023-KY0003). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Clinical staging and molecular subtype of all patients followed the Guidelines of the Chinese Society of Clinical Oncology (17). Three days before the CT simulation, patients in the DIBH group were trained by a physical therapist to hold their breath. The CT scans started after the chest had stabilized at the maximum height. A minimal breath-hold duration of at least 30 seconds was considered suitable (18). FB patients maintained smooth breathing during scanning. Real-time position management (RPM; Varian Medical Systems, Palo Alto, CA, USA) was used to measure the patients' respiration. An overview of the detailed procedure is shown in *Figure 1*.

Highlight box

Key findings

- DIBH enables a considerable reduction of radiation therapy doses to the heart.
- Δ HH is an independent predictor of DIBH benefit.

What is known and what is new?

- DIBH have showed the dosimetric benefits to the heart and cardiac substructures.
- We showed that anatomic characteristics correlate with cardiac doses and may inform patient selection for DIBH.

What is the implication, and what should change now?

- This study may contribute to optimizing of RT in breast cancer patients. Prospective clinical trials are warranted to confirm our findings.

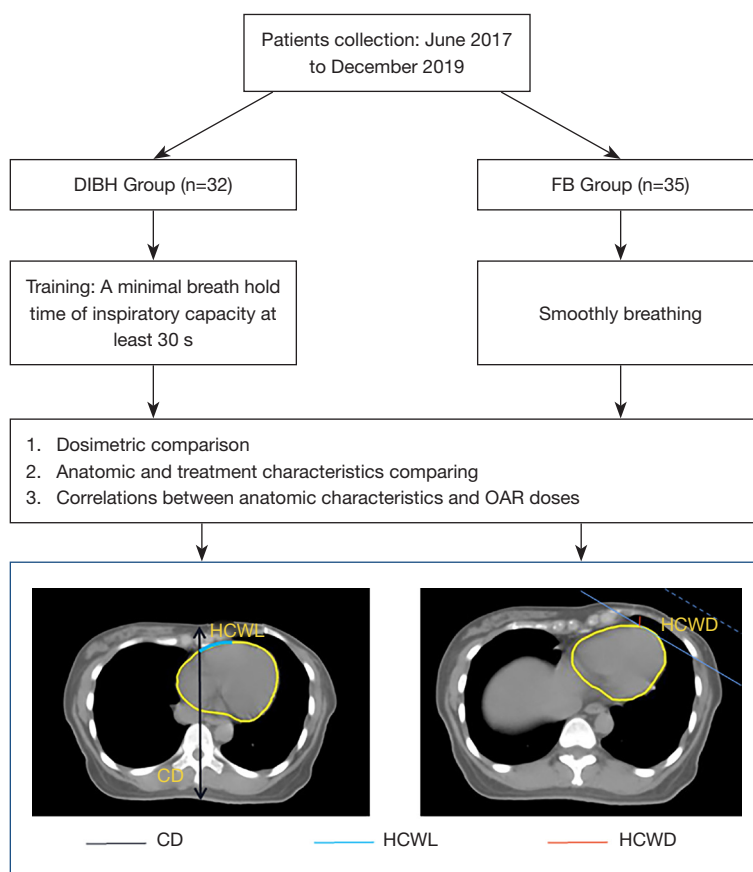


Figure 1 Flow chart for enrollment of left-sided breast cancer patients using DIBH and FB radiotherapy planning. DIBH, deep inspiration breath hold; FB, free breathing; OAR, organ at risk; CD, chest depth; HCWL, heart chest wall length; HCWD, heart chest wall distance.

Dosimetric assessment

The target regions and organs at risk (OARs), including heart, lungs, LAD, LV, and right ventricle (RV), were contoured according to the Radiation Therapy Oncology Group guidelines (19). In patients who underwent mastectomy, RT volumes included the chest wall, while, in patients after BCS, target volumes comprised the whole breast. Regional lymph nodes were irradiated in patients with high-risk features. All patients received 3-dimensional conformal RT. The Eclipse treatment planning system (TPS; Eclipse version 13.6, Varian Medical Systems) was used for contouring and planning. The prescribed dose was defined as 50 Gy in 25 fractions to the planning target region. Additionally, patients after BCS received a 10 Gy sequential boost dose to the tumor bed. Before RT delivery, weekly cone-beam computed tomography was performed to verify position and examine the treatment reproducibility.

