

Investigation of cardiac and pulmonary doses in patients with left sided breast cancer treated by radiotherapy with deep inspiration breath hold technique

S. Parlar^{1*}, G. Var², R. Cosar³, M. Dogan³, Y. Ozguven¹, D. Nurlu³, M. CemUzal³

¹Trakya University, Vocational School of Health, Radiotherapy Department, Edirne/Turkey,

²Ministry of Health Ankara City Hospital, Department of Radiation Oncology, Ankara/Turkey

³Trakya University Faculty of Medicine, Department of Radiation Oncology, Edirne/Turkey

ABSTRACT

► Original article

*Corresponding author:

Sule Parlar, Ph.D.,

E-mail:

suleparlar@trakya.edu.tr

Received: June 2021

Final revised: September 2021

Accepted: October 2021

Int. J. Radiat. Res., April 2022;
20(2): 369-375

DOI: 10.52547/ijrr.20.2.17

Keywords: left sided breast irradiation, deep inspiration breath hold, cardiac dose, radiotherapy.

Background: Cardiac disease is a documented risk factor in left breast irradiation. In an attempt to reduce cardiac toxicity, different treatment techniques adapted to respiratory cycle phases have been developed. The aim of this study is to investigate the feasibility of the voluntary breath hold technique when irradiating the left breast in selected patients. **Materials and Methods:** The study included 20 patients with left sided breast cancer. For each patient, two computed tomography (CT) scans were acquired, one with the free breathing (FB) technique and one with the voluntary deep inspiration breath hold (DIBH) technique. Treatment plans were created using a field-in-field intensity-modulated radiation therapy technique. A dosimetric comparison was made between the two techniques for the heart, left anterior descending (LAD) coronary artery, ipsilateral lung and contralateral breast. **Results:** The average of the mean dose of the heart decreased from 7.7 Gy to 5.8 Gy and V_{20Gy} (%) from 12.8% to 8.3% using the DIBH technique ($p=0.009$, $p<0.001$). The DIBH technique demonstrated significantly smaller maximum heart distance (2.0 cm vs. 0.9 cm, $p < 0.001$) and 8.0% reduction in LAD mean dose. Furthermore, D_{mean} for the ipsilateral lung was reduced from 12.8 Gy to 12.2 Gy and V_{20Gy} (%) from 25.6% to 22.8%. **Conclusions:** In the treatment plans made using the DIBH technique, a significant reduction in the radiation dose delivered to the heart has been observed. In order to reduce long-term morbidity and mortality risks from cardiovascular disease affecting the survival of patients with left sided breast cancer, irradiation techniques such as the DIBH should be considered, especially for premenopausal patients.

INTRODUCTION

In a meta-analysis of early-stage breast cancer (ESBC) randomised studies, it was reported that every four local and/or regional recurrences prevented by adjuvant radiotherapy (RT) after mastectomy or breast-conserving surgery (BCS) would prevent one death from breast cancer in the course of 15 years, in the absence of death from another cause (1, 2). However, contrary to this contribution of RT to survival, the incidence of contralateral breast cancer and non-breast cancer deaths were higher in irradiated patients than in non-irradiated patients (3). It was also reported in many studies that irradiated heart and lung volumes and doses are associated with long-term morbidity and mortality (4-8). It has also been reported that mean lung doses in breast cancer RT are associated with radiation pneumonia (9-11). Studies conducted on US SEER cancer registries in patients who were irradiated for breast cancer from 1970 to early 1980

by the standard RT regimens at the time reported that deaths from heart disease and lung cancer were appreciably increased 10 to 20 years afterwards (4, 5). Opposed tangential fields were used for breast or chest wall irradiation by the free breathing (FB) technique. Irradiated heart volumes and doses, especially those of the left anterior descending (LAD) coronary artery developing stenosis during follow-up, were held responsible for increased mortality (12). Darby *et al.* reported mean cardiac doses at RT as 6.6 Gy for left sided tumours, 2.9 Gy for right-sided tumours, and 4.9 Gy overall (range, 0.03 to 27.72). She also stated that for every 1 Gy increase in the cardiac mean dose, the rate of major coronary disease in the heart increases by 7.4% (7).

In an attempt to reduce cardiac toxicity, different treatment techniques adapted to respiratory cycle phases have been developed (13-17). For instance, the real-time position management (RPM) system ensures irradiation of the PTV with gating in a particular phase of respiration. When the active

breath control (ABC) system is used, the PTV is irradiated with the deep inspiration breath hold (DIBH) technique. In the absence of these systems, one can use the voluntary DIBH but, in this case, it is imperative to closely monitor the patient holding her breath at a special phase of respiration during irradiation⁽¹⁸⁾. With these techniques, significant reductions in the doses of the heart, lung and contralateral breast can be achieved^(13, 14, 19-21). In a study comparing tangential field-in-field (FiF) forward IMRT to a six-beam inverse IMRT planning for left breast irradiation with reproducible DIBH technique, it was reported that cardiac and contralateral breast radiation exposures were significantly reduced with tangential FiF planning⁽²²⁾.

