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Chemotherapy-Related Cardiac Dysfunction: Quantitative Cardiac Magnetic Resonance Image Parameters and Their Prognostic Implications

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Objective: To quantitatively analyze the cardiac magnetic resonance imaging (CMR) characteristics of chemotherapy-related cardiac dysfunction (CTRCD) and explore their prognostic value for major adverse cardiovascular events (MACE).
Materials and Methods: A total of 145 patients (male:female = 76:69, mean age = 63.0 years) with cancer and heart failure who underwent CMR between January 2015 and January 2021 were included. CMR was performed using a 3T scanner (Siemens). Biventricular functions, native T1 T2, extracellular volume fraction (ECV) values, and late gadolinium enhancement (LGE) of the left ventricle (LV) were compared between those with and without CTRCD. These were compared between patients with mild-to-moderate CTRCD and those with severe CTRCD. Cox proportional hazard regression analysis was used to evaluate the association between the CMR parameters and MACE occurrence during follow-up in the CTRCD patients.
Results: Among 145 patients, 61 had CTRCD and 84 did not have CTRCD. Native T1, ECV, and T2 were significantly higher in the CTRCD group (1336.9 ms, 32.5%, and 44.7 ms, respectively) than those in the non-CTRCD group (1303.4 ms, 30.5%, and 42.0 ms, respectively; P = 0.013, 0.010, and < 0.001, respectively). They were not significantly different between patients with mild-to-moderate and severe CTRCD. Indexed LV mass was significantly smaller in the CTRCD group (65.0 g/m^2 vs. 78.9 g/m^2; P < 0.001). According to the multivariable Cox regression analysis, T2 (hazard ratio [HR]: 1.14, 95% confidence interval [CI]: 1.01–1.27; P = 0.028) and quantified LGE (HR: 1.07, 95% CI: 1.01–1.13; P = 0.021) were independently associated with MACE in the CTRCD patients.
Conclusion: Quantitative parameters from CMR have the potential to evaluate myocardial changes in CTRCD. Increased T2 with reduced LV mass was demonstrated in CTRCD patients even before the development of severe cardiac dysfunction. T2 and quantified LGE may be independent prognostic factors for MACE in patients with CTRCD.
Keywords: Cardiotoxicity; Magnetic resonance imaging; T1 mapping; T2 mapping; Late gadolinium enhancement

INTRODUCTION

With the decline in the mortality and morbidity rates of cancer patients due to advancements in medical care, life expectancy is becoming increasingly significant [1]. After tumor recurrence, cardiovascular disease is the most critical factor affecting cancer patients [2], leading to fatal outcomes [3]. Cancer treatment-associated cardiac dysfunction encompasses various types of cardiac damage caused by cancer therapies such as chemotherapy (CTx), targeted agents, and immunotherapy [4]. Chemotherapy-related cardiac dysfunction (CTRCD) is a severe side effect of cancer treatment. The occurrence of heart failure in these cases has a fatality rate more than triple that of idiopathic dilated cardiomyopathy [5].

Expert consensus for cardiac evaluation after cancer

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Korean Journal of Radiology
KJR

therapy defined cancer therapy-related cardiac dysfunction based on decreased left ventricular ejection fraction (LVEF) using echocardiography [6,7]. A recent guideline suggested the definition of cancer therapy related to cardiac dysfunction based on patient symptoms and functions, and grouped them into severities: mild, moderate, and severe [4]. However, echocardiography is operator-dependent and cannot detect myocardial damage prior to cardiac dysfunction [8]. Cardiac magnetic resonance imaging (CMR) provides functional assessment of both ventricles with high diagnostic accuracy and reproducibility [9]. In addition, CMR tissue characterization techniques provide pixel-based quantification of T1 and T2 values, as well as calculated extracellular volume (ECV) of the myocardium and the presence or pattern of late gadolinium enhancement (LGE), which enables noninvasive identification of histopathological changes in the myocardium, such as myocardial fibrosis, edema, or inflammation in CTRCD [10,11]. We hypothesized that the CMR tissue characteristics and functional data would differ between patients with and without CTRCD. Additionally, we suggest that CMR could potentially predict major adverse cardiovascular events (MACE) in patients with CTRCD. Therefore, this study aimed to quantitatively analyze the CMR characteristics of CTRCD and explore their prognostic value for MACE in CTRCD patients.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Severance Hospital (approval number: 4-2020-1332). The requirement for informed consent was waived owing to the retrospective study design.

Patients

A total of 204 CMR scans of cancer patients suspected of non-ischemic heart failure based on their symptoms and left ventricular function (LVEF < 60%) on echocardiography were consecutively enrolled between January 2015 and January 2021. The exclusion criteria were other heart diseases that could cause heart failure such as coronary artery and valvular heart disease (n = 39), treatment with target agents or immunotherapeutic agents (n = 15), poor image quality due to motion artifacts (n = 2), and pediatric patients (age < 18 years) (n = 1). Fifty-seven patients were excluded. We categorized them as non-CTRCD or CTRCD based on their CTx history. Two patients did not meet the CTRCD diagnostic criteria [4,12]. Thus, 84 were non-CTRCD patients and 61 were CTRCD patients. Both groups were subgrouped according to severity based on LVEF (< 40% or not). Patients with a new LVEF reduction of < 40% were assigned to the severe group, and those with a new LVEF reduction of ≥ 10%, < 60%, were assigned to the mild to moderate group [4,12,13]. Figure 1 illustrates the patient selection process.

