

Dose Sparing with Breath-Holding Compared with Free Breathing in Right Sided Breast Cancer Irradiation

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Abstract

Background: Deep inspiration breath-hold (DIBH) technique is superior to the free breathing (FB) in irradiation of breast and chest wall. The radiation exposure of liver, lungs and heart is decreased considerably when right breast cancer (RBC) is treated with DIBH. The present study aimed to reduce the toxicity of RBC irradiation to risk organs.

Method: This prospective clinical study included 120 female patients who were randomly allocated into 2 Arms, arm A received FB, arm B received DIBH, each comprising 60 cases. The comparison of both arms, treatment plans evaluation and dose volume histograms were analyzed to assess doses to clinical target volume (CTV), boost and risk organs (liver, ipsilateral lung and heart). A study of alanine transaminase (ALT) and aspartate transaminase (AST) as pre, during and 3 months post-treatment were done. Statistical Package of Social Services version 24 was used to analyze data. Statistical analysis was determined using the chi square and Mann-Whitney U test and $P \leq 0.05$ was considered statistically significant.

Results: The mean, minimum and maximum doses of CTV and boost in both arms showed no significant difference. Mean, minimum and maximum doses of liver and right lung in both arms showed significant difference, doses in DIBH technique were less than FB. Mean and maximum doses of heart in both arms showed significant difference, while the minimum dose of heart did not. Pre-, during, and 3 months post-treatment ALT and AST values showed no significant difference.

Conclusion: In RBC patients DIBH is an efficient method for lowering liver, ipsilateral lung and heart radiation exposure.

Keywords: Breast neoplasms, Deep inspiration breath hold, Radiotherapy, Dose reduction

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Introduction

With an age-specific incidence rate of 48.8/105, breast cancer (BC) is still the most prevalent form of cancer in women in Egypt, in spite of the disparity in incidence rates of BC between developed and underdeveloped countries. In 2050, over 46,000 incident cases are predicted.¹ Egypt is one of the most populous countries in the Middle East and North Africa region, with a total population exceeding 102 million in 2020. Also, Egypt represents nearly 1.31% of the global population and ranked 14th among countries sorted by population. The highest incidence cancers were, in order, hepatic, breast, bladder, non-Hodgkin lymphoma, lung, leukemia, and prostate cancers.² The models of BC treatment are surgical resection, systemic treatment and radiation therapy (RT). RT offers many benefits, but it also often carries a risk of toxicity. Deep inspiration breath-hold (DIBH) technique is far superior to the free breathing (FB) technique in RT to breast and chest wall. The increase in distance between the target and organs at risk (OAR) contributes to a reduction in radiation exposure. The use of DIBH technique has been shown to significantly reduce doses to the liver, lungs and heart including its substructures through proper patient selection and training, without compromising planned target volume coverage or causing any unacceptable overdosing or under dosing.³

Variations in breath holding among various fractions (from 1 day to the next) are the cause of variations in interfraction breath holding. Variations in respiration maneuvers (abdominal versus costal), patient posture (e.g. arching the spine), internal organ motion and drift or shift of organs from gravity or relaxation are possible causes. Breath-hold variation within the same fraction (i.e., from beam-on to beam-off) is the cause of intrafraction breath-hold variation. Drift or organs shift brought on by gravity or relaxation, patient fatigue, respiration maneuvers (abdominal versus costal), patient posture and internal organ motion are possible reasons.⁴