It was stated that the DIBH technique, which is used with different devices, was used in only 20% of European cancer centres in 2000 and in only 4% of centres in England in 2012, despite its heart-sparing effect^(21, 23). Their use has been limited due to the cost of the device required for DIBH and patient-specific disposable materials (e.g., ABC). The application rate of the tools is estimated to be low, as these commercially available devices are costly to buy and service. The device without the DIBH technique can be used in clinics to overcome resource limitations. Also, due to the current coronavirus epidemic, different approaches have been recommended for left sided breast cancer RT, especially with respiratory gating systems. In the article on the COVID-19 pandemic published in March 2020, it is recommended to avoid the use of the ABC device in breast cancer RT due to the risk of contamination and to minimize the use of devices that require decontamination⁽²⁴⁾. Even, in line with the recommendations of the worldwide radiation oncology community regarding the pandemic, an article was published about the rapid transition to the voluntary DIBH technique in patients with breast cancer⁽²⁵⁾.

It is very costly for RT clinics to obtain special devices for the DIBH. In addition, considering the pandemic, sanitary measures to use the voluntary DIBH technique are recommended, even if DIBH equipment is available. Such equipment was not present at our clinic when the study was performed. In this study, the reliability and compatibility of the voluntary DIBH technique was checked in young and cooperative patients with left breast cancer without the use of additional equipment. Additionally, the OARs doses were compared between the FB and DIBH techniques in treatment plans.

MATERIALS AND METHODS

Patient selection

The study included 20 consecutive, premenopausal women aged 27–47 years (mean

age $\pm$ SD, 40.3 $\pm$ 8.4 year) with early stage (T1-2, N0, M0) left sided breast cancer. All of them had BCS previously, and their Eastern Cooperative Oncology Group (ECOG) performance score was 0–1. None of them had previous breast irradiation or had any comorbidity. The capability to maintain a voluntary breath hold for a period of 5 to 20 seconds was performed as a first evaluation. They were asked initially to breathe freely, then to inhale deeply at a level fully below their maximum inspiration volume and to keep their breath for at least 20 seconds. This process was repeated a few times in succession in order to provide stability for the DIBH. As a final evaluation, they underwent a treatment simulation consisting of six consecutive DIBH commands with 5 second intervals. Patients who were able to execute reliable breath holds were told to practise holding their breath during 20 seconds if possible, three times a day while lying down at home until computed tomography (CT) simulation day. The study was approved by Faculty of Medicine Scientific Research Ethics Committee (Date: 19.06.2013, Registration number: 2013/106).

CT simulation and immobilisation

All selected patients were positioned on the simulation couch in the supine position, and a breast board was used to immobilise the patients. According to our clinical protocol of delineation, modified from the Radiation Therapy Oncology Group (RTOG) guidelines, the borders of the whole breast were determined⁽²⁶⁾. CT markers on the patient's treatment field were first defined in FB. Then, the patient was told to breathe deeply and hold her breath. In the meantime, the lateral and midline shifts were noted and marked on the skin. Breath hold consistency was checked by the range moved by the laser from all the markers in the DIBH. First, a CT scan was performed in the FB technique, followed by the scan using the DIBH technique. Axial images were acquired with 5 mm slice thickness from the mandible to the bottom of the lung, without using IV contrast during the Toshiba (Toshiba Medical Systems Corporation, Otawara, Japan) CT simulation (Model; Asteion S4, gantry aperture 72 cm, field of view 50 cm). Similar CT scans were obtained in a row, both with the FB technique and the DIBH technique for each patient. Figure 1 shows axial CT slices from the identical level of the breast in a patient.

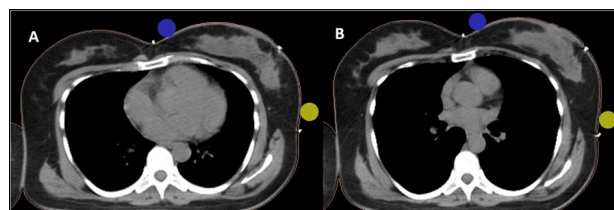


Figure 1. Free breathing (FB) (A) and deep inspiration breath hold (DIBH) (B) axial CT scans of the same level of the breast on CT scans.

Delineation of target volumes and organs at risk

Target volumes (CTV and PTV) and OARs (heart, LAD, ipsilateral lung and contralateral breast) were contoured using a FocalSim (v4.8, Elekta Instrument AB, Stockholm, Sweden) according to the RTOG guidelines (26). The CTV contour included the entire parenchyma of the left breast, which was retracted 5 mm from the skin surface to account for dose build-up. The PTV contour included CTV with a 5 mm peripheral margin to contain for daily set-up uncertainties. In case the PTV overlapped the lung tissue, the overlapping part of the PTV was subtracted. The heart was delineated from the pulmonary trunk range to the cardiac apex to contain the pericardium and myocardium of the atria and ventricles, except the aorta, pulmonary artery/vein, and superior vena cava. The anterior interventricular groove was taken as a guide if the LAD artery was not visible due to the lack of contrast medium from the atrioventricular notch near the pulmonary trunk to the lower cardiac apex. A 0.5 cm margin was added around the LAD artery for uncertainties for heart and respiration movement uncertainties. The ipsilateral lung was contoured, excluding the mediastinum. The contralateral breast glandular structure was also contoured similarly to the left breast. Contralateral breast contouring could only be performed in 10 patients because the contralateral breast lateral parts of the other 10 patients stayed outside of the field-of-view (72 cm). For delineation concordance, the same physician and physicist performed all contouring procedures together, as well as treatment planning procedures.

