

Cardiac computed tomography-derived myocardial tissue characterization after anthracycline treatment

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Abstract

Aims Understanding cardiac function after anthracycline administration is very important from the perspective of preventing the onset of heart failure. Although cardiac magnetic resonance and echocardiography are recognized as the ‘gold standard’ for detecting cardiotoxicity, they have many shortcomings. We aimed to investigate whether cardiac computed tomography (CCT) could replace these techniques, assessing serial changes in cardiac tissue characteristics as determined by CCT after anthracycline administration.

Methods and results We prospectively investigated 15 consecutive breast cancer patients who were scheduled to receive anthracycline therapy. We performed echocardiography and CCT before and 3, 6, and 12 months after anthracycline treatment. The mean cumulative administered anthracycline dose was 269.9 ± 14.6 mg/m² (doxorubicin-converted dose). Of the 15 enrolled patients who received anthracycline treatment for breast cancer, none met the definition of cardiotoxicity. The CCT-derived extracellular volume fraction tended to increase after anthracycline treatment and had relatively similar dynamics to the left ventricular ejection fraction and global longitudinal strain as determined by echocardiography.

Conclusions Our findings indicated that CCT could provide adequate information about the characteristics of myocardial tissue after anthracycline administration. CCT may improve the understanding of cardiotoxicity by compensating for the weaknesses of echocardiography. This technique could be useful for understanding cardiac tissue characterization as a ‘one-stop shop’ evaluation, providing new insight into cardiooncology.

Keywords Cardiooncology; Cardiotoxicity; Anthracycline; Cardiac computed tomography

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Introduction

Cardiac magnetic resonance (CMR) imaging is regarded as ‘the gold standard’ diagnostic imaging method for detecting cardiotoxicity caused by anticancer drug use, and its use is recommended in many guidelines.^{1–3} However, the long examination times, the high medical costs, and the limited number of facilities that can accommodate this method limit the widespread use of CMR imaging.

We previously reported that cardiac computed tomography (CCT) enables comprehensive assessment in the non-invasive evaluation of patients with takotsubo cardiomyopathy⁴ and achieved extracellular volume (ECV) quantification using CCT in takotsubo cardiomyopathy patients.⁵ Given the above background, we recently reported a similarity between CCT and CMR in cancer therapy-related cardiac dysfunction (CTRCD) cases in terms of consistency between the ECV maps from CCT and CMR and between late iodine enhancement in CCT and late gadolinium enhancement

(LGE) in CMR.^{6,7} Moreover, regarding late cardiac function in patients after using anthracycline treatment, we demonstrated that CCT may be comparable with echocardiography because the ECV determined by CCT behaved the same as left ventricular (LV) ejection fraction (EF) (end-diastolic volume and end-systolic volume) and LV-global longitudinal strain (GLS) as determined by echocardiography⁸; the clinical application of CCT in the cardiooncology area is expected in the coming years.^{9,10}

In the present study, to enhance the clinical usefulness of CCT in cardiooncology, we investigated serial changes in the CCT-derived ECV fraction in anthracycline-treated breast cancer patients.

Methods

The current study was a prospective, single-centre, observational study that explored clinical data in patients with breast cancer scheduled to receive anthracycline therapy.

Ethical consideration

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Institutional Review Board of Kumamoto University (Approval No. Rinri 1730), and written informed consent was obtained from each patient or the family of the patient. This study was registered with the University

Hospital Medical Information Network Clinical Trials Registry (UMIN000047554).

