Cardiac MRI in the Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy
A Systematic Review

Paaladinesh Thavendiranathan, MD, MSc; Bernd J. Wintersperger, MD; Scott D. Flamm, MD, MBA; Thomas H. Marwick, MBBS, PhD, MPH

During the past 30 years, there has been a significant decrease in cancer mortality rates, predominantly attributable to improvements in treatment options. However, survivors are at increased risk of premature cardiac disease, both because of the overlap in risk factors for cancer and cardiovascular disease and the cardiotoxic effects of cancer chemotherapy. Two chemotherapeutic agent classes that are commonly associated with cardiotoxicity are the anthracyclines and tyrosine kinase inhibitors, both of which can cause left ventricular (LV) dysfunction and heart failure (HF). Mechanisms of cardiac injury from cancer therapy have been summarized elsewhere. Briefly, anthracycline cardiotoxicity has been attributed to reactive oxygen species formation, transcriptional changes in intracellular adenosine triphosphate production in cardiac myocytes, and, more recently, through interaction with cardiac topoisomerase IIβ. Trastuzumab cardiotoxicity seems to be because of inhibition of cardiomyocyte human epidermal growth factor receptor 2, resulting in ATP depletion and contractile dysfunction. Other proposed mechanisms include immune-mediated destruction of cardiomyocytes. At the tissue level, early anthracycline toxicity has been associated with myocardial inflammation, vacuolization, and cell swelling/edema. These changes seem to occur before myocardial functional abnormalities. Later stages of toxicity are associated with myocardial inflammation, vacuolization, and cell swelling/edema. These changes seem to occur before myocardial functional abnormalities. Unfortunately, the use of myocardial biopsy is not feasible for diagnostic purposes in this setting. However, once HF manifests, the 2-year mortality can be as high as 60%. This emphasizes the importance of early recognition of cardiac injury and institution of cardioprotective therapy in an effort to prevent development of HF and allow uninterrupted completion of cancer therapy. Thus, the diagnosis is dependent on either direct evidence of myocardial damage or functional disturbance. Either signal may be identified by imaging or biomarker measurements.

A commonly used definition of cardiotoxicity is a >5% reduction in LV ejection fraction (EF) to <55% with HF symptoms, or a >10% asymptomatic reduction to <55%. Cardiovascular imaging, therefore, has an important role in the identification of cardiotoxicity and, more importantly, in the detection of early cardiac injury using newer techniques. Although no established definition of early cardiac injury exists, in this article it is defined as the presence of myocardial changes without significant reduction in LVEF. However, despite multiple candidate imaging modalities, the best modality for these purposes is unknown.

Multiple gated acquisition scans are commonly used to monitor cardiotoxicity using LVEF. Despite being a reproducible technique, its lack of sensitivity to small changes in LVEF limits its use in the detection of early cardiac injury. Echocardiography is also commonly used to monitor cardiotoxicity, although it too is relatively insensitive to small changes in LVEF. Its most promising application, however, is in the use of myocardial strain and strain rate imaging to detect early cardiac injury. Nonetheless, the challenges of acoustic window with echocardiography will remain.

Biomarkers may also play a role in the detection of cardiotoxicity. In particular, troponin I release with anthracycline or trastuzumab therapy has been shown to be a marker of subsequent LV dysfunction. However, the need for multiple repeated measurements and the poor recovery in LV function in patients with proven troponin release limit its use in routine practice. Cardiac MRI (CMR) is considered the reference standard for measurement of ventricular volumes and function, making it ideally suited to assess cardiotoxicity. However, more uniquely the ability for myocardial tissue characterization provides a noninvasive biopsy of the underlying histopathological myocardial changes, potentially allowing for recognition of early cardiac injury. Additional strengths include lack of ionizing radiation and absence of acoustic window limitations. In this systematic review of published works, recent abstracts, and ongoing clinical trials, we summarize the existing data on the use of CMR for the following
clinically important scenarios: (1) detection of early cardiac injury, (2) identification of cardiotoxicity during or <1 year of treatment, (3) detection of late consequence of therapy (>1 year post-treatment), and (4) monitoring response to cardio-protective therapy.

