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Detection of the Early Cardiotoxic Effects of Doxorubicin-Containing Chemotherapy Regimens in Patients with Breast Cancer through Novel Cardiac Magnetic Resonance Imaging: A Short-term Follow-up

Afsaneh Maddah Safaei[1], Tara Molanaie Kamangar[1], Sanaz Asadian[2], Nahid Rezaeian[2], Ebrahim Esmati[1], Kasra Kolahdouzan[1], Leila Hosseini[2], Marzieh Lashkari[1], Fatemeh Jafari[1], Farnaz Amouzegar Hashemi[1]

[1]Department of Radiation Oncology, Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Radiology, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

***Corresponding author:**
Nahid Rezaeian,
Department of Radiology,
Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences,
Tehran, Iran.

nahid6069@yahoo.com

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ABSTRACT

Objectives: Many patients with breast cancer (BC) require cardiotoxic anthracycline-based chemotherapy. We intended to assess the early cardiotoxic effects of doxorubicin utilizing cardiac magnetic resonance (CMR) imaging.

Material and Methods: Forty-nine patients including 21 otherwise healthy females with BC at a mean age (±SD) of 47.62 ± 9.07 years and 28 normal controls at a mean age (±SD) of 45.18 ± 4.29 years were recruited. They underwent CMR and transthoracic echocardiography at baseline and 7 days after four biweekly cycles of doxorubicin and cyclophosphamide. Biventricular functional, volumetric, global strain, and tissue characterization findings were analyzed and compared with those of 28 controls.

Results: In post-chemotherapy CMR, 4 patients (19.04%), three symptomatic and one asymptomatic, exhibited evidence of doxorubicin cardiotoxicity. Significant differences in biventricular ejection fraction, left ventricular end-systolic volume index, and all 3D global strain values were noted after chemotherapy in comparison with the baseline (all $P < 0.05$). More than half of the study population showed a significant change in all right ventricular global strain values. One patient (4.76%) exhibited evidence of diffuse myocardial edema in post-chemotherapy CMR, and 3 patients (14.28%) showed myocardial fibrosis. The study participants were clinically followed up for 4–10 months (mean = 7 months). Overall, 8 patients (38.09%) complained of dyspnea on exertion and fatigue on follow-up. None of the CMR markers was associated with the development of symptoms.

Conclusion: Our investigation revealed striking changes in CMR parameters in the follow-up of BC patients treated with cardiotoxic chemotherapy. These exclusive CMR features assist in the early initiation of preventive cardiac strategies.

Keywords: Breast cancer, Doxorubicin, Cardiac magnetic resonance imaging, Cardiotoxicity

INTRODUCTION

Breast cancer (BC) is the most prevalent cancer among women and comprises about 30% of cancers in this population group. In 2018, about 2.1 million new cases were diagnosed, and 626 thousand patients died of BC worldwide.[1] The treatment protocols vary based on the

different characteristics of the tumor and the stage of the disorder on diagnosis and include surgery, chemotherapy, radiation therapy, and hormone therapy. Due to decreased disease-related mortality in these patients, many cases die of other causes rather than BC itself. Cardiovascular disease is the predominant cause of mortality in patients with BC, accounting for the death of 24% of cases over 65 years of age and 12.5% of all age groups.[2,3] This higher risk could be due to chemotherapy regimens containing cardiotoxic trastuzumab and anthracyclines; the direct impact of radiation on the heart, especially in left-sided BC; and the presence of cardiovascular risk factors, including obesity and inactive lifestyle in BC.[1-4] Despite their known cardiac toxicity profile, anthracycline-containing regimens remain the cornerstone of BC chemotherapy due to their significant effect in the reduction of BC recurrence.[5]

There is no universally accepted definition for cardiotoxicity; it has, nevertheless, been defined as a decline of more than 10% in the left ventricular ejection fraction (LVEF) to a final value of <55% in asymptomatic subjects or a drop of at least 5% in LVEF to a final value of <55% in symptomatic patients.[6,7] Anthracycline-induced cardiotoxicity has been classified as acute, subacute, and chronic. Acute toxicity occurs within 1 week of chemotherapy induction and is usually transient, self-limiting, and reversible.

