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A Comparative Dosimetric Study for the Treatment of Left-Sided Breast Cancer using Three-Dimensional Conformal Deep Inspiration Breath-Hold and Free-Breathing Intensity-Modulated Radiotherapy Techniques

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ABSTRACT

Introduction: Most women with left-sided breast cancer are at an increased risk of heart morbidity and mortality from the adjuvant radiotherapy due to an increase in heart absorbed dose during radiotherapy treatment. This study aimed to compare free-breathing intensity-modulated radiotherapy (FB-IMRT) and three-dimensional conformal deep inspiration breath-hold (3DCRT-DIBH) techniques in terms of the cardiac dose.

Material and Methods: In total, 15 women with left-sided breast cancer underwent FB and DIBH computed tomography (CT) scans in the same supine position. For DIBH CT, 3D-CRT plans were created using two opposing wedged tangential fields and for FB-CT, 4-5 IMRT optimized tangential fields were created. All plans were evaluated using the dose-volume histogram. The data were analyzed in SPSS software version 20 (IBM, IL).

Results: The FB-IMRT plans were more homogeneous and had more dose coverage and fewer hotspots, than the 3DCRT-DIBH plans; however, the planning target volume V95% was clinically acceptable for both techniques**.** Furthermore, the 3DCRT-DIBH plans were much faster and require fewer monitor units. A significantly lower mean dose of heart, left lung, left anterior descending coronary artery, right lung, and V10% left lung were observed in 3DCRT-DIBH plans, compared to FB-IMRT plans. Moreover, FB-IMRT plans showed a significant further dose reduction in heart V25% and V30%**.**

Conclusion: The majority of the patients with left-sided breast cancer who treated with the DIBH technique were getting sufficient benefits of radiotherapy, and DIBH was a comprehensive strategy for reducing cardiac doses during radiotherapy treatment.

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Introduction

The radiotherapy treatment is the clinical option to treat the whole left-sided breast cancer after breast-conserving surgery (mastectomy). If not treated, the microscopic tumor that remains after surgery will lead to recurrence or metastases (or both) [1]. Left-sided breast cancer radiotherapy treatment is associated with cardiotoxicity, compared to the right-sided breast cancer treatment, and the rates of cardiac morbidity and mortality [2-5] increased with an extrapolated heart mean dose (HMD) and left anterior descending coronary artery (LAD) [6,7]. The cardiac radiotherapy risk is depended on the patient's anatomy, target, shape volume, and internal mammary node irradiation [8-14]. Many different techniques of radiotherapy treatment have been developed with the criteria for improving target volume dose coverage and reducing high radiation doses to the cardiac volume. This study selected three-dimensional conformal radiotherapy in deep inspiration breath-hold (3DCRT-DIBH) and free-breathing intensity-modulated radiotherapy (FB-IMRT) techniques to evaluate the heart radiation toxicity during left-sided breast cancer treatment. The 3DCRT-DIBH was begun with deep inspiration, which pushed the diaphragm downward and the ribs anteriorly. This increases the size of the thoracic cavity, thereby filling the lungs with the air [15]. The most popular systems that used to implement the DIBH technique are real-time position management (RPM) device from Varian medical systems (USA) and

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active breathing control (ABC) device from Elekta (Sweden u). The RPM is a respiratory gating technology that is used for self-held breath-hold which includes voluntary DIBH by the patient. The patients breathe to reach a predefined threshold and instructed to perform deep inspiration (20 sec at a time). The ABC is a breathing device for forcing DIBH by spirometry-based active breathing coordinator that was used to measure the respiratory (lung) volume during inhalation by stopping the flow of air at a prespecified volume for a pre-defined period [16, 17].

The FB-IMRT is one of the radiotherapy techniques that is progressively applied to the left-sided breast with the specific goal of improving breast volume dose coverage and reducing high radiation doses to the adjacent normal healthy tissues. The IMRT treatment planning is the planning process in which the clinical objectives are defined within the optimizer, and the treatment planning system (TPS) finds the mathematical solution by modifying the plan automatically. The TPS algorithm optimizes the beam parameters that result in the desired dose distribution. During IMRT optimization, the fluencies of each field was optimized by changing the beamlet weights. The fluence is derived during the optimization process and represents the mathematical solution of how best to weight the beamlets to achieve the optimal dose. The desired fluence pattern is converted to the leaf motion pattern for delivery. The treatment field arrangement is the same as that used for the 3D-CRT plan by taking into account the breathing motion and possible swelling of the breast during the radiation treatment. The skin flash was added by extending the fluence beyond the skin surface at least 2 cm [18-20]. This study as a technical note aimed to investigate the impact of the 3DCRT-DIBH technique to reduce heart radiation toxicity during left-sided breast cancer radiotherapy, compared to FB-IMRT.

