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Extracellular volume measured by whole body CT scans predicts chronic cardiotoxicity in breast cancer patients treated with neoadjuvant therapies based on anthracyclines: A retrospective study

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ABSTRACT

Introduction: Neoadjuvant chemotherapies for breast cancer (BC) are effective but potentially cardiotoxic, and expose long survivors at risk of chemotherapy-related cardiac dysfunction (CTRCD). Unfortunately, early screening for CTRCD has actual diagnostic limits. Myocardial extracellular volume (mECV) is a radiological marker used in cardiac CT scans and cardiac magnetic resonance for diagnosis and follow-up of CTRCD. It can be measured in whole-body CT (WB-CT) scan, routinely performed in patients at high risk of relapse, to evaluate CTRCD occurrence during oncological follow-up.

Methods: 82 WB-CT scans were examined at baseline (T_0) and during oncological follow-up at first year (T_1) and fifth year (T_5) after the end of neoadjuvant treatment. mECV was measured at 1 min (PP) and 5 min (DP) after contrast injection. 31 echocardiograms were retrieved in T_1 to perform a linear correlation between mECV and left ventricular ejection fraction (LVEF).

Results: mECV values in T_0 were similar between the two groups both in PP and in DP. Significant results were found for PP values in T_1 (37.0 % vs 32 %, $p = 0.0005$) and in T_5 (27.2 % vs 31.2 %, $p = 0.025$). A cut-off value of 35 % in PP proved significant in T_1 (OR = 12.4, $p = 0.004$), while mECV was inversely correlated with LVEF both in PP (adj-S = −3.54, adj-p = 0.002) and in DP (adj-S = −2.51, adj-p = 0.0002), suggesting a synergistic action with the age at diagnosis ($p < 0.0001$, respectively).

Conclusions: WB-CT scans performed during oncological reassessment in patients at high-risk of recurrence could be used for CTRCD screening in cardiovascular low-risk patients, especially in aging patients with mECV values above 35 %.

1. Introduction

Breast cancer (BC) management has achieved improvements in neoadjuvant chemotherapy (NACT), exceeding a 70 % 10-year survival in Europe, providing survival rates of 89 % and 62 % in local and regional diseases, respectively [1,2]. However, despite progresses in oncological therapies and diagnostic tools [3], the occurrence of cardiovascular disease (CVD) is still an issue for cancer patiens [4,5] being a potential consequence of cancer treatments [6]. For long-surviving patients, cancer therapeutics-related cardiac dysfunction (CTRCD) caused by potential cardiotoxic drugs could undermine the oncological outcomes. Despite their renowned cardiotoxicity, anthracyclines (AC), represent the first option for the high-risk patients with triple negative BC and very selected luminal-like BCs [2]. Analogously, in human epidermal growth factor receptor 2 (Her-2) positive BC, anti-Her-2-based schemes with Trastuzumab (T) are used in both neoadjuvant and adjuvant settings [7,8]. In the latter, the combination of AC + T is still used in some cases, although modern protocols suggest to de-escalate AC in patients with low risk Her-2 positive BC or to use anti-Her-2 dual blockade [2,7,9,10]. CTRCD has been widely reported as

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an adverse event of both drugs, ranging between 5-48 % and 1.7–44 %, for AC and T, respectively [10–12], although moderate-to-severe CTRCDs are found in 5.8 % and 6.2 % of cases, respectively [10] and 7.0 % of events are observed when used sequentially [10]. Reliable biomarkers for CTRCD early detection are still lacking, as Troponins I/T (Tn I/T) are burdened by a consistent rate of false positive and negative results, while Brain Natriuretic Peptides (BNP) are tardive markers of heart failure [13,14]. Both biomarkers have low overall sensitivity and positive predictive value (69 % and 52 %, respectively) [15]. Echocardiography is limited by interference of breast surgical scar and by a tardive increase of left ventricular ejection fraction (LVEF) [16–18]. A recent echocardiographic technique, the Speckle Tracking, aimed at studying the residual elasticity of cardiac tissue by measuring the reduced Global Longitudinal Strain (GLS) [13,19], has proven unsuccessful in guiding the choice of cardio-protective therapy [19,20]. Among the new markers under investigation [16–18] stands the myocardial extracellular volume (mECV), a radiological marker reflecting the expenditure of the contrast mean in the myocardial interstitial space [21,22]. It may increase in the presence of edema and interstitial fibrosis [21–23] and it is utilized as an early predictor of myocardial injury in cardiac Magnetic Resonance Imaging (cMRI) [23] or Computed Tomography (CT) scan [24,25]. Normal values range between 20 and 30 % and greater values are considered pathological [23]. Although mECV assessment is already widely validated in cMRI, its costs prevent its routine use in cardio-oncology [24,26]. Conversely, CT scan provides acceptable results concordant with histological findings [24–26]. Indeed, patients who underwent AC treatments showed a significant correlation with mECV values when adjusted for age [27,28]. Therefore, the evaluation of mECV values in whole body (WB)-CT scan used for disease restaging in symptomatic patients and selected high risk patients, might be useful for early detection of asymptomatic and unexpected damage to cardiac tissue in low cardiovascular risk patients [4]. However, studies are limited as they measure mECV values only in a delayed phase, in 7–10 min after contrast medium injection, thus leading to a loss of information on its early spread in cardiac tissue.