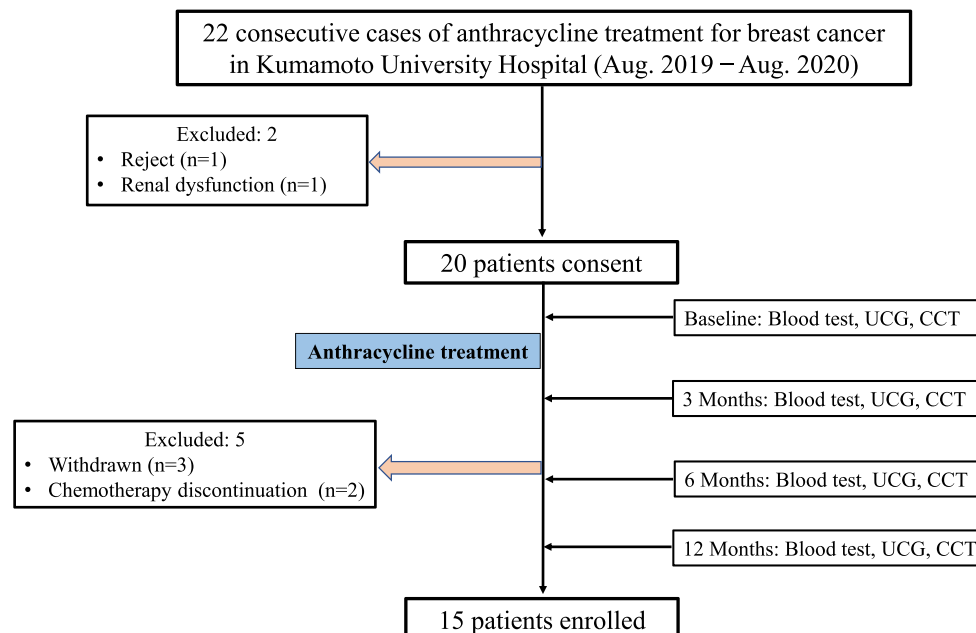
Study subjects

We prospectively investigated 22 consecutive patients who were diagnosed with breast cancer and scheduled to receive anthracycline therapy at Kumamoto University Hospital between August 2019 and July 2020. We recorded each patient's medical history and relevant clinical characteristics. We excluded two patients: one who refused to participate in the study ($n = 1$) and one who had renal dysfunction ($n = 1$). We performed blood tests, echocardiography, and CCT before and 3, 6, and 12 months after anthracycline treatment. During the observation period, we excluded five patients because of withdrawal of consent ($n = 3$) and discontinuation of chemotherapy ($n = 2$). The remaining 15 patients were enrolled in this study. The study flow chart is shown in *Figure 1*.

Clinical parameters

Baseline demographic data, cardiovascular risk factors, and medications on enrolment were documented. Hypertension was defined as blood pressure $> 140/90$ mmHg or the taking of antihypertensive medication, as previously described.^{11–13} Diabetes mellitus was defined as the presence of symptoms of diabetes and a casual plasma glucose

Figure 1 Study flowchart. CCT, cardiac computed tomography; UCG, ultrasound cardiography.



concentration ≥ 200 mg/dL, a fasting plasma glucose concentration ≥ 126 mg/dL, and a 2-h plasma glucose concentration ≥ 200 mg/dL on the oral glucose tolerance test (75 g) or the taking of medication for diabetes mellitus. Dyslipidaemia was defined as a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL (≥ 3.63 mmol/L), a high-density lipoprotein cholesterol concentration < 40 mg/dL (1.04 mmol/L), or a triglyceride concentration ≥ 150 mg/dL (≥ 1.7 mmol/L). Blood samples were obtained under stable and fasting conditions in the early morning. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m².¹⁴ The estimated glomerular filtration rate was calculated using the Japanese Society of Nephrology formula.¹⁵

Blood biomarkers

Blood samples were collected by venipuncture from every patient at each point as described in *Figure 1*. Serum high-sensitivity troponin-T (hsTnT) concentration levels and plasma B-type natriuretic peptide (BNP) concentration levels were analysed using commercially available assays (Roche Diagnostics, Tokyo, Japan and Abbott Japan, Matsudo, Japan, respectively).