Materials and Methods

Patient Selection and Data Collection

Totally, 15 mastectomy women with left-sided breast cancer were selected consecutively for radiotherapy from April to October 2018. The patients were within the age range from 34 to 65 years and eligible for the DIBH treatment. Table 1 summarizes the patient data collected based on the clinical practice guidelines in oncology for left-sided breast cancer. The anatomical parameters, such as central lung distance (CLD), maximal heart distance (MHD), maximal heart length, and chest wall shape were significant in DIBH patient selection (Figure.1) [21-24].

Table 1. Summary of the patient clinical data

Items	Patient collected data
Anatomical variation	Maximum heart distance (MHD)
	Maximal heart length (MHL)
	Central lung distance (CLD)
	Chest wall shape
Others	Age, weight (obesity), height, smoking
	Comorbidities (diabetes, hypertension)
	Histological diagnosis
	Surgery type
	Medical imaging diagnosis (CT, MRI, PET)
	Chemotherapy details and Prescription
	DIBH eligibility

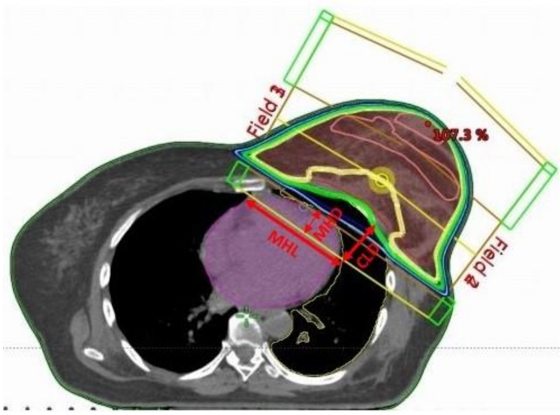

Figure 1. Anatomical parameters measured for left breast irradiation

Table 2. Planning clinical goals

Structure	Objective
PTV	95% of volume receive 95% of the prescribed dose (47.5 Gy) Maximum dose, 105% of prescribed dose
CTV	Uniform dose
Heart	V25 Gy ≤ 10% (QUANTEC) V30 Gy < 10% Heart Mean dose (HMD) <8 Gy
LAD	Mean dose 20 Gy Maximum Dose ≤ 50 Gy
Ipsilateral Lung	V20 Gy (%) ≤33%, ≤30 % (with DIBH) V10 Gy (%) ≤68%, ≤63 % (with DIBH) Mean (Gy) ≤20Gy, ≤18 Gy (with DIBH)
Contralateral Lung	V20 Gy (%) ≤8%
Contralateral Breast	Mean Dose (Gy) ≤5Gy

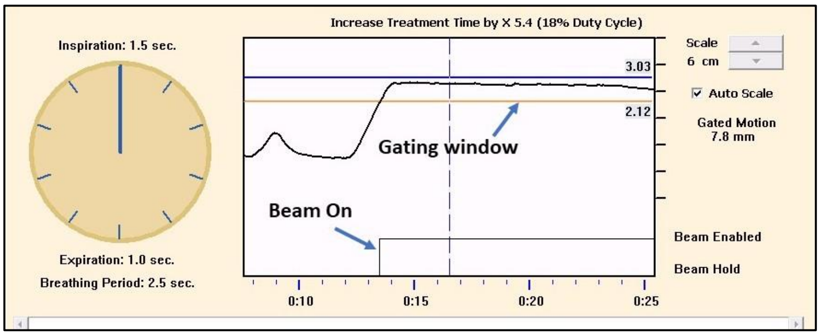

Figure 2. The DIBH gating curve acquired by the RPM

Computed Tomography Simulation of deep inspiration breath-hold patients

The procedures of computed tomography (CT) simulation of patients using the DIBH technique require a helical CT scan that is acquired sequentially in 2.5 mm slices for both FB and DIBH scans. Moreover, it needs an RPM system, which is an external motion-tracking system used to observe the patients' respiratory cycle. The patients were placed in a supine position on a CT-simulator couch and immobilized with their arms upon a breast board. In addition, some degree of tilt was applied to isolate breast tissue underneath the level of the head of the clavicle. The patient's head was positioned with the chin up and might be turned slightly to the contralateral side if necessary. With the help of the radiotherapy team, the patients were coached on the breath-hold technique by providing verbal instructions to hold their breath for up to 20 sec. The RPM system was a respiratory gating based on the motion of external infrared radiation (IR) reflected marker box placed on the patient's chest or abdomen skin where the respiratory motion was monitored by an IR tracking camera mounted in the room's wall which resulting in a real-time visual image of the tracing box motion. The amplitude gating threshold lines were determined to the levels just above and below the breath-hold level (Figure 2). The typical workflow was the acquisition of a "free-breathing scan" before the acquisition of a "breath-hold" scan in which all enrolled patients completed two CT simulation scans one in FB and the other in DIBH.

