RESEARCH ARTICLE

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Comparison Between Breath-Hold and the Inspiratory Phase of Free Breathing in Left Breast Cancer Radiotherapy: Target Volume Coverage and Organ Sparing

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Abstract

Background: Cardiac mortality and coronary events associated with left breast radiotherapy are correlated with the mean radiation dose to the heart. **Methods:** This prospective phase II study included left breast cancer patients receiving adjuvant locoregional radiotherapy with intensity-modulated radiation therapy (IMRT) following surgery. Patients were treated using the respiratory gating (RPM) technique (Varian Medical Systems, USA). Dosimetric outcomes were compared between deep inspiration breath-hold (DIBH) and the inspiratory phase of free breathing (FB) in the same patients, focusing on target volume coverage and sparing of critical organs (lungs, heart, and coronary arteries). The prescribed dose was 50 Gy in 25 fractions over five weeks to the chest wall or breast and/or lymph nodes, with an additional boost of 10 Gy in five fractions over one week to the tumor bed in breast-conserving surgery (BCS) cases. Two treatment plans were generated per patient: one for DIBH and another for the inspiratory phase of FB. **Results:** Between February 2020 and August 2022, 60 patients with a mean age of 50 years were enrolled in the study. The dosimetric analysis showed that the mean heart dose was lower in the DIBH group (4.8 Gy) compared to the FB group (6.4 Gy) with a statistically significant difference ($p < 0.0001$). Similarly, the mean dose to the left anterior descending artery (LAD) was significantly reduced in DIBH (14 Gy) compared to FB (20.5 Gy) ($p < 0.0001$). Regarding target volume coverage, the mean planning target volume (PTV) V95% was slightly higher in DIBH (97.3%) than in FB (96.5%) ($p = 0.0062$). The mean left lung V20 was comparable between the two techniques, with values of 14.4% in DIBH and 14.35% in FB ($p = 0.85$), indicating no significant difference in lung dose sparing. However, the mean left ventricular dose was significantly lower in DIBH (6 Gy) compared to FB (8.1 Gy) ($p < 0.0001$), further supporting the advantage of DIBH in reducing cardiac radiation exposure. **Conclusion:** DIBH plans demonstrated superior target coverage and significantly improved cardiac and coronary sparing compared to FB inspiratory phase plans. However, FB plans remained within acceptable dose constraints. No significant differences were observed in lung dose sparing or beam-on time.

Keywords: RPM- left breast- FB inspiratory phase- patients not able to do DIBH

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Introduction

Breast cancer is the most common cancer in women and the leading cause of cancer-related deaths among females [1]. Although radiation therapy improves local control and survival rates in breast cancer, some researchers have raised concerns that its toxicities, particularly cardiac-related complications, may offset these survival benefits [2]. Studies indicate that patients with left-sided breast tumors who undergo radiation therapy face a higher risk of cardiac mortality [3]. Cardiac mortality and coronary event rates are strongly correlated with the mean radiation dose to the heart, with estimates suggesting that for every 1 Gy increase in the heart's mean dose, the risk of heart disease and coronary events rises by 4–7%. Furthermore, no safe dose threshold has been identified below which the risk of cardiac events is eliminated [4]. Several heart-sparing techniques are available, including prone positioning, deep inspiration breath-hold (DIBH), and respiratory gating to minimize heart exposure; partial breast irradiation, which targets only the lumpectomy cavity; and advanced radiation techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and proton therapy [5]. Among these methods, DIBH is considered the most effective technique for cardiac sparing during radiotherapy [6]. While DIBH generally results in lower radiation doses to the heart, left anterior descending

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artery (LAD), and lungs, in certain cases, free breathing (FB) or prone positioning may yield comparable or even superior dosimetric outcomes [7].

A recent study by Korreman et al. [9] highlighted challenges associated with DIBH, reporting that 16.7% of patients were unsuitable for this technique [8]. Common limitations include an inability to hold their breath long enough during CT simulation or treatment due to poor lung function or performance status, difficulty complying with training, or failure to achieve reproducible breath-hold during treatment sessions. Additionally, some patients may not derive significant dosimetric benefits from DIBH over FB. For these individuals, 4D gated treatment delivery may be a viable alternative, although its accuracy, reproducibility, and impact on treatment efficiency require further evaluation [9].