CMR Protocol

All included patients underwent CMR (3T, Prisma fit, Siemens Healthineers) using a six-element body matrix coil and spine matrix coil array. One slice of two-chamber, four-chamber, and short-axis cine images, including the whole ventricles, were obtained with a retrospectively electrocardiogram (ECG)-gated and balanced steady-state free precession (true fast imaging with steady-state precession [TrueFISP]) sequence.

Native T1 mapping images were acquired using a modified look-locker inversion-recovery 5(3)3 (MOLLI) sequence in three short-axis planes (apical, mid, and base of the left ventricle [LV]). A nonselective inversion pulse (TrueFISP single-shot readout sequence in the mid-diastolic phase) was applied. T2 mapping images were acquired using a T2-prepared single-shot TrueFISP sequence along the same three short-axis planes of the LV used for native T1 mapping.

LGE images were obtained 10 min after contrast injection (0.2 mmol/kg of gadolinium contrast, meglumine gadoterate [Dotarem], Guerbet). A normal myocardium was represented using a phase-sensitive inversion recovery-prepared TrueFISP sequence with the inversion time adjusted to null. The LGE images covered the entire LV along the same short-axis planes with cine or T1 mapping images. A fast low-angle shot sequence with different inversion times (150–650 ms to null) determined the inversion time before LGE imaging. Hematocrit levels were evaluated immediately before CMR. Post-contrast T1 mapping images were acquired 15 min after contrast injection along the same three short-axes of LV images used for T1 with a scheme "4(1)3(1)2" using three inversion pulses.

CMR Analysis

Cvi42 MR analysis software (Circle Cardiovascular Imaging Inc.) was used to evaluate the CMR data. We evaluated ventricular function using end-systolic and end-diastolic volumes from short-axis cine images by manually delineating the endocardial and epicardial borders of the

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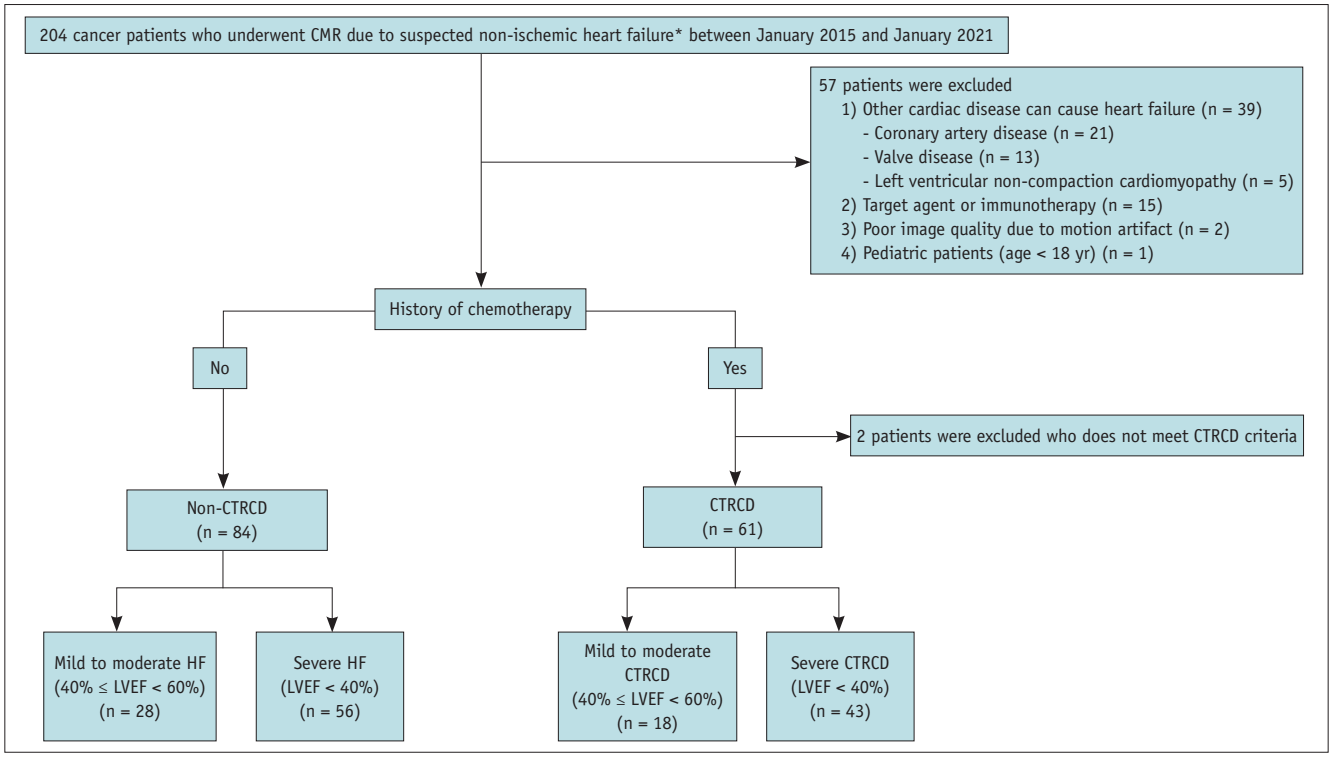