Target and Organs at Risk Contouring

The clinical target volume (CTV) consisted of the reconstructed breast/chest including the tumor bed, and the planning target volume (PTV) was CTV with anterior margin of 5 mm from the skin edge. The chest wall and all organs at risk (OAR) (both lungs, heart, left anterior descending artery, and contralateral breast) were contoured successfully on a 3D image according to the radiation therapy oncology group (RTOG) breast and cancer contouring atlas (2009) [25-27] using several contouring tools in Eclipse™ TPS (version 15.6). It was recommended to perform the contouring by the same oncologist to maintain the consistency of contouring, especially when delineating smaller structures.

Treatment Planning

Both 3D-CRT and IMRT treatment plans were created on Eclipse™ TPS (version 15.6) with the analytical anisotropic algorithm (AAA) from Varian medical systems (USA) using 6-10 MV photon. The radiotherapy dose (RT) was given at 2 Gy over 25 sessions according to the clinical protocols. Table 2 summarizes the main planning of the clinical goals.

3D-DIBH Conformal Planning

An isocenter treatment technique was used with two opposing medial and lateral tangential beam fields to ensure that the breast tissue was covered. Moreover, multi-leaf collimators (MLCs) were utilized to shape the treatment field. The medial tangential field gantry angle ranged from 315° to 305°, and lateral tangential field gantry angle was within the range between 125° and 130°. It is worth mentioning that the dynamic wedge was used to prevent hotspots and improve homogeneity. Moreover, the photon beam energy (6 MV) was used to achieve homogenous dose distribution. There were no definitive rules to find the optimal beam angle, and it depended on the patient anatomy (breast and/or chest wall concavity and the deep valley between the breasts).

FB-IMRT Planning

The 'sliding window' IMRT technique with photon beam energy (6 MV) was used for FB-IMRT planning with 5 isocenter non-coplanar beams with gantry angles (320°,300° 110°, 125°) using Eclipse™ TPS (version 15.6). The collimator rotation was required to prevent the treatment field, split and minimize the MLCs tongue and groove effect, and block the lung and heart volume.

Plan geometry had been created after contouring, and the optimal fluences were created by the dose-volume optimizer algorithm. During the optimization, the optimal fluence was created and used as an input to the leaf motion calculator. Moreover, the optimal fluence was converted to an actual fluence and leaf motions that were scaled in terms of monitor units (MUs).

The actual fluence was used for the final 3D dose calculation using AAA. The MUs and dose distribution were displayed after the calculation. Due to respiration, the patient's chest was moved in the air during radiation delivery to prevent skin toxicity (skin overdose or underdose). Additionally, the "Skin Flash" tool was used by extending the optimal fluence beyond the patient body surface, and the optimization objectives were defined in terms of clinical goals (Table 3). The normal tissue objective (NTO) was used to control the dose distribution outside the PTV, which limited the high dose level in healthy tissue and minimized hotspots around the PTV. In total, four parameters within the NTO were defined before optimization. Distance from target border, start dose, end dose, and dose fall-off (Figure 3) showed the dose distribution and beam arrangement with axial, coronal, and sagittal views for each technique for DIBH and FB.

Table 3. Optimization constraints for IMRT plans

	Volume %		Objectives Gy	Priority
PTV	Upper	٠	52	200
	Lower	100	50	200
Heart	Upper	5	30	100
	Upper	20	10	100
	Upper	40	5	100
Lt. Lung	Upper	30	20	95
	Upper	20	15	95
Rt. Lung	Upper	8	15	80
	Mean		5	80
Rt. Breast	Mean		5	80
NTO	Distance from target border			0.3 cm
	start dose			100%
	end dose			65%
	fall-off			0.3

Upper Objectives: Maximum allowed dose
Lower Objectives: Minimum dose request (Used for targets only)

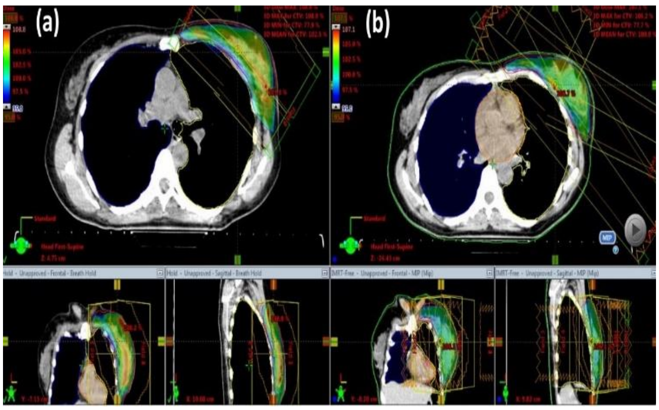

Figure 3. Dose distribution and beam arrangement on axial, coronal, and sagittal views of one patient with (a) tangent-based 3-D conformal during deep inspiration breath-hold (3DCRT-DIBH) technique (b) Intensity modulated radiotherapy during free breathing (FB-IMRT) technique