The presentation of acute cardiotoxicity may consist of non-specific repolarization abnormalities in electrocardiography, transient acute LV dysfunction, troponin elevation, and myopericarditis.[8] Subacute cardiotoxicity may appear up to some weeks after chemotherapy, manifesting as pericarditis, myocarditis, and acute heart failure. Chronic toxicity is considered the most common and insidious form of cardiotoxicity; it happens within the 1st year after the completion of chemotherapy or after this period. It usually presents as LV dysfunction that deteriorates into dilated cardiomyopathy or congestive heart failure unless diagnosed and treated early.[9] Various strategies have been used for the early diagnosis of cardiotoxicity, including 2D and 3D echocardiography, tissue Doppler imaging, cardiac magnetic resonance (CMR) imaging,[10] and the assessment of serum cardiac biomarkers. Although 2D transthoracic echocardiography (TTE) is the most appropriate method for the detection of cardiotoxicity, it has inadequate sensitivity for detecting subclinical myocardial damage.[6] CMR is a non-invasive technique with excellent spatial and temporal resolutions for the comprehensive assessment of myocardial function, tissue characterization, and strain analysis.[11] Feature tracking CMR (FT-CMR) is a novel method for myocardial deformation analysis that detects early changes in myocardial function.[12,13]

The prevention, timely detection, and management of cancer-related heart disease pose a formidable challenge to most oncologists. As was mentioned before, CMR confers new powerful features for the early discovery of cardiotoxicity that requires further evaluation. In the present study, we aimed to determine the role of CMR parameters in the early detection of doxorubicin-related cardiac dysfunction in patients with BC.

MATERIAL AND METHODS

The current investigation was conducted as a prospective study in the Tehran Cancer Institute, in collaboration with Rajaie Cardiovascular Medical and Research Center, from April 2019 to December 2019. Twenty-one female patients with a pathologic diagnosis of invasive ductal carcinoma or invasive lobular carcinoma of the breast without a history of previous cardiovascular disease and 28 healthy controls (14 women) were recruited. All the patients with BC were followed up for 4–10 months to detect any evidence of cardiac signs and symptoms, including resting or exertional dyspnea, chest pain, fatigue, and palpitation after the last cycle of chemotherapy.

According to standard guidelines, the study subjects were candidates for adjuvant chemotherapy with doxorubicin. The exclusion criteria consisted of a history of pacemaker and cardioverter-defibrillator implantation, the presence of metallic foreign bodies (contraindications for CMR), known allergic reactions to gadolinium-based contrast media, a history of cardiovascular disease and risk factors like hypertension, the use of any medication, age <18 years old, and impaired renal function tests. Informed written consent was obtained from all the participants after they had received comprehensive explanations about the benefits and potential harms of the study. All the patients received the chemotherapy regimen with cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2; cumulative dose = 350–450 mg/m^2) for 4 cycles every 2 weeks followed by paclitaxel (80 mg/m^2) for 4 cycles every 3 weeks. They were monitored for any cardiovascular symptoms and presumable side effects relating to the treatment.

TTE and CMR were acquired at baseline, within a few hours of chemotherapy, and 7 days after 4 biweekly cycles of doxorubicin and cyclophosphamide.

Standard 2D-TTE was performed with a commercial ultrasound instrument (Philips EPIQ 7). The images were digitally saved and analyzed off-line using Q-Lab software. LVEF was estimated through the Simpson rule. LV global longitudinal strain (GLS) was determined through the speckle-tracking method in the standard apical views (2-, 3-, and 4-chamber views) at a frame rate of 40–90 Hz (mean = 60 frames/second). The endocardial borders of LV wall were automatically tracked and manually adjusted. TTE was performed before and after chemotherapy by a single expert cardiologist, blinded to the patients' medical conditions.

CMR examinations were conducted with a Siemens MAGNETOM Avanto (Siemens, Germany) 1.5 T with specific cardiac coils. Cine images were taken during end-expiratory breath-holds in a stack of short- and long-axis windows through balanced steady-state free precession sequences. CMR data consisted of end-systolic and end-diastolic volume indices, stroke volume, and EF for both ventricles. The body surface area was calculated through the Haycock method. Strain analysis was accomplished off-line with FT software cvi42 (Canada). Endocardial and epicardial lines in the end-diastolic frame were manually traced, and automatic border tracking was performed within all cardiac phases for feature detection.

