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ORIGINAL ARTICLE

Dosimetric Analysis of Tangential-Based Volumetric Modulated Arc Therapy Implemented Using Deep Inspiration Breath-Hold Technique in the Left Breast Cancer Patients with Breast-Conserving Surgery

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OBJECTIVE

We aimed to report the dosimetric effects of integrating the deep inspiration breath-hold technique (DIBH) into tangential-based volumetric modulated arc therapy (TVMAT) in left breast cancer patients who underwent breast-conserving surgery (BCS).

METHODS

Sixty-one patients who underwent BCS were included in the study. Patients were divided into two groups according to whether irradiation was applied only to the breast or to the breast + regional lymph nodes (RLN). DIBH-TVMAT and free-breath (FB)-TVMAT plans were generated using a mono-isocentric technique with two partial arc rotations for each patient. The same gantry angles were used for both FB-TVMAT and DIBH-TVMAT plans. DIBH-TVMAT and FB-TVMAT plans were evaluated, and dosimetric parameters were compared.

RESULTS

The mean cardiac dose in the FB-TVMAT and DIBH-TVMAT plans was 8.8 Gy and 5 Gy, respectively, indicating a 42% dose reduction in patients receiving only breast radiotherapy (RT) (p=0.000). Left lung volumes that received 5 Gy and 20 Gy were also significantly in favor of DIBH-TVMAT (p=0.001; p=0.003). A 23% reduction was encountered in the maximum dose applied to the left anterior descending coronary artery (LADCA) after the DIBH-TVMAT plan in patients who received RT to the breast and RLN (p=0.000). The addition of supraclavicular lymph nodes to the treatment field revealed an increase in the heart volume that received 5 Gy and the ipsilateral lung volumes that received 5, 10, and 20 Gy.

CONCLUSION

The technique integrating DIBH with TVMAT provides a significant dose reduction not only to the heart and LADCA but also to the bilateral lungs and contralateral breast without sacrificing target volume dose coverage.

Keywords: Breast cancer; deep inspiration breath hold (DIBH); radiotherapy; tangential-based volumetric modulated arc therapy (TVMAT).

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INTRODUCTION

Breast cancer is one of the most common three cancer types worldwide, as well as being the most common cancer type among females.[1] Adjuvant radiotherapy is the standard treatment method in patients undergoing breast-conserving surgery because it reduces the risk of local recurrence and prolongs overall survival.[2–4] Besides its important role in the treatment regimen and numerous benefits, it shows important side effects in normal tissue. Particularly, the anterior heart is exposed to an intense dose during left breast (LB) irradiation.[5] Besides the anterior heart, the left anterior descending coronary artery (LADCA), lungs, and contralateral breast are also exposed to considerable radiation.[6] Darby et al.[7] reported that some changes may occur in the heart exposed to ionizing radiation within follow-ups. Ischemic heart disease may develop within long-term follow-up periods due to exposure of the heart and LADCA to radiation dose and decrease the quality of life. Besides, it has been detected that the risk for various cardiac events, coronary artery disease, and furthermore lung cancer has proceeded for long years depending on treatment and dosage in the patients who received radiotherapy (RT) for LB cancer compared with right breast radiation.[8] Because the risk for fatal cardiovascular diseases increases due to the proximity of the treatment field to the heart and coronary vessels in LB cancer radiotherapy. The anterior part of the heart and LADCA are exposed to high doses during irradiation, particularly in the use of classical treatment methods.[8–11]

Modern treatment techniques have been developed and are currently still developed to decrease heart, LADCA, lungs, and contralateral breast doses in the radiotherapy of particularly LB cancer and reduce the risk for potential subsequent cardiac toxicity, ischemic diseases, radiation pneumonia, and furthermore a secondary cancer.[12] Respiratory motion seriously affects dose distribution in RT for LB cancer. Respiratory motion causes differences in the distance between the volume that receives a high dose and the heart. Deep inspiration breath-hold technique (DIBH) eliminates the impact of breathing motion by detaching the heart, LADCA, and lungs from the target volume.[13] However, the voluntary breath-hold technique alone without definite standardization may not be optimal because of differences during treatment and between RT fractions. This problem can be solved by management and monitoring of breathing. The use of an infrared surface marker placed without the need for an invasive intervention and a camera system that monitors this marker during treatment and compares it with the reference position has a higher safety than voluntary breath-holding or other systems.[14–17]

On the other side, it is known that the use of intensity-modulated radiation therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) as modern RT techniques provides a highly confirmed dose distribution on the target volume and decreases doses to organs-at-risk such as the heart and lungs.[18–20] In recent years, IMRT is commonly used instead of three-dimensional conformal RT (3DRT) due to the achievement of regular dose distribution on the target volume after breast-conserving surgeries and reduction of doses to organs-at-risk in breast cancer.[21–25] VMAT is one of the novel treatment techniques and has been noticed to provide better conformity and homogeneity on target volume coverage with simultaneous modulation of multileaf collimator (MLC) movement compared to IMRT and also to present advantages in dose distribution to organs-at-risk and delivery time reduction.[24] Despite the advantage of delivering a high dose to the target volume and a low dose to the organs-at-risk, it has been reported that standard VMAT may cause malignancies by increasing doses to the contralateral breast and contralateral lung compared with tangential-based methods. Therefore, VMAT cannot be the first treatment option in breast cancer.[25] Tangential VMAT (TVMAT) is a very novel treatment method developed by modifications on VMAT considering its disadvantages. Even though it seems similar to tangential-based treatments, they provide high dose at the target volume, low dose to organs-at-risk, and delivery time reduction. Moreover, it eliminates the disadvantages of VMAT in the contralateral organs. Yu et al.[26] have also reported that doses to OAR in VMAT were higher than in TVMAT.

There are only a limited number of studies that compare the techniques DIBH-TVMAT and free breath (FB)-TVMAT based on respiratory monitoring. To our knowledge, our comparison will be the study with the largest number of patients that has dosimetrically compared TVMAT applied using the DIBH technique with TVMAT applied using the FB technique. In addition, it has been aimed to demonstrate that TVMAT applied using the DIBH technique reduces the dose to organs at risk such as the heart, left lung, LADCA, and right breast and can be safely implemented.