The doses to the heart, LV, RV, and LAD were analyzed using the Dmean and maximum dose (Dmax). Additionally, a DVH was created to evaluate the dosimetric parameters of 5 and 20 Gy to the ipsilateral lung and 25 Gy to the heart.

Anatomic and treatment characteristics

According to previous studies, the study parameters anatomic variables were selected from the treatment scan fields (20,21). The chest depth (CD), heart chest wall length (HCWL), and heart chest wall distance (HCWD) were calculated (showed in *Figure 1*). And the distance between the ipsilateral lung and breast (DBIB) was defined as the distance between the mass centers of ipsilateral lung and the PTV breast (21). The heart height (HH), the heart and ipsilateral lung volumes were also analyzed in both groups. The difference between values and the average value of FB groups were denoted with “ Δ ”, for example, Δ HH.

Statistical analysis

Statistical analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a P value of <0.05 was considered statistically significant. The *t*-test, U-test, and chi-squared test were performed to compare the variables between the groups. Pearson's test was used for correlation analysis for differences between values in two groups and dose parameters (Dmean and Dmax). Relationships between anatomic variables and protective dose reduction (20%) were analyzed. Receiver operator characteristic (ROC) curve analyses were used for predicting parameter thresholds.

Results

Baseline characteristics

The study group included 67 patients (32 managed with DIHB and 35 with FB) treated between June 2017 and December 2019. The median age of the DIBH and FB groups was 48.5 years (range, 27–66 years) and 52 years (range, 35–73 years), respectively. The baseline characteristics, including age, clinical stage, histopathological grade, type of RT field, and systemic adjuvant treatment, were not different between the groups (Table 1).

Radiation dose distribution to OARs and cardiac substructures

The Dmean values in the DIBH group were lower than in the FB group for the heart (4.68 vs. 6.69 Gy, $P<0.001$), LAD (12.28 vs. 20.06, $P=0.000$), LV (4.71 vs. 7.76 Gy, $P<0.001$), and RV (5.66 vs. 8.67 Gy, $P=0.000$), corresponding to a decrease by 30.0%, 38.7%, 39.3%, and 34.7%, respectively. The Dmax values in the DIBH group were also lower than in the FB group for the heart (38.19 to 45.28 Gy, $P<0.001$), LAD (45.30 to 50.85 Gy, $P=0.000$), LV (31.37 to 44.03 Gy, $P=0.000$), and RV (35.96 to 49.96 Gy, $P<0.001$), corresponding to decrease by 15.6%, 10.9%, 28.8%, and 28.0%, respectively. Patients in the DIBH group also showed a significantly lower heart V25 than those in the FB group (2.60% and 6.23%, respectively, $P=0.008$). In contrast, the Dmean, V5, and V20 of the ipsilateral lung did not differ significantly between the groups (Table 2).

Anatomical characteristics

DIBH, compared with FB, resulted in higher ipsilateral lung

volume (1,671 vs. 1,022 cc, $P<0.001$), HH (8.59 vs. 7.28 cm, $P<0.001$), DBIB (12.73 vs. 10.78 cm, $P<0.001$), CD (19.97 vs. 19.18 cm, $P=0.052$), and HCWD (1.57 vs. 1.35 cm, $P=0.004$) (Table 3). DIBH decreased the heart volume (505 vs. 558 cc, $P=0.010$) and HCWL (3.26 vs. 3.93 cm, $P<0.001$). The different value of HH, DBIB, CD, HCWL, and HCWD between DIBH and FB groups were 1.31, 1.95, 0.79, -0.67, and 0.22 cm, respectively.

Correlations between anatomic characteristics and organ at risk doses

Δ HH, Δ DBIB, and Δ HCWL between the FB and DIBH correlated with Heart, LAD, LV and RV Dmean and Dmax values (Table 4). A clear negative correlation was observed between these parameters and Δ HH, Δ DBIB, and Δ HCWL ($P<0.05$). In contrast, Δ HCWD correlated only with the heart Dmean ($P<0.05$) and not with other dose-volume parameters ($P>0.05$).