Thereafter, 3D CMR strain was acquired from the 2-, 3-, and 4-chamber views and a stack of short-axis planes from the base to the apex of LV [Figure 1]. In addition, 2D right ventricular (RV) strain values were collected from RV free wall in the 4-chamber and short-axis sequences. Image brightness was optimized to obtain a higher contrast to distinguish between endocardium and blood in the ventricular cavity.

Strain percentage was defined as the rate of changes in dimensions from end-diastole to end-systole. Longitudinal strain depicts LV shortening from the base to the apex throughout a cardiac cycle. Circumferential strain is an illustration of LV contraction along LV circular perimeter. Radial strain shows myocardial deformation toward the center of the ventricular cavity and determines LV wall thickening throughout systole; hence, unlike the other ones, it is depicted as a positive value. However, for simplicity, all strain values were depicted as absolute values. A reduction of more than 15% in strain values from pre- to post-chemotherapy states was defined as significant.

Tissue characterization sequences consisted of short-tau inversion recovery (STIR) and late gadolinium enhancement (LGE) [Figure 2]. Myocardial edema was defined in STIR sequences by utilizing a stack of short-axis images (slice thickness = 12 mm). Endocardial and epicardial outlines were manually traced, and the signal intensity of the myocardium was compared with that of the skeletal muscle. A signal intensity ratio of >1.9 was considered a positive value for myocardial edema. In addition, localized regions with myocardial inflammation were determined using the color threshold of the software.

LGE images were captured 10 min after the injection of gadoterate meglumine (Dotarem; 0.15 mmol/kg) through segmented inversion-recovery methods and additionally single-shot free-breathing sequences in the same sections as function views. The inversion time was assessed with a Look-Locker image, and the presence of myocardial fibrosis was evaluated visually by an expert independently.

