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A Comparative Study of 3-D Conformal Radiotherapy Treatment Plans with and Without Deep Inspiration Breath-Hold Technique for Left-Sided Breast Cancer

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ABSTRACT

Introduction: The rate of cardiac diseases have increased among patients who underwent radiotherapy for left-sided breast cancer. The study's aim was evaluate the dose to organs at risk in free-breathing 3-dimensional conformal (FB-3DCRT) against 3-dimensional conformal deep inspiration breath-hold (3DCRT-DIBH) in patients with left-sided breast cancer.

Material and Methods: In total, 15^{th} female patients diagnosed with left-sided breast cancer were included in this study from December 2017 to December 2018. All selected patients were subjected to FB and DIBH computed tomography (CT) scans. The 3DCRT plans were created on both DIBH and FB scans for each selected patient. Various doses were obtained from dose-volume histograms and then compared. The data were analyzed in SPSS software (version 20) (IBM; IL). P-value less than 0.05 was considered statistically significant.

Results: The results obtained from the DIBH and FB conditions were compared. The average maximum dose and V95% for planning target volume was approximate for both DIBH and FB, and the average mean doses to the heart, left anterior descending artery, and left lung were decreased by 40.50% (P=0.0003), 54.30% (P=0.02), and 18.50% (P=0.0002) in DIBH, respectively. Moreover, the heart V25% and V30% were decreased by 36% (P=0.06) and 35.8 % (P=0.03) in DIBH, respectively. Regarding the left lung, a decrease by 18.10% in V10 % (P=0.0006) and 18% in V20% (P=0.0002) was also observed in DIBH.

Conclusion: The 3DCRT-DIBH for patients with left-sided breast cancer maintained the benefits of radiotherapy while minimizing cardiac risks. All patients completed their treatment smoothly.

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Introduction

The majority of left-sided breast cancer women are treated by adjuvant radiotherapy after undergoing primary surgery to reduce the early-stage locoregional recurrence rate and locally advanced breast cancers that demonstrated improvement in overall survival. However, left-sided breast cancer radiotherapy treatment was associated with higher mean cardiac radiation dose. Many studies also showed the increased rate of morbidity and mortality in patients with extrapolated mean cardiac radiation dose, compared to patients with right-sided breast cancer [1,2].

If the cardiac absorbed dose could be decreased, the major coronary problems and cardiac deaths would decrease as well. Respiratory and breathing motion during radiotherapy can make the tumor to move out of the radiotherapy treatment field. As a result, it will become difficult to give the tumor's prescribed radiation dose accurately. And this, in turn, can lead to an underdosing in the cancer cells and unnecessary overdosing in the adjacent healthy tissues [3-6].

In recent years, many techniques and clinical solutions have been considered to decrease cardiac toxicity, such as prone positioning in which the patients are treated lying on their stomach. The radiation is directed at the breast tissue, which hangs through an opening in the prone breast board and the contralateral breast does not hang through the prone breast board. This method decreases the contact distance between the breast tissue and chest walls and reduces the radiation toxicity to nearby organs, including the lungs and the heart; however, this method was less beneficial to patients with small breast cancer.

The intensity-modulated radiotherapy (IMRT) is another practice of breast cancer radiotherapy treatment which has been progressively used in recent years. It has an advantage of improving the target dose homogeneity, dose distribution, and

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sparing normal tissue structures that receive high doses either in inverse (tangential fields IMRT) or forward planning (field-in-field technique).

Furthermore, the volume modulated arc therapy (VMAT) is an additional form of IMRT that has developed in recent years. In VMAT, the linear accelerator gantry rotates 360 degrees around the patient during radiotherapy treatment. The advantages of this therapy over the IMRT technique include shorter treatment time and fewer monitor units [7].