Fig. 1. Patient selection process. A total of 204 CMR scans of cancer patients who suspected non-ischemic heart failure were initially enrolled, of which 59 patients were excluded. Finally, 145 patients were included and categorized them based on their CTx history. Non-CTRCD and CTRCD patients were subgrouped according to severity based on LVEF (< 40% or not). *Based on their symptoms and left ventricular function (LVEF < 60%) on echocardiography. CMR = cardiac magnetic resonance imaging, CTRCD = chemotherapy-related cardiac dysfunction, HF = heart failure, LVEF = left ventricular ejection fraction, CTx = chemotherapy

LV. The ventricular volume and mass at the end of the systolic and diastolic phases, stroke volume, and LVEF were automatically calculated. The LV mass between the diastolic and systolic phases was checked to ensure that they were almost identical, and the end-diastolic phase data were used for analysis [14,15]. Global native T1, T2, post-contrast T1, and ECV values were measured at 16 myocardial segments, except for the apical segment. The ECV was measured using the following equation:

ECV (%) = (ΔR1 of myocardium/ΔR1 of the LV blood pool) x (1 – hematocrit) x 100.

The same CMR protocol measured the reference value for native T1, ECV, and T2 as 1219.0 ± 29.1 ms, 25.7% ± 2.4%, and 39.6 ± 2.0 ms, respectively. LV blood pool T1 values were measured using a circular region of interest > 10 mm^2, avoiding the papillary muscle. A motion-corrected T1 map provided by Siemens software was used for this analysis, and a 10% offset method was used to avoid partial volume artifacts. Segments with visible artifacts were excluded from the analysis. Additionally, one expert radiologist analyzed the presence and patterns of LGE and divided them into four types of LGE patterns: mesocardial, right ventricle (RV) insertion, mixed (mesocardial and RV insertion), and others. A total of 143 images were evaluated for LGE quantification, except for two missed data. In short-axis LGE images, LGE quantification indicated that the relative LGE area of LV volume, excluding papillary muscles and trabeculae, was automatically measured with the 5-standard deviation (SD) method [16,17]. Two investigators analyzed all images (J.H.K. and Y.J.H. in training, with 12 years of experience in cardiovascular radiology).

Patient Follow-Up

The patient outcome of interest in this study was a MACE during the follow-up period. The end of the follow-up period was April 28, 2022. MACE were defined as a composite of hospitalization for heart failure, cardiovascular shock or death, heart transplantation, implantable cardioverter-defibrillator (ICD) insertion, or major arrhythmia (ventricular tachycardia, ventricular fibrillation, and complete

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Korean Journal of Radiology
KJR

atrioventricular heart block) [18,19]. Follow-up clinical event data were collected by reviewing electronic medical records.

Statistical Analysis

Continuous variables with normal distribution were presented as mean ± SD and compared using Student's *t*-test. Continuous variables with non-normal distribution were presented as median (range) and compared using the Mann–Whitney U test. Two-way analysis of variance (ANOVA) was used for comparison between subgroups (i.e., mild to moderate vs. severe heart failure) of the CTRCD and non-CTRCD groups. The intraclass correlation coefficient (ICC) was calculated using a two-way mixed effects model with absolute agreement and multiple raters. ICC < 0.5, 0.5–0.75, 0.75–0.9, and > 0.9 were poor, moderate, good, and excellent reliability, respectively [20].

Univariable and multivariable Cox proportional hazard models were used to examine the relationship between CMR parameters and MACE. The multivariable Cox regression model included all significant variables ($P < 0.05$) in the univariable analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a Cox model. The proportional hazard assumption was tested using the Schoenfeld residual method. Statistical significance was set at $P < 0.05$. Statistical Package for the Social Sciences (SPSS) software (ver. 26, SPSS Inc.) and R software (version 4.0.5; R Foundation for Statistical Computing) were used for all statistical analyses.

RESULTS

Patients

A total of 145 patients (male: female ratio = 76:69, mean age = 63.0 years), 61 with CTRCD, and 84 without CTRCD were included. In the CTRCD group, 40 (65.6%) patients underwent anthracycline (AC) CTx. Among the non-CTRCD patients, 56 had severe heart failure (LVEF < 40%), and others had borderline systolic LV function (40 ≤ LVEF < 60%). CTRCD patients were divided into two groups according to CTRCD severity [4]. Eighteen patients had mild to moderate CTRCD (i.e., LVEF reduction by ≥ 10 percentage points to an LVEF of 40%–49%, or heart failure symptom with abnormal cardiac biomarker with LVEF < 60%), and 43 had severe