It is currently unknown how harmful breast RT is to the liver. In order to prevent RT-induced liver disease (RILD), studies evaluating hepatic

malignancies indicate that the dosage limitations for normal liver volumes are $D_{mean} \leq 28-32$ Gy in 2 Gy fractions. Usually, RILD is detected two to three months after RT is finished. More than or equal 2 fold increase in alkaline phosphatase (ALP) (classic type) or ≥ 5 -fold increase in aspartate transaminase (AST)/alanine transaminase (ALT) (non-classic type) level after RT is the definition of RILD.⁵ The heart, lungs, and liver radiation exposure is decreased considerably when right breast cancer (RBC) is treated with DIBH.⁶ The liver was significantly displaced by the DIBH from the high-dose target region, resulting in a 63% reduction in liver volume in the high-dose region to 50 cc.⁷ Furthermore, the cardiac substructure radiation doses, which involves both ventricles, the right coronary artery (RCA) region, both atria, and the lungs, are efficiently decreased when the DIBH technique is used during RBC irradiation. In RBC radiation, the DIBH may result in a considerable sparing of these structures.⁸ In our study, we chose RBC irradiation to apply DIBH technique because the liver dose is no less important than the heart dose in left BC (LBC) irradiation. Also, some previous studies have reported the significance of DIBH technique in RBC irradiation dosimetric outcomes such as reducing dose to OAR: liver, heart and right lung which is always an important aim in RT. The effect on the liver is particularly important, especially since previous studies found that an increased dose to the liver, as a risk organ, affects liver enzymes and consequently impacts the patient clinically. The aim of the present study was to investigate how DIBH technique impacted the liver, heart, and right lung doses in RBC RT.

Methods

The present prospective clinical study included a total of 120 female patients with BC, who fulfilled the inclusion criteria, based on the clinical flow over a 10-month period. The retrospective sample size analysis showed that 120 patients (60 per group) was sufficient to detect a moderate effect size ($d = 0.6$) with 80% power at a 0.05 significance level. The study was conducted from January 2024 to March 2025. The patients were

randomly allocated into 2 Arms, arm A (1st) received FB, arm B (2nd) received DIBH, each compromising 60 cases. Even numbers of cases were in the first arm and odd numbers were in the second arm. Patient assignment was based on the order of presentation without any influence from investigators. RBC patients who underwent breast conserving surgery were included, while cases with insufficient data in medical files, patient refusal, non-cooperative patients and patients with elevated liver enzymes were excluded from the study. All cases that met the eligibility criteria and attended the department during the study period were included in the study. Every participant provided written informed consent. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The Faculty of Medicine International Review Board (IRB) and the Zagazig University Ethical Committee approved this study (ethics code: ZU- IRB # 37/23-Jan-2024).

All patients underwent most comfortable treatment positioning, simulation and fixation through thermoplastic mask in the supine position and underwent computed tomography (CT). Next, the CT images were transferred electronically to the treatment planning system or through CD applications. Patients with RBC underwent CT simulation after breast conserving surgery, the first group with FB and the second group with DIBH technique. The patients were trained by an educated nurse to hold their breath (e.g., for 20 seconds) at specific lung volume during CT simulation and radiation treatment time. They were provided with videos and instructed to repeat the exercise at home three times a day at least one week before CT simulation. Coaching patients led to decreased treatment time and reduced anxiety which is a challenge to DIBH technique. Most of the patients were cooperative and committed. Digitally reconstructed radiograph (DRR) was used to ensure accurate radiation delivery. While a comprehensive motion monitoring or gating system were not incorporated in this study, visual coaching, patient compliance and daily DRR formed the cornerstone of our

reproducibility strategy.

Radiation oncologists used the treatment planning system to contour patients. Target volume and OAR delineation was done according to Radiation Therapy Oncology Group (RTOG) and reference atlas contours in order to reduce interobserver variation and achieve accurate delineation. Breast clinical target volume (CTV) was the entire mammary gland, includes the lumpectomy CTV lumpectomy CTV includes seroma and surgical clips (placed in the lumpectomy cavity during surgery) when present included in delineation. The dose reaching OAR was minimized by shielding them using MLC without interference with the target coverage. A comparison of both arms, the treatment plans evaluation and dose volume histograms (DVHs) were analyzed to assess dose to CTV, boost and OAR (liver, ipsilateral lung and heart). Radiotherapy was delivered using a linear accelerator (Linac) in 25 fractions to a prescribed dose of 50 Gy, followed by a 10 Gy boost administered in 5 fractions. All patients underwent a study of ALT and AST as baseline, weekly during treatment delivery and three months later.