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MATERIALS AND METHODS

Sixty-one patients were included in the study. The patients were selected according to the following inclusion criteria:

The patients;

1. who had undergone breast-conserving surgery between January 2016 and January 2020 and received adjuvant RT
2. who could hold their breath in deep inspiration after breath-hold guidance
3. whose CT images could be taken in both deep inspiration and free-breath
4. with good performance status

The exclusion criteria for the patients were as follows:

1. who could not hold their breath in deep inspiration after breath-hold guidance
2. who had undergone mastectomy
3. who had previously received RT for breast or another field

Breast RT was performed in 44 patients, whereas 17 patients received RT to breast, Level I, II, and III axillary lymph nodes, supraclavicular lymph nodes (SCLN), and internal mammary lymph nodes (IMLN). All the patients who received lymph node irradiation were Stage II or III. The patients were fixed with hands over head in the supine position on the carbon fiber breast board using elbow boards. Radiopaque markers were placed into the imaging area before the imaging procedure. Computed tomography (CT) slices were acquired with a 16-slice CT scanner (Siemens Somatom Emotion Duo). The CT acquisition slice was 3 mm in thickness. The imaging field started from the first cervical vertebra of the upper spine and elongated to the second lumbar vertebra of the lower spine.

Breath-Hold Guidance

Each patient was guided about breath-holding by a training nurse one week before CT imaging. Breath-hold guidance involved instruction of the patients on how to hold their breath and how to initiate breathing. CT scans were obtained by holding breath at deep inspiration and free-breathing in the successful patients in breath-holding. The breath-holding level was encountered by breath-hold monitoring with an infrared reflecting block and cameras inserted into the xiphoid process using the real-time position management (RPM) System (Varian Medical System, Palo Alto, USA). The field of the infrared reflecting block was marked on the patient's skin. A test procedure was performed prior to CT imaging by having the patients hold their breath twice for 20 seconds. CT imaging was initiated in DIBH in the patients who completed the test procedure successfully. At the onset of the imaging session, a gating window was specified as 1.5 mm below and above the breath-hold level to medium to be used during treatment. Immediately after this procedure, free-breath images were obtained in the same position. CT scan images, the respiratory curve, and gating window were recorded after CT imaging and analyzed in the Eclipse Version 13.6.23 Treatment Planning System (Varian Medical System, Palo Alto, USA).

The Determination of the Target Volume and Organs-at-risk

The determinations of the organs-at-risk and target volume were carried out according to the delineation guidelines of the Radiation Therapy Oncology Group (RTOG)[27] and the Danish Breast Cancer Cooperative Group.[4] Primarily the heart, LADCA, right and left lungs, esophagus, right breast, and spinal cord were contoured as the organs-at-risk. The clinical target volume (CTV) was contoured for each patient by the same radiation oncologist in both DIBH and FB. The CTV included LB glandular tissue of the patients who would receive only breast irradiation whereas LB glandular tissue, Level I-III lymph nodes, IMLN, and SCLN were included in the patients who would receive irradiation to the regional lymph nodes. The breast glandular tissue was determined utilizing the sternum and mid-axillary line at medial and lateral aspects in the CT images, respectively. The latissimus dorsi muscle was excluded from the treatment field. All the patients received an additional boost dose to the tumor bed. Seroma and surgical clips were contoured for the determination of the tumor bed to be applied boost dose (gross tumor volume after lumpectomy). The cranial and caudal margins of SCLN were contoured as the caudal aspects of the cricoid cartilage and clavicular head, respectively. The thyroid gland and trachea were definitely excluded from the treatment field. Axillary lymph nodes were contoured taking the pectoralis major and minor muscles as a reference. The cranial and caudal margins of IMLN were specified as the superior aspect of the 1st rib and cranial aspect of the 4th rib, respectively. The planning target volume (PTV) was generated by adding a 5-mm margin to the CTV through three-dimensional expansions. The PTV was cropped from the skin by a 3-mm margin.

Treatment Planning

All patients were distributed into two groups. The treatment plans were created separately for each patient both in DIBH and FB.

DIBH-TVMAT and FB-TVMAT plans were designed using a mono-isocentric technique with two partial arc rotations for patients whose only breast and tumor bed would be irradiated. The first arc started at 275.8–309.3 degrees and stopped at 131.6–172.5 degrees in DIBH-TVMAT plans. The second arc was fully inverted to the first arc. The same entrance and exit angles were used in FB-TVMAT plans. The collimation angles of 30 and 330 degrees were used in the first and second arcs, respectively.

DIBH-TVMAT and FB-TVMAT plans were also designed using a mono-isocentric technique with two partial arc rotations for patients whose breast, tumor bed, and RLN would be irradiated. The first arc started at 285–311.4 degrees and stopped at 124.3–175 degrees in DIBH-TVMAT plans. The second arc was fully inverted to the first arc. The same entrance and exit angles were used in FB-TVMAT plans. The collimation angles of 30 and 330 degrees were used in the first and second arcs in this group, respectively.

The total dose defined for the breast was 50 Gy with 2 Gy per fraction per day for the group in which RT was applied to only the breast. A dose of 60 Gy with 2.4 Gy per fraction per day was defined for the tumor bed by the simultaneous integrated boost (SIB) technique. The purpose of the treatment plan was described as receiving 95% of the defined dose by at least 98% of PTV applied as 50 Gy whereas that was receiving 95% of the defined dose by at least 98% of PTV applied as 60 Gy.

The total dose defined for breast+RLN was 50 Gy with 2 Gy per fraction per day for the group in which RT was applied to breast and RLN. A dose of 60 Gy with 2.4 Gy per fraction per day was defined for the tumor bed by SIB technique. The purpose of the treatment plan was described as receiving 95% of the prescribed dose by at least 98% of PTV applied as 50 Gy whereas that was receiving 95% of the prescribed dose by at least 98% of PTV applied as 60 Gy.

The treatment planning was created for each patient primarily with DIBH-TVMAT. The treatment plans were created using Eclipse Version 13.6.23 Treatment Planning System (TPS) (Varian Medical System, Palo Alto, USA). The treatment plans were performed using 6MV photon energy. Gantry settings were the same for DIBH-TVMAT and FB-TVMAT. The first essential target of the treatment plan was 98% coverage of PTV by 98% of the defined dose. The second essential target of the plan was to keep the doses at the lowest possible level for the organs-at-risk while the first essential target was achieved. No bolus dose was administered to any of the patients. The target volumes, dose concentrations for the organs-at-risk, and our priorities were as shown in the table (Table 1). The optimization was stopped when these criteria were met, and the plan was accepted as the final plan (Figs. 1, 2). Similar conformity and homogeneity were achieved for each plan. In addition, quality assurance (QA) was carried out for each plan. The grid size for dose calculation was 2.5 mm. The progressive resolution optimizer (Version 13.6.23) and analytical anisotropic algorithm (Version 13.6.23) were used for the optimizations of TVMAT.