Table 1. Baseline characteristics of patients

Clinical features	All patients (n = 145)	Non-CTRCD (n = 84)	CTRCD (n = 61)	*P**
Age, yr	63.0 ± 12.8	67.0 ± 10.5	57.6 ± 13.8	< 0.001
Sex (male:female)	76:69 (52.4:47.6)	50:34 (59.5:40.5)	26:35 (42.6:57.4)	0.056
Height, cm	162.9 ± 8.8	162.9 ± 9.4	162.8 ± 8.2	0.933
Weight, kg	62.1 ± 12.7	61.6 ± 13.6	62.7 ± 11.7	0.603
BSA, m^2	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.620
Left thoracic radiation therapy	18 (12.4)	3 (7.1)	15 (24.6)	0.181
Hypertension	75 (51.7)	45 (53.6)	30 (49.2)	0.536
Diabetes mellitus	51 (35.1)	27 (32.1)	24 (39.3)	0.411
Hyperlipidemia	19 (13.1)	9 (10.7)	10 (16.4)	0.034
Smoking	40 (27.6)	24 (28.6)	16 (26.2)	0.711
NT-proBNP, pg/mL	1159.5 (10, 7000)	1028.0 (10, 70000)	1378 (36, 70000)	0.820
Troponin T, μg/mL	21.5 (3, 1388)	18.5 (3, 1388)	23 (5, 336)	0.988
Type of cancer				
Breast cancer	34 (23.4)	9 (10.7)	25 (41.0)	< 0.001
Lymphoma	16 (11.0)	3 (3.6)	13 (21.3)	0.002
Sarcoma	10 (6.9)	4 (4.8)	6 (9.8)	0.322
Genitourinary cancer	23 (15.9)	22 (29.8)	1 (1.7)	< 0.001
Esophagus/stomach cancer	16 (11.0)	14 (16.7)	2 (3.3)	0.023
Head and neck cancer	11 (7.6)	8 (9.5)	3 (4.9)	0.358
Lung cancer	4 (2.8)	4 (4.8)	0 (0.0)	0.139
Others	31 (21.4)	20 (23.8)	11 (18.0)	0.527

Data are shown as patient number (%), mean ± standard deviation, or median (range).
*Non-CTRCD vs. CTRCD.
CTRCD = chemotherapy-related cardiac dysfunction, BSA = body surface area, NT-proBNP = N-terminal prohormone of brain natriuretic peptide

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Table 2. Functional and tissue parameters in patients

	Non-CTRCD (n = 84)				CTRCD (n = 61)				
	Mild to moderate HF (n = 28)	Severe HF (n = 56)	*P**	Total	Mild to moderate CTRCD (n = 18)	Severe CTRCD (n = 43)	*P*†	Total	*P*‡
Clinical features									
Age, yr	68.0 ± 9.8	67.3 ± 11.4	> 0.999	67.0 ± 10.5	48.5 ± 15.8	61.5 ± 9.9	0.002	57.6 ± 13.8	< 0.001
Height, cm	162.6 ± 10.3	162.6 ± 9.4	> 0.999	162.9 ± 9.4	165.0 ± 7.5	161.7 ± 8.5	0.702	162.7 ± 8.1	0.933
Weight, kg	56.7 ± 11.4	63.1 ± 15.0	> 0.999	61.6 ± 13.6	66.5 ± 10.7	61.7 ± 12.0	0.844	62.3 ± 11.9	0.603
BSA, m^2	1.6 ± 0.2	1.7 ± 0.2	> 0.999	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.611	1.7 ± 0.2	0.620
Functional data									
LVEDVi, mL/m^2	83.0 ± 19.7	147.0 ± 39.0	< 0.001	125.7 ± 45.3	83.1 ± 20.1	122.5 ± 36.5	< 0.001	110.3 ± 37.0	0.031
LVESVi, mL/m^2	41.6 ± 12.1	108.1 ± 36.1	< 0.001	86.0 ± 43.7	39.8 ± 12.6	90.0 ± 33.3	< 0.001	74.4 ± 36.8	0.094
SV, mL	68.9 ± 20.1	63.3 ± 18.4	> 0.999	65.2 ± 19.0	73.9 ± 20.1	54.0 ± 18.9	0.001	60.1 ± 20.9	0.131
LVEF, %	50.2 ± 6.1	26.9 ± 7.3	< 0.001	34.6 ± 13.0	51.9 ± 6.9	27.7 ± 8.2	< 0.001	34.7 ± 13.3	0.965
CO, L/min	4.5 ± 1.1	4.6 ± 1.3	> 0.999	4.6 ± 1.2	5.8 ± 1.6	4.3 ± 01.4	< 0.001	4.8 ± 1.6	0.415
RVEDVi, mL/m^2	79.1 ± 20.7	88.4 ± 31.3	0.860	85.3 ± 28.4	68.9 ± 15.8	78.4 ± 28.9	> 0.999	75.5 ± 25.8	0.034
RVESVi, mL/m^2	39.0 ± 15.4	52.8 ± 26.0	0.065	48.2 ± 23.8	30.9 ± 7.5	48.7 ± 27.2	0.036	43.2 ± 24.4	0.218
RVSV, mL	68.7 ± 18.4	60.5 ± 18.2	0.345	63.2 ± 18.6	68.5 ± 21.4	51.4 ± 17.8	0.007	56.7 ± 20.5	0.048
RVEF, %	52.7 ± 9.5	43.3 ± 12.0	0.009	46.4 ± 12.0	56.1 ± 9.0	43.1 ± 16.1	0.002	47.2 ± 15.5	0.758
RVCO, L/min	4.5 ± 1.1	4.4 ± 1.4	> 0.999	4.5 ± 1.3	5.4 ± 1.6	4.2 ± 1.4	0.008	4.5 ± 1.6	0.759
LV mass (diastolic), g	95.3 ± 27.7	149.8 ± 45.8	< 0.001	131.7 ± 48.0	113.7 ± 27.9	110.7 ± 37.1	> 0.999	111.6 ± 34.3	0.004
Indexed LV mass, (diastolic), g/m^2	57.6 ± 13.8	66.6 ± 24.7	< 0.001	78.9 ± 26.4	65.0 ± 13.9	66.6 ± 17.9	> 0.999	65.0 ± 18.5	< 0.001
Myocardial tissue characterization									
Native T1, ms	1248.6 ± 68.4	1335.3 ± 70.9	< 0.001	1303.4 ± 83.7	1322.4 ± 61.0	1347.3 ± 74.8	> 0.999	1336.9 ± 69.5	0.013
ECV, %	28.6 ± 3.7	31.6 ± 5.2	0.100	30.5 ± 4.8	31.6 ± 3.4	32.7 ± 4.3	> 0.999	32.5 ± 4.0	0.010
T2, ms	41.5 ± 2.1	42.5 ± 2.1	> 0.999	42.0 ± 2.4	43.6 ± 3.6	44.6 ± 4.7	> 0.999	44.7 ± 4.6	< 0.001
LGE quantification, %	8.1 ± 10.4	12.6 ± 13.2	0.282	11.0 ± 12.4	9.0 ± 8.9	13.7 ± 10.2	0.716	12.4 ± 10.0	0.270
LGE pattern									
Total	10	41		51 (60.7)	9	33		42 (67.7)	
Mesocardial	2	13		15 (17.9)	1	4		5 (8.1)	
RV insertion	1	2		3 (4.0)	0	6		6 (9.7)	
Mixed	5	21		26 (31.0)	2	16		18 (21.4)	
Others	2	5		7 (8.3)	6	7		13 (15.5)	

Data are mean ± standard deviation, n, or patient number (%).

*Mild to moderate HF vs. Severe HF, †Mild to moderate CTRCD vs. Severe CTRCD, ‡Non-CTRCD vs. CTRCD.

CTRCD = chemotherapy-related cardiac dysfunction, HF = heart failure, BSA = body surface area, LVEDVi = indexed left ventricular end-diastolic volume, LVESVi = indexed left ventricular end-systolic volume, SV = stroke volume; LVEF = left ventricular ejection fraction, CO = cardiac output, RVEDVi = indexed right ventricular end-diastolic volume, RVESVi = indexed right ventricular end-systolic volume, RVSV = right ventricular stroke volume, RVEF = right ventricular ejection fraction, RVCO = right ventricular cardiac output, LV = left ventricle, ECV = extracellular volume fraction, LGE = late gadolinium enhancement, RV = right ventricle

Korean Journal of Radiology
KJR

CTRCD (LVEF < 40%) (Fig. 1). Breast cancer was the most common type of cancer (n = 34). The number of breast cancer and lymphoma patients was higher in the CTRCD group than in the non-CTRCD group (P < 0.001 and P = 0.002, respectively). Eighteen patients (12.4%) underwent left thoracic radiation therapy, including the heart, but there was no significant difference between the non-CTRCD group and CTRCD groups (Table 1). The median diagnostic duration from completion of CTx to CMR was 848 days. Finally, 41 (67.2%) of the CTRCD patients were diagnosed with CTRCD more than one year after the completion of CTx.

CMR Parameters: CTRCD vs. Non-CTRCD

There were no significant differences in the incidence of heart failure (LVEF < 40%) between the CTRCD and non-CTRCD groups (69.4% vs. 66.7%, P = 0.731).

Left ventricular end-diastolic volume (LVEDV) and right ventricular end-diastolic volume (RVEDV) indexed to the body surface area (i.e., LVEDVi and RVEDVi) were significantly higher in the non-CTRCD group than in the CTRCD group (P = 0.031 and 0.034, respectively). However, the two groups had no significant difference in either ventricular ejection fraction (LVEF: 34.6% vs. 34.7%, right