Additionally, deep inspiration breath-hold (DIBH) is another way to minimize the heart absorbed dose during left breast cancer radiation treatment by reducing its volume and movement in the radiation treatment fields [8-11]. Controlled DIBH and voluntary DIBH were the most common modalities of DIBH. The controlled DIBH can be achieved with active techniques using spirometry-based active breathing coordinator. Active breathing coordinator (ABC) device (Elekta, Stockholm, Sweden) is known as an example of this modality. The ABC process begins when the patient takes a deep inspiration breath and pushes enough air to fill his/her lungs and hold it. The volume of the taken air will be measured by the ABC device, and the ABC's valve (in the breathing tube) will lock off at the predefined air volume and then the patient will not be allowed to breathe again during the breath-hold. The valve automatically opens at the end of the breath-hold procedure.

The other clinical modality of DIBH is voluntary breath-hold. In this modality, the patients were instructed to carry out deep inspiration breathhold which usually takes ≥ 20 seconds at a time. When the patients capture a deep breath, the lungs are filled with air and this pushes back the heart to move away from the chest when radiation is being delivered. Once they exhale, the machine automatically closes off the radiation.

Figure 1. Varian real-time position management system

The treatment procedure is usually completed in a few successive breaths. The voluntary DIBH can be achieved using a Varian real-time position management (RPM) system (Figure.1) (Varian Medical Systems, Palo Alto, CA, USA). This system reflects the marker box that is placed on the patient's chest based on the motion of the external infrared (IR) and can be detected using an IR tracking camera that produces a real-time visual image. The respiratory motion is measured as a waveform, and the gating thresholds can be defined through it. The beam can be stopped automatically during the treatment when the patient's breathing falls outside the predefined threshold [12-15].

Materials and Methods

Patient Selection

The major challenge in this study was patient selection which required some degree of effective patient cooperation for the procedures to be implemented correctly. In total, 15th consecutive female patients with left-sided breast cancer were diagnosed and treated from December 2017 to December 2018 according to our center protocol for DIBH. This protocol included the patient selection methodology policy, the gating thresholds, the marker block location at patient's surface, the patient position on the CT couch, patient coaching's instructions, and DIBH CT scan procedures. The inclusion criteria were the ability to perform consistent breath-hold and keep DIBH ≥20 sec. On the other hand, the patients who had respiratory problems that prevented them from keeping their breath-hold ≥20 sec were excluded from the study.

Deep inspiration coaching and CT-Simulation

The selected patients were given instructions and coached by the radiotherapy staff to ensure that they could evenly stable their breath and hold their deep inspiration for about ≥20 sec during the CT-scan and treatment [16,17]. The patients were immobilized in the supine position, placed on a carbon fiber breast board with both arms abducted above the head, and underwent free-breathing (FB) and DIBH CT-scans in the same position. In this study, GE Discovery RT 16-slice advanced radiation therapy planning computed tomography (CT) system is used for simulation and scanning (GE Healthcare, Chicago, Illinois, United States).

The RPM system (Varian Medical Systems, Palo Alto, CA, USA) was an external motion tracking system that used to observe the patients' DIBH (Fig.1). A Perspex box containing six IR reflecting markers was placed on the patient's chest at the level of the diaphragm outside the treatment area. It was detected by an IR camera located at the end of the CT couch to register the patient's respiratory cycle by detecting the anterior-posterior motion of the marker box.

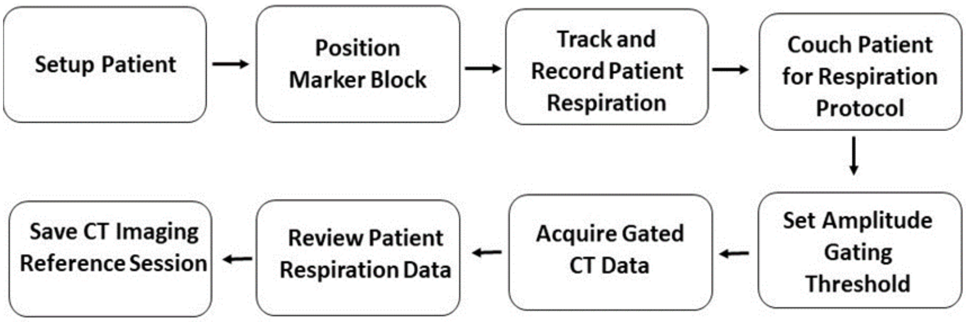

Figure 2. Deep inspiratory breath-hold imaging process

The patient's breathing trace was observed on the RPM workstation. Verbal instructions were given to the patients via the intercom to breathe in and hold their breath for approximately 20 sec. Subsequently, they were instructed to breathe normally. The amplitude gating threshold lines were determined to a level just above and just below the breath-hold level. The breath-in and breath-hold processes were repeated several more times until the patients could achieve the same amplitude multiple times and feel comfortable to the DIBH technique. A helical CT was acquired sequentially in 2.5-mm slices for both FB and DIBH scans (Figure.2)