Given these challenges, our study aimed to address this gap by comparing the dosimetric differences between DIBH-IMRT and the inspiratory phase of FB-IMRT in terms of target coverage and organ-at-risk (OAR) sparing (heart, lungs, and LAD). The goal was to explore a potential alternative technique for patients unable to perform DIBH effectively.

Materials and Methods

Patient Selection

This prospective phase II dosimetric feasibility study was conducted at the Kasr Al-Aini Center of Clinical Oncology & Nuclear Medicine (NEMROCK) and Fayoum University Hospital. The study included patients with left breast cancer who were receiving adjuvant locoregional radiotherapy with the intensity-modulated radiation therapy (IMRT) technique following either breast-conserving surgery (BCS) or modified radical mastectomy (MRM). Eligible patients were cognitively and physically fit to undergo radiotherapy using the respiratory gating (RPM) technique. The study compared dosimetric outcomes between deep inspiration breath-hold (DIBH) and the inspiratory phase of free breathing (FB) in the same patients, focusing on target volume coverage and the sparing of critical organs at risk (lungs, heart, and coronary arteries). Between February 2020 and May 2022, a total of 75 patients were screened for eligibility. Fifteen patients were excluded due to their inability to perform the DIBH technique: five had cardiac comorbidities, three were noncompliant with instructions, and seven were unable to sustain breath-holding. Consequently, 60 patients were included in the final analysis, as illustrated in Figure 1.

Eligible patients were female, aged ≤60 years, with pathologically confirmed non-metastatic left breast cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Each patient underwent two CT simulations: one in free breathing (FB-CT) and another in DIBH using the RPM Varian system.

Primary Endpoint

The primary endpoint of the study was the comparison of the mean heart dose between the DIBH and FB inspiratory phase treatment plans.

Secondary Endpoint

The secondary endpoints of the study included:

1- Heart Dose Constraints: Comparison of various heart dose parameters between DIBH and FB, including heart V5, V10, V15, V20, V25, V30, and V40.

2- Target Volume Coverage: Evaluation of planning target volume (PTV) coverage by comparing PTV V95% and V98% between both modalities.

3- Lung Dose Parameters: Assessment of lung dose exposure by comparing lung volumes, including both lungs V20%, V5%, and mean lung doses between the two modalities.

4- Left Anterior Descending Artery (LAD) Exposure: Comparison of LAD dosimetric parameters, including mean dose, maximum dose, V15%, V30%, and V40%.

5- Left Ventricular Dose Parameters: Evaluation of left ventricular dose exposure by comparing mean dose, V5%, V15%, and V23% between DIBH and FB.

Respiratory Gating System

The Real-time Position Management (RPM) system, developed by Varian Medical System (USA) in the early 2000s, utilizes two reflectors attached to an external marker cube, which is placed on the patient's abdomen. The motion of this cube marker, which reflects the patient's breathing pattern, is detected by an infrared camera and assessed by the scanner's controlling software based on predefined criteria. The RPM system continuously monitors the patient's breathing, and if the breath-hold level deviates from the set threshold, a beam-hold situation is triggered. This system enhances treatment accuracy by ensuring real-time monitoring of the patient's progress and maintaining high reproducibility.

Patient Positioning, Immobilization, and CT Scanning

A planning CT scan was performed with the patient in the supine position. Patients were positioned on a breast board elevated at 5 degrees, with each hand grasping a designated column for stabilization. The head was tilted to the right to allow proper exposure of the supraclavicular region. The xiphisternal junction was marked with external radio-opaque markers and permanent tattoos to ensure localization and setup accuracy. CT scans covered the region from the mandible (C3–C4 vertebrae) to below the costophrenic angles to include the lung volume, using a 2.5 mm slice thickness. Each patient underwent two CT simulations: one with DIBH using the RPM Varian system and another with free breathing (FB). Maximum intensity projection (MIP) was constructed from the inspiratory phases on CT. Before scanning, patients were trained on the RPM system. They were positioned on a flat table in the CT planning room with an infrared reflecting marker box placed near the xiphoid process to track respiratory movements. The RPM system analyzed the patient's breathing pattern and motion using an infrared tracking camera and a reflective marker box. Gating thresholds were set to activate and deactivate the radiation beam when the breast target was in the desired phase of the respiratory cycle.

Target Volumes and Organs at Risk (OAR) Contouring

Delineation was performed following the RTOG breast atlas consensus guidelines [10]. OARs were contoured based on their radiological anatomy. Whole-breast irradiation was used for patients who underwent breast-conserving surgery, while the chest wall was treated in patients who underwent modified radical mastectomy. Patients with ≥N1 disease received treatment to the peripheral chain lymph nodes (PCLN), including the supraclavicular lymph nodes (SCLN) and level III axilla. SCLN irradiation was included for patients with positive nodes (N1) or those who had received neoadjuvant chemotherapy.

Treatment Planning

All patients' plans were created using the IMRT technique with a prescribed dose of 50 Gy in 25 fractions (2 Gy per fraction). IMRT fields were designed based on the CT simulation geometry to ensure uniform dose distribution across the breast volume, provide adequate tumor bed coverage, minimize the mean heart dose, limit high-dose regions (hot spots), and reduce lung exposure. The planning process involved adjustments to beam weights, multi-leaf collimators (MLC), collimator angle rotation, and iterative beam shaping to optimize dose distribution.

Plan Acceptance

Treatment plans were reviewed to ensure appropriate total dose delivery, fractionation, and beam arrangement. The beam eye view was assessed for optimal beam configuration and anterior dose fall-off. Dose distribution was evaluated on axial CT slices using isodose lines and dose color wash. The cumulative Dose Volume Histogram (DVH) was analyzed to ensure adherence to dose constraints.

A treatment plan was approved if at least 95% of the planning target volume (PTV) received 95% of the prescribed dose while maintaining the lowest tolerable doses to OARs [11].

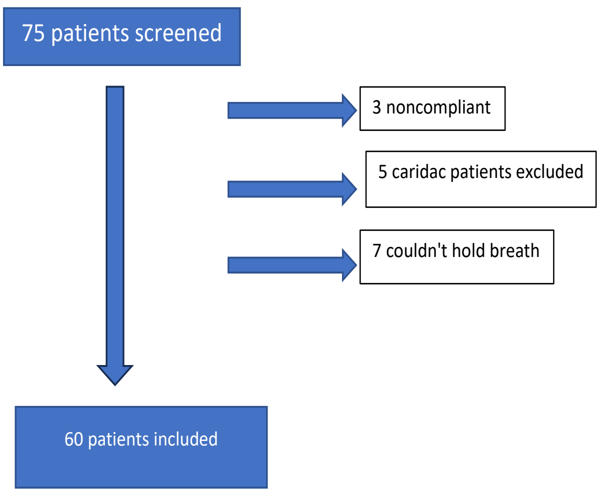

Figure 1. Diagram Illustrating the Recruitment Process.

Ethical Considerations

The research protocol was reviewed and approved by the Research Ethics Committee and the Scientific Research Committee of the Department of Clinical Oncology, Faculty of Medicine, Cairo University. Final approval was granted by the Faculty of Medicine Research Ethics Committee at Cairo University (Approval Code: MD-55-2020).

Results

Patient Characteristics

All included patients were female, with a mean age of 50 ± 9.6 years. Forty-four patients (73.3%) underwent conservative breast surgery, while 16 patients (26.7%) underwent modified radical mastectomy. Regarding disease stage, 19 patients (31.7%) were classified as stage I, 19 patients (31.7%) as stage II, and 22 patients (36.6%) as stage III. Stage IV patients were excluded from the study. In terms of molecular subtypes, 40 patients (66.6%) were classified as luminal A-like, 10 patients (16.6%) as HER2-enriched, 5 patients (8.3%) as luminal B, and 5 patients (8.3%) as triple-negative breast cancer (TNBC). These patient characteristics are summarized in Table 1.

Total Lung Volumes and Chest Wall Displacement

The arithmetic mean for total lung volume was 3927.03 ± 624 cc for DIBH vs. 2179.4 ± 365 cc for the FB inspiratory phase ($P < 0.0001$). The arithmetic mean for chest wall displacement was 1.99 ± 0.4 cm for DIBH (range: 1.18–3.6 cm) vs. 0.77 ± 0.2 cm for the FB inspiratory phase (range: 0.37–1.44 cm) ($P < 0.0001$).

Feasibility for Patients

The arithmetic mean for beam-on time was 2.4 ± 0.6 min for DIBH vs. 2.3 ± 0.4 min for the FB inspiratory phase, while the median value was 2.3 min for DIBH vs. 2.25 min for the FB inspiratory phase ($P = 0.76$).