Table 1 Critical organ dose limitations for DIBH-TVMAT and FB-TVMAT

Structure	Parameter	Objective
PTV	V98 Gy (%)	≥98%
	D98 Gy (%)	≥98%
	D5 Gy (%)	≤110%
Heart	V25 Gy (%)	≤25%
	D_{mean} (Gy)	≤9 Gy[a], ≤10 Gy[b]
	D_{max} (Gy)	≤50 Gy
LADCA	D_{max} (Gy)	≤50 Gy
Left lung	V10 Gy (%)	≤50%
	V20 Gy (%)	≤20%
Right lung	D_{mean} (Gy)	≤5 Gy
Right breast	D_{mean} (Gy)	≤6 Gy
Esophagus	D_{mean} (Gy)	≤34 Gy

[a]: If supraclavicular irradiation was not performed; [b]: If supraclavicular irradiation was performed. DIBH: Deep inspiration breath-hold technique; TVMAT: Tangential-based volumetric modulated arc therapy; FB: Free-breath; PTV: Planning target volume; LADCA: Left anterior descending coronary artery

Dosimetric Evaluation

All DIBH-TVMAT and FB-TVMAT plans were evaluated, and dosimetric parameters were determined. The heart volumes that received 5, 10, 25, and 30 Gy doses, mean and maximum doses (V5, V10, V25, V30, D_{mean}, D_{max}), and the values of LADCA (V4, V5, V10, V25, V30, D_{mean}, D_{max}), left lung (V5, V10, V20), right lung (D_{mean}, $D_{2\%}$), and right breast (D_{mean}) as the organs-at-risk were obtained from the dose-volume histogram (DVH). These values were compared comprehensively only in the group that received irradiation to breast and breast+RLN (Figs. 3, 4). In addition, dosimetric analyses and comparisons were carried out for the organs-at-risk after SCLN irradiation for these two groups. Equivalent doses of 2 Gy fractionation (EQD2) were calculated for the organs-at-risk and target volumes to perform an accurate dosimetric comparison since the SIB technique was implemented.

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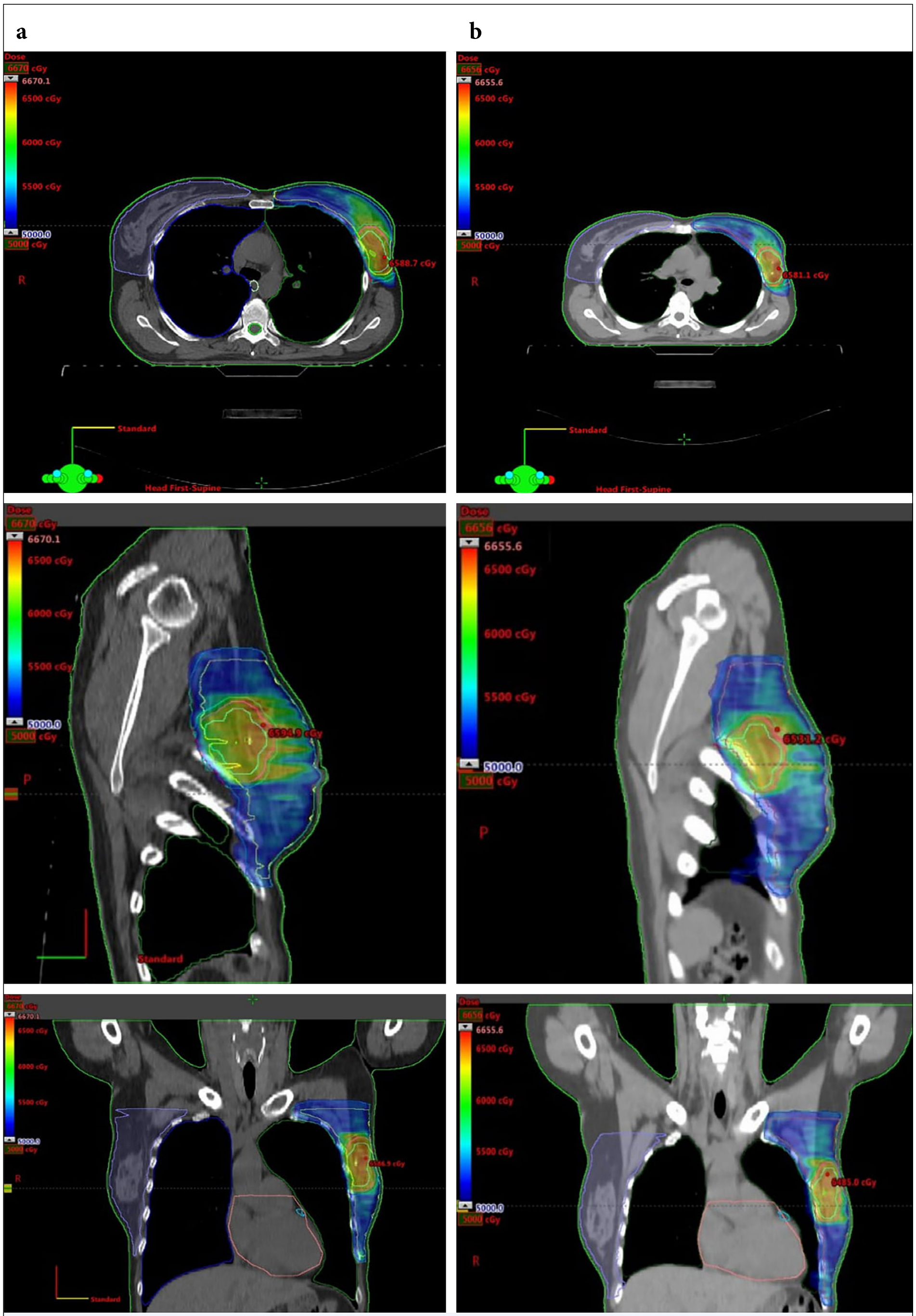

Fig. 1. The dose distribution in the axial, sagittal and coronal views of the case applied 50 Gy to the breast and 60 Gy to the tumor bed by simultaneous integrated boost (SIB) technique after left breast-conserving surgery. (a) TVMAT plan with deep inspiration breast-hold technique. (b) TVMAT plan with free-breathing technique.
TVMAT: Tangential-based volumetric modulated arc therapy.

Statistical Analysis

Data were analyzed using IBM SPSS Version 24.0 (SPSS Inc., IL, USA) statistical software. The distribution normality of the continuous variables was tested using visual (histogram and probability analyses) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Mean and standard deviation were used for normally distributed data. The doses determined for

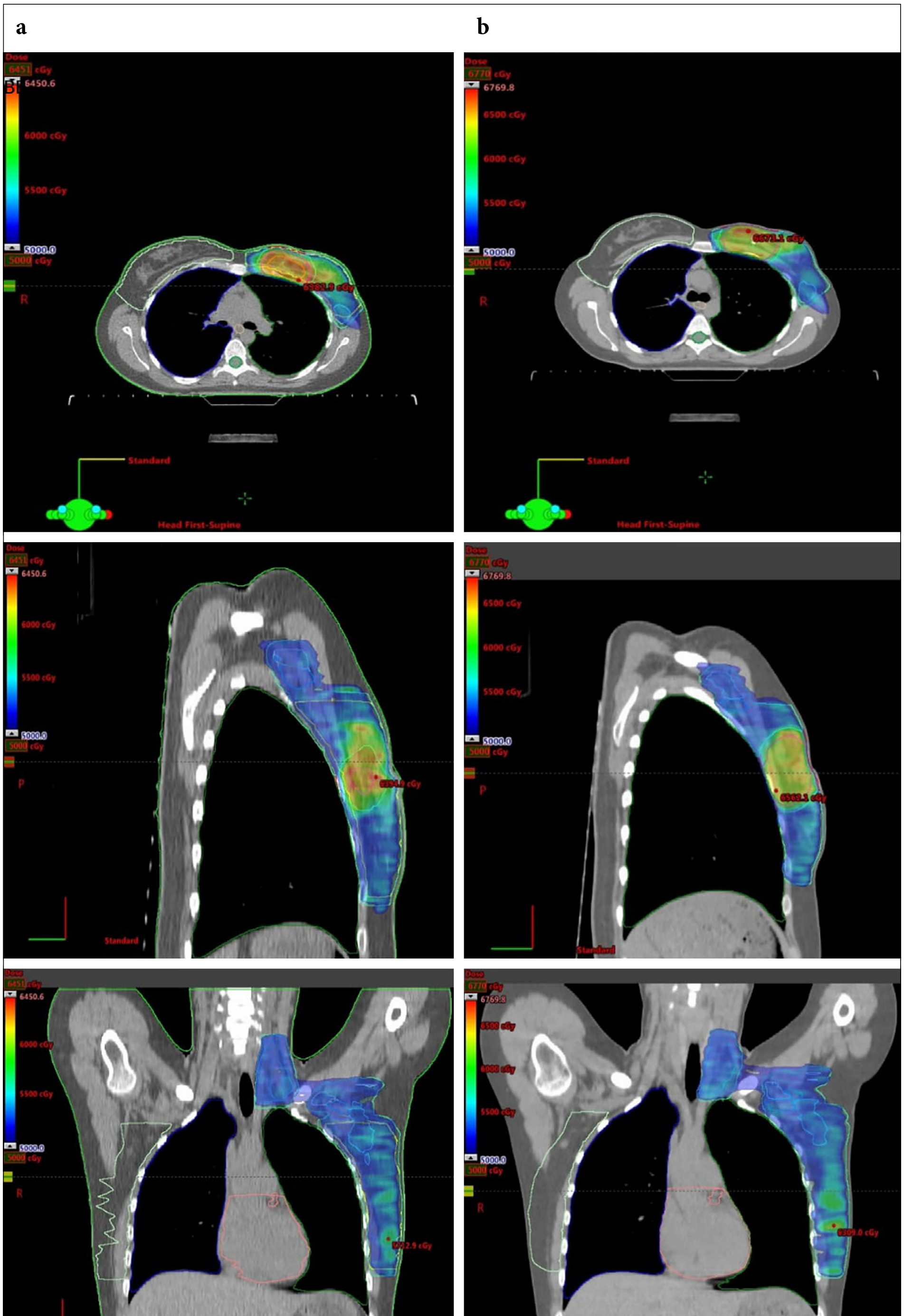

Fig. 2. The dose distribution in the axial, sagittal and coronal views of the case applied 50 Gy to the breast and regional lymph nodes, and 60 Gy to the tumor bed by simultaneous integrated boost (SIB) technique after left breast-conserving surgery. (a) TVMAT plan with deep inspiration breast-hold technique. (b) TVMAT plan with free-breathing technique.

the treatment plan of each patient group created using DIBH-TVMAT and FB-TVMAT were analyzed with a Paired-sample T-test. The dosimetric analyses following supraclavicular irradiation between two groups were carried out using an Independent T-test. A p-value of <0.05 was accepted as the statistical significance level.

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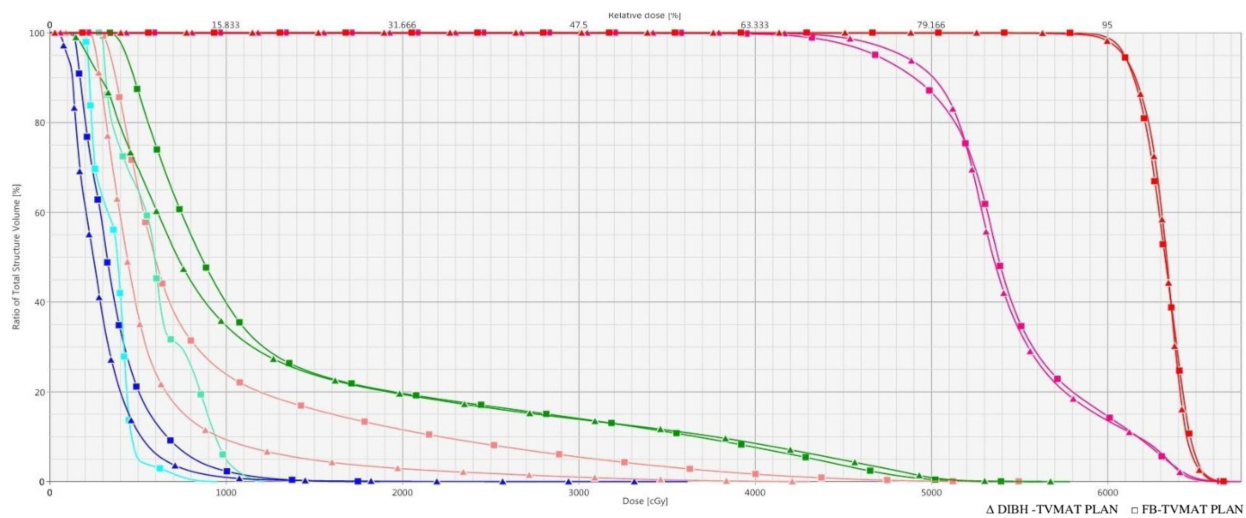

Fig. 3. The dosimetric comparison between dose-volume histograms of organs-at-risk and target volumes in DIBH-TVMAT and FB-TVMAT plans of the case applied 50 Gy for the breast and 60 Gy for the tumor bed after left breast-conserving surgery.
DIBH: Deep inspiration breath-hold technique; TVMAT: Tangential-based volumetric modulated arc therapy; FB: Free-breath.