Contouring

The contouring of clinical target volume (CTV) and critical structures (i.e., heart, left anterior descending (LAD) region, and lungs) were performed according to clinical practice guidelines [18-20]. The planning target volume (PTV) was created by expanding CTV by 5 mm in all directions but no closer than 3 mm to the skin in both CTs. Both FB and DIBH CT scans were contoured by the same oncologist using the treatment planning system (Eclipse™ v. 15.6) automatic delineation tools (Varian Medical Systems, Palo Alto, CA, USA).

Table 1. Clinical criteria planning

PTV D95	≥95 %
PTV D05	≤110 %
Ipsilateral lung V20 Gy	≤33 %; ≤30 % (with DIBH)
Ipsilateral lung V10 Gy	≤68 %; ≤63 % (with DIBH)
Ipsilateral lung mean dose	≤20 Gy; ≤18 Gy (with DIBH)
Heart V25 Gy	≤25 %
Heart maximum point dose	≤50 Gy
Heart mean dose, left breast	≤8 Gy
Left anterior descending maximum point dose	≤50 Gy

Treatment planning

Both FB and DIBH CT scans were planned by the same medical physicist to ensure plan uniformity. A total dose of 50.4 Gy in 28 fractions over 5-6 weeks was prescribed according to the clinical practice guidelines in oncology for left breast cancer [21-23]. Table 1 summarizes the main planning clinical criteria [24]. All patients were treated by the field-in-field technique which is also known as a forward IMRT planning technique. The beam directions used in the field-in-field technique were the same as those for 3D conformal planning with two opposed tangential beams.

A 3-D dose distribution was first calculated for equally weighted open fields without any wedges. Therefore, the dose distribution was inhomogeneous in breast treatment planning. These isodose surfaces are usually between 100 and 125 %. The MLC segments were designed to block these surfaces permitting the customization of tissue compensation. Subsequently, each segment was given a weight, and a dose distribution was calculated in this study. Segment weights were optimally modified so that hotspots were minimized without compromising acceptable coverage to the breast volume.

The field-in-field technique produces a lower hotspot and reduces the time of treatment, thereby reducing the total body exposure due to leakage radiation, compared to wedged fields without compromising coverage to the breast volume. The 6-10 MV photon beam energy was used for DIBH and FB. The dose distributions were calculated using the (Eclipse™ v. 15.6) treatment planning system supported by the anisotropic analytical algorithm (AAA) for both DIBH and FB treatment plans. The absorbed dose was normalized as 100% as the mean absorbed dose in the PTV. All patients were treated by Varian Medical Systems (Clinac iX™) linear accelerator equipped with a multi-leaf collimator (MLC) with 120 leaves (Varian Medical Systems, Palo Alto, CA, USA).

Dosimetric Evaluation

Various doses were obtained from the dose-volume histograms to evaluate the functional parameters for comparison of the plans. The coverage (D95%), homogeneity index, (HI) and dose conformity index (CI) of the PTV on FB and DIBH scans for each patient were recorded according to:

$$\text{Homogeneity index (HI)} = \frac{(D2\%-D98\%)}{D50}\ ; (HI\ ideal\ is\ zero)$$

$$\text{Conformity index (CI)} = \frac{V95\%}{PTV\ volume}\ ; (CI\ ideal\ is\ 1.0)$$

Where D2%, D98%, and D50% were doses received by 2%, 98%, and 50% of the volume, respectively. In addition, V95% was the volume of PTV covered by the 95% isodose lines, and the significant dose of organs at risk (OAR) was determined according to General QUANTEC Guidelines for heart volume and left-sided lung on both FB and DIBH scans.

