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Review article

Role of advanced cardiovascular imaging in chemotherapy-induced cardiotoxicity

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ABSTRACT

The development of cardiotoxicity induced by cancer treatments has emerged as a significant clinical problem, both in the short run, as it may influence drug administration in chemotherapeutic protocols, and in the long run, because it may determine adverse cardiovascular outcomes in survivors of various malignant diseases. Therefore, early detection of anticancer drug-related cardiotoxicity is an important clinical target to improve prevention of adverse effects and patient care. Today, echocardiography is the first-line cardiac imaging techniques used for identifying cardiotoxicity. Cardiac dysfunction, clinical and subclinical, is generally diagnosed by the reduction of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). However, myocardial injury detected by echocardiography is preceded by other alterations, such as myocardial perfusion and mitochondrial and metabolic dysfunction, that can only be recognized by second-level imaging techniques, like cardiac magnetic resonance (CMR) and nuclear imaging, which, using targeted radiotracers, may help to provide information on the specific mechanisms of cardiotoxicity. In this review, we focus on the current and emerging role of CMR, as a critical diagnostic tool of cardiotoxicity in the very early phase, due to its availability and because it allows the contemporary detection of functional alterations, tissue alterations (mainly performed using T1, T2 mapping with the evaluation of extracellular volume-ECV) and perfusional alteration (evaluated with rest-stress perfusion) and, in the next future, even metabolic changes.

Moreover, in the subsequent future, the use of Artificial Intelligence and big data on imaging parameters (CT, CMR) and oncoming molecular imaging datasets, including differences for gender and countries, may help predict cardiovascular toxicity at its earliest stages, avoiding its progression, with precise tailoring of patients' diagnostic and therapeutic pathways.

1. Introduction

Cancer and heart disease are the leading cause of morbidity and mortality in the industrialised world [1]. Advanced cancer therapy

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Table 1
Cardiotoxicity diagnostic criteria.

Society	Diagnostic Criteria	Year of publication
ASE/ EACVI	Decrease in LVEF of >10%, to LVEF <53% Relative drop in GLS >15% from baseline suggests subclinical LV dysfunction	2014
ESC	Decrease in LVEF of >10% from baseline, to LVEF <50% Decrease in GLS of >15% from baseline may suggest risk of cardiotoxicity	2016
ESMO	LVEF drop by ≥ 10–15%, or to <50% Symptomatic heart failure regardless of LVEF	2020
IC-OS	For asymptomatic patients: **Mild:** LVEF ≥50% and new relative decrease in GLS by >15% from baseline, and/or new rise in cardiac biomarkers (cardiac troponin I/T > 99th percentile, BNP >35 pg/mL, NT-proBNP ≥125 pg/mL). New reduction in LVEF by ≥ 10% or <10%, to absolute 40% < LVEF <50%, and new relative decrease in GLS by >15% from baseline, and/or new rise in cardiac biomarkers. **Severe**: new LVEF reduction to <40%. For symptomatic patients: mild heart failure symptoms or more.	2021
ESC	Asymptomatic: **Mild:** LVEF ≥50% and decline in GLS >15% and/or new rise in cardiac biomarkers. **Moderate:** new decrease in LVEF by 10% to a LVEF of 40–49% or new decrease by <10% to a LVEF of 40–49% and decline in GLS by 15% or new rise in cardiac markers **Severe**: new decrease in LVEF to <40% Symptomatic: **Mild:** Mild HF symptoms, no intensification of therapy required **Moderate**: Required intensification of Diuretics and HF therapy **Severe**: hospitalization for HF **Very Severe:** HF requiring inotropic or mechanical support and consideration of transplantation **ICI myocarditis:** cTn rise, with 1 major or 2 minor criteria, after exclusion of ACS and acute intectious myocarditis **Major criteria:** - CMR diagnosis **Minor criteria:** - Clinical syndrome - Ventricular arrhytmia and/or new conduction system disease - Decline in LV systolic function - Other immune-related adverse event - Suggestive CMR	2022

ASE = American Society of Echocardiography; EACVI = European Association of Cardiovascular Imaging; ESC = European Society of Cardiology; ESMO = European Society of Cardiology; IC-OS = International Cardio- Oncology Society; LVEF = left ventricular ejection fraction; GLS = global longitudinal strain; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-BNP.
ICI: immune checpoint inhibitors.

leads to improved patient survival, and long-term cancer survivors are expected to increase by approximately 30% in the next decade [2]. The clinical disruption of increasingly performing therapies also has a downside, including direct and indirect cardiovascular insult [3]. The incidence of cancer therapeutics-related cardiac dysfunction shows a wide variability in the duration of treatment, the type of chemotherapeutic agents used, and patient comorbidities [4].

Specifically, anthracyclines-induced cardiotoxicity has been categorised as acute, early–onset chronic progressive and late-onset types. Acute cardiotoxicity occurs in less than 1% of patients during or immediately after the infusion of anthracycline, manifesting as a temporary and acute reduction of contractility. The early-onset chronic progressive type occurs in 1.6%–2.1% of patients, usually a few months after therapy. While late-onset chronic progressive anthracycline-cardiotoxicity occurs at least one year after completion of treatment in 1.6%–5% of patients, cardiac dysfunction may be observed in patients from 10 to 20 years after the last cycle of therapy [5]. Also, radiation therapy is known to be cardiotoxic in patients whose radiation beam affects the mediastinal area.

In these settings, advanced cardiac imaging, especially Echocardiography and Cardiac Magnetic Resonance, plays a central role in assessing patients before treatment initiation and during the follow-up period. The aim of this review is to present the state of the art of Advanced Imaging Techniques as a milestone in the early diagnosis and follow-up of cardio-oncological patients.

2. Cardiotoxicity

2.1. Definition and guidelines

The 2022 European Society of Cardiology (ESC) guidelines define the term cancer therapy-related cardiac dysfunction (CTCRD) in patients with oncological diseases, cardiac injury, cardiomyopathy and Heart Failure (HF) [6]. This document includes a broad spectrum of possible presentations and various cancer therapies, including chemotherapy, target agents, immune therapies and radiation therapy. Unlike previous position statements by the European Association of Cardiovascular Imaging (EACVI) and the European Society for Medical Oncology (ESMO) [7], ESC guidelines clearly differentiate the several clinical expressions of cardiotoxicity and their respective management in the broad spectrum of cancer therapy-related cardiovascular toxicity (CTR-CVT) including valvular, pericardial and vascular disease.

In these settings, cardiac imaging, especially Transthoracic Echocardiogram (TTE), has a crucial role in evaluating patients before the beginning of the treatment and throughout the follow-ups [8]. ESC guidelines validate TTE with the integration of global longitudinal strain (GLS) as a first-line modality to perform before starting treatment in patients with a high and very high risk of CTR CVT.

CTRCD can be defined as the presence or absence of symptoms [9]. In the latter asymptomatic group of patients, ESC guidelines indicate three risk classes based on the severity of the relative reductions of ejection fraction (EF) and GLS (>15%) (Table 1).

Previous position papers included all imaging modalities (Echocardiography, MRI, Nuclear imaging), and the choice of the modalities was exclusively related to the expertise of the centre and the modality availability [10]. However, in 2022 ESC guidelines, CMR imaging is recommended as an alternative modality of choice in patients with bad acoustic windows due to body habitus [11].

2.2. Chemotherapeutic agents

Several cancer treatments are associated with cardiotoxicities, such as anthracyclines, 5-fluorouracil, cyclophosphamide, tyrosine kinase inhibitors, immune checkpoint inhibitors, HER-2 antagonist, and radiation therapy [12].

Anthracyclines (Doxorubicin, Idarubicine) are commonly used in hematologic lymphoproliferative disease (Hodgkin and non-Hodgkin Lymphoma, acute lymphoblastic leukaemia) and solid malignant tumours (breast cancer, osteosarcoma, etc.), are associated with dose-dependent cardiotoxicity. Cardiotoxicity occurs in 90% of adults within one year.

