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Dosimetric Efficacy of Voluntary Deep Inspiration Breath-Hold in the Radiotherapy of Left Breast Cancer Patients Using the UK START Trial

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ABSTRACT

Introduction: Deep inspiration breath-hold (DIBH) technique is widely administered to left breast cancer (LBC) patients to reduce the cardiopulmonary radiation doses. The UK standardization of breast cancer radiotherapy (UK START) dose prescription was found comparable to the conventional schedule. The current study compared voluntary DIBH and free-breathing (FB) methods in the cardiopulmonary radiation doses of LBC patients with supraclavicular irradiation treated with the UK START trial.
Material and Methods: Computed tomography (CT) scans were acquired for a group of 50 LBC patients in DIBH and FB and a radiotherapy plan was created on each scan. The dose-volume histogram parameters of the heart and lung were analyzed against their relevant first clinical acceptance criteria using one-sample t-test. Additionally, the correlation between the ipsilateral lung volume expansion and the cardiopulmonary dosimetric benefits was assessed.
Results: The cardiopulmonary radiation doses were significantly reduced in DIBH compared with FB. For DIBH, the mean difference between the mean heart dose (MHD), Heart V_{16Gy}, and Lung V_{16Gy} and their first acceptance criteria was -62.6 cGy, -0.63%, and -2.18% ($p < 0.001$), respectively. In contrast, the first acceptance criteria of the cardiopulmonary dosimetric parameters were not accomplished with the FB method. In addition, the difference in MHD and heart V_{20Gy} between DIBH and FB plans showed a moderate correlation with ipsilateral lung volume expansion ($r = 0.51$ and 0.5, respectively).
Conclusion: DIBH technique should be served to all locally advanced LBC patients, and the ipsilateral lung volume expansion could be a predictor for the cardiac-sparing radiotherapy in LBC.

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Introduction

Radiotherapy is a substantial treatment modality that is given to breast cancer patients after breast surgery as radical treatment to diminish the likelihood of tumor relapse [1,2]. The conventional dose regimen for breast cancer radiotherapy has been 50 Gy with 25 fractions that has been used over the last decades. The UK standardization of breast cancer radiotherapy (START) trialists group introduced a hypofractionation dose regimen (40 Gy/15 fractions). They found that such a hypofractionation regimen is comparable to the conventional schedule [3]. In addition, the American society for radiation oncology (ASTRO) guideline preferred the hypofractionation regimens such as 42.56 Gy in 16 fractions or 40.05 Gy in 15 fractions in whole breast radiotherapy [4].The administration of radiotherapy in left-sided breast cancer (LBC) has been shown to raise the coronary diseases due to increasing the mean dose of the cardiac structures [5,6]. In addition, the irradiated lung volume is directly correlated to the deterioration of its functions [7]. These studies were designed to ensure sufficient irradiation to the target volumes while minimizing feasibly the irradiated volumes of the organs at risk to avoid late toxicity [8].

Several studies have shown that in LBC radiotherapy, deep inspiration breath-hold (DIBH) has dosimetric priority over the conventional free breathing (FB) method, where it can provide a sufficient reduction in irradiated cardiopulmonary volumes. These studies were planned on the basis of scanning the patients at the same computed tomography (CT) session in DIBH and FB.

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Subsequently, target volumes and risk organs were delineated to create two plans for dosimetric comparison purposes. The studies have been conducted on patients with or without regional lymph nodes irradiation, and have been undergone whether breast conservative breast surgery (BCS), modified radical mastectomy (MRM), or both operations [9–13].

A previous study discussed the benefits of DIBH radiotherapy with right-sided breast cancer patients, and the authors found a superiority of DIBH technique over FB in the reduction of the ipsilateral lung and the right coronary artery dosimetric parameters especially in the patients with regional nodal irradiation [14].

