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Chemotherapy-induced cardiotoxic effect in breast cancer patients treated with trastuzumab (Herceptin) by MRI

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Abstract

Background Chemotherapy-associated cardiomyopathy is a well-known cardiotoxicity of contemporary cancer treatment. As cancer outcomes improve, cardiovascular disease has become a leading cause of morbidity and mortality among cancer survivors. The objective of this study was to evaluate the role of CMR in the detection of early cardiotoxic changes and in the identification of patients at risk of developing CTRCD.

Patients and methods Fifty patients diagnosed breast cancer examined by echocardiography and cardiac MRI before the start of chemotherapeutic regimen followed by 2 and 4 months post-chemotherapy.

Results By echocardiography, all measures were within normal range at the start and at the first follow-up. Twenty (40%) patients show decreased LVEF at second follow-up reaching up to 50% with milder affection of the other parameters. CMR examination shows decreased LVF at second and third follow-up ($p = 0.005$). There was significant elevation of T2 value for 10 patients at first follow-up (p value 0.04) and for 22 patients at second follow-up (p value 0.01) in correlation with baseline. The T1 mapping and ECV showed elevation at first and second follow-up as compared to baseline ($p = < 0.05$).

Conclusion T1 and T2 mapping is superior to echocardiography in early detection of the cardiotoxic effects of chemotherapy applied for breast cancer patients and can guide the management and patient lifestyle.

Keywords Cardiotoxic, MRI, Trastuzumab, CMR, Chemotherapy, Cardiomyopathy

Background

Several years ago, cancer therapy-induced cardiotoxic reactions were first recognized with the use of anthracyclines, but after that it was identified that such cancer therapy-related cardiac dysfunction (CTRCD) can be induced by other cancer therapies as well including Herceptin (trastuzumab) and immunotherapeutic agents [1–3].

Cardiotoxicity is a general term which refers to cardiac injury due to myocyte damage, which may or may not be accompanied by physiologic changes. Cardiac dysfunction is a more specific term which means the presence of a measurable systolic function decline [4].

Chemotherapeutic agents are classified into two types: Type I and Type Il [4–7]:

Type I: All types of anthracyclines (doxorubicin, epirubicin and idarubicin) are classified in this type [8, 9]. However, the characteristic agent is doxorubicin. This group of agents leads to permanent, irreversible damage which is also cumulative dose related.

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Type II: The characteristic agent of this type is trastuzumab which is intended in our study. The damage caused by this group of agents is usually reversible and is unrelated to dose.

The risk of developing CTRCD is defined based on the cardiac review and evaluation committee criteria as a ≥ 10% reduction in left ventricular ejection fraction from baseline to < 55% in the absence of heart failure symptoms, or a reduction of ≥ 5 to < 55% with symptoms by CMR and 2DE separately [10].

Multiple factors are known to increase the risk of developing CTRCD including: patient-related factors (age and pre-existing CV disease), CV risk factors (obesity, diabetes, tobacco use and sedentary lifestyle), CV risk factors metabolic abnormalities and hypersensitivity to the drugs as well as prior chemotherapy and/or radiotherapy [11].

The most commonly discussed form of CTRCD is HF. However, cancer therapy-related cardiac complications may present in different ways, including myocardial ischemia, changes in blood pressure, arrhythmias (including bradycardia, tachyarrhythmias and atrio-ventricular (AV) blocks), pericarditis, pericardial effusion, or pericardial thickening [11, 12].

Trastuzumab is one of the monoclonal antibody-based tyrosine kinase inhibitors or what is called targeted cancer therapy. Their function is to bind a specific target and block its action. One of these targets is the human epidermal growth factor II (HER-2), which is a member of the epidermal growth factor receptor family. Trastuzumab (trade name of Herceptin) is the most commonly used tyrosine kinase inhibitor in the clinical practice especially in breast cancer and results in type II CTRCD [5, 13].

Chemotherapeutic regimens which include only trastuzumab lead to lower rates of CTRCD than combine trips to trastuzumab and anthracyclines. At the ultrastructure level, trastuzumab-related cardiotoxicity is characterized by monocyte dysfunction rather than necrosis [14].

Imaging modalities

Echocardiography is the most popular imaging technique for assessing patients before, during and then after potentially cardiotoxic medication. Its widespread accessibility, repeatability, adaptability, absence of radiation exposure and safety for individuals with concurrent renal illness all contribute to this [15].