Treatment planning

Treatment plans were produced using a field in field intensity-modulated radiation therapy (FiF-IMRT) technique for both the FB and the DIBH techniques at CMS XIO TPS (v.4.8 Computerized Medical Systems, St. Louis, MO, USA) (figure 2). To achieve dose homogeneity, low-weight segments obtained using 6 MV or 15 MV photon beams were added to the primary treatment fields. The prescription dose of 50 Gy in 25 fractions was planned for PTV. The goal of treatment was to obtain at least 95% of the PTV volume (95% of 50.0 Gy), receiving 47.5 Gy. An electron or photon 10 Gy boost to the tumour bed was not contained in the doses analysed. Plan quality was evaluated using factors calculated according to the formulas below: Homogeneity Index (HI) = $(D_{2\%} - D_{98\%}) / D_{50\%}$ (27); Conformity Index (CI) = $V_{47.5} / PTV$ (28); and Conformity Number (CN) = $(TV_{RI} / TV) * (TV_{RI} / V_{RI})$ (29). Where TV_{RI} means target volume covered by the reference isodose and V_{RI} means volume of the reference isodose. Cumulative dose-volume histograms (DVHs) of FB and DIBH plans were computed and compared for each patient. The

treatment plans were calculated with the "Superposition" algorithm in CMS XIO. The dose-volume parameters of the OARs evaluated in this study are given in table 1.

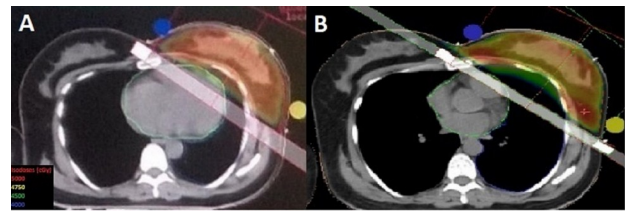


Figure 2. Representative dose distributions of the techniques planned: Free breathing (FB) (A) and deep inspiration breath hold (DIBH) (B).

Table 1. Comparison parameters of target volume (PTV) and volumes of organs at risk (OAR).

Structures	Parameters
PTV	Volume, D_{max} $V_{47.5Gy}(\%)$, HI, CI, CN
Ipsilateral Lung	Volume, D_{max} , D_{mean} , D_{min} $V_{5Gy}(\%)$, $V_{10Gy}(\%)$, $V_{15Gy}(\%)$, $V_{20Gy}(\%)$, $V_{25Gy}(\%)$, $V_{30Gy}(\%)$, $V_{50Gy}(\%)$
Heart	Volume, D_{max} , D_{mean} , D_{min} $V_{5Gy}(\%)$, $V_{10Gy}(\%)$, $V_{15Gy}(\%)$, $V_{20Gy}(\%)$, $V_{25Gy}(\%)$, $V_{30Gy}(\%)$, $V_{50Gy}(\%)$ Maximum Heart Distance (MHD)
LAD	D_{max} , D_{mean} , D_{min} $V_{25Gy}(\%)$
Contralateral breast	Volume, D_{mean}

Treatment delivery

The treatment of the 20 patients selected for the study was performed with the voluntary DIBH technique using a Elekta Synergy linear accelerator (Elekta, AB, Stockholm, Sweden). After setting the FB lasers precisely, as in CT simulation to assess breath hold reproducibility, the patient was told to breathe deeply and hold. Meanwhile, the location of the DIBH markers and their distance to the FB lasers were checked. Before each beam-on and during irradiation, their superpositions were checked from a zoom camera in the control room. Before each beam-on, the patient was told to breathe deeply through the control room intercom. Simultaneous electronic portal images were taken daily for all patients and compared with DRRs. If the error value was above 5 mm for at least two consecutive days, shifting was performed. When the irradiation was over, the patient was told to breathe normally before starting subsequent segment irradiation.

Statistical analysis

The "one-sample Kolmogorov-Smirnov" test was used to analyse the normal distribution of all data from DVHs. Wilcoxon signed-rank tests were used to analyse the differences in dose volume values obtained using FB and DIBH techniques. $P < 0.05$ was accepted as statistically significant.

RESULTS

The treatment of the 20 patients selected for the study was performed with the DIBH technique. In all plans, the longest segment irradiation time for the DIBH technique was 20.4 seconds. In one patient, mismatch of laser cross lines and skin markers was detected due to her inability to hold her breath during beam-on time, and irradiation was interrupted. There was no compliance problem with the remaining treatments of this or any other patient. Table 2 summarizes of dose parameters of target volume and OARs in FB and DIBH techniques. All techniques resulted in similar dose coverage ($V_{47.5\text{Gy}}$ (%)) of the PTV. PTV coverage was better with DIBH plans as compared to FB plans. Dose conformity was significantly better using the DIBH technique.