Hypothesizing different trends between portal and delayed phase,

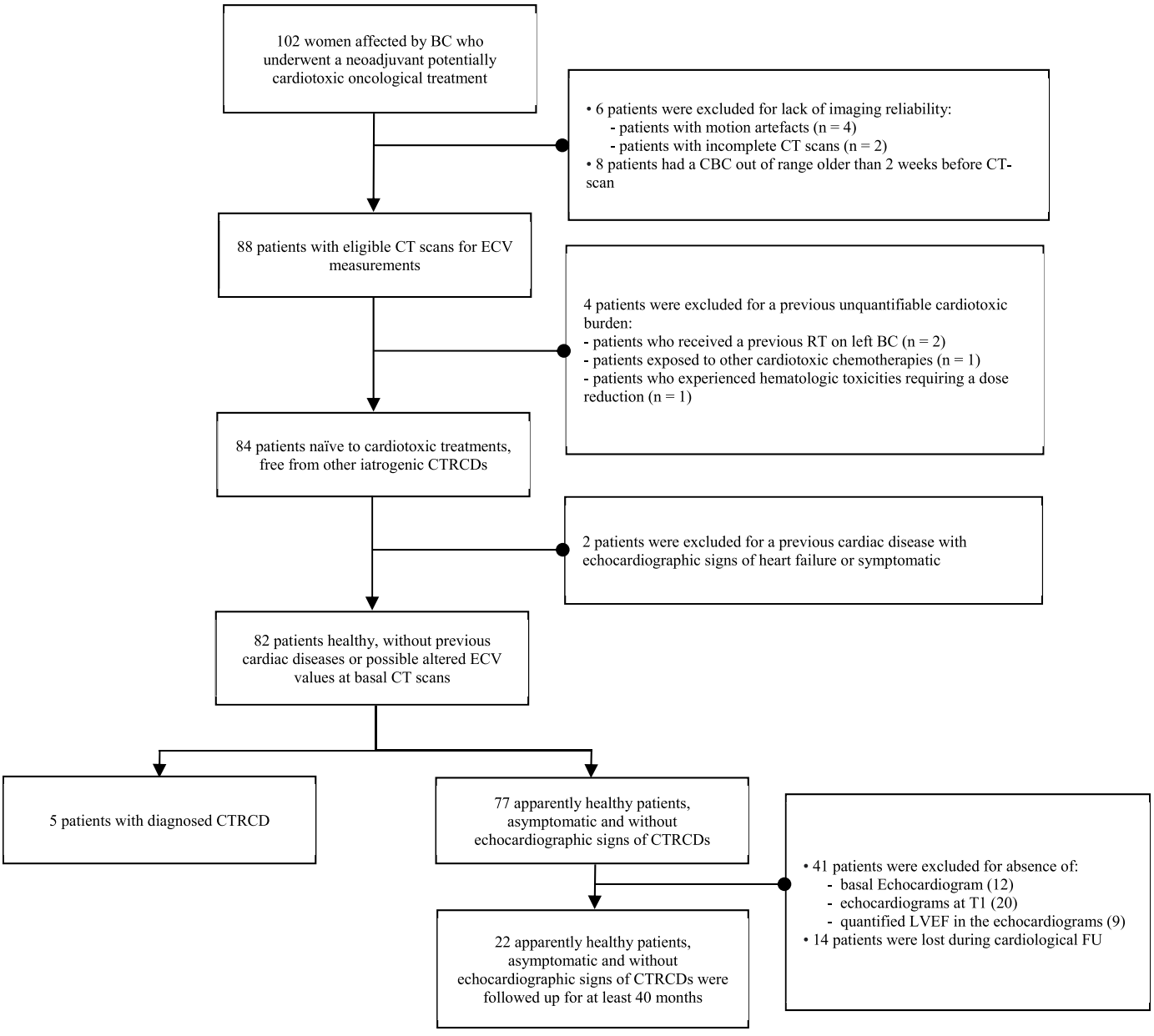

Fig. 1. Flowchart of exclusion criteria.

we evaluated the differences in mECV values in BC patients exposed to cardiotoxic drugs.

2. Methods

2.1. Study design

We retrospectively evaluated 102 women affected by BC, who were treated with neoadjuvant chemotherapy, based on AC or T, between January 2010 and July 2016 at the Oncology Department of Tor Vergata University Hospital. Patient eligibility was checked according to the following criteria:

- Age $\geq$18 years
- A WB-CT scan performed before treatment (T_0), after 12 $\pm$ 3 months (T_1) and after 60 $\pm$ 6 months (T_5);
- A complete blood cell count (CBC) not older than 2 $\pm$ 1 weeks from the beginning of NACT;
- An echocardiogram performed at T_0 and at T_1.

Exclusion criteria were (a) patients with personal history of any cardiovascular disease, (b) patients who received a reduced dose of NACT due to toxicity, (c) patients relapsing or with a second tumor requiring an additional oncological treatment and (d) patients who developed a CTRCD before T_1 time point.

Eighty-two patients were found eligible and were divided in two observational arms based on the cardiotoxic occurrence, the CTRCD group and the non-CTRCD group, to perform a retrospective association study (Fig. 1).

2.2. Definition of CTRCD

Included patients were studied retrospectively in a follow up of 5 years for cardiotoxicities occurring after the first year of follow up. CTRCDs were defined in agreement with European society of cardiology (*ESC) guidelines for cardio-oncology 2022* [13] as (1) onset of symptomatic HF (2) asymptomatic drop of LVEF >10 % from baseline and under the value of 53 % at ultrasonography (US), (3) onset of other relevant cardiac diseases such as myocardial infarction, moderate-to-severe valvulopathy, arrhythmias or cardiopathies.

2.3. CT acquisition protocols

WB-CT scans were performed with a 128-layer CT scanner (GE-Healthcare; Revolution EVO, CT, General Electrics Medical System, Milwaukee, WI, USA) using a multi-step spiral acquisition following a cranial–caudal direction, including abdomen, part of the thorax, heart and cranium. In contrast with standard cardiac CT protocol, all acquisitions were performed without ECG gating during the oncological reassessments. Imaging acquisition included a baseline scan and three subsequent scans before the administration of 100–120 mL of iodinated contrast medium (Iomeron 350 mg/mL, Bracco Imaging) followed by 30–50 mL of saline at 3 mL/s. Post-contrast scans were acquired applying a threshold of 120 HU placing a region of interest (ROI) in the descending aorta at the thoracic-abdominal passage,

In this way, three phases were obtained:

- Arterial phase, generally about 15–18 s after contrast injection;
- Portal phase, 1 min after contrast injection (Fig. 2-A);
- Delayed phase, about 5 min after contrast injection (Fig. 2-B).

Radiation doses were reported using the following formula: dose length product (DLP) expressed in mGy $\times$ cm (DLP value for each patient were extracted).

The WB-CT images were evaluated by two radiologists with 15 years of experience in cardiovascular radiology, blinded to each other refer-