Plan Evaluation

The dose-volume histogram was calculated for each structure, and the significant dose of PTV and OARs on both FB and DIBH scans were calculated according to general QUANTEC guidelines.

Statistical Analysis

The data were analyzed in SPSS software (version 20, IBM; IL). Moreover, the paired sample t-test was used to evaluate the significance of differences. A p-value less than 0.05 was considered statistically significant to obtain the differences between FB-IMRT and 3D-DIBH treatment techniques using a two-tailed test.

Results

Planning Target Volume and Contralateral Breast Dose

Both 3D-DIBH and FB-IMRT had shown optimum target coverage and homogeneity with a superior V 95% (%), conformity index [28], and homogeneity index (HI) [29] which were clinically acceptable**.** Lower MUs were observed using a 3D-DIBH technique (on average 275 MUs, P=0.003), compared to the number of MUs in the IMRT technique. The contralateral breast mean dose was reduced by 3.87 Gy (P=0.0002) for the 3D-DIBH technique, compared to IMRT. Table 4 tabulates the dose parameters to target.

Heart Dose

The 3D-DIBH, FB-IMRT, heart, and LAD dose parameters were demonstrated in Table 4. For the 3D-DIBH technique, the HMDwas reduced on average by 7.12 Gy (P=0.002), and the minimum heart dose was reduced by 1.73 Gy. Moreover, the heart V25% and V30% were reduced by 2.8% (P=0.003) and 1.64% (P=0.001), respectively, in the FB-IMRT technique. The contoured average heart volume of the 3D-DIBH technique was 504.4 cm^3 that was seemed to be smaller, compared to the FB-IMRT technique with an average heart volume of 555.9 cm^3 (P<0.007). Regarding the LAD region, the LAD mean and maximum doses were reduced on average by 2.61 Gy and 9.66 Gy, respectively, in the 3D-DIBH technique. There was no significant difference in terms of the contoured volumes of the LAD region in the DIBH condition which were 2.85 cm^3 (P=0.10) and 2.43 cm^3 for 3D-DIBH and FB-IMRT, respectively. The MHD was reduced by 0.9 cm in the DIBH technique, except for four patients whose hearts were fully excluded from the beam limits.

Table 4. PTV, Heart and Lung dose evaluation

	FB IMRT		DIBH 3DCRT			
	Mean	SD	Mean	SD	Mean Δ	P-value
PTV and Contralateral breast						
PTV MD	53.5	0.675	53.54	0.368	-0.04	0.007 *
PTV V95% %	98.05	1.22	95.05	0.15	3	0.007 *
PTV CI	0.98	0.012	0.95	0.001	0.03	0.012 *
PTV HI	0.09	0.019	0.14	0.021	-0.05	0.012 *
PTV MU	1184	282.6	275	18.4	909	0.003*
Contralateral Breast Mean Dose Gy	4.27	1.02	0.4	0.05	-3.87	0.0002*
Heart						
Heart volume	555.9	94.2	504.4	114.2	51.5	0.007*
Heart V30%	0.47	1.5	2.11	0.57	-1.64	0.00١ *
Heart V25%	0.59	1.79	3.39	0.60	-2.8	0.003*
HMD Gy	9.58	2.21	2.46	1.10	7.12	0.002*
Heart Maximum Dose Gy	41.17	3.25	46.60	1.91	-5.43	0.01 *
Heart Minimum Dose Gy	2.04	0.95	0.31	0.12	1.73	0.01 *
MHD cm	1.8	0.07	0.9	0.04	0.9	0.05 *
LAD						
LAD Mean Gy	11.53	10.8	8.92	9.1	2.61	0.005 *
LAD MAX Gy	46.56	10.7	36.9	13.1	9.66	0.03 *
LAD volume cm^3	2.43	0.4	2.58	0.4	-0.24	0.10*
Lungs						
Lt. Lung volume cm^3	918.3	269.8	1646	260.9	-727.7	0.0002*
Lt. Lung V10%	27.95	11.6	15.09	4.8	12.86	0.004*
Lt. Lung V20%	12.05	5.4	13.31	4.6	-1.26	0.0016 *
Lt. Lung Mean Dose Gy	11.53	1.9	9.74	1.8	1.79	0.02 *
CLD cm	2.53	0.27	2.98	0.26	-0.45	0.03 *
Rt. Lung Mean dose Gy	3.45	1.44	0.3	0.14	3.15	0.0003 *