Table 2. Dose volume histograms (DVHs) parameters for free breathing (FB) and deep inspiration breath hold (DIBH) plans.

	DIBH Mean $\pm$ SD	FB Mean $\pm$ SD	p
PTV			
Volume (cc) mean	988,25 $\pm$ 408,54	1022,5 $\pm$ 404,37	0,313
D_{max}	54,96 $\pm$ 1,33	55,19 $\pm$ 1,12	0,852
$V_{47.5\text{Gy}}$ (%)	88,32 $\pm$ 4,15	89,92 $\pm$ 3,83	<0,001
HI	0,16 $\pm$ 0,20	0,25 $\pm$ 0,22	0,001
CI	0,56 $\pm$ 0,07	0,49 $\pm$ 0,09	0,010
CN	0,22 $\pm$ 0,06	0,19 $\pm$ 0,03	0,010
HEART			
Volume (cc) mean	442,55 $\pm$ 94,58	503,00 $\pm$ 95,47	0,001
D_{max}	50,58 $\pm$ 2,10	50,97 $\pm$ 2,50	0,940
D_{mean}	5,81 $\pm$ 1,52	7,74 $\pm$ 2,40	0,009
D_{min}	0,38 $\pm$ 0,10	0,40 $\pm$ 0,08	0,808
$V_{5\text{Gy}}$ (%)	14,89 $\pm$ 3,92	20,69 $\pm$ 4,84	<0,001
$V_{10\text{Gy}}$ (%)	11,09 $\pm$ 3,25	16,07 $\pm$ 4,79	<0,001
$V_{15\text{Gy}}$ (%)	9,51 $\pm$ 3,03	14,44 $\pm$ 4,31	<0,001
$V_{20\text{Gy}}$ (%)	8,29 $\pm$ 2,84	12,84 $\pm$ 3,96	<0,001
$V_{25\text{Gy}}$ (%)	7,43 $\pm$ 2,46	12,44 $\pm$ 4,90	<0,001
$V_{30\text{Gy}}$ (%)	6,66 $\pm$ 2,52	10,19 $\pm$ 3,35	<0,001
$V_{50\text{Gy}}$ (%)	0,34 $\pm$ 0,57	0,69 $\pm$ 0,84	0,118
MHD (cm)	0,9195 $\pm$ 0,50	1,9975 $\pm$ 0,61	<0,001
LAD			
D_{max}	50,04 $\pm$ 1,83	50,30 $\pm$ 2,81	0,049
D_{mean}	33,57 $\pm$ 6,04	36,48 $\pm$ 6,13	0,159
D_{min}	2,92 $\pm$ 0,95	3,07 $\pm$ 0,90	0,643
$V_{25\text{Gy}}$ (%)	68,75 $\pm$ 12,84	71,38 $\pm$ 11,56	0,520
IPSILATERAL LUNG			
Volume (cc) mean	1843,49 $\pm$ 542,78	1187,65 $\pm$ 185,62	0,001
D_{max}	53,20 $\pm$ 1,64	53,74 $\pm$ 1,39	0,433
D_{mean}	12,19 $\pm$ 2,70	12,83 $\pm$ 2,37	0,867
D_{min}	0,18 $\pm$ 0,07	0,23 $\pm$ 0,08	0,005
$V_{5\text{Gy}}$ (%)	31,98 $\pm$ 5,79	34,42 $\pm$ 5,80	0,005
$V_{10\text{Gy}}$ (%)	27,39 $\pm$ 4,97	29,61 $\pm$ 5,28	0,004
$V_{15\text{Gy}}$ (%)	24,66 $\pm$ 4,51	27,10 $\pm$ 5,14	0,046
$V_{20\text{Gy}}$ (%)	22,83 $\pm$ 4,18	25,36 $\pm$ 4,83	0,014
$V_{25\text{Gy}}$ (%)	21,23 $\pm$ 4,37	24,42 $\pm$ 5,71	<0,001
$V_{30\text{Gy}}$ (%)	20,08 $\pm$ 3,71	22,19 $\pm$ 4,95	0,008
$V_{50\text{Gy}}$ (%)	4,68 $\pm$ 4,60	5,97 $\pm$ 4,40	0,167
CONTRALATERAL BREAST*			
D_{mean}	1,29 $\pm$ 1,29	0,95 $\pm$ 1,03	0,241

Abbreviations: FB, Free breathing; DIBH, deep inspiration breath hold; PTV, Planning target volume; D_{max} , maximum dose administered to volume; D_{mean} , mean dose administered to volume; D_{min} , minimum dose administered to volume; $V_{47.5\text{Gy}}$ (%), organ volume receiving 47,5 Gy; HI, Homogeneity Index; CI, Conformity Index; CN, Conformity Number; $V_{5\text{Gy}}$ (%), $V_{10\text{Gy}}$ (%), $V_{15\text{Gy}}$ (%), $V_{20\text{Gy}}$ (%), $V_{25\text{Gy}}$ (%), $V_{30\text{Gy}}$ (%) and $V_{50\text{Gy}}$ (%), organ volume receiving 5, 10, 15, 20, 25, 30 and 50 Gy; LAD, left anterior descending artery; SD, standard deviation. * Right breast values were calculated for only 10 patients with suitable imaging on their CT-sim scan.