We further constructed the ROC curve to evaluate the predictive value of Δ HH, Δ DBIB, and Δ HCWL for >20% Dmean reduction. The highest efficiency was shown for Δ HH, with the area under the curve (AUC) values of 0.818, 0.725, 0.821, and 0.820 for heart, LAD, LV, and RV Dmean, respectively (all statistically significant; Table 5 and Figure 2).

Discussion

Breast cancer patients have benefited from advanced radiation technologies through improved treatment outcomes and longer survival times. However, quality of life (QoL) problems caused by Side-effects should not be overlooked. Thus, DIBH application for reducing cardiac irradiation deserves further investigation.

In this study, DIBH allowed better separation of the heart and LAD to Radiation field, and reduced the irradiated heart volume. We showed that DIBH reduces the Dmean and Dmax to the heart, LAD, LV, and RV. We found that Δ HH has a strong correlation with cardiac mean dose reduction. These results may inform patient selection for DIBH.

Some studies have showed the benefit of DIBH for reducing the mean and maximum dose to the heart and to the LAD (22,23). However, previous studies demonstrated that patients do not benefit equally from DIBH (24). Owing to the complexity of this procedure, it is essential to select patients who will benefit most from it. The predictive value of anatomical and volume parameters for heart exposure

Table 1 Patient characteristics

Characteristics	Total (n=67)	DIBH group (n=32)	FB group (n=35)	P value
Age (years), median [range]	49.0 [27–73]	48.5 [27–66]	52 [35–73]	0.082
Clinical stage, n (%)				
I	6 (9.0)	2 (6.3)	4 (11.4)	
II	25 (37.3)	15 (46.9)	10 (28.6)	
III	30 (44.8)	12 (37.5)	18 (51.4)	0.403
IV	6 (9.0)	3 (9.4)	3 (8.6)	
Histopathological grade, n (%)				
1–2	32 (47.8)	15 (46.9)	17 (48.6)	
3	12 (17.9)	4 (12.5)	8 (22.9)	0.443
Unknown	23 (34.3)	13 (40.6)	10 (28.6)	
Vascular invasion, n (%)				
Yes	17 (25.4)	8 (25.0)	9 (25.7)	0.946
No	50 (74.6)	24 (75.0)	26 (74.3)	
Lymph node metastasis, n (%)				
Yes	49 (73.1)	24 (75.0)	25 (71.4)	0.742
No	18 (26.9)	8 (25.0)	10 (28.6)	
Neoadjuvant chemotherapy, n (%)				
Yes	16 (23.9)	6 (18.8)	10 (28.6)	0.346
No	51 (76.1)	26 (81.3)	25 (71.4)	
Adjuvant chemotherapy, n (%)				
Yes	61 (91.0)	31 (96.9)	30 (85.7)	0.242
No	6 (9.0)	1 (3.1)	5 (14.3)	
Targeted therapy, n (%)				
Yes	28 (41.8)	16 (50.0)	12 (34.3)	0.193
No	39 (58.2)	16 (50.0)	23 (65.7)	
Endocrine therapy, n (%)				
Yes	34 (50.7)	17 (53.1)	17 (48.6)	0.710
No	33 (49.3)	15 (46.9)	18 (51.4)	
RT, n (%)				
Breast/chest wall only	5 (7.5)	2 (6.3)	3 (8.6)	
Breast/chest wall and lymph nodes, except IMC	46 (68.7)	23 (71.8)	23 (65.7)	0.853
Breast/chest wall and lymph nodes, including IMC	16 (23.8)	7 (21.9)	9 (25.7)	
Boost, n (%)				
No	59 (88.1)	29 (90.6)	30 (85.7)	0.809
Yes	8 (11.9)	3 (9.4)	5 (14.3)	

DIBH, deep inspiratory breath hold; FB, free breathing; RT, radiation; IMC, internal mammary chain.

