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Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient

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ABSTRACT

Cancer therapy can be associated with both cardiac and vascular toxicity. Advanced multi-modality imaging can be used to stratify patient risk, identify cardiovascular injury during and after therapy, and forecast recovery. Echocardiography continues to be the mainstay in the evaluation of cardiac toxicity. Particularly, echocardiography-based strain imaging is useful for risk stratification of patients at baseline, and detection of subclinical left ventricle (LV) dysfunction during therapy. Cardiac magnetic resonance (CMR) serves a complementary role in the patient with poor echocardiographic or equilibrium radionuclide angiographic image quality or in situations where a more accurate and precise LV ejection fraction measurement is needed to inform decisions regarding discontinuation of chemotherapy. New CMR techniques like T1 and T2 mapping and positron emission tomography (PET) imaging will help us better understand the structural, pathological, and metabolic myocardial changes associated with ventricular dysfunction or release of serum biomarkers. CMR may also be helpful in the evaluation of vascular complications of cancer therapy. Stress echocardiography, stress CMR, computed tomography, and PET are excellent imaging options in the evaluation of ischemia in patients receiving therapies that could potentially cause vasospasm or accelerated atherosclerosis. (J Am Coll Cardiol Img 2018;11:1173–86)

The field of oncology has advanced remarkably. In some instances, cancer is either cured or converted to a chronic disease. Nevertheless, some of the old and new emerging cancer therapies are associated with development of cardiovascular toxicities (1,2), which may have the potential to offset the gains in survival obtained with these cancer treatment advances (3). Much of the focus on cardiovascular toxicities has been in the early detection of myocardial damage and prediction of cancer therapeutics-related cardiac dysfunction (CTRCD). However, because the toxicities associated with cancer therapies are much broader (**Table 1**) (4), this report discusses advanced multi-modality imaging and how it can be used to stratify patients' risk before cancer therapy is started, identify early cardiovascular injury during therapy, predict recovery from injury, and detect cardiovascular injury in long-term cancer survivors (**Central Illustration**).

CLINICAL CASE

A 51-year-old female with left-sided, high-risk, early stage human epidermal growth factor receptor 2-positive (HER2+) breast cancer was referred to the

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

CTRCD = cancer therapeutics-related cardiac dysfunction

EDV = end-diastolic volume

ERNA = equilibrium radionuclide angiocardiography

ESV = end-systolic volume

GLS = global longitudinal strain

GCS = global circumferential strain

HER2+ = human epidermal growth factor receptor 2-positive

cardio-oncology clinic. Her treatment plan included mastectomy, epirubicin, 300 mg/m^2, 17 cycles of trastuzumab, radiation therapy (50 Gy), and hormone therapy. She had no known cardiovascular risk factors, was not receiving medications, and had excellent functional capacity. Imaging and biomarker assessments were performed prior to cancer therapy, throughout her treatment, and 1 year later (Table 2). Her baseline blood pressure was 138/80 mm Hg, cardiac examination was unremarkable; her left ventricular ejection fraction (LVEF) by 3-dimensional (3D) echocardiography was 61%; global longitudinal strain (GLS) was −21.3%; and global circumferential strain (GCS) was −20.3%. Several questions were raised during her initial consultation and follow-up: How does cardiac imaging play a role in identifying cardiovascular toxicity risk in this patient? What is the best method to detect early cardiac injury from treatment? What are the predictors of ventricular function recovery after cardiotoxicity?

ASSESSMENT OF BASELINE RISK OF CARDIOVASCULAR COMPLICATIONS IN PATIENTS RECEIVING CANCER THERAPY

ASSESSING RISK OF CTRCD AND HEART FAILURE. American Society of Clinical Oncology guidelines recommend risk stratification for cardiac dysfunction prior to initiation of potentially cardiotoxic cancer treatment. We refer the readers to their discussion of which patients with cancer are at increased risk of developing cardiac dysfunction (5). From an imaging standpoint, patients with borderline cardiac function (LVEF of 50% to 55%, a history of myocardial infarction, and presence of other cardiac comorbidities, e.g., ≥moderate valvular heart disease) before the start of anthracycline or trastuzumab therapy are at a 3.6- to 11.8-fold increased risk for developing cardiac dysfunction (5). The expert consensus for multi-modality imaging evaluation of the adult patient during and after cancer therapy recommends a baseline echocardiogram, with the calculation of LVEF, ideally using 3D echocardiography and GLS if the technology is available and the operators are comfortable with their performance and interpretation (6). The latter is a reflection of the superior reproducibility of 3D LVEF and GLS measurements (7,8). In addition to LVEF, pre-treatment measurements of GLS appear to identify patients at elevated risk of major adverse cardiac events in the context of anthracycline therapy (9,10). Similarly, every 1% difference in baseline circumferential strain has been associated with 31% increased odds of cardiotoxicity in women receiving breast cancer therapy (11).

Cardiac magnetic resonance (CMR) is usually not used as a first-line tool for risk stratification because of its cost and lack of wide availability. However, in patients with a nondiagnostic echocardiogram, unexplained dilation of the left or right ventricles, or morphological abnormalities raising concern for infiltrative cardiomyopathy, CMR can complement the echocardiographic evaluation to assess for a potential cause. To date, however, there are no data to determine whether pre-treatment CMR parameters identify patients at risk for cardiotoxicity.

CORONARY ARTERY DISEASE RISK. Stress echocardiography may be useful in the evaluation of patients with intermediate or high probability of coronary artery disease (CAD) who are undergoing regimens that may be associated with ischemia (e.g., 5-fluoracil, capecitabine, bevacizumab, sorafenib, and sunitinib) (6). Cardiac computed tomography (CCT) has changed the landscape of coronary assessment in the field of cardiology. Its role in cardio-oncology is primarily restricted to assessment of coronary calcium and obstructive CAD (12). Both nuclear and positron emission tomography stress testing represent alternatives for the evaluation of CAD in these patients. Stress CMR can detect the presence and extent of inducible myocardial ischemia with high diagnostic accuracy (13). The attraction of stress echocardiography and stress CMR is the lack of radiation exposure. However, stress echocardiography may be challenging in patients who have had mastectomies, breast expanders, or implants. In those situations, the use of ultrasonic enhancing agents may improve visualization of the myocardial segments and accuracy of interpretation (14). CMR may not be feasible in the presence of certain breast tissue expanders because of their ferromagnetic components (6).

