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CARDIAC COUNTERCLOCKWISE ROTATION IS A RISK FACTOR FOR HIGH-DOSE IRRADIATION TO THE LEFT ANTERIOR DESCENDING CORONARY ARTERY IN PATIENTS WITH LEFT-SIDED BREAST CANCER WHO RECEIVING ADJUVANT RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY

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ABSTRACT

Patients irradiated for left-sided breast cancer have higher incidence of cardiovascular disease than those receiving irradiation for right-sided breast cancer. Most abnormalities were in the left anterior descending (LAD) coronary artery territory. We analyzed the relationships between preoperative examination results and irradiation dose to the LAD artery in patients with left-sided breast cancer. Seventy-one patients receiving breast radiotherapy were analyzed. The heart may rotate around longitudinal axis, showing either clockwise or counterclockwise rotation (CCWR). On electrocardiography, the transition zone (TZ) was judged in precordial leads. CCWR was considered to be present if TZ was at or to the right of V3. The prescribed dose was 50 Gy in 25 fractions. The maximum (Dmax) and mean (Dmean) doses to the LAD artery and the volumes of the LAD artery receiving at least 20 Gy, 30 Gy and 40 Gy (V20Gy, V30Gy and V40Gy, respectively) were significantly higher in CCWR than in the non-CCWR patients. On multivariate analysis, TZ was significantly associated with Dmax, Dmean, V20Gy, V30Gy, and V40Gy. CCWR is a risk factor for high-dose irradiation to the LAD artery. Electrocardiography is useful for evaluating the cardiovascular risk of high-dose irradiation to the LAD artery.

Key Words: breast cancer, breast-conserving surgery, breast radiotherapy, cardiac toxicity, coronary artery

INTRODUCTION

Most patients with early breast cancer are given breast-conserving treatment, consisting of wide excision and postoperative radiotherapy. Postoperative radiotherapy reduces the risk of local recurrence and results in long-term survival similar to that obtained with mastectomy.[1-3)]

Breast cancer patients receiving radiotherapy have a 1.27 to 1.76-fold higher mortality rate from cardiac disease than those not given radiotherapy.[1,4)] Borger *et al.* reported that patients irradiated for left-sided breast cancer with tangential fields have a higher incidence of cardiovascular

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disease than those with right-sided cancer.[5] The hazard ratio associated with left-sided versus right-sided breast cancer was 1.38 (95% confidence interval, 1.09–2.15). Bouillon *et al.* reported that patients irradiated for left-sided breast cancer have a 1.56-fold higher mortality from cardiac disease than those given right-sided irradiation.[4] Approximately 90% of abnormalities on single photon emission computed tomography myocardial perfusion stress tests or echocardiograms in patients irradiated for left-sided breast cancer were in the left anterior descending (LAD) coronary artery territory.[6,7] It would be useful if patients with a high risk of receiving high-dose to the LAD artery could be identified in advance.

Patients underwent various preoperative examinations. If high-risk patients can be identified by these examinations, it would not be necessary to perform additional examinations. This would be advantageous in terms of reducing costs. We analyzed the relationships between preoperative examination results and irradiation dose to the LAD artery in patients with left-sided breast cancer who received tangential radiotherapy.

MATERIALS AND METHODS

Patients and preoperative evaluations

The eligibility criteria of this cross-sectional study were presence of left-sided breast cancer, breast-conserving surgery performed at our institute, no prior thoracic radiotherapy, no prior thoracic surgery, and no underlying diseases, such as interstitial pneumonia or dermatomyositis, contraindicating radiotherapy, written informed consent, in patients without heart disease. Institutional review board approval was waived because this study was a part of routine clinical practice. Written informed consent was obtained from each patient before the radiotherapy. Between February 2007 and October 2013, 71 patients met the criteria. Mammography, contrast-enhanced computed tomography (CT) from chest to pelvis, contrast-enhanced magnetic resonance imaging (MRI) of the breast, breast ultrasound, upright chest X-ray, electrocardiography (ECG), respiratory function tests and blood examinations are routinely performed at our institution to