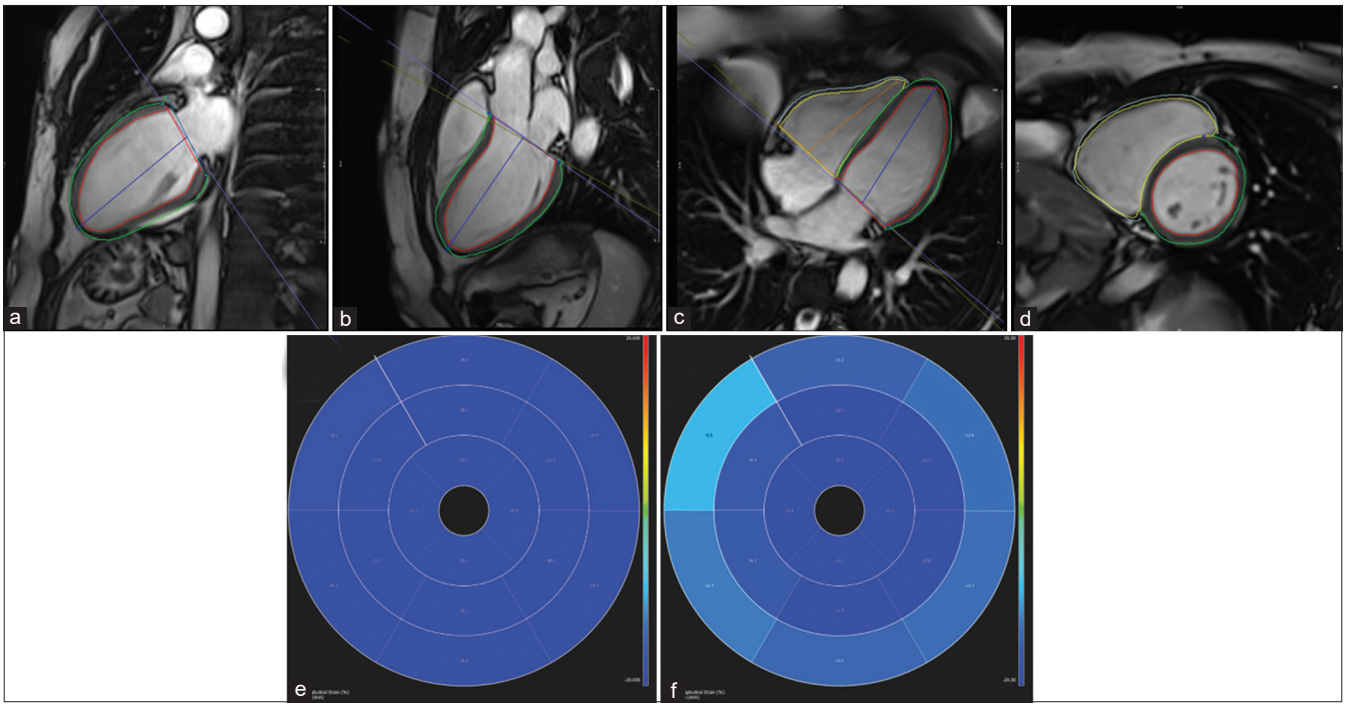

Figure 1: 52-year-old woman with breast cancer who presented after four biweekly cycles of chemotherapy. Endocardial (red) and epicardial (green) borders of the LV are traced in a) 2-chamber, b) 3-chamber, c) 4-chamber, as well as the D: short-axis plane and RV endocardial (yellow) and epicardial borders (blue) in c) 4-chamber and d) short-axis level to extract deformation parameters. (e and f) bull's eye map of a global longitudinal strain of different LV regions according to 16 segments AHA model before and after chemotherapy shows decrease LV strains after chemotherapy. LV: Left ventricle, RV: Right ventricle, AHA: American heart association.

Cardiotoxicity based on LVEF was defined[8] as a decline of more than 10% to a final value of <55% in asymptomatic patients or a decline of at least 5% to a final value of <55% in symptomatic patients.

Statistical analysis

Data were investigated with SPSS software, version 26. Categorical variables were displayed as frequencies and percentages, while continuous variables were reported as the mean ± the standard deviation (SD). Normality was evaluated through the Shapiro–Wilk method for continuous variables. The mean values were compared through the paired *t*-test and the Wilcoxon signed-rank method. Binary logistic regression analyses were conducted to assess any correlation between CMR parameters and dichotomous categorical variables. $P < 0.05$ was assumed significant in all the tests performed.

RESULTS

The present study enrolled 49 subjects, consisting of 21 women with BC, at a mean age (±SD) of 47.62 ± 9.07 years and 28 normal controls at a mean age (±SD) of 45.18 ± 4.29 years. Left-sided BC was reported in 52.38% ($n = 11$) of the patients with BC. During the short-term follow-up, 5 patients (23.8%) developed dyspnea on exertion and 3 (14.28%) reported fatigue. Table 1 demonstrates the demographic characteristics of the study population.

The normal controls consisted of 14 women (50%). A comparison of CMR parameters between the patient group and the normal controls showed no difference, except for RV global radial strain (GRS) ($P < 0.001$) and RV global circumferential strain (GCS) ($P < 0.001$) [Table 2].

In post-chemotherapy CMR, 4 patients (19.04%), 3 (14.28%) symptomatic and 1 (4.76%) asymptomatic, exhibited evidence of doxorubicin cardiotoxicity.

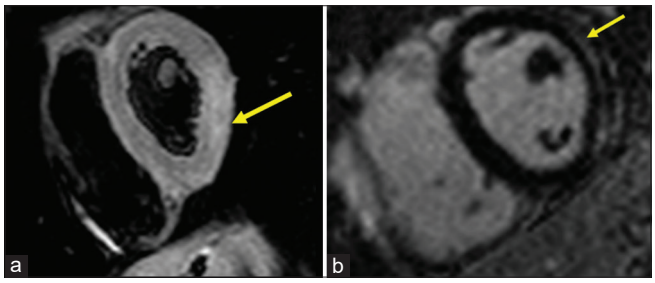

Figure 2: A 48-year-old woman patient with breast cancer shows evidence of myocarditis on CMR images after four biweekly cycles of chemotherapy. a) STIR sequence of basal LV short-axis shows inferolateral LV wall edema (yellow arrow) b) LGE sequence at the same level demonstrates subepicardial fibrosis of LV lateral wall (yellow arrow). STIR: Short tau inversion recovery, LV: Left ventricle, LGE: Late gadolinium enhancement.

The next step was a comparison of CMR parameters between baseline and post-chemotherapy among the patients with BC, which demonstrated a significant difference in biventricular

Table 1: Baseline Characteristics of the study participants.