Statistical analysis

The collected data were computerized and statistically analyzed by computer using Statistical Package for the Social Sciences version 24 (SPSS). For qualitative variables presented by number and percentage, chi-square test was used to investigate the statistical difference between qualitative variables. For quantitative continuous variables presented by mean $\pm$ SD, t-test and Mann-Whitney test were used to investigate the statistical significance of the difference between mean values of the two groups. The results were considered statistically significant when the significant probability was less than 0.05 ($P < 0.05$). P -values less than 0.005 were highly significant. P -value ≥ 0.05 was considered statistically insignificant.

Results

Baseline demographic, clinical, and treatment characteristics were comparable between the FB and DIBH groups, with no statistically significant

Table 1. Demographic and tumor characteristics

	Group A (FB) (n=60)	Group B (DIBH) (n=60)	P-value
Age (years)			
Mean $\pm$ SD	44.21 $\pm$ 7.05	42.10 $\pm$ 8.10	0.130
Range	(37-52)	(34-51)	
Menopausal state			
Pre - menopausal	43 (71.66%)	40 (66.66%)	0.55
Post - menopausal	17 (28.33%)	20 (33.33%)	
Residence			
Urban	36 (60%)	30 (50%)	0.27
Rural	24 (40%)	30 (50%)	
Type of BCS			
Lumpectomy	45 (75%)	50 (83.33%)	0.26
Quadrantectomy	15 (25%)	10 (16.66%)	
Tumor location			
UOQ	36 (60%)	32 (53.33%)	0.39
UIQ	15 (25%)	13 (21.66%)	
LOQ	9 (15%)	15 (25%)	
Tumor grade			
Grade I	15 (25%)	20 (33.33%)	0.36
Grade II	28 (46.66%)	29 (48.33%)	
Grade III	17 (28.33%)	11 (18.33%)	
Tumor size			
T1c	25 (41.66%)	20 (53.33%)	0.59
T2	30 (50%)	33 (55%)	
T3	5 (8.33%)	7 (11.66%)	
Laterality			
Right	60 (100%)	60 (100%)	0.99
Left	0 (0%)	0 (0%)	
Nodal status			
N0	27 (45%)	19 (31.66%)	0.431
N1	25 (41.66%)	28 (46.66%)	
N2	5 (8.33%)	8 (13.33%)	
N3	3 (5%)	5 (8.33%)	
LVI			
Present	17 (28.33%)	20 (33.33%)	0.55
Absent	43 (71.66%)	40 (66.66%)	
PNI			
Present	17 (28.33%)	20 (33.33%)	0.55
Absent	43 (71.66%)	40 (66.66%)	
Histology			
IDC	51 (85%)	53 (88.33%)	0.59
ILC	9 (15%)	7 (11.66%)	
ER receptors			
Positive	53 (88.33%)	51 (85%)	0.59
Negative	7 (11.66%)	9 (15%)	
PR receptors			
Positive	40 (66.66%)	42 (70%)	0.69
Negative	20 (33.33%)	18 (30%)	
HER2Neu			
Positive	9 (15%)	15 (25%)	0.17
Negative	51 (85%)	45 (75%)	
Ki-67			
Low	43 (71.66%)	46 (76.66%)	0.53
High	17 (28.33%)	14 (23.33%)	

Variables are presented by number and percentage. Chi-square test was used. *P*-values less than 0.05 are significant. *P*-values less than 0.005 are highly significant. BCS: Breast conserving surgery; UOQ: Upper outer quadrant; UIQ: Upper inner quadrant; LOQ: Lower outer quadrant; LVI: Lymphovascular invasion; PNI: Perineural invasion; SD: Standard deviation; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; n: Number; DIBH: Deep inspiration breath-hold; FB: Free breathing