Trastuzumab is a monoclonal antibody that acts on the erbB-2 protein kinase receptor, which is also present in the cardiomyocyte and works in the regulation of multiple functions such as cell apoptosis, mitosis, cell adhesion, cell hypertrophy, angiogenesis and adrenergic sensitivity.

Sunitinib is a tyrosine kinase inhibitor (AMP-activated protein kinase) and platelet-derived growth factor receptor that plays a role in cardiomyocyte function and survival [13].

Mitoxantrone is a DNA topoisomerase-II inhibitor with antineoplastic, anti-inflammatory and immunomodulatory activity. Cardiotoxicity is dose-dependent and occurs in 2% of cancer patients with systolic and diastolic dysfunction [14].

Ciclofosfamide has cardiac toxicity associated with cumulative doses, such as fulminant myocarditis and arrhythmia [15].

Fluorouracil, methotrexate and taxanes were correlated to arrhythmia and myocardial ischemia.

With novel cancer therapies, immunotherapy has several cardiotoxic effects.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target the host immune negative regulation receptors, such as CTLA-4/ipilumab (cytotoxic T lymphocyte-associated protein4), nivolumab or pembrolizumab, programmed cell death receptor1(PD-1), and programmed cell death ligand1(PD-L1) as avelumab or atezolizumab.

Radiation therapy cardiotoxicity is noticeable in patients in whom the radiation beam affected the mediastinal area, mainly in bulky lymphomas and in women treated at the breast, with a cumulative dose of more than 30Gy and a daily fractioning of more than 2Gy, which may contribute to pericardial effusion in the acute phase. New radiotherapy techniques have reduced the risk of direct cardiac damage for optimised radiation beam balance, including 3-dimensional (3D) treatment planning with dose-volume histograms [16,17].

2.3. Comorbidities in cardiotoxicity and risk assessment

Among the risk factors for anthracycline-induced cardiotoxicity, it is helpful to distinguish cumulative drug overdose from pre-existing cardiovascular (CV) diseases such as diabetes, hypertension, coronary artery disease and peripheral vascular disease. Before starting any cardiotoxic treatment, patients should undergo an appropriate risk assessment. Within the risk factors for cardiotoxicity, we can identify genetic predispositions such as female gender and the black race, previous or concomitant mediastinal radiation in combination with other agents (such as trastuzumab), electrolyte disturbances (hypocalcaemia and hypomagnesemia), hemochromatosis and liver disease [18,19].

Finally, many cancer patients have undiagnosed coronary artery disease at the time of cancer diagnosis. This underlying disease and the risk of adverse coronary events may be aggravated by cancer and the toxicity of multiple chemotherapeutic agents that induce further inflammation with the pathogenetic evolution of coronary artery disease.

2.4. Etiopathogenesis and clinical scenario

Left ventricular dysfunction is the morphological and functional pattern usually correlated to damage from cardiotoxicity. However, it represents the outcome of different pathophysiological mechanisms of oncological treatments, with unpredictable pictures of inflammation, ischemia, myocyte apoptosis and myocardial fibrosis. There are different hypotheses underlying the mechanism of cardiotoxicity from anthracyclines. It is accepted that anthracycline's cardiotoxicity results from a multifactorial process related to oxidative stress, mitochondriopathy, changes in iron and calcium homeostasis and the respiratory chain [20].

The generation of free radicals is recognized as the primary cause: the resultant cellular damage is myocyte death with myocardial fibrosis in the context of chronic dilated cardiomyopathy. Cardiotoxicity from anthracyclines is reversible if it is diagnosed early and managed appropriately.

Tyrosine kinase inhibitors are known to inhibit the production of human epidermal growth factor with myocyte injury and altered systolic function that can often be transient. Trastuzumab is the most frequently used monoclonal antibody associated with cardiotoxicity, usually reversible after chemotherapy cessation.

Several chemotherapeutic drugs are related to the ischemic cascade, such as VEGF inhibitors; the role of coronary endothelial dysfunction is outlined as the basis of the mechanism that can be studied with perfusion imaging and can often be evaluated as alterations of microcirculation [21].

Recent studies have shown that Anthracyclines cardiotoxicity may present as a direct vascular injury, with increased thickening of the arterioles and loss of smooth muscle cells; finally, this vascular remodelling may contribute to the onset of myocardial perfusion defects [22,23].

Furthermore, pericardial disease, whose frequency is well correlated with doses of anthracyclines and tyrosine kinase inhibitors, may include acute toxicity clinical scenarios such as acute pericarditis with pericardial effusion rate often in association with myocardial inflammation. In contrast, the later chronic pictures with pericardial involvement often appear to be identifiable in combined therapies with mediastinal radiotherapy and evolution in constricting pericarditis. Among the late effects of radiotherapy-related damage are pericardial constrictive, accelerated atherosclerosis, myocardium damage, defects in the conduction system, and diastolic and valvular dysfunction. Other pictures related to cardiotoxicity are cardiac masses such as thrombi, pulmonary hypertension, and light-chain cardiac amyloidosis.

Among immune-related adverse events (IRAEs), colitis is the most common fatal event, but myocarditis correlated to ICI has a higher associated mortality, ranging from 25% to 50% [24,25]. Other cardiovascular toxicities have also been reported, including myocardial infarction, vasculitis and pericardial disease [26,27]. The clinical presentation in most cases of myocarditis is displayed within the first two months after initiation of ICI, ranging from asymptomatic elevations in cardiac biomarkers to severe decompensation with end-organ damage.

3. Imaging

3.1. Echocardiography

Echocardiography represents the first imaging approach in the management of oncologic patients for accessibility, versatility, low cost, widespread availability, patient acceptability, absence of ionising radiation and safety in patients with chronic renal disease. However, clinical practice and growing literature demonstrate the high variability of the LVEF as the main parameter of cardiac function, approximately 10%. In this context, three-dimensional (3D) TTE seems more accurate and reproducible, with a lower inter-observer variability (about 5–6%) [28].

In cardiotoxicity management, several studies showed that the approach based only on LVEF evaluation is inadequate for detecting early cardiac injury, especially in young patients [29]. Therefore, more sensitive parameters based on myocardial deformation and myocardial tissue characterisation have been proposed for early recognition of cardiac injury.

Myocardial deformation (or strain) is analysed with speckle tracking echocardiography: it is a dimensionless index concerning the total deformation of the ventricle during the whole cardiac cycle.

Strain is measured as a percentage of its initial length: the parameters can be measured in longitudinal (global longitudinal strain or GLS), radial, and circumferential directions (global circumferential strain or GCS).

Recent studies on cardiotoxicity highlight that myocardial deformation modifications manifest earlier than a change in LVEF [30].

In literature, it is reported that a decrease of peak global longitudinal strain (GLS) of 10–15% is an early biomarker of cardiotoxicity, with greater accuracy than 3D GLS vs 2D GLS [31,32] (see Fig. 1).

A partial decline in GLS, more than 15% indicates subclinical LV dysfunction. It, therefore, deserves cardiological evaluation with the integration of cardioprotective drugs and modulation of the chemotherapeutic dosage. Abnormalities in a longitudinal strain of the free right ventricular wall were detected in 75% of patients in a six-month follow-up after cardiotoxic treatment, with LVEF dropping from>10% to >53% [33]. This functional parameter could be helpful as an early marker for subclinical RV toxicity, but preliminary results should be validated in clinical trials with a more extended follow-up.

The main limitations in echocardiography are currently attributable to the wrong acoustic window and the differences in reprocessing depending on different software with GLS inter-vendor variability of up to 3.7% In some cases, contrast echocardiography may also be employed to improve endocardial border detection in patients with suboptimal image quality. Lastly, pharmacological stress-echo, mainly with dobutamine, has shown, in some cases, subclinical functional alterations of LV induced by chemotherapy drugs; non-homogeneously confirmed literature data limit its use in the management of cardiotoxicity in the early phase [34].