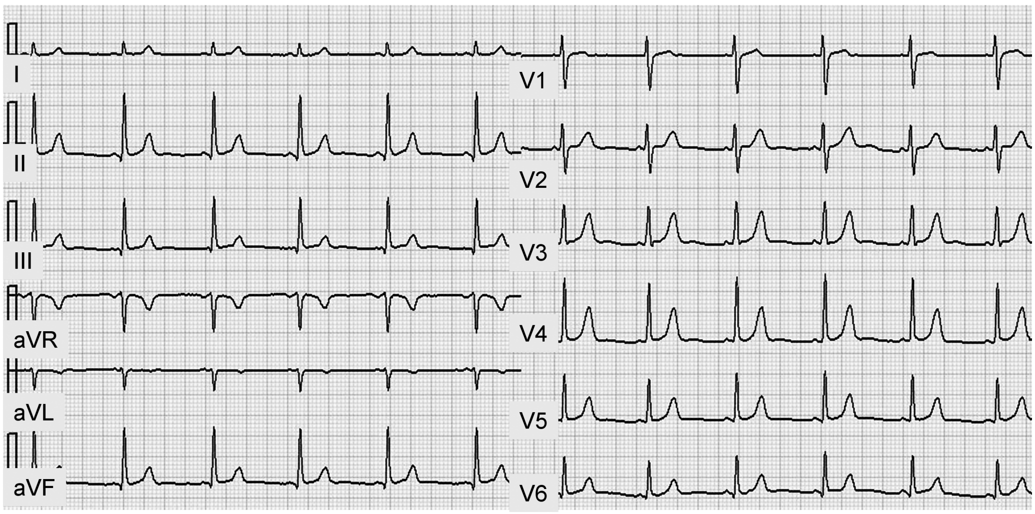

Fig. 1 The transition zone (TZ) was taken as the point where the R and S waves of 6 precordial leads were of equal amplitude. This patient's TZ was at V2

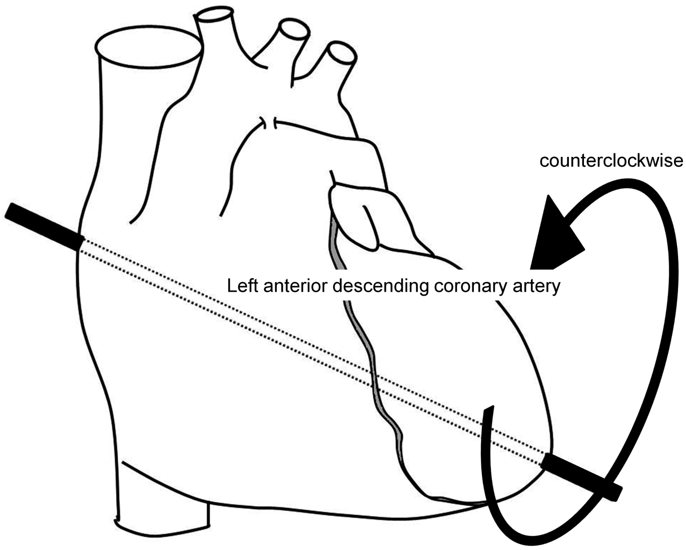

Fig. 2 Diagram of counterclockwise rotation of the heart around its longitudinal axis

determine the stage and to evaluate whether the patient will be able to undergo surgery under general anesthesia. In the present study, we focus on ECG and CT scout view data.

On ECG, the transition zone (TZ) was judged in precordial leads. The TZ was taken as the point where the R and S waves of 6 precordial leads were of equal amplitude (Fig. 1). Usually, the TZ is at V3 to V4. The heart may rotate around longitudinal axis, showing either clockwise or counterclockwise rotation (CCWR) as viewed from the apex (Fig. 2). CCWR is defined as a TZ at or to the right of V3 according Minnesota Code 9-4-1. Patients were divided into two groups: TZ at or to the right of V3 and TZ at or to the left of V4.

The cardiothoracic ratio (CTR) was measured in the CT scout view. CTR was defined as: cardiac width/thoracic width × 100 (%). CTR is generally evaluated on upright chest X-rays. However, because our patients were irradiated in the supine position, CTR in the scout view was used. Patients were divided into two groups: CTR ≥ 50 and CTR < 50%.

Body mass index (BMI) was used a physique index. BMI was defined as: weight/(height × height) (kg/m^2). The Japanese Society for the Study of Obesity proposed that the standard BMI in Japanese be taken as 22.[8)] Patients were divided into two groups: BMI ≤ 22 and BMI > 22 kg/m^2.