VASCULAR TOXICITY. Many agents used in cancer treatment such as tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, antimetabolites, and radiation therapy are associated with direct vascular toxicity, whereas hormone therapy can increase the risk of atherosclerotic vascular events (15,16). Potential vascular toxicities include hypertension, CAD, peripheral arterial disease, pulmonary hypertension, and venous thrombosis (16). Although certain clinical risk factors for these toxicities have been described (e.g., pre-existing hypertension), unlike cardiomyopathy,

there have been no reports that have examined vascular imaging parameters to identify patients at risk (16). The area of vascular risk in cancer survivors, however, has gained significant attention with the description of clonal hematopoiesis (CH) as a risk factor for atherosclerotic vascular disease (17). CH is an expansion of myeloid and lymphoid cells that carry recurrent somatic mutations. CH appears to be identified in approximately 10% of patients 70 to 79 years of age (18), with a 4-fold increased incidence in patients receiving cancer therapy when compared with untreated patients (19). Patients with CH are at a 2.0- to 2.6-fold higher risk of coronary or cerebrovascular disease (20). Therefore, identifying patients with CH and performing targeted vascular imaging may be a novel future approach to risk stratification.

TABLE 1 Cardiovascular Toxicities Where Imaging Plays a Role in Risk Stratification, Detection, or Prognosis

Toxicity	Agents	Imaging Recommended
CTRCD, myocarditis	Anthracyclines Alkylating agents Antimetabolites Antimicrotubule agents Monoclonal antibody-based tyrosine kinase inhibitors Proteasome inhibitors Small-molecule tyrosine kinase inhibitors Immune therapy	3D Echo (ideally) or 2D Echo GLS CMR
Valvular heart disease	Radiation-induced heart disease	2D Echo CT CMR
Pericardial disease	Methotrexate Arsenic trioxide Antimetabolites Antimicrotubule agents Radiation therapy	2D Echo CT CMR
Coronary artery disease	Antimetabolites Antimicrotubule agents; Monoclonal antibody-based tyrosine-kinase inhibitors Small-molecule tyrosine kinase inhibitors	Stress echocardiography CCT Stress CMR PET
Pulmonary hypertension	Small-molecule tyrosine kinase inhibitors	2D Echo
Vascular toxicity	Anthracyclines Tyrosine kinase inhibitors Monoclonal antibodies Proteasome inhibitors Antimetabolites	Vascular ultrasonography CMR CT

2D = 2-dimensional; CCT = cardiac computed tomography; CMR = cardiac magnetic resonance; CT = computed tomography; CTRCD = chemotherapy-related cardiac dysfunction; Echo = echocardiography; GLS = global longitudinal strain; PET = positron emission tomography.

EARLY IDENTIFICATION OF CARDIOVASCULAR INJURY DURING CANCER THERAPY. Early detection of CTRCD. ***Evaluation of LV volume and function.*** Historically, planar equilibrium radionuclide angiocardiography (ERNA) and single-photon emission computed tomography (SPECT)-ERNA provided reliable and accurate means of calculation of LVEF. However, although extensive research exists in the cancer setting, these techniques have almost been abandoned due to the concern for radiation exposure, especially during repeated examinations. In addition, modern multiple gated acquisition scans may not allow optimal patient positioning for LVEF assessments (6). The limits of agreement between multiple gated acquisition scans and CMR for LVEF are wide (−19.4% to 16.5%). At an LVEF threshold of 50% to define cardiotoxicity, there is a risk of misclassifying 35% of cancer patients (21). It is also important to note the additional limitation of ERNA due to its inability to evaluate right ventricular, valvular function, or pericardial disease.

Although CCT has the capability of providing a measurement of LV volumes and LVEF, it comes at the cost of radiation exposure. Therefore, CCT does not have a routine role in the surveillance of cardiac function during cardiotoxic cancer therapy.

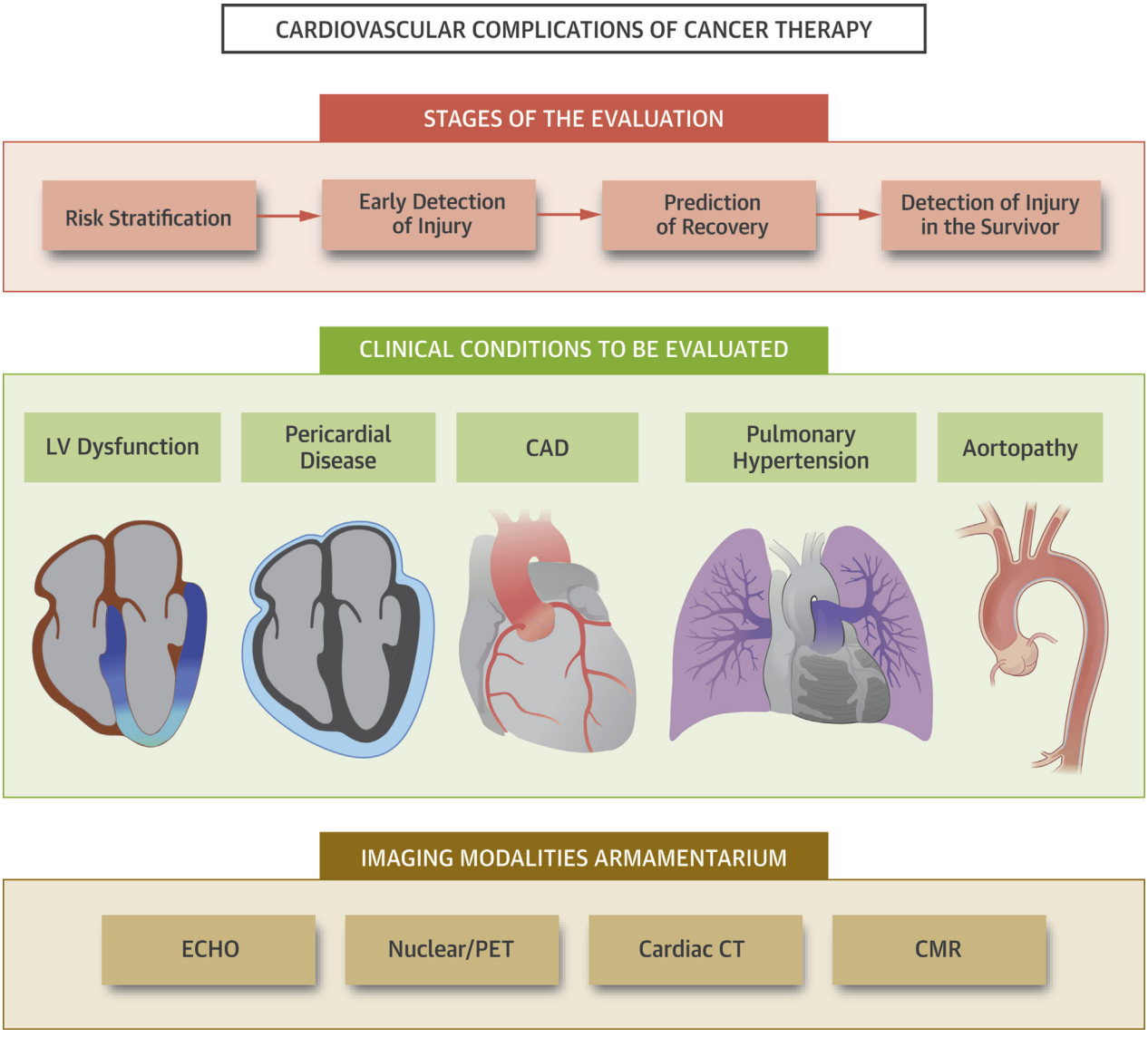
Surveillance and detection of CTRCD is currently performed by using echocardiography-derived LVEF and, more recently, strain imaging (6). The overall goals are: 1) correct adjudication of stage B heart failure, so that modern heart failure therapy can be initiated; 2) accurate calculation of LV volumes in the assessment of LV remodeling; and 3) potential identification of situations where changes in loading conditions may be playing a role in changes in LVEF or strain.