Target Volume and Organs at Risk Dosimetry
Cardiac Doses

The arithmetic mean for the heart mean dose was 4.8 ± 1.05 Gy for DIBH vs. 6.4 ± 1 Gy for the FB inspiratory phase ($P < 0.0001$) (Figure 2A). The mean heart V5, V10, V15, V20, V25, V30, and V40 were higher in the

Table 1. Patients' Characteristics.

Item	Age		Type of surgery		Staging			Molecular type			
	Mean & SD	Median	BCS	MRM	I	II	III	luminal		Her2neu	TNBC
								A	B	enriched	
Number	50 (±) 9.6	54	44	16	19	19	22	40	5	10	5
Percentage	-	-	73.30%	26.70%	31.66%	31.66%	36.60%	66.60%	8.30%	16.60%	8.30%

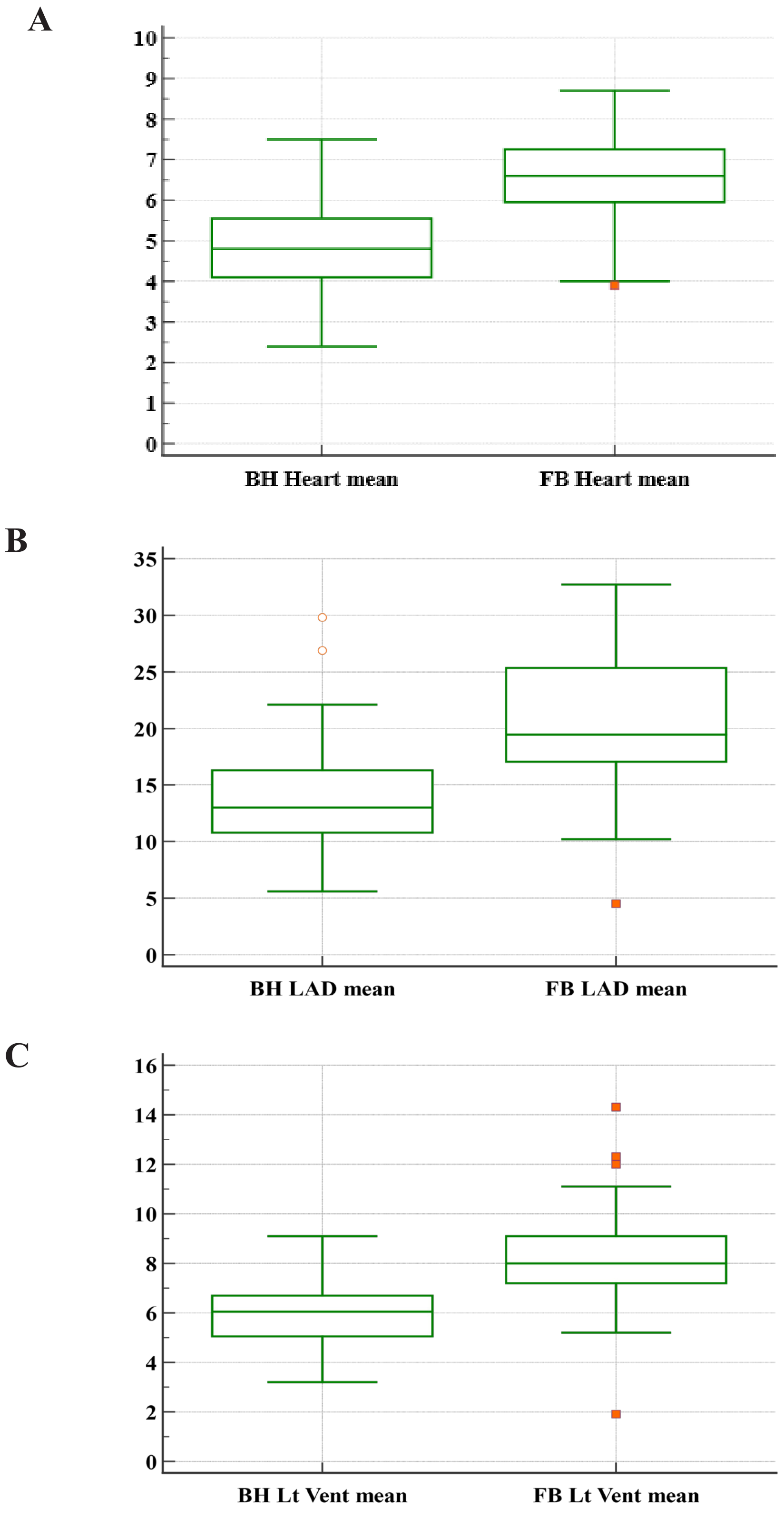

Figure 2. A, Box plot showing comparison of the heart mean dose between BH & FB inspiratory phase. B, Box plot showing comparison of LAD mean between BH & FB inspiratory phase. C, Box plot showing comparison of left ventricular mean between BH & FB inspiratory phase