For all patients, the DIBH technique significantly decreased the radiation doses in most of the heart parameters compared with the FB technique (table 2). Heart volumes decreased approximately 12% in the DIBH technique as compared to that in the FB technique ($p = 0.001$). Similarly, the DIBH technique significantly decreased mean heart dose compared to the FB technique ($p = 0.009$). The mean heart dose was decreased from 7.7 Gy to 5.8 Gy. With the DIBH technique, the mean heart dose was found to be decreased by 24.9%. When cardiac sub-volumes were examined, a reduction in dose was achieved in all sub-volumes, as expected, by the DIBH technique (figure 3). All dose differences between the two techniques were statistically significant.

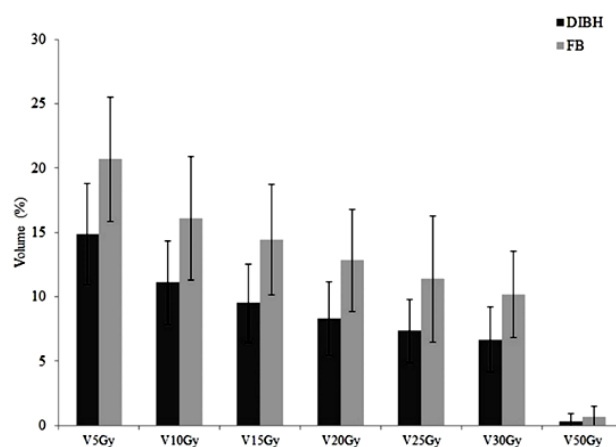


Figure 3. Cardiac sub-volume doses for free breathing (FB) and deep inspiration breath hold (DIBH) techniques. V5Gy, V10Gy, V15Gy, V20Gy, V25Gy, V30Gy and V50Gy, organ volume receiving 5, 10, 15, 20, 25, 30 and 50 Gy. Error bars represent standard deviation (SD).

Maximum heart distance (MHD) was 0.4-2.00 cm (mean 0.9 cm, SD 0.5) for the 20 patients evaluated in the DIBH technique (table 2). In the FB technique, this value was found to be 0.8-2.8 cm (mean 2.0 cm, SD 0.6). The MHD value was significantly reduced by using the DIBH technique ($p \leq 0.001$). In other words, the depth of the heart within the treatment field was decreased. The statistically significant decrease in MHD can be better seen in the box plot (figure 4).

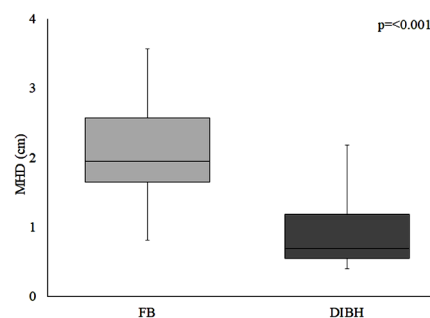


Figure 4. Box plot showing the mean maximum heart distance (MHD) in the free breathing (FB) and deep inspiration breath hold (DIBH) techniques. The boxes point out the 25th and 75th percentiles of MHD dose, meantime horizontal lines in the boxes point out the median. Error bars indicate standard deviation for excessive values.

In table 2, the mean (range) and p-values of D_{mean} , D_{max} and $V_{25\text{Gy}}(\%)$ of the LAD artery are shown for both the FB and DIBH techniques. The D_{mean} and $V_{25\text{Gy}}$ values found for the LAD artery were lower with the DIBH technique as compared to that with the FB technique. The mean LAD artery doses were reduced by 8.0% with the DIBH technique, but the difference was not statistically significant (figure 5).

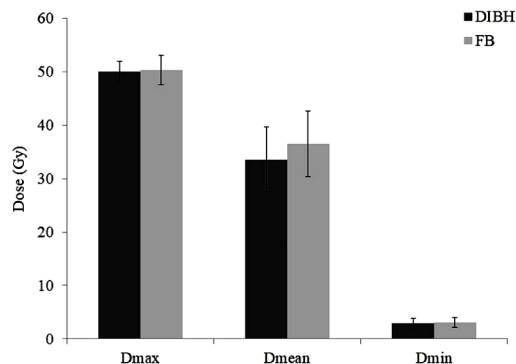


Figure 5. Left anterior descending (LAD) coronary artery doses for the free breathing (FB) and deep inspiration breath hold (DIBH) techniques. Error bars represent standard error. D_{max} , maximum dose administered to volume; D_{mean} , mean dose administered to volume; D_{min} , minimum dose administered to volume; $V_{25\text{Gy}}$, organ volume receiving 25Gy. Error bars represent standard deviation (SD).