Simulation of radiotherapy planning

Radiopaque markers were placed at the midline, the mid-axillary line, 1 cm below the infra-mammary fold, and at the level of head of the clavicle. All patients were in the supine position on a breast board with both arms above their heads. Images were obtained using a CT scanner with 16 detector arrays (LightSpeed Xtra, GE Healthcare, Waukesha, WI, USA). Patients were scanned with 2.5-mm slices from the clavicle to the mid-abdomen while breathing freely without cardiac gating over 40 seconds. All CT images were transferred to Eclipse External Beam Planning 6.5 (Varian Medical Systems Palo Alto, CA, USA). Two opposed tangential fields were set up according to the clinically determined borders. The reference point was set as the midpoint of the nipple and the posterior border of the field. None of the reference points was on the lung parenchyma or the border between the lung and chest wall. Each patient's plan was normalized to this reference point. A 6-MV in energy photon beam was used. The prescribed dose was 50 Gy in 25 fractions. Beam weighting and physical wedges were used to achieve the maximum dose to the target ≤ 7% above the prescribed dose, if needed. Corrections for tissue inhomogeneities were used in all cases (Batho power-law method).

The LAD artery was delineated in the anterior interventricular groove down to the apex of the heart with reference to contrast-enhanced CT scans which had been obtained for preoperative evaluation.[9] In many cases, the LAD artery was identified non-contrast CT, but in some cases, it was difficult to identify the LAD artery. However, the delineation of the LAD artery is not difficult if anatomical knowledge is applied while observing cranial and caudal slices and contrast-enhanced CT.

Statistical analysis

The dose-volume histogram (DVH) was calculated for each patient. The volumes of the LAD artery receiving at least 20, 30 and 40 Gy (V20Gy, V30Gy and V40Gy, respectively), and the maximum and mean doses (Dmax and Dmean, respectively) of the LAD artery were calculated. Dosimetric parameters were compared using the Mann-Whitney *U* test. The TZ, CTR, and BMI were estimated employing multiple linear regression analysis. As the TZ is not an interval variable, we created dichotomous categorical variables (TZ at or to the right of V3 and TZ at or to the left of V4). A p value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

The median age was 55, range 33 to 77, years old. Of the 71 patients, 34 (48%) had a TZ at or to the right of V3. The other 37 (52%) patients had TZ at or to the left of V4. The mean CTR on scout view was 50.9 ± 4.8%. The mean BMI was 22.7 ± 4.2 kg/m^2.

The average Dmax, Dmean, V20Gy, V30Gy and V40Gy are shown in Table 1. Dmax, Dmean, V20Gy, V30Gy, and V40Gy were significantly higher in patients with TZ at or to the right of V3 than in those with TZ at or to the left of V4 (p = 0.0002, 0.0002, 0.0017, < 0.0001 and < 0.0001, respectively). There were no statistically significant differences in Dmax, Dmean, V20Gy, V30Gy, or V40Gy between patients with CTR ≥ 50 and those with CTR < 50%. Dmax,

Table 1 Dosimetric parameters

		TZ[a]		CTR[b] (%)		BMI[c] (kg/m^2)	
	Total	At or right of V3	At or left of V4	≥ 50	< 50	≤ 22	> 22
Number of patients	71	34	37	41	30	36	35
Maximum dose (Gy)	42.9	46.3[e]	39.4[e]	43.9	41.3	45.6[f]	39.9[f]
Mean dose (Gy)	16.2	19.6[e]	12.7[e]	16.3	16.1	17.9	14.3
V20Gy[d] (%)	34.4	41.5[e]	27.1[e]	35.5	32.6	38.0	30.4
V30Gy[d] (%)	26.9	35.7[e]	17.8[e]	26.8	26.9	31.7[f]	21.5[f]
V40Gy[d] (%)	17.7	26.4[e]	8.7[e]	16.9	19.0	23.5[f]	11.4[f]

[a] TZ = transition zone; [b] CTR = cardiothoracic ratio; [c] BMI = body mass index;
[d] V20Gy, V30Gy, and V40Gy = percentage of left anterior descending artery volume receiving ≥ 20, ≥ 30, and ≥ 40 Gy, respectively.
[e] Significant differences (p < 0.05) between TZ at or right of V3 and at or left of V4.
[f] Significant differences (p < 0.05) between BMI ≤ 22 and BMI > 22.