FB inspiratory phase than in DIBH. The mean values for DIBH vs. FB inspiratory phase were as follows:

- Heart V5: 37.7% ± 14.4 vs. 46.5% ± 10
- Heart V10: 7.2% ± 3.5 vs. 15.7% ± 6
- Heart V15: 2.38% ± 2.1 vs. 7% ± 2.8
- Heart V20: 1.18% ± 1.5 vs. 4.3% ± 2.04
- Heart V25: 0.6% ± 1 vs. 3.06% ± 1.7
- Heart V30: 0.43% ± 0.7 vs. 2.09% ± 1.4
- Heart V40: 0.04% ± 0.1 vs. 0.5% ± 0.7

All comparisons were statistically significant ($P < 0.0001$).

The mean LAD (left anterior descending artery) mean

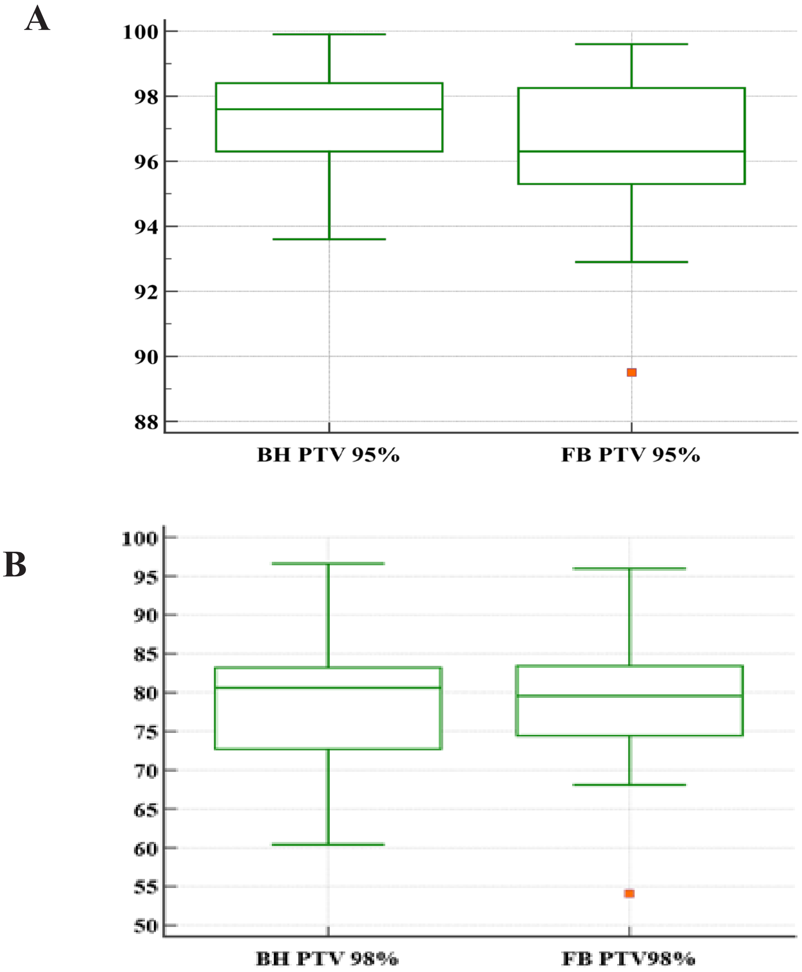

Figure 3. A, Box plot showing comparison of the PTV D95 between BH & FB inspiratoty phase. B, Box plot showing comparison between PTV V98% between BH & FB inspiratory phase.

dose was 14 ± 4.7 Gy for DIBH vs. 20.5 ± 6.1 Gy for the FB inspiratory phase (P < 0.0001) (Figure 2B).

• LAD maximum dose: 32.7 ± 10.4 Gy for DIBH vs. 41.5 ± 6.7 Gy for the FB inspiratory phase (P < 0.0001).

• LAD V15: 35.4% ± 21.6 for DIBH vs. 60.3% ± 18.1 for the FB inspiratory phase (P < 0.0001).