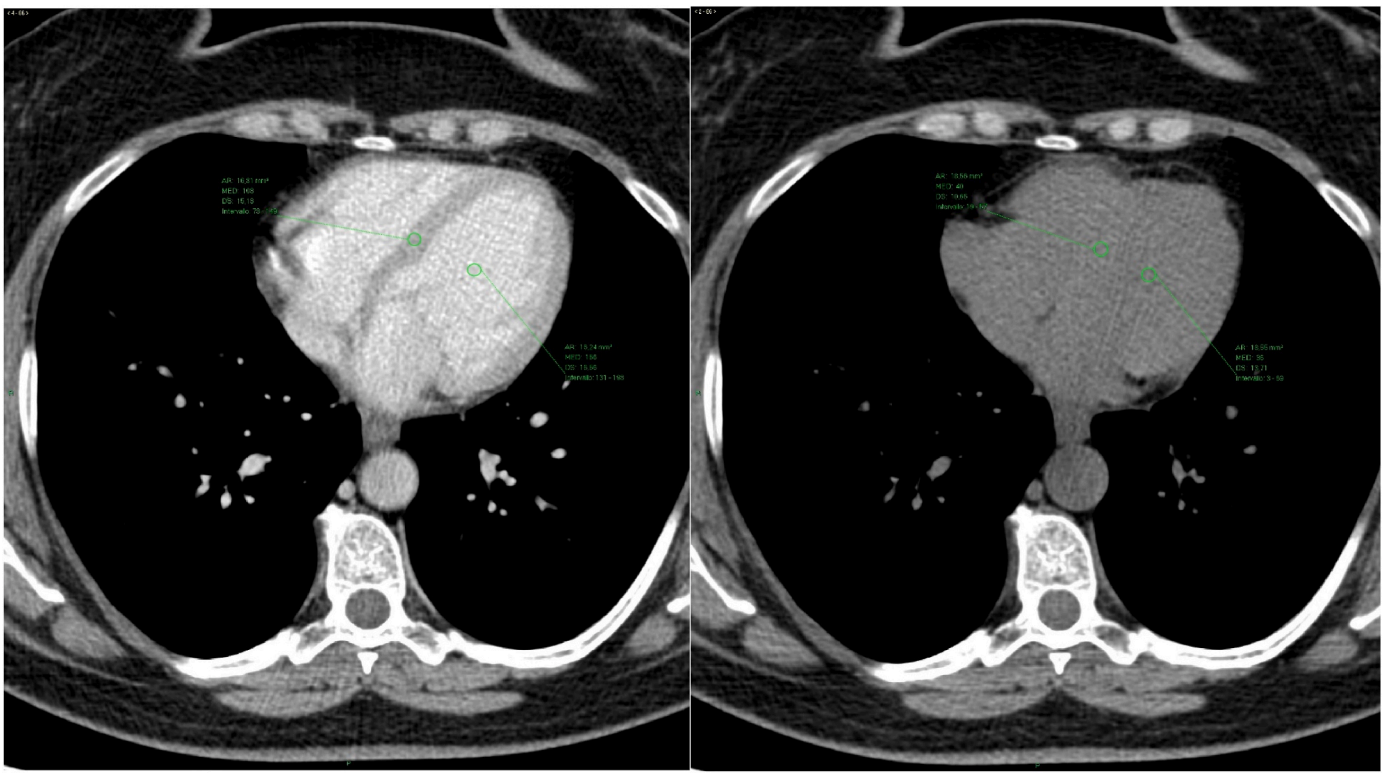

Fig. 2. ROI (green arrows) located in the interventricular septum and left intraventricular blood pool in CT scans acquired (A) during the portal phase (1 min after contrast medium injection) and (B) in the delayed phase (5 min after contrast medium injection), respectively, and in the portal phase. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ring to a third radiologist for solving discrepancies. One ROI was drawn in the thickest portion of the middle septum and another one of equal proportions in the "blood" pool of the left ventricle, avoiding the papillary muscles. ROIs were measured in the three phases (basal, portal, and delayed phase) at T_0, T_1 and T_5. Hounsfield units (HUs) obtained were included in the following formula [29]:

$$ECV = (1\text{–haematocrit}) \bullet \left[\left(Humyo_{post} - Humyo_{pre}\right) \Big/ \left(Hublood_{post} - Hublood_{pre}\right)\right]$$

resulting in ECV values measured in PP and DP.

2.4. Statistical analysis

The quantitative and normally distributed variables were presented as mean ± standard deviation (SD), otherwise, data was described with median ± interquartile range (IQR). ANOVA test was performed after Shapiro–wilk's tests and Mauchly's test that confirmed normality and sphericity, respectively. Welch's t-tests for paired data were conducted between the independent groups with different or not known variances, whereas, for not normally distributed populations, a Wilcoxon test for paired data was used. A multiple linear regression was performed together with the interaction tests for the predictors, whereas the residual analysis was performed to check the goodness of the results. Finally, Fisher's exact test and odds ratio were used to find a possible predictive cut-off of ECV. All the tests and plots were performed with a two-sided $\alpha = 0.05$ as significance level, using Rstudio software v 4.0.4.

3. Results

In the overall selected population (n = 82) median age was 45 ± 4.5 (±IQR) years, with a baseline (T_0) LVEF 65 % ± 3.5 % versus T_1-LVEF of 60 % ± 2.5 %. All patients were apparently healthy and asymptomatic before starting the oncological treatments, reporting a mean LVEF>50 % at the echocardiogram. Post-menopausal women were 37 % of the whole cohort, with 4.5 ± 2.3 years (median ± IQR) from the menopausal age; the known smokers were 26.8 % and smoked about 19 ± 5.1 pack/years; patient's comorbidities were type-2 diabetes (19.5 %), hypertension (17.1 %), hypercholesterolemia (31.7 %). Body Mass Index (BMI) reported in the population was 22.4 ± 2.6 (median ± IQR), with 17.1 % of underweighted patients (BMI<19.5) and 17.1 % of overweighted (BMI>30) individuals. In the control group, only 22 patients reported complete clinical data on LVEF values.

Among the 82 selected patients, 5 cases of CTRCD were recorded with a median time-to-event ranging between 14 and 23 months. Indeed, 2 patients suffered of >15 % LVEF reduction, 1 patient reported arrhythmia (atrial fibrillation) and massive pericarditis, and 1 patient reported an asymptomatic LVEF decrease under 50 % (LVEF 40 %). On the other hand, 77 patients remained apparently healthy and asymptomatic during the 5-year FU. Consequently, the *CTRCD-arm* (n = 5) was compared with the apparently healthy *non-CTRCD arm* (n = 77), assessing the general trends in mECV values.

3.1. Analysis in CTRCD-arm at T_1 and T_5 in the portal phase (PP) and delayed phase (DP) settings

We observed different trends in mECV values among the different time points (T_0, T_1, T_5) in the PP setting, showing a significant difference after the ANOVA test (F = 14.14, p = 0.0007). At the pairwise analysis, we found increased mECV values with a relative difference (RD) of 23.5 % from T_0 to T_1 (30.0 % vs 37.0 %, $t_4 = 4.17$, p = 0.014), while no significant variations were observed between T_0 and T_5 (30.0 % vs 28.4 %, $t_4 = 1.04$, p = 0.36) (Fig. 3A). Conversely, a significant decrease of mECV was registered from T_1 to T_5 (RD -23.3 %, $t_4 = -10.6$, p = 0.0004).

The analyses were performed also in the DP setting (Fig. 3B), showing a significant difference among the three groups (F = 7.84, p = 0.007), confirmed at the subgroup analyses, with a significant increase (RD = 45.6 %) of mECV from T_0 to T_1 (26.0 % vs 37.8 %, $t_4 = -4.4$, p = 0.012). Similarly, a significant result from T_0 to T_5 ($t_4 = -4.7$, $p < 0.01$) was detected (Fig. 3B). Noteworthy, no significant variations were detected when T_1 and T_5 were compared ($t_4 = 1.0$, p = 0.38) in the DP setting.

3.2. Comparisons between CTRCD-arm vs non-CTRCD in the PP and in the DP setting

The direct comparison of mECV values between the CTRCD-arm and the non-CTRCD arm was performed at each time point in both PP and DP setting. No difference was found in T_0 confirming the initial absence of cardiac damage both in PP ($t_{80} = 1.64$, p = 0.11) and DP ($t_{80} = -1.1$, p = 0.28) (Fig. 4). At T_1, a significant difference was detected, showing a relative increase of 14 % (p = 0.0005) in the CTRCD group values. Surprisingly, at T_5 we observed lower mECV values for the CTRCD group with a statistically significant relative reduction of 12.7 % of the mean values ($t_{6.5} = -2.88$, p = 0.025) (Fig. 4-A). Conversely, no significant differences were observed in the DP setting (Fig. 4-C and D).