Table 2 Summary of multivariate analysis

	Regression coefficient	Standard error	*p* value	Adjusted R^2
Maximum dose				
TZ[a]	6.276	1.823	0.0010	
CTR[b]	0.246	0.198	0.2185	0.221
BMI[c]	–0.556	0.223	0.0154	
Mean dose				
TZ[a]	6.512	1.661	0.0002	
CTR[b]	0.087	0.180	0.6309	0.219
BMI[c]	–0.391	0.203	0.0595	
V20Gy[d]				
TZ[a]	13.313	4.069	0.0018	
CTR[b]	0.456	0.441	0.3054	0.191
BMI[c]	–1.116	0.498	0.0287	
V30Gy[d]				
TZ[a]	17.066	4.172	0.0001	
CTR[b]	0.146	0.452	0.7484	0.243
BMI[c]	–1.115	0.511	0.0329	
V40Gy[d]				
TZ[a]	17.190	4.101	< 0.0001	
CTR[b]	–0.086	0.444	0.8478	0.275
BMI[c]	–0.973	0.502	0.0572	

[a] TZ = transition zone; [b] CTR = cardiothoracic ratio; [c] BMI = body mass index;
[d] V20Gy, V30Gy, and V40Gy = percentage of left anterior descending artery volume receiving ≥ 20, ≥ 30, and ≥ 40 Gy, respectively.

V30Gy and V40Gy were significantly higher in patients with BMI ≤ 22 kg/m^2 than those with BMI > 22 kg/m^2 (p = 0.0008, p = 0.0273 and 0.0034, respectively). There were no statistically significant differences in Dmean, or V20Gy between patients with BMI ≤ 22 and those with BMI > 22 kg/m^2.

On multivariate analysis, TZ and BMI were significantly associated with Dmax, V20Gy and V30Gy. TZ was the only factor associated with Dmean and V40Gy (Table 2).

DISCUSSION

Darby *et al.* reported that although both mean heart dose and mean LAD coronary artery dose were correlated with the rate of major coronary events, mean heart dose was a better predictor.[10] However, the treatment in this report was based on two-dimensional planning. They simulated a treatment plan based on the CT scan of a woman with typical anatomy. Therefore, true individual CT-based radiotherapy information was unavailable for the women studied. The authors noted this as a study limitation. In another article, they reported that it is not known which part of the heart is the most radiosensitive or which structure or structures at risk should be chosen as a reference point for the tolerant dose in clinical practice.[11] The use of three-dimensional (3D) planning would elucidate which structure is a better predictor of the risk of major coronary events after long-term patient follow up. Using 3D treatment planning, physicians may be able to decrease the dose delivered to the heart with the use of multileaf collimators to a certain extent depending on the tumor location. Therefore, in this 3D treatment era, the dose delivered to the LAD, which is located the closest to the chest wall, may be more important than that delivered to the entire heart.

The deep inspiration breath-hold (DIBH) technique is one of the methods to reduce the cardiac dose.[12-15] Dmax and Dmean to the LAD artery are reportedly reduced approximately 50–60% with the DIBH technique.[12,13] DIBH technique is useful for reducing cardiac dose in breast cancer radiotherapy but also in lung cancer radiotherapy.[16] This technique is useful, but is highly time-consuming and throughput is thus decreased. Blank reported that technicians were mostly involved during the first irradiation with verification for conventional tangential radiotherapy in free breath and 42 minutes on average. Attendance time of technicians for daily routine treatment without verification was 15 minutes. Occupation time of the accelerator room is the largest in overall room occupation time (42%).[17] This study examined tangential breast radiotherapy during free breathing. When the DIBH technique used, the time in the accelerator is longer. While early breast cancer is not uncommon, it may be difficult to irradiate all cases with left-sided breast cancer using the DIBH technique in many institutions. Applying the DIBH technique to high-risk patients is the most realistic approach. If only high-risk patients to be irradiated with the DIBH technique, it is necessary to recognize these patients before performing the planning CT scans for radiotherapy. Patients were scanned while breathing freely for conventional tangential radiotherapy, but were scanned in deep inspiration breath-hold for the DIBH technique.