• LAD V30: 8.1% ± 14.2 for DIBH vs. 26.7% ± 22.8 for the FB inspiratory phase (P < 0.0001).

• LAD V40: 1.2% ± 3.9 for DIBH vs. 7% ± 13.2 for the FB inspiratory phase (P = 0.0003).

For the left ventricle:

• Left ventricle V5: 54.5% ± 18.2 for DIBH vs. 67.4% ± 15.8 for the FB inspiratory phase (P < 0.0001).

• Left ventricle V15: 3.1% ± 3.9 for DIBH vs. 9.8% ± 6.2 for the FB inspiratory phase (P < 0.0001).

• Left ventricle V23: 1.24% ± 2.1 for DIBH vs. 4.7% ± 3.1 for the FB inspiratory phase (P < 0.0001).

• Left ventricle mean dose: 6 ± 1.3 Gy for DIBH vs. 8.1 ± 1.8 Gy for the FB inspiratory phase (P < 0.0001) (Figure 2C).

Target Volume Doses

The arithmetic mean for PTV V95% was 97.3% ± 1.3 for DIBH vs. 96.5% ± 1.9 for the FB inspiratory phase (P = 0.0062) (Figure 3A). The arithmetic mean for PTV V98% was 78.2% ± 8.6 for DIBH vs. 79.3% ± 7 for the FB inspiratory phase (P = 0.23) (Figure 3B).

Lung Doses

The mean total lung dose was 5.9 ± 1.3 Gy for DIBH vs. 6 ± 1.5 Gy for the FB inspiratory phase (P = 0.38).

• Left lung mean dose: 10.3 ± 1.7 Gy for DIBH vs. 10.5 ± 2 Gy for the FB inspiratory phase (P = 0.13).

• Right lung mean dose: 2.1 ± 1.1 Gy for DIBH vs. 2.1 ± 1.3 Gy for the FB inspiratory phase (median: 1.7 Gy for DIBH vs. 1.6 Gy for the FB inspiratory phase, P = 0.27).

• Left lung V20: 14.4% ± 2.9 for DIBH vs. 14.3% ± 4 for the FB inspiratory phase (P = 0.85) (Figure 4).

• Left lung V5: 59.9% ± 13.9 for DIBH vs. 63.8% ± 16.2 for the FB inspiratory phase (P = 0.01).

• Right lung V20: 0.0005% ± 0.0019 for DIBH vs. 0.65% ± 3.6 for the FB inspiratory phase (P = 0.49).

• Right lung V5: 0.09% ± 0.1 for DIBH vs. 9.9% ± 13.8 for the FB inspiratory phase (P < 0.0001).

Discussion

This prospective phase II dosimetric feasibility study is the first in Egypt to explore an alternative radiation technique for patients with left breast cancer who are

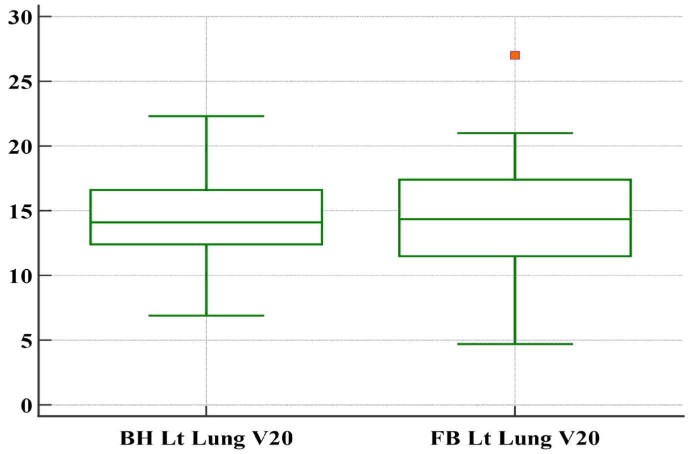

Figure 4. Box Plot Showing Comparison of Left Lung V20 between BH & FB Inspiratory Phase

unable to perform deep inspiration breath-hold (DIBH) during treatment. We investigated the feasibility of delivering radiation during the inspiratory phase of free breathing (FB) as an alternative approach to spare organs at risk (OAR) while maintaining adequate target coverage. The effectiveness of this technique was evaluated through a dosimetric comparison with DIBH. While both strategies met tolerance constraints, DIBH provided significantly better cardiac sparing, with no significant differences in lung dose reduction or beam-on time.