3.2. CMR

The ESC 2022 Guidelines suggest that Cardiac Magnetic Resonance (CMR) role should be related to patients or situations in which the echocardiogram is non-available or the patient has a bad acoustic window [6,8]. Undeniably, CMR plays a crucial role in cardiotoxicity diagnosis as an evaluation of acute, subacute and chronic interstitial damage and individuation of cardiac prognostic markers in systolic dysfunction, heart failure and others disease.

3.2.1. Functional parameters

CMR represents the gold standard technique for evaluating LV volumes and EF; it is a valid method for monitoring cardiac function during or after oncologic treatments and identifying small changes in LV volume and EF, thanks to higher accuracy and reproducibility compared to 2D-echo. CMR-derived measures of LVEF are usually employed as the endpoint in randomised trials aimed at evaluating the role of cardioprotective agents in preventing cardiotoxicity [35]. CMR variability in LVEF measurement is estimated at 2.4–7.3% [36], but the limitations are mainly related to the execution time and high costs and make the method difficult to access.

A reduction in global systolic function by CMR after 88 months was detected in 91 patients undergoing chemotherapy based on anthracycline. The study identified a close negative correlation between myocardial mass loss measured in CMR and cumulative pharmacological dose; patients with mass <57 g/m^2 had a higher percentage of MACE and, therefore, hospitalisations for heart failure, defibrillator implants and cardiovascular mortality [37].

CMR is also the gold-standard method for evaluating RV morphology and function, with obvious advantages over 2D echocardiography in intracavitary, trabecular and wall anatomical details, volumetric quantification, and spatial resolution. Functional alterations in post-chemotherapy RV are associated with a further appreciable decline in LVEF in patients with combined therapy with trastuzumab. Furthermore, observational studies report a close correlation between RV failure, morbidity, and mortality in HF patients [38].

Moreover, CMR allows for the examination of the atrial function; the prognostic role of LA (left atrial) volume and function as LAEF (left atrial ejection fraction) as an early marker of cardiotoxicity was investigated, remarking that reduction of LAEF correlates with changes in LVEF in the first 6 months of trastuzumab treatment. (see Fig. 2) [39].

Myocardial deformation is another parameter that could be used in the early phase of cardiotoxicity: indices may also be extrapolated using different CMR image techniques. Tissue tagging is the standard reference for systolic and diastolic strain by tags which follow the myocardium during contraction in long- and short-axis cine. Still, limitations are connected to the need for dedicated sequences and time-consuming image post-processing. In this setting, CMR feature tracking (CMR-FT) allows a simple calculation using a block-matching approach with regions of interest tracked along the cardiac cycle; it's directly applied in post-processing to long- and short-axis cine.

CMR-FT allows, along with the echo, to analyse the torsional myocardial deformations along the three dimensions (longitudinal,

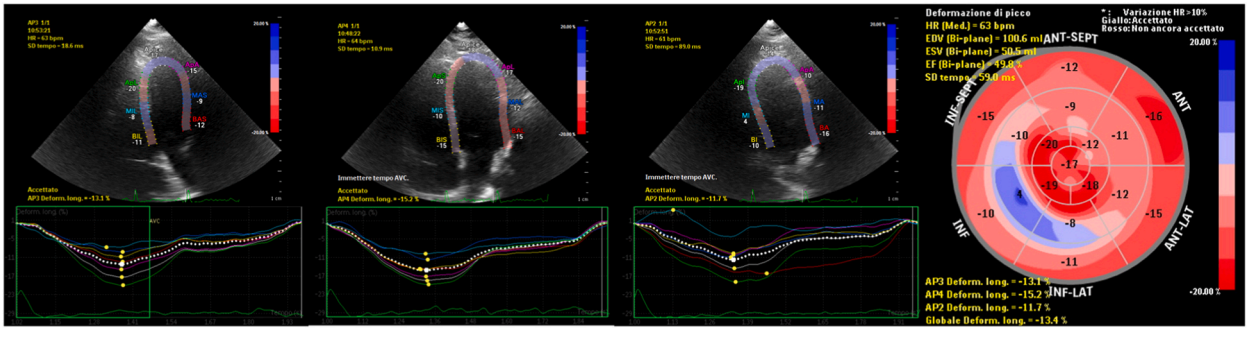

Fig. 1. GLS (global longitudinal strain) evaluated by speckle tracking technique in 3, 4 and 2-chamber apical view: GLS alteration in a patient with HL (Hodgkin Lymphoma) after six cycles of chemotherapy.

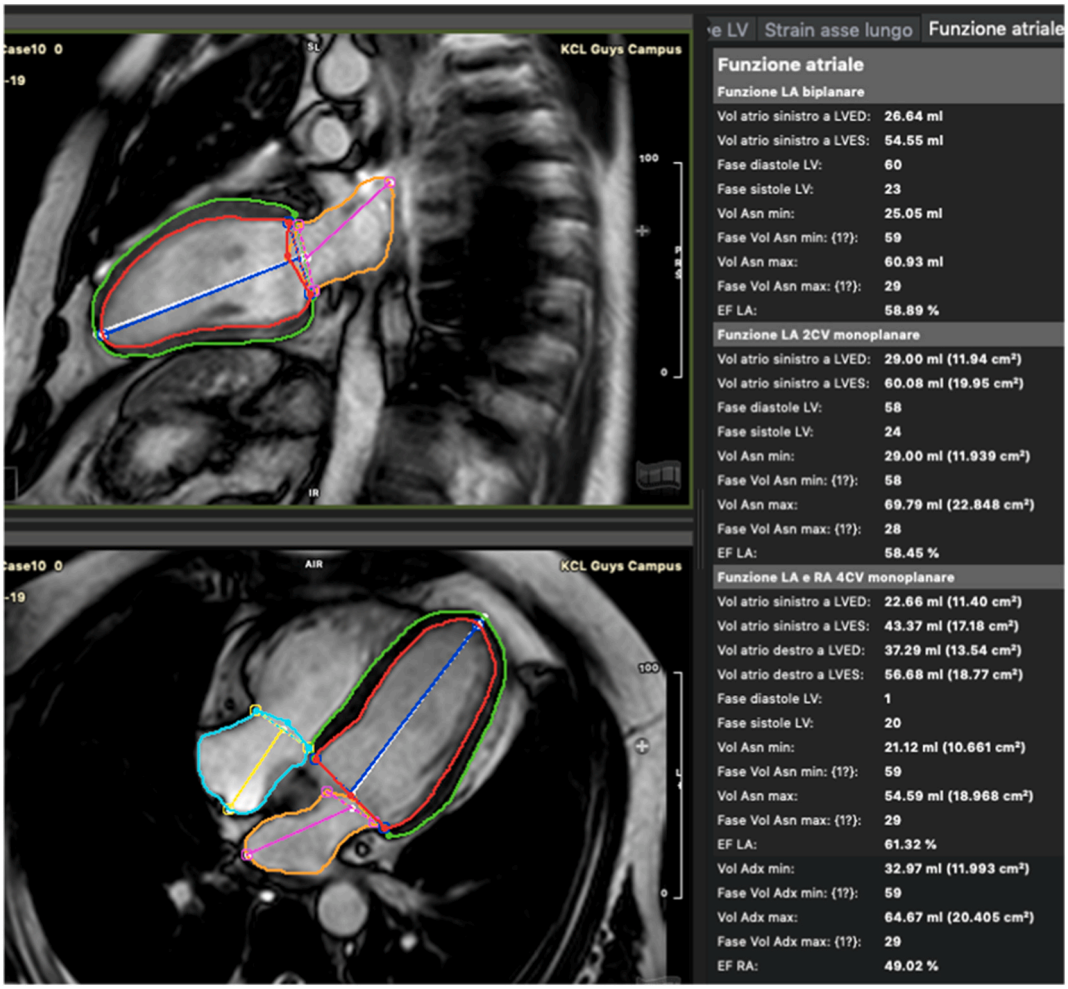

Fig. 2. Atrial function-Artificial Intelligence by software Circle Cardiovascular Imaging (CVI) detected left ventricle, left atrial and right atrial contours on all phases of the selected 2CV and 4CV slices.

radial and circumferential) appreciable in subclinical changes in cardiac function.