Patient characteristics	Value
Pathology	
IDC	20 (95.2%)
ILC	1 (4.8%)
Grade 1/2/3	6 (28.6%)/10 (47.6%)/5 (23.8%)
ER+	13 (61.9%)
PR+	9 (42.9%)
Her2+	0
Side	Right 10 (47.61%), Left 11(52.38%)
Symptoms	Symptomatic 8 (36.36%), Asymptomatic 14 (63.63%)
Dyspnea	5 (22.7%)
Chest Pain	0
Peripheral Edema	0
Fatigue	3 (14.28%)
Past Medical History	
DM	0
HTN	0
HLP	0
CAD	0
Lab Data	
Cardiac TNI	4 (19.04%)

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, ER+: Estrogen receptor positivity, PR+: Progesterone receptor positivity, DM: Diabetes mellitus, HTN: Hypertension, HLP: Hyperlipidemia, CAD: Coronary Arterial disease, TNI: Troponin I

Table 2: Comparison of mean±SD among normal controls and patients before and after chemotherapy.

	Normal control	Before chemotherapy	After chemotherapy
N	28	21	21
Age mean±SD	45.18±4.29	47.62±9.07	-
LVEF	58.17±1.70	60.15±7.90	54.60±6.85
RVEF	55.64±1.116	55.06±7.23	50.58±5.80
LVEDVI	66.38±5.66	65.36±10.74	63.42±12.43
RVEDVI	63.60±2.99	63.92±15.16	61.47±15.24
LVESVI	27.62±3.46	25.71±6.42	28.21±6.95
RVESVI	28.85±1.62	29.36±8.98	31.41±8.84
LVGLS	18.07±1.35	17.72±3.39	15.14±3.30
LVGCS	18.69±2.18	19.30±2.98	16.68±4.02
LVGRS	39.82±7.77	44.53±8.89	36.34±11.60
RVGLS	23.57±4.48	25.94±5.42	21.36±6.80
RVGCS	17.68±1.78	12.84±3.49	8.72±3.75
RVGRS	31.05±7.75	22.20±6.90	14.76±5.77

N: Number, LV: Left ventricle, EF: Ejection fraction, GLS: Global longitudinal strain, GCS: Global circumferential strain, GRS: Global radial strain, RV: Right ventricle, EDVI: End-diastolic volume index, ESVI: End-systolic volume index

Table 3: CMR findings in breast cancer patients before chemotherapy with doxorubicin and 2 weeks after the fourth course of chemotherapy.

	Mean difference Pre- and post-chemotherapy (95% CI)	*P* value	*t*
LV			
GLS	2.58 (1.61–3.55)	≤0.001	5.578
GCS	2.62 (1.32–3.91)	≤0.001	4.22
GRS	8.18 (4.35–12.02)	≤0.001	4.45
EF	5.54 (3.31–7.78)	≤0.001	5.18
EDVI	1.94 (−2.63–6.52)	0.387	0.88
ESVI	−2.49(−4.41–0.57)	0.014	−2.71
RV			
GLS	4.58 (2.17–6.98)	0.001	3.97
GCS	4.12 (2.51–5.73)	≤0.001	5.34
GRS	7.43(4.25–10.61)	≤0.001	4.88
EF	4.48(7.25–1.71)	0.003	−3.37
EDVI	2.45 (−3.55–8.44)	0.41	0.85
ESVI	−2.04 (−5.24–1.15)	0.19	−1.33

GLS: Global longitudinal strain, GCS: Global circumferential strain, GRS: Global radial strain, EDVI: End-diastolic volume index, ESVI: End-systolic volume index, SV: Stroke volume, EF: Ejection fraction, CMR: Cardiac magnetic resonance, LV: Left ventricle, RV: Right ventricle

EF, LV end-systolic volume index, and all 3D global strain values (all *P*s < 0.05). The results are depicted in Table 3.

Significant deteriorations in RV strain values were noted in GLS (12/21, 57.14%), GCS (14/21, 66.66%), and GRS (15/21, 71.42%). In addition, significant LV strain reductions were seen in GLS (10/21, 47.61%), GCS (8/21, 38.09%), and GRS (12/21, 57.14%).

One patient (4.76%) demonstrated evidence of diffuse myocardial edema in post-chemotherapy CMR in STIR/T2-weighted sequences, and 3 patients (14.28%) showed signs of mid-myocardial fibrosis in post-chemotherapy CMR in LGE sequences.