The introduction of additive echocardiographic markers for the identification of subclinical myocardial dysfunction has thus received substantial scientific attention. The usefulness of echocardiographic measurements of diastolic function has been investigated following chemotherapy, but the findings are conflicting; thus, diastolic tests really are not usually advised for this indication. Diastolic dysfunction frequently occurs before systolic failure [16, 17].

Myocardial strain imaging can identify early myocardial injury [18]. Cardiac stress imaging can accurately measures the cardiac systolic function not only EF due to the ability of estimation of the myocardial displacement or strain in all three dimensions (longitudinal, radial and circumferential) [19–21].

Cardiovascular magnetic resonance (CMR) imaging

T1-weighted and T2-weighted CMR techniques have been successful in identifying myocardial infarction and provide valuable information for the early detection of cardiotoxicity. For example, T1-weighted and T2-weighted images have shown vascular dysfunction and edema in addition to changes in quantitative measures of tissue dysfunction in patients with myocardial infarction [22]. Delayed enhancement CMR imaging is rapid and standard in clinical practice but may yield variable results due to T2 effects [23].

Recent advances in CMR techniques have enabled quantitative mapping of magnetic relaxation values (T1 and T2), which overcome many of the disadvantages of qualitative techniques. Although there is an increased scan time associated with quantitative mapping of tissue, T1/T2 readings may be immediately examined on several scanners and on various pictures without the need to provide a contrast agent [24].

CMR plays an important role in the diagnosis of myocardial fibrosis. LGE can accurately recognize myocardial scars, while T1 mapping is another novel technique applied for the assessment of chronic diffuse myocardial fibrosis [25]. A recent CMR technique developed from a pre- and a post-contrast T1 measurement allows quantification of the ECV which is a marker of myocardial interstitial fibrosis [26, 27].

Patients and methods

This prospective study was carried out in the period from November 2019 until June 2022 on 50 patients receiving cardiotoxic chemotherapy (trastuzumab) that were referred to the Department of Radiology, Faculty of Medicine, Minia University, for treatment of breast cancer patients scheduled to undergo treatment with trastuzumab "Herceptin." All patients had written the informed consent. The study was approved by the Ethics Committee of the Faculty of Medicine, Minia University.

Inclusion criteria: adult female patient (> 18 years) prepared for trastuzumab regimen and able to tolerate three CMR examinations, each one last about 45 min.

Exclusion criteria: patient's age (< 18 years), previous start of chemotherapy which was intended to be studied,

pre-existing symptomatic HF, recent acute coronary syndrome, persistent atrial fibrillation, patients with cardiac pacemakers, implantable hearing aids, intracranial metal clips, metallic bodies in the eye, insulin pumps, extreme claustrophobia, renal insufficiency (GFR < 30 ml/min/1.73 m^2), inability to sustain a breath-hold, morbid obesity and clinically unstable patients.

Methods

All patients were subjected to full history taking, clinical cardiac examination and ECG examination. A written consent was taken from all patients.

A. Echocardiography

2D Echocardiography for assessment of LVEF, EDV, ESV, LVEDV and LVESV before the start of the chemotherapy (baseline), after 2 (early follow-up) and 4 months (late follow-up).

B. CMR

Imaging schedule

Serial CMR was performed at three time points:

- Baseline: Before the start of chemotherapy.
- Early follow-up: 2 months after the start of chemotherapy.
- Late follow-up: 4 months after the start of chemotherapy.

CMR protocol and standard parameters

All CMR examinations were performed in Radiology Department, Faculty of Medicine, Minia University Hospital, using clinical MRI system (Ingenia 1.5 T Philips) equipped with a body phased-array 18-channel receiver coil and ECG gating.