Currently, CMR strain imaging tools are mainly used in the research field. GCS is the strain parameter with the best interobserver agreement and inter-study reproducibility. At the same time, GLS can help identify early LV dysfunction and the predictive role of mortality in ischemic and non-ischemic cardiomyopathy [40].

In a study that has compared the prognostic value of CMR/echo in women with HER2+ early-stage breast cancer receiving sequential anthracycline/trastuzumab (6 and 5 monitoring for echo and CMR from baseline until 15 months post -treatments), changes in CMR and 2D-echo strain, LVEF and LVESVi (left ventricular end-systolic volume) were prognostic for subsequent CTRCD. 2D-echo GLS showed the highest discriminatory value increase over baseline clinical risk factors for subsequent cancer therapeutics-related cardiac dysfunction (CTCRD). Still, feature tracking by CMR GLS/GCS showed an additional confirmatory diagnostic and prognostic marker for cardiotoxicity, especially when accurate measurements and highly reproducible of LVESVi, LVEF and FT were preserved [41] (see Fig. 3a–d).

3.2.2. Myocardial tissue characterisation

Additionally, CMR permits the study of tissue characterisation, unlike the other methods included in the CTRCD path, allowing for a single examination to diagnose subclinical damage pictures in a broad range of myocardial pathologies. Within damages caused by anti-neoplastic agents, CMR allows the identification of acute cardiotoxical features such as oedema and inflamed areas, detectable in the early stages of cardiotoxicity; also, CMR allows the identification of focal and/or diffuse fibrosis patterns, that usually characterize later scenarios. In acute-subacute cardiotoxicity, areas of increased myocardial water, such as oedema and inflammation, are detected by dark blood T2 W sequences with visual analysis. However, a semi-quantitative calculation with a ratio signal is possible by positioning 2 ROI in the affected myocardium and the neighbouring muscle tissue. The semiquantitative analysis of T2 shows a relative limit to the presence of systemic inflammatory processes.

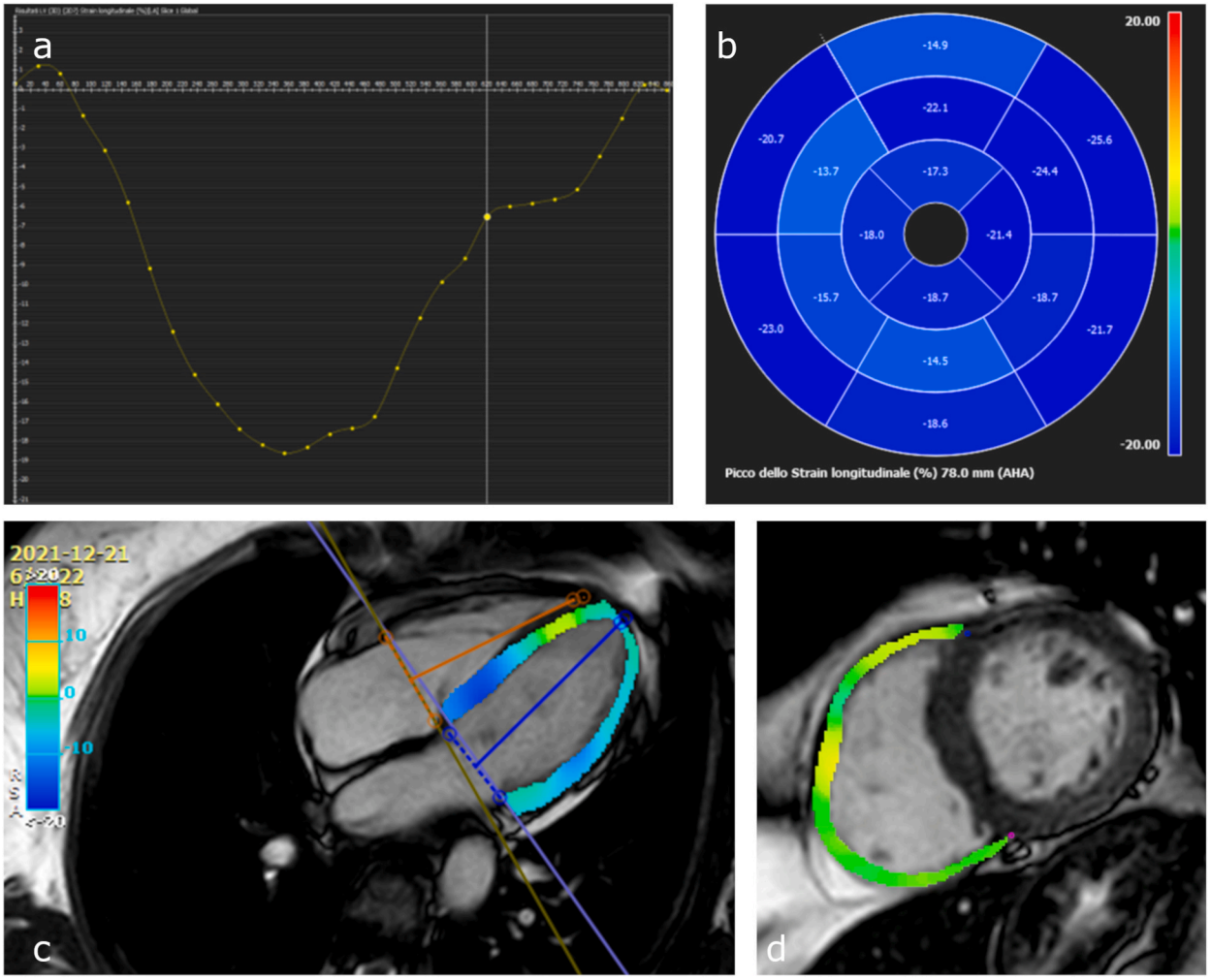

Fig. 3. Assessment of myocardial deformation by Circle Cardiovascular Imaging, reprocess of multiplanar cine bright blood with semi-automated Feature Tracking: Artificial Intelligence icon tools generate strain curve (a), polar maps (b) about longitudinal (GLS) and circumferential strain (GCS) for left and right ventricles (c,d).

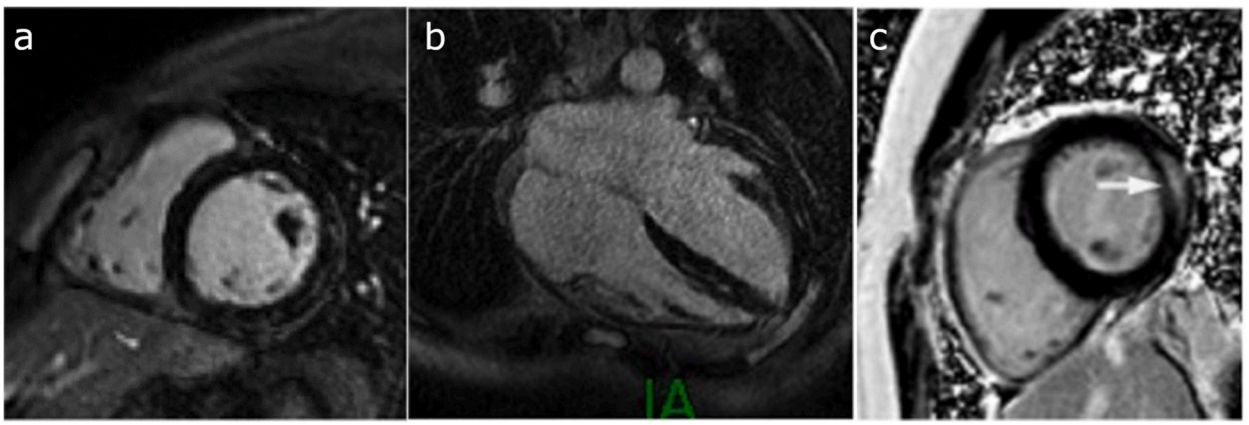

Fig. 4. Inversion recovery T1 weighted with gadolinium-Delayed enhancement (DE): a,b short and 4-chamber long axis evidence subepicardial-mesocardial DE in the context of myo-pericarditis due to acute cardiotoxicity in a patient undergoing the first cycle of anthracyclines for leukaemia; c short axis shows mesocardial DE due to chronic cardiotoxicity by Trastuzumab, located along the ventricular lateral wall.