The mean ± SD echocardiographic GLS values before and after chemotherapy were 19.74 ± 2.53 and 19.64 ± 2.35, correspondingly, (P = 0.81), and the mean ± SD echocardiographic EF values before and after chemotherapy were 55 ± 0 and 53.81 ± 3.41, respectively (P = 0.066).

The study participants were followed up for their symptoms for 7 months (4–10 months) after the last cycle of chemotherapy. Six patients (28.57%) recovered from their previous symptoms, while 3 (14.28%) developed new symptoms. Overall, 8 patients (38.09%) complained of dyspnea on exertion and fatigue on follow-up.

The logistic regression analysis of the association between changes in CMR parameters and the presence or absence of clinical symptoms such as dyspnea and fatigue showed that none of the CMR markers was significantly associated with the development of symptoms.

DISCUSSION

In the present investigation, CMR parameters in patients suffering from BC before and after chemotherapy were compared. In addition, the CMR findings of the patients were compared with those of normal controls. The main findings of our research are as follows:

Chemotherapy-induced cardiotoxicity was detected in 4 out of 21 patients with BC based on the available guidelines. After chemotherapy, there were significant changes in all FT-CMR-derived strain values as well as biventricular EF and LV end-systolic volume index. Moreover, RV strain values revealed significant deteriorations in more than half of the patients with BC. Further, CMR tissue characterization images illustrated myocardial edema in one and mid-myocardial LV fibrosis in three of our patients with BC after chemotherapy.

In our study population, about 19% of the patients exhibited subacute cardiotoxicity after doxorubicin chemotherapy: Three patients with symptoms and one patient without symptoms. In a prospective study, Cardinale *et al*.[14] assessed follow-up echocardiograms in patients with BC receiving adjuvant treatment with doxorubicin, cyclophosphamide, and docetaxel and demonstrated early LV dysfunction in 9% of the patients. We think that differences in terms of ethnicity among our study population, the brand of doxorubicin, and the associated oncologic regimens, including cyclophosphamide and paclitaxel, may have contributed to the high rate of cardiotoxicity in our study population. Some previous studies have recommended that the anthracycline chemotherapy regimen be discontinued if there is a fall of >10% in LVEF to a final value of below 53% with a view to preventing the further aggravation of LV dysfunction and progression to heart failure.[15,16] Therefore, the detection of an early decline in EF with CMR as the gold standard method can reduce the rate of cardiotoxicity by timely interventions.

The results of our study showed that all absolute biventricular strain parameters, including GLS, GCS, and GRS, significantly decreased after 4 cycles of doxorubicin administration. In an investigation by Lunning *et al*.,[17] similar findings were reported with the use of CMR. It has also been previously revealed that LVGLS is superior to LVEF and all other conventional echocardiographic parameters in predicting mortality in patients suffering from heart failure with reduced EF,[18] and a 10–15% decrease in this parameter appears to be useful for predicting cardiotoxicity and congestive heart failure.[19] Further studies may result in the definition of more detailed criteria, including FT-CMR strain parameters in the diagnosis of cardiotoxicity. Although it leads to an increased incidence of cardiotoxicity, the treatment strategies would be initiated promptly that ultimately bears a better outcome.

In our investigation, patients with BC had almost comparable strain values with normal controls before chemotherapy. Nonetheless, we noticed a significant change in biventricular strain values after chemotherapy. Considering that only four patients were classified as cases of chemotherapy-related cardiotoxicity, we suppose that utilizing FT-CMR parameters may assist in the earlier detection of cardiac insult by chemotherapeutic agents. Moreover, we believe that diagnosing disturbances in ventricular deformation parameters might confer the early initiation of protective cardiac strategies.

As was already discussed, our patients experienced a significant decline in EF and strain parameters in RV and LV. The overwhelming majority of the previous studies have examined strain parameters in LV, but the significant difference in strain and EF parameters in RV early after chemotherapy with doxorubicin needs further elaboration. Notably, more than half of our study participants had a decline of >15% in GLS, GCS, and GRS in RV after chemotherapy, which is outstanding despite the small sample size of our investigation. In a study by Calleja *et al*.,[20] 40% of patients with BC showed abnormal post-chemotherapy RV strain patterns in echocardiography, in favor of RV dysfunction. In another study, patients with concomitant RV and LV dysfunction had a low rate of improvement in LV dysfunction during follow-up by comparison with those without RV dysfunction (17% vs. 40%).[21] Therefore, CMR with its superiority over echocardiography in the assessment of RV function and morphology could provide valuable data for predicting the outcome and yielding appropriate preventive approaches.