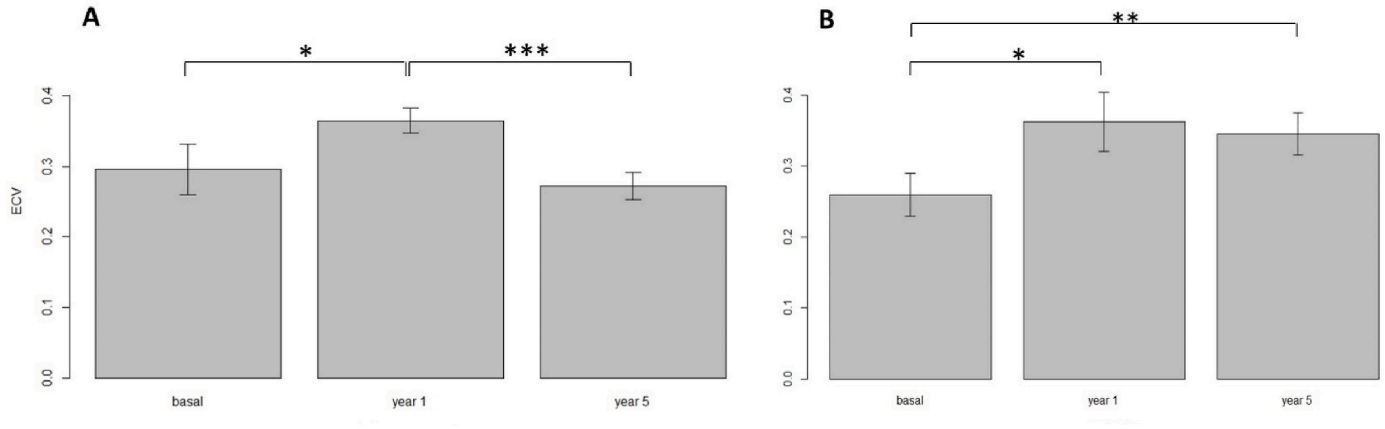

Fig. 3. Trend of mECV values in CTRCD group during oncological follow up. mECV mean values measured in patients with CTRCDs at different timepoint during the follow up, at baseline (T_0), at first year (T_1) and at fifth year (T_5) in **A.** Portal phase and **B.** Delayed Phase. Comparisons were performed with a 2-sided Wilcoxon test. * ($p < 0,05$), ** ($p < 0.01$), ***($p < 0.001$).

A

FU year	Portal Phase		
	CTRCD (Mean + SD)	Non-CTRCD (Mean + SD)	*p-value*
Baseline (T_0)	30.0% ± 3%	26.9% ± 4%	*0.11*
First year (T_1)	36.5% ± 2%	32% ± 5%	*0.0005***
Fifth year (T_5)	27.2% ± 2%	31.2% ± 5%	*0.025**

FU year	Delayed Phase		
	CTRCD (Mean + SD)	Non-CTRCD (Mean + SD)	*p-value*
Baseline (T_0)	26.0% ± 3%	28.7% ± 5%	*0.28*
First year (T_1)	36.3% ± 4%	34,6% ± 7%	*0.29*
Fifth year (T_5)	34,6 ± 3%	31,8% ± 7%	*0.07*

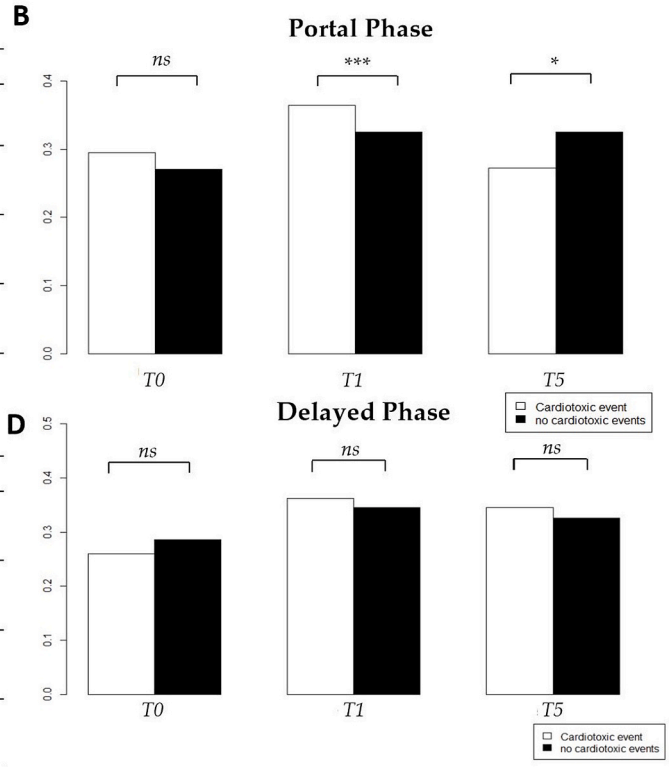

Fig. 4. Comparison of mECV values between CTRCD and non-CTRCD group. The mECV values of patients with CTRCD were compared with ethe values of apparently healthy patients at T_0, T_1 and T_5 both in PP (**A-B**) and DP setting (**C-D**). The results are presented as values (mean ± SD) in tables (**A-C**), whereas they are graphed in barbplot in **B-D**. Of note, in T_1 and in T_5 we observed a statistically significant reduction of mECV values for patients with CTRCD in PP ($p = 0.0005$) and in DP ($p = 0.025$), whereas no significant difference was observed in DP settings ($p = 0.29$ and $p = 0.07$, respectively.). Comparisons were performed with 2-sided welch's *t*-test.

3.3. Correlation between LVEF and mECV values at T_1 in general sample and CTRCD group

Correlation analyses were conducted on the two arms after all echocardiograms were retrieved and all patients with incomplete information were excluded (Fig. 1). As a result, we confirmed from general population a sample (GS) of 27 patients (median age 45 ± 4 years), gathering data for their Cardiac Risk Factor (CRF) useful for the further analyses. A cardiotoxicity (CarTox, n = 5) group and a non-CarTox group (n = 22) were defined, and their baseline CFR and characteristics are enlisted in Table 1.

3.3.1. Correlations in the General Sample

Firstly, we analyzed the GS without further distinctions considering ECV in the PP phase (PP-ECV) at the T_1 time point. As a result, no significant correlation was found between changes in LVEF (Δ-LVEF) nor in PP-ECV ($s = -0.04$, $R^2 = 0.002$, $p = 0.83$), when simple regression was performed. Of note, after the multiple regression the adjusted values of PP-ECV became strongly significant (adj-S = −3.54; adj-p = 0.002) while a significant interaction ($p = 0.002$) between PP-ECV and age at diagnosis (AD) was found, suggesting a possible synergistic effect between these two predictors on the final outcome of Δ-LVEF (Table 2A).