Echocardiography

Echocardiography was performed at each point as described in *Figure 1*. The methodology of the echocardiography was described previously.¹⁶ In brief, LVEF was measured using the modified Simpson's method. The LVEF and E/e' ratio, which were assessed by tissue Doppler, were measured by echocardiography (Vivid-E95®; GE-Vingmed Ultrasound, Horten, Norway; Aplio500®; Canon, Tokyo, Japan; EPIQ 7G®; Philips, Bothell, WA, USA) as previously reported.^{17,18} LV-GLS was assessed using 2DS vendor-independent software (TomTec Imaging Systems, Germany). Speckles were tracked frame by frame throughout the LV myocardium over the course of one cardiac cycle; basal, mid, and apical regions of interest were then created and manually adjusted whenever needed. All sonographers were blinded to the patient's clinical history and data to minimize bias.

Cardiac computed tomography

Cardiac computed tomography was performed at each point as described in *Figure 1*. The methodology for the CCT scans was described previously.^{6–8} In brief, all CCTs were performed using a 320-detector row scanner (Aquilion One Genesis edition; Canon Medical Systems, Otawara, Japan). First, electrocardiogram-gated unenhanced CCT was performed. Then, coronary CT angiography was performed using

550 mg/kg contrast material, and delayed phase CCT was performed 7 min after contrast material injection. The parameters for CT scanning and image reconstruction for ECV analysis were as follows: 120 kVp, 750 mA, 0.275 ms/rot, a model-based iterative reconstruction algorithm (Forward projected model-based Iterative Reconstruction Solution), 18.0-cm display field of view, section thickness: 0.5 mm. Each original dataset of 0.5-mm axial images was processed for multiplanar reformation in the short-axis plane with a section thickness of 5.0 mm. Regions of interest were placed in the septum and blood pool in the mid-left ventricular unenhanced and delayed phase CCT short-axis images. For ECV measurement, a septal segment was chosen because improved accuracy has previously been demonstrated using septal regions of interest compared with analysis of all mid-ventricular segments on short-axis images.^{19,20} The ECV value was calculated as follows: ECV (%) = $(1 - \text{haematocrit}) \times (\Delta\text{myo} \div \Delta\text{blood pool}) \times 100$, where $\Delta\text{myo} = \text{myocardial HU (postcontrast)} - \text{precontrast}$ and $\Delta\text{blood pool} = \text{left ventricular blood pool HU (postcontrast)} - \text{precontrast}$.

Anthracycline administration regimen

In FEC therapy, fluorouracil, epirubicin, and cyclophosphamide were administered at 500, 100, and 500 mg/m², respectively; in EC therapy, epirubicin and cyclophosphamide were administered at 90 and 600 mg/m², respectively; and in AC therapy, doxorubicin and cyclophosphamide were administered at 60 and 600 mg/m², respectively, usually every 3 weeks (or every 2 weeks for dose-dense therapy). Trastuzumab and radiation therapy were used sequentially after anthracycline-containing regimen.

Definition of cancer therapy-related cardiac dysfunction

A decrease in the LVEF > 10 percentage points and to a value $< 53\%$ was defined as CTRCD, according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging expert consensus.²¹ The utility of echocardiography in the detection of CTRCD was described in the expert consensus above.²¹

Anthracycline equivalence dose

The anthracycline equivalent dose was calculated based on a position paper.¹ In brief, the relative cardiotoxicity of epirubicin to doxorubicin was 0.7.

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of the distribution of continuous data. Continuous variables with a normal distribution are expressed as the mean \pm standard deviation. Categorical data are presented as numbers or percentages. Differences between two groups were tested using Fisher's exact test or the χ^2 test for categorical variables and the Mann–Whitney *U* test for continuous variables, as appropriate. The data on the effect of anthracycline administration on each parameter described in *Figure 3* were analysed with one-factor analysis of variance with repeated measures followed by the post hoc Bonferroni multiple comparisons test. A *P* value < 0.05 was considered to denote statistical significance. Statistical analyses were performed using SPSS Version 27 (IBM Inc., Armonk, NY, USA).