The average ipsilateral lung volume was risen from 1187.7 cc to 1843.5 cc ($p = 0.001$), indicating a mean 55.6% increase for all patients with the DIBH technique (table 2). The D_{mean} value for the ipsilateral lung was also found to be lower by using the DIBH technique. As with cardiac doses, ipsilateral lung sub-volumes doses were significantly lower with the DIBH technique. The mean values for $V_{20\text{Gy}}$ were 25.4% and 22.8% for the FB and DIBH techniques, respectively, which is equivalent to an average 10.2% (range 1.4–34.7%) decrease in the DIBH. The higher dose reduction with the DIBH was obtained in $V_{30\text{Gy}}$ (12.1%, range 0.8–35.0) (figure 6). The contralateral breast D_{mean} average doses, which were obtained for only 10 patients, were found as 1.3 Gy with the DIBH technique and 0.9 Gy with the FB technique, but the difference was not statistically significant.

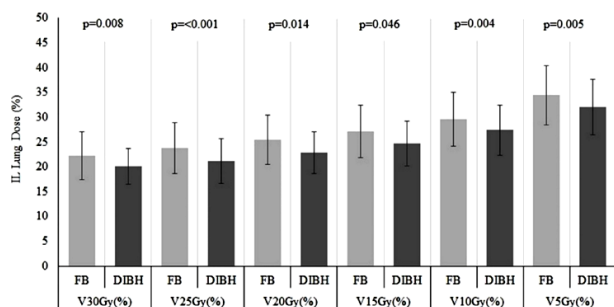


Figure 6. Ipsilateral lung (IL) doses in the free breathing (FB) and deep inspiration breath hold (DIBH) techniques. $V_{30\text{Gy}}(\%)$, $V_{25\text{Gy}}(\%)$, $V_{20\text{Gy}}(\%)$, $V_{15\text{Gy}}(\%)$, $V_{10\text{Gy}}(\%)$ and $V_{5\text{Gy}}(\%)$ organ volume receiving 30, 25, 20, 15, 10 and 5 Gy. Error bars represent standard deviation (SD).

DISCUSSION

Dosimetric comparisons of several RT planning techniques have been evaluated in a great number of studies on women with left sided ESBC in order to find out which one is more advantageous for OARs doses. As the cure rate and life expectancy of patients with ESBC is very high, radiation-related cardiac and pulmonary late toxicities have to be minimised, especially for relatively young patients with left sided breast cancer. It has been reported that the rate of subsequent ischemic heart disease increases with heart and LAD doses (7).

Different DIBH techniques have been suggested to decrease the cardiac dose by move away the breast and chest wall far from the heart throughout irradiation (15, 16, 30, 31). Hayden *et al.* showed statistically significant reductions in the mean heart dose, MHD and mean LAD dose utilising the DIBH technique (32). In a similar multicentre study on 101 patients from the UK, it is stated that the mean heart dose is effectively halved in breast RT using the voluntary breath hold technique (16). In the review by Bergom *et al.*, it is reported that the DIBH caused 25–67% and 20–73% reductions in both mean heart doses and mean LAD doses, respectively, when the FB and DIBH plans of the same patient were compared (19). In addition, Corradini's results show that the minimum risk for both major coronary disease and secondary lung cancer is in three-dimensional conformal RT plans using the DIBH technique (2). In our study, whilst the average heart volume was 503 cc in the FB technique, the heart was stuck due to the enlargement of the lung in the DIBH technique; its volume decreased to 442.5 cc on average ($p = 0.001$). Accordingly, the mean heart dose decreased from 7.7 Gy to 5.8 Gy ($p = 0.009$) with a rate of 24.9%. Similarly D_{mean} and $V_{25\text{Gy}}(\%)$ values for the LAD artery were lower with the DIBH technique as compared to that with the FB technique, but none of the differences was statistically significant. In contrast, the difference for MHD was significant ($p < 0.001$). Vikstrom *et al.* reported that the MHD value reduced from 1.3 cm to 0.3 cm with the DIBH technique. They also found that a lower mean MHD resulted in a lower mean heart dose achieved with the DIBH technique (33). Our results are parallel with other published articles indicating a decrease in the cardiac and LAD artery doses by using the DIBH. However, our heart and LAD artery doses for both FB and DIBH techniques were found to be higher than previously published articles. This was probably due to the bigger breast volume of our patients and the larger constraints on PTV coverage we applied for treatment planning. Additionally, contouring the LAD artery was especially difficult. It was often badly visualised, because we did not use contrast medium. Also, there were irregularities due to cardiac and respiratory motion.

In our study, the mean ipsilateral lung volume increased by 1.5 times with the DIBH technique compared to that with the FB technique ($p = 0.001$). Significant increases in lung volume caused by the DIBH technique were reported in similar studies ^(13, 32-34). We found ipsilateral lung D_{mean} dose lower with the DIBH as compared to that with the FB technique, but the difference was not significant. Meanwhile, the differences between $V_{5-30\text{Gy}}$ (%) values were significantly lower with the DIBH. In his study of NTCP on early clinical and radiological pulmonary complications following breast cancer RT, Rancati reported that the mean lung doses were robust parameters that correlated with the risk of pneumonitis ⁽⁹⁾. Marks *et al.* suggested that V20 should be limited to 30-35% and the mean lung dose to 20-23 Gy, so the risk of RP does not exceed 20% in conventional fractionation ⁽³⁵⁾. The average $V_{20\text{Gy}}$ (%) values of our patients were significantly lower with the DIBH technique as compared to those with the FB technique (22.8% vs. 25.5%).

