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Usefulness of cardiac magnetic resonance for early detection of cancer therapeutics-related cardiac dysfunction in breast cancer patients

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ABSTRACT

Background: Prognosis of breast cancer patients has been improved along with the progress in cancer therapies. However, cancer therapeutics-related cardiac dysfunction (CTRCD) has been an emerging issue. For early detection of CTRCD, we examined whether native T1 mapping and global longitudinal strain (GLS) using cardiac magnetic resonance (CMR) and biomarkers analysis are useful.

Methods: We prospectively enrolled 83 consecutive chemotherapy-naïve female patients with breast cancer (mean age, 56 ± 13 yrs.) between 2017 and 2020. CTRCD was defined based on echocardiography as left ventricular ejection fraction (LVEF) below 53% at any follow-up period with LVEF>10% points decrease from baseline after chemotherapy. To evaluate cardiac function, CMR (at baseline and 6 months), 12-lead ECG, echocardiography, and biomarkers (at baseline and every 3 months) were evaluated.

Results: A total of 164 CMRs were performed in 83 patients. LVEF and GLS were significantly decreased after chemotherapy (LVEF, from 71.2 ± 4.4 to 67.6 ± 5.8%; GLS, from −27.9 ± 3.9 to −24.7 ± 3.5%, respectively, both $P < 0.01$). Native T1 value also significantly elevated after chemotherapy (from 1283 ± 36 to 1308 ± 39 msec, $P < 0.01$). Among the 83 patients, 7 (8.4%) developed CTRCD. Of note, native T1 value before chemotherapy was significantly higher in patients with CTRCD than in those without it (1352 ± 29 vs. 1278 ± 30 msec, $P < 0.01$). The multivariable logistic regression analysis revealed that native T1 value was an independent predictive factor for the development of CTRCD [OR 2.33; 95%CI 1.15–4.75, $P = 0.02$].

Conclusions: These results indicate that CMR is useful to detect chemotherapy-related myocardial damage and predict for the development of CTRCD in breast cancer patients.

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1. Introduction

Breast cancer is one of the most frequent cancers [1]. However, the prognosis of breast cancer patients has been improved along with the progress in cancer therapies, inevitably resulting in a large population of long-term survivors [2]. Some breast cancer patients who are at a certain risk of relapse require receiving chemotherapy including anthracycline and/or HER2 inhibitors [3]. However, these anti-cancer drugs sometimes cause cardiac dysfunction, namely cancer therapeutics-related cardiac dysfunction (CTRCD) and subsequent cardiac adverse events including heart failure after chemotherapy [4,5]. Furthermore, early detection and robust treatment of CTRCD are important for the improvement of left ventricular (LV) function [6,7]. Thus, in the setting of progressive increase in cancer-survivors, the predictive factors of CTRCD are needed.

Cardiac magnetic resonance (CMR) imaging is one of the gold standard imaging modalities to evaluate cardiac function with a significant impact on management of heart failure patients [8]. Especially, parametric mapping is useful to non-invasively detect myocardial edema and fibrosis, and has been reported to predict mortality in various cardiac diseases [9–11]. In the field of cardio-oncology, the usefulness was previously reported for early detection of myocardial change after chemotherapy and/or radiation therapy [12–15]. CMR may be potentially the early marker of chemotherapy-induced cardiac damage, however, these studies have several limitations including the insufficiency of pre-treatment and longitudinal assessment, and use of multiple chemotherapeutic regimes for various cancer. Furthermore, there are few clinical data regarding the usefulness of native T1 value for prediction of CTRCD [16,17].

Thus, we hypothesized that CMR is useful for prediction of CTRCD, and performed this prospective study with comprehensive cardiac assessments including CMR in breast cancer patients.

2. Methods

2.1. Human studies

This study was conducted following the ethical principles in the Declaration of Helsinki and the protocol was approved by the Ethics Committee of our institution (No.2017–1-866). All participants provided a written informed consent.

2.2. Study protocol

Fig. 1 shows the study flowchart in this study. We prospectively screened 214 consecutive breast cancer patients who visited out-patient cardio-oncology clinic at our institution to evaluate cardiac function before chemotherapy between August 2017 and March 2020. Of those, we excluded the patients with heart disease (cardiomyopathy, valvular heart disease, and ischemic heart disease), or previous chemotherapy for any cancer. Finally, we enrolled 83 chemotherapy-naïve female patients (mean age 56 years; range, 28–82 years) who were assessed for their cardiac function with cardiac MRI and completed 12 months follow-up. To evaluate their cardiac function, echocardiography, high-sensitive cardiac troponin T (Elecsys high-sensitive Troponin T, Roche Diagnostics GmbH, Rotkreuz, Switzerland) (hs-cTnT), and B-type natriuretic peptide (the Alinity i system, Abbott Laboratories, Illinois, USA) (BNP) were assessed every 3 months (at Visit 1–5). Moreover, cine and parametric mapping were also acquired using CMR (at Visit 1 and 3) (Fig. 2).