Literature Review
The search method adhered to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for reporting systematic reviews.28 A MEDLINE (1970 to June 2013) search was performed using the OVID search engine using the key words neoplasms, antineoplastic agents, cardiac toxicity, CMR, and their variations. All citations were screened for inclusion by using a hierarchical approach of assessing the title, abstract, and article (Figure 1). References of all selected articles and reviews were screened to identify additional studies. Any study of ≥10 patients that used CMR as the primary method to detect cardiotoxicity was included. No language or humans-only restrictions were imposed. Conference proceedings from Society of Cardiovascular Magnetic Resonance, European Society of CMR, American College of Cardiology, American Heart Association and, European Society of Cardiology Meetings were screened for relevant abstracts between 2009 and 2013. Any relevant studies from these meetings are referred to as preliminary studies in this review. The World Health Organization International Clinical Trials registry (clinicaltrials.org) was searched with above mentioned key words to identify relevant ongoing trials. Preliminary studies and ongoing trials are summarized in the Appendix Tables I and II in the online-only Data Supplement and the references for the preliminary studies are only provided in the Supplement. All relevant data were extracted using a standard data form, and primary authors were contacted when necessary to clarify study components.

Detection of Early Cardiac Injury
Ventricular Volumes, Systolic Function, and Mass
Prediction of subsequent cardiac toxicity15,20 based on small early changes in LV volumes, mass, or function has been difficult with echocardiography or multiple gated acquisition. In contrast, the high accuracy and precision of CMR may allow identification of early cardiac injury by showing subtle changes that do not meet current criteria for cardiotoxicity (Table 1).19,29 A preliminary study by Smith et al of 28 anthracycline-treated breast cancer patients illustrated that a significant increase in LV mass on day 3 of therapy (likely because of edema) predicted subsequent drop in LVEF at 1 year (Appendix Table I in the online-only Data Supplement). Another preliminary study by Grover et al of 36 patients with breast cancer demonstrated a significant increase in LV end-systolic volume by CMR as the earliest indicator of cardiac injury that occurred even before a rise in troponin or fall in global longitudinal strain.

An ongoing observational study is examining whether early change in CMR LVEF and volumes between baseline and 3 months in 150 patients receiving anthracycline therapy (with or without trastuzumab) could predict the degree of LVEF drop by 24 months (Appendix Table II in the online-only Data Supplement).36

Myocardial Strain
Early reduction in myocardial strain or strain rate using echocardiography has been shown to predict subsequent

![Figure 1. Literature search flow diagram.](http://circimaging.ahajournals.org/)}
Similarly, CMR-based techniques such as spatial modulation of magnetization have shown a decline of mid-wall circumferential strain at 1 month of therapy in 53 asymptomatic patients treated with anthracyclines and have remained reduced at 6 months (Table 1). However, whether these early changes predicted subsequent cardiotoxicity was not reported. An ongoing trial in 50 patients with lymphoma with CMR will provide additional data on the