All patients were scanned using an identical imaging protocol as follows:

(1) Scout images (axial, coronal and sagittal) using real-time interactive planning: imaging parameters were: FOV 450 × 450 mm^2, TR/TE 2.1/0.82 ms, slice thickness 10 mm, acquisition matrix 192 × 96, voxel size = 2.38 × 4.69 × 10 mm^3 and flip angle 50°. (2) Cine images using a breath-hold bSSFP with a retrospective ECG gating in LV LAx planes (2 Ch, 3 Ch and 4 Ch) as well as in contiguous SAx slices. (3) Native myocardial Tl mapping before IV contrast agent administration using a breath-hold MOLL1 sequence in three SAx planes at different LV levels. (4) Myocardial T2 mapping in three SAx plane using a breath-hold turbo SE (TSE) sequence. IV contrast agent administration (injection of 0.2–03 mmol/kg body weight gadolinium-based contrast agent)

NB: A breath-hold look-locker T1-scout sequence was acquired in one mid-ventricular SAx plane before LGE acquisition to determine the accurate T1 for nulling normal myocardial signal intensity.

(5) LGE After about 6–10 min of IV contrast agent administration using breath-hold TI-weighted inversion recovery PSIR sequences along the same planes of the cine bSSFP images. (6) Myocardial post-contrast T1 mapping after 10 min of IV contrast agent injection using a breath-hold MOLLI sequence with the same planning and CMR parameters as the native map in order to acquire the myocardial ECV maps.

CMR analysis

All the MRI images were transferred to a commercial off-line workstation for further analysis. The software we used for post-processing was IntelliSpace Portal (ISP) workstation (Version 9.1, Philips Healthcare, Best, The Netherlands).

The collected CMR parameters included standard morphological and functional parameters for LV as well as tissue characterization parameters (LV global TI and T2 Mapping) as well as the number of abnormal LV segments and percentage of healthy myocardium.

Ventricular volumes and function: Results for ventricular EDV index (EDVi), ESV index (ESVi), EF, SV and LV mass index (LVi) were quantitatively, evaluated in SAx-cine images through manually tracing the epi- and endocardial borders on successive images at end-diastole and mid-systole.

Myocardial TI, T2 mapping and ECV fraction: Epicardial and endocardial contours were manually traced in three SAx slices (basal, mid-ventricular and apical). ECV fraction was reported in percentage and measured using the native and post-contrast Tl values as well as patient's hematocrit value. Checking the presence of enhancement: LGE images were checked at the different planes for the presence or absence of enhancement in each segment.

Statistical analysis

The analysis of the data was carried out using the IBM SPSS 26.0 statistical package software (IBM; Armonk, New York, USA). Normality of the data was tested using the Shapiro–Wilk tests. Data were expressed as mean and standard deviation for quantitative measures, in addition to both number and percentage for categorized data McNemar test used to compare frequencies on multiple measures. A p-value less than 0.05 was considered significant.

Results

Regarding the demographic data, the mean age of study population was 44.8 years, 35 patients were female, and 15 patients were male. The mean body mass index (BMI) of the cohort study was 25.3 kg/m^2.

Echocardiography findings

All patients underwent echocardiography examination before the start of chemotherapy, two- and four-month follow-up. All measures were within normal range including LVEF, EDV, ESV, LVEDV and LVESV at the start and at the first follow-up. Twenty (40%) patients show decreased LVEF at second follow-up reaching up to 45% with milder affection of the other parameters (Fig. 1).

CMR findings

- Fifty patients prepared for cardiotoxic chemotherapy regimen were enrolled in our study with mean age 44.8 years, 60% being female and 40% being male.
- They underwent prospective CMR at baseline of start of the chemotherapy, 2 months and 4 months thereafter as follow-up.
- All patients showed normal CMR volumetric, functional and tissue characterization parameters at the baseline study.
- LVEF was within normal range at baseline. However, it tended to decrease at first follow-up which was followed by a significant reduction at the second follow-up in comparison with the baseline with $p=0.005$
- Compared to the baseline, there was a significant increase of LVESV at the first and second follow-up with $p=<0.0001$ for both (Table 1).
- The LVMi was also decreased significantly at the first follow-up ($p=0.016$) but no significant interval changes at the second follow-up (60%)
- There was no significant correlation between changes at first follow-up in LVEF and LVMi (Pearson's correlation coefficient $=-0.048$, $p=0.740$).
- LVEDV shows mild increase at the first follow-up with no significant interval changes at the second follow-up ($p=<0.99$)

Table 1 Demographic data of the studied group

Demographic data	Studied group ($n=50$)
Age	
Mean ± SD	44.8 ± 12.92
Range	21–74
Sex	
Male: (N%)	20 (40%)
Female: (N%)	30 (60%)
BMI	
Mean ± SD	25.3 ± 1.42
Range	21–30

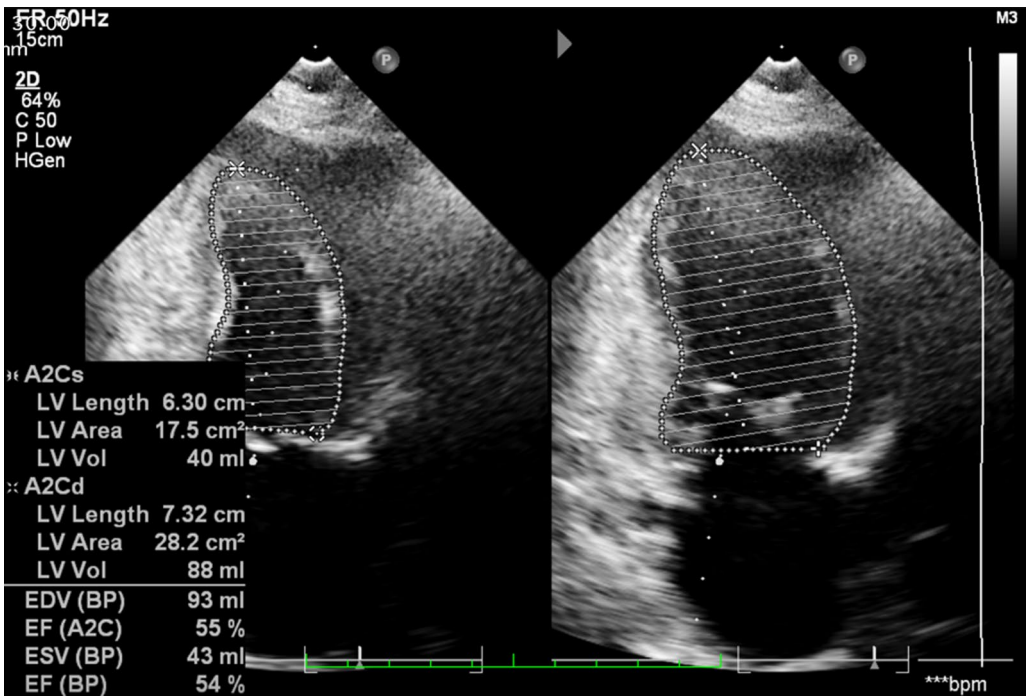


Fig. 1 Echocardiographic study shows elevated EDV, ESV and reduced ejection fraction (54%) of the previously examined patient at second echo follow-up

- LVESV shows mild increase at the first follow-up more appreciated at the second follow-up ($p = < 0.001$)
- Only two patients (4%) showed at second follow-up; anterior, anteroseptal and anterolateral mid-segmental, subpericardial LGE (Fig. 2).

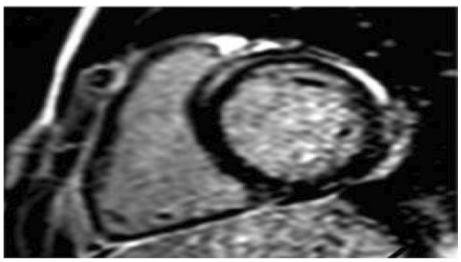


Fig. 2 LGE image at the mid-ventricular level of the same case showing subpericardial enhancement of the anterior, anteroseptal and anterolateral segments [second follow-up CMR]

- The T1 mapping and ECV showed mild elevation at first follow-up, which was followed by significant elevation at second follow-up as compared to baseline. Values are expressed as p, probability [significance < 0.05] (Fig. 3).
- There was significant elevation of T2 value for 10 patients (20%) at first follow-up (p value 0.04) and for 22 patients (44%) at second follow-up (p value 0.01) in correlation with baseline (Figs. 1, 4, 5 and Tables 2, 3).