A group of authors showed that changes in T1 weighted signal intensity could be used as an early marker of anthracycline-related subclinical injury [42]. Several studies exhibit a correlation between a reduced percentage of focal fibrosis by late gadolinium enhanced (LGE) in CTRCD and a reduced worse outcome (see Fig. 4a–c). However, one of the inherent limitations of LGE is related to the detection of diffuse pathology as diffuse myocardial fibrosis; therefore, a myocardial segment that presents regular abolition of the signal could hide a cardiopathic substrate [43,44]. For these reasons, an increase in interstitial fibrosis secondary to collagen deposition has been reported in anthracycline-related cardiotoxicity.

The native and post-contrast T1 sequences, exploiting the T1 relaxation times, can identify interstitial fibrotic remodelling with or without edemogens substrate and report good reproducibility on various heart diseases [45].

Also, CMR imaging with gadolinium can quantify the ECV-extracellular volume derived from pre- and post-contrast T1 measurements, which correlates with histological findings of myocardial fibrosis [46]. A study identified elevated ECV as interstitial myocardial fibrosis within 3months after the first cycle of cardiotoxicity chemotherapy [47,48]. Anthracycline-treated patients displayed elevated myocardial ECV since it closely correlates with diastolic dysfunction and increased left atrial volume [49]. Furthermore, it has been supposed that decreased cardiomyocyte size may contribute to increased ECV [50]. Moreover, scientists compared myocardial native T1 mapping and ECV in patient's pre-post-anthracycline treatment with three years follow-up. The study showed a significant increase in ECV after treatment (27.8+-0.7% to 30.4+-0.7%, $p < 0.01$), regardless of the oncological picture and cardiovascular comorbidities. At the same time, the native T1 was elevated in the pre- and post-treatment group of patients subjected to anthracyclines, compared to the control groups [51,52]. Majors toxical effects occurs early, in the first year of the therapy and ECV by T1 mapping native and enhanced sequences is a marker of risk stratification [53] (see Fig. 5).

CMR can also identify myocardial oedema and inflammation by parametric T2 mapping techniques, with a close correlation between long T2 relaxation times and the increased share of interstitial water, the earliest marker and a role in the therapeutic management of the reversible phase of cardiotoxicity-induced remodelling. A recent study investigated early anthracycline cardiotoxicity by multiparametric CMR mapping in a porcine model suggesting the potential technical at an early stage before the development of myocardial damage. In this study, myocardial T2 values already increased after anthracycline therapy compared to the native T1 and ECV parameters, as well as LVFE, which remained normal. This really interesting aspect is related to the close correlation between the reduction of the anthracycline dose, the tendency to normalise the T2 values, and the regression of histological changes. At the same time, continuation leads to alteration of native T1 and ECV values, global systolic dysfunction and development of fibrosis [54] (Table 2).

3.2.3. *Microvascular dysfunction*

New myocardial perfusion defects have been found in cancer patients undergoing SPECT approximately 6–24 years after

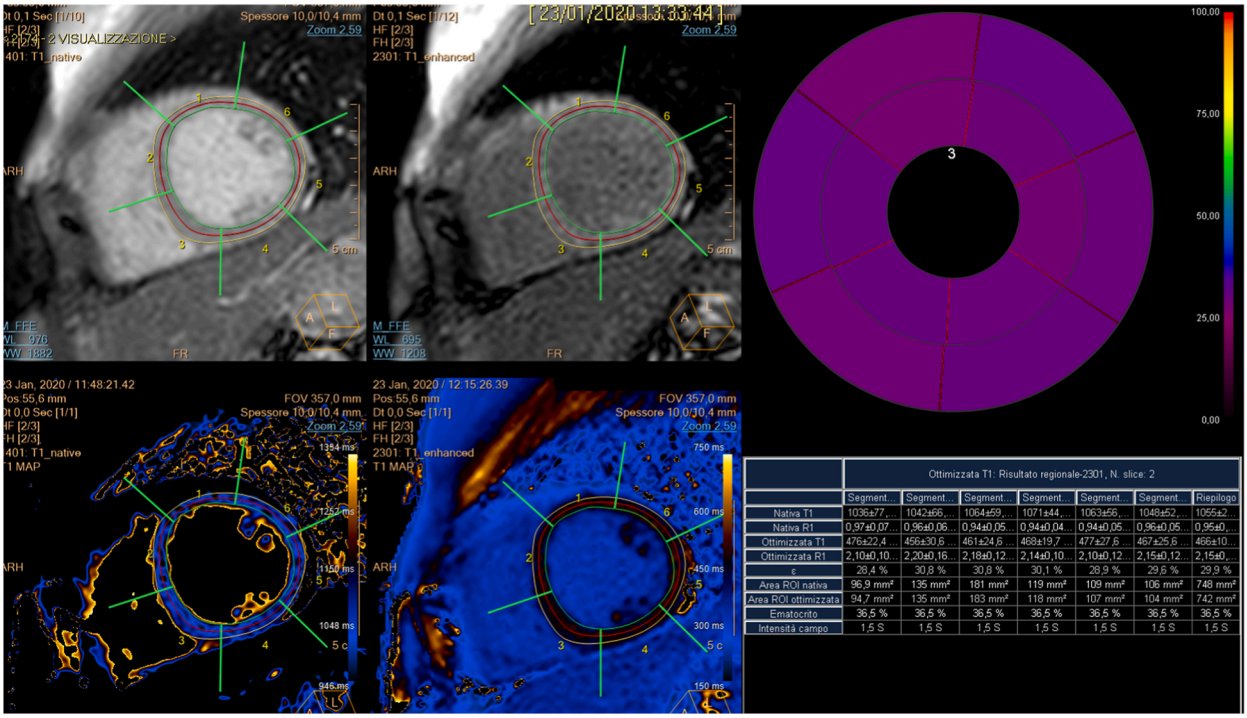

Fig. 5. T1 mapping (native/enhanced) post-processing with maps and results for segmentation along 1 out of 3 main plans acquired (middle left ventricle): diffuse increase of T1 native and ECV (extracellular volume) as interstitial remodelling with oedema and fibrosis in a patient with HL (Hodgkin Lymphoma) two months after chemotherapy with anthracyclines.

Table 2
CMR protocol for Cardiotoxicity.

Cardiotoxicity: CMR Protocol		
	SEQUENCES	**FINDINGS**
Scout/Anatomy	- Axial T1 weighted TSE Black Blood	- Localization of cardiac planes
Function	- bSSFP (Bright blood) performed in Long Axis 2, 3 and 4 chambers	- Evaluation of morphology and functional parameters as EF
	- bSSFP biventricular short axis	- Post-processing strain analysis for GLS and GCS.
Tissue Characterization	- T1 Native (MOLLI)	- Interstitial remodelling
	- T2 STIR or SPAIR (black blood) performed in short axis and long axis 4 chambers	- Evaluation of GLS, oedema and inflamed areas, secondary to therapy
	- T2 mapping	
Tissue Characterization after contrast/Scar imaging	- T1 weighted TSE and phase-sensitive inversion recovery gradient echo after contrast (Early and delayed enhancement)	- Evaluation of hyperemic and flogistic areas
	- T1 enhanced (MOLLI) in bi-plane short axis for base, middle and apex of ventricles	- Macroscopic and interstitial (ECV) fibrosis

GLS: global longitudinal strain, GCS: global circonferential strain, TSE: Turbo spin echo, bSSFP: balance Steady-state free precession (1.5 T MR).

chemotherapy cycles. This data suggests the added value of CMR stress in the early diagnosis of vascular damage and microcirculation dysfunction through impairments in myocardial blood flow and myocardial perfusion reserve in whose quantification new pixel-wise perfusion maps will come into play, which has at present not been explored in cancer patients [55,56].