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Cancer</th>
<th>n</th>
<th>Age/Sex</th>
<th>Treatment</th>
<th>Imaging Timing</th>
<th>Findings</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunning et al[30]</td>
<td>Strain (feature tracking)</td>
<td>Non-Hodgkin lymphoma</td>
<td>10</td>
<td>Median (range)</td>
<td>Doxo (300 mg/m²)</td>
<td>Baseline, 3 mo post-Doxo</td>
<td>Significant reduction in circumferential strain post-therapy. Trend toward GLS reduction</td>
<td>...</td>
</tr>
<tr>
<td>Drafts et al[29]</td>
<td>LV volumes, EF and circumferential (circ) strain (SPAMM)</td>
<td>Breast and heme</td>
<td>53</td>
<td>Mean±SE, 50±2 y</td>
<td>Anth (Doxo equivalent 50–375 mg/m²), radiotherapy 0%</td>
<td>Baseline, 1, 3, and 6 mo</td>
<td>By 6 mo significant increase in LVE SV (42±3 to 54±3), reduction in LVEF (58±1% to 53±1%), and circ strain (-17.7±0.4% to -15.1±0.4%)</td>
<td>...</td>
</tr>
<tr>
<td>Ylänen et al[31]</td>
<td>LVEF</td>
<td>Multiple pediatric</td>
<td>62</td>
<td>Median, 7.8 y</td>
<td>Anth (80–419 mg/m²), radiotherapy 11%</td>
<td>Median, 7.8 y post-therapy</td>
<td>LVEF and RVEF &lt;55% in 79% and 80%, respectively. Significant dilation of LV and RV in 15% to 100% of patients. LV mass normal</td>
<td>...</td>
</tr>
<tr>
<td>Armstrong et al[19]</td>
<td>LVEF and mass</td>
<td>Multiple pediatric</td>
<td>114 (5% with previous CM)</td>
<td>Median (range)</td>
<td>Radiotherapy 32% ± Anth (0 to &gt;350 mg/m²)</td>
<td>Median 27.8 y postcancer diagnosis</td>
<td>LVEF &lt;50% in 14%. LVEF and LV mass 2 SD below normal in 32% and 48% of patients</td>
<td>...</td>
</tr>
<tr>
<td>Neilan et al[32]</td>
<td>LVMI</td>
<td>Multiple</td>
<td>91, all with known Anth CM, (82% stage C HF)</td>
<td>43±18 y</td>
<td>Anth (276±18 mg/m²), radiotherapy 33%</td>
<td>Median 88 mo post-therapy</td>
<td>Inverse relationship between LVMI and Anth dose (r=−0.67) For 27 mo f/u, CV events* more common with lower LVMI (HR, 0.87). LVMI of &lt;57 gm/m²—sens 100%, spec 85% to predict CV events</td>
<td>...</td>
</tr>
<tr>
<td>Chaosuwannakit et al[33]</td>
<td>LVE SV, LVEF</td>
<td>Breast, lymphoma, or leukemia</td>
<td>40</td>
<td>52±11 y, 70% women</td>
<td>Anth, trastuzumab (in combination or alone), radiotherapy 0%</td>
<td>Baseline and 4 mo after treatment initiation</td>
<td>Significant increase in LVE SV (49.7±18.2 to 54.9±12.5 mL) and LVEF (58.6±6.3 to 53.9±6.4%) at 4 mo</td>
<td>...</td>
</tr>
<tr>
<td>Oberhoizer et al[14]</td>
<td>LV and RV function</td>
<td>Multiple</td>
<td>28</td>
<td>Mean 16.4 y, 53% women</td>
<td>Anth 202 (81–462) mg/m²</td>
<td>0–20 y post-therapy (average 3 y)</td>
<td>Reduction in LVEF in 15/28 to &lt;55%</td>
<td>...</td>
</tr>
<tr>
<td>Wassmuth et al[34]</td>
<td>Early gadolinium enhancement imaging to measure relative enhancement (RE)</td>
<td>Multiple</td>
<td>22</td>
<td>Mean age 43 y, 77% women</td>
<td>Dixo (67±25 mg/ m²) or epirubicin (76±19 mg/m²), radiotherapy 9%</td>
<td>Pretherapy 3 d and 28 d post</td>
<td>LV EF drop 67.8±1.4% to 58.9±1.9% at 28 d. Increase in RE to ≥5 on d 3 associated with drop in LVEF on d 28 and persistent EF reduction at 6 mo (subgroup)</td>
<td>...</td>
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</table>

Anth indicates anthracycline; CM, cardiomyopathy; CMR, cardiac MRI; CV, cardiovascular; Dixo, doxorubicin; EF, ejection fraction; GLS, global longitudinal strain; heme, hematologic; HF, heart failure; HR, hazard ratio; LV, left ventricular; LVE SV, LV end-systolic volume; LVMI, LV mass index; LVEF, LV ejection fraction; RV, right ventricular; RVEF, RV ejection fraction; SPAMM, spatial modulation of magnetization.

*Mean±SD unless otherwise stated.
†Cardiovascular deaths, appropriate implantable cardioverter defibrillator therapy, admission for decompensated HF.
use of myocardial strain to identify early injury and predict subsequent cardiotoxicity.37

Myocardial Inflammation
Myocardial inflammation detected with CMR based on early gadolinium enhancement using T1-weighted fast-spin echo sequences has been used as a marker of myocardial injury in patients with myocarditis (Figure 2).38 Using this method in 22 asymptomatic patients receiving anthracyclines for solid or hematologic malignancies, a ratio of signal intensity (SI) differences between myocardium and skeletal tissue between pre- and postcontrast acquisition ≥5 on day 3 was associated with a reduction in LVEF at 28 days (Table 1).35 Also, there was a modest (r=−0.57) correlation between increased SI at day 3 and lower LVEF at 6 months.35 These changes may be attributable to either an increase in extracellular distribution volume or enhanced water exchange between the compartments because of early myocardial injury.

These findings seem to be confirmed by a preliminary study by Kotwinski et al of 51 patients with breast cancer treated with anthracyclines (with or without trastuzumab; Appendix Table I in the online-only Data Supplement). Among the 20% with cardiotoxicity, a higