FULL PAPER

Helical tomotherapy with a complete-directional-complete block technique effectively reduces cardiac and lung dose for left-sided breast cancer

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Objectives: To evaluate the feasibility and optimal restricted angle of the complete-directional-complete block (CDCB) technique in helical tomotherapy (HT) by including regional nodal irradiation (RNI) with the internal mammary node (IMN) in left-sided breast cancer.

Methods: Ten left-sided breast cancer patients treated with 50 Gy in 25 fractions were compared with five-field intensity-modulated radiation therapy (5F-IMRT) and six types of HT plans. In the HT plans, complete block (CB), organ-based directional block (OBDB) and CDCB with different restricted angles were used.

Results: The conformity index (CI) between the $CDCB_{0,10,15,20}$ and 5F-IMRT groups was similar. Compared to CB, OBDB and 5F-IMRT, $CDCB_{20}$ resulted in a decreased ipsilateral mean lung dose. The low-dose region (V_5) of the ipsilateral lung in OBDB (84.0%) was the highest among all techniques ($p < 0.001$). The mean dose of the heart in CB was significantly reduced (by 11.5–22.4%) compared with other techniques. The V_{30} of the heart in $CDCB_{20}$ (1.9%) was significantly lower than that of CB, OBDB and 5F-IMRT. Compared to the

mean dose of the left anterior descending (LAD) artery of 5F-IMRT (27.0 Gy), $CDCB_0$, $CDCB_{10}$, $CDCB_{15}$, $CDCB_{20}$ and OBDB reduced the mean dose effectively by 31.7%, 38.3%, 39.6%, 42.0 and 56.2%, respectively. Considering the parameters of the organs-at-risk (OARs), $CDCB_{10,15,20}$ had higher expectative values than the other techniques ($p = 0.01$).

Conclusions: HT with the CDCB technique is feasible for treating left-sided breast cancer patients. The $CDCB_{10-20}$ techniques not only achieved similar planning target volume coverage, homogeneity and dose conformity but also allowed better sparing of the heart and bilateral lungs.

Advances in knowledge: For left-sided breast cancer patients whose RNI field includes the IMN, heart avoidance is an important issue. The CDCB technique achieved good PTV coverage, homogeneity and dose conformity and allowed better sparing of the mean dose of the lung, the LAD artery, and the heart and reduced the V_{30} of the heart.

INTRODUCTION

Thorsen et al[1] demonstrated that internal mammary node irradiation (IMNI) results in a statistically significant increase in the 8-year overall survival (OS) of approximately 4% compared to patients without IMNI in patients with early-stage axillary node-positive breast cancer. Furthermore, 1 and 1.6% of the absolute benefits to the 10-year

OS by regional node irradiation (RNI) with IMNI were reported in the MA.20 trial and in the European Organisation for Research and Treatment of Cancer (EORTC) trial, respectively.[2–4]

However, cardiotoxic effects, coronary atherosclerosis, pneumonitis and pulmonary fibrosis could potentially

increase, especially in patients with left-sided breast irradiation.[2,5] Conventionally, parallel-opposed tangential photon beams matching megavoltage photons and electron fields cause the anterior of the heart and the proximal left anterior descending (LAD) artery to receive high radiation doses.[6] The rates of major coronary events were shown to increase linearly with the mean dose to the heart by 7.4% per gray (Gy).[7] Additionally, a slight increase in pneumonitis and pulmonary fibrosis with RNI has recently been reported.[2]

The tangent angles techniques can have a limited dose to the ipsilateral lung and the contralateral breast, but it is difficult to generate a concave dose distribution conforming to the breast target.[8] Intensity-modulated radiation therapy (IMRT) techniques have demonstrated advantages in target conformity and homogeneity for breast irradiation while sparing the anterior heart and ipsilateral lung tissue from high doses of radiation, but they also involve the organs exposed in the low-dose region.[9]

The purpose of this study was to develop an optimal treatment plan by using the complete-directional-complete block (CDCB) technique with different angle restrictions to minimize the risk of cardiac, LAD artery and lung irradiation for patients with left-sided breast cancer who were treated with whole-breast irradiation and RNI.

METHODS AND MATERIALS

Patient selection and structure delineation

Ten patients with locally advanced left-sided breast cancer who received radiotherapy were enrolled, and CT images were obtained. Each patient received treatment planning via inverse planning by different techniques in the same CT images. Prospective data were collected after receiving approval from the Institutional Review Board of the Far Eastern Memorial Hospital

(FEMH-IRB- 104105-E). The staging characteristics for the selected patients are listed in Table 1.

The patients were scanned with a CT scanner (GE, Discovery VCT PET/CT Imaging System) with 2.5 mm slice spacing, and then the image sets were transferred to a treatment planning system (Pinnacle3 Version7.6C) for targeting and organ delineation. Clinical target volumes (CTVs) included the whole breast/chest wall, the axillary (levels II and III) region, the supraclavicular fossa (SCF), and IMNs (in the first-to-third interspaces) and were obtained as per published guidelines.[10] For the regional nodes, planning target volumes (PTVs) were expanded by 5 mm from the regional nodal CTV. For the breast/chest wall, an 8 mm isotropic margin was added to the CTV to account for setup uncertainty and respiratory motion. A virtual bolus 10 mm in thickness was used to cover the flash region of the PTV that extends into the surrounding air and was included in the body contour in the IMRT and tomotherapy plans. Organ-at-risk (OAR) volumes were contoured for each lung, the heart and the contralateral breast. The heart and LAD artery were contoured according to the validated University of Michigan cardiac atlas.[11]

All plans in this study were optimized with at least 95% of the PTV encompassed by the prescribed dose (Dp) of 50 Gy in 25 fractions. The maximum dose was less than 110% of the Dp, and dose volume points and penalties were adjusted throughout the optimization process to best meet OAR dose constraints without compromising the PTV coverage.