Statistical Analysis

The data were analyzed in SPSS software (version 20) (IBM; IL). In addition, a paired sample t-test was used to compare the sample mean differences. P-value less than 0.05 was considered statistically significant. As a result of the comparison between the DIBH and FB techniques, the percent relative reduction for mean heart dose, mean LAD dose, mean left lung dose, and lung V20 can be calculated according to:

$$V20 = 100 \times \frac{X_{FB}-X_{DIBH}}{X_{FB}}$$

Where X is a given quantity of organ volume or dose.

Results

Table 2 depicts the comparison of average dose parameters to target volumes and OARs for FB and DIBH which were clinically acceptable and yielded the same coverage of the PTV. Moreover, (Figure.3) illustrates the same CT planning axial image of the left-sided breast cancer patient in FB (3a) and DIBH CT-scans (3b), where the target volume of the breast covered by 95% of the prescribed dose. According to the results, the average maximum dose prescribed to the whole left-sided breast was 53.69 Gy, and the V95 % was obtained at 95.8% (P=0.0006) in DIBH condition. Regarding FB condition, the average maximum dose was 53.47Gy, and V95% was estimated at 96.2%.

Table 2. Comparison of volume and dosimetric data using free breathing and deep inspiration breath-hold plans

		Deep inspiration breath-hold	Free breathing	P-value
Planning target volume of the breast	Max. Dose Gy	53.69	53.47	< 0.05 *
	V 95 %	95.8	96.2	< 0.05 *
	CI	0.95	0.95	< 0.05 *
	HI	0.13	0.14	< 0.05 *
Heart	Mean Dose Gy	2.28	4.18	< 0.05 *
	V25 %	2.24	3.49	< 0.05 *
	V30 %	1.97	3.07	< 0.05 *
Left anterior descending	Mean Dose Gy	14.86	32.51	< 0.05 *
Left Lung	Mean Dose Gy	8.91	10.93	< 0.05*
	V10 %	16.07	19.61	< 0.05 *
	V20 %	13.29	16.21	< 0.05 *

* P-value less than 0.05 is considered statistically significant

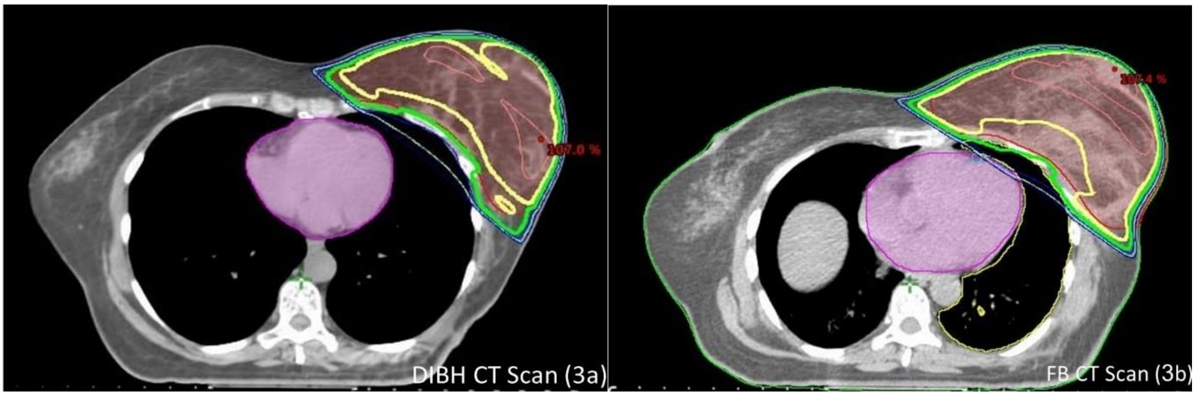

Figure 3. 3D-conformal dose distribution for deep inspiratory breath-hold CT Scan (3a), Free-breathing CT Scan (3b)