Between February 2020 and May 2022, 75 patients were screened for this study. Of these, 15 patients were excluded due to their inability to perform the DIBH technique for various reasons. The final analysis included 60 patients, each of whom underwent two CT simulations: one with free breathing (FB-CT) and another with DIBH using the RPM Varian system.

Both treatment plans remained within the tolerance dose limits for OARs. However, DIBH was significantly more effective in sparing the heart, left anterior descending artery (LAD), and left ventricle. The arithmetic mean of the heart dose was 4.8 Gy for DIBH vs. 6.4 Gy for the FB inspiratory phase ($P < 0.0001$). These findings are consistent with a recent single-institution dosimetric study comparing DIBH and FB in left breast cancer radiotherapy, where all dosimetric parameters for cardiac structures were significantly reduced ($P < 0.01$ for all). That study reported a mean heart dose (Dmean) of 1.3 Gy (range: 0.5–3.6) in the DIBH group vs. 2.2 Gy (range: 0.9–8.8) in the FB group ($P < 0.001$). Similarly, the Dmean for the left ventricle was 1.5 Gy (range: 0.6–4.5) with DIBH vs. 2.8 Gy (range: 1.1–9.5) with FB ($P < 0.001$), and the LAD Dmean was 4.1 Gy (range: 1.2–33.3) in DIBH vs. 14.3 Gy (range: 2.4–37.5) in FB ($P < 0.001$) [12]. Both techniques were equivalent in their ability to spare lung dose bilaterally. The mean left lung V20 was 14.4% for DIBH vs. 14.3% for FB inspiratory phase ($P = 0.85$), aligning with findings from a recent dosimetric study published in the Journal of Radiation Research. That study, which investigated parameters for selecting left breast cancer patients for intensity-modulated radiotherapy (IMRT) with DIBH, reported a mean total lung dose of 4.3 Gy in DIBH vs. 4.5 Gy in FB, a statistically insignificant difference ($P = 0.39$) [13]. Additionally, beam-on time was similar in both plans.

Although there was a small but statistically significant difference in target coverage between the two strategies, both remained well within acceptable clinical practice parameters. This minor difference is consistent with findings from another dosimetric study comparing DIBH and FB in left breast cancer radiotherapy, which reported a PTV V95% of 95.2% ± 6.3% for DIBH vs. 95.6% ± 4.1% for FB, a non-significant difference [14].

The study had some limitations, including a small sample size and heterogeneous patient characteristics. We recommend conducting future studies with larger cohorts to validate these findings.

In conclusion, patients who are unable to perform the DIBH procedure may still benefit from radiation delivery during the inspiratory phase of free breathing. This technique provides a viable alternative that achieves comparable lung sparing and target coverage while offering a potential reduction in cardiac complications.

Author Contribution Statement

Conceptualization, H.M.& S.H.; methodology, S.H. & H.M.; CT planning & Delineation, S.H.; Delineation & Plan acceptance, H.M. & S.H.; Physics plans, M.A.; writing-original draft preparation, S.H.; writing-review and editing, S.H. & H.M & L.K.; visualization, H.M. &S.H.; supervision, HM. All authors have read and approved the final version of the manuscript for publication.

Acknowledgements

Approval

This study is part of an approved MD student thesis.

Ethical approval

The study was approved by the Cairo University Ethical Committee. The research protocol was reviewed and accepted by the Research Ethics Committee and the

Scientific Research Committee of the Department of Clinical Oncology, Faculty of Medicine, Cairo University. It was also approved by the Research Ethics Committee of the Faculty of Medicine, Cairo University (Approval Code: MD-55-2020).

Data Availability Statement

The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflict of interest

The author declares no conflict of interest

Abbreviations

BCS: Breast conservation surgery
DIBH: Deep inspiration breath-hold
3DRT: 3D-Conformal radiotherapy
DVH: Dose–volume histogram
FB: Free breathing
HER2: Human epidermal growth factor receptor 2
IMRT: Intensity-modulated radiotherapy
LAD: Left anterior descending artery
LV: Left ventricle
MLC: Multi leaf collimator
MRM: Modified radical mastectomy
OAR: Organs at risk
PTV: planning target volume
RPM: Real-time position management
RTH: Radiotherapy
SD: Standard deviation
TNBC: Triple-negative breast cancer
VMAT: volumetric modulated arc therapy

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