Table 2. Therapeutic data

	Group A (FB) (n=60)	Group B (DIBH) (n=60)	P-value
Chemotherapy			
None	15 (25%)	17 (28.33%)	0.603
AC	20 (33.33%)	15 (25%)	
AC/Taxol	25 (41.66%)	28 (46.66%)	
Radiation target			
Whole breast	27 (45%)	19 (31.66%)	0.295
WB + SC	30 (50%)	36 (60%)	
WB + SC + Axilla	3 (5%)	5 (8.33%)	
Hormonal			
None	7 (11.66%)	9 (15%)	0.758
Anastrozole	8 (13.33%)	6 (10%)	
Letrozole	2 (3.33%)	5 (8.33%)	
Tamoxifen	1 (1.66%)	1 (1.66%)	
Anastrozole + Zoladex	4 (6.66%)	7 (11.66%)	
Letrozole + Zoladex	14 (23.33%)	10 (16.66%)	
Tamoxifen + Zoladex	24 (40%)	22 (36.66%)	
Trastuzumab			
Yes	9 (15%)	15 (25%)	0.17
No	51 (85%)	45 (75%)	
Pertuzumab			
Yes	6 (10%)	10 (16.66%)	0.28
No	54 (90%)	50 (83.33%)	

Variables are presented by number and percentage. Chi-square test was used. *P*-values less than 0.05 are significant. *P*-values less than 0.005 are highly significant; FB: Free breathing; AC: Adriamycin-cyclo phosphamide; WB+SC: Whole breast + supraclavicular; DIBH: Deep inspiration breath-hold; n: Number

differences observed between the two arms (Tables 1 and 2). Most patients in both groups were premenopausal, from urban areas, and presented with invasive duct carcinoma located predominantly in the upper outer quadrant. T2

and N1 stages were the most frequently encountered tumor stages, while grade 2 tumors represented the predominant histopathological grade (46.66% in FB vs. 48.33% in DIBH). Estrogen receptors (ER)⁺, progesterone receptors

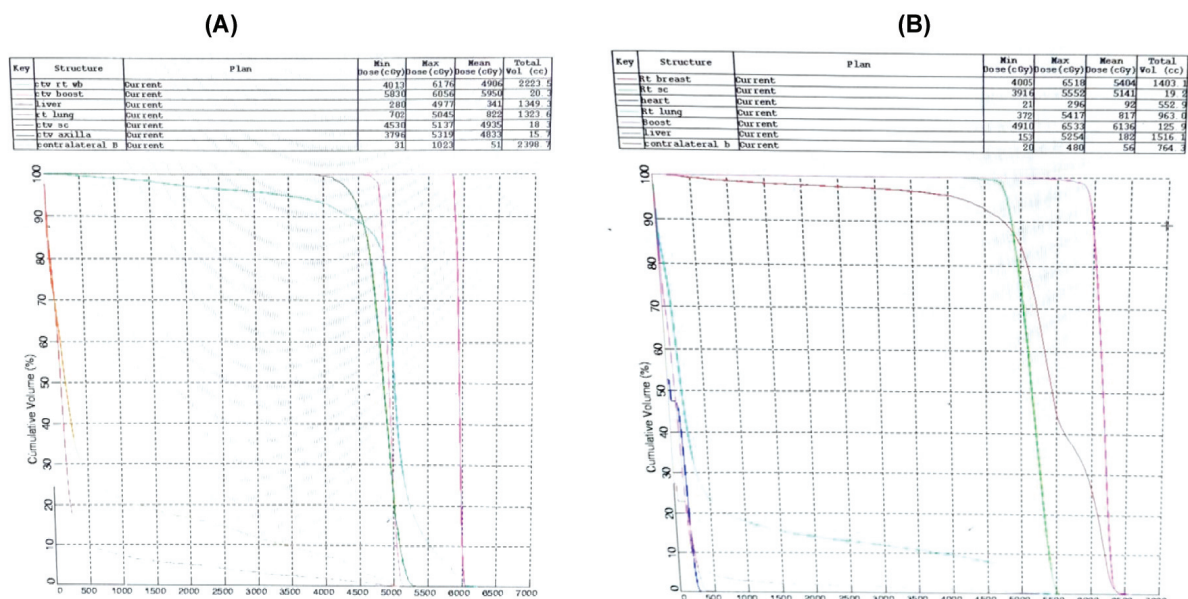


Figure 1. This figure shows the dose volume histogram indicating dose to target and OARs) DVH in FB (Free breathing) technique. B) DVH in DIBH technique.