In our study, all patients were relatively young women highly adaptable to respiratory training. In only one patient, mismatch of laser cross lines and skin markers was detected due to her inability to hold her breath during beam-on time, and irradiation was interrupted. However, in the voluntary DIBH technique without the use of a respiratory monitor, it is important that the entire team is trained in this regard. A multicentre study by Barlett *et al.* indicated that the set-up process and repeatability data should be routinely checked when applying new RT techniques ⁽¹⁶⁾. They also showed in their study that the voluntary breath hold is reproducible and feasible for patients and radiographers, but it will likely require some additional treatment time ⁽¹⁶⁾. In another study, Kunheri *et al.* stated that respiratory monitoring systems used in patients with breast cancer are relatively easier to use clinically compared to other modern RT techniques, such as IMRT, which is preferred as another alternative method for reducing cardiac doses ⁽³⁶⁾. As a disadvantage, the duration of treatment time with the DIBH technique is longer than other treatment modalities, and the deviation between fractions that can be determined with daily portal graphics are also more substantial.

CONCLUSION

Our data confirmed that left breast irradiation with the voluntary DIBH technique results in important decreases in heart and LAD doses when compared to the FB technique. Patients' compliance and their training along with the treatment team are essential for the use of this technique. In order to reduce mortality risk from cardiovascular diseases affecting long-term survival of patients with left sided ESBC, the use of the DIBH technique must be

considered, even in the absence of DIBH equipment.

ACKNOWLEDGMENT

None

Ethical considerations: Ethics approval code; TÜTF GOKAEK 2013/106.

Author contributions: All authors contributed in Designing and Conducting the research in addition to writing the article.

Conflict of interest: The authors declare that they have no competing interests.

Funding: This work was financially supported by the Trakya University Scientific Research Projects (TUBAP project no: 2013/123).

REFERENCES

- Koivumaki T, Fogliata A, Zeverino M, Boman E, Sierpowska J, Moeckli R, *et al.* (2018) Dosimetric evaluation of modern radiation therapy techniques for left breast in deep-inspiration breath-hold. *Phys Med*, **45**: 82-7.
- Corradini S, Ballhausen H, Weingandt H, Freislederer P, Schonecker S, Niyazi M, *et al.* (2018) Left-sided breast cancer and risks of secondary lung cancer and ischemic heart disease : Effects of modern radiotherapy techniques. *Strahlenther Onkol*, **194**(3): 196-205.
- Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, *et al.* (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, **366**(9503): 2087-106.
- Darby SC, McGale P, Taylor CW, Peto R (2005) Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol*, **6**(8): 557-65.
- Henson KE, McGale P, Taylor C, Darby SC (2013) Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer*, **108**(1): 179-82.
- Jacobse JN, Duane FK, Boekel NB, Schaapveld M, Hauptmann M, Hoening MJ, *et al.* (2019) Radiation Dose-Response for Risk of Myocardial Infarction in Breast Cancer Survivors. *Int J Radiat Oncol Biol Phys*, **103**(3): 595-604.
- Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, *et al.* (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*, **368**(11): 987-98.
- Kunheri B, Kotne S, Nair S, Makuny D (2017) A dosimetric analysis of cardiac dose with or without active breath coordinator moderate deep inspiratory breath hold in left sided breast cancer radiotherapy. *Journal of Cancer Research and Therapeutics*, **13**(1): 56-61.
- Rancati T, Wennberg B, Lind P, Svane G, Gagliardi G (2007) Early clinical and radiological pulmonary complications following breast cancer radiation therapy: NTCP fit with four different models. *Radiother Oncol*, **82**(3):308-16.
- Gokula K, Earnest A, Wong LC (2013) Meta-analysis of incidence of early lung toxicity in 3-dimensional conformal irradiation of breast carcinomas. London, England; *Radiation Oncology*, **8**: 268.
- Okutan M, Franko A, Köksal C, Göksel E, Karaman Ş, Akpınar YE, *et al.* (2020) The evaluation of lung doses for radiation pneumonia risk in stereotactic body radiotherapy: A comparison of intensity modulated radiotherapy, intensity modulated arc therapy, cyberknife and helical tomotherapy. *Int JRR*, **18**(4): 633-40.
- Nilsson G, Holmberg L, Garmo H, Duvernoy O, Sjogren I, Lagerqvist B, *et al.* (2012) Distribution of coronary artery stenosis after radiation for breast cancer. *Official Journal of the American Society of Clinical Oncology*. **30**(4): 380-6.
- Bruzzaniti V, Abate A, Pinnaro P, D'Andrea M, Infusino E, Landoni V, *et al.* (2013) Dosimetric and clinical advantages of deep inspiration breath-hold (DIBH) during radiotherapy of breast cancer. *J Exp Clin Cancer Res*, **32**: 88.