There are two types of DIBH the moderate DIBH such as the active breath coordinator system (ABC from Elekta, Stockholm, Sweden) and the voluntary DIBH (vDIBH) such as the real-time position management system (RPM from Varian Medical systems, Palo Alto, Ca, USA). The ABC is a spirometry-based device, which monitor the breathing pattern by measuring the lung volume through the air flow entering the lung of the patient who is performing the breath-hold. Alternatively, the RPM system utilizes a camera to monitor the displacement of a marker block placed on the abdomen of the patient, and the marker contains six dots that reflects the infrared (IR) rays produced by an IR emitter back to the camera [12].

Almost dosimetric comparisons studies were performed with the conventional dose fractionation except single study was performed with the UK START trial with the moderate DIBH technique [15]. However, UK START trialist group approved that the dose prescription of 40.05 Gy in 15 fractions was comparable to the conventional scheme [3]. A recent study was performed by our group employing the RPM system to compare between DIBH and FB methods in LBC patients with the UK FAST trial [16]. Another study was performed with dose regimen 50.4 Gy in 28 fractions using the RPM system [9]. However, according to our knowledge no dosimetric comparison study was performed with the UK START trial using the RPM system.

The aim of the current study was therefore to assess the efficacy of vDIBH technique in the radiotherapy of LBC patients treated with the UK START trial. Additionally, the correlation between the lung volume expansion due to DIBH and its relevant dosimetric benefits was assessed.

Materials and Methods

Patient Selection

The current study was approved by Baheya hospital research ethics committee. In a retrospective manner, fifty female LBC patients who were referred to receive their post-operative radiotherapy from June 2019 to May 2020 were enrolled in the current study. Out of the 50 selected patients, 35 patients underwent MRM, and 15 patients underwent BCS. The patient selection was based on the cooperative conditions including the ability to receive the instructions of the DIBH methodologies and the ability to hold the breath for more than 15 seconds. Patients with hearing problems and intellectual disabilities were excluded from the study and completed their treatment in FB.

Patient training and CT-Simulation

All patients were immobilized with a supine breast board from Q-Fix (Avondale, PA, USA) with two hand support sticks, and it was tilted by 10°. Additionally, two indexers were used to fix the breast board on distinct coach positions to ensure the reproducibility of the superior-inferior and left-right shifts. The breast board angle was elevated in BCS patients, especially for large breast patients, to avoid the probable contouring overlap between the breast and supraclavicular lymph nodes.

CT scans were acquired and reconstructed every 4 mm using a CT simulator (Siemens, SOMATOM Definition AS, VA48A). The average scan time was 15 seconds and the slice thickness was 4 mm. A CT-FB (

Figure 1a) was acquired for all patients before acquiring the CT-DIBH (

Figure 1b) to avoid the lung tissue stretch that would be resulted from the DIBH training. The DIBH training session was lasting 30 minutes before the CT scan. The DIBH technique was done using the RPM system, and a six dots reflector marker block was positioned on the abdomen of the patients (Figure 2). The patient was instructed to take three consecutive deep breaths and exhale them before performing the DIBH. Subsequently, the breath-hold level was defined with a gating window of 5 mm.