Planning designed by helical tomotherapy with complete-directional-complete block

The image sets with targets and OARs were transferred to a Tomotherapy Hi Art Planning system (v. 4.0.4. Tomotherapy, Inc., Madison, Wisconsin, USA). A field width of 2.5 cm, a pitch

Table 1. The staging characteristics of the selected patients

Patient	Stage	Without neoadjuvant treatment			Postneoadjuvant treatment			ER	PR	Her2/neu	Surgical technique
		pT	pN	M	ypT	ypN	M				
1	IIIC	2	3a	0	-	-	-	0%	0%	3+/3+	BCT
2	IIB	2	1	0	-	-	-	95%	95%	2+/3+	BCT
3	IIA	2	0 (i+)	0	-	-	-	1%	1%	0/3+	BCT
4	IIIC	2	3	0	-	-	-	90%	90%	2+/3+	MRM
5	IIIA	2a	2a	0	-	-	-	0%	0%	3+/3+	MRM
6	IIIC	2	3	0	-	-	-	0%	0%	0/3+	MRM
7	IIA	1b	1	0	-	-	-	0%	0%	0/3+	BCT
8	ypIIA	-	-	-	from 1c to 1a	from 1 to 1	0	90%	90%	1+/3+	BCT
9	ypIIB	-	-	-	from 3 to 3	from 3a to 0	0	1%	0%	3+/3+	MRM
10	ypIA	-	-	-	from 4b to 1b	from 2 to 0 (i+)	0	0%	0%	3+/3+	MRM

BCT, breast-conserving surgery; MRM, modified radical mastectomy.
i+: ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph nodes.

Figure 1. The CDCB. The CB was a rectangular structure with the ends connected 3 cm away from the margin of the planning target volumes (PTV). The CB was designed to disable beamlets from entering or exiting through this structure. The directional-blocking area of the CDCB was determined by the intersection of where the CB and the beam aperture passed through the 0.5 cm margin of the PTV of the IMNs. Directional block was used to close the beamlets if the blocked structure was proximal to the target in order to limit the beamlet entrance direction. The CDCB restricts the beamlets to enter within limited angles, and beam angles of 0, 10, 15 and 20 degrees were used as the restricted angles according to the geometric center of the IMNs (in the first to third interspaces) and were used to determine the optimal design of the CDCB.
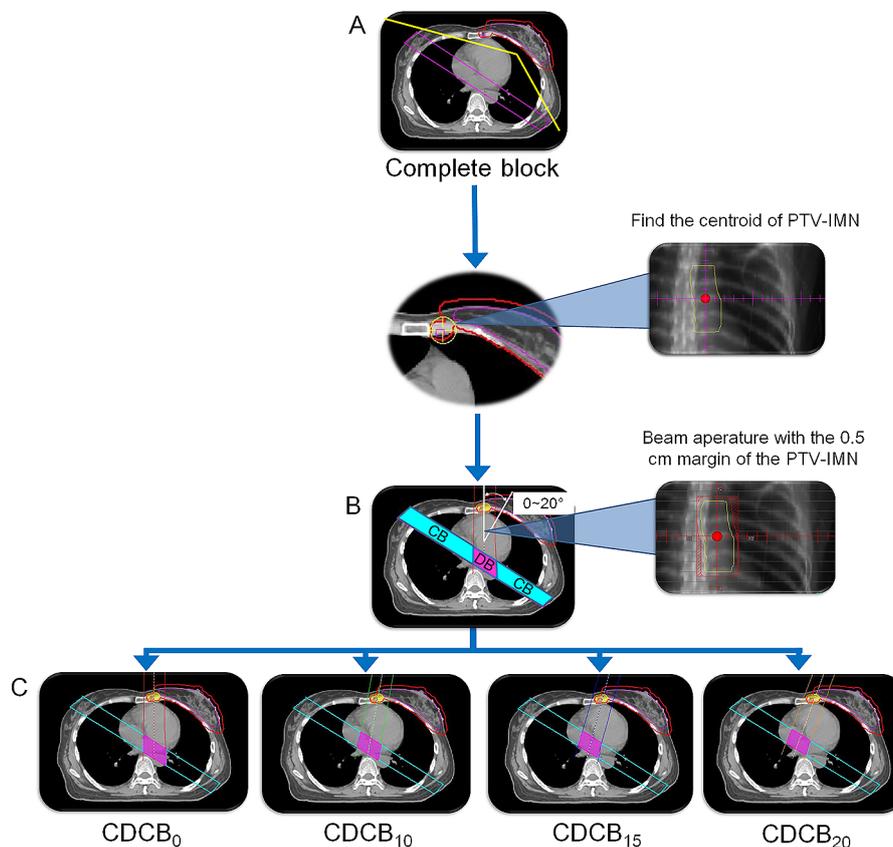
of 0.215 and a maximum modulation factor of 2.6 were used for all tomotherapy plans.