Table 2 Estimated cardiac doses for DIBH and FB

Parameter	DIBH group (median)	FB group (median)	Reduction	P value
Left lung mean dose (Gy)	14.13	13.76	+2.6%	0.461
Left lung V20 (%)	24.19	24.68	-2.0%	0.470
Left lung V5 (%)	58.90	56.92	+3.4%	0.247
Right lung mean dose (Gy)	1.33	1.20	+9.8%	0.224
Heart mean dose (Gy)	4.68	6.69	-30.0%	<0.001*
Heart max dose (Gy)	38.19	45.28	-15.6%	<0.001*
Heart V25 (%)	2.60	6.23	-58.2%	0.008*
LAD mean dose (Gy)	12.28	20.06	-38.7%	0.000*
LAD max dose (Gy)	45.30	50.85	-10.9%	0.000*
LV-mean (Gy)	4.71	7.76	-39.3%	<0.001*
LV-max (Gy)	31.37	44.03	-28.8%	0.000*
RV-mean (Gy)	5.66	8.67	-34.7%	0.000*
RV-max (Gy)	35.96	49.96	-28.0%	<0.001*

*, significant differences. DIBH, deep inspiratory breath hold; FB, free breathing; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle.

Table 3 Median and standard deviation values of anatomic parameters

Parameter (CT-based)	DIBH group (median)	FB group (median)	Reduction	P value
HH (cm)	8.59	7.28	1.31 cm	<0.001*
DBIB (cm)	12.73	10.78	1.95 cm	<0.001*
CD (cm)	19.97	19.18	0.79 cm	0.052
HCWL (cm)	3.26	3.93	-0.67 cm	<0.001*
HCWD (cm)	1.57	1.35	0.22 cm	0.004*
Heart volume (cc)	505	558	-53 cc	0.010*
Ipsilateral lung volume (cc)	1,671	1,022	649 cc	<0.001*

*, significant differences. CT, computed tomography; HH, heart height; DBIB, the distance between ipsilateral lung and breast; CD, chest depth; HCWL, heart chest wall length; HCWD, heart chest wall distance; DIBH, deep inspiratory breath hold; FB, free breathing.

was also shown in some studies, including CD, maximum heart depth, tumor bed site, and heart volume in the radiation field (20,25). We demonstrated that out of various analyzed anatomical measures, Δ HH was the best and independent predictor of the Dmean to the heart, LAD, LV, and RV. Hence, this simple measure may identify patients necessitating effective heart protection.

A limitation of breath-holding techniques is their reproducibility, which may affect clinical outcomes (26). Current approaches to overcome this problem include

surface-guided radiotherapy, RPM, and image-guided radiation therapy (27,28). DIBH also requires specific training and patient compliance, therefore, treatment efficacy with this technique may be variable. The predictive value of anatomical parameters for heart exposure dose has been highly regarded. This study offered information on potential utility of predictors for patients benefiting from DIBH. We studied some similar research (29,30). The investigation of comparing those parameters from FB and DIBH scans in some patients worthy of further study.

Table 4 Correlations between delta values of anatomic parameters and radiation doses

Variable	Δ HH	P value	Δ DBIB	P value	Δ HCWD	P value	Δ HCWL	P value
Heart								
Dmean	-0.72	<0.001*	-0.52	0.000*	-0.26	0.037*	-0.45	0.000*
Dmax	-0.61	<0.001*	-0.37	0.002*	-0.13	0.284	-0.45	0.000*
LAD								
Dmean	-0.52	0.000*	-0.40	0.000*	-0.19	0.118	-0.26	0.033*
Dmax	-0.58	<0.001*	-0.39	0.001*	-0.22	0.080	-0.31	0.012*
LV								
Dmean	-0.65	<0.001*	-0.65	<0.001*	-0.21	0.088	-0.40	0.001*
Dmax	-0.53	0.000*	-0.29	0.016*	-0.23	0.058	-0.39	0.001*
RV								
Dmean	-0.49	0.000*	-0.39	0.001*	-0.14	0.277	-0.32	0.008*
Dmax	-0.55	0.000*	-0.51	0.000*	-0.23	0.062	-0.31	0.012*

*, significant differences. Dmean, mean dose; Dmax, maximum dose; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle; HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWD, heart chest wall distance; HCWL, heart chest wall length.