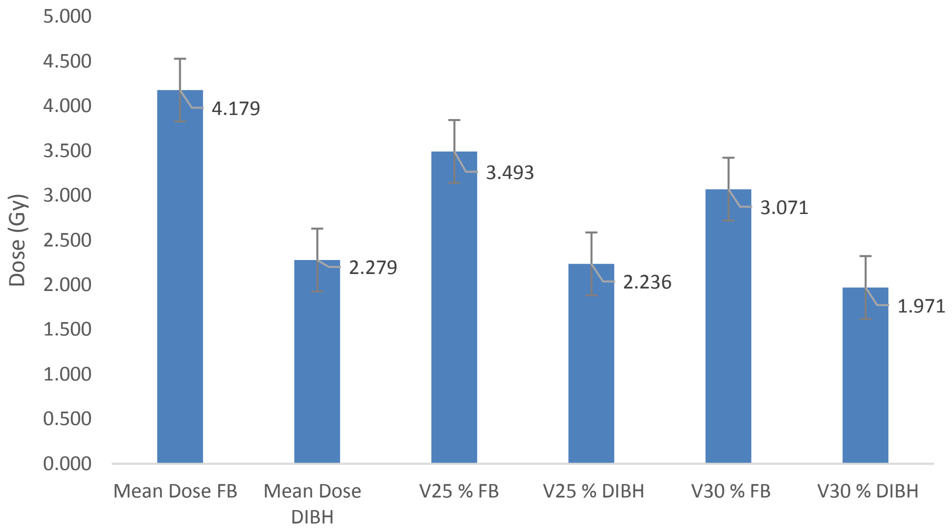

Figure 4. Heart dose statistics

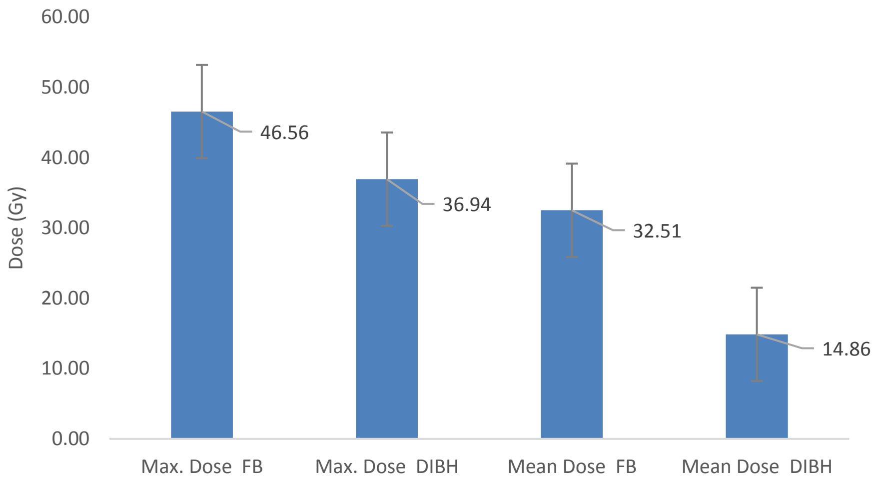

Figure 5. Left anterior descending dose statistics

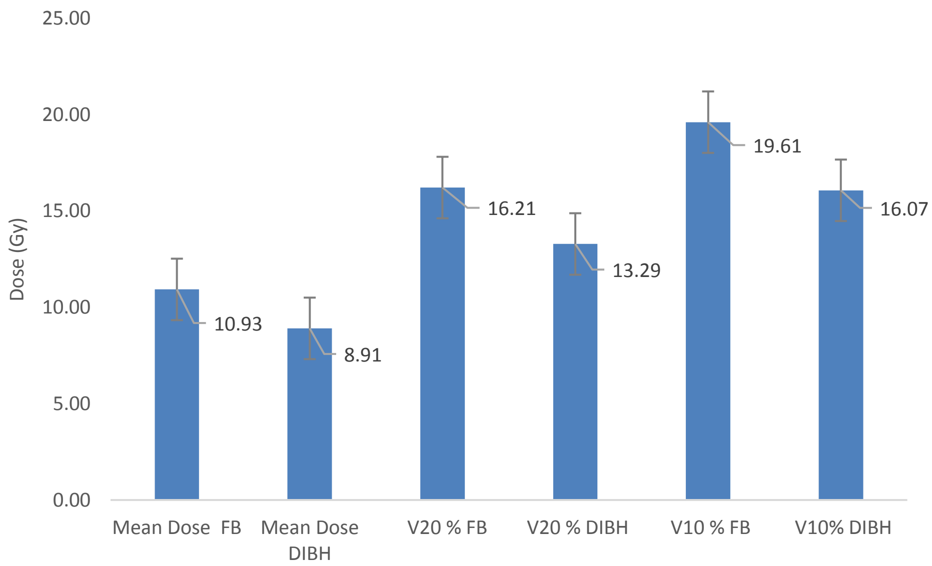

Figure 6. Left lung dose statistics

The DIBH also led to a significant reduction in mean heart dose (Figure.4) and V25% and V30% values of the heart. The average mean doses to the heart were 2.28 and 4.18 Gy in DIBH and FB conditions, respectively (P=0.0003). In addition, the average heart V25% was 2.24% in DIBH and 3.49% in FB conditions (P=0.06). The average V30% of the heart were 1.97% and 3.07% in DIBH and FB conditions, respectively (P=0.03).

A significantly lower mean dose in LAD (Figure.5) was observed in DIBH (14.86 Gy), compared to FB (32.51 Gy), P=0.002). Moreover, regarding DIBH, a little dose reduction (8.91 Gy) was observed in the mean dose left lung (Figure.6), and the V10% and V20% were determined at 16.07% and 12.29%, respectively. Additionally, FB lung mean dose, V10%, and V20% were estimated at 10.93 Gy, 19.61%, and 16.21%, respectively.

Discussion

According to the results, the cancer patients treated with DIBH technique had lower mean heart doses than those treated with the FB technique [25]. Many dosimetric study comparisons demonstrated the benefits of DIBH, specifically for cardiac structures dose parameters. A significant improvement in both mean heart doses (the relative dose reduction range: 25–67%) and mean LAD doses (the relative dose reduction range: 20–73%) were observed in DIBH, compared to FB (Table 3).