The best method for measuring LVEF to identify early cardiovascular injury is still unclear.

CMR can identify small changes in LVEF that appear to parallel the changes in myocardial strain (22). However, whether such small early changes predict subsequent CTRCD or are just the result of hemodynamic variability is unclear (23). CMR may be useful clinically in situations where there is concern regarding echocardiographic or ERNA calculation of LVEF or in situations where a more accurate and precise LVEF measurement is needed to inform decisions regarding chemotherapy discontinuation (6).

Interestingly recent work in female patients receiving therapy for breast cancer has suggested that nadir LVEF values are identified by 3D echocardiography earlier than 2D echocardiography, suggesting that 3D measured LVEF may be a useful method to identify early cardiac injury (24). For adjudication of stage B heart failure during cancer therapy, based on a single study, 3D LVEF appears to identify more

CENTRAL ILLUSTRATION **Cardiovascular Complications of Cancer Therapy**



Plana, J.C. et al. J Am Coll Cardiol Img. 2018;11(8):1173–86.

Stages of the evaluation and clinical conditions to be evaluated and imaging modalities available. CAD = coronary artery disease; CMR= cardiovascular magnetic resonance; CT = computed tomography; PET = positron emission tomography.

patients who meet CTRCD criteria than 2D LVEF does (25). Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally, 3D echocardiography) (6). It is important to recognize that, although ideal, the technique or the expertise in interpretation may not be widely available outside academic centers. In such scenarios, ultrasound-enhancing agents should be used to enhance 2D echocardiography when 2 contiguous LV segments are not well visualized on noncontrast apical images (6). The LV volumes obtained will be larger with closer correlation with CMR. The recently published clinical applications of ultrasonic enhancing agents in echocardiography reported a study examining baseline pre-chemotherapy echocardiograms in female patients, where 51% of contrast-enhanced diastolic volumes were classified as abnormal, despite the LV dimensions being within

the normal range by unenhanced 2D volume measurements. To account for this change in normal range, the document proposed an end diastolic volume upper limit cutoff of 83 ml/m^2 for women and 98 ml/m^2 for males (26). Armstrong et al. (27) compared LV volumes measured using 2D and 3D echocardiography to volumes measured using CMR. They found that, although the 3D calculated left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were closer to those calculated by using CMR, there was still underestimation (mean EDV: 12.4 ml/m^2; mean ESV: 5.3 ml/m^2; $p < 0.001$ for both).

LV volumes and EF are not fixed for a given individual. They fluctuate, reflecting dynamic changes in loading conditions and inotropic state. A reduction in LVEF can be due to either an increase in LVESV or reduction in LVEDV. In patients treated with anthracycline and/or trastuzumab, the primary driver for a reduction in LVEF is an increase in LVESV (22,28–30) Patients may exhibit potential reductions in LVEDV caused by intravascular volume depletion (reduced preload) from cancer therapy-related poor oral intake, vomiting, or diarrhea. Two recent studies of various cancers in patients receiving chemotherapy demonstrated that 16% to 19% of patients who met criteria for CTRCD showed only an isolated reduction in LVEDV without a "significant" increase in LVESV (23,31). This has important implications for clinical management of subclinical LV dysfunction and CTRCD and is a cause for further investigation. However, several concepts should be considered when interpreting these data. First, up to 6% variability in LVEF and 21 ml in LVEDV can occur with CMR measurements due to variability in contouring the basal short axis slice. However, newer software analysis tools allow tracking the motion of the mitral and aortic valves' planes through the cardiac cycle, minimizing the variability in LV volumes calculations. This is particularly important in longitudinal studies where even the acquisition of the basal slice could be different due to variability in image setup (32,33). Second, based on cardiac physiology, a reduction in LVEDV does not occur in isolation. It is associated with a sympathetic reflex that increases inotropy, which in turn will increase the slope of the end-systolic pressure-volume relationship. In addition, the reduction in stroke volume results in reduced systemic pressure with subsequent reduction in afterload. In combination, the LVESV also decreases. This concept is supported by recent work in which healthy individuals subjected to 2.0% to 3.5% intravascular volume depletion had a reduction in both LVEDV and LVESV without a statistically significant reduction in LVEF or circumferential strain (34). Therefore, the lack of a reduction in LVESV associated with a reduction in LVEDV seen in these recent studies suggests a concomitant reduction in myocardial contractility to explain the reduction in LVEF. Finally it is important to recognize without making CMR the technique to routinely follow patients during cancer therapy that our echocardiography techniques do not have the ability to identify small changes in ventricular volumes during cancer therapy (8). Hence, using ventricular volumes as surrogates for intravascular status would not be practical in routine clinical practice.

TABLE 2 Temporal Changes in Cardiac Function, Biomarkers, and Symptoms in the Clinical Case Presented

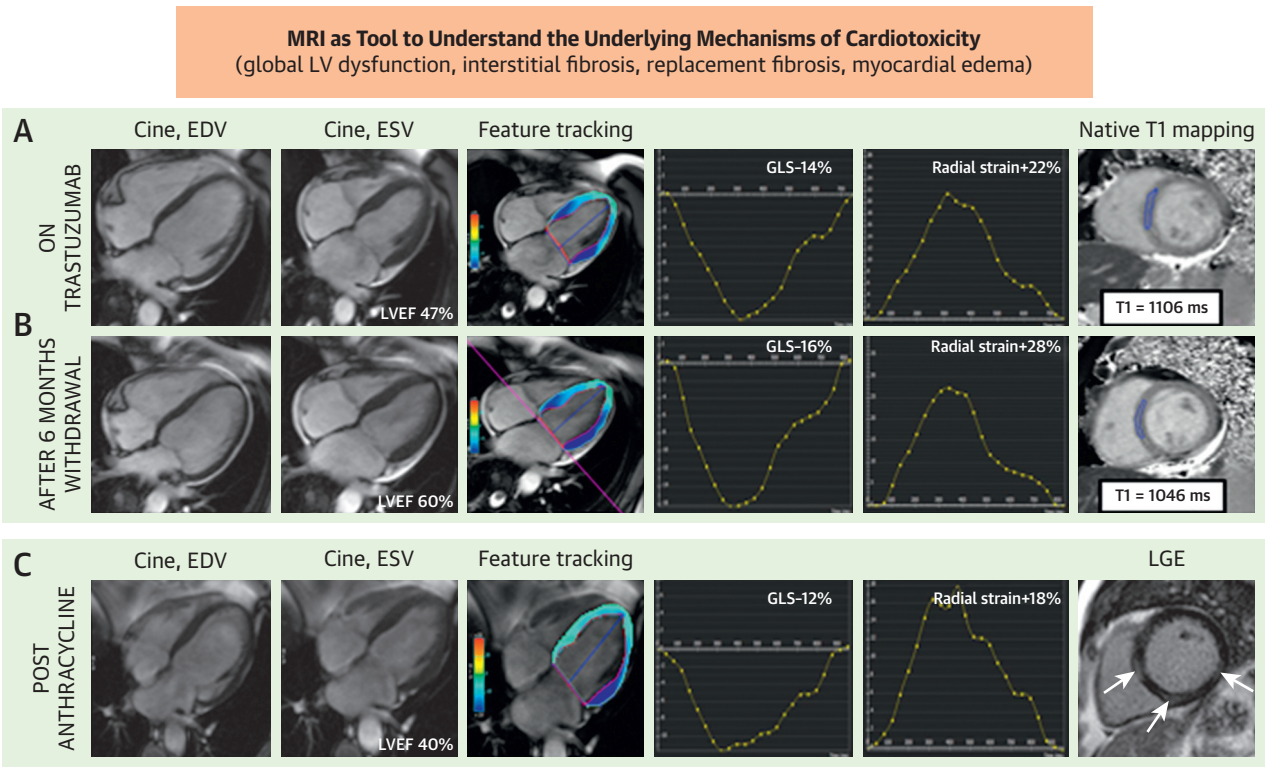
Intervals of Follow-Up	3D EF	2D EF	GLS	HsTpI, ng/ml	NYHA Functional Class
Pre-cancer therapy	61	64	−21.5	2	I
Post-anthracycline therapy	53	55	−17.9	48	I
1 month into trastuzumab (Herceptin) therapy	48	47	−15.1	102	II–III
6 weeks	56	60	−19.2	17	I
6 months	53	54	−17.8	8	I
9 months	53	58	−18.1	3	I
12 months	53	55	−17.1	2	I
24 months	52	54	−17.9	-	I

EF = ejection fraction; HsTpI = highly sensitive troponin I; NYHA = New York Heart Association; other abbreviations as in Table 1.

The findings of potential volume dependency of LVEF measurements further emphasize the importance of repeating cardiac imaging 2 to 3 weeks later upon discovery of subclinical LV dysfunction or CTRCD, before consideration of changes to cancer therapy or initiation of cardiac medications (6). It also is important to perform surveillance imaging at times when patients' intravascular volumes are less likely to be depleted, such as the day before the next chemotherapy cycle.

Evaluation of LV deformation: strain imaging. Negishi et al. (35) found that the strongest predictor of CTRCD was delta 2D-based GLS during treatment. An 11% reduction (95% confidence interval [CI]: 8.3% to 14.6%) half way through trastuzumab therapy was the optimal cutoff, with a sensitivity of 65% and a specificity of 94% for subsequent cardiotoxicity. GLS was an independent early predictor of later reductions in LVEF, incremental to usual predictors in patients at risk for trastuzumab-induced cardiotoxicity. Their findings served as the scaffolding for the subsequently published expert consensus that recommends the use of GLS for the surveillance of

FIGURE 1 CMR Tools to Understand Underlying Mechanisms of Cardiotoxicity

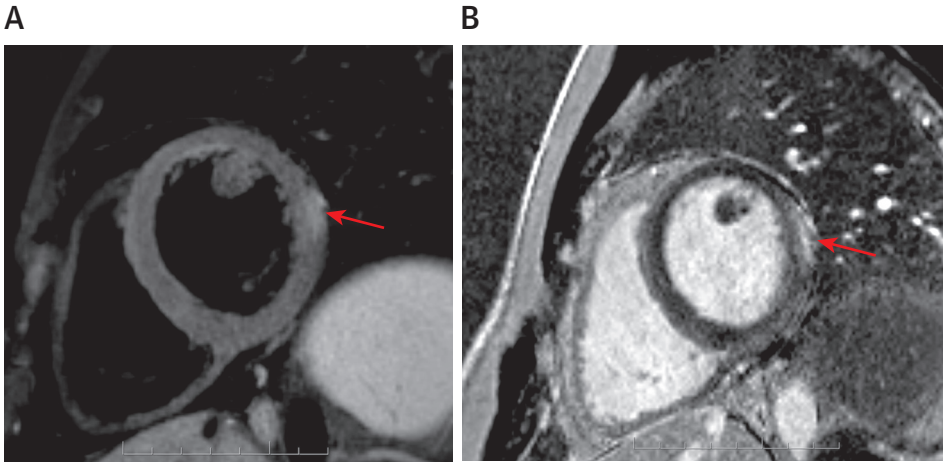


CMR studies in a patient during **(A)** and after 6-month withdrawal of trastuzumab **(B)**: end-diastolic (EDV) frame, end-systolic (ESV) frame, feature tracking analysis and curves for GLS and radial strain and native T1 mapping. At 6-month withdrawal, both EDV and ESV are reduced, ejection fraction increased, global longitudinal and radial strain improved, and native T1 values were reduced. This case demonstrated the reversible nature of trastuzumab cardiomyopathy. **(C)** CMR study in a patient with anthracycline-cardiomyopathy, with reduced EDV and ESV, reduced ejection, impaired global longitudinal strain, and presence of subepicardial and mid-wall late gadolinium enhancement (LGE) in the septum, inferior, and inferolateral walls. CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction.

subclinical LV dysfunction for patients being treated with anthracyclines or trastuzumab with a reduction of >15% compared to baseline illustrating a clinically significant change (6). Nevertheless, the association between GLS and subsequent CTRCD might have been potentially misinterpreted, postulating first, that GLS falls before LVEF in patients receiving cardiotoxic therapies and, second, that there is a compensatory increase in GCS in response to the reduction in GLS in order to initially preserve LVEF. Recent work (36) can help us understand the relationship between LVEF and its determinants: GCS, GLS, LV internal dimension, and wall thickness. The model showed that GCS contributes more than twice as much to LVEF than GLS. For the LVEF to be maintained, a reduction of GLS needs to be compensated by an increase in GCS or wall thickness or reduced LV diameter. In the above- mentioned study by Negishi et al. (35), LVEF, GLS, and GCS decreased in parallel from baseline to 12 months, from 58 ± 5.5% to 55 ± 5.3%; from −20.7% to −18.3%; and from −17.8% to −15.9%, respectively. Global radial strain decreased from 50.9% to 45.7%. Other studies have also demonstrated simultaneous reductions in all these parameters (11,37).

Six-month data from the study by Negishi et al. (35) can help us understand the limitations of using 2D echocardiography and the role of 2D-based strain for the early detection of subclinical LV dysfunction. LVEF decreased from 64 ± 4.6% to 58 ± 5.5% (a 6 absolute point reduction in LVEF), which is below the 10-point threshold ability of 2D-based echocardiography to discriminate sequential changes in LVEF (8). At the 12-month follow-up, LVEF continued to deteriorate, reportedly at 55 ± 5.3% (9 absolute point reduction in LVEF), very close to the threshold, giving the reader the ability to recognize the change. In parallel, there was a

FIGURE 2 Myocarditis Identified by CMR



(A) Focal area of myocardial edema is shown in a T2-weighted sequence (SPAIR) image **(arrow)**. **(B)** Subepicardial enhancement **(arrow)** on late gadolinium-enhanced images, reflective of myocardial cell death. Subepicardial enhancement is a pattern often seen in myocarditis. SPAIR = spectral attenuated inversion recovery; other abbreviation as in Figure 1.

reduction in GLS from −20.7 ± 2.6% to −18.3 ± 2.1% at 6 months (2.4 absolute point reduction, 11.6% relative reduction compared to baseline), which remained unchanged at 12 months. The lower intra- and inter-observer variability values of GLS allow easier recognition of the change in systolic function than LVEF. The relative mean error for GLS was 1.7 (below the 2.4 change noted during surveillance), making 2D-based strain well suited for the identification of subclinical LV dysfunction (38).

Using CMR, Drafts et al. (22) initially reported on the behavior of LVEF and GCS at 1, 3, and 6 months in 53 patients receiving low-dose anthracyclines (50 to 375 mg/m^2) for the treatment of breast cancer, leukemia, and lymphoma. LVEF and GCS decreased from baseline to 6 months 58 ± 1% to 53 ± 1% ($p = 0.0002$) and from −17.7 ± 0.4% to −15.1 ± 0.4% ($p = 0.0003$), respectively (22).

In 101 patients receiving cardiotoxic agents in the setting of various malignancies, Jordan et al. (31) subsequently published data incorporating CMR mid-wall Eulerian GCS, including this time GLS (n = 34, using high-temporal resolution 2- and 4-chamber cine views), and LVEF. Overall, GLS declined from −15.44 to −14.79 ($p = 0.069$), GCS from −17.99% to −17.23% ($p = 0.0052$), and LVEF from 59.2% to 56.7% ($p = 0.0002$), respectively.

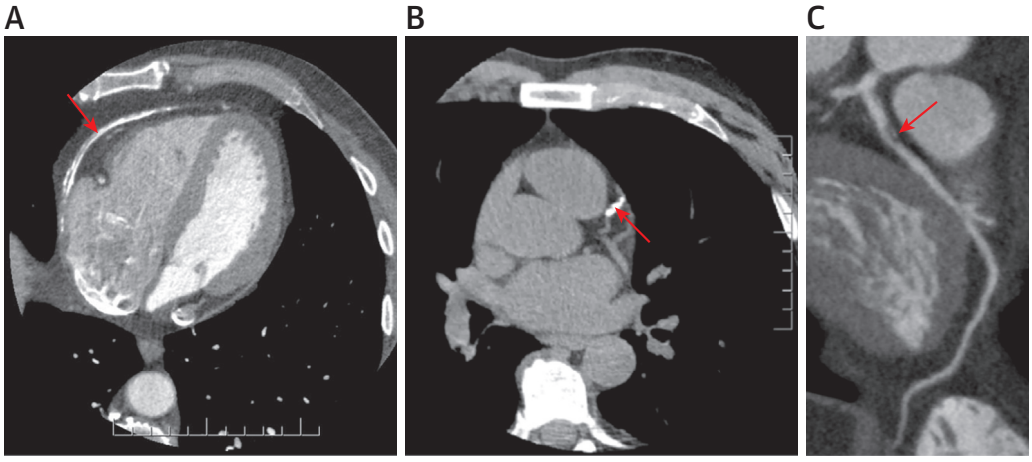
LV mass was unchanged by CMR in the patients who developed CTRCD. The diameter of the ventricle increased only slightly during and after anthracycline therapy (22).

Data from these echocardiographic and CMR studies suggest that the reduction in LVEF may be explained by the parallel reduction in GLS and GCS, with slight contribution from the increase in LV internal dimension. The apparent misconception that GLS changes before LVEF appears to be explained by the inability of 2D-based echocardiography to recognize changes <10%. Larger studies ideally using CMR-based LVEF and strain are needed to study this concept further.

The significant interest in triplane and 3D speckle tracking is currently limited by the poor correlation of values of this technique compared with 2D-based strain. There are 2 explanations: the limited feasibility due to poor tracking of the segments and the differences in acquisition rates (low volumes per second compared to the high frame rates attainable with its 2D counterpart). We are hopeful that technology will evolve over time and overcome these challenges (39).