3.2.4. Pericardial disease

Pericardial disease following cancer therapy is not uncommon as it is with acute pericarditis. Some patients undergoing radiotherapy may progress to chronic pericardial inflammation or constrictive pericarditis. In these cases, CMR assesses the morphology by dark-blood imaging and evaluates hemodynamic effects of constrictive type with white blood cine imaging and real-time during free breathing (especially in the short axis) (see Fig. 6a–f). Myocardial tagging on CMR can document adhesion between the parietal and

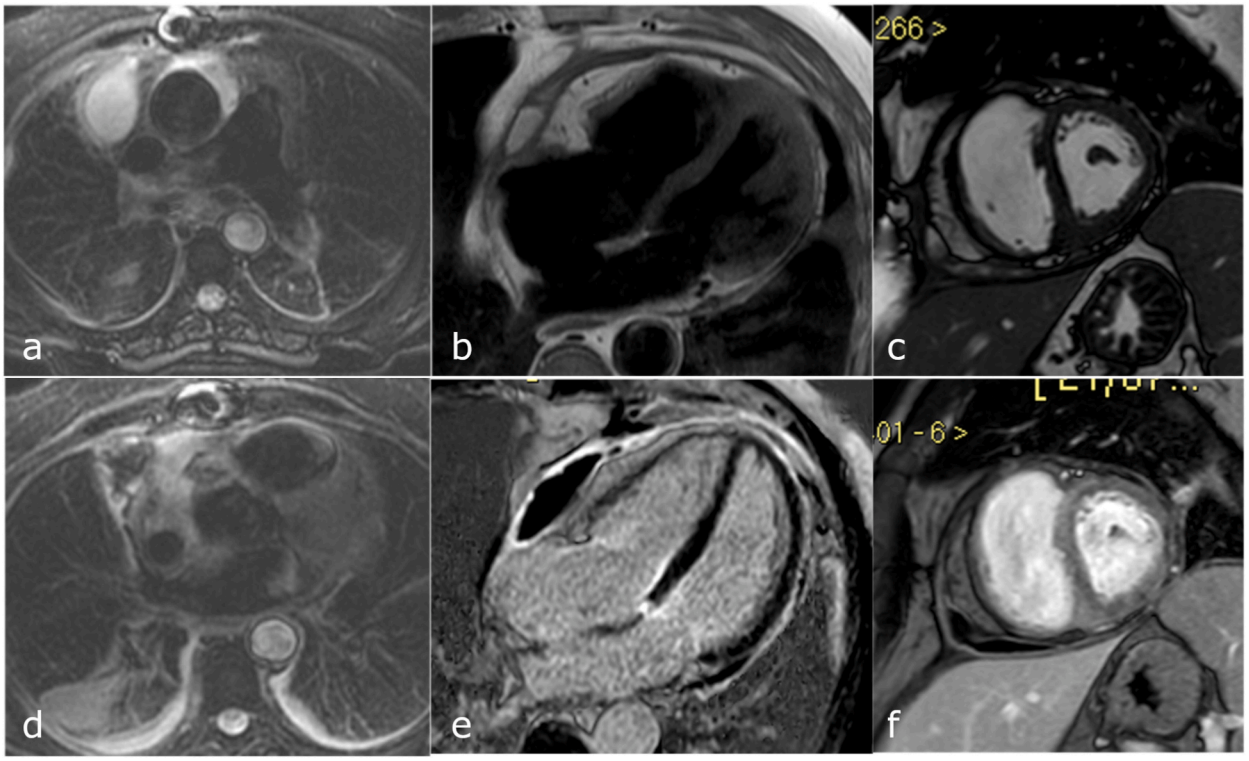

Fig. 6. (a, d): axial T1 W after gadolinium contrast in a patient subjected to Anthracycline chemotherapy and radiotherapy with acute mediastinitis and perimyocarditis; (b,c,e,f): follow-up CMR 4 months after acute cardiotoxicity with evidence of chronic effusive-constrictive pericarditis with thickened pericardium>4 mm (b axial black blood T1 W), S-shaped intraventricular septal motion during the cardiac cycle (c short axis bSSFP Cine), fibrotic thickening of the leaflets (e long axis four chambers late gadolinium enhancement-LGE) and areas of ongoing inflammation (f short axis early gadolinium enhancement).

visceral pericardium. At the same time, LGE is correlated with active inflammation because chronic constrictive pericarditis shows greater degrees of fibrosis and calcification and, therefore, should not exhibit contrast impregnation [57]. These technical data can change therapeutic management.

3.2.5. Chronic damage from cardiotoxicity

CMR allows the identification of further structural and functional alterations in valvular heart disease secondary to chronic cardiotoxicity with direct and indirect flow analysis. Axial valve plane by cine sequences allows to extrapolate off the valve planimetry in case of stenosis and the identification of foci of endocarditis; aorto-mitral curtain thickening and calcification is a marker of previous cardiac irradiations, and it is associated with adverse prognosis [58].

Advanced cardiac imaging as CMR can identify typical morphological and tissue patterns in cancer patients who develop accumulation cardiomyopathies such as amyloidosis and iron overload. In patients with suspected amyloidosis, CMR shows a concentric hypertrophic LV pattern and bi-atrial dilatation through multiplanar cine sequences. Tissue analysis demonstrates extensive interstitial remodelling through native and enhanced T1 mapping sequences and the presence of late gadolinium enhancement LGE with concentric subendocardial or transmural ventricular distribution.

In patients with iron overload, CMR represents a valid biomarker to evaluate cardiac iron stores with T2* and R2 sequences for quantifying iron levels. These sequences are performed without an infusion of contrast medium, and R2* is more accurate in quantifying iron in cases of severe accumulation [59]. In the initial forms of iron accumulation, the most frequently encountered cardiac morphological pattern is the restrictive. In later stages, the evolution is dilated cardiomyopathy with systolic dysfunction.

3.3. CT

Coronary-CT (CCT) has a broader diagnostic spectrum allowing for evaluation in the first instance of the pericardium and coronary arteries that may undergo modifications even in patients undergoing chemotherapy, providing an accurate assessment of vascular toxicities, the second most common group of collateral effects. Notably, in arterial toxicity, CCT allows us to rule out acute coronary

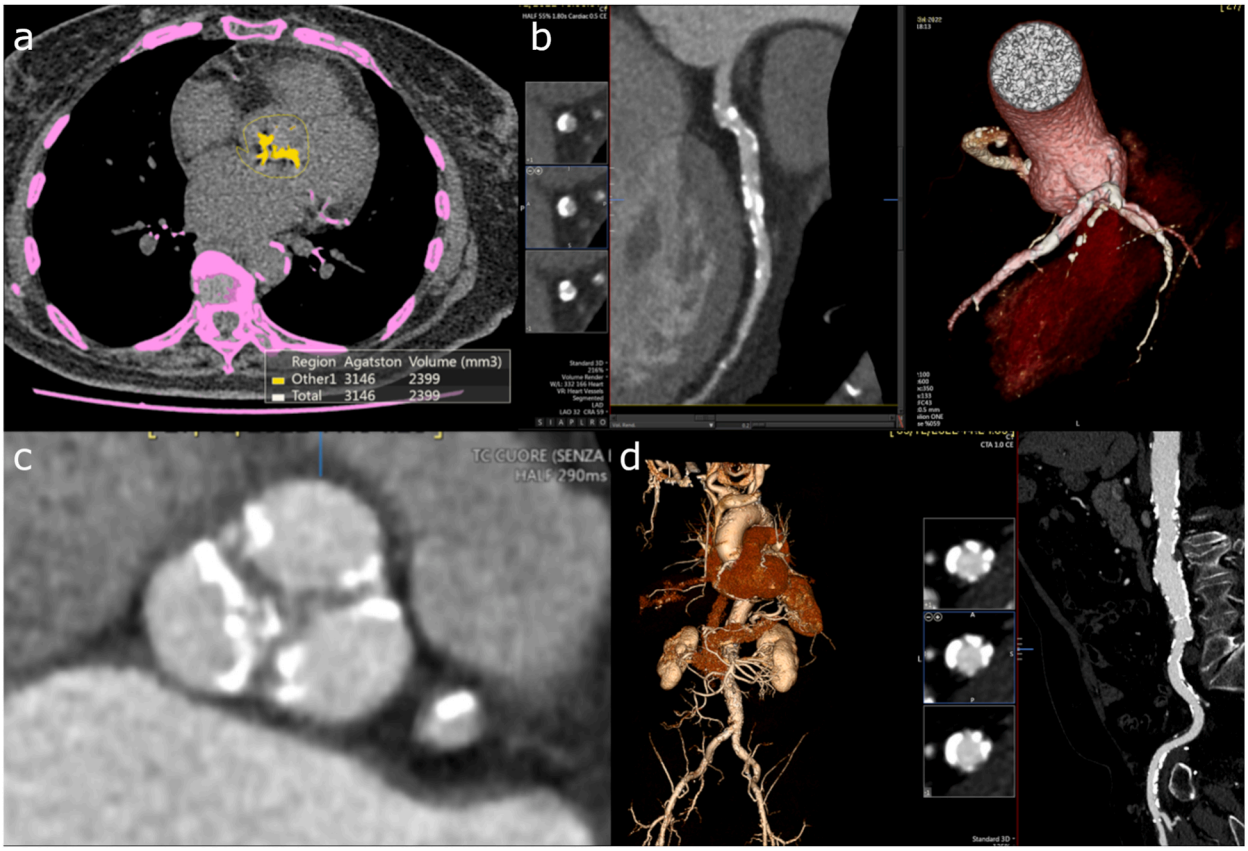

Fig. 7. Potential applications of cardiac computed tomography in visualising the entire spectrum of cardiovascular disease induced by cancer treatments. Coro CTA: (a, c) baseline and postcontrast scans for morphological evaluation of aortic valve with calcium quantification by Agatston score; (b) MPR-curved and 3D volume in calcific atheromasia of LAD (left anterior descendent); (d) Angio-CT: extensive aortic vascular disease in patients monitored in the long term after chemotherapy (tyrosine kinase inhibitors).

syndrome for vasospasm, accelerated atherosclerosis or thrombosis.; but another proposed use is to rule out obstructive CAD when myocarditis is suspected or in patients with decreased left ventricular function after cardiac toxicity. Another useful indication is correlated to the evaluation of coronary atherosclerosis before the beginning of the therapy, which allows identifying the risk class for further clinical management [60]. Therefore, CCT analysis at baseline pre-chemotherapy enables the identification of calcified plaques in patients, with a basal scan correct, which permits a classification of the risk class by Agatston calcium score [61].

Coronary CT identifies the accurate analysis of the plaque in relation both to the densitometric values (precise calculation of the calcified, fibrotic and lipid percentage) and to the morphological values (positive remodelling, lipid core) and the semiautomatic evaluation of the residual luminal area from which any critical issues may arise.

In patients with non-Hodgkin's lymphoma undergoing radiotherapy, an increased risk of developing coronary artery disease is mainly addressed in the follow-up of patients undergoing radiotherapy, according to a hypothetical etiopathogenetic mechanism in which the radiant damage would seem to induce an inflammatory vascular pattern from which the atheromatous disease originates. The vessels mainly affected are the common trunk and the left anterior descendant [62] (see Fig. 7a–d).

Cardiac CT can assess ischemic burden allowing the identification of hemodynamically significant coronary lesions; this is possible by estimating fractional flow reserve by FFR-CT and CT perfusion imaging at rest/stress. In this context, FFR-CT is an emerging non-invasive tool that provides relevant prognostic information and allows therapeutic strategy optimisation [63].

CCT also allows us to evaluate heart chambers and functionality and to operate a tissue analysis of vitality, thanks to the increased space-time resolution of the latest generation scanners.

Among the advantages of the imaging technique, we find beyond the high spatial and temporal resolution, the accessibility, and the short duration of the investigation. The principal limit is still correlated to the radiation dose, which, even if small, is added to the further single-beam procedures that use ionising radiations.

3.4. Nuclear imaging

3.4.1. MUGA-multiple gated acquisition

MUGA is a scintigraphic technique that uses technetium-99m-pertechnetate labeled red blood cells to evaluate cardiac function.

ESC guidelines recommend the use of MUGA when TTE is non diagnostic and CMR is non available. MUGA shows reduced intra-interobserver variability compared to 2D echocardiography, good correlation with 3D methods but reduced correspondence with CMR in the calculation of volumes and FE [64,65].

MUGA has advantages over TTE when patients cannot tolerate echocardiography, such as after thoracic radiation or mastectomy in relation to patient discomfort for chest wall compression during scanning and it can lead to reduced image quality.

In literature studies, MUGA turns out to be accurate, available and with an interobserver variability of $<$5%. On the other hand, poor electrocardiography-base triggering in case of arrhythmias, high cost and overexposure to ionising radiation (in particular for younger patients) represent limitations to the routine use of this method [66]. An average MUGA scan gives 5–15 mSv of radiation compared to the annual 3.6 mSv exposure from background radiation [67].

Radionuclide molecular imaging is a candidate to help identify subclinical toxicity allowing intervention before clinical disease is manifest. At first, radiotracers can be 111 In-antimyosin or 123I- metaiodobenzylguanidine (123I-MIBG) [68].

111 In-antimyosin is a molecular tracer which binds to exposed cardiac myosin correlated to cardiomyocyte necrosis. In a study of 20 patients, 8 developed a cardiomyopathy post-doxorubicin. In patients who have developed cardiomyopathy, there was a higher overall uptake of 111 In-antimyosin post chemotherapy [69].

A follow-up study showed that this increase in uptake of 111 In- antimyosin also occurred in patients who did not incur a decrease in LVEF, suggesting its efficacy in detecting pre-clinical cardiotoxicity [70].

3.4.2. SPECT

Single-photon electron computed tomography (SPECT) was one of the principal methods for cardiotoxicity screening until the recent guidelines.

Nowadays, current guidelines focus on identification of reduced LVEF and GLS, while evaluation of ischemia, a strength of nuclear imaging, plays a role in the development of cardiotoxicity.

In this context, SPECT myocardial perfusion imaging (MPI) contributes with a prognostic role for the detection of obstructive CAD in the post-radiation/chemotherapy population, as well as being useful in risk stratification. Nuclear scan uses a pharmacological stress protocol with dypiridamole or dobutamine and TC-99m-tetrofosmin as a nuclear marker injected in two phases after pharmacological stress and later in rest protocol.

SPECT MPI does not require physical exercise, is not limited by sonographic windows, and can be performed in the immediate post-radiation. Patients with extensive risk factors for CAD undergoing high-risk oncologic surgery would benefit from traditional SPECT imaging to better aid with cardiac risk stratification.

3.4.3. PET-positron emission tomography

PET MPI has a high temporal and spatial resolution (images can be sliced at 5 mm instead of 12–15 mm in SPECT), as well as accuracy and sensitivity, offering attenuation correction on all scans. Cardiac PET often uses rubidium-82 as tracer; myocardial perfusion by PET has a 95% sensitivity and specificity, higher than SPECT (respectively 87 and 73%). Further advantages are related to the lower radiation dose than in the past (4 mSV) and protocol duration time ($<$1 h than 2 days in SPECT). PET MPI is the gold standard technique in the diagnosis of myocardial metabolism and evaluation of microvascular function due to the ability to assess ischemia

beyond the epicardial coronaries through measurement of the myocardial perfusion reserve (MPR) [71].

MPR represents the ratio of absolute myocardial blood perfusion at peak hyperemia to resting perfusion and is analogous to the coronary flow reserve (CFR) in coronary angiography. This marker is abnormally reduced in coronary territories perfused by vessels with critical luminal stenosis. However, reduced myocardial perfusion reserve could be attributed to coronary microvascular dysfunction (CMD) [72].