Table 5 Predictive values of particular anatomic parameters for cardiac doses

Parameter	Δ HH		Δ DBIB		Δ HCWL	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
Heart Dmean	0.818	0.717, 0.919	0.729	0.597, 0.860	0.685	0.545, 0.824
LAD Dmean	0.725	0.602, 0.848	0.664	0.533, 0.796	0.585	0.446, 0.724
LV Dmean	0.821	0.720, 0.922	0.735	0.607, 0.862	0.715	0.587, 0.842
RV Dmean	0.820	0.717, 0.924	0.774	0.658, 0.890	0.705	0.580, 0.830

Dmean, mean dose; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle; HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWL, heart chest wall length; AUC, the area under the curve; CI, confidence interval.

Our study has a few limitations. First, it was retrospective, conducted in a single center, and included patients who underwent both mastectomy and BCS. Additionally, some patients were administered nodal RT, including internal mammary lymph node RT, which increases cardiac exposure. Due to small patient samples, we could not perform stratified analyses considering these variables. Second, the doses to the OARs in each fraction were less strictly controlled than in prospective studies. Currently, advanced RT techniques, such as intensity-modulated RT and volumetric-modulated arc therapy, have been employed in DIBH planning. However,

we have identified a reliable predictor for the DIBH benefit. It is imperative, however, that these observations are confirmed within prospective studies.

Conclusions

DIBH significantly reduces cardiac doses in left-sided BC patients undergoing RT. Δ HH may help select patients who will benefit most from DIBH. Future prospective studies are warranted to determine more robustly the dosimetric and clinical benefits of DIBH.