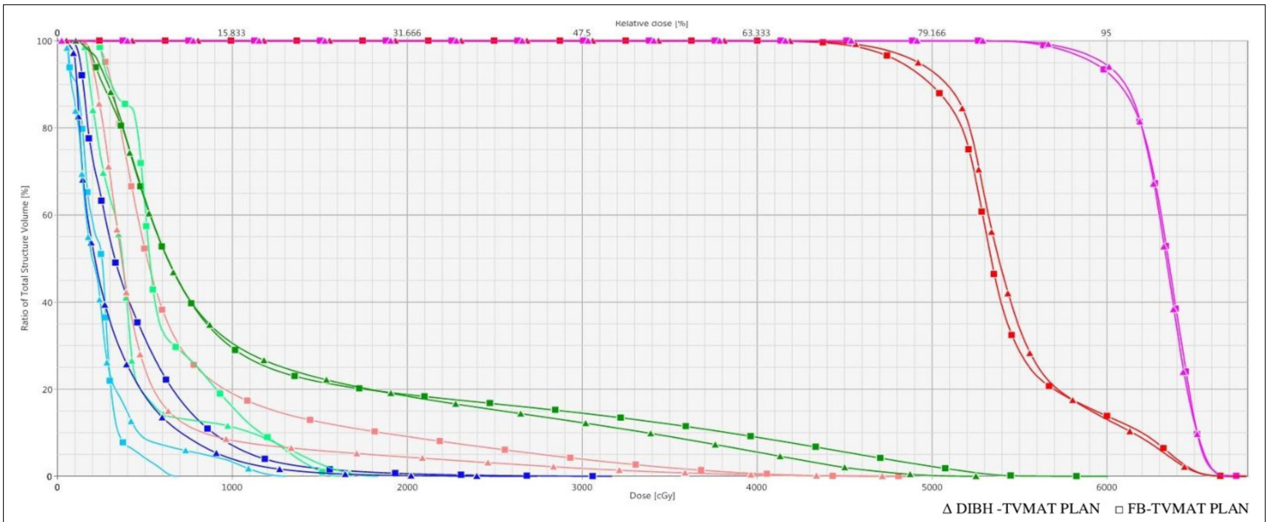

Fig. 4. The dosimetric comparison between dose-volume histograms of organs-at-risk and target volumes in DIBH-TVMAT and FB-TVMAT plans of the case applied 50 Gy for the breast and regional lymph nodes and 60 Gy for the tumor bed after left breast-conserving surgery.

Informed Consent and Ethics Committee Approval
Informed consents were obtained from all patients. Institutional evaluation board approval and Ethics Committee Approval were obtained for the present study.

RESULTS

The median age of the 44 patients who received RT for only the breast was 54 (36–74) years. Invasive ductal carcinoma was present in 33 (75%) of the patients who received RT for the breast. Of those patients, 22 (50%) had a Grade 2 tumor, whereas 25 (56.8%) patients were evaluated to be in the Luminal A group. Thirty (68.2%) of the patients who received RT for the breast were Stage IA. The median age of the 17 patients who received RT for the breast+RLN was 49 (29–63) years. Ten (58.8%) were premenopausal. The patient and tumor characteristics were summarized in Table 2.

Table 2 Patient and tumor characteristics

Characteristics	Group with irradiated breast n=44 (100%)		Group with irradiated breast+RLN n=17 (100%)	
	n	%	n	%
Median age (range)	54 (36–74)		49 (29–63)	
Menopause status				
Premenopausal	16	36.4	10	58.8
Postmenopausal	28	63.6	7	41.2
Histopathological type				
Ductal invasive	33	75	17	100
Ductal in situ	6	13.6		
Other	5	11.4		
Molecular subtype				
Luminal A	25	56.8	12	70.6
Luminal B	12	27.3		
HER2+	2	4.5	1	5.9
Triple negative	5	11.4	4	23.5
Histopathological grade				
G1	13	29.5		
G2	22	50	11	64.7
G3	9	20.5	6	35.3
Stage				
IA	30	68.2		
IB	13	29.5		
2A	1	2.3	7	41.2
2B	7	41.2		
3A	3	17.6		
Neoadjuvant chemotherapy				
Yes	2	4.5	4	23.5
No	42	95.5	13	76.5

RLN: Regional lymph nodes

The Comparison between DIBH-TVMAT and FB-TVMAT in the Patients Who Received RT for Only the Breast

The values obtained for the organs-at-risk and PTV were listed in Table 3.

Heart and LADCA: The comparison between the two plans regarding heart values revealed that the mean heart dose was 5 Gy in the DIBH plan, whereas it was found to be 8.8 Gy in the FB plan (p=0.000). According to this result, the mean heart dose decreased by 3.7 Gy (42%) after the implementation of DIBH. The heart volume that received 25 Gy was 1.2% in the DIBH plan, whereas that volume was 7% in the FB plan (p=0.000). The maximum heart doses were 36.4 Gy and 49.3 Gy in the plans applied with DIBH and FB techniques (p=0.000), respectively. These results indicated a 25% reduction. The comparison in terms of mean LADCA doses showed that the mean LADCA dose in DIBH plans was 14.8 Gy, whereas it was 21.9 Gy in FB plans. An increase of averagely 7.1 Gy corresponding to 32% was detected in FB plans (p=0.000). An average 22% reduction was encountered in LADCA maximum doses in DIBH plans.

Ipsilateral lung, Contralateral lung, and right breast: Ipsilateral lung volumes that received 5 Gy in DIBH and FB plans were found to be 59% and 65%, respectively (p=0.001). The V20 value for the DIBH technique was 18.6% Gy, whereas that value was 19.7% Gy for the FB technique (p=0.003). Thus, an improvement of 5% was achieved by the DIBH technique in V20 values. Even though the lung volume that received 10 Gy showed a 2% decrease by the DIBH technique, no statistical significance was detected (p=0.2).