On the other hand, in the DP, ECV absolute values (DP-ECV) were significantly correlated with Δ-LVEF ($S = -0.29$, $r = -0.2$, $R^2 = 0.14$, $F_{28} = 4.6$, $p = 0.04$) showing an inverse relationship at T_1 (Table 2B and Fig. 5A). The values were found to be still statistically significant when regression analysis was performed, and an interaction between DP-ECV and AD was found (adj-$R^2 = 0.55$, $F_{26} = 4$. Residual SE = 0.04, Fig. 5A). Notably, also DP-ECV resulted to be even more significant when the interaction test was performed ($p < 0.0001$), suggesting, also in this case, an additional and synergistic effect. DP-ECV did not show any additional significant interaction with other patient's characteristics, (data not shown).

Table 1
Characteristics and cardiac risk factor (CRF) of the general sample (GS).

Variables	Arm CarTox (n = 5)	Arm non-CarTox (n = 22)	p-value
Age (years, median ± IQR)	45 ± 7	45 ± 4	*0.72*
Menopause (RF)	2 (0.4)	5 (0.2)	*0.60*
Type of carcinoma			
Infiltrating ductal (RF)	2 (0.4)	14 (0.56)	–
Infiltrating lobular (RF)	1 (0.2)	4 (0.16)	–
Poorly differentiated (RF)	1 (0.2)	7 (0.28)	–
Mucinous (RF)	1 (0.2)	0	–
Comorbidities			
DiabetesMellitus (RF)	2 (0.4)	4 (0.2)	*0.24*
Hypertension (RF)	2 (0.4)	4 (0.2)	*0.17*
Smoking (RF)	2 (0.4)	6 (0.2)	*0.84*
Hypercolesterolemia (RF)	1 (0.2)	8 (0.3)	*0.54*
Treatment choice			
Doxorubicin	3	17	*0.77*
Trastuzumab	2	8	
Baseline LVEF (mean ± SD)	0.70 ± 0.03	0.65 ± 0.06	*0.13*
1st year LVEF (mean ± SD)	0.65 ± 0.05	0.65 ± 0.05	*0.28*
Hematocrit (%), mean ± SD	35.4 ± 0.05	36.2 ± 0.07	*0.76*

IQR: Interquartile range; RF: Relative Frequence; SD: Standard Deviation.

3.3.2. Correlations in the CarTox arm

The CarTox arm was analyzed to investigate whether PP-mECV and

Table 2
Results from analysis of linear regressions. The reported values are referring to simple linear regression (S-value; p-value; R^2-value) and to multiple regression with interaction test (adjusted values) between LVEF and the prognosticators (**A**) PP-ECV or (**B**) DP-ECV. Noteworthy a significant interaction was found between the ECV values measured both in portal phase (PP-ECV) and in delayed phase (DP-ECV) with the age at diagnosis (AD). Considering these synergies with AD, a stronger effect was found between (**A**) PP-ECV and LVEF (-3.54 vs -0.04, adj-*S* vs S) and a higher predictive capability of the model was described (0,25 vs 0.002, adj-R^2 vs R^2). Similar results were observed for PP-ECV (**B**), with an even higher predictive capability (0.55 vs 0.14, R^2 vs adj-R^2). R^2: coefficients of determination; S: linear coefficient (slope).

Prognosticators	S	p-value	R^2	Adj-R^2	Adj-S	Adj-p
A)						
PP-ECV (1min)	−0.04	0.83	0.002	0.25	−3.54	0.002
Age at Diagnosis (AD)	0.0006	0.63	0.008		0.03	0.008
Interaction test (AD*PP-ECV)	–	–	–		0.007	0.002
B)						
DP-ECV (5min)	−0.29	0.04	0.14		−2.51	0.0002
Age at Diagnosis (AD)	0.0006	0.63	0.16	0.55	0.03	0.0002
Interaction test (AD*DP-ECV)	–	–	–		0.007	<0.0001

DP-mECV could have a role in the clinical diagnosis of CTRCD. Unfortunately, no significant result was observed. Indeed, despite a clear trend towards decrease of the LVEF values while increasing DP-ECV at the first year ($S = -1.13$, Adj-$R^2 = 0.83$, $F_3 = 15.68$), the relationship was not statistically significant ($p = 0.058$, Fig. 5B). Importantly, this analysis had a low statistical power ($\beta = 0.66$), and the Spearman's rank coefficient was also significantly high ($r = -0.87$).

3.4. Definition of a predictive value for mECV values predicting CTRCDs

A reliable PP-ECV value able to distinguish patients who are developing a CTRCD from those who are still apparently healthy was evaluated. We found that a PP-ECV greater than 35 %, measured at T_1, predicted a risk to develop a CTRCD 12-fold higher than the non-CTRCD group (OR = 12.4, V = 0.49, p = 0.004, Fig. 5C).

3.5. Correlations in the AC-treated group and T-treated group

A last analysis was performed on the subgroups of patients receiving A (n = 20) or T (n = 10). The two subgroups were unrefined for CTRCD, because the number of events was too low (3 and 2 patients, respectively). However, also in this case, in the A-treated group we observed a non-significant trend for the PP-ECV ($S = 0.24$, $R^2 = 0.16$, $F = 3.4$, $p = 0.082$) and for DP-ECV ($S = -0.14$, $R^2 = 0.017$, $F = 0.32$, $p = 0.58$) during the first year follow up, whereas a significant inverse correlation was found between mECV values and Δ-LVEF when age at diagnose (AD) and menopause status were considered within an interaction test (Table 3). No positive result was obtained when T was analyzed (Table 3).

4. Discussion

Our investigation evaluated thoracic CT scans performed within a WB-CT oncological reassessment providing evidence of detectable and reliable measures of mECV whose values were differently expressed in patients who eventually developed CTRCD and who did not.

This approach provides promising data suggesting its use for CTRCD screening in long-survivors at low risk for cardiac events at baseline. Although 98 % of CTRCDs are generally expected within the first year [30], we suppose that the incidence of 2 % of late cardiotoxicity [30] might be underestimated because retrospective studies with longer follow up are few. In a previous study from our group, a significant increase of mECV values was observed in both acute and chronic cardiotoxicity settings[25]. In the present study, we analyzed the changes in mECV values in patients who developed cardiac dysfunction (CTRCD arm) and in those who did not (non-CTRCD arm), analyzing different phase, PP and DP. Indeed, significant increases from T_0 to T_1 were observed both in PP ($p = 0.014$) and in the DP phase ($p = 0.012$). These findings suggest that the maximum peak of mECV values for the CTRCD group arises at T_1, defining mECV measurements as a useful monitoring tool in the first year of follow up. These data are in agreement with previous evidences [28,31,32]. Noteworthy, a consistent mECV reduction from T_1 to T_5 was observed in the PP setting (RD -23.3 %, $p = 0.0004$) but not in the DP ($p = 0.38$), where mECV values remained stably high. Probably, the differences observed between PP and DP are caused in T_1 by myocardial edema for a (sub)acute inflammation, whereas in T_5 the chronic cardiotoxicity reflected myocardial fibrosis. Indeed, both conditions cause a slow contrast medium wash-out in DP as expected [28,31,32], while the hypovascularization within the scar could account for the slow wash-in observed in PP, as described in analogous diseases [33,34].