Tissue characterization. CMR may facilitate our understanding of the pathogenesis of CTRCD. Myocardial tissue changes such as intracellular and interstitial edema and fibrosis may precede the alterations in LV volumes, reduction in LVEF, or changes in myocardial strain and may represent early markers of myocardial injury. Multiple CMR imaging sequences such as T1- and T2-weighted imaging, as well as newer T2 and T1 mapping sequences, can help identify intracellular and interstitial edema and are now part of our armamentarium (**Figure 1**) (40,41).

FIGURE 3 Cardiac Computed Tomography for Assessment of CAD



(A) Pericardial calcification in patients who had previously undergone chest radiation. **(B)** Significant proximal coronary artery disease involving the LAD artery. **(C)** Mixed plaque in the proximal LAD in a patient experiencing chest pain during treatment with 5-fluorauracil. LAD = left anterior descending artery; other abbreviations as in Figure 1.

Native T1 mapping or a combination of pre- and post-contrast T1 mapping can be used to calculate extracellular volume fraction (ECV) as a marker of edema or interstitial fibrosis (42). Post-contrast T1-weighted imaging (late gadolinium enhancement [LGE]) can be used to identify myocardial replacement fibrosis.

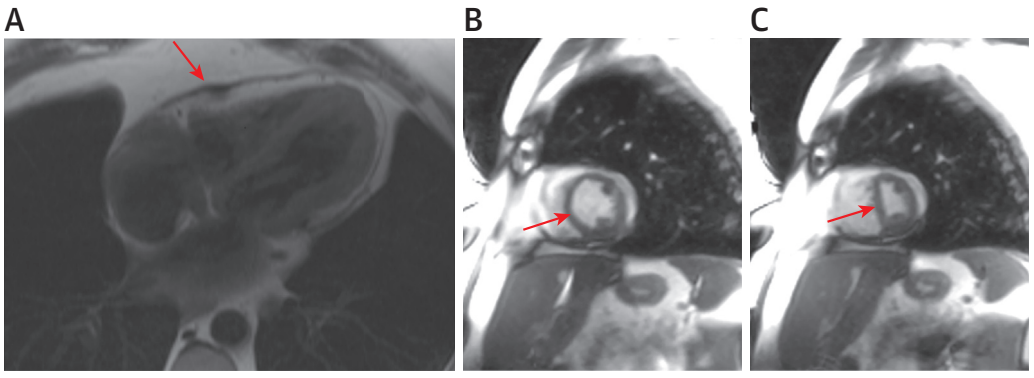
Several small studies using CMR have shown myocardial edema early following anthracycline therapy, by using T2-weighted sequences (30,43). The presence of edema has been associated with persistent reduction in RV function in follow-up examinations (30). CMR studies have also demonstrated presence of focal and replacement fibrosis with variable patterns (epicardial, mid-wall, insertion points) and incidence. Nevertheless, this finding has not been consistent in published reports (41). Also, there is accumulating evidence of the presence of diffuse interstitial fibrosis measured by native T1 mapping and ECV in anthracycline-induced cardiomyopathy. It manifests independently of the presence of cardiovascular comorbidities and is associated with impaired diastolic function (44,45). In cancer survivors, an increase in ECV has been associated with higher anthracycline doses and lower exercise capacity (46). In this latter cohort, the increase in ECV is likely a marker of interstitial fibrosis.

Some CMR studies have described subepicardial LGE of the lateral wall in patients with trastuzumab cardiomyopathy, suggesting an underlying myocarditis, however, this has not been reproduced in other studies (47,48). Although the presence of LGE has been associated with prognosis in a range of ischemic and nonischemic cardiomyopathies, there are no similar data in patients with CTRCD (49). However, LGE imaging may have value in evaluating patients receiving cancer immunotherapy with a clinical suspicion of myocarditis. Cardiotoxicity related to immunotherapy includes heart failure, Takotsubo-like syndrome, and fulminant myocarditis with fatal outcome (50). CMR is known to be a valuable modality for detection of myocarditis, using the Lake Louise criteria (51). Although this has not been formally evaluated in the setting of immune therapy, a recent case series of 35 patients with immune therapy-mediated myocarditis identified LGE in a mid-myocardial, subepicardial, or diffuse pattern in 77% of the patients (**Figure 2**) (52).

Myocardial metabolism. PET imaging provides a unique assessment of myocardial metabolism, which may identify the earliest myocardial or vascular changes related to toxicity. Although changes in fluorodeoxyglucose uptake appear to identify patients at risk of doxorubicin-mediated cardiotoxicity (53), the use of PET imaging to identify early cardiotoxicity is still limited to the research realm.

Complementary role of biomarkers. Several biomarkers have been proposed for early detection of CTRCD.

FIGURE 4 Assessment of Pericardial Constriction Using CMR



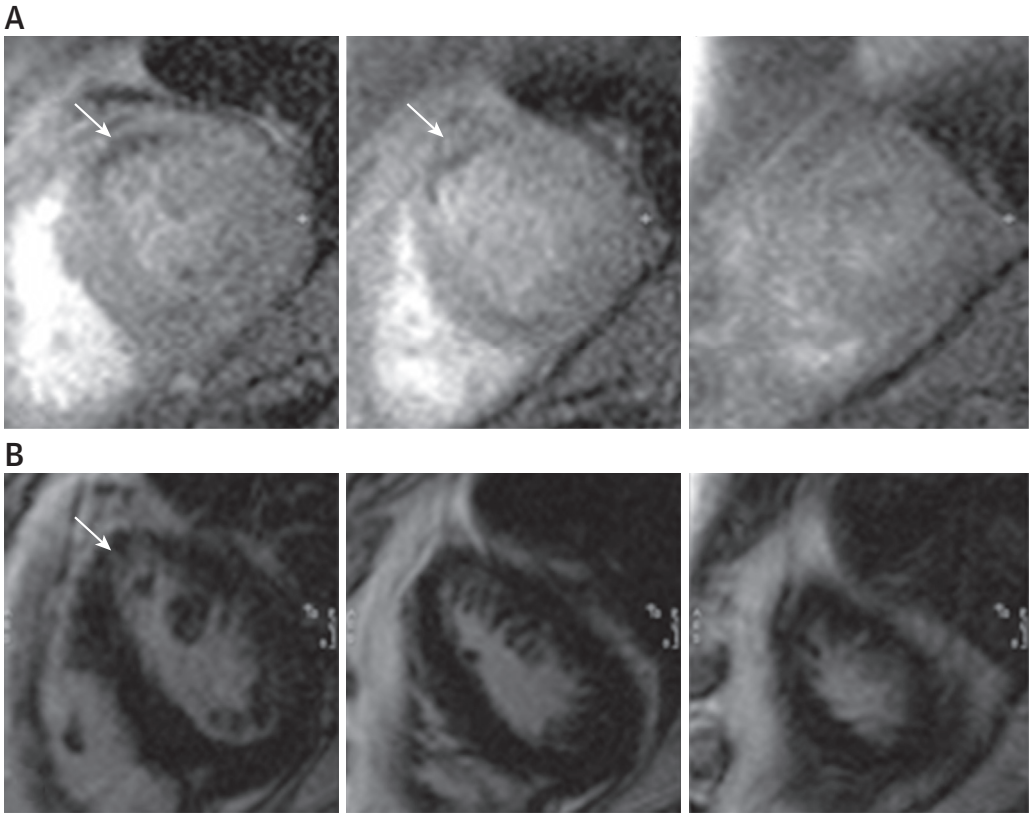
(A) T1-weighted spin echo sequence demonstrates thickening of the pericardium **(arrow)**. **(B, C)** Real-time cine sequence showing normal position of the interventricular septum at expiration, but shifted **(B)** into the LV during inspiration **(C)**. This respirophasic septal shift is a hemodynamic feature of constrictive physiology. LV = left ventricle; other abbreviations as in Figure 1.

The biomarkers most studied are troponin (Tn), resulting from cardiomyocyte damage and natriuretic peptides, reflecting elevation in left ventricular filling pressure and wall stress. Tn is recognized as a highly efficient predictor of early and long-term cardiac toxicity. Cardinale et al. (54-56) had previously demonstrated that Tn subunit I (TnI) positivity soon after initiating regimens containing anthracyclines is a strong predictor of LVEF reduction and poor cardiac outcome, particularly in patients showing persistent (>1 month) Tn positivity. Cardinale et al. (57) also showed that, in trastuzumab-treated patients, TnI evaluation provided an opportunity to recognize patients at risk of developing trastuzumab-induced CTRCD, and among them, those who were less likely to recover from it despite optimal therapy for heart failure. There is debate regarding the clinical usefulness of the measurement of natriuretic peptides because of discordant results (1,2). Notably, data for the complementary role of biomarkers to imaging in cancer patients are limited but encouraging. Sawaya et al. (58) showed a negative predictive value of 91% when a decrease in GLS (<19%) was combined with an elevation of ultrasensitive TnI in breast cancer patients receiving doxorubicin and trastuzumab. Similarly, the combination of elevated TnI and myeloperoxidase levels was shown to identify a group of patients with breast cancer at increased risk for cardiotoxicity better than each individual biomarker alone (59). A combined multimodality imaging and biomarker approach in selected individuals may thus be of interest for risk prediction and to guide therapy.

DETECTION OF PULMONARY HYPERTENSION. Pulmonary hypertension can occur during cancer treatment due to venous thromboembolism, compression by the tumor, or due to use of tyrosine kinase inhibitors such as dasatinib. Echocardiography remains the primary method to screen for pulmonary hypertension during treatment through the measurement of right ventricular systolic pressure from the tricuspid regurgitation jet.

VASCULAR TOXICITY. There has been growing interest in expanding our understanding of the effects of cancer therapeutics in the cardiovascular system beyond the heart. Arterial stiffness by pulse wave velocity (PWV) can identify vascular changes in the asymptomatic subclinical stage: vascular ultrasonography can be used to assess both the local and carotid-femoral arterial stiffness, whereas CMR can be used to assess both local and central arterial stiffness. Di Lisi et al. (60) recently reviewed cancer therapy-induced vascular toxicity. Useful imaging biomarkers in this context are the noninvasive flow-mediated dilation (flow hyperemia-mediated dilation) of the brachial artery to detect endothelial dysfunction and increased intima-media thickness of the common carotid artery measured by ultrasonography. Using CMR, the thoracic aortic PWV, a marker of vascular stiffness, appears to increase steadily after the administration of anthracyclines. Although adjusting for baseline heart rate had minimal impact on the change in velocity over time, participants with a higher systolic blood pressure had a higher PWV at rest and a faster increase in PWV, highlighting the interaction between the effects of the

FIGURE 5 Stress CMR for the Assessment of Inducible Myocardial Ischemia and Viability



(A) Significant peri-infarct ischemia **(white arrow)** in the basal to mid-cavity of the anterior wall (LAD territory) in a 57-year-old male with a history of chemotherapy and radiation for small-cell lung cancer. Basal, mid-, and apical short-axis slices are from stress first-pass perfusion images using a gradient echo (GRE) sequence after adenosine infusion and administration of 0.1 mmol/kg gadolinium chelate contrast agent. **(B)** Corresponding basal, mid-, and apical short-axis slices from late gadolinium- enhanced images using an inversion recovery (IR)-GRE sequence 15 to 20 min after contrast administration. There is a focal subendocardial infarction in the mid-cavity anterior wall **(arrow)**. Abbreviations as in Figure 4.

chemotherapeutic agents and the baseline risk factors of the patient. Aortic distensibility also can be assessed by gated CT, but both the radiation burden and the lower temporal resolution (which may lead to underestimation of distensibility) limit its use in this context (61). Despite these interesting findings, whether these early changes result in subsequent symptomatic vascular disease remains unknown.

PREDICTION OF RECOVERY OF CARDIOVASCULAR TOXICITY

CTRCD. Once there is a reduction in myocardial function identified during cancer therapy, there are very few data for predictors of recovery other than the timing of heart failure therapy initiation (62). In patients receiving sequential anthracycline and trastuzumab-based therapy, nadir GLS value greater than −15.8% may identify patients at higher risk of lack of LVEF recovery (hazard ratio [HR]: 0.39; 95% CI: 0.18 to 0.74) (63). Similarly, in anthracycline-treated patients, lower LVEF at initiation of HF treatment may be associated with lack of recovery of ventricular function (64). The only other imaging predictors of ventricular function recovery is larger left atrial volume (odds ratio [OR]: 0.94; 95% CI: 0.88 to 0.99) (65). These parameters together suggest that those who have more severe myocardial dysfunction, as measured by EF, strain, or atrial remodeling at initiation of HF therapy, are less likely to have recovery of heart function.