For the complete block (CB) helical tomotherapy (HT) plans (HT-CB), the designs of the directional and CB were reported in the previous study.[8] For tomotherapy plans with CDCB, the CB was modified to improve in-dose conformality while sparing the lungs and heart from high doses of radiation as follows: (1) the CB was a rectangular structure with the ends connected 3 cm away from the margin of the PTV. It was designed to disable beamlets from entering or exiting through this structure; and (2) the directional-blocking area of the CDCB was determined by the intersection of where the CB and the beam aperture passed through the 0.5 cm margin of the IMN. Directional block was used to close the beamlets if the blocked structure was proximal to the target to limit the beamlet entrance direction. The CDCB restricts the beamlets to enter only within limited angles, and beam angles of 0, 10, 15 and 20 degrees were used as the restricted angles according to the geometric center of the IMN and were used to determine the optimal design of the CDCB (Figure 1). The heart, lungs and contralateral breast are referred

to as the "organ-based directional block (OBDB)" to limit the primary beam from entering through these structures.

Five-field IMRT planning
Five-field IMRT (5F-IMRT) plans were generated for a Versa HD accelerator. The 5F-IMRT plans were executed on a Pinnacle treatment planning system (Pinnacle3 v. 9.8C) with a 0.2 cm calculation grid. Five fixed angles of 6 MV coplanar fields consisted of one anteroposterior beam, two medial beams (300 ~ 320 degrees) and two lateral beams (120 ~ 150 degrees), which were modulated using the direct machine parameter optimization technique available in the Pinnacle system. The maximum number of segments was set to 40, and the minimum segment MUs was set to 4.

Plan evaluation parameters
The uniformity index (UI) of the PTV was defined as the ratio of the minimum dose received in 5 and 95% of the PTV.[12] The conformity index (CI) of the PTV was defined as CI= $(TV_{PIV})^2$/$(TV \times PIV)$, where PIV is the prescription isodose volume, TV_{PIV} is target volume covered by the PIV, and TV is the target

Table 2. Averages of the ten patients' dose volume histogram parameters as a percentage of the conformity and uniformity indexes for the planning target volumes of left-sided breast cancer patients with irradiation of the whole breast/chest wall, the axillary (levels II and III) region, the supraclavicular field, and the internal mammary nodes by using different treatment techniques for comparison

Technique		CB	$CDCB_0$	$CDCB_{10}$	$CDCB_{15}$	$CDCB_{20}$	OBDB	5F-IMRT	*p* value
PTV volume	Parameters	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
$825.838 \pm$ 267.38 ml (548.5– 1844.0 ml)	CI	0.66 ± 0.06	0.69 ± 0.05	0.69 ± 0.05	0.69 ± 0.05	0.69 ± 0.05	0.73 ± 0.04	0.66 ± 0.07	<0.001
	UI	1.06 ± 0.01	1.07 ± 0.01	1.07 ± 0.01	1.07 ± 0.01	1.07 ± 0.01	1.06 ± 0.01	1.07 ± 0.01	<0.001
	$D_{5\%}$	53.35 ± 0.40	53.68 ± 0.35	53.69 ± 0.35	53.89 ± 0.38	53.73 ± 0.29	53.17 ± 0.41	53.97 ± 0.26	<0.001
	$D_{95\%}$	50.22 ± 0.20	50.19 ± 0.14	50.17 ± 0.19	50.26 ± 0.14	50.16 ± 0.21	50.17 ± 0.21	50.22 ± 0.44	0.091
	$V_{95\%}$	99.10 ± 0.50	98.82 ± 0.45	98.71 ± 0.48	98.57 ± 0.76	98.69 ± 0.64	98.80 ± 0.42	98.80 ± 0.55	<0.001
	$V_{109\%}$	0.35 ± 0.40	0.54 ± 0.52	0.65 ± 0.56	1.37 ± 1.48	0.83 ± 0.69	0.23 ± 0.51	1.07 ± 0.91	<0.001

CB, complete block; CDCB, complete-directional complete block; CI, conformity index; Dx%, the minimum doses delivered to x% of the planning target volume; 5F-IMRT, 5-field intensity-modulated radiotherapy; OBDB, organ-base-directional block; UI, uniformity index; Vx%, the volume of the PTV receiving x% of the prescribed dose.
Data are presented as the mean ± standard deviation.

volume.[13] Furthermore, $V_{109\%}$ was calculated to assess dose homogeneity.

The normal tissue dose metrics were calculated for the plan comparisons. Additionally, the tomotherapy plan with OBDB that assigned OARs as "directionally" blocked structures was also compared with the CB, CDCB$_{0,10,15,20}$ and 5F-IMRT plans.

Statistical methods
The treatment variables between groups were assessed by t-tests and chi-square tests. A generalized estimating equation (GEE) model was used to study the outcomes for dependent variables under different conditions. The statistical analyses were performed using the SPSS statistical package (v. 20.0, IBM Corporation, Armonk, NY, USA). *P* values had a significance level of 0.05. To determine whether the differences between all possible pairings of the planning techniques were statistically significant, we conducted Bonferroni tests that generated the presented *p* values.

RESULTS
Planning target volume
The comparisons of the treatment plans are summarized in Tables 2 and 3. There were no statistically significant differences in the $D_{95\%}$ of the PTV between all seven planning techniques. However, the $V_{95\%}$ of the CB plan (99.10±0.5%) was significantly higher than that of CDCB$_{10}$-$_{20}$ ($p < 0.05$). There were no significant differences in terms of PTV coverage as measured by the $V_{95\%}$ among the CDCB$_0$ and CDCB$_{20}$, OBDB and 5F-IMRT plans. Additionally, the estimated *p* values for the compared treatment modalities.