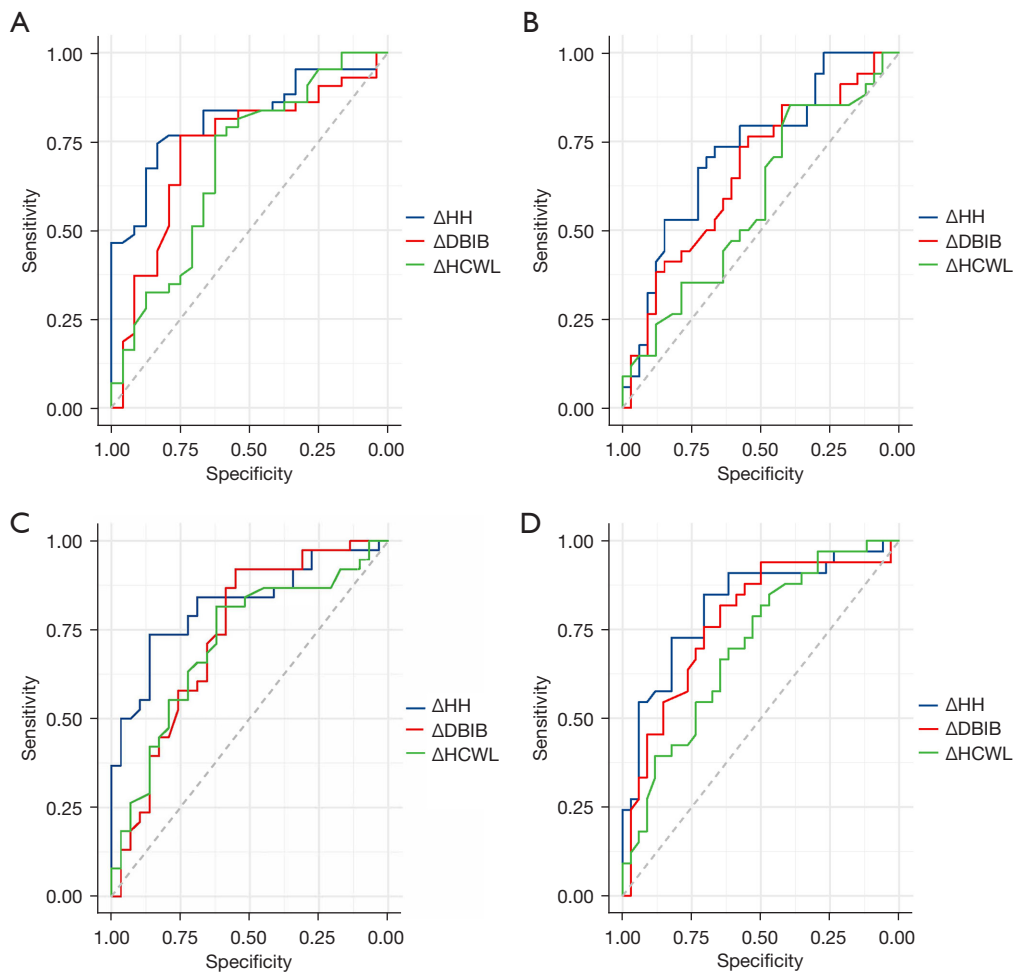


Figure 2 Receiver operating characteristic curves predicting for >20% reduction in mean heart dose (A), mean LAD dose (B), mean LV dose (C), and mean RV dose (D). HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWL, heart chest wall length; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle.

Acknowledgments

Funding: This work was supported by The Basic Ability Enhancement Program for Young and Middle-aged Teachers of Guangxi (No. 2020KY03036), Guangxi Medical University Foundation (No. GXMUYSF201918), Foundation of Guangxi Health and Family Planning Commission (No. Z20190581), and the Foundation of the Second Affiliated Hospital of Guangxi Medical University (No. hbrc202104).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://gs.amegroups.com/>

[article/view/10.21037/gc-23-160/rc](https://gs.amegroups.com/article/view/10.21037/gc-23-160/rc)

Data Sharing Statement: Available at <https://gs.amegroups.com/article/view/10.21037/gc-23-160/dss>

Peer Review File: Available at <https://gs.amegroups.com/article/view/10.21037/gc-23-160/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gc-23-160/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Second Affiliated Hospital of Guangxi Medical University Ethics Committee (approval No. 2023-KY0003) and individual consent for this retrospective analysis was waived.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Clarke M, Collins R, Darby S, 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;366:2087-106.
- Cao L, Xu C, Yi P, et al. Asparaginyl endopeptidase (AEP) regulates myocardial apoptosis in response to radiation exposure via alterations in NRF2 activation. *Am J Cancer Res* 2021;11:1206-25.
- Schubert LK, Gondi V, Sengbusch E, et al. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. *Radiother Oncol* 2011;100:241-6.
- Roumeliotis M, Long K, Phan T, et al. Including internal mammary lymph nodes in radiation therapy for synchronous bilateral breast cancer: an international survey of treatment technique and clinical priorities. *Breast Cancer Res Treat* 2018;171:471-5.
- Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. *CA Cancer J Clin* 2021;71:7-33.
- Banfill K, Giuliani M, Aznar M, et al. Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions. *J Thorac Oncol* 2021;16:216-27.
- Gee HE, Moses L, Stuart K, et al. Contouring consensus guidelines in breast cancer radiotherapy: Comparison and systematic review of patterns of failure. *J Med Imaging Radiat Oncol* 2019;63:102-15.
- Taylor C, McGale P, Brønnum D, et al. Cardiac Structure Injury After Radiotherapy for Breast Cancer: Cross-Sectional Study With Individual Patient Data. *J Clin Oncol* 2018;36:2288-96.
- Bergom C, Bradley JA, Ng AK, et al. Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification. *JACC CardioOncol* 2021;3:343-59.
- Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-98.
- Nilsson G, Holmberg L, Garmo H, et al. Distribution of coronary artery stenosis after radiation for breast cancer. *J Clin Oncol* 2012;30:380-6.
- Skyttä T, Tuohinen S, Boman E, et al. Troponin T-release associates with cardiac radiation doses during adjuvant left-sided breast cancer radiotherapy. *Radiat Oncol* 2015;10:141.
- Piroth MD, Baumann R, Budach W, et al. Heart toxicity from breast cancer radiotherapy : Current findings, assessment, and prevention. *Strahlenther Onkol* 2019;195:1-12.
- Bergom C, Currey A, Desai N, et al. Deep Inspiration Breath Hold: Techniques and Advantages for Cardiac Sparing During Breast Cancer Irradiation. *Front Oncol* 2018;8:87.
- Latty D, Stuart KE, Wang W, et al. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. *J Med Radiat Sci* 2015;62:74-81.
- Shim JG, Kim JK, Park W, 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;15:105-10.
- Li JB, Jiang ZF. Chinese Society of Clinical Oncology Breast Cancer Guideline version 2021: updates and interpretations. *Zhonghua Yi Xue Za Zhi* 2021;101:1835-8.
- Yamauchi R, Mizuno N, Itazawa T, et al. Dosimetric evaluation of deep inspiration breath hold for left-sided breast cancer: analysis of patient-specific parameters related to heart dose reduction. *J Radiat Res* 2020;61:447-56.
- Li XA, Tai A, Arthur DW, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG Multi-Institutional and Multiobserver Study. *Int J Radiat Oncol Biol Phys* 2009;73:944-51.
- Register S, Takita C, Reis I, et al. Deep inspiration breath-hold technique for left-sided breast cancer: An analysis