In this study, the relative dose reduction for average mean dose heart and LAD were 45.50% and 54.30%, respectively, when the patients underwent DIBH as opposed to FB technique. Accordingly, the DIBH showed a significant dose reduction in mean dose to the heart (2.28 Gy) and LAD region (14.86 Gy), compared to FB. The difference between mean heart dose and mean LAD region dose was noticeable due to the fact that the LAD was located in the anterior part of the heart that was irradiated to the tangential treatment fields used in whole breast radiotherapy.

What DIBH distinguishes was the ability to reduce the heart, LAD region, left lung dose, and at the same time kept the PTV dose coverage and improved the PTV dose homogeneity. This feature is not found in the FB technique. (Figure.7) depicts the percent relative dose reduction that observed at OARs when using DIBH technique. No significant differences were found according to the PTV coverage and D95 for both the DIBH and FB scans.

However, with DIBH, a more dose homogeneity was generally achieved, compared to the FB. This is due to the avoidance of heart irradiation during FB treatment plans [26-28], where, the heart irradiation avoidance led to a decrease in the PTV coverage and homogeneity [29], thereby potentially increasing the risk for recurrence or metastases [30,31]. Due to the small sample sizes, it was impossible to achieve the statistical power to show this effect in this study.

Table 3. Mean Left anterior descending and heart dose reduction in previous studies, including free breathing and deep inspiration breath-hold techniques for left-sided breast cancer radiotherapy treatment