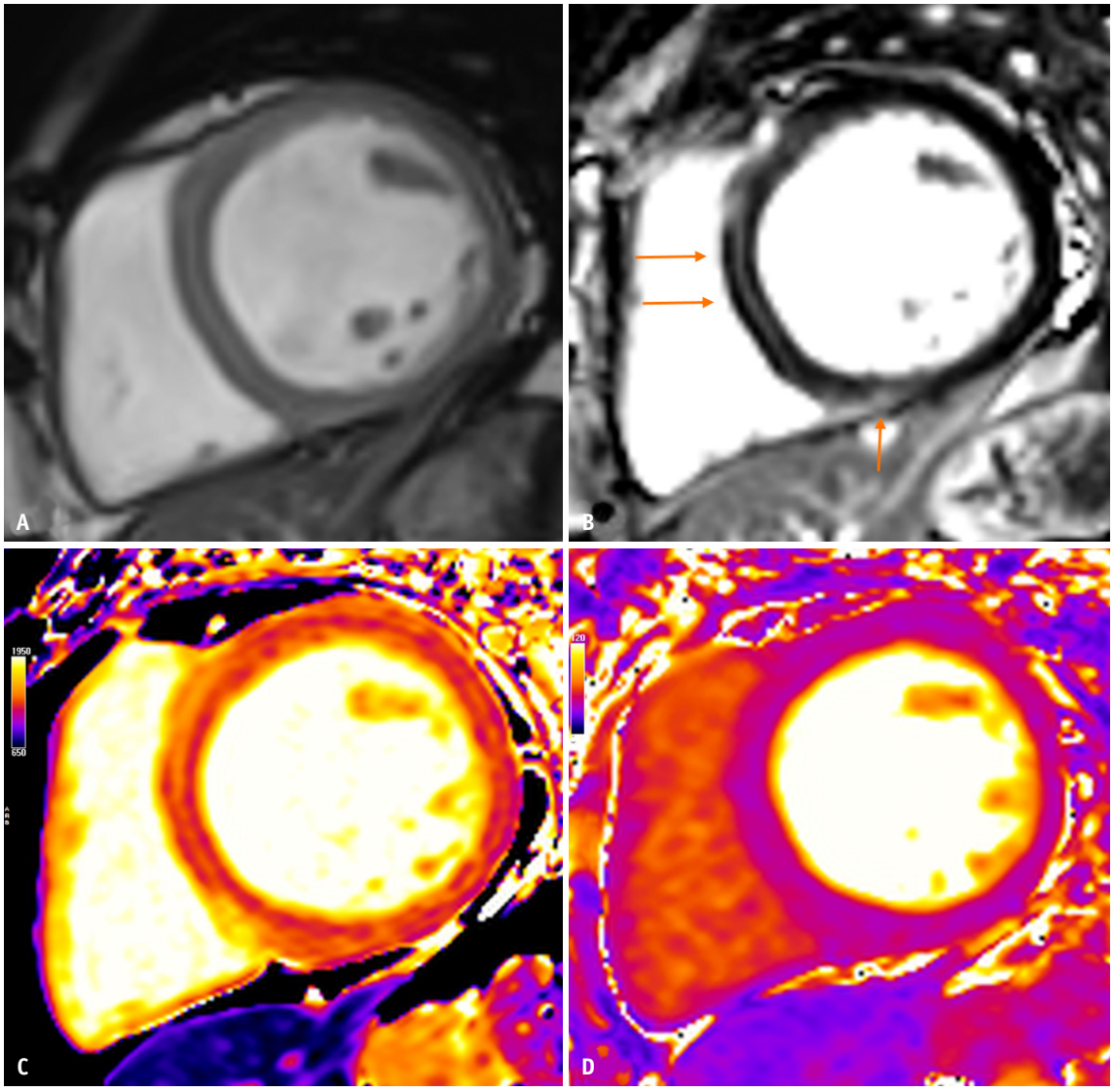

Fig. 2. A 50-year-old female with breast cancer underwent radical mastectomy and CTx (AC) from July to December 2006, who presented severe CTRCD. CMR images show globally enlarged LV (LVEDVi = 105.8 mL/m^2), reduced LV function (LVEF: 32.3%) and indexed LV mass (49.0 g/m^2) in cine image **(A)**, mesocardial and RV insertion LGE (arrows) **(B)**, increased native T1 (1304.3 ms) **(C)**, and increased T2 (45.7 ms) **(D)** and ECV (27.0%). CTx = chemotherapy, AC = anthracycline, CTRCD = chemotherapy-related cardiac dysfunction, CMR = cardiac magnetic resonance imaging, LV = left ventricle, LVEDVi = indexed left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, RV = right ventricle, LGE = late gadolinium enhancement, ECV = extracellular volume fraction

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ventricular ejection fraction [RVEF]: 46.4% vs. 47.2%).

Indexed LV mass was significantly smaller in the CTRCD group than in the non-CTRCD group (65.6 vs. 78.9 g/m^2, P < 0.001). In the non-CTRCD group, indexed LV mass was significantly larger in patients with severe heart failure than in those with mild to moderate heart failure (66.6 vs. 57.6 g/m^2, P < 0.001). However, in the CTRCD group, it was similar between the severe and mild to moderate CTRCD patients without a significant difference (66.6 vs. 65.0 g/m^2, P > 0.999) (Table 2).