Discussion

Cancer survivors are increasing nowadays however with increased incidence of cardiovascular complications mainly due to the cardiotoxic effect of chemotherapy. Such cardiotoxic changes may adversely affect the clinical condition of cancer survivors. Therefore, monitoring cancer patients using cardiac imaging has been increasingly implemented in the cardio-oncology field, which

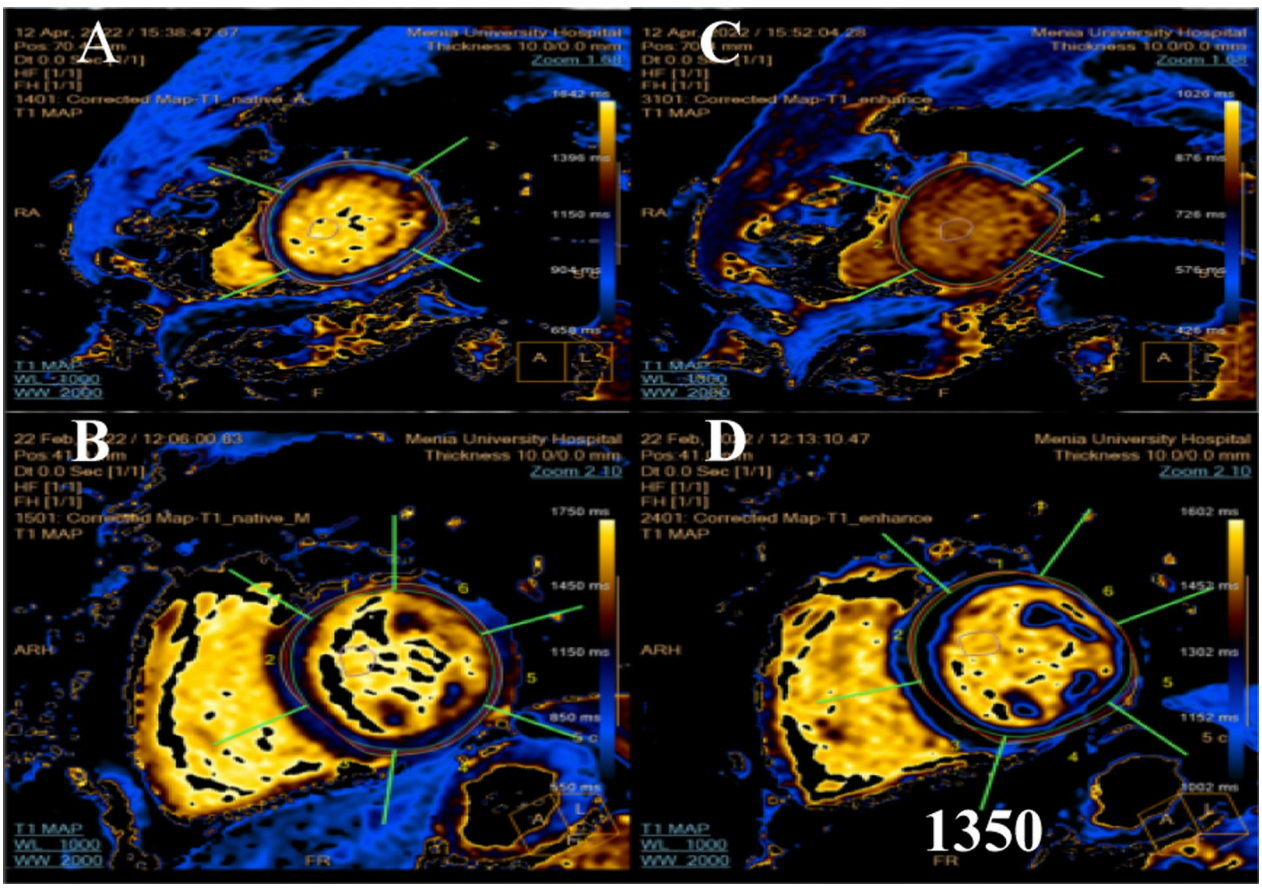


Fig. 3 Pre-contrast (**A**, **B**) and post-contrast (**C**, **D**) T1 mapping images at the apical (**A** and **C**), mid-ventricular (**B** and **D**) levels [second follow-up CMR] showing elevated T1 values