Deep inspiratory breath-hold study		Mean left anterior descending dose (Gy)			Mean heart dose (Gy)		
Real-time position management	Number of patients	*FB	**DIBH	Reduction	FB	DIBH	Reduction
Borst et al. [35]	19	11.4	5.5	52%	5.1	1.7	67%
Vikstrom et al. [36]	17	18.1	6.4	65%	3.7	1.7	54%
Hayden et al. [37]	30	33.7	21.9	35%	6.9	4.0	42%
Hjelstuen et al. [38]	17	25.0	10.9	56%	6.2	3.1	50%
Bruzzaniti et al. [39]	8	9.0	2.7	70%	1.7	1.2	29%
Lee et al. [40]	25	26.3	16.0	39%	4.5	2.5	44%
Reardon et al. [41]	10	2.5	1.8	29%	1.6	0.9	45%
Bolukbasi et al. [42]	10	4.0	5.0	20%	4.9	3.7	25%
Verhoeven et al. [43]	17	30.9	22.4	28%	3.5	1.6	54%
Joo et al. [44]	32	40.8	23.7	42%	7.2	2.8	61%
Mulliez et al. [45]	12	17.6	10.9	38%	4.0	2.2	45%
Lawler and Leech [46]	28	10.9	5.2	52%	1.8	1.2	33%
McIntosh et al. [47]	10	-	-	43%	-	-	48%
Johansen et al. [48]	16	-	-	-	6.5	2.5	62%
Stranzl et al. [49]	11	-	-	-	4.0	2.5	38%
Stranzl and Zurl [50]	22	-	-	-	2.3	1.3	44%

* Free breathing
** Deep inspiratory breath-hold techniques

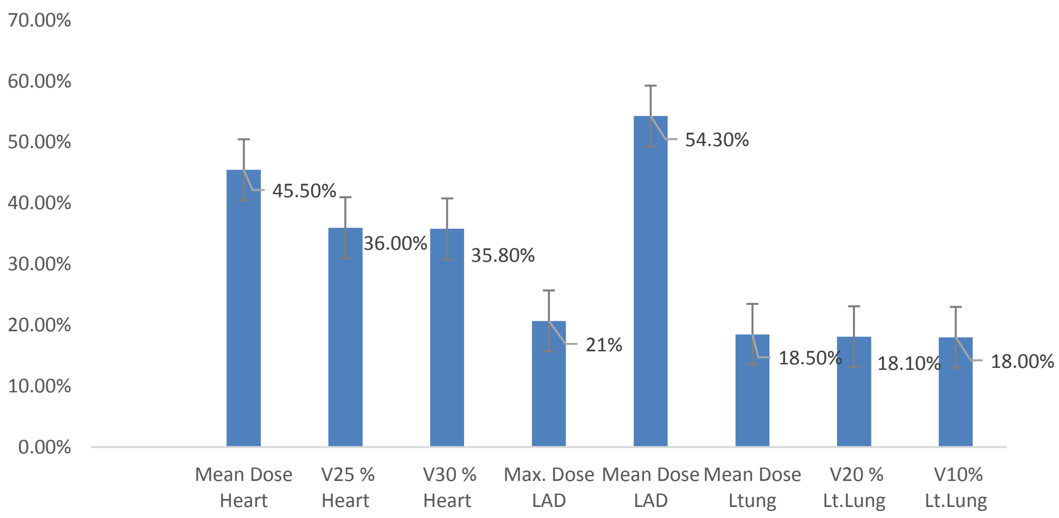

Figure 7. Organs at risk dose reduction

Some studies revealed that the whole heart dose may not be the main reason for all types of radiation-induced cardiac morbidity and mortality, and there was a relationship between doses to particular cardiac substructures and later damages to those substructures. A literature review by Correa et al. [32] demonstrated that the LAD region was an important structure which was related to cardiac morbidity and a wide range of mean LAD dose (5 to 46.3 Gy) due to the small LAD volume; moreover, there was a reproducible and variation in LAD contouring [33].

Other study reported that the left ventricle V5 was a predictor of acute cardiac diseases, compared to mean heart dose [34]. Therefore, there is a need to conduct more studies to determine exactly the most important predictor of all types of radiation-induced cardiac morbidity and mortality during the left breast radiotherapy treatment. Accordingly, it is suggested to maintain the dose in the heart and LAD as low as possible during the clinical practice. Regarding the left lung, although the volume of the lungs increased with DIBH, a small reduction was observed in the left lung doses in DIBH, compared to FB, especially the mean dose and V20. The reason for this reduction was the attempt to improve the PTV coverage dose.

Conclusion

The results of this study demonstrate that the DIBH for left-sided breast cancer radiotherapy was an impactful method leading to a considerable dose reduction in the heart and the LAD-region. Moreover, all patients would benefit from the DIBH technique and they completed their treatment smoothly. However, some patients benefited more from DIBH than others depending on their anatomy and level of their inspiration.

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