Native T1 was significantly increased in both CTRCD and non-CTRCD groups (1336.9 ms vs. 1303.4 ms, P = 0.013). ECV and T2 were increased in the CTRCD group with significant differences (32.5%, 44.7 ms vs. 30.5%, 42.0 ms, P = 0.010 and < 0.001, respectively). In the non-CTRCD group, native T1 and ECV were significantly higher in those with severe heart failure than in those with mild to moderate heart failure (1335.3 ms, 31.6% vs. 1248.6 ms, 28.6%, P < 0.001 and 0.100). In the CTRCD group, native T1, ECV, and T2 were increased regardless of the severity of CTRCD (1322.4 ms, 31.6%, 43.6 ms vs. 1347.3 ms, 32.7%, 44.6 ms, P > 0.999, in all of these parameters). Native T1, ECV, and indexed LV mass showed excellent interobserver agreement (ICC: 0.962, 0.902, and 0.994, respectively). T2 showed good interobserver agreement (ICC: 0.753).

In the analysis of LGE, 51 (60.7%) non-CTRCD and 42 (67.7%) CTRCD patients exhibited myocardial LGE. The most common LGE pattern was the mixed type (both mesocardial and RV insertions) in both groups. There was no significant difference in LGE quantification between the groups (11.0% vs. 12.4%, P = 0.270) (Table 2). Figure 2 shows the representative CMR images of patients with severe CTRCD.

Table 3. Univariable and multivariable analysis of the association between CMR parameters and MACE in the CTRCD patients

	HR (95% CI)	*P*
Univariable analysis		
NT-proBNP	1.00 (1.00–1.00)	0.001
Troponin T	1.01 (1.00–1.01)	0.002
LVEDVi	1.02 (1.01–1.04)	0.001
LVESVi	1.03 (1.01–1.04)	< 0.001
LVEF	0.95 (0.90–0.99)	0.026
RVEDVi	1.04 (1.02–1.05)	< 0.001
RVESVi	1.03 (1.01–1.05)	< 0.001
RVEF	0.95 (0.92–0.98)	0.003
Native T1	1.01 (1.00–1.02)	0.021
ECV	1.19 (1.06–1.35)	0.005
T2	1.15 (1.04–1.28)	0.010
LGE quantification	1.07 (1.02–1.13)	0.007
Multivariable analysis*		
LVEF	0.99 (0.97–1.08)	0.856
RVEF	0.96 (0.90–1.02)	0.171
Native T1	1.00 (0.99–1.01)	0.635
ECV	1.15 (0.94–1.39)	0.171
T2	1.14 (1.01–1.27)	0.028
LGE quantification	1.07 (1.01–1.13)	0.021

*Cox proportional hazards model adjusting for NT-proBNP, Troponin-T, LVEDVi, LVESVi, RVEDVi, and RVESVi which are significant in univariable analysis: variables remaining in the final model are shown.
CMR = cardiac magnetic resonance imaging, MACE = major adverse cardiovascular events, CTRCD = chemotherapy-related cardiac dysfunction, HR = hazard ratio, CI = confidence interval, NT-proBNP = N-terminal prohormone of brain natriuretic peptide, LVEDVi = indexed left ventricular end-diastolic volume, LVESVi = indexed left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, RVEDVi = indexed right ventricular end-diastolic volume, RVESVi = indexed right ventricular end-systolic volume, RVEF = right ventricular ejection fraction, ECV = extracellular volume fraction, LGE = late gadolinium enhancement

Association between CMR Parameters and MACE

In the CTRCD group, MACE occurred in 12 patients, including two hospitalizations for heart failure, seven arrhythmias (three ventricular arrhythmias, one atrioventricular block, and three ICD insertions), and three cardiogenic deaths. Among the 12 MACE patients, 10 (83.3%) were in the severe CTRCD group. The median follow-up duration for outcomes after CMR was 149 days.

In the univariable Cox proportional hazard analysis in the CTRCD patients, clinical factors such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin-T, functional factors such as indexed both ventricular end-diastolic and end-systolic volume and ejection fraction, as well as myocardial tissue character parameters (native T1, ECV, T2, and LGE quantification) were associated with increased risk of MACE. In the multivariable analysis, after adjusting biventricular volume factors, only T2 (HR: 1.14; 95% CI: 1.01–1.27; P = 0.028) and LGE quantification (HR: 1.07; 95% CI: 1.01–1.13; P = 0.021) were significantly associated with MACE (Table 3).

DISCUSSION

This study aimed to characterize myocardial tissue using quantitative CMR parameters in CTRCD and explore their prognostic values. Our data suggest that CMR provides noninvasive tissue characterization to identify diffuse myocardial changes for predicting MACE in cancer patients.

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Although many studies have been published in the field of cardio-oncology, studies on the characteristic CMR features and their prognostic values in CTRCD are insufficient. Our data included a relatively large cohort and suggested the CMR characteristics of CTRCD. Even in mild to moderate CTRCD, increased T2 and decreased LV mass indicate myocardial tissue change before the severe decline in LVEF. In addition, T2, which represents myocardial edema and inflammation, and quantification of LGE, which indicates the volume of focal myocardial fibrosis, were predictive of MACE in CTRCD patients.