A typical dose distribution for the plans is displayed in Figure 2A–G. There were no differences in PTV coverage with the 95% isodose for the HT techniques compared to the 5F-IMRT. However, the CB provided better coverage of $V_{95\%}$ than 5F-IMRT (99.10 ± 0.50 *vs* 98.29 ± 0.54, $p = 0.026$). The $V_{109\%}$ in CDCB$_{15}$ and 5F-IMRT had the highest values. The OBDB plan had better conformity (0.73) than the other plans. The UIs in the CB and OBDB plans were worse than those of the other techniques. Additionally, the OBDB plan had the lowest $D_{5\%}$.

Normal tissue irradiation
The CDCB$_{15}$ and CDCB$_{20}$ plans had the lowest ipsilateral mean lung dose, V_5, V_{10} and V_{20}. For the contralateral lung, the CB and CDCB$_0$ plans had the lowest mean dose. The CDCB$_0$ and CDCB$_{15}$ plans had the lowest V_{20} values in the contralateral lung. Interestingly, 5F-IMRT had the lowest contralateral mean breast dose. The OBDB plan had the highest heart mean doses (10.41 ± 1.72 Gy) and V_5 (88.81±14.1%) compared to the other techniques. Compared to the other techniques, the CDCB$_{20}$ and OBDB plans had lower mean doses in the LAD artery (Tables 4 and 5).

The current study predicted the optimal radiation technique strategy for left-sided advanced breast cancer by summing the specific weights of each parameter in each technique and then comparing the sums with the highest one and checking the comparisons by t-test. The specific weight for the comparison of each parameter in each technique was defined as "0", "1" and "2" when the p values were > 0.05, ≤ 0.05 and ≤ 0.001, respectively. The sums of the expectations provided by the parameters of the OARs in CB, CDCB$_0$, CDCB$_{10}$, CDCB$_{15}$, CDCB$_{20}$, OBDB and 5F-IMRT were 22, 33, 52, 58, 61, 17 and 19, respectively. CDCB$_{20}$ was better than CDCB$_0$, OBDB and 5F-IMRT. In addition, CDCB$_{20}$ was slightly better than CB. However, there were no differences among CDCB$_{10}$, CDCB$_{15}$ and CDCB$_{20}$. A range

Table 3. The presented *p* values describe the statistical relevance of the differences in $V_{95\%}$, conformity index and uniformity index of the planning target volume between all possible pairs of the studied planning techniques

Parameters	PTV		
	$V_{95\%}$	CI	UI
A *vs* B	0.097	<0.001	0.017
A *vs* C	0.004	0.003	0.021
A *vs* D	0.004	<0.001	<0.001
A *vs* E	0.005	0.002	0.023
A *vs* F	1.000	<0.001	1.000
A *vs* G	1.000	1.000	0.028
B *vs* C	1.000	1.000	1.000
B *vs* D	1.000	1.000	0.710
B *vs* E	1.000	1.000	1.000
B *vs* F	1.000	0.014	0.202
B *vs* G	1.000	1.000	1.000
C *vs* D	1.000	1.000	1.000
C *vs* E	1.000	1.000	1.000
C *vs* F	1.000	0.001	0.257
C *vs* G	1.000	1.000	1.000
D *vs* E	1.000	1.000	1.000
D *vs* F	1.000	0.001	0.030
D *vs* G	1.000	1.000	1.000
E *vs* F	1.000	<0.001	0.100
E *vs* G	1.000	1.000	1.000
F *vs* G	1.000	0.003	<0.001

A, CB; B, CDCB$_0$; C, CDCB$_{10}$; D, CDCB$_{15}$; E, CDCB$_{20}$; F, OBDB; G, 5F-IMRT.

Data are presented as the mean ± standard deviation.

of 10–20 degrees for the CDCB technique was considered the optimal restricted angle. (Table 6)

DISCUSSION

Breast cancer patients treated with RNI by IMRT have demonstrated dosimetric benefits compared with conventional delivery.[14–16] HT has also been confirmed to have smaller hotspots than three-dimensional (3D) plans[9] and with much greater dose homogeneity than the IMRT plan.[8] However, these reports also claimed that HT plans designed with the directional block technique delivered a significantly greater volume of low-dose radiation to the lungs, contralateral breast and other normal tissues when compared with 3D or IMRT plans. Recently, the HT plan using the CB technique for early-stage left-sided breast irradiation was shown to decrease the volume of low-dose radiation delivered to the OARs.[8] Nevertheless, the problem with using CB in RNI, especially IMNI, is the inadequate CI for the coverage of IMN. In the current study, the OBDB technique had the best CI value as a result of to the degrees of freedom of the beamlet entrance.