Results

Clinical characteristics of enrolled patients

Patient characteristics, such as demographics, chemotherapy regimens, anthracycline doses, and cardiovascular risk profile, are shown in *Table 1*. Fourteen patients received epirubicin and cyclophosphamide therapy (EC therapy). One patient received doxorubicin and cyclophosphamide therapy (AC therapy). The cumulative anthracycline dose in all patients was 269.9 ± 14.6 mg/m² (doxorubicin-converted dose). Five patients received trastuzumab therapy, and two patients received radiation therapy. The LVEF was $66.6 \pm 3.2\%$ at baseline.

Serial changes in blood biomarkers

None of the 15 patients treated with anthracycline developed CTRCD during the observation period. In all patients, obstructive coronary artery disease was excluded by CCT angiography.

Figure 3A,B shows serial changes in plasma BNP level and serum hsTnT level, respectively. Plasma BNP levels tended to increase slightly, but no significant change was observed. Serum hsTnT levels increased significantly 3 months after anthracycline treatment (*P* < 0.01 , vs. baseline) and then gradually decreased to the normal range. Case by case delineations were shown in Supporting Information, *Figure S2*.

Serial changes in echocardiographic parameters

Figure 3C,D shows LVEF and GLS determined by echocardiography, respectively. LVEF decreased significantly 3 months after anthracycline treatment (*P* < 0.01 , vs. baseline) and con-

Table 1 Baseline characteristics of enrolled patients

	All patients (n = 15)
Age (years)	62.1 \pm 10.3
BMI (kg/m ²)	22.7 \pm 4.2
BSA (m ²)	1.54 \pm 0.13
Breast cancer profile	
Cancer stage	
0–I (%)	6 (40)
II–IV (%)	9 (60)
Unknown (%)	0 (0)
Chemotherapy	
FEC (%)	0 (0)
EC (%)	14 (93)
AC/FAC (%)	1 (7)
Anthracycline dose ^b (mg/m ²)	269.9 \pm 14.6
Molecular target therapy ^a	5 (33)
Trastuzumab (%)	5 (33)
Bevacizumab (%)	0 (0)
Pertuzumab (%)	4 (27)
Lapatinib (%)	0 (0)
Radiation therapy (%)	2 (13)
Cardiovascular risk profile	
Hypertension (%)	6 (40)
Diabetes mellitus (%)	2 (13)
Dyslipidaemia (%)	10 (67)
CKD (%)	1 (7)
Prechemotherapy LVEF (%)	66.6 \pm 3.2
Prechemotherapy BNP (pg/mL)	13.5 \pm 7.6

Data are presented as the mean \pm SD, or number (percentage). AC, doxorubicin and cyclophosphamide; BMI, body mass index; BNP, plasma B-type natriuretic peptide concentration level; BSA, body surface area; CKD, chronic kidney disease; EC, epirubicin and cyclophosphamide; FAC, fluorouracil, doxorubicin and cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; LVEF, left ventricle ejection fraction.

^aOverlaps possible.

^bDoxorubicin-converted dose.

tinued to decrease during the observation period. GLS decreased significantly 6 months after anthracycline treatment (*P* < 0.01 , vs. baseline) and continued to decrease during the observation period. *Figure S1* shows more echocardiographic data concerning the LV systolic and diastolic function.

Serial changes in cardiac computed tomography-derived extracellular volume fractions

Representative CCT-derived ECV images are described in *Figure 2*. *Figure 3E* shows serial change in GLS determined by echocardiography and in ECV determined by CCT. ECV gradually increased, and a significant difference was observed 12 months after anthracycline treatment. *Table S1* shows clinical characteristics of enrolled patients according to ECV changes. ECV increase and decrease groups show the group in which ECV increased (*n* = 8) and the group in which ECV decreased (*n* = 7) at the third month compared with baseline, respectively. Prechemotherapy LVEF in ECV increase group was significantly lower than in ECV decrease group.