Native T1, ECV, and T2 significantly increased in the CTRCD group compared to the non-CTRCD group, which means diffuse myocardial change corresponded well with the results of previous studies [9,10]. Previous studies have also suggested the potential of CMR to detect CTRCD in preclinical and clinical stages through T1 and T2 mapping and ECV [7,9,10,21]. In animal model studies, T2 prolongation histopathologically represents myocardial edema with preserved myocardial tissue structure in the early stages of CTx. In later stages, increased T1 and ECV are prominent with myocardial fibrosis [10]. Serial myocardial damage leads to destruction of the myocardial structure and subsequent cardiac dysfunction with decreased LVEF. Galán-Arriola et al. [22] found that only T2 prolongation (with normal T1 and ECV) indicated a reversible stage of AC cardiotoxicity and that the damaged myocardial tissue became irreversible with increased T1 and ECV.

Higher T2, indicating myocardial edema or inflammation, was found in the severe CTRCD group as well as the mild to moderate CTRCD group. In addition, T2 was associated with a prognosis for MACE in CTRCD patients. A recent comprehensive review of T2 mapping indicated that T2 elevation can be used as an indicator of arrhythmogenicity in hypertrophic cardiomyopathy and autoimmune cardiac diseases. Moreover, T2 elevation is a reliable predictor of increased morbidity and mortality in patients with myocarditis, amyloidosis, and heart involvement in systemic diseases such as systemic sclerosis [23]. T2 has also been demonstrated to independently predict adverse clinical outcomes in patients undergoing heart transplantation [24]. Meanwhile, shorter T2 is related to a better prognosis of treated dilated cardiomyopathy with reverse remodeling of the LV [25]. Contrary to our findings, other previous reports showed that T1 and ECV were significant prognostic factors in patients who underwent CTx [26], and an early decrease in native T1 after the first administration of AC was a predictor for the development of CTRCD after completion of CTx [27].

LV mass is another important parameter in CMR for quantifying cardiotoxicity. Left ventricular hypertrophy (LVH) refers to an increased LV mass resulting from ventricular wall thickening, dilatation of the ventricle, or both. An increase in myocardial mass is an early mechanism for maintaining the ejection fraction and reducing stress on the ventricular wall. Myocardial fibrosis is an essential pathophysiological feature of LVH. Initially, myocardial fibrosis causes diastolic dysfunction but can progress to systolic dysfunction, clinically manifesting as heart failure [28-30]. Unlike idiopathic dilated cardiomyopathy, cardiomyocyte apoptosis and atrophy may reduce LV mass after CTx [31]. Jordan et al. [32] demonstrated that CTx contributes to worsening heart failure symptoms with reduced LV mass independent of LVEF. Furthermore, LV mass provides prognostic information for CTRCD and is inversely associated with MACE [33]. Consistent with previous studies, we found a tendency for smaller LV mass in the CTRCD group than in the non-CTRCD group. In the subgroup analysis, patients with severe CTRCD did not demonstrate increased LV mass, unlike patients with severe heart failure. However, LV mass was not a significant prognostic factor for MACE in this study.

We observed that the quantified LGE value was a factor for MACE in CTRCD patients. The presence and quantification of LGE were related to focal myocardial fibrosis and a higher potential for adverse outcomes in patients with heart failure [34,35]. Harries et al. [36] showed that LGE was associated with LV remodeling and reduced LVEF in late-onset AC cardiomyopathy.

The timing of diagnosis is also critical for the prognosis of CTRCD. Late-onset chronic cardiotoxicity (> 1 year after the completion of CTx) is usually irreversible and refractory to traditional heart failure therapy, causing poor outcomes [37]. Similarly, most MACE occurred in patients with severe CTRCD in this study. However, because early identification and treatment initiation of CTRCD are essential for recovering LVEF [38], these myocardial characterizing factors will help detect and manage CTRCD.

This study had some limitations. As this was a retrospective study, some associated factors, such as the cumulative dose of CTx and cancer stage, were not thoroughly evaluated. Second, our study population was from a single center, limiting the statistical power. More extensive data from multicenter studies using standard

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CMR protocols are required to confirm our findings. Third, this study was purposely restricted to patients with CTx; therefore, our results cannot be generalized to newer cancer therapies, such as targeted agents.

In conclusion, quantitative parameters from CMR have the potential to evaluate myocardial changes in CTRCD. Increased T2 and decreased LV mass in the mild-to-moderate CTRCD group may indicate diffuse myocardial changes in CTRCD, even before the development of severe heart dysfunction. T2 and quantified LGE may be independent prognostic factors for MACE in patients with CTRCD.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Dr. Hye-Jeong Lee, and Dr. Jin Hur, the contributing editors of the *Korean Journal of Radiology*, and the Statistical Consultant for *Korean Journal of Radiology*, Prof. Kyunghwa Han, were not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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Conceptualization: Yoo Jin Hong. Data curation: Jinhee Kim. Formal analysis: Kyunghwa Han. Funding acquisition: Hye-Jeong Lee, Jin Young Kim. Investigation: Jin Hur. Methodology: Young Jin Kim. Project administration: Yoo Jin Hong. Resources: Byoung Wook Choi. Software: Kyunghwa Han. Supervision: Yoo Jin Hong. Validation: Yoo Jin Hong. Visualization: Jinhee Kim. Writing—original draft: Jinhee Kim. Writing—review & editing: Yoo Jin Hong.

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