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Table 3 Dosimetric parameters and differences between DIBH-TVMAT and FB-TVMAT plans regarding doses to organs-at-risk including heart, left lung, right lung and right breast obtained from dose-volume histogram in the patients applied radiotherapy for only the breast (Δ)

Structure	Parameter	DIBH-TVMAT	FB-TVMAT	Δ (DIBH-FB)	p
Heart	V5 Gy (%)	29.5±12.2	64.5±39.6	−34.9 (54%)	0.000
	V10 Gy (%)	7.7±3.7	23.6±5.5	−15.8 (66%)	0.000
	V25 Gy (%)	1.2±1.2	7±2.8	−5.7 (81%)	0.000
	V30 Gy (%)	0.5±0.7	4.7±2.3	−4.2 (89%)	0.000
	D_{mean} (Gy)	5±1	8.8±1.4	−3.7 (42%)	0.000
	D_{max} (Gy)	36.4±7.2	49.3±4.8	−12.8 (25%)	0.000
LADCA	V5 Gy (%)	80.6±22.1	94±10.8	−13.3 (14%)	0.000
	V10 Gy (%)	50.1±24.2	61.6±19.3	−11.4 (18%)	0.002
	V25 Gy (%)	21.9±23.4	40.8±19.7	−18.8 (46%)	0.000
	V30 Gy (%)	15.4±21.3	34.5±20.1	−19 (55%)	0.000
	D_{mean} (Gy)	14.8±6.9	21.9±7	−7.1 (32%)	0.000
	D_{max} (Gy)	36.9±8	48±7.3	−11 (22%)	0.000
Left lung	V5 Gy (%)	59.1±10.7	65.1±11.1	−5.9 (9%)	0.001
	V10 Gy (%)	30.8±4.4	31.6±3.9	−0.8 (2%)	0.2
	V20 Gy (%)	18.6±1.8	19.7±1.4	−1 (5%)	0.003
Right lung	D_{mean} (Gy)	3.3±0.8	3.9±1.1	−0.6 (15%)	0.000
	$D2_{\%}$ (Gy)	11.9±5.7	12.5±4.7	−0.5 (4%)	0.4
Right breast	D_{mean} (Gy)	5±1.5	5.5±1.6	−0.4 (7%)	0.003
PTV	V95 Gy (%)	98±1.7	98±1.3	0 (0%)	0.4

The mean right lung values for DIBH and FB treatment plans were found to be 3.3 Gy and 3.9 Gy, respectively (p=0.000). The ipsilateral lung $D_{2\%}$ value was detected to be 11.9% in DIBH plans. That value corresponded to an average dose reduction of 4% compared with FB plans. However, no statistical significance was determined (p=0.4).

A 0.5 Gy (7%) reduction was detected between DIBH and FB plans regarding the mean right breast dose (p=0.003).

The Comparison between DIBH-TVMAT and FB-TVMAT in the Patients Who Received RT for the Breast+Regional Lymph Nodes

The values obtained for the organs-at-risk and PTV were listed in Table 4.

Breast and LADCA: The mean heart dose was found to be 5.5 Gy in the treatment plan using the DIBH technique. A dose reduction of 3.4 Gy corresponding to 38% was encountered compared with FB (p=0.000). The most significant dose reductions were noticed in the values of the volume that received 25 Gy. The mean values in DIBH and FB plans were 6.4% and 1.2%, respectively. This result indicated an 81% reduction (p=0.000). The same reduction was determined also in the values of heart V5, V25, and V30. The comparison regarding mean LADCA doses showed reductions of 6.2 Gy (27%) and 11.4 Gy (23%) in the D_{mean} and D_{max} values, respectively (p=0.000; p=0.000). A reduction of 27% was also detected in the volume that received a 25 Gy dose (V25) compared with the FB plan (V25) 27% (p=0.000).

Ipsilateral lung, Contralateral lung, and Right Breast: The most surprising results were obtained in the left lung doses of the group that received breast+RLN irradiation. The comparison between DIBH and FB plans indicated an average 7% reduction only in the lung volume that received a 5 Gy dose, and this reduction was found statistically significant (p=0.001). However, the reduction in the values of V10 and V20 was not statistically significant.

The evaluation of the right lung doses revealed a reduction of 0.8 Gy corresponding to 18% in the mean lung dose applied in the DIBH plan (p=0.007). The comparison between DIBH and FB plans regarding $D_{2\%}$ values showed a 9% reduction; however, that result was not found statistically significant (p=0.2). Another noticeable organ-at-risk was the right breast. A 0.3 Gy reduction was detected in the mean contralateral breast dose by the comparison between DIBH and FB plans; however, this reduction was not evaluated to be statistically significant (p=0.2).

Table 4 Dosimetric parameters and differences between DIBH-TVMAT and FB-TVMAT plans regarding doses to organs-at-risk including heart, left lung, right lung and right breast obtained from dose-volume histogram in the patients applied radiotherapy for the breast and regional lymph nodes (Δ)

Structure	Parameter	DIBH-TVMAT	FB-TVMAT	Δ (DIBH-FB)	p
Heart	V5 Gy (%)	37.5±12	62.9±10.1	−25.3 (40%)	0.000
	V10 Gy (%)	7.3±4.6	23.5±6.8	−16.1 (68%)	0.000
	V25 Gy (%)	1.2±1.5	6.4±2.3	−5.2 (81%)	0.000
	V30 Gy (%)	0.6±1	4.3±1.9	−3.6 (83%)	0.000
	D_{mean} (Gy)	5.5±1	8.9±1.2	−3.4 (38%)	0.000
	D_{max} (Gy)	37.7±9	51.8±4.6	−14.1 (27%)	0.000
LADCA	V5 Gy (%)	93.5±9.7	97.6±5.1	−4 (4%)	0.1
	V10 Gy (%)	52.5±28.1	62±19.4	−9.4 (15%)	0.1
	V25 Gy (%)	25.7±20.9	41.7±22.2	−15.9 (38%)	0.004
	V30 Gy (%)	18.4±17.1	35.8±22.5	−17.3 (48%)	0.002
	D_{mean} (Gy)	16.5±6.7	22.7±8	−6.2 (27%)	0.000
	D_{max} (Gy)	37.9±8.6	49.3±13.9	−11.4 (23%)	0.000
Left lung	V5 Gy (%)	72.4±7.9	78.3±6.9	−5.9 (7%)	0.001
	V10 Gy (%)	36.4±4.7	36.7±2.4	−0.2 (0.5%)	0.8
	V20 Gy (%)	20.2±1.5	20.3±0.9	−0.08 (0.3%)	0.1
Right lung	D_{mean} (Gy)	3.5±0.9	4.3±1.4	−0.8 (18%)	0.007
	$D_{2\%}$ (Gy)	11.5±3.8	12.8±4.9	−1.2 (9%)	0.1
Right breast	D_{mean} (Gy)	5.3±2	5.6±1.9	−0.3 (5%)	0.2
PTV	V95 Gy (%)	98±1.4	98±1.2	0 (0%)	0.2

The Comparison between the Effects of DIBH-TVMAT and FB-TVMAT Techniques Applied in Supraclavicular Lymph Node Irradiation for the Organs-at-risk

Heart and LADCA: The integration of SCLN into the treatment field had no impact on the heart volumes that received 10, 15, 25, and 30 Gy doses, as well as D_{mean} and D_{max} dose values, in the irradiated patients using the DIBH-TVMAT technique. However, mean V5 values were found to be 37.5% and 29.5% in the DIBH-TVMAT plan, and the only increased value of V5 was statistically significant after SCLN irradiation (p=0.002) (Table 5). On the other side, differently from the DIBH-TVMAT, no impact of SCLN irradiation using the FB-TVMAT plan was encountered on the dosimetric parameters of the heart. Similarly, with heart doses, a statistically significant increase was detected only in the V5 value using the DIBH-TVMAT plan after SCLN irradiation in the comparison between LADCA doses regarding SCLN irradiation (p=0.002). No impact of SCLN irradiation using the FB-TVMAT plan was encountered on LADCA regarding the dosimetric parameters (Table 6).