OAR: Organs at risk; DIBH: Deep inspiration breath hold; DVH: Dose volume histogram

Table 3. Treatment and dosimetric characteristics

Group A	Group B (FB) (n=60)	P-value (DIBH) (n=60)	
Mean CTV	51.36 ± 10.40	51.60 ± 9.90	0.199
Min CTV	31.81 ± 11.32	32.81 ± 9.78	0.608
Max CTV	62.66 ± 1.94	62.64 ± 2.11	0.955
Mean boost	59.35 ± 8.30	59.47 ± 7.80	0.427
Min boost	43.09 ± 10.94	42.08 ± 8.72	0.580
Max boost	62.64 ± 1.58	62.77 ± 1.78	0.677
Mean Rtlung	10.72 ± 2.40	7.79 ± 1.14	<0.001
Min Rtlung	5.42 ± 1.87	4.85 ± 1.13	0.045
Max Rtlung	51.76 ± 5.09	48.73 ± 3.76	<0.001
Mean liver	2.03 ± 1.60	1.10 ± 0.52	<0.001
Min liver	2.89 ± 1.07	2.43 ± 0.90	0.0121
Max liver	47.86 ± 2.39	46.62 ± 2.98	0.0133
Mean heart	1.40 ± 0.19	0.92 ± 0.15	<0.001
Min heart	0.33 ± 0.08	0.31 ± 0.10	0.387
Max heart	3.45 ± 0.52	3.12 ± 0.90	0.0154

Variables are presented by mean ± SD. T-test and Mann-Whitney test were used. *P*-values less than 0.05 are significant. *P*-values less than 0.005 are highly significant. Min: Minimum; Max: Maximum; FB: Free breathing; DIBH: Deep inspiration breath-hold; n: Number; CTV: Clinical target volume

(PR)⁺, human epidermal growth factor receptor 2(Her-2) negative disease was the most common molecular subtype in both groups. No significant differences were detected regarding menopausal status, tumor characteristics, pathological findings, receptor status, or proliferative activity (Ki-67 expression) between the study arms. Chi-square testing confirmed balanced baseline characteristics across both groups.

Chemotherapy was administered in 75% of the FB group and 71.66% of the DIBH group, predominantly using the AC-Taxol regimen, while adjuvant hormonal therapy was received by 88.33% and 85% of patients, respectively. Whole breast and regional nodal irradiation was performed in 33 FB patients and 41 DIBH patients. Target volume dose parameters showed no significant differences between groups ($P > 0.05$). T-test and Mann-Whitney test were used to assess significant difference in tables 3 and 4. According to table 3, the mean, minimum and maximum doses of CTV and boost in the patients in both arms showed no significant difference ($P > 0.05$). Regarding OARs, all values were below than the tolerance dose. However, DIBH significantly reduced doses to OAR compared with FB, including the mean liver dose (1.10 vs. 2.03 Gy, $P < 0.001$), mean right lung dose (7.79 vs. 10.72 Gy, $P < 0.001$), and mean heart dose (0.92 vs. 1.40

Gy, $P < 0.001$). Maximum heart dose was also significantly lower with DIBH (3.12 vs. 3.45 Gy, $P = 0.015$). Despite these dosimetric advantages, ALT and AST levels before, during, and 3 months after radiotherapy showed no significant differences between both groups ($P > 0.05$).

Discussion

In the present prospective study, the patients were randomly allocated into 2 arms, arm A received RT with FB technique, arm B received RT with DIBH technique, each compromising 60 cases. The primary endpoint was the assessment of dosimetric parameters to CTV, boost, liver, lung and heart. The secondary endpoint was the assessment of pre-and post-treatment values of liver enzymes, intended as an early indicator of potential subclinical liver response to RBC irradiation. Much evidence has supported DIBH effectiveness in reducing the dose to the heart and other surrounding normal tissues in LBC patients.