When the CTRCD and non-CTRCD groups were compared in the PP setting at T_5, even lower values were observed (27.2 % vs 31.2 %, $p = 0.025$). Also in this case, hypovascularization and ischemic disease with vessel obstruction after the CTRCD event could be hypothesized [33,34]. Remarkably, a statistically significant cut-off value ($V = 0.49$, $p = 0.004$) of 35 % predicted a 12-fold increased risk of developing CTRCD in patients with higher PP-ECV values. Indeed, all patients with CTRCD clustered in the lower-right "high-risk" quadrant, suggesting the same prognostic pattern, whereas, in DP setting, the relationship resulted not significant ($p = 0.29$).

A linear regression analysis was performed between mECV values and changes in cardiac contractility in the first year follow up (T_1). Analyzing the GS with a multiple regression analysis, a significant relationship was found when the interaction test with patient's AD was performed, both for PP-ECV and for DP-ECV. This suggests that AD and mECV should be considered synergistically to better explain the inverse relationship between Δ-LVEF and mECV. Noteworthy, when we analyzed the linear regression for the CTRCD group, despite the lack of statistical significance due to a low statistical power, we found a strong inverse correlation, indicating that results are promising. Lastly, correlation analyses were performed for the trastuzumab-treated women with negative results both in PP and DP setting, while for anthracyclines-treated women a significant inverse relationship with Δ-LVEF was found at the multiple regression after the interaction test between AD with both PP-ECV and DP-ECV, suggesting a synergistic model.

Although our data on non-CTRCD patients are consistent with those reported in the literature, to our knowledge we are the first to show data in CTRCD patients, reporting at baseline a range of mECV values (PP = 26.9–30 % and DP = 26–28.7 %) similar to previous observations [24,35,36]. Although our patients are younger (median 45 ± 4 years) than those described in other studies reported so far [24,26,36], the role of AD in reducing cardiac contractility and increasing the risk of CTRCD was already described [10,13,37,38]. In a similar study on patients treated with AC, a cumulative cardiotoxicity incidence of 1.2 % per year was observed in patients younger than 55 years, reaching a 10.6 % risk in patients over-75 years [39], thus suggesting a synergy between drug cardiotoxicities and AD. On this regard, the cumulative risk added by CRFs has been recently evaluated in the cardio-oncological guidelines when risk stratification is assessed at baseline [13,38]. Indeed, CRF correction and cardiac prevention lead to reduced CTRCD incidence in AC-treated elderly patients [13,40,41]. Actually, mECV values are already largely used in CMR, and several studies focusing on AC-induced CTRCDs confirmed that these values remain persistently increased even years after the end of treatment [28,42,43]. However, CMR cannot be used routinely in the follow-up of BC patients being expensive and time-consuming, whereas, CT scan is part of the oncological