2.3. MRI acquisition protocol

All MRI examinations were performed by using a 3.0 T whole-body MR scanner (Ingenia 3.0 T, Phillips Healthcare, Best, the Netherlands). Imaging protocols included MRI with cine and parametric maps (pre- and post-contrast T1 maps, and T2 map). Cine images were acquired at 25 frames per slice per beat in short-axis, long-axis (2-chamber and 4-chamber views). Post-contrast T1 mapping were acquired 10 min after 0.1 mmol/kg × body weight (kg) of gadolinium-based contrast agent (Gadovist, Bayer Vital GmbH, Leverkusen, Germany) administration. All T1 maps were acquired using a modified Look-Locker inversion recovery (MOLLI) sequence [18]. Details of the CMR parameters are provided in Table S1. According to the recommendation of Society for Cardiovascular Magnetic Resonance, we recruited 18 female control subjects (mean age 49 years; range, 26–76 years) without heart disease or malignancy, and their CMR images were acquired using the same scanner and protocol in order to establish normative values of parametric mappings [19].

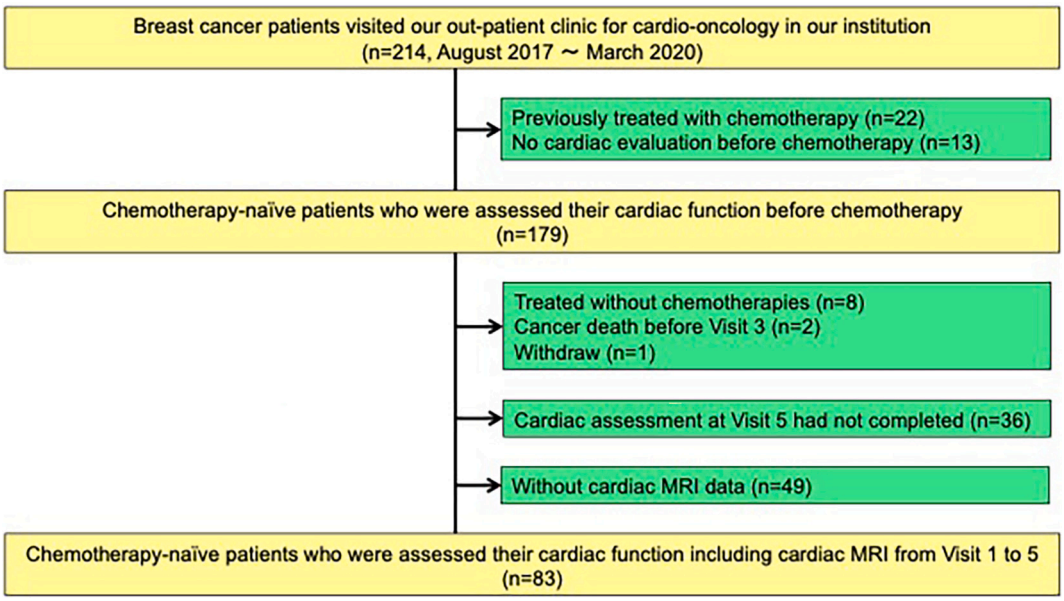

Fig. 1. Patients flow chart.
MRI = magnetic resonance imaging.

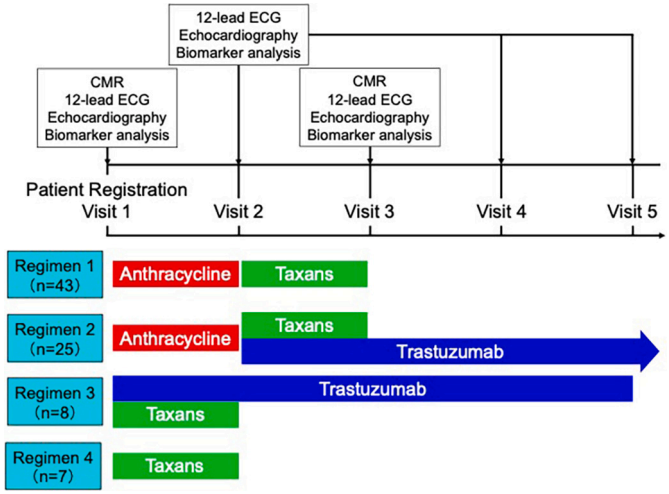

Fig. 2. Study protocol.
CMR (at Visit 1 and 3), echocardiography, 12-lead ECG, and high-sensitive cardiac troponin T, and BNP (at Visit 1 to 5) were assessed.
CMR = cardiac magnetic resonance; ECG = electrocardiogram; Visit 1 = baseline; Visit 2–5 = 3,6,9, and12 months after initiation of chemotherapies, respectively.

2.4. CMR image analysis

We analyzed all CMR images by using a commercially available workstation (Vitrea; Canon Medical Systems, Otawara, Japan). Volumetric, strain, and parametric mapping analyses were performed by 2 blinded reviewers independently. We obtained LVEF, LV end-diastolic volume index, LV end-systolic volume index, stroke volume index, and cardiac index from the short-axis cine images stacks. Feature tracking for strain analysis was performed using the same workstation. In radial and circumferential strain, epi- and endocardial contours of LV short-axis cine images were automatically detected. In longitudinal strain analysis, epi- and endocardial contours of LV long-axis cine images were drawn at end-diastolic phase manually and propagated automatically. After automatic tracking, 1st reviewer adjusted contours, and then 2nd reviewer modified contours, if necessary, under consensus reading. When we measured T1 and T2 value in myocardium and in blood using pre- and post-contrast T1 and T2 mapping (T1 myo-pre, T1 myo-contrast, T1 blood-pre, and T1 blood-contrast, respectively), regions of interest to evaluate parametric mapping were >100 mm2 and placed on mid-ventricular septum. Extracellular volumes were calculated by using the following formula; (1-hematocrit) × (1/T1 myo-contrast - 1/T1 myo-pre) / (1/T1 blood-contrast - 1/T1 blood-pre) [20].