Numerous studies have modified the way that RT is daily administered to LBC patients, and the DIBH technique is now a cornerstone in the care of certain LBC patients.^{9, 10} Prior studies have provided dose–response data that inform normal tissue complication probability modeling in radiation oncology:

Table 4. Pre- and Post-treatment liver enzymes assessment

	Group A (FB) (n=60)	Group B (DIBH) (n=60)	P-value
Pre-treatment			
AST	19.8 ± 8.85	20.27 ± 8.92	0.742
ALT	19.28 ± 8.10	23.43 ± 11.64	0.147
During treatment			
AST	20.17 ± 8.91	20.51 ± 8.46	0.744
ALT	20.86 ± 6.98	22.80 ± 7.73	0.151
3 months post-treatment			
AST	21.34 ± 5.86	22.52 ± 7.19	0.326
ALT	20.88 ± 7.04	21.50 ± 9.48	0.685

Variables are presented by mean ± SD. T-test and Mann-Whitney test were used. *P*-values less than 0.05 are significant. *P*-values less than 0.005 are highly significant. ALT: Alanine transaminase; AST: Aspartate transaminase; n: Number, FB: Free breathing; DIBH: Deep inspiration breath-hold

- **Liver:** The threshold for clinically significant RILD typically occurs when mean liver dose exceeds 30 Gy in conventional fractionation.¹¹

- **Lung:** Rades et al. reported that the risk of grade ≥2 radiation pneumonitis correlates with mean lung dose above 13 Gy and risk increases steeply beyond 20 Gy.¹²

- **Heart:** Although right breast irradiation generally results in lower heart doses compared with left-sided treatments, some exposure still occurs, particularly to RCA and atrial structures. Even low doses (e.g., 1–5 Gy) may contribute to late cardiovascular events though the evidence is stronger for left-sided cases.¹³

Our study shows that the DIBH approach can assist in lowering liver dose in RBC patients. The liver in the high-dose target location was substantially shifted by DIBH, leading to reduced liver volume in that location. Although the incidence of liver radiation exposure in the both groups (mean dose of liver is 2.03 ± 1.60 Gy in FB group, while in DIBH is 1.10 ± 0.52 Gy, $P < 0.001$) was lower than the dose limit (28 Gy), in our opinion, steps should be taken to minimize, as possible, exposure to normal tissue, while maintaining PTV coverage. We must remember that the methods currently in use may not be relevant enough or carefully selected to detect liver toxicity caused by radiation. In our study, pre-, during, and 3 months post-treatment ALT and AST values showed no significant difference between both groups ($P > 0.05$), and within three months of the end of treatment, no patient

exhibited signs or symptoms of RILD or had liver function test results that met the criteria for the condition. While no significant changes in liver enzymes were observed, this supports the safety of the technique, and dosimetric improvements may still offer long-term benefits not immediately detectable in short-term clinical parameters. Further liver dose reduction is recommended even though these dosages are currently considered safe, especially in patients who were previously treated by hepatotoxic chemotherapy regimens, as well as those with synchronous or metachronous liver tumors, and cases where in addition to breast radiation, stereotactic radiotherapy are used to treat liver metastases. As a dosimetric study, it was not the intended outcome to experience nausea or other symptoms of acute toxicity.⁶

Reduction of ipsilateral lung dose with the use of the DIBH technique is another significant finding of our study. In keeping with earlier researches,^{9, 10} DIBH during RT considerably decreased the average mean dose to the right lung when compared with FB (mean dose in FB is 10.72 ± 2.40 Gy vs. 7.79 ± 1.14 Gy in DIBH, $P < 0.001$). By expansion, DIBH lowers the ipsilateral lung dose so that less tissue is exposed to radiation in the treated area.¹⁴ In order to avoid pneumonitis as a result of RT and secondary lung cancer, it is crucial for BC patients to minimize their lung exposure. Even though the risk of radiation pneumonitis is already minimal, normal tissue-sparing radiation techniques can further lower it. While our cohort did not exhibit signs of pneumonitis, reducing mean lung dose (by 2.9