Figure 2 Cardiac computed tomography (CCT) imaging. ECV, extracellular volume; GLS, global longitudinal strain as determined by UCG; hsTnT, high-sensitivity troponin-T; LVEF, left ventricular ejection fraction as determined by UCG.

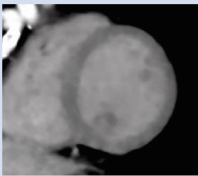
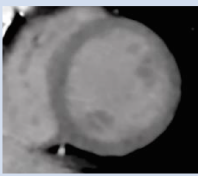
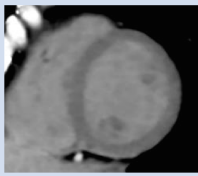
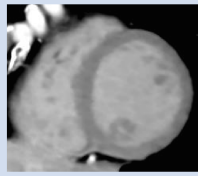
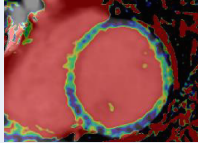
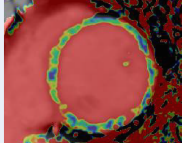
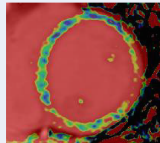
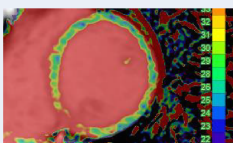
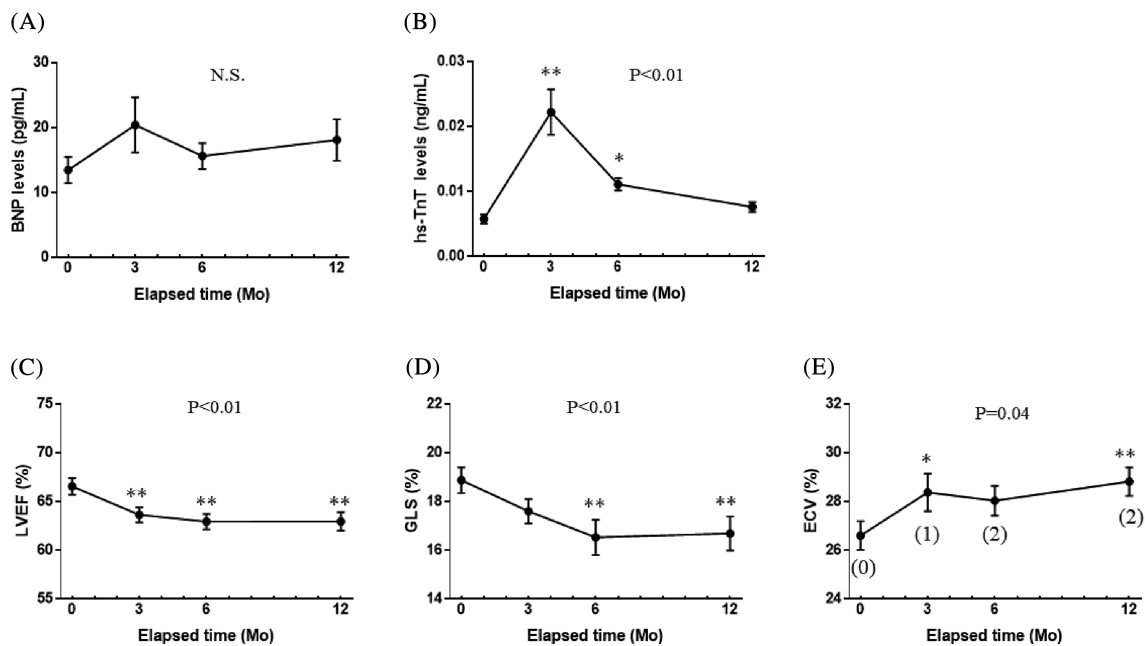
	Baseline	3 Month	6 Month	12 Month
CCT Image				
CCT ECV Map				
ECV (%)	24.0	27.9	26.2	29.1
LVEF (%)	65.4	63.0	60.6	65.1
GLS (%)	23.8	20.1	19.0	18.7
hsTnT (ng/mL)	0.0030	0.0106	0.0077	0.0042