2.5. Echocardiography acquisition

All echocardiographic images were acquired by experienced cardiologists and sonographers, using the commercially available ultrasound system (Philips EPIQ 7, Philips Healthcare, Best, the Netherland) with standard acquisition. All measurements of standard echocardiographic parameters were quantified according to the recommendations of the American Society of Echocardiography [21]. LVEF was calculated using Biplane Disk Summation. These measurements were made in the apical four- and two-chamber views at end-diastole and end-systole, respectively. The endocardial tracing was completed manually, and LV volume and ejection fraction were calculated automatically. Images for 2-dimensional speckle-tracking were acquired in the DICOM format using a frame rate of 50 fps. The data were transferred for off-line analysis (Tomtec 2D Cardiac Performance analysis; TomTec Imaging Systems, Munich, Germany) for GLS using a semi-automatic algorithm on the software platform. Strain analysis was performed by 2 blinded reviewers independently, one cardiologist and one cardiac sonographer (Y.T. and J.F, with 10 and 16 years of experience, respectively). Quantitative measurements were performed in a blinded manner.

2.6. Clinical outcomes and follow-up

The primary outcome was the development of CTRCD defined as a decrease in LVEF >10% points and to a value <53% in LVEF measured by echocardiography at any visit during the study period [22,23]. Furthermore, the predictive parameters for CTRCD were investigated. Temporal changes in clinical data and difference in myocardial damage among anti-cancer drugs were also evaluated. Follow-up visits were planned every 3 months (Visit 2–5) and completed 12-months follow-up (Fig. 2).

2.7. Statistical analysis

All statistical analyses were performed with JMP® Pro 14.2.0 (SAS Institute Inc., Cary, NC, USA). No power analysis was performed because of the lack of previous studies on this topic. Continuous variables are presented as means±standard deviations or medians with interquartile range. Continuous variables were compared by Welch's *t*-test and categorical variables were presented as numeral with percentage and were compared by the Fisher's exact test. Biomarker levels were log-transformed to normalize their distribution. Group comparisons for continuous variables were performed by the Kruskal-Wallis test for multiple groups. The temporal changes in clinical data from Visit 1 to 5 were compared by Bonferroni-corrected paired *t*-tests using the data at Visit 1 as reference. Univariable and multivariable logistic regression was used to determine variables associated with CTRCD. Missing values at completely at random were addressed using pairwise deletion methods. Two-sided *P*-value of <0.05 was considered as statistically significant.

3. Results

3.1. Patient characteristics

We finally included 83 consecutive chemotherapy-naïve breast cancer patients (all female, mean age 56; range 28–82 years) who were scheduled for chemotherapy. All of them completed 12 months follow-up (Visit 1 to 5). Baseline characteristics are summarized in Table 1. Some patients received beta-blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers for their hypertension. There were no differences in breast cancer laterality, and 81.9% of patients received anthracycline drugs at the cumulative dose of 280 (IQR 240, 280) mg/m^2, and 20.1% of patients received anthracycline followed by sequential trastuzumab.

3.2. CMR parameters

A total of 164 CMRs were performed in 83 patients. One patient could not use contrast agents because of her known allergy, so only native T1 value, T2 value, and cine were available in this patient. Another one with artificial joint was unable to undergo 3.0 T MRI. Thus, in this patient, only cine images were acquired using a 1.5T scanner. CMR at Visit 3 could not be performed in 2 patients due to their general condition. Finally, a total of 164 CMRs (83 CMRs at Visit 1 and 81 at Visit 3) were performed in 83 patients. As shown in Table S2, the CMR data of the breast cancer patients were compared with control subjects. Native T1 and T2 value before chemotherapy were significantly elevated compared with the control subjects (1283 ± 36 vs. 1257 ± 32, $P < 0.01$; 46.5 ± 2.5 vs. 44.8 ± 1.1, $P < 0.01$, respectively). Table 2 shows the temporal changes in CMR data in the breast cancer patients. The volumetric analysis showed significant changes in LVEF and LV end-systolic and end-diastolic volume index after chemotherapy. The decreases in

Table 1
Baseline clinical characteristics.