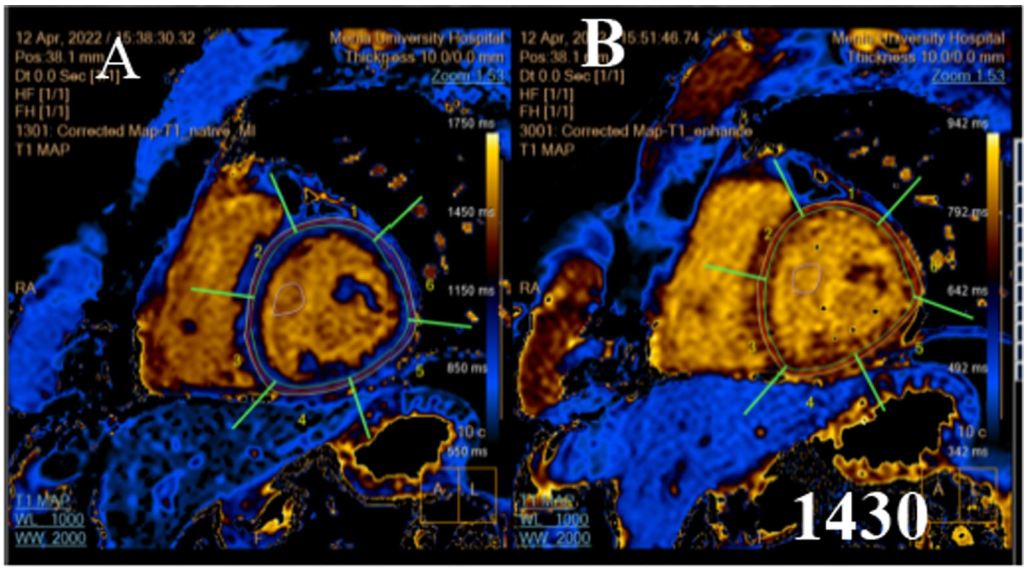
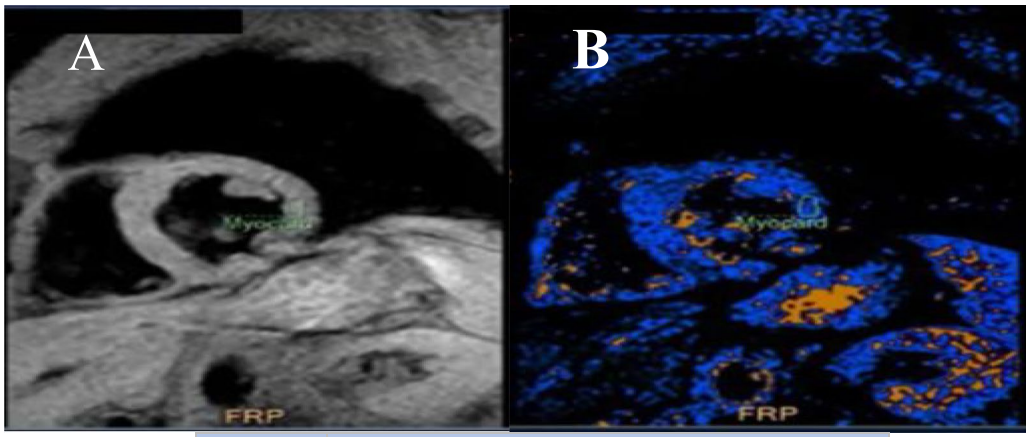


Fig. 4 Pre-contrast (**A**) and post-contrast (**B**) T1 mapping images at the mid-ventricular level [second follow-up CMR] show elevated T1 values



C	T2 Mapping Local Results
	Myocardial T2
T2	60.5± 2.4 ms
R2	30.5 ±10.4 Hz
ROI Area	55.0 mm^2
Filed strength	1.5 T

Fig. 5 T2 mapping sequence of the same case shows elevated T2 values (**A**), short-axis dark blood radial bSSFP at mid-ventricular level (**B**) corresponding T2 color mapping (**C**) T2 mapping values [at second CMR follow-up]

Table 2 Changes in functional parameters by CMR versus echo for all enrolled patients

	CMR		Echo		*P* value
	First follow-up	Second follow-up	First follow-up	Second follow-up	
LVFF	49 ± 5.6	42 ± 5.5	65 ± 4.2	45 ± 5.3	First: 0.005* Second: 0.109
LVEDV	97 ± 10	118 ± 14	68 ± 5	77 ± 6.3	First: > 0.99 Second: > 0.99
LVESV	45 ± 5.7	53 ± 6.2	30 ± 5	37 ± 2.2	First: < 0.001* Second: < 0.001*

Data expressed as mean + SD & median (IQR); p, probability; * significance < 0.05