14. Latty D, Stuart KE, Wang W, Ahern V (2015) Review of deep inspiration breath-hold techniques for the treatment of breast cancer. *Journal of Medical Radiation Sciences*, **62**(1): 74-81.
15. Bartlett FR, Colgan RM, Carr K, Donovan EM, McNair HA, Locke I, et al. (2013) The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiotherapy and Oncology*, **108**(2): 242-7.
16. Bartlett F, Donovan E, McNair H, Corsini L, Colgan R, Evans P, et al. (2017) The UK HeartSpare Study (Stage II): multicentre evaluation of a voluntary breath-hold technique in patients receiving breast radiotherapy. *Clinical Oncology*, **29**(3):e51-e6.
17. Osman SO, Hol S, Poortmans PM, Essers M (2014) Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiotherapy and Oncology*, **112**(1): 17-22.
18. de Boer HC, van den Bongard DJ, van Asselen B (2016) Automated daily breath hold stability measurements by real-time imaging in radiotherapy of breast cancer. *Radiother Oncol*, **119**(1): 61-4.
19. Bergom C, Currey A, Desai N, Tai A, Strauss JB (2018) Deep inspiration breath hold: Techniques and Advantages for Cardiac Sparing During Breast Cancer Irradiation. *Front Oncol*, **8**: 87.
20. Osman SO, Hol S, Poortmans PM, Essers M (2014) Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiother Oncol*, **112**(1): 17-22.
21. Bartlett FR, Colgan RM, Carr K, Donovan EM, McNair HA, Locke I, et al. (2013) The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol*, **108**(2): 242-7.
22. Bolukbasi Y, Saglam Y, Selek U, Topkan E, Kataria A, Unal Z, et al. (2014) Reproducible deep-inspiration breath-hold irradiation with forward intensity-modulated radiotherapy for left-sided breast cancer significantly reduces cardiac radiation exposure compared to inverse intensity-modulated radiotherapy. *Tumori*, **100**(2): 169-78.
23. van der Laan HP, Hurkmans CW, Kuten A, Westenberg HA (2010) Current technological clinical practice in breast radiotherapy; results of a survey in EORTC-Radiation Oncology Group affiliated institutions. *Radiotherapy and Oncology*, **94**(3): 280-5.
24. Simcock R, Thomas TV, Mercy CE, Filippi AR, Katz MA, Pereira JJ, et al. (2020) COVID-19: Global radiation oncology's targeted response for pandemic preparedness. *Clinical and Translational Radiation Oncology*, **2020**(22): 55-68.
25. Barnett E, Comsa D, Zhang B, Pestill T, Bradley C, Proctor L, et al. (2020) A rapid transition to voluntary breath hold from device-assisted moderate deep inspiration breath hold for patients receiving breast radiotherapy during the COVID-19 pandemic. *Adv Radiat Oncol*, **5**(4): 675-8.
26. RTOG Breast Cancer Atlas [Available from: <https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx> [accessed 17th August 2019].
27. ICRU (2010) International Commission on Radiation Units and Measurements: Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU Report 83. *J ICRU*, **10**: 1-106.
28. Paddick I (2000) A simple scoring ratio to index the conformity of radiosurgical treatment plans. *Journal of neurosurgery*. **93**(3): 219-22.
29. Feuvret L, Noël G, Mazeron J-J, Bey P (2006) Conformity index: a review. *Int J Radiat Oncol Biol Phys*, **64**(2): 333-42.
30. Bergom C, Currey A, Desai N, Tai A, Strauss JB (2018) Deep inspiration breath hold: techniques and advantages for cardiac sparing during breast cancer irradiation. *Frontiers in Oncology*, **8**: 87.
31. Boda-Heggemann J, Knopf A-C, Simeonova-Chergou A, Wertz H, Stieler F, Jahnke A, et al. (2016) Deep inspiration breath hold—based radiation therapy: a clinical review. *Int J Radiat Oncol Biol Phys*, **94**(3): 478-92.
32. Hayden AJ, Rains M, Tiver K (2012) Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. *J Med Imaging Radiat Oncol*, **56**(4): 464-72.
33. Vikstrom J, Hjelstuen MH, Mjaaland I, Dybvik KI (2011) Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. *Acta Oncol*, **50**(1): 42-50.
34. Shim J-G, Kim J-K, Park W, Seo J-M, Hong C-S, Song K-W, et al. (2012) Dose-volume analysis of lung and heart according to respiration in breast cancer patients treated with breast conserving surgery. *Journal of Breast Cancer*, **15**(1): 105.
35. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. (2010) Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys*, **76**(3): 570-6.
36. Kunheri B, Kotne S, Nair SS, Makuny D (2017) A dosimetric analysis of cardiac dose with or without active breath coordinator moderate deep inspiratory breath hold in left sided breast cancer radiotherapy. *Journal of Cancer Research and Therapeutics*, **13**(1): 56.