CI: Conformity Index HI: Homogeneity Index MD: Maximum Dose
MHD Gy: Maximum Heart Dose MHD cm: maximal heart distance CLD cm: central lung distance
* Significant difference between plans if P<0.05

Lung Dose

In the 3D-DIBH technique, the left lung volume increased on average by 727.7cm^3 (44.2%, P=0.0002). Moreover, the mean left lung dose was reduced on average by 1.79 % (P=0.0003), and the V20% was reduced on average by 1.26 % in the FB-IMRT (P=0.7). Additionally, V10% was reduced by 12.86% (P=0.004), and the contralateral lung mean dose was reduced by 3.15 Gy (3.45Gy vs. 0.3 Gy P=0.0003). The CLD increased in the DIBH technique by 0.45 cm, which was 2.53 cm in the FB-IMRT technique and 2.98 cm in the DIBH technique. Table 4 summarizes the dose parameters to the lungs.

Discussion

In general, there are a lot of dosimetric studies conducted on the cardiac dose reduction during left-sided breast cancer radiotherapy (Table 5). This study investigated the relationship of the individual patient anatomical structure, as well as cardiac and lung received doses by comparing two different treatment techniques, namely 3D-DIBH and FB-IMRT. The results revealed that in the 3D-DIBH technique, due to the separation, the distance was increased between the chest wall and heart, and the heart volume size was reduced from 555.9 cm^3 to 504.4 cm^3. Moreover, the MHD was reduced from 1.8 cm to 0.9 cm, and as a result of increasing the separation distance, a significant reduction was observed in the HMD from 9.58 Gy to 2.46 Gy, compared to the FB-IMRT technique.

Regarding LAD, since LAD was placed in the frontal part of the heart, it was closer to the chest wall, and during the free-breathing treatment, the larger volume heart led the LAD into the tangential treatment fields in which it was exposed to more radiation dose. Therefore, in the DIBH technique, the mean LAD dose was reduced from 11.53 Gy to 8.92 Gy on average. However, in general, an unacceptable maximum LAD dose appeared in both techniques since the steep dose gradient at the treatment field edge could produce a high dose at the LAD inferior part. Figures 4 and 5 illustrate the relationship between LAD dose variation, heart volume, and HMD. Although the maximum heart dose was reduced with FB-IMRT plans on average from 46.60 Gy to 41.17 Gy in all patients, the heart volume received low doses with IMRT due to the phenomenon of "low-dose bath" that cannot be avoided in IMRT.

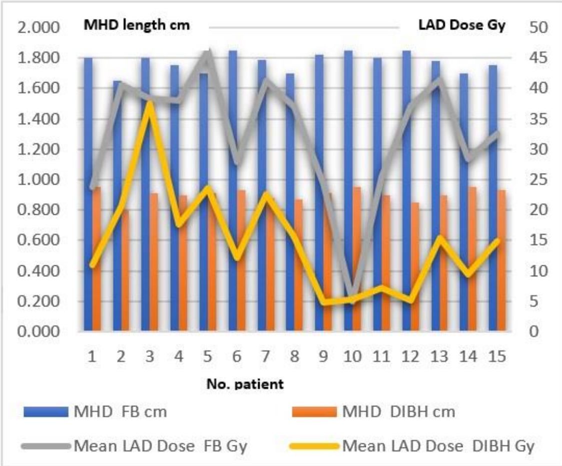

Figure 4. The variation of mean LAD dose with MHD in 15 patients

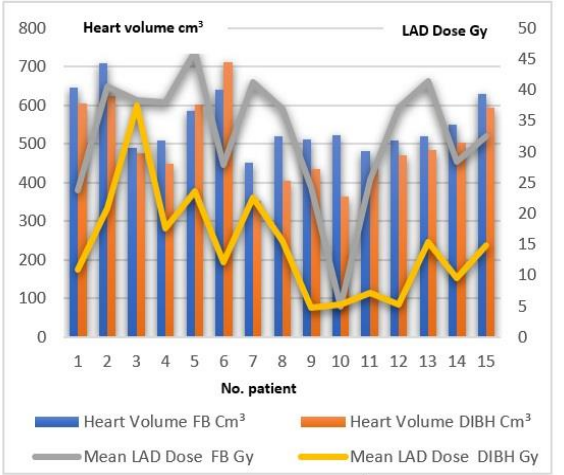

Figure 5. The variation of mean LAD dose with heart volume in 15 patients

The heart V25% and V30% showed superior results with FB-IMRT plans, compared to 3D-DIBH. The influence of MHD in cardiac dose reduction is shown in figures 6 and 7, which explains the relationship between heart volume, HMD and MHD. However, the CLD was strongly associated with lung dose. During DIBH, the CLD was increased from 2.53 cm to 2.98 cm, and due to the expansion of left lung volume for all patients, it was increased on average from 918.3 cm^3 to 1646 cm^3.