- of predictors for organ-at-risk sparing. *Med Dosim* 2015;40:89-95.
21. Lin H, Liu T, Shi C, et al. Feasibility study of individualized optimal positioning selection for left-sided whole breast radiotherapy: DIBH or prone. *J Appl Clin Med Phys* 2018;19:218-29.
 22. Dumane VA, Saksornchai K, Zhou Y, et al. Reduction in low-dose to normal tissue with the addition of deep inspiration breath hold (DIBH) to volumetric modulated arc therapy (VMAT) in breast cancer patients with implant reconstruction receiving regional nodal irradiation. *Radiat Oncol* 2018;13:187.
 23. Misra S, Mishra A, Lal P, et al. Cardiac dose reduction using deep inspiratory breath hold (DIBH) in radiation treatment of left sided breast cancer patients with breast conservation surgery and modified radical mastectomy. *J Med Imaging Radiat Sci* 2021;52:57-67.
 24. Ferini G, Valenti V, Viola A, et al. A Critical Overview of Predictors of Heart Sparing by Deep-Inspiration-Breath-Hold Irradiation in Left-Sided Breast Cancer Patients. *Cancers (Basel)* 2022;14:3477.
 25. Cao N, Kalet AM, Young LA, et al. Predictors of cardiac and lung dose sparing in DIBH for left breast treatment. *Phys Med* 2019;67:27-33.
 26. Kron T, Bressel M, Lonski P, et al. TROG 14.04: Multicentre Study of Feasibility and Impact on Anxiety of DIBH in Breast Cancer Patients. *Clin Oncol (R Coll Radiol)* 2022;34:e410-9.
 27. Lu W, Li G, Hong L, et al. Reproducibility of chestwall and heart position using surface-guided versus RPM-guided DIBH radiotherapy for left breast cancer. *J Appl Clin Med Phys* 2023;24:e13755.
 28. Rossi M, Laaksomaa M, Aula A. Patient setup accuracy in DIBH radiotherapy of breast cancer with lymph node inclusion using surface tracking and image guidance. *Med Dosim* 2022;47:146-50.
 29. Ferini G, Molino L, Tripoli A, et al. Anatomical Predictors of Dosimetric Advantages for Deep-inspiration-breath-hold 3D-conformal Radiotherapy Among Women With Left Breast Cancer. *Anticancer Res* 2021;41:1529-38.
 30. S Nair S, Devi VNM, Sharan K, et al. A Dosimetric Study Comparing Different Radiotherapy Planning Techniques With and Without Deep Inspiratory Breath Hold for Breast Cancer. *Cancer Manag Res* 2022;14:3581-7.
- (English Language Editor: L. Huleatt)

Cite this article as: Zhu H, Sun H, Zhang J, Xie Y, Jassem J, Franco P, Sun W, Liu W, Yue H. Cardiac exposure in left-sided breast cancer patients undergoing deep inspiratory breath hold radiation therapy. *Gland Surg* 2023;12(5):677-686. doi: 10.21037/gs-23-160