Ipsilateral Lung, Contralateral Lung, and Right Breast: SCLN irradiation was found to significantly affect mean left lung, V5, V10, and V20 values in both DIBH-TVMAT and FB-TVMAT plans (p=0.000; p=0.000; p=0.02, respectively). An adverse result was monitored in the right lung. SCLN irradiation showed no statistically significant effect on right lung D_{mean} doses with DIBH and FB planning (p=0.2; p=0.2, respectively). Even though reductions were encountered in mean right breast doses using both DIBH and FB plans, these reductions were not statistically significant (p=0.5; p=0.8, respectively) (Table 5, 6).

DISCUSSION

The present study was carried out using the RPM system as one of the most reliable and easily applicable methods of the DIBH technique. All patients showed compliance with the DIBH procedure throughout the study. To our knowledge, it is the largest single-center patient study in which DIBH was integrated into the TVMAT technique with breath monitoring, and dosimetric analyses were carried out in patients irradiated for breast+RLN after breast-conserving surgery. The impact of SCLN irradiation has also been evaluated comprehensively in the study. Both DIBH-TVMAT and FB-TVMAT planning were reviewed, and dosimetric parameters of the doses to organs-at-risk were compared. According to the study outcomes, both whole-breast and breast+RLN

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Table 5 The dosimetric parameters of the organs-at-risk including heart, left lung, right lung and right breast obtained from dose-volume histogram for DIBH-TVMAT plan in the patients with and without supraclavicular lymph node RT

Structure	Parameter	Deep inspiration breath-hold		p
		No SCLN (n=44)	SCLN (n=17)	
Heart	V5 Gy (%)	29.5±12.2	37.5±12	0.02
	V10 Gy (%)	7.3±3.7	7.7±4.6	0.7
	V25 Gy (%)	1.2±1.2	1.2±1.5	0.9
	V30 Gy (%)	0.5±0.7	0.6±1	0.5
	D_{mean} (Gy)	5±1	5.5±1	0.1
	D_{max} (Gy)	36.4±7.2	37.7±9	0.5
LADCA	V5 Gy (%)	80.6±22.1	93.5±97	0.02
	V10 Gy (%)	50.1±24.2	52.5±28.1	0.7
	V25 Gy (%)	21.9±23.4	25.7±20.9	0.5
	V30 Gy (%)	15.4±21.3	18.4±17.1	0.6
	D_{mean} (Gy)	14.8±6.9	16.5±6.7	0.4
	D_{max} (Gy)	36.9±8	37.9±13.9	0.7
Left lung	V5 Gy (%)	59.1±10.7	72.4±7.9	0.000
	V10 Gy (%)	30.8±4.4	36.7±4.7	0.000
	V20 Gy (%)	18.6±1.8	20.2±1.5	0.02
Right lung	D_{mean} (Gy)	3.3±0.8	3.5±0.9	0.2
Right breast	D_{mean} (Gy)	5±1.5	5.3±2	0.5

RT: Radiotherapy; SCLN: Supraclavicular lymph nodes

Table 6 The dosimetric parameters of the organs-at-risk including heart, left lung, right lung and right breast obtained from dose-volume histogram for FB-TVMAT plan in the patients with and without supraclavicular lymph node RT

Structure	Parameter	Free-breathing		p
		No SCLN (n=44)	SCLN (n=17)	
Heart	V5 Gy (%)	62.9±10.1	64.5±39.6	0.9
	V10 Gy (%)	23.5±6.8	23.6±5.5	0.1
	V25 Gy (%)	6.4±2.3	7±2.8	0.5
	V30 Gy (%)	4.3±1.9	4.7±2.3	0.3
	D_{mean} (Gy)	8.8±1.4	8.9±1.2	0.7
	D_{max} (Gy)	49.3±4.8	51.8±4.6	0.06
LADCA	V5 Gy (%)	94±10.8	97.6±5.1	0.08
	V10 Gy (%)	61.6±19.3	62±19.4	0.9
	V25 Gy (%)	40.8±19.7	41.7±22.2	0.8
	V30 Gy (%)	34.5±20.1	35.8±22.5	0.8
	D_{mean} (Gy)	21.9±7	22.7±8	0.7
	D_{max} (Gy)	48±7.3	49.3±8.6	0.5
Left lung	V5 Gy (%)	65.1±11.1	78.3±6.9	0.000
	V10 Gy (%)	31.6±3.9	36.4±2.4	0.000
	V20 Gy (%)	19.7±1.4	20.3±0.9	0.004
Right lung	D_{mean} (Gy)	3.9±1.1	4.3±1.4	0.2
Right breast	D_{mean} (Gy)	5.5±1.6	5.6±1.9	0.8

irradiations applied in combination with TVMAT and DIBH were found to significantly reduce the doses applied to the heart, LADCA, ipsilateral, and contralateral lungs. In both DIBH and FB planning, dramatic decreases were noticed not only in mean heart doses but also in V5, V10, V25, V30, and D_{max} values of the heart in both groups. The reduced doses of the contralateral breast were detected by the implementation of DIBH in patients irradiated for only the breast, while a 5% reduction was monitored in patients irradiated for breast+RLN; however, this reduction was not found statistically significant.

Many retrospective studies have demonstrated that RT implemented to breast+RLN using the DIBH technique in LB cancer patients caused significant reductions in doses applied to the heart and coronary veins.[28–31] Al-Hammadi et al.[32] included patients who had undergone both breast-conserving surgery and mastectomy in their single-center study that evaluated dosimetric parameters in patients who applied the voluntary DIBH technique. In some patients, the RLN was included in the irradiation area, while in other parts, RT was applied only to the breast/chest wall. In that study, patients were not divided into groups for the evaluation of dosimetric parameters, although different fields were irradiated, and statistical analyses were carried out for all patients. Similarly, with our study, the mean heart dose regressed from 6.1 Gy to 3.2 Gy, indicating a 50% reduction was encountered. The mean LADCA doses in DIBH and FB plans were found to be 23 Gy and 14.8 Gy, respectively. The differences between V10, V20, and V30 values were found statistically non-significant according to the dosimetric comparison between voluntary breath-hold and free-breathing plans in the left lung. However, right lung and right breast doses were not tested. In our study, left lung V5 and V20 values were detected to be reduced after DIBH-TVMAT planning in the group that implemented RT for only the breast, whereas significant reductions were determined only in V5 values of the group irradiated for breast+RLN. D_{mean} values of the right lung and right breast were monitored to be significantly decreased by the DIBH-TVMAT technique in the group that implemented RT for only the breast. Contrarily, only the right lung D_{mean} dose significantly decreased in the group that applied RT to breast+RLN.