Figure 2. Axial dose distribution for the 5F-IMRT plan (A) and the HT plans: (B) OBDB, (C) CB, (D) CDCB$_0$, (E) CDCB$_{10}$, (F) CDCB$_{15}$, and (G) CDCB$_{20}$.
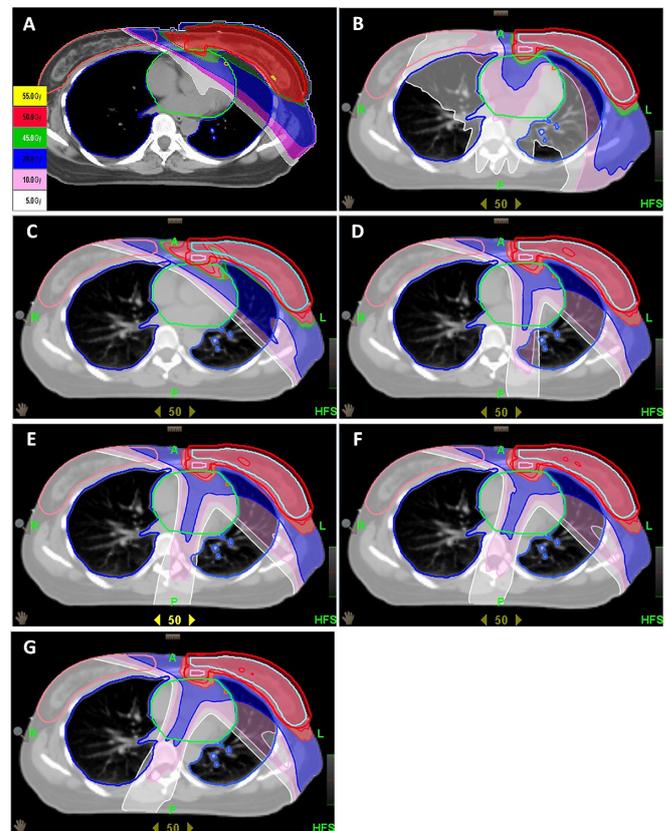
The average mean heart dose (MHD) is approximately 4 Gy for standard left-tangential irradiation without involving the IMN.[17] However, when using different techniques to irradiate the IMN, the increased to 7.0–16.7 Gy,[9,18–23] as shown in Table 7. Through tight heart dose constraints in the whole-breast IMRT plan, the MHDs could be decreased to 2 Gy.[24] Breast cancer treated by rotational techniques without a special design may expose the heart to a relatively high MHD (7.0 to 14.4 Gy).[9,18,19,22] However, when specially designed, rotational techniques such as VMAT are able to easily reduce the MHD on average from 10 Gy to ≤6.5 Gy when compared with 3D conformal planning.[23] The OBDB technique has a better conformity for PTV coverage than others but with worse MHDs (10.4 Gy) and V_5 of the heart (88.8%) compared with other techniques. With the CB or angular restriction techniques, the V_5 of the heart could decrease by 55 to 69% when compared with OBDB. The angular restriction techniques have lower V_{30} and V_{40} of the heart than CB, OBDB and 5F-IMRT. Additionally, a recent review of the literature recommends that the V_{25} of the heart should be less than 10% for a probability of cardiac mortality below 1%.[25] In the current study, the V_{25} of the heart in all techniques ranged from 3.41 to 5.45%, which made all plan designs safer but still exposed patients to a significant risk of major coronary events. Darby et al[7] found that the incidence of ischemic heart disease increases linearly with the mean dose to the heart with no apparent threshold below which there was no risk. Jagsi R et al[26] reported that IMRT with a deep

Table 4. Comparison of dosimetric parameters in normal organs-at-risk for left-side-breast cancer patients with irradiation of the whole breast/chest wall, the axillary (levels II and III) region, the supraclavicular field, and the internal mammary nodes by using different treatment techniques

Technique	Parameters	CB	CDCB$_0$	CDCB$_{10}$	CDCB$_{15}$	CDCB$_{20}$	OBDB	5F-IMRT	p value
Organs		Mean ± SD	Mean ± SD	Mean ±S D	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Ipsilateral lung	Mean (Gy)	15.82 ± 1.82	14.03 ± 1.38	13.14 ± 1.41	12.78 ± 1.43	12.77 ± 1.29	15.07 ± 2.29	15.69 ± 1.54	<0.001
	V$_5$ (%)	56.15 ± 3.95	58.29 ± 4.66	54.82 ± 4.04	54.10 ± 3.90	54.03 ± 3.95	84.14 ± 8.56	60.64 ± 5.93	<0.001
	V$_{10}$ (%)	48.02 ± 4.43	45.48 ± 4.26	42.80 ± 4.12	41.51 ± 4.01	41.67 ± 3.51	50.73 ± 11.71	43.97 ± 3.73	<0.001
	V$_{20}$ (%)	34.31 ± 4.88	27.80 ± 4.50	25.80 ± 4.41	24.80 ± 4.46	24.93 ± 4.07	26.56 ± 5.93	30.56 ± 4.02	<0.001
Contralateral lung	Mean (Gy)	1.10 ± 0.24	1.14 ± 0.20	1.21 ± 0.24	1.41 ± 0.24	1.64 ± 0.21	6.04 ± 0.79	0.87 ± 0.11	<0.001
	V$_{20}$ (%)	0.15 ± 0.18	0.07 ± 0.06	0.10 ± 0.08	0.08 ± 0.08	0.10 ± 0.09	0.84 ± 0.77	0.13 ± 0.10	<0.05
Contralateral breast	Mean (Gy)	2.81 ± 1.54	2.81 ± 1.23	2.53 ± 1.33	2.53 ± 1.35	2.52 ± 1.34	4.56 ± 0.76	1.75 ± 0.99	<0.001
Heart	Mean (Gy)	5.09 ± 1.30	5.68 ± 1.27	6.11 ± 1.31	6.20 ± 1.43	6.23 ± 1.40	10.41 ± 1.72	6.11 ± 1.36	<0.001
	V$_5$ (%)	19.98 ± 5.67	30.23 ± 6.29	33.15 ± 7.20	33.70 ± 7.74	33.94 ± 7.60	88.81 ± 14.14	34.56 ± 14.45	<0.001
	V$_{25}$ (%)	5.07 ± 2.20	3.41 ± 1.76	3.59 ± 1.77	5.33 ± 5.0	5.37 ± 5.36	5.45 ± 2.57	4.72 ± 1.73	<0.001
	V$_{30}$ (%)	3.58 ± 1.67	2.11 ± 1.27	2.12 ± 1.18	2.14 ± 1.20	1.93 ± 1.16	3.49 ± 1.74	3.56 ± 1.47	<0.001
	V$_{40}$ (%)	1.47 ± 0.88	0.63 ± 0.57	0.67 ± 0.49	0.70 ± 0.51	0.55 ± 0.46	1.16 ± 0.72	1.56 ± 1.03	<0.001
LAD	Mean (Gy)	22.85 ± 6.36	18.44 ± 5.95	16.67 ± 5.52	16.31 ± 5.58	15.66 ± 5.26	11.83 ± 3.24	27.00 ± 9.63	<0.001
	Maximum (Gy)	45.49 ± 5.41	43.73 ± 6.56	40.66 ± 9.29	40.08 ± 10.12	39.70 ± 10.33	34.93 ± 9.07	47.70 ± 3.61	<0.001