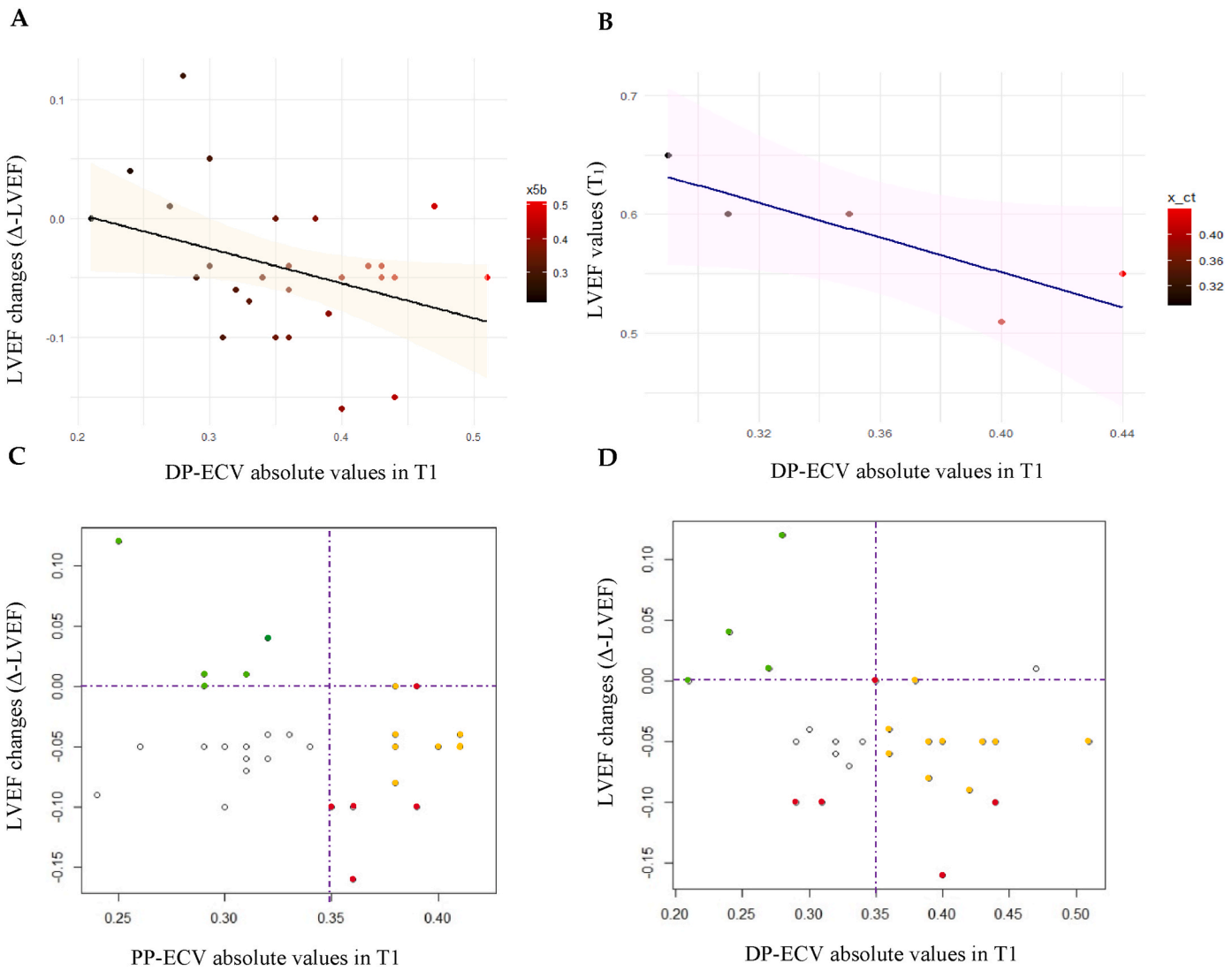

Fig. 5. Linear regressions between ECV values in delayed phase and LVEF changes evaluated at T_1. The trends of ECV values at T1 negatively correlates with the changes of LVEF from T_0 to T_1 both in the GS (**A**) and in the CTRCD group (**B**). Of note in PP setting (**C**), patients are clustered in significant groups, suggesting subgroup of patients with different prognoses. Indeed, green points could be patients probably healthy and at lower risk to develop a CTRCD (lower ECV and higher LVEF values), whereas yellow points could be patients developing a CTRCD or at higher risk (higher ECV and lower LVEF values). Importantly patients with a diagnosed CTRCD (red) were all located in the lower right quadrant, confirming its high risk and the predictivity of PP-ECV > 35 %. In DP setting (**D**), although more patients(yellow) were located in the lower right high-risk quadrant the patients with a CTRCD were scattered, do not confirming its predictive role in DP-ECV. A dotted line on 0.35 was chosen as a cut-off for CTRCD prediction as shown in PP and as reference for DP. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reassessment [28,42,43]. We described for the first time, to the best of our knowledge, the differences in mECV values, measured by WB-CT scan, between patients who developed CTRCD and those who did not, highlighting their predictive role for CTRCD and myocardial remodeling and the ability to differentiate between acute and chronic damage. Moreover, the use of WB-CT scan imagines allowed us to follow the patients for a long time (5 years).

We must acknowledge important limitations: the reduced sample size, the limited rate of CTRCD, the possible presence of selection biases and the lack of a control arm not exposed to cardiotoxic drugs. Moreover, we considered together severe and mild cases, leading to heterogeneity of results, whereas a larger study with adequate number of documented CTRCDs could better differentiate in mild, moderate and severe cases. Among the technical limitations, the ECG-synchronization was not performed when the image were acquired reducing somehow the accuracy and precision. However, the choice of centering the ROI in the septum drastically reduced motion artefacts.

5. Conclusions

In the present study we provided evidence supporting the use of WB-CT scans as a preliminary assessment for CTRCD when considering mECV evaluation, in apparently healthy women, whereas an intensive cardiological follow up could be reserved to second level examinations. Indeed, cardiac damage in young women after anthracycline treatment is a slow and multifactorial process. These patients, after significant initial cardiac distress, continue to accumulate tissue insults due to the presence of CRF, becoming at greater risk to develop CTRCD and, therefore, they need to be monitored. In this context, DP-ECV values could be monitored over time to predict the incidence of CTRCD, particularly when they increase above 35 %, revealing a 12-fold increased risk. Our study shows that increasing values of DP-ECV combined with decreasing values of PP-ECV could be used to differentiate acute from chronic damage, when measured at the first and fifth year after anthracycline therapy. However, more evidences will be needed to

Table 3
Linear regressions performed in the subgroup treated with Anthracyclines (A) and Trastuzumab (T). Strong and significant correlations were found at multiple regression only for patients treated with A. The model predictivity reached high levels in A-treated women for DP-ECV setting (63 %), confirming the goodness of the results. No significant result was achieved for analyses on T.

Subgroups	S	R [2]	p-value	Adj-S	Adj R^2	Adj-p
Anthracyclines:						
PP-ECV (1 min)	−0.14	0.02	0.5	3.23	**0.39**	**0.0035**
Age at Diagnosis (AD)	0.001	0.03	0.45	0.024		**0.0016**
Interaction test (DA*PP-ECV)	–		–	0.007		**0.002**
DP-ECV (5 min)	0.24	0.16	0.08	−2.71	**0.63**	**0.0003**
Age at Diagnosis (AD)	0.001	0.03	0.45	0.01		**0.0003**
Interaction test (DA*DP-ECV)	–	–	–	0.06		**0.0001**
Trastuzumab:						
PP-ECV (1 min)	0.18	0.04	0.57	−0.78	−0.39	0.97
Age at Diagnosis (AD)	−0.0008	0.03	0.62	0.0008		0.89
Interaction test (DA*PP-ECV)	–	–	–	−0.009		0.92
DP-ECV (5 min)	−0.16	0.006	0.83	0.02	−0.43	0.76
Age at Diagnosis (AD)	−0.0008	0.03	0.62	0.002		0.84
Interaction test (DA*DP-ECV)	–	–	–	0.02		0.76

assess the utility for thorax CT scan in helping clinicians to decide whether a cardiac CT should be performed as a second level examination. Moreover, the clinical utility of our findings requires confirmation, including a histopathological one, in larger ad hoc prospective studies.

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Ethic declaration

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

CRediT authorship contribution statement

R. Rosenfeld: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **S. Riondino:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **M. Cerocchi:** Writing – original draft, Visualization, Software, Resources, Investigation, Data curation, Conceptualization. **A. Luciano:** Visualization, Software, Resources, Investigation, Data curation. **G. Idone:** Visualization, Validation, Software, Resources, Investigation. **D. Lecis:** Visualization, Validation, Software, Resources, Investigation. **F. Illuminato:** Visualization, Validation, Software, Resources, Investigation. **A. Tolomei:** Visualization, Validation, Software, Resources, Investigation. **F. Torino:** Writing – original draft, Supervision, Project administration. **M. Chiocchi:** Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Data curation, Conceptualization. **M. Roselli:** Validation, Supervision, Resources, Project administration.