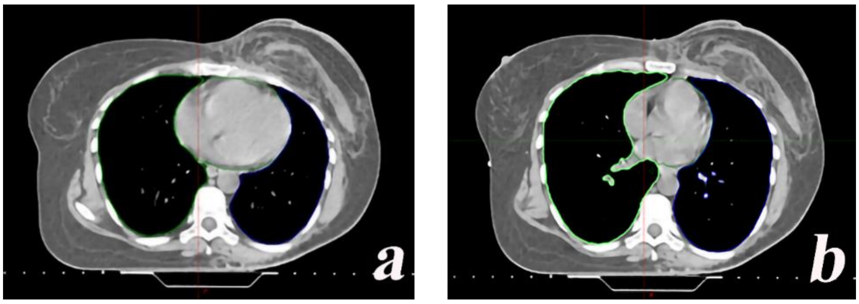
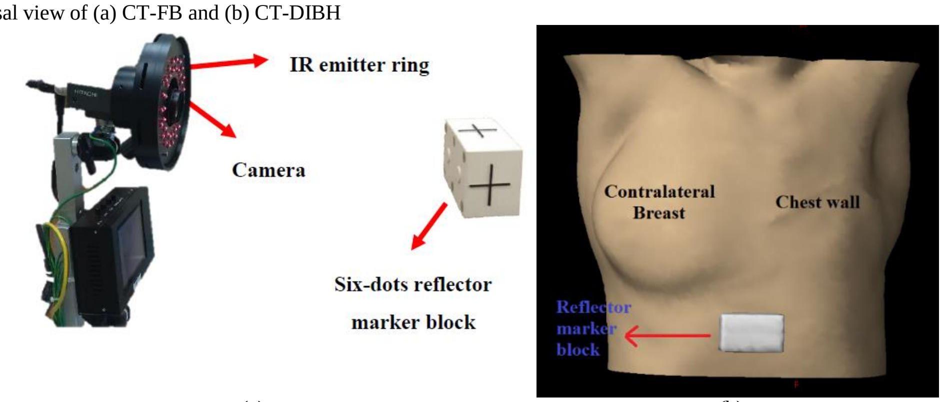


Figure 1. Transversal view of (a) CT-FB and (b) CT-DIBH



(a) (b)

Figure 2. (a) RPM System including the IR emitter ring, which emits IR to the reflector marker block that accordingly reflects the IR to the camera at the center of the IR emitter ring. (b) Position of the reflector marker block midway between the xiphoid process and umbilicus.

Table 1. Departmental clinical acceptance criteria for hypofractionation scheme whole breast radiotherapy

	Dosimetric parameter	Acceptance criteria
Heart	MHD (cGy)	≤ 320 – 400
	$V_{16Gy} – V_{20Gy}$	≤ 5%
Lung	$V_{16Gy} – V_{18Gy}$	≤ 20% - 30%
PTV	$D_{90\%}$	≤ 95% - 90%
	$D_{107\%}$	≤ 2%

MHD: Mean heart dose; V_x: the relative volume of the organ received at least X Gy; PTV D_x: The relative dose delivered to volume X of the PTV.

Table 2. Paired sample t-test results of the comparison between the CT-DIBH and CT-FB in the organs at risk dosimetric parameters

Structure	Dosimetric Parameter	CT-DIBH	CT-FB	RR (%)	p-value
Heart	MHD (Gy)	2.57	4.07	36.86	< 0.001
	V_{16Gy} (%)	4.37	8.44	48.22	< 0.001
	V_{20Gy} (%)	3.85	7.84	50.89	< 0.001
Lung	V_{16Gy} (%)	17.82	21.36	16.57	< 0.001
	V_{18Gy} (%)	17.16	20.63	16.82	< 0.001

RR: Relative reduction; MHD: Mean heart dose; V_x: the volume of the organ received at least X Gy.

Table 3. Dosimetric comparisons studies using the ABC system

Study	No. of patients	No. of CT-DIBH	No. of CT-FB	RR in MHD (%)	RR in lung V_{20Gy} (%)	Dose regimen (Gy/fxn)
Wang et al.[31]	20	20	20	58.51**	7.69*	50/25
Nissen and Appelt [32]	227	144	83	48.07**	16.19^{*1} 9.92^{*2}	50/25
Swanson et al. [33]	87	87	87	40.48**	17.65**	45/25
Eldredge-Hindy et al. [21]	86	86	86	66.67**	13.33*	50.40/28
Chi et al. [34]	31	31	31	44.33*	29.23*	50/25
Mohamad et al. [22]	22	22	22	61.42**	16.87**	50.40/28
Kunheri et al. [15]	45	45	45	48.54**	8.75^{n}	40/15
Lin et al. [35]	369	107	262	52.45**	25.00**	50/25

RR: Relative reduction; MHD: Mean heart dose; Lung V_{20Gy} the volume of the lung received at least 20 Gy of the prescribed dose.
^{1} Supraclavicular field; ^{2} No supraclavicular field
* $p < 0.05$; ** $p < 0.001$; ^{n} non-significant.