CB, complete block; CDCB, complete-directional-complete block; 5F-IMRT, 5-field intensity- modulated radiotherapy; LAD, left anterior descending oronary artery; OBDB, organ-base-directional block; V$_x$, the volume of the organ receiving x Gy.
Data are presented as the mean ± standard deviation.

Table 5. The presented *p* values describe the statistical relevance of the differences in dose parameters in the ipsilateral lung, the heart and the left anterior descending artery between all possible pairs of the studied planning techniques

Parameters	Ipsilateral lung				Heart						LAD
	D_{mean}	V_5	V_{10}	V_{20}	D_{mean}	V_5	V_{25}	V_{30}	V_{40}	D_{mean}	D_{max}
A *vs* B	<0.001	0.105	0.035	<0.001	0.048	<0.001	<0.001	<0.001	<0.001	<0.001	1.000
A *vs* C	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.027
A *vs* D	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	1.000	<0.001	0.003	<0.001	0.027
A *vs* E	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	1.000	<0.001	<0.001	<0.001	0.014
A *vs* F	1.000	<0.001	1.000	0.001	<0.001	<0.001	1.000	1.000	1.000	<0.001	<0.001
A *vs* G	1.000	0.642	0.041	0.058	0.002	0.006	1.000	1.000	1.000	0.095	1.000
B *vs* C	<0.001	<0.001	<0.001	0.009	0.321	0.132	1.000	1.000	1.000	0.001	1.000
B *vs* D	<0.001	<0.001	<0.001	<0.001	0.174	0.084	1.000	1.000	1.000	<0.001	1.000
B *vs* E	<0.001	<0.001	<0.001	<0.001	0.180	0.052	1.000	1.000	1.000	<0.001	0.975
B *vs* F	1.000	<0.001	1.000	1.000	<0.001	<0.001	0.008	0.002	0.001	<0.001	0.001
B *vs* G	0.043	1.000	1.000	1.000	1.000	1.000	0.016	<0.001	0.001	0.001	0.036
C *vs* D	0.001	0.003	0.007	<0.001	1.000	0.943	1.000	1.000	1.000	0.663	1.000
C *vs* E	0.034	0.012	0.456	0.163	1.000	0.099	1.000	0.109	0.001	<0.001	1.000
C *vs* F	0.083	<0.001	0.488	1.000	<0.001	<0.001	0.017	0.002	<0.001	0.002	0.004
C *vs* G	<0.001	0.116	1.000	0.025	1.000	1.000	<0.001	<0.001	<0.001	<0.001	0.051
D *vs* E	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.408	1.000	0.014	1.000
D *vs* F	0.008	<0.001	0.153	1.000	<0.001	<0.001	1.000	0.003	<0.001	0.011	0.025
D *vs* G	<0.001	0.046	1.000	0.005	1.000	1.000	1.000	<0.001	0.001	<0.001	0.061
E *vs* F	0.007	<0.001	0.159	1.000	<0.001	<0.001	1.000	<0.001	<0.001	0.041	0.106
E *vs* G	<0.001	0.045	1.000	0.006	1.000	1.000	1.000	<0.001	<0.001	<0.001	0.041
F *vs* G	1.000	<0.001	1.000	1.000	<0.001	<0.001	1.000	1.000	0.407	<0.001	<0.001

A, CB; B, CDCB$_0$; C, CDCB$_{10}$; D, CDCB$_{15}$; E, CDCB$_{20}$; F, OBDB; G, 5F-IMRT.

inspiration breath hold technique reduced the percentage of the left ventricle receiving ≥5 Gy by approximately 10% for patients with left-sided disease in whom IMN was targeted and suggested a potential benefit for preservation of the cardiac ejection fraction. For these reasons, the best approach seems to be keeping the dose to the heart as low as possible, avoiding direct irradiation altogether and using a special design and cardiac-sparing techniques whenever possible.[23,26–29]

The coronary artery dose estimates for females who received breast cancer radiotherapy were between 6 and 43 Gy.[30] Patients with unfavorable anatomy may receive radiation doses greater than 30 Gy to parts of the distal LAD artery.[31] The Danish Breast Cancer Cooperative Group proposed potential benefits from respiratory gating to decrease the LAD constraint to a maximum dose of 20 Gy.[32] The higher radiation doses to the coronary artery or LAD were strongly associated with more frequent injury.[33] One of the reasons for this is that mid- or distal LAD coronary artery segments remained in the radiation fields in some females.[27] The maximum dose values of the LAD in the current study were 35–48 Gy. In a study by Taylor et al,[33] the left-versus-right ratios for injury to these segments from tangential radiotherapy after breast-conserving surgery were approximately three for the LV

apex and approximately six for the mid- or distal LAD segment, indicating that the sparing priority should be the LAD segment. CB has a better MHD and V_5 of the heart than the other plans. However, the CB technique also resulted in the second highest mean and maximum doses in the LAD. In contrast, OBDB has a better mean and maximum dose in the LAD in all techniques. However, OBDB resulted in the highest MHD (10 Gy) and V_5 of the heart (88.8%). Darby et al[7] demonstrated a dose–effect relationship based on the MHD. Additionally, the volume of the left ventricle receiving 5 Gy (LV-V_5) seems to be a better predictor for acute coronary events than the MHD.[34] Therefore, CBCD$_{20}$ is better than CB and OBDB for heart protection. Moreover, the parameter priority for reducing the risk of cardiac injury would be maximum dose of LAD,[33] followed by V_5 of the heart,[34] the MHD,[7] and V_{25}.[25]