DETECTION OF CARDIOVASCULAR DISEASE IN LONG-TERM CANCER SURVIVORS

DETECTION OF CTRCD. The high risk for adult onset CTRCD after treatment for childhood and adolescent neoplasia warrants early detection when intervention is expected to be of greater benefit. Children's Oncology Group long-term follow-up guidelines recommend periodic evaluation by echocardiography. Conventionally, the measurement has been obtained using 2D echocardiography. In cancer survivors, compared with CMR, the sensitivity and false negative rate improved from 25% and 75% to 53% and 47%, respectively, when using 3D echocardiography instead of 2D echocardiography, reducing the misclassification rate of stage B heart failure patients as normal from 11% to 5% (27). However, in a larger cohort of 1,820 adult survivors of childhood cancer, although only 5.8% of the patients had abnormal 3D LVEF (<50%), 32.1% of survivors with normal 3D LVEF had cardiac dysfunction by GLS (28%) or by diastolic assessment (8.7%) or both. Abnormal GLS was associated with the dose of chest radiation and anthracycline-based chemotherapy received. Interestingly, survivors with the metabolic syndrome were twice as likely to have abnormal GLS or diastolic dysfunction. The authors concluded that the use of modern echocardiography may allow identification of a subset of survivors who may benefit from early medical intervention (66).

CMR-based ECV has been examined as a measure of subclinical cardiac injury in both pediatric and adult cancer survivors. In pediatric cancer survivors, ECV appears to be associated with total anthracycline dose, markers of adverse ventricular remodeling, and lower maximum V_{O_2} (46). In adults treated with anthracyclines, ECV fraction is increased in cancer survivors compared to that in controls, with higher values in those with reduced versus those with preserved LVEF (45). Elevated ECV is also correlated with measures of worse diastolic dysfunction such as higher lateral annular E′ velocity and E/e′ ratio. Compared to matched controls and a separate cohort of patients who underwent imaging prior to cancer therapy, ECV values appeared to be elevated, particularly in those receiving anthracycline-based therapy (44). These data suggest that increased ECV may occur in cancer survivors with preserved or reduced LVEF and that it identifies a cohort of patients with potentially vulnerable myocardium. Whether these abnormalities have future implications for the cardiovascular health of patients remains to be determined.

In addition to LV dysfunction, recent studies of lymphoma survivors have also described right ventricular (RV) systolic dysfunction. The association between LV function (LV GLS) and RV function (tricuspid annular plane systolic excursion), indicated a global long-term cardiotoxic effect. However, RV dysfunction (6.2%) was less prevalent than LV dysfunction (30.8%) ($p < 0.001$) (67,68).

DETECTION OF PERICARDIAL DISEASE. Pericardial disease can be seen as a long-term consequence of radiation therapy to the chest. Echocardiography remains the primary modality for screening for pericardial constriction in patients with suggestive symptoms (69). Cardiac CT can help assess the presence and extent of pericardial calcification (**Figure 3**). In patients in whom echocardiography is not diagnostic, CMR also provides an assessment of the presence of pericardial thickening, pericardial effusion, its extent, and an assessment of the constrictive physiology (**Figure 4**) (69).

DETECTION OF VASCULAR TOXICITY. Radiation-induced cardiovascular disease appears to be associated with damage to endothelial cells through transient increases in oxidative stress, impaired vascular wall homeostasis, endothelial dysfunction and apoptosis of endothelial cells with subsequent inflammatory response leading to increased expression of matrix metalloproteinases, adhesion molecules, and proinflammatory cytokines and, downregulation of vasculoprotective nitric oxide, leading to accelerated atherosclerosis, increased blood viscosity and unstable platelet aggregates (70). Arterial stiffness is a precursor of atherosclerosis and is increased in irradiated arteries, in keeping with radiation-induced damage. Early and late changes in markers of aortic stiffness with breast cancer therapy was measured using CMR at baseline and at, 4, and 14 months post-therapy measuring aortic PWV and distensibility at ascending aorta and proximal descending aorta. The study demonstrated that acute changes are observed in PWV and distensibility at the ascending aorta following contemporary breast cancer chemotherapy and partially reverse a year after therapy is discontinued, with more severe effects seen with anthracyclines (71). Childhood cancer survivors show reduced vascular health (72), and increased arterial stiffness following chemotherapy (73). The long-term effects of radiation therapy on arterial stiffness may have a role on increasing cardiovascular risk in women treated for breast cancer (74).

The assessment of coronary calcium and obstructive CAD can be achieved robustly by using CCT (Figure 3) and stress CMR (Figure 5). In survivors, a coronary calcium score may help with risk stratification and may guide intensity of risk factor modification.

DISCUSSION OF THE PATIENT'S CASE

Our patient had no conventional cardiovascular risk factors. Although her baseline 3D LVEF and GLS were normal, her GCS was mildly reduced, which may be a pre-treatment risk of CTRCD (Table 2).(11) She had a reduction in 3D LVEF immediately post anthracycline but it did not meet CTRCD criteria. However, she had >15% relative reduction in GLS, meeting criteria for subclinical LV dysfunction (6). Given the absence of convincing data for intervention with isolated reduction in GLS, no cardiac therapy was instituted. She presented 1 month later with stage C heart failure. Her lowest GLS was measured at 15.1%, suggesting that there is a reduced chance of completed LVEF recovery (63). With 2 trastuzumab cycles held and initiation of beta-blockers and angiotensin-converting enzyme inhibitors (ACEi), her LVEF and GLS improved; however, despite ~2 years of cardiac medications, her GLS and LVEF remains mildly reduced.

OUTCOMES IN CARDIO-ONCOLOGY AND FUTURE DIRECTIONS

The goal for the cancer patient is to fully administer the prescribed regimen with no interruptions, aiming at cure or remission, with a survival free of cardiovascular morbidity and mortality. This brings us to the question of the optimal outcome to follow in cardio-oncology?

We propose to strengthen the partnership between imaging, oncology and heart failure specialists and, very importantly, the cancer patient, so as a group we can come to an agreement as to the outcomes we believe will matter, so we can use them effectively to understand and mitigate the cardiovascular toxicity of old and new agents. We anticipate that the oncologists will include the ability to deliver full and uninterrupted regimens. The imagers would like to include LV volumes, LVEF, and mass and deformation indices. Our heart failure colleagues will obviously be interested in the accurate adjudication of cardiomyopathy, heart failure, and cardiovascular mortality, as well as the use of biomarkers (Tn, BNP, and N-terminal pro-B-type natriuretic peptide) and tests evaluating functional exercise capacity (6-min walk test and maximum Vo_2). The patient would likely add quality of life to the above-mentioned metrics.

Regardless of our field of expertise, we have one shared goal: cancer survival without cardiovascular disease. We look forward to continuing the advancement of the field of multimodality imaging with the hope of achieving this goal through the demonstration of impact on outcomes.

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