Table 4 Dosimetric comparisons studies using vDIBH methods

Study	No. of patients	No. of CT-DIBH	No. of CT-FB	RR in MHD (%)	RR in lung V_{20Gy} (%)	Dose regimen (Gy/fxn)
Stranzl et al. [20]	11	11	11	37.50**	14.00*	50/25
Johansen et al. [36]	16	16	16	61.56*	NA	50/25
Vikström et al. [29]	17	17	17	54.05*	18.03*	50/25
Hjelstuen et al. [37]	17	17	17	50.00**	26.52**	50/25
Hayden et al. [26]	30	30	30	42.44**	4.74^{n}	50/25
K. H. Sung et al. [38]	22	22	22	49.15**	NA	50.4/28
Yang et al. [27]	28	28	28	50.00*	0.40^{n}	50.4/28
Rochet et al. [25]	35	35	35	64.00**	16.46*	50/25
Tanguturi et al. [30]	146	110	38	46.09**	8.56*	50/25
Joo et al. [23]	32	32	32	61.46**	11.64**	50/25
Hepp et al. [39]	20	20	20	47.22**	29.41**	50/25
Schönecker et al. [40]	13	13	13	52.01*	26.29*	50/25
Saini et al. [11]	33	33	33	43.75**	5.08**	42.56/16
Simonetto et al. [19]	89	89	89	35.00**	NA	50/25
Vuong et al. [28]	29	29	29	49.33**	11.03^{1n} 18.66^{2*}	50/25
Morsy et al. [9]	15	15	15	40.50**	18.00**	50.4/28
Chang et al. [10]	21	21	21	41.08**	14.67^{n}	50/25

RR: Relative reduction; MHD: Mean heart dose; Lung V_{20Gy} the volume of the lung received at least 20 Gy of the prescribed dose; NA: not available
^{1} Supraclavicular field; ^{2} No supraclavicular field.
* $p < 0.05$; ** $p < 0.001$; otherwise, ^{n} non-significant.

Treatment planning

The target volumes, heart, and the ipsilateral lung were contoured following the RTOG-1005 breast cancer atlas [17]. For research purposes, and in a retrospective manner, the chest wall and supraclavicular lymph nodes were contoured while the axillary and internal mammary lymph nodes were excluded. The chest wall was contoured from the caudal border of the clavicle head cranially to the end of the contralateral breast caudally, and from the sternal-rib junction medially to the latissimus dorsi muscle laterally. The radiotherapy plan was prescribed to 40.05 Gy in 15 fractions (the START trial scheme) for the whole breast or chest wall plus the supraclavicular lymph nodes.

The radiotherapy plans were created with field-in-field forward intensity-modulated radiotherapy technique on the CT-DIBH and CT-FB scans using the treatment planning system (Eclipse™, version 13.6, Varian Medical Systems). The treatment beams were adjusted to be tangential with 6 MV energies for the small separation patients, and 15 MV energy was utilized for patients of large separation. Two subfields per field were used to improve the dose homogeneity within the PTV by increasing the dose to the areas that were not covered with 100% of the prescribed dose. The PTV was intended to receive the same dose coverage in the DIBH-CT and FB-CT plans. The algorithm used in dose calculations was the anisotropic analytical algorithm (AAA) with grid size 2.5 mm. The dose rate was set to 600 MU/minute and the treatment plans were transferred via the oncology information system (ARIA, Varian Medical Systems) to the linear accelerator (Clinac iX™, Varian Medical Systems).

Data collection and statistical analysis

The DVH data were collected on a spread sheet and analyzed using Statistical Package for Social Sciences software (SPSS V20, IBM; Inc.). Paired sample t-test was performed to compare between CT-DIBH and CT-FB plans in the ipsilateral lung volume, the ipsilateral lung volume received at least 16 Gy (V16Gy), mean heart dose (MHD), and the heart V20Gy. In addition, we calculated the relative dose reduction (%) of the MHD and lung V16Gy using ((1). Moreover, the average MHD and lung V16Gy in the current study were compared with similar previously published studies with the active breath coordinator (ABC) system (

Table 3) and with vDIBH methods (Table 4).

$$\text{Relative Dose Reduction (\%)} = \frac{X_{FB} - X_{DIBH}}{X_{FB}} \quad (1)$$

The dosimetric parameters of CT-DIBH were tested against their first clinical acceptance criteria (

Table 1) using one-sample t-test to determine the mean difference between the risk organs doses for the DIBH technique and the departmental acceptance criteria to study the efficacy of the DIBH technique.

A Pearson correlation test was performed to show the correlation between the absolute reduction in the heart and lung dosimetric parameters between the CT-DIBH and CT-FB plans and the ipsilateral lung volume expansion ((2). Values of Pearson correlation coefficient (r) range from -1 to 1, where the sign indicates the direction of the relationship. The absolute value of r indicates the strength, and the strength of the correlation was classified according to

Evan's correlation guide [18] into very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.00). A p-value of less than 0.05 was considered statistically significant, and all tests were two-tailed.

$$\text{ILV expansion} = \frac{LV_{DIBH} - LV_{FB}}{LV_{DIBH}} \quad (2)$$

Where ILV is the ipsilateral lung volume, Dose Reduction (%) is the relative dose reduction between the CT-DIBH and the CT-FB plans, X_{FB} is the dosimetric parameter calculated on the CT-FB scan, and X_{DIBH} is the dosimetric parameter calculated on the CT-DIBH scan.

Results

All dosimetric parameters in the CT-DIBH plans were significantly lower than the CT-FB plans ($p < 0.001$) when the PTV coverage was kept to be the same in both scans (Table 2). The average PTV D90% was 95% ± 1.2% and the average maximum point dose was 107.6% ± 0.5%.

The OARs dosimetric parameters were below the first criteria when planning with the DIBH technique. The mean difference between the first clinical acceptance criteria and the calculated MHD in the CT-DIBH was -62.6 cGy ($p < 0.001$). For the heart V16Gy and V20Gy, the mean difference was -0.63% ($p = 0.07$) and -1.2% ($p < 0.001$), respectively. For the lung V16Gy and V18Gy, the mean difference was -2.18% ($p < 0.001$) and -2.84% ($p < 0.001$), respectively. On the other hand, CT-FB plans could not accomplish the optimal dosimetric parameters for the OARs as shown in **Error! Reference source not found.**.

The average MHD and lung V16Gy in the current study were compared with similar previously published studies with the active breath coordinator (ABC) system (Table 3) and with vDIBH methods (Table 4).

The average ipsilateral lung volume in DIBH scans was 1826.82 ± 304 cm3 and it was significantly higher than the FB scans where it was 1073.12 ± 267.7 cm3 ($p < 0.001$) and the average relative lung expansion was 41.26%. There was a positive moderate correlation between the ipsilateral lung volume expansion and the reduction in MHD, the heart V16Gy and V20Gy between the CT-DIBH and the CT-FB plans ($r = 0.51$, $p < 0.001$), ($r = 0.49$, $p = 0.001$), and ($r = 0.50$, $p = 0.003$), respectively (**Error! Reference source not found.**). There was no correlation between the reduction in the lung doses and the lung volume expansion ($p > 0.05$).

Discussion

Different studies confirmed that the DIBH technique could minimize the cardiopulmonary radiation toxicity compared to the conventional FB method [9–13]. The reduction in cardiac doses was substantially due to the increase in the separation between the posterior border of the tangential fields and the cardiac structures [19]. In addition, most of the studies that conducted dosimetric comparisons between DIBH and FB method in breast cancer radiotherapy found a significant reduction in lung doses [12,13].

Most studies were performed using the conventional dose regimen of breast cancer radiotherapy (50 Gy/25 fractions), nevertheless, two studies only were conducted with the hypofractionation dose regimens [11,15]. However, the UK START trialist group approved that the dose prescription of 40.05 Gy in 15 fractions was comparable to the conventional scheme [3]. Furthermore, dosimetric comparisons between DIBH and FB were performed by our group to assess the safety of treating LBC patients in FB with the UK FAST trial dose prescription [16].

According to our knowledge, this is the first study to compare DIBH and FB methods in LBC patients with the UK START trial using the RPM system. Our results are consistent with previous studies, which reported that DIBH reduced the cardiopulmonary structures in comparison to the FB method. The relative reduction in MHD in the present study was about 38%, which goes in line with that reported with Stranzl et al. [20] and comparable to other studies [12,13]. Conversely, other studies showed a higher relative reduction in MHD (higher than 60%) due to setting inclusion criteria before conducting their studies [21–23].

Korreman et al. demonstrated in a pilot study that the DIBH technique was superior in the cardiac dose reduction compared to other respiratory gating management methods [24]. Our results were consistent with their results in terms of cardiac dose reduction with improvement in relative dose reduction. In their work, the relative reduction in heart volume that received 50% of the prescribed dose was 90% whereas the present study achieved a reduction of about 51%. In addition, they conducted their investigation on small sample size (17 patients), eight of them were right-sided breast cancer patients, which perhaps accentuated the relative reduction percent. While our study was composed of 50 patients all of them were LBC scanned in DIBH and FB at the same CT-simulation session to avoid statistical bias.

Our results showed a significant reduction in the ipsilateral lung V_{16Gy} and V_{18Gy} with 17% in DIBH compared with FB plans. These results were comparable to previous studies, where a significant reduction in the intermediate dose delivered to the ipsilateral lung volume was shown in DIBH compared to FB plans [22,25]. On the other hand, other studies found no significant reduction in the ipsilateral lung doses between both methods [10,15,26,27]. A previous publication supposed that only patients who underwent BCS and without regional nodal irradiation had a significant reduction in lung volume received an intermediate dose of the prescription when using DIBH [28]. In contrast, we retrospectively planned all patients with the additional supraclavicular field and found a significant reduction in lung doses.

The ipsilateral lung volume was increased by about 41% when scanning the patients in DIBH compared with the FB, which in agreement with previous reports

[20,29]. The increase in lung volume causes the heart to be pushed away from the tangential beams, and this explains the correlation between heart dosimetric parameters and ipsilateral lung volume expansion. This is in good agreement with a previous work that discussed the correlation between the difference in lung volume expansion and the difference in MHD measured for DIBH and FB plans [30].

In contrast, there was no correlation between ipsilateral lung volume expansion and the relative reduction in lung V_{16Gy} and V_{18Gy}, and this disagreed with a similar published work [28]. This contradiction could be explained by the inclusion of more lung volume within the tangential fields in patients who exhibited a pigeon-shaped chest wall after performing the deep inspiration.

Our results displayed that the DIBH technique accomplished the first clinical acceptance criteria of the UK START trial for the OARs of LBC patients without compromising the PTV coverage. However, the insignificant decrease that was shown in the heart V_{16Gy} concerning its clinical acceptance criterion exploits the importance of training the patients on the DIBH technique. As a result of increasing the training session period, the lung volume could be expanded more, which was positively correlated with cardiac dose reduction. Consequently, and otherwise contraindicated, we highly recommend considering the DIBH technique as the standard approach of treating LBC patients provided adequate training on the DIBH process before CT scanning to get the most advantage of such a technique.

Conclusion

The DIBH technique should be the standard of care for the radiotherapy of LBC patients due to its superiority on the FB method in the significant reduction in heart and lung dose without compromising the target coverage. In addition, the ipsilateral lung volume expansion could be a predictor for cardiac-sparing radiotherapy for LBC patients.

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