	Overall (n = 83)	CTRCD (n = 7)	Non-CTRCD (n = 76)	P value
Age, yrs.	55.7 ± 12.6	50.4 ± 9.9	56.1 ± 12.8	0.19
Female, n(%)	83 (100)			
Body mass index, kg/m^2	23.5 ± 4.3	21.7 ± 3.5	23.6 ± 4.3	0.22
Creatinine, mg/dL	0.61 ± 0.11	0.62 ± 0.07	0.61 ± 0.11	0.66
LDL cholesterol, mg/dL	115.7 ± 34.7	110.3 ± 62.5	116.1 ± 32.7	0.86
HbA1c, %	5.9 ± 1.4	5.9 ± 0.9	5.9 ± 1.4	0.89
High-sensitive Cardiac troponin T, ng/mL	0.005 [0.003, 0.007]	0.004 [0.003, 0.005]	0.005 [0.003, 0.007]	0.07
BNP, pg/mL	15.9 [8.5, 23.8]	16.8 [12.0, 51.7]	15.4 [7.9, 23.7]	0.34
Cardiovascular risk factors				
Hypertension, n(%)	29 (34.9)	4 (57.1)	25 (32.9)	0.23
Dyslipidemia, n(%)	20 (24.1)	2 (28.6)	18 (23.7)	0.67
Diabetes mellitus, n (%)	12 (14.5)	2 (28.6)	10 (13.2)	0.27
Current or ex-smoker, n(%)	14 (16.9)	2 (28.6)	12 (15.8)	0.34
Medication				
Beta-blocker, n(%)	3 (3.6)	1 (14.3)	2 (2.6)	0.23
RAS inhibitors, n(%)	12 (14.5)	1 (14.3)	11 (14.5)	>0.99
Statins, n(%)	10 (12.1)	0 (0.0)	10 (13.2)	0.59
Diuretics, n(%)	1 (1.2)	0 (0.0)	1 (1.3)	>0.99
Breast cancer				
Left side, n(%)	40 (48.2)	5 (71.4)	35 (46.1)	0.25
Early stage, n(%)	61 (73.5)	6 (85.7)	55 (72.4)	0.67
Breast cancer therapy				
Surgery, n(%)	79 (95.2)	7 (100)	72 (94.7)	>0.99
Radiation therapy, n (%)	62 (75.6)	6 (85.7)	56 (74.7)	>0.99
Endocrine therapy, n (%)	49 (59.8)	5 (71.4)	44 (58.7)	0.70
Neoadjuvant, n(%) / Adjuvant, n(%)	39 (49.4) / 40 (50.6)	5 (71.4) / 2 (28.6)	34 (47.2) /38 (52.8)	0.26
AC, n(%)	68 (81.9)	7 (100)	61 (80.3)	0.34
AC regimen, n(%) / FEC regimen, n(%)	17 (25.0) / 51 (75.0)	3 (42.9) / 4 (57.1)	14 (23.0) / 47 (77.0)	0.35
AC dose, mg/m^2	280 [240, 280]	280 [240, 280]	280 [246, 280]	0.27
Tmab, n(%)	33 (39.8)	2 (28.6)	31 (40.8)	0.70
AC + Tmab, n(%)	25 (30.1)	2 (28.6)	23 (30.3)	>0.99

Results are expressed as mean ± SD, median (interquartile range), or n (%). Comparison between patients with CTRCD and those without CTRCD (P < 0.05) is considered significant.
AC, anthracycline; BNP, B-type natriuretic peptide; CTRCD, cancer therapeutics-related cardiac dysfunction; HbA1c, hemoglobin A1c; LDL cholesterol, low density lipoprotein cholesterol; RAS, renin-angiotensin-aldosterone system; Tmab, trastuzumab.

each strain parameter after chemotherapy were also significant. Furthermore, parametric mapping variables were significantly elevated after chemotherapy especially in patients with elevation in hs-cTnT, but not in those without (Figs. S1 and S2).

3.3. Development of CTRCD

Among the 83 patients, 7 (8.4%) developed CTRCD during the follow-up period, and almost all CTRCDs developed after Visit 3 (Table S3, Fig. 3). The baseline characteristics were comparable between the patients who developed CTRCD (CTRCD group) and those who did not (non-CTRCD group) (Table 1). There were no significant differences in baseline characteristics, such as age, BMI, comorbidity, and medication. Furthermore, breast cancer therapy was comparable between the 2 groups. All the patients with CTRCD had received anthracycline. All the patients with CTRCD were asymptomatic and were treated with beta-blockers and/or angiotensin converting enzyme inhibitors and their LVEF improved within 6 months. Fortunately, they

Table 2
Temporal changes in cardiac MRI data during follow-up.

	Visit 1 (n = 83)	Visit 3 (n = 81)	P value
Volumetric analysis			
LVEF, %	71.2 ± 4.4	67.6 ± 5.8	<0.01
LVEDVi, mL/m^2	61.4 ± 11.7	65.7 ± 13.1	<0.01
LVESVi, mL/m^2	17.8 ± 4.9	21.5 ± 7.0	<0.01
SVi, mL/m^2	43.6 ± 8.0	44.1 ± 8.2	0.70
CI, L/min/m^2	3.0 ± 0.6	3.2 ± 0.7	0.06
LV mass index, g/m^2	43.9 ± 8.3	44.4 ± 7.5	0.40
Strain analysis			
LV GLS, %	−27.1 ± 3.9	−24.7 ± 3.5	<0.01
LV GRS, %	71.5 ± 20.2	64.0 ± 21.3	<0.01
LV GCS, %	−20.6 ± 2.8	−19.5 ± 3.1	<0.01
RV GLS, %	−33.8 ± 5.7	−31.6 ± 5.4	<0.01
Tissue imaging analysis			
Native T1 value, msec	1283 ± 36	1308 ± 39	<0.01
T2 value, msec	46.4 ± 2.5	47.8 ± 2.6	<0.01
ECV fraction, %	30.7 ± 5.4	31.7 ± 3.0	<0.01

All results are expressed as mean ± SD or n (%). CI, cardiac index; ECV fraction, extra cellular volume fraction; LVEDVi, left ventricular end-diastole volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systole volume index; LV GCS, left ventricular global circumferential strain; LV GLS, left ventricular global longitudinal strain; LV GRS, left ventricular global radial strain; RV GLS, right ventricular global longitudinal strain; SVi, stroke volume index.