Al-Hammadi et al.[32] also determined that the mean left lung and V20 values decreased after the exclusion of the supraclavicular fossa from the RT field in patients who applied both DIBH and FB. On the other side, our study results indicated a significant decrease in V5, V10, and V20 values of the ipsilateral lung in both DIBH-TVMAT and FB-TVMAT plans. Additionally, similar to this study, the exclusion of SCLN from the RT field had no impact on mean and maximum heart doses in the planning with both DIBH and FB. Furthermore, dosimetric parameters of the right lung and right breast were not affected by the exclusion of SCLN from the RT field. Only heart V5 and LADCA V5 values were detected to be increased after the addition of SCLN to the irradiated field in DIBH planning. Even though most parameters appeared to be correlated, some values seemed to be higher in that study. We used the parameters in our study obtained by the implementation of 60 Gy RT to the tumor bed using the SIB technique. Al-Hammadi et al.[32] implemented 50 Gy RT in all patients, and calculations were carried out on this dosage in their study. The groups were not differentiated in performing dosimetric evaluations and statistical analyses. This aspect is an important factor for the different outcomes of their study.

Lin et al.[33] also included patients with both left and right breast cancer in their large case series. In this study, the comparisons were conducted without differentiation regarding treatment planning techniques and tumor laterality. The concurrent evaluation of the right and LB treatment plans indicated a 50% reduction in mean heart doses using DIBH compared with FB. In our study, an improvement was achieved in both heart and organ-at-risk doses after using DIBH, according to the evaluation of only LB.

On the other hand, 3-D conformal, IMRT, hybrid IMRT, and standard VMAT techniques were compared in some studies.[34–36] The applicability of novel techniques has been researched also in recent studies.[37–39] In one of those studies, Dumane et al.[40] treated breast cancer patients with a breast implant using DIBH-TVMAT while regional lymph nodes were also added to the RT field and compared dosimetric parameters. In their study, they implemented 50 Gy RT in all patients. Mean heart doses in DIBH and FB plans were 8.2 Gy and 5.3 Gy, respectively. In other words, a mean reduction of 2.9 Gy was detected. In our study, the mean heart dose decreased from 8.9 Gy to 5.5 Gy according to the comparison between DIBH-TVMAT and FB-TVMAT plans in patients who received RT to breast+RLN. In other words, a mean reduction of 3.4 Gy was determined. In addition, a boost dose of 60 Gy RT was administered to the tumor bed. Similarly, in this study, the reduction in the value of V5 of the ipsilateral lung using the DIBH-TVMAT plan was significant, whereas the reduction in the V20 value was statistically non-significant in the group that had RLNs added to the RT field. However, the contralateral breast D_{mean} dose reduction was not found statistically significant in that study, whereas we identified a decrease in contralateral breast D_{mean} values.

Virén et al.[41] implemented 50 Gy RT to the breast in their study on LB cancer and compared the standard tangential field-in-field (FinF) plan, tangential intensity-modulated radiotherapy plan, TVMAT plan with two dual arcs, and continuous VMAT (CVMAT) plan with a dual arc using FB without the DIBH technique. They reported that CVMAT decreased ipsilateral lung, heart, and LADCA doses more than other techniques, whereas it increased the low doses applied to the contralateral lung and breast volumes. Contrarily, they stated that TVMAT increased both dose coverage and homogeneity without increasing low contralateral lung and breast dose-volumes. They noted that TVMAT could be a safe treatment method for this reason. Yu et al.[26] have shown the superiority of the TVMAT technique, particularly in patients that had RLNs added to the treatment field. TVMAT planning has been recommended considering its contribution to dose homogeneity and its therapeutic effect.

Yu et al.[26] included 14 patients who underwent breast-conserving surgery and 50 Gy RT to the breast in their study and compared DIBH-TVMAT and FB-TVMAT planning. The use of 4 partial arcs was preferred in the study. We used 2 partial arcs in our study to shorten the treatment process and thereby increase the quality of breath-holding. In that study, the mean heart dose after 50 Gy RT in DIBH-TVMAT and FB-TVMAT plans were 7.9 Gy and 3.2 Gy, respectively. A 50% reduction was observed in ipsilateral lung V30 value, whereas mean contralateral lung and contralateral breast doses were similar to our study.[42]

Another crucial subject is the system applied for breath-holding. Voluntary breath-holding is a system completely left to the patient's initiative without the requirement of any equipment and progresses with coaching instructions. It can be performed in institutions that do not have adequate equipment. Bartlett et al.[43] compared ABD-DIBH and voluntary BH in their study carried out with 23 patients and reported that set-up errors were insignificant. However, although these errors appear to be insignificant, errors that may emerge due to the patient's initiative should not be underrated. The

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ABC system is a spirometer-based system. It forces the patient to hold their breath. Therefore, it may be discomforting for the patient. Besides, it is not suitable for patients with anxiety. This situation may affect dose distribution. The patient does not experience such complaints with the use of the RPM system. Hamming et al.[44] evaluated the accuracy and applicability of surface-guided RT accompanied by cone-beam CT-based monitoring. The comparison between CBCT and SGRT data revealed positioning errors below 5 mm, and SGRT has been reported to be a reliable option for patients.

The limitation of our study was the non-use of an intravenous contrast agent during CT simulation. Wennstig et al.[45] evaluated the interobserver differences during contouring coronary arteries. They reported in their study that minimal differences may occur between observers in contouring performed without contrast enhancement.

CONCLUSION

Compared with FB-RT, the DIBH technique provides significant dose reduction applied to the heart, LADCA, ipsilateral lung, contralateral lung, and contralateral breast. The DIBH technique, accompanied by RPM, not only increases patient comfort but also minimizes both intrafractional and interfractional variability thanks to monitoring. Thereby, it assures regular dose distribution in the target volume and decreases toxicity. Besides, the TVMAT technique increases homogeneity and dose coverage as well as VMAT. However, it does not increase the doses to the volumes of the organs-at-risk in contrast to VMAT. The technique in which DIBH was integrated into TVMAT in LB cancer patients may be accepted as the standard treatment approach in due course.

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