Table 3 Changes of myocardial tissue characterization for all enrolled patients

	T2 value	ECV apex	ECV mid	ECV base	T1 value
Baseline	51.9 + 2.40	0.23 + 0.01	0.23 + 0.01	0.23 + 0.01	1100 + 25
Mean SD Range	48.4–55.4	0.21–0.25	0.21–0.25	0.21–0.25	49–65.25
First follow-up	53.5 + 4.59	0.26 + 0.04	0.25 + 0.03	0.26 + 0.04	1250 + 60
Mean SD Range	48.4–67.4	0.21–0.35	0.21–0.37	0.21–0.38	50.25–66.38
Second follow-up	55.5 + 5.28	0.30 + 0.03	0.29 + 0.03	0.29 + 0.04	1500 + 50
Mean SD Range	48.4–67.4	0.24–0.39	0.23–0.37	0.23–0.39	52.23–64.39

may provide early diagnosis and prevention of chemotherapy-related cardiovascular complications through allowing early use of different cardioprotective measures [28, 29].

Recently, a significant increase in cancer survivors has been observed but with an increased risk of premature cardiac disease. The cardiotoxic effect of cancer chemotherapy is not the only reason for this observation but also the overlap in risk factors for cancer and CV disease [27, 30]. Therefore, the use of cardiac imaging with this group of patients is increasingly important for early recognizing and preventing complications that occur after treatment with cancer chemotherapy [31]. However, the detection of chemotherapy-related cardiotoxicity is still challenging, mainly because of the length of the period, during which cardiac dysfunction may occur as well as the frequent absence of clinical symptoms. Moreover, the currently used definition of CTRCD depends mainly on the changes of LVEF, which on the one hand does not demonstrate the early cardiotoxic changes and on the other hand is mainly measured by echocardiography, which has several limitations [32].

Although 2D TTE is still considered the standard cardiac imaging modality, because of its availability, low cost and absence of ionizing radiation, it does not achieve the accuracy of CMR in the measurement of cardiac function due to the underestimation of LV volumes together with its lower spatial resolution and hence its lower reproducibility [33].

Our study shows normal ranges at baseline examination but reduced parameters at the follow-up mainly the second one in comparison with early detection of reduced LV parameters by CMR.

Cardiac magnetic resonance imaging (CMR) is the gold standard for the noninvasive assessment of LV volumes and LVEF and playing an important role as a part of the multimodality imaging for better diagnosis of cardiotoxicity and understanding the mechanism of CRCD. Thus, CMR can evaluate changes over time in morphological, functional and tissue characterization parameters so detect early myocardial affection [30, 34].

During follow-up of the chemotherapy included in this study, the LVEF tended to decrease at 2 months, followed by a significant reduction at 4 months after initiation of chemotherapy. This finding is consistent with another study conducted on breast cancer patients treated with trastuzumab and also found that the LVEF started to decrease at 3 months, followed by a significant reduction at 6 months after initiation of therapy [35].

CMR allows myocardial tissue characterization through the use of recent myocardial T1 and T2

mapping techniques. They allow quantitative assessment of diffuse myocardial tissue alteration [36].

An increased native T1 indicates the presence of diffuse myocardial fibrosis and edema. An increased T2 is useful for the diagnosis of acute inflammatory processes such as myocarditis [37].

Our study analyzed T1 and T2 mapping CMR in breast cancer patients treated by chemotherapy (Herceptin) trastuzumab. Furthermore, the predictive value of CMR for early identification of CTRCD was analyzed.

The tissue characterization parameters (native T1 and T2 maps) showed significant elevation among our cohort of patients during second follow-up after initiation of chemotherapy. The elevation in native T1 map at 4 months was also reported by Haslbauer et al., who reported a significant elevation in native T1 map within 4 months after initiation of chemotherapy and remained elevated until > 12 months. The same group found also a significant elevation in T2 map within 4 months after initiation of chemotherapy which was followed by later recovery. They assumed that native T1 map is the most effective predictor of chemotherapy-induced cardiotoxicity, while T2 map is considered the second valid predictor of early cardiotoxicity [38]. This observation is similar to our findings, as we found significant elevation in T2 map after 4 months among breast cancer patients.