Figure 3 Serial changes in plasma BNP concentration level, serum hsTnT concentration level, LVEF, GLS, and ECV in anthracycline-treated patients. All data are expressed as the mean \pm standard deviation. Zero indicates baseline. The numbers in parenthesis indicate the number of late iodine enhancement (LIE) patients. BNP, plasma B-type natriuretic peptide concentration levels; ECV, extracellular volume fraction; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction. * $P < 0.05$ vs. baseline, ** $P < 0.01$ vs. baseline.



Discussion

The main purpose of this study was to investigate serial changes in potent factors related to myocardial impairment, including myocardial tissue characterization determined by CCT-derived ECV fraction in anthracycline-treated breast cancer patients, and the main findings of this study were as follows: first, serum hsTnT concentration increased at peak within 3 months after anthracycline treatment, but gradually decreased to the normal range; second, LVEF and GLS as determined by echocardiography decreased after anthracycline treatment and tended to keep decreasing gradually; third, the CCT-derived ECV fraction tended to continue to increase after anthracycline treatment and had relatively similar dynamics to the abovementioned LVEF and GLS.

Great strides have been made in cancer treatment, which has greatly improved the prognosis of cancer patients. Especially for cancer chemotherapy, in addition to 'classic' anthracycline anticancer drugs and platinum preparations, molecular targeted therapies and immune checkpoint inhibitors continue to be developed, and these preparations also contribute to extending the lifespan of cancer patients. The effects of these drugs on the cardiovascular system can force cancer treatment to be discontinued and can sometimes lead to fatal cardiovascular complications. Therefore, oncocardiology-specialized cardiovascular evaluation and therapeutic intervention are required for cancer treatment.²²

Since the contrast of the tissue is clear on CMR imaging, many T1 mapping techniques have been reported for assessing myocardial oedema and fibrosis. It has been reported that potential myocardial damage caused by anthracyclines shows a high signal on T1 mapping.²³ In addition, it has been reported that in cardiomyopathy caused by trastuzumab, a large distribution of LGE is observed in the middle layer of the myocardium on the lateral wall,²⁴ and CMR may be useful for early diagnosis. On the other hand, patients with indwelling internal metals, such as non-MRI-conditional pacemakers and implantable cardioverter defibrillators, cannot be examined with CMR, and there are many problems in terms of cost and convenience. Recently, this information was comprehensively reviewed.^{25,26}

Echocardiography is highly versatile and can be used to repeatedly evaluate cardiac function. Conventionally, LVEF has been used as the standard for the diagnosis of CTRCD, but in recent years, it has been reported that early CTRCD can be detected using the GLS, which is known as the myocardial strain method, as an index. Many guidelines recommend measuring GLS values.¹⁻³ Recently, we reported that left atrium reservoir function as determined by echocardiography may be an optimal indicator of CTRCD.¹⁶ Echocardiography has numerous advantages, such as wide availability, lack of radiation, and the ability to assess haemodynamics and cardiac structures; however, its major limitations include inter-observer variability, intraobserver variability, test-retest vari-

ability, intervendor variability,²⁷ image quality, and technical requirements.¹ Contrast echocardiography and real-time 3D echocardiography have been used to reduce interobserver variability and improve the quality of image rendering, but they have not yet become widespread in clinical practice.²⁸

Regarding CCT, CMR and echocardiography were originally superior in morphological evaluation, and the usefulness of CCT has been considered to be poor from the perspective of cardiac function evaluation.²⁹ Therefore, in the cardiooncology field, contrast-enhanced CT has been useful for diagnosing deep vein thrombosis and pulmonary embolism.³⁰ However, our previous report demonstrated consistency between CCT and CMR in CTRCD cases,^{6,7} showing that in patients with significant LV dysfunction as detected by echocardiography after anthracycline therapy, CCT could detect changes in myocardial tissue characterization. These previous reports indicated that CCT may be comparable with CMR, indicating that CCT could effectively evaluate CTRCD.