Assessing CMD is particularly important in cancer patients receiving ischemia-provoking therapy, especially drugs with cardiotoxicity from microvascular pathology [73].

The high cost and low availability limit the use of the method in cardio-oncology. However, research has focused its attention in addition to perfusion on the role of CMD as a biomarker of alteration of myocardial metabolism and recent animal studies involving mice showed an increase in myocardial Fludeoxyglucose (FDG) uptake by PET in mice treated with sunitinib (tyrosine kinase inhibitor) than in untreated mice group. These studies identified several significant clinical correlations in the close association between FDG uptake and myocardial fibrosis on tissue analysis and on the preventive role of drugs as endothelin receptor antagonist to avoid deregulation of myocardial metabolism and cardiac fibrosis as well as improve recovery of diastolic function impaired by sunitinib [74].

Also, several radiotracers that are already used for oncology indications may provide specific added value to the clinical pre-stratification of cardiac toxicity [75]. For example, Ga-FAPI (fibroblast activating protein) gets upregulated in atherosclerosis and fibrosis and can be a potential early marker of ICI myocarditis [76,77]; instead, 89 Zr-DFO-CD4 or-CD8 may be useful to detect inflammation at earliest stages, useful in immunotherapy and in cases of accelerated atherosclerosis, with high-risk plaques that rise the chance of myocardial infarction [78,79].

4. Future directions

The assessment of the mechanisms of anticancer drug cardiotoxicity by imaging is a cornerstone in the future of cardio-oncology. In this context, the knowledge of perfusion, metabolic and mitochondrial dysfunctions underlying the cardiotoxicity's damage can be strategic to identify the signs of early cardiotoxicity through imaging (see Fig. 8).

A group of researchers compared findings by PET, SPECT and CMR with early perfusion, metabolic and mitochondrial function imaging, suggestive of cardiotoxicity. They underline that most studies have been conducted in animal models and their clinical relevance in clinical practice is still questionable and partially unknown [80].

For this reason, CMR is an excellent technique as it allows us to obtain much information through a multiparametric study. The association between 3D rapid functional sequences and tissue characterisation sequences such as T1 mapping will speed up the investigation and expand the role of CMR in diagnosing patients with suspected cardiotoxicity by modifying clinical and therapeutic management.

Also, thanks to stress CMR, with a vasodilator drug, it is possible to detect microcirculatory dysfunction, and, in the future, it should be possible to detect metabolic dysfunction. Translational CMR studies cardiac metabolism altered by oxidative stress induced by chemo-radiotherapy, with mitochondrial dysfunction. Phosphorus magnetic resonance spectroscopy (31P-MRS) measures earlier metabolic dysfunction through myocardial phosphocreatine to adenosine triphosphate ratio (Pcr/ATP), marker impaired in patients with heart failure risk factors and animal model of anthracycline-related cardiotoxicity. PCr/ATP ratio always precedes and predicts contractile dysfunction in animal models, but a recent study evidences a predictive role of mortality in dilated cardiomyopathy [81]. Another metabolic CMR imaging technique is hyperpolarised 13C. It has considerable potential in preclinical cancer diagnosis studies, grading and therapeutic response monitoring, including in lymphoma and breast cancer. Pyruvate, a 13C-labeled substrate, is the primary product of glycolysis. The technique increases the signal-to-noise ratio for detecting hyperpolarised 13C-labeled metabolites by several orders of magnitude and facilitates dynamic and non-invasive imaging of 13C-pyruvate to 13C-lactate exchange over time. Hyperpolarised MRI has a well-defined potential to quantify metabolic alterations in cardiovascular disease but, at the moment, is not used in daily clinical practice [82].

Molecular imaging, through PET and SPECT, is an excellent alternative to CMR, especially in cases where the exclusion of one of the three etiopathological causes (metabolic, mitochondrial and perfusion dysfunctions) is of fundamental importance. Nonetheless there is a very large choice of molecular tracer, technique's limits are related to the fact that molecular traces have been studied in animal experiments and to the radiation and cost of the imaging techniques. Therefore, 18F-FDG PET in patients with cardiotoxicity allows us to evaluate the early disfunctions associated with antineoplastic agents and to manage their condition.

Additionally, 18F-FDG uptake may be useful as an alternative or even more specific cardiac marker in a hybrid version with CMR, allowing the simultaneous detection of vascular metabolic and functional imaging [83,84].

Also, Artificial Intelligence (AI) has various potential uses in managing cardiotoxicity. At first, the Radiomic application extracts and selects radiomic features based on dimensions, shape, signal density and spatial resolution of voxel signal in a specific tissue. In this context, exciting AI stake reworking imaging applications generated full-dose PET images from low-dose images [85,86]. At the same time, the interesting clinical challenge for practical use will be the employment of the latest generation CCT, such as a photon counting technology and radiomic for information about vulnerability plaque coronaries, perivascular-epicardial fat inflammation (the most robust predictive marker of cardiac mortality), myocardial tissue characterisation (extracellular volume and quantification scar) and perfusion imaging.

Moving forward, the theragnostic platform will take advantage of the addition of novel nanoparticles in CT, containing inorganic contrast agents as specific peptides or antibodies, to detect the molecular and cellular target. New techniques of CT as dual-energy technology, in addition to molecular contrast, can facilitate myocardial tissue characterisation by allowing for material

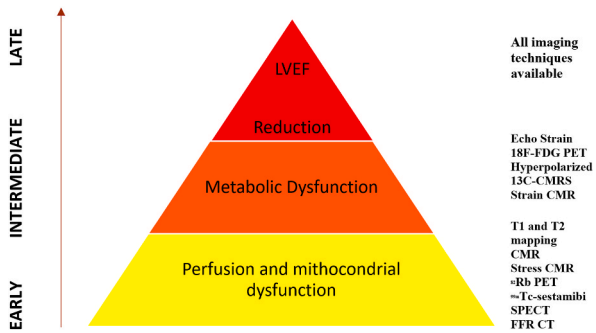

Fig. 8. Detection of CTRCD (cancer treatment-related cardiac dysfunction) using non-invasive imaging. The progress of CTRCD can be divided into three phases: early, intermediate and late. The early phase is characterised by perfusion and mitochondrial dysfunction; in this phase, CMR allows Tissue characterisation for oedema and fibrosis (especially T1 and T2 mapping) and perfusion CMR (Rest/Stress) for microvascular dysfunction. The intermediate phase exhibits a metabolic dysfunction, with impaired diastolic and strain parameters, that can be practically evaluated with Echo and CMR techniques. In the late stage, reduced LVEF represents only the tip of the iceberg and is correlated to consolidated tissue damage.

decomposition analysis [87].

Furthermore, other AI applications can help the clinical deployment of molecular imaging targeting approaches in the timely detection of cardiotoxicity with the accuracy of segmentation algorithms and predict adverse cardiovascular outcomes in patients subjected to imaging targeting as nuclear biomarkers- PET radiotracers targeting FAP (fibroblast activating protein) and PD 1 (death protein1) [88,89].

5. Conclusion

The continuous development and application of new cancer therapies have resulted in a higher survival rate, which inevitably carries the side effects of cardiotoxicity. Nowadays, advanced imaging such as CMR and Molecular Nuclear Imaging, including new techniques such as metabolic and molecularly targeted imaging, may help to understand the pathophysiological mechanism correlated to cardiotoxicity to ensure better prevention and specific therapeutic pathways, trying to reduce oxidative stress. Further, clinical trials are needed to decide when and how to embrace CMR and nuclear imaging for early diagnosis and clinical management of cardiac dysfunction.

Finally, in the subsequent future use of Artificial Intelligence (AI) and big data on imaging parameters (CT, CMR) and oncoming molecular imaging datasets, including differences for gender and countries, may help predict cardiovascular toxicity at their earliest stages, avoid its progression, with precise tailoring of patients' diagnostic and therapeutic pathways.

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