The risks of early and late radiogenic lung sequelae for patients with breast cancer are strongly related to the volume of the irradiated lung and the dose. A mean lung dose (MLD) >15.0 Gy and a V_{20} >31.1% for breast cancer patients treated with RT can easily cause Grade one radiation pneumonitis; therefore, the MLD should remain between 12 and 15 Gy and the V_{20} should remain below 24% to avoid lung toxicity.[35] The addition of SCF

Table 6. The sum of the specific weights of each parameter in each technique for left-sided advanced breast cancer, comparison with the highest sum and a check by t-test. The specific weight for the comparison of each parameter in each technique is defined as "0", "1" and "2" when p values were > 0.05, ≤ 0.05 and ≤ 0.001, respectively

		CB	$CDCB_0$	$CDCB_{10}$	$CDCB_{15}$	$CDCB_{20}$	OBDB	5F-IMRT
Ipsilateral lung	Mean	0	3	6	8	8	0	0
	V_5	2	2	6	8	9	0	2
	V_{10}	0	1	4	5	4	0	1
	V_{20}	0	2	4	7	5	1	0
	V_{40}	0	4	4	5	5	7	0
Contra. lung	Mean	8	5	6	4	2	0	11
	V_{20}	0	1	1	1	1	0	1
Contra. breast	Mean	2	2	3	3	3	0	2
Heart	Mean	10	2	2	2	2	0	2
	V_{30}	0	4	5	5	6	0	0
	V_{40}	0	4	6	4	7	0	0
LAD	Mean	0	3	5	6	9	9	0
SUM		22	33	52	58	61	17	19
p value		0.06	0.015	0.211	0.60		0.003	0.03

and IMN irradiation will increase the MLD and V_{20}, which are associated with a 2.5-fold higher risk of radiation pneumonitis and a two-fold risk of radiogenic fibrosis.[35] Furthermore, SCF irradiation showed a strong association with the incidence of radiation pneumonitis (OR = 5.07).[36]

Compared to conventional techniques or 3D-CRT, IMRT can reduce mean lung V_{20} by approximately 4–10%.[16,22,37] However, the ipsilateral lung V_5 will increase approximately 9–68%,[16,22,37,38] and the lung V_5 could be as high as 85.8%.[38] Lancellotta et al reported a better lung V_{20} by using the 3D-CRT technique than by using HT.[22] Similarly, HT with a special design can provide lower ipsilateral lung V_{20} more easily than 3D-CRT[9,39] or IMRT.[8,18,39] Nevertheless, the ipsilateral lung V_5 in HT without a special design could be as high as 70–99.3%.[19,22,40,41] In contrast, the low-dose volume of the lung could be reduced efficiently from 33.1 to 24.7% by HT with the CB technique when compared with IMRT.[8] Additionally, the CB or CDCB techniques used here not only meet the MLD (12.7–15.8 Gy) and V_{20} (24.8–34.3%) criteria but also decreased the ipsilateral lung V_5 (54.0–58.3%) and the contralateral lung V_5 (2.1–6.3%).

An overview analysis suggests that patients receiving radiation may have an elevated incidence of contralateral breast cancer compared with those who did not receive radiation.[42,43] The mean dose to the contralateral breast during RNI using the OBDB technique treatment by HT was 4.3 to 4.8 Gy.[9,18,22] The OBDB technique has better conformity for PTV (CI = 0.73) than the others; however, it could expose the other organs to a higher mean contralateral breast dose (4.6 Gy), contralateral lung dose (6.0 Gy) and heart dose (10.4 Gy). In contrast, the other techniques have lower mean doses of 2.5–2.8 Gy, 1.1–1.6 Gy and 5.1–6.2 Gy for the contralateral breast, contralateral lung and heart, respectively. However, Nichols et al[19] reported that the

mean dose to the contralateral breast was 1.8 Gy by the same technique. Nevertheless, the MHD, ipsilateral V_5 of the lung and contralateral V_5 of the lung in their report were higher, at 14.4 Gy, 99 and 82%, respectively.[19] Similarly, the breast treated with RNI by a different arc therapy, such as volumetric-modulated arc therapy (VMAT), appears to have a lower contralateral breast dose (1.5–3.2 Gy). Nonetheless, this technique also has a higher MHD (9–13 Gy) and ipsilateral lung dose (4 Gy).[19–21] Therefore, awareness of the potential risks of scatter dose to the contralateral breast or other organs by HT with the OBDB technique or arc therapy is prudent.