Declaration of competing interest

All authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

[1] Duggan C, Trapani D, Ilbawi AM, et al. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. Lancet Oncol 2021;22(11):1632–42. https://doi.org/10.1016/S1470-2045(21)00462-9.
[2] Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol 2019;30(8):1194–220. https://doi.org/10.1093/annonc/mdz173.
[3] DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA A Cancer J Clin 2019;69(6):438–51. https://doi.org/10.3322/caac.21583.
[4] Murphy SL. Mortality in the United States, vol. 427. NCHS Data Brief; 2021 Dec. p. 1–8.
[5] Gaidai O, Cao Y, Loginov S. Global cardiovascular diseases death rate prediction. Curr Probl Cardiol 2023;48(5):101622. https://doi.org/10.1016/j.cpcardiol.2023.101622.
[6] Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: JACC: CardioOncology state-of-the-art review. JACC CardioOncology 2022;4(1):19–37. https://doi.org/10.1016/j.jaccao.2022.01.101.
[7] Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13(1):25–32. https://doi.org/10.1016/S1470-2045(11)70336-9.
[8] von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377(2):122–31. https://doi.org/10.1056/NEJMoa1703643.
[9] Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372(2):134–41. https://doi.org/10.1056/NEJMoa1406281.
[10] López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, et al. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. Eur Heart J 2020;41(18):1720–9. https://doi.org/10.1093/eurheartj/ehaa006.
[11] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016 2016;37(36):2768–801. https://doi.org/10.1093/eurheartj/ehw211.
[12] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97(11):2869–79. https://doi.org/10.1002/cncr.11407.
[13] Lyon AR, López-Fernández T, Couch LS, et al. ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European society for therapeutic radiology and oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): developed by the task force on cardio-oncology of the European society of cardiology (ESC). Eur Heart J 2022. https://doi.org/10.1093/eurheartj/ehac244. Published online August 26, 2022: ehac244.
[14] Pudil R, Mueller C, Čelutkienė J, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the cardio-oncology study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. Eur J Heart Fail 2020;22(11):1966–83. https://doi.org/10.1002/ejhf.2017.
[15] Michel L, Mincu RI, Mahabadi AA, et al. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis. Eur J Heart Fail 2020;22(2):350–61. https://doi.org/10.1002/ejhf.1631.
[16] Rosenfeld R, Riondino S, Formica V, Torino F, Martuscelli E, Roselli M. MiRNAs and circRNAs for the diagnosis of anthracycline-induced cardiotoxicity in breast cancer patients: a narrative review. J Personalized Med 2022;12(7):1059. https://doi.org/10.3390/jpm12071059.
[17] Lok DJA, Van Der Meer P, de la Porte PWBA, et al. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. Clin Res Cardiol Off J Ger Card Soc 2010;99(5):323–8. https://doi.org/10.1007/s00392-010-0125-y.
[18] Loria V, Dato I, Graziani F, Biasucci LM. Myeloperoxidase: a new biomarker of inflammation in ischemic heart disease and acute coronary syndromes. Mediat Inflamm 2008;2008:135625. https://doi.org/10.1155/2008/135625.
[19] Negishi T, Thavendiranathan P, Penicka M, et al. Cardioprotection using strain-guided management of potentially cardiotoxic cancer therapy: 3-year results of the SUCCOUR trial. JACC Cardiovasc Imaging 2023;16(3):269–78. https://doi.org/10.1016/j.jcmg.2022.10.010.
[20] Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. J Am Coll Cardiol 2021;77(4):392–401. https://doi.org/10.1016/j.jacc.2020.11.020.
[21] Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19(1):75. https://doi.org/10.1186/s12968-017-0389-8.
[22] Harries I, Liang K, Williams M, et al. Magnetic resonance imaging to detect cardiovascular effects of cancer therapy. JACC CardioOncology 2020;2(2):270–92. https://doi.org/10.1016/j.jaccao.2020.04.011.
[23] Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 Mapping and Extracellular Volume (ECV) in clinical practice: a comprehensive

review. J Cardiovasc Magn Reson 2017;18(1):89. https://doi.org/10.1186/s12968-016-0308-4.
[24] Monti CB, Zanardo M, Bosetti T, et al. Assessment of myocardial extracellular volume on body computed tomography in breast cancer patients treated with anthracyclines. Quant Imag Med Surg 2020;10(5):93444–944. https://doi.org/10.21037/qims.2020.04.05.
[25] Chiocchi M, Cerocchi M, Di Tosto F, et al. Quantification of extracellular volume in CT in neoadjuvant chemotherapy in breast cancer: new frontiers in assessing the cardiotoxicity of anthracyclines and trastuzumab. J Personalized Med 2023;13(2):199. https://doi.org/10.3390/jpm13020199.
[26] Tu C, Shen H, Liu R, et al. Myocardial extracellular volume derived from contrast-enhanced chest computed tomography for longitudinal evaluation of cardiotoxicity in patients with breast cancer treated with anthracyclines. Insights Imaging 2022;13:85. https://doi.org/10.1186/s13244-022-01224-5.
[27] Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol 2013;111(5):717–22. https://doi.org/10.1016/j.amjcard.2012.11.022.
[28] Jordan JH, Vasu S, Morgan TM, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. Circ Cardiovasc Imaging 2016;9(8):e004325. https://doi.org/10.1161/CIRCIMAGING.115.004325.
[29] Miller CA, Naish JH, Bishop P, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circ Cardiovasc Imaging 2013;6(3):373–83. https://doi.org/10.1161/CIRCIMAGING.112.000192.
[30] Cardinale D, Biasillo G, Salvatici M, Sandri MT, Cipolla CM. Using biomarkers to predict and to prevent cardiotoxicity of cancer therapy. Expert Rev Mol Diagn 2017;17(3):245–56. https://doi.org/10.1080/14737159.2017.1283219.
[31] Ferreira de Souza T, Quinaglia AC, Silva T, Osorio Costa F, et al. Anthracycline therapy is associated with cardiomyocyte atrophy and preclinical manifestations of heart disease. JACC Cardiovasc Imaging 2018;11(8):1045–55. https://doi.org/10.1016/j.jcmg.2018.05.012.
[32] Naresh NK, Misener S, Zhang Z, et al. Cardiac MRI myocardial functional and tissue characterization detects early cardiac dysfunction in a mouse model of chemotherapy-induced cardiotoxicity. NMR Biomed 2020;33(9):e4327. https://doi.org/10.1002/nbm.4327.
[33] Mahnken AH, Koos R, Katoh M, et al. Assessment of myocardial viability in reperfused acute myocardial infarction using 16-slice computed tomography in comparison to magnetic resonance imaging. J Am Coll Cardiol 2005;45(12):2042–7. https://doi.org/10.1016/j.jacc.2005.03.035.
[34] Ko SM, Hwang SH, Lee HJ. Role of cardiac computed tomography in the diagnosis of left ventricular myocardial diseases. J Cardiovasc Imaging 2019;27(2):73–92. https://doi.org/10.4250/jcvi.2019.27.e17.
[35] Sado DM, Flett AS, Banypersad SM, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart Br Card Soc 2012;98(19):1436–41. https://doi.org/10.1136/heartjnl-2012-302346.
[36] Capra D, Monti CB, Luporini AG, et al. Computed tomography-derived myocardial extracellular volume: an early biomarker of cardiotoxicity in esophageal cancer patients undergoing radiation therapy. Insights Imaging 2020;11(1):120. https://doi.org/10.1186/s13244-020-00922-2.
[37] Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol Off J Eur Soc Med Oncol 2020;31(2):171–90. https://doi.org/10.1016/j.annonc.2019.10.023.
[38] Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020;22(11):1945–60. https://doi.org/10.1002/ejhf.1920.
[39] Bowles EJA, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012;104(17):1293–305. https://doi.org/10.1093/jnci/djs317.
[40] Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131(22):1981–8. https://doi.org/10.1161/CIRCULATIONAHA.114.013777.
[41] Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol Off J Am Soc Clin Oncol 2010;28(25):3910–6. https://doi.org/10.1200/JCO.2009.27.3615.
[42] Reiter U, Reiter C, Kräuter C, Fuchsjäger M, Reiter G. Cardiac magnetic resonance T1 mapping. Part 2: diagnostic potential and applications. Eur J Radiol 2018;109:235–47. https://doi.org/10.1016/j.ejrad.2018.10.013.
[43] Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume fraction from T1 measurements in healthy volunteers and mice: relationship to aging and cardiac dimensions. JACC Cardiovasc Imaging 2013;6(6):672–83. https://doi.org/10.1016/j.jcmg.2012.09.020.