Table 5. Dose parameters of LAD and heart in previous studies using FB IMRT and 3DCRT DIBH techniques for left-sided breast cancer radiotherapy treatment

Study	# Patients	Mean LAD dose (Gy)			Mean heart dose (Gy)		
		FB	DIBH	Reduction	FB	DIBH	Reduction
Mast ME, et al [30]	20	14.9	9.6	35.5%	2.7	1.8	33.3%
Sripathi LK , et al [31]	15	17.08	22.4	-31.1%	11.94	3.3	72.3%
Chi F, et al [32]	31	18.87	15.57	17.5%	2.82	1.56	44.6%
Reardon KA, et al. [33]	10	-	-	69.9%	-	-	43.25%

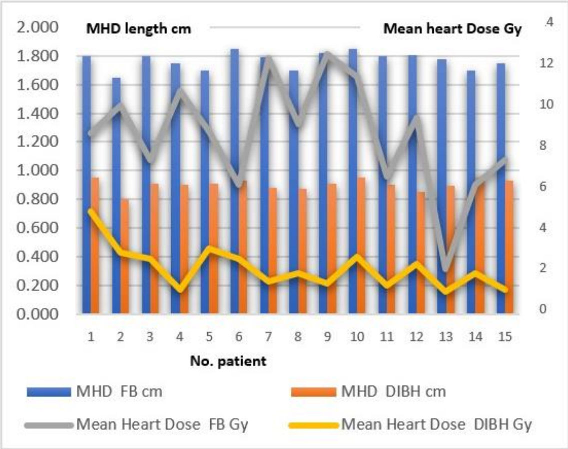

Figure 6. The variation of heart mean dose with MHD for 15 patients

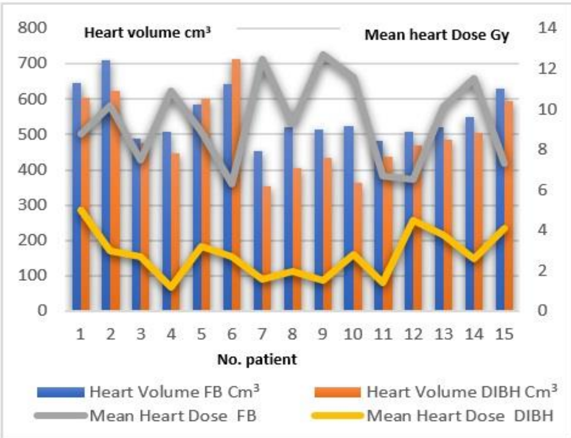

Figure 7. The variation of heart mean dose with heart volume for 15 patients

Moreover, the volume of the left lung receiving 10% of the prescription dose was reduced from 27.95% to 15.09%, and the left lung mean dose was reduced from 11.53 Gy to 9.74 Gy. In addition, the volume of left lung receiving 20% of the prescription dose was slightly reduced by 10.4%, compared to the FB-IMRT technique. Figures 8 and 9 depict the relationship of the left lung volume with MHD HMD dose and CLD.

Regarding the contralateral lung, there was a significant reduction in the mean dose received from 3.45 Gy to 0.3 Gy in the DIBH plan, compared to the FB-IMRT. The dosimetric analysis of 3DCRT-DIBH and FB-IMRT plans showed that IMRT plans produced a better uniform dose distribution and homogeneity within the treated volume of the left breast and optimum target coverage (V95%) of approximately 98.05% with significant superior in CI and homogeneity index HI, compared to the DIBH plans. However, the MUs number amount needed to deliver during the beam-on with 3D-CRT plans were lower than IMRT plans by approximately one-quarter, of that needed to where this mean that the 3D-CRT DIBH techniques dose delivery was much faster than FB-IMRT appropriate for breath-hold techniques. Moreover, there was a reduction in total body exposure that produced from MLC leakage radiation.

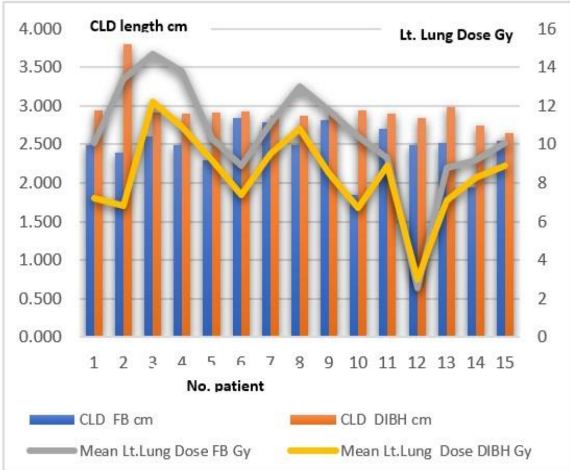

Figure 8. The variation of mean Lt. Lung dose with CLD for 15 patients

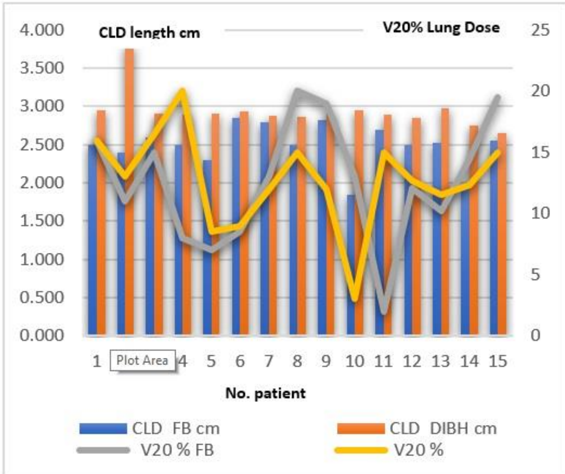

Figure 9. The variation of V20% Lt. Lung dose with CLD for 15 patients

The skin toxicity was the other consideration in IMRT due to the patient position, uncertainty, patient respiration, and degree of breast swelling during treatment that led to the overdosing of surrounding healthy tissues or underdosing of treated volume. Therefore, the TPS provided a “Skin Flash” tool that helps to reduce these uncertainties by spreading the fluence beyond the patient skin surface. For contralateral breast, the DIBH technique led to a significant reduction in the mean dose from 4.27 Gy to 0.4 Gy, compared to the FB-IMRT plans.

Conclusion

In general, the majority of the patients with left-sided breast cancer who were treated with the DIBH technique were getting clinical benefits of radiotherapy, and all patients selected for DIBH concluded their treatment smoothly. Furthermore, the DIBH is considered a comprehensive strategy for reducing cardiac doses during radiotherapy treatment, less cost-effective, and relatively easy to perform in both treatment planning and patient set-up, compared to the FB-IMRT technique.

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References

1. Early Breast Cancer Trialists Collaborative Group (EBCTCG). Effect of RT after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomized trials. Lancet. 2011; 378:1707‑16.
2. Rutqvist LE, Johansson H. Mortality by laterality of the primary tumour among 55,000 breast cancer patients from the Swedish Cancer Registry. British journal of cancer. 1990 Jun;61(6):866-8.
3. Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. British journal of cancer. 2013 Jan;108(1):179-82.
4. Gyenes G, Rutqvist LE, Liedberg A, Fornander T. Long-term cardiac morbidity and mortality in a randomized trial of pre-and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiotherapy and oncology. 1998 Aug 1;48(2):185-90.
5. Taylor C, Correa C, Anderson S. Late side-effects of breast cancer radiotherapy:Second cancer incidence and non-breast-cancer mortality among 40,000 women in 75 trials.San Antonio Breast Cancer Symp. 2015; S5:08.
6. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. The Lancet. 2000 May 20;355(9217):1757-70.
7. Van den Bogaard VA, Ta BD, van der Schaaf A, Bouma AB, Middag AM, Bantema-Joppe EJ, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. Journal of Clinical Oncology. 2017 Apr 10;35(11):1171.
8. Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 1950s‑1990s. International Journal of Radiation Oncology* Biology* Physics. 2007 Dec 1;69(5):1484-95.
9. Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. International Journal of Radiation Oncology* Biology* Physics. 2013 Aug 1;86(5):860-6.
10. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. New England Journal of Medicine. 2015 Jul 23;373(4):307-16.
11. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. New England Journal of Medicine. 2015 Jul 23;373(4):317-27.
12. Dess RT, Liss AL, Griffith KA, Marsh RB, Moran JM, Mayo C, et al. Ischemic cardiac events following treatment of the internal mammary nodal region using contemporary radiation planning techniques. International Journal of Radiation Oncology* Biology* Physics. 2017 Dec 1;99(5):1146-53.
13. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. New England Journal of Medicine. 2013 Mar 14;368(11):987-98.
14. Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation. 2017 Apr 11;135(15):1388-96.
15. Latty D, Stuart KE, Wang W, Ahern V. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. Journal of medical radiation sciences. 2015 Mar;62(1):74-81.
16. Bruzzaniti V, Abate A, Pinnarò P, D’Andrea M, Infusino E, Landoni V, et al. Dosimetric and clinical advantages of deep inspiration breath-hold (DIBH) during radiotherapy of breast cancer. Journal of Experimental & Clinical Cancer Research. 2013 Dec;32(1):88.
17. Vikström J, Hjelstuen MH, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. Acta Oncologica. 2011 Jan 1;50(1):42-50.
18. Ahunbay EE, Chen GP, Thatcher S, Jursinic PA, White J, Albano K, et al. Direct aperture optimization‑based intensity-modulated radiotherapy for whole breast irradiation. International Journal of Radiation Oncology* Biology* Physics. 2007 Mar 15;67(4):1248-58.
19. Bhatnagar AK, Brandner E, Sonnik D, Wu A, Kalnicki S, Deutsch M, et al. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. Breast cancer research and treatment. 2006 Mar 1;96(1):41-6.
20. Hong L, Hunt M, Chui C, Spirou S, Forster K, Lee H, et al. Intensity-modulated tangential beam irradiation of the intact breast. International Journal of Radiation Oncology* Biology* Physics. 1999 Jul 15;44(5):1155-64.
21. Johansen S, Vikström J, Hjelstuen MH, Mjaaland I, Dybvik KI, Olsen DR. Dose evaluation and risk estimation for secondary cancer in contralateral breast and a study of correlation between thorax shape and dose to organs at risk following tangentially breast irradiation during deep inspiration breath-hold and free breathing. Acta Oncologica. 2011 May 1;50(4):563-8.

22. Kong FM, Klein EE, Bradley JD, Mansur DB, Taylor ME, Perez CA, et al. The impact of central lung distance, maximal heart distance, and radiation technique on the volumetric dose of the lung and heart for intact breast radiation. International Journal of Radiation Oncology* Biology* Physics. 2002 Nov 1;54(3):963-71.
23. Levitt SH, Aeppli DM, Nierengarten ME. The impact of radiation on early breast carcinoma survival: A Bayesian analysis. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1996 Sep 1;78(5):1035-42.
24. Johansen S, Vikström J, Hjelstuen MH, Mjaaland I, Dybvik KI, Olsen DR. Dose evaluation and risk estimation for secondary cancer in contralateral breast and a study of correlation between thorax shape and dose to organs at risk following tangentially breast irradiation during deep inspiration breath-hold and free breathing. Acta Oncologica. 2011 May 1;50(4):563-8.
25. Gentile MS, Usman AA, Neuschler EI, Sathiaseelan V, Hayes JP, Small Jr W. Contouring guidelines for the axillary lymph nodes for the delivery of radiation therapy in breast cancer: evaluation of the RTOG breast cancer atlas. International Journal of Radiation Oncology* Biology* Physics. 2015 Oct 1;93(2):257-65.
26. Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, et al. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncologica. 2013 May 1;52(4):703-10.
27. Feng M, Moran JM, Koelling T, Chughtai A, Chan JL, Freedman L, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. International Journal of Radiation Oncology* Biology* Physics. 2011 Jan 1;79(1):10-8.
28. Feuvert L, Noel G, Mazeron JJ, Bey P. Conformity index: a review. International Journal of Radiation Oncology* Biology*Physics. 2006 Feb 1;64(2):333-42.
29. Kataria T, Sharma K, Subramani V, Karrthick KP, Bisht SS. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. Journal of medical physics/ Association of Medical Physicists of India. 2012 Oct;37(4):207.
30. Mast ME, Van Kempen-Harteveld L, Heijenbrok MW, Kalidien Y, Rozema H, Jansen WP, et al. Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further?. Radiotherapy and Oncology. 2013 Aug 1;108(2):248-53.
31. Sripathi LK, Ahlawat P, Simson DK, Khadanga CR, Kamarsu L, Surana SK, et al. Cardiac dose reduction with deep-inspiratory breath hold technique of radiotherapy for left-sided breast cancer. Journal of medical physics. 2017 Jul;42(3):123.
32. Chi F, Wu S, Zhou J, Li F, Sun J, Lin Q, et al. Dosimetric comparison of moderate deep inspiration breath-hold and free-breathing intensity-modulated radiotherapy for left-sided breast cancer. Cancer/Radiothérapie. 2015 May 1;19(3):180-6.
33. Reardon KA, Read PW, Morris MM, Reardon MA, Geesey C, Wijesooriya K. A comparative analysis of 3D conformal deep inspiratory‑breath hold and free-breathing intensity-modulated radiation therapy for left-sided breast cancer. Medical Dosimetry. 2013 Jun 1;38(2):190-5.