To take into account the parameters of the OARs in CB, $CDCB_0$, $CDCB_{10}$, $CDCB_{15}$, $CDCB_{20}$, OBDB and 5F-IMRT, the sums of the expectations were calculated to be 22, 33, 52, 58, 61, 17 and 19, respectively (Table 6). $CDCB_{10-20}$ was better than CB, $CDCB_0$, OBDB and 5F-IMRT. However, there are some limitations in the current study. First, we did not use cardiac-sparing techniques (such as breath hold, treatment in a prone position, treatment during deep inspiration (including the use of breath-hold and gating techniques)) for planning during the current study. In the current study, the maximum dose of LAD ranged from 39.7 to 47.7 Gy for all techniques. One of the reasons for this is that mid- or distal LAD coronary artery segments remained in the radiation fields. Taylor et al[33] reported that the left-versus-right ratio for injury to these segments from tangential radiotherapy was approximately six for the mid- or distal LAD segment, indicating that irradiating these segments causes injury. Additionally, the Danish Breast Cancer Cooperative Group proposed potential benefits from respiratory gating to decrease the LAD constraint to a maximum dose of 20 Gy.[32] Moreover, using the breath hold technique for the left-side-breast with RNI, remarkably low doses to the OARs have been reported.[44] Therefore, where possible, these segments should be excluded from fields using

Table 7. Comparison of the planning parameters of the target and OARs for helical tomotherapy (HT) and HT/volumetric modulated arc therapy (VMAT) plans in this study and plans for other studies in the literature for locoregional irradiation, including the internal mammary chain in left-sided breast cancer

Author	Goddu[9]	Caudrelier[18]	Sakumi[21]	Nichols[19] HT	Nichols[19] VMAT	Tyran[20]	Dumane[23]	Current study (HT) OBDB	CB	CDCB$_{10}$	CDCB$_{15}$	CDCB$_{20}$
Target volumes	Breast/chest-wall + IMC+SCV + AX											
Patient number	10[a]	10[a]	5[a]	15[a]		10[a]	10[b]	10[a]				
Dp	50.4	50	50/45 (breast/LN)	50.4		50/46.95 (breast/LN)	50.4	50				
Technique	HT	HT	VMAT	HT	VMAT	VMAT	VMAT	OBDB	CB	CDCB$_{10}$	CDCB$_{15}$	CDCB$_{20}$
PTV												
$V_{95\%}$ (%)	98	99	95.2/98.7/99.4 (breast/clavicular/IMN)			96.0/96.0 (breast/LN)	96.3	98.8	99.1	98.7	98.6	98.7
$V_{107\%}$ (%)		31.1				(breast/LN)						
$V_{109\%}$ (%)	1.5							0.2	0.4	0.7	1.4	0.8
D_{95} (Gy)				49.8	49.3		48.89	50.2	50.2	50.2	50.3	50.2
CI		0.56		0.719	0.778	0.8 (combine)		0.73	0.66	0.69	0.69	0.69
Ipsilateral lung												
D_{mean} (Gy)	11.9	8.3	12.7			15.2	15.3	15.1	15.8	13.1	12.8	12.8
V_5 (%)	73.7	35.4	74.6	99.3	96.9	86.7	84.3	84.1	56.2	54.8	54.1	54.0
V_{10} (%)	34.7	9.2	44.5			55.3	46.9	50.7	48.0	42.8	41.5	41.7
V_{20} (%)	17.6		18.9	29.9	32.3	25.4	24.7	26.6	34.3	25.8	24.8	24.9
Contralateral lung												
D_{mean} (Gy)	4.2	6.2	4.0			4.0	3.6	6.0	1.1	1.2	1.4	1.6
Heart												
D_{mean} (Gy)	12.2	7	11.4	14.4	12.9	8.6	6.5	10.4	5.1	6.1	6.2	6.2
V_5 (%)		38.3	90.3				39.0	88.8	20	33.2	33.7	33.9
V_{25} (%)							0.7	5.5	5.1	3.6	5.3	5.4
V_{30} (%)	1.5	1.5	3.0			1.3		3.5	3.6	2.1	2.1	1.9
V_{40} (%)								1.2	1.5	0.7	0.7	0.6
Contralateral breast												
D_{mean} (Gy)	4.3	4.8	3.1	1.8	1.5	3.2	4.2	4.6	2.8	2.5	2.5	2.5

HT, helical tomotherapy; VMAT, volumetric modulated arc therapy

a. left-sided breast cancer patients

b. five left-sided and five right-sided breast cancer patients

cardiac-sparing techniques.[23,26–29]However, cardiac V_{40} ranged from 0.55 to 1.47%, and $CDCB_{20}$ reduced cardiac V_{40} by 53–63% compared with CB, OBDB and IMRT in the current study. For some institutes that do not use the breath hold technique, the CDCB technique provides a chance to possibly decrease cardiac toxicity.

Second, lying prone causes the breast to fall away from the chest wall, which allows for cardiac avoidance.[45] However, in general, Asian females have smaller breast volumes compared to Caucasian females.[46] For females with large breast volumes, using the prone positioning can ensure that the breast is far away from the chest wall and is expected to result in minimal cardiac doses. However, in females with smaller breast volumes, it can be theorized that the change between breast tissue and the chest wall is limited. Moreover, lying prone is described as uncomfortable,[47] and patients may not be able to maintain their position throughout treatment; therefore, reproducibility of treatment is challenging, and as a result the OAR dose may increase.[48] The prone position was not used in the current study based on these published observations.

CONCLUSIONS

HT with the CDCB technique successfully reduced radiation doses to the heart, LAD artery and lung compared to IMRT, OBDB and CB. Considering the balance with the minimal dose to the critical organs and the best homogeneity and conformity of the PTV, the optimal angle for CDCB is 10–20 degrees. Clinical studies of left-sided breast irradiation with angle-restricted HT are warranted in the future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of our hospital (FEMH-IRB-104105-E).

CONSENT FOR PUBLICATION:

Consent to publish has been obtained from the applicable persons and is available.

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