In the present study, we first demonstrated the clinical usefulness of CCT in the cardiooncology field in terms of serial changes in the CCT-derived ECV fraction in patients administered anthracycline. Interestingly, prechemotherapy LVEF in ECV increase group was significantly lower than in ECV decrease group (*Table S1*). These results were consistent with and may complement previous reports that prechemotherapy LVEF was one of predictor of CTRCD onset.^{2,31}

Cardiac computed tomography is not only simply and easily performed in clinical practice but also well validated and inexpensive, which indicates that the method can be widely applied. Moreover, this novel CT imaging method can be performed in conjunction with standard coronary artery evaluation and cancer follow-up, possibly contributing to an examination cost reduction. In other words, CCT may compensate for the weaknesses of echocardiography. ECV evaluation by CCT involves an increase in the radiation dose, and it provides little functional information over echocardiography despite the increased radiation exposure. It is well known that the increase in ECV is closely correlated with tissue fibrosis and oedema, and an increase in ECV is also observed in the myocardium where abnormalities cannot be detected by LGE in CMR.³² Therefore, an increase in ECV value has the potential to detect myocardial damage that cannot be detected by echocardiography or biomarkers. CCT may be an important way to effectively identify patients with suspected CTRCD by echocardiographic functional evaluation and then assess the characteristics of myocardial tissue. It is highly likely that combining CCT and echocardiography will result in improved evaluation of myocardial properties as well as increased diagnostic ability. In other words, CCT and echocardiography can complement each other to improve the diagnostic ability of cardiotoxicity. Importantly, large-scale clinical trials are essential to examine the usefulness of CCT and to show the role of CT-ECV in clinical studies in the cardiooncology field.

Study limitations

The present study has some limitations. First, it was a single-centre study with a very small population. Therefore, a larger multiracial and multicentre study is required. Second, we could not compare patients receiving anthracycline and patients receiving no drugs because of the lack of a control group (non-cancer group/non-anthracycline group). Third, verification of CTRCD by using other drug classes, such as trastuzumab, is mandatory. Moreover, the effects of concomitant agents must be verified. Furthermore, in the present study, 2 out of 15 patients had a history of radiation therapy, and thus, the effect of LV systolic/diastolic dysfunction associated with radiation therapy³³ cannot be ruled out. Finally, no patients in the study developed CTRCD; thus, it is not clear that changes in ECV derived by CCT have any clinical significance. Hence, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Additional detailed, large-scale clinical studies may be required to verify our theories.

Conclusions

Despite these limitations, we have clearly and for the first time demonstrated serial changes in the CCT-derived ECV fraction in patients after anthracycline administration. This simple but novel method could be useful for understanding cardiac tissue characterization as a 'one-stop shop' evaluation, providing new insight into cardiooncology.

Acknowledgements

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Conflict of interest

Prof Matsushita belongs to the endowed division sponsored by Abbott Medical Japan LLC, Boston Scientific Corporation, Cardinal Health Japan G.K., Fides-one, Inc., Getinge AB, GM Medical Co., Ltd., ITI, Japan Lifeline Co., Ltd., Kaneka Medix Corporation, Kikuchi Medical Association, Koninklijke Philips N.V., Medtronic Japan Co., Ltd., Nipro Corporation, and

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Serial changes in left ventricle (LV) volume (A), E/e' (B) and E/A (C) in echocardiographic data.

LVEDV: LV end-diastolic volume, LVESV: LV end-systolic volume.

Figure S2. Serial changes in plasma BNP concentration level, serum hsTnT concentration level, LVEF, GLS, and ECV in anthracycline-treated patients (case by case delineation)

0 month indicates baseline.

Abbreviations as shown in Figure 3.

Table S1. Baseline characteristics of enrolled patients according to ECV changes.

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