Our study confirms and extends the knowledge about the value of T2 and T1 to detect chemotherapy-related myocardial injury. Interestingly, we found a more pronounced increase in T1 compared to T2 in our patients with chemotherapy. This finding is most likely related to the fact that we performed the first follow-up CMR 2 months after chemotherapy initiation, which was followed by 4-month follow-up, whereas Galán-Arriola et al. performed weekly CMR [39]. We presume that we imaged the patients at a later time point of myocardial injury when T2 had already normalized, but T1 was still elevated. Similar to Galán-Arriola et al., we observed that the T1 increase was paralleled by a LV dysfunction quantified by reduction of LVEF.

Myocardial fibrosis due to collagen deposition from acute or chronic disease is associated with several forms of cancer treatment, including the administration of anthracycline chemotherapy and trastuzumab. Increases in interstitial fibrosis can impair both LV diastolic and systolic function. Pathological myocardial fibrosis due to cancer therapy tends to be diffuse [40], while LGE may detect focal areas of myocardial fibrosis. Quantitative assessment of interstitial myocardial fibrosis using mapping techniques shows increased native T1 and extracellular volume (ECV) fraction measures. ECV fraction measures are obtained by acquiring T1 assessments before and after GBCA administration and accounting for heart rate and serum hemoglobin [41].

In our study, diffuse myocardial fibrosis could be detected at each follow-up by calculating ECV fraction at basal, mid-ventricular and apical segments. We found significant ECV fraction elevation at the apical segments at first follow-up, but significant elevation at more and variable LV segments at second follow-up 4 months post-chemotherapy initiation compared to the baseline study. This is matched with Muehlberg et al. found; ECV was higher at the end of chemotherapy than at baseline and 48 h after the first dose of anthracyclines, because of the loss in LV mass [42]. In the animal model proposed by Hong et al., no detectable changes in LVEF and native T1 were observed after 6 weeks, while ECV changed significantly within the first three weeks. Therefore, ECV could serve as an early marker of myocardial damage [43].

In a study of women with breast cancer treated with anthracyclines ± trastuzumab, the presence of myocardial edema was demonstrated through T2 mapping in 49% of the sample from 1 to 4 months after the start of therapy [44]. Our study shows similar results with elevated T2 values gradually from first to second follow-up. The values of T2 mapping are sensitive to myocardial edema which may be represented early before elevation of T1 mapping and ECV values.

The pattern, incidence and prognostic significance of LGE in patients receiving chemotherapeutic agents are not matching between the degree of cardiac toxicity and dose of therapeutic regimen. One group was studied by retrospective and prospective methods shows that the presence of LGE in the context of established cardiomyopathy in patients during and at end of therapy with anthracyclines and trastuzumab with no significant interval changes among follow-ups [45, 46].

The pattern of LGE shows different non-specific patterns include subepicardial or myocarditis-like, and the incidence ranged between 94 and 100%. A study included 10 patients with non-Hodgkin lymphoma, showed new or progressive midmyocardial LGE in 30% of patients 3 months after fulfillment of therapy which represent early myocardial damage, while preserved LVEF [47].

Limitations of study

Limitations of the study include the small sample size and short follow-up duration. Therefore, studies with larger cohorts and longer follow-up are recommended for the validation of our findings.

Conclusion

Echocardiography is mandatory as a guideline in evaluation of the cardiac function before the initiation of the chemotherapeutic regimen of breast cancer patients and

follow-up as an available widespread non-cost diagnostic tool. But the early prediction of the cardiotoxic effects of the chemotherapy by T1 and T2 mapping will guide the management, planning and the outcome of the patient life.

Abbreviations

ACE	Angiotensin-converting enzyme
CMR	Cardiac magnetic resonance
CTRCD	Cancer therapy-related cardiac dysfunction
ECV	Extracellular volume
EF	Ejection fraction
GBCA	Gadolinium-based contrast agent
HER-2	Human epidermal growth factor II
LGE	Late gadolinium enhancement
MRI	Magnetic resonance imaging
TTE	Trans-esophageal echocardiography
3D	Three dimensional

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Author contributions
MAM was involved in writing, revision and editing. ASE was involved in revision and editing. AFZ was involved in data collection and statistics. TEE was involved in data collection and writing. MFA was involved in writing and editing. All authors have read and approved the manuscript.

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Availability of data and materials
The data are available on a reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional review board of the Faculty of Medicine, Minia University, Egypt.

Consent for publication
Written informed consent was obtained from all subjects (patients) in this study.

Competing interests
The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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