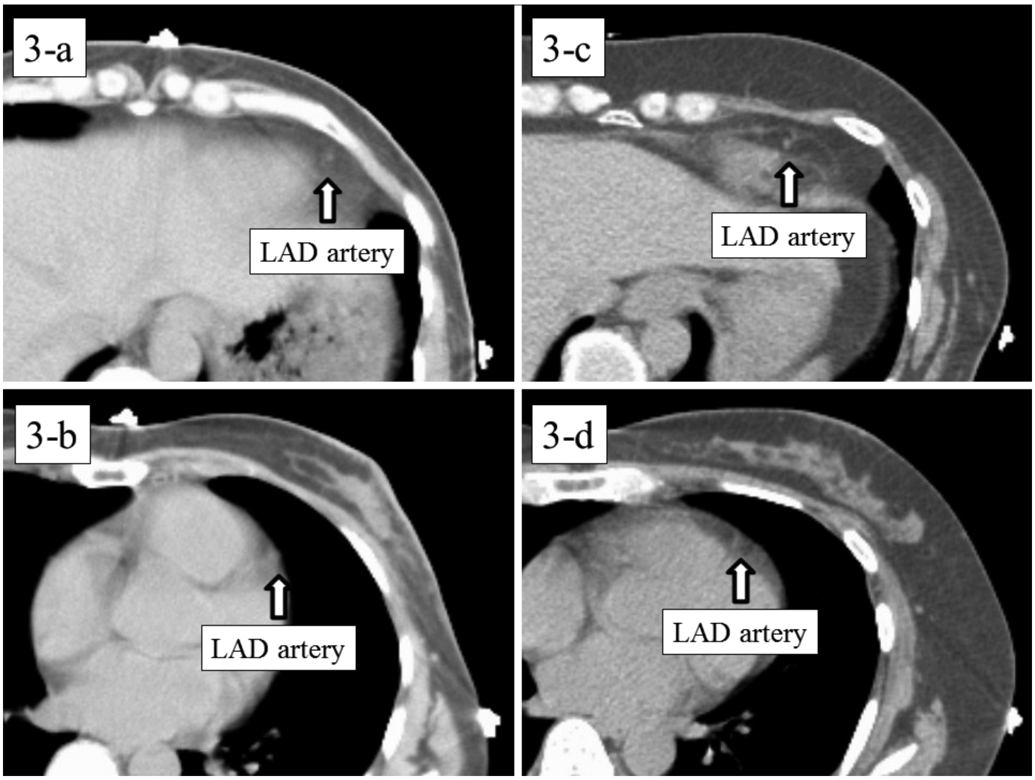

Fig. 3 CT images at the level of the cardiac base and apex in a patient whose body mass index (BMI) was 19.1 kg/m^2 (3-a, b). CT images at the level of the cardiac base and apex in a patient whose BMI was 27.0 kg/m^2 (3-c, d).

Taylor CW *et al.* reported that maximum heart distance (MHD) was correlated with mean heart dose and mean LAD coronary artery dose.[18] MHD is the maximum distance between the anterior cardiac contour and the posterior tangential field edges on beam's eye view. Because measuring MHD is easy, this method is useful. However, the MHD can be measured after the creation of a treatment plan. All patients underwent various examinations preoperatively. If high-risk patients can be identified based on these examinations, there would be no need for additional examinations. This would be advantageous in terms of reducing costs.

The heart may rotate around longitudinal axis, showing either clockwise or counterclockwise rotation as viewed from the apex. The LAD artery of a patient with CCWR is closer to the chest wall than that of a non-CCWR patient. This may cause the LAD artery to receive a higher dose. Dmax, Dmean, V20Gy, V30Gy, and V40Gy were significantly higher in patients with TZ at or to the right of V3 than patients with TZ at or to the left of V4. Because the full length of the LAD artery is near the chest wall in patients with CCWR, doses to this artery were high not only in high-dose region but also moderate-dose region.

Patients with large CTR have large hearts relative to their physiques. If CTR is large, doses to the LAD artery would presumably be high. However, there were no statistically significant differences in Dmax, Dmean, V20Gy, V30Gy, or V40Gy between patients with CTR ≥ 50 and those with CTR < 50%.

Patients with lower BMI were thinner and had little pericardial fat. For patients with large amounts of pericardial fat, this fat tissue provides insulation between the LAD artery and chest wall and increases the distance between the two (Fig. 3). On multivariate analysis, BMI were significantly associated with Dmax, V20Gy and V30Gy. There were marginal significant differences in Dmean and V40Gy between patients with BMI ≤ 22 and those with BMI > 22 kg/m^2.

This study was limited in that wall motion, respiratory motion, and chest wall deformity were not considered in great detail. However, we believe that we could take into account the average delineation caused by wall and respiratory motion, because the planning CT scan was performed over 40 seconds.

CCWR is a risk factor for high-dose irradiation to the LAD artery and low BMI is an additional risk factor. ECG is useful for evaluating the risk of high-dose irradiation to the LAD artery.

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