Gy in our study) may contribute to minimizing long-term pulmonary toxicity and second malignancy risks, particularly in younger patients or those receiving concurrent systemic therapy. According to Grantzau et al., after breast irradiation, smokers are primarily more likely to develop secondary lung cancer, and the median interval between receiving treatment for BC and being diagnosed with secondary lung cancer was 12 years. Despite the growing number of long-term survivors after BC treatment, advancements in normal tissue-sparing radiation techniques are still required.⁶

Furthermore, the radiation doses to the cardiac substructures, including the RCA region, both atria and both ventricles are effectively decreased when the DIBH technique is used during RBC irradiation.⁸ Compared with FB, the mean heart dose in the present study was lower with DIBH (mean dose in FB is $1.40 \pm 0.19\text{Gy}$ vs. $0.92 \pm 0.15\text{Gy}$ in DIBH, $P < 0.001$). Our findings are in concordant with those of prior studies. According to Conway et al.,¹⁰ DIBH can decrease the amount of radiation dose to heart in RBC RT. Furthermore, in almost all patients, DIBH was able to lower cardiac mass within RT fields.⁸ Nevertheless, DIBH did not result in a significant decrease in the heart dosage according to Essers et al. study.⁹ DIBH has a well-established heart-sparing effect on patients with LBC, and this method can result in a considerable obvious dose reduction. Even though cardiac exposure is already minimal in patients with RBC, every attempt should be made to achieve maximal cardiac protection because even minimal cardiac exposure reductions may have long-term, clinically real advantages.¹⁵ Implementing DIBH does not come with a significant cost. According to an Indian study, DIBH can lower cardiac complications in patients with LBC at a reasonable cost.^{16, 17}

The DIBH approach has certain downsides: DIBH treatment delivery takes more time than FB and setup is more complicated. With more experience, we hope to ultimately reduce the time required for DIBH setup. Short follow-up period, three months, was a limitation also as it was insufficient for assessing late toxicity. While we

acknowledge that a three-month follow-up ALT and AST levels may not capture late onset RILD, the aim was not to establish a diagnosis of RILD, but rather to observe short-term biochemical changes that may correlate with liver radiation dose. Future studies with longer follow-up and imaging are warranted to fully assess the risk of RILD. Another limitation of this study is the use of even/odd sampling method for group assignment. Although sampling method was intended to imitate random allocation, it lacks the unpredictability of true randomization and may be susceptible to allocation bias. Additionally, since all patients underwent breast-conserving surgery without lymph node boost, the findings may not be generalizable to mastectomy cases or nodal irradiation. Nonetheless, we might have to accept the limitation of this method if our aims are to protect the surrounding normal organs and to decrease co morbidities and mortalities. Further studies are warranted to assess the economic impact, long-term cardiac and hepatic outcomes, and workflow implications of DIBH in clinical practice. The strength of the present study lies in the prospective and the presence of serial liver function test results, pre-, during, and three months post-treatment assessment as an early indicator of potential subclinical liver response to RBC irradiation.

Conclusion

DIBH is an efficient method for lowering radiation doses to the liver, ipsilateral lung, and heart in RBC patients. Future prospective studies with more large cohorts with long term monitoring of toxicity and clinical findings should be designed to find out the dosimetric benefits gained from applying DIBH with RBC-RT.

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Authors' Contribution

N.G.E, D.A.H, N. N.H.A, M.I.S and A.E: Study design; data acquisition; data analysis and interpretation; drafting and critical reviewing of the manuscript. All authors read and approved the final manuscript version and agreed with all parts of the work in ensuring that any queries about the accuracy or integrity of any component of the work are appropriately investigated and handled.

Conflict of Interest

No potential conflict of interest relevant to this article was reported. The authors alone are responsible for the content and writing of the paper.

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