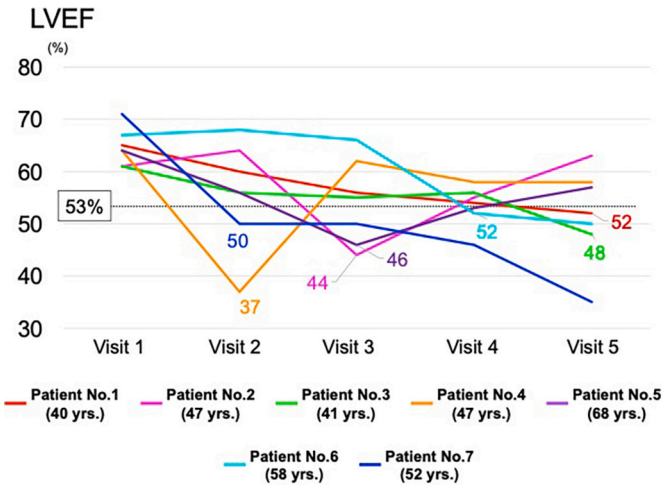

Fig. 3. Temporal changes in LVEF in patients with CTRCD.
Among the 83 patients, 7 (8.4%) developed CTRCD during the follow-up period.
CTRCD = cancer therapeutics-related cardiac dysfunction, LVEF = left ventricular ejection fraction.

completed planned chemotherapy as originally scheduled. Additionally, several cardiac adverse events except LV dysfunction were noted during the follow-up period (Table S4). Although it was unclear whether any events were related to chemotherapies, additional cardiac therapies were required in those patients. Especially, chemotherapy was interrupted during medical therapy for arrhythmia in the patient with the development of ventricular tachycardia.

As shown in Table 3, the comparison was made for various parameters at Visit 1 and 2 between the patients with and those without CTRCD. Of note, native T1 and T2 values at Visit 1 in the CTRCD group were significantly elevated compared with the non-CTRCD group (1352 ± 29 vs. 1278 ± 30, $P < 0.01$; 49.8 ± 3.1 vs. 46.1 ± 2.2, $P = 0.03$, respectively) (Fig. 4). The significant diference in native T1 value remained to after chemotherapy (at Visit 3) (1341 ± 25 vs. 1304 ± 38, $P < 0.01$). Furthermore, in the CTRCD group, serum levels of hs-cTnT, but not BNP at Visit 2, were significantly elevated compared with the

Table 3
Comparison of various parameters at Visit 1 and 2 (CMR at Visit 3) between patients with and those without CTRCD.

	Visit 1		P value	Visit 2 (CMR at Visit 3)		P value
	CTRCD	Non-CTRCD		CTRCD	Non-CTRCD	
Biomarkers						
High-sensitive Cardiac troponin T, ng/mL	0.004 (0.003, 0.005)	0.005 (0.003, 0.007)	0.07	0.033 (0.023, 0.037)	0.015 (0.009, 0.022)	<0.01
BNP, pg/mL	16.8 (12.0, 51.7)	15.4 (7.9, 23.7)	0.33	23.5 (9.4, 54.8)	12.7 (7.0, 21.5)	0.26
12-lead ECG						
Heart rate, beats per minutes	73.9 ± 6.9	69.9 ± 11.0	0.21	79.4 ± 9.8	77.4 ± 11.3	0.63
PR interval, msec	156 ± 28	158 ± 21	0.82	150 ± 27	159 ± 21	0.44
Corrected QT interval, msec	437 ± 29	432 ± 20	0.63	457 ± 30	436 ± 20	0.12
Echocardiography						
LVDd, mm	45 ± 4.5	44.8 ± 3.6	0.89	48.7 ± 3.8	45.0 ± 4.2	0.04
LVDs, mm	29.9 ± 4.5	28.3 ± 2.7	0.40	33.1 ± 3.6	29.1 ± 3.3	0.02
LVEF, %	64.7 ± 3.5	67.6 ± 4.4	0.08	55.9 ± 10.2	64.0 ± 4.1	0.08
LAVI, mL/m^2	25.3 ± 4.4	26.5 ± 6.6	0.52	28.2 ± 10.6	28.0 ± 7.6	0.96
E/e'	7.61 ± 2.2	7.91 ± 2.4	0.74	8.13 ± 3.0	7.84 ± 2.1	0.81
RVFAC, %	45.5 ± 6.7	45.8 ± 4.4	0.93	44.4 ± 6.4	44.9 ± 5.0	0.83
GLS, %	−18.9 ± 1.1	−20.3 ± 2.5	0.02	−18.0 ± 2.8	−19.6 ± 2.7	0.19
CMR						
Heart rate, beats per minutes	77.4 ± 9.4	69.0 ± 9.3	0.12	70.2 ± 5.5	71.5 ± 9.1	0.65
LVEF, %	66.1 ± 4.0	71.7 ± 4.2	0.02	58.8 ± 6.7	68.5 ± 4.9	0.02
LVEDVi, mL/m^2	64.7 ± 12.7	61.1 ± 11.7	0.52	74.1 ± 21.1	64.9 ± 12.0	0.34
LVESVi, mL/m^2	22.1 ± 5.3	17.4 ± 4.7	0.09	31.1 ± 11.3	20.5 ± 5.7	0.07
SVi, mL/m^2	42.6 ± 7.9	43.7 ± 8.1	0.77	43.1 ± 11.2	44.2 ± 8.0	0.82
CI, L/min/m^2	3.3 ± 0.6	3.0 ± 0.6	0.31	3.1 ± 0.8	3.2 ± 0.7	0.78
LV mass index, g/m^2	52.3 ± 16.9	43.0 ± 6.7	0.24	54.8 ± 14.4	43.3 ± 5.6	0.11
LV GLS, %	−22.3 ± 3.9	−27.4 ± 3.6	0.04	−20.1 ± 1.6	−25.1 ± 3.3	<0.01
LV GCS, %	−18.4 ± 1.9	−20.8 ± 2.8	0.04	−14.3 ± 2.3	−19.9 ± 2.8	<0.01
LV GRS, %	53.8 ± 7.6	73.0 ± 20.2	<0.01	40.7 ± 9.9	66.0 ± 20.8	<0.01
RV GLS, %	−31.7 ± 4.5	−34.0 ± 5.8	0.33	−28.5 ± 2.9	−31.9 ± 5.5	0.05
Native T1 value, msec	1352 ± 29	1278 ± 30	<0.01	1341 ± 25	1304 ± 38	<0.01
T2 value, msec	49.8 ± 3.1	46.1 ± 2.2	0.03	49.2 ± 2.9	47.6 ± 2.5	0.20
ECV fraction, %	33.5 ± 3.1	30.1 ± 3.6	0.11	34.1 ± 5.1	31.6 ± 2.8	0.34

Results are expressed as mean ± SD, median (interquartile range), or n (%). Various Parameters (at Visit 1 and 2) are shown in Table 3, and follow-up CMR data (at Visit 3) was shown exceptionally.
12-lead ECG, 12-lead electrocardiogram; BNP, B-type natriuretic peptide; CI, cardiac index; CTRCD, cancer therapeutics-related cardiac dysfunction; ECV fraction, extra cellular volume fraction; GLS, global longitudinal strain; LAVI, left atrial volume index; LVEDVi, left ventricular end-diastole volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systole volume index; LV GCS, left ventricular global circumferential strain; LV GLS, left ventricular global longitudinal strain; LV GRS, left ventricular global radial strain; RVFAC, right ventricular fractional area change; SVi, stroke volume index.

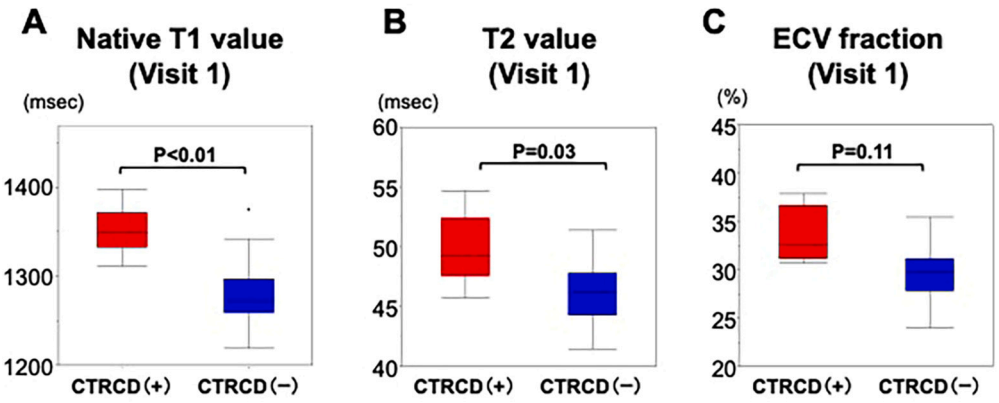

Fig. 4. The comparison of parametric mapping before chemotherapy between the patients with and without CTRCD.
The results of parametric mapping before chemotherapy in the CTRCD and the non-CTRCD groups are shown in red and blue box plot, respectively. Native T1 value before chemotherapy in the CTRCD group were significantly elevated compared with the non-CTRCD group.
(panel A = Native T1 value (at Visit 1); panel B = T2 value (at Visit 1); and panel C = ECV fraction (at Visit 1), respectively). CTRCD = cancer therapeutics-related cardiac dysfunction; ECV = extracellular volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

non-CTRCD group (0.033[0.023–0.037] vs. 0.015[0.009–0.022] ng/mL, $P < 0.01$; 23.5[9.4–54.8] vs. 12.7[7.0–21.5] pg/mL, $P = 0.26$, respectively).