Our results demonstrated significant deteriorations in biventricular EF and LV end-systolic volume index despite the absence of meaningful differences between EF and LVGLS derived by TTE before and after chemotherapy. A previous study reported that conventional 2D echocardiography had a sensitivity of 25% for detecting LVEF reductions below 50% after anthracycline chemotherapy in comparison with CMR, and an improvement to a sensitivity of 53% was seen using 3D echocardiography.[22] Our research underscored the power of CMR in the early detection of chemotherapeutic cardiotoxicity.

In our study, about 19% of the participants had signs of myocardial edema or focal mid-wall fibrosis in post-chemotherapy contrast-enhanced CMR, along with a meaningful rise in cardiac troponin, indicating the probable occurrence of myocarditis induced by chemotherapy. In an animal model, the earliest sign of doxorubicin-induced cardiomyopathy was the prolongation of T2 at 6 weeks after the initiation of chemotherapy before any detectable change in T1 mapping, extracellular volume, and LV motion.[23,24] This finding depicts the exclusive power of CMR in revealing tissue evidence of myocardial inflammation and fibrosis, non-invasively.

We could not detect a statistically significant relationship between symptom development during the follow-up period and CMR parameters. We believe that large-scale studies are needed for evaluating the predictive role of CMR parameters in this regard.

We noted a significant difference in RVGCS and RVGRS values between normal controls and patients with BC before chemotherapy. The previous studies have evaluated the reproducibility and reliability of the FT-CMR method and proposed more research on this issue.[13] Given that most of the strain values were comparable between our two study groups, we postulate that our finding may be a technical bias. Accordingly, we recommend more studies with a larger sample size.

The early diagnosis of treatment-related cardiotoxicity in patients afflicted by cancer is essential in that cardiac side effects are reversible in the early stages, and this necessitates adherence to the standard guidelines for cardiac care in these patients. In a large cohort study on patients with BC, from 2009 to 2014, guideline-adherent cardiac monitoring was identified only in 46.2% of the patients.[24] CMR, albeit considered the gold standard for the evaluation of cardiac function, has not been incorporated into these guidelines for chemotherapy-related cardiotoxicity screening. According to Kolla *et al*.,[25] CMR use for chemotherapy-related cardiotoxicity screening increased from 0.9% in 2011 to only 2.9% in 2014. In a remarkable study by Thavendiranathan *et al*. on 331 anthracycline-treated BC patients with associated heart failure risk markers, cardioprotective treatment was initiated based on either GLS or EF decline. Their results revealed that the arm with GLS-guided therapy had a notably lower reduction in LVEF after 1-year follow-up. They concluded that the application of GLS in surveillance for CTRCD has an impressive effect on the treatment strategies to prevent cardiac dysfunction.[26] On the strength of its ability to detect subtle, yet potentially perilous, cardiac changes early in the course of the disease, CMR confers the prevention and management of the upcoming cardiac morbidity and, thus, enhances the quality of life and survival in this susceptible group of patients with cancer.

Limitations

The notable drawbacks of our study were the low case volume and the lack of a long-term CMR-based follow-up. In addition, in view of the advent of T1 mapping and extracellular volume quantification techniques, we recommend that further studies incorporating these techniques be designed with longer follow-ups.

CONCLUSION

FT-CMR enables us to detect subclinical cardiotoxicity induced by chemotherapeutic agents more readily and earlier

than echocardiography. Further, CMR tissue characterization sequences can identify myocardial edema and fibrosis, indicative of post-chemotherapy myocarditis, which confers the opportunity to initiate preventive and curative strategies before significant cardiac morbidity endangers the lives of patients with BC.

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Availability of data and materials

The data sets used during the current study are available from the corresponding author on reasonable request.

Ethical Approval

All the procedures performed in this study were in keeping with the ethical standards of the institutional research committee of Tehran University of Medical Sciences and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

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Conflicts of interest

There are no conflicts of interest.

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