3.4. Predictive factors for CTRCD

To investigate the predictive factors for the development of CTRCD, univariable logistic regression analysis using variables at Visit 1 was performed (Table S5). Table 4 shows variables associated with a P value of <0.05 in univariable logistic regression analysis and native T1 and T2 value before chemotherapy were significant variables [Odds ratio (OR) 2.03; 95% confidence interval (CI) 1.26–3.26, P < 0.01, OR 1.86; 95%CI 1.19–2.90, P < 0.01, respectively]. Regarding cardiac structure at visit 1, LV end-systolic volume index and LV mass index were also significant [OR 1.23; 95%CI 1.01–1.50, $P = 0.04$, OR 1.10; 95%CI 1.00–1.22, $P < 0.05$, respectively]. In the systolic function, there was significance only in LV GLS [OR 1.42; 95%CI 1.08–1.86, $P = 0.01$]. Of note, multivariable analysis with stepwise selection revealed that native T1 value was an independent predictive factor for the development of CTRCD [OR 2.33; 95%CI 1.15–4.75, $P = 0.02$]. In the selected study population with patients treated with anthracycline alone ($n = 43$), the results were almost the same (data not shown).

Table 4
Logistic regression analysis associated with the development of CTRCD.

	Univariable analysis		Multivariable analysis	
	Odds ratio [95% Confidence Interval]	P value	Odds ratio [95% Confidence Interval]	P value
Variables at Visit 1				
LVESVi, mL/m^2	1.23 [1.01–1.50]	0.04	1.15 [0.81–1.64]	0.42
LV mass index, g/m^2	1.10 [1.00–1.22]	<0.05		
LV GLS, %	1.42 [1.08–1.86]	0.01		
Native T1 value (per 10 msec), msec	2.03 [1.26–3.26]	<0.01	2.33 [1.15–4.75]	0.02
Native T2 value, msec	1.86 [1.19–2.90]	<0.01		

LVESVi, left ventricular end-systolic volume index; LV GLS, left ventricular global longitudinal strain; hs-cTnT, high-sensitive cardiac troponin T; LVEF, left ventricular ejection fraction.

Furthermore, the combination of native T1 value before chemotherapy (at Visit 1) and cardiac troponin after chemotherapy (at Visit 2) highly predicted CTRCD (Fig. S4).

3.5. Temporal changes in clinical data

Table S6 summarizes the temporal changes in cardiac clinical data. Serum levels of hs-cTnT were significantly elevated after Visit 2 (Fig. S3A), whereas plasma levels of BNP were comparable during the follow-up period. Transient changes in heart rate were also noted, which returned to baseline level at Visit 4. After initiation of chemotherapy, LVEF measured by echocardiography was significantly decreased from Visit 2, although most of them were in the normal range (Fig. S3B).

3.6. Difference in the extent of cardiac damage among chemotherapy drugs

The breast cancer patients were divided into 4 groups by chemotherapy drugs as follows; anthracycline alone, anthracycline and trastuzumab, trastuzumab alone, and other anticancer drugs (Table S7). Elevation in hs-cTnT was noted in the patients treated with anthracycline regimens, but not in those treated without anthracycline regimens. The elevation in native T1 values and extracellular volume fraction after chemotherapies were noted in those treated with anthracycline and trastuzumab regimens. There were no changes in LVEF or the values of parametric mappings in the patients with other anticancer drugs, such as docetaxel or paclitaxel.

4. Discussion

Subsequent cardiac adverse events including CTRCD after chemotherapy deteriorates patients' outcome. Therefore, early detection of subclinical CTRCD is important for cancer management. This prospective study provided three important findings; [1] among the 83 consecutive chemotherapy-naïve breast cancer patients, CTRCD developed in 7 (8.4%), [2] parametric mappings detected myocardial damage after anthracycline, and [3] native T1 value before chemotherapy was an independent predictive factor for the development of CTRCD.

4.1. Limited predictability for CTRCD using GLS or biomarkers analysis

The incidence of CTRCD development in this study (8.4%) was comparable to that in the previous large cohort studies [24–26]. All the patients with CTRCD received anthracycline, and the elevation in hs-cTnT were noted. Although previous studies showed the usefulness of cardiac troponin to predict CTRCD [27,28], hs-cTnT elevation was noted in 51 of 68 (75.0%) patients received anthracycline in this study. Thus, it was difficult to predict CTRCD based on cardiac troponin alone because of its low positive predictive value. Previous studies also showed the usefulness of GLS for early detection of CTRCD and suggested that cut-off value was the relative change in GLS of >15% to detect subclinical myocardial dysfunction [22,29,30]. However, changes in GLS before development of CTRCD was noted in only one (14.2%) among 7 patients who developed CTRCD in this study. Several conditions, such as surgical wound and breast implant, often lead to poor imaging quality and deteriorate the accuracy of GLS analysis [31]. Furthermore, it might be difficult to perform echocardiography at an appropriate phase when reduction was noted only for GLS, but not for LVEF, due to individual differences in the time-course of ventricular dysfunction.

4.2. Detection of chemotherapeutic myocardial damage using parametric mapping

Parametric mapping variables were significantly elevated after anthracycline therapy, suggesting that the development of myocardial injury was caused by the therapy. Anthracycline and trastuzumab are generally recognized to cause CTRCD by distinct mechanisms. Anthracycline causes myocyte death via reactive oxygen species and topoisomerase 2 inhibition, while trastuzumab causes myocyte dysfunction via inhibition of myocyte repair process [32]. Interestingly, in our study, patients treated with both anthracycline and trastuzumab showed the most elevated values in native T1 value, ECV fraction, and LVEF after chemotherapy. This finding was consistent with the clinical practice that the risk of heart failure is increased after anthracycline and trastuzumab compared with anthracycline alone [23,33]. Thus, the imaging biomarkers may reveal the additional myocyte toxicity caused by combination of anticancer drugs. Although the risk of anthracycline-induced CTRCD was dose-dependent, some individuals receiving a lower dose of anthracycline developed CTRCD because of variable susceptibility to anthracycline [32,34]. In this study, dose effect of anthracycline could not be assessed because of a standardized chemotherapy regimen.

4.3. Predictive value for the development of CTRCD

We showed the relationship between elevated native T1 values before chemotherapy and the development of CTRCD. Previous studies showed that elevated native T1 value was related to poor prognosis in various cardiac diseases [16–18]. Importantly, it remained to be an independent risk factor for the development of CTRCD in multivariable analysis. Our study showed similar results in anthracycline-induced cardiomyopathy. However, it is not clearly known why native T1 value elevated in the patients with CTRCD before chemotherapy. Previous studies showed that elevated native T1 value was related to poor prognosis even though in patients with preserved LVEF [35]. Furthermore, in first-degree relatives of patients with HCM who were identified sarcomere–gene mutations, but had no evidence of LVH, native T1 value was higher than healthy control [36]. Thus, it is possible that elevated native T1 value in pre-treatment breast cancer patients without history of cardiovascular disease reflect general risk based on factors which we cannot recognize such as past life-style, underlying myocardial characteristics, susceptibility to anthracycline, and genetic factors. Cardiac evaluation using CMR may provide more predictive information to identify patients at risk for CTRCD. More importantly, combined evaluation of native T1 value before chemotherapy and cardiac troponin T as a biomarker for myocardial damage highly predict CTRCD as shown in Fig. S4. Thus, close follow up using cardiac troponin may be required in patients with elevated native T1 value before chemotherapy. Furthermore, several studies regarding primary prevention for CTRCD using cardioprotective drugs were performed, but no expected results were shown [37,38]. Risk stratification strategy using native T1 value before chemotherapy may be useful for primary prevention for CTRCD using cardioprotective drugs.

4.4. CMR acquisition and analysis

Although accuracy of CMR measurements is generally better than that of echocardiography, the definition of CTRCD based on CMR measurement only at Visit 3 may have overlooked patients with CTRCD because CTRCD developed often after Visit 3. Thus, CTRCD was defined as a decrease in LVEF>10% points and to LVEF<53% by echocardiography in this study.

There are known various factors influencing the accuracy of T1-measurement using MOLLI method, including protocol parameters, sequence design, patients' heart rate, arrhythmia, and respiratory motion [39]. It is also known that native T1 values are variable based on scanner, age, and sex [23,40]. However, MOLLI technique requires tightly controlled setting of CMR protocol to provide accurate and reproducible results [18]. In this study, all female patients demonstrated sinus rhythm and could hold their breath during the acquisition. All serial CMR exams were conducted using the same MR scanner and protocols by the same trained MR technologists. Therefore, measurement errors for the CMR quantification could be minimized.

Native T1 values were significantly elevated in pre-treatment breast cancer patients compared with control subjects. These results are consistent with the previous studies and may indicate the link between heart failure and malignancy via myocardial inflammation-mediated pathway [13,41,42].

4.5. Study limitations

This study has several limitations. First, some patients without CMR data were excluded. Although CMR can provide a non-invasive assessment of cardiac function, structure, and tissue characteristics, the limitation of accessibility should be solved. Furthermore, the novel CMR imaging technique, parametric mapping is available in few institutions in Japan. Second, sample size of this prospective, single-center study is small, but this is the first study in Japan using the novel CMR imaging technique, especially in 3T scanner. Third, the long-term prognosis was unknown. Fourth, no histological validation of parametric mapping was performed because an invasive myocardial biopsy was limited in asymptomatic patients.

4.6. Conclusions

In conclusions, native T1 value before chemotherapy can reveal high-risk patients for CTRCD in chemotherapy-naïve breast cancer patients. A future multi-center prospective study with a larger number of patients is needed.

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Disclose conflicts of interest

None.

CRediT authorship contribution statement

Yosuke Terui: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. **Koichiro Sugimura:** Conceptualization, Methodology, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Hideki Ota:** Investigation. **Hiroshi Tada:** Resources. **Kotaro Nochioka:** Resources. **Haruka Sato:** Resources. **Yuko Katsuta:** Resources. **Junko Fujiwara:** Investigation. **Narumi Harada-Shoji:** Resources. **Akiko Sato-Tadano:** Resources. **Yoshiaki Morita:** Resources. **Wenyu Sun:** Investigation. **Satoshi Higuchi:** Investigation. **Shunsuke Tatebe:** Resources. **Shigefumi Fukui:** Resources. **Saori Miyamichi-Yamamoto:** Resources. **Hideaki Suzuki:** Resources. **Nobuhiro Yaoita:** Resources. **Nobuhiro Kikuchi:** Resources. **Miku Sakota:** Resources. **Yasuhiko Sakata:** Resources, Writing – review & editing. **Takanori Ishida:** Resources, Writing – review & editing. **Kei Takase:** Writing – review & editing. **Satoshi Yasuda:** Writing – review & editing, Supervision, Project administration. **Hiroaki Shimokawa:** Conceptualization, Writing – review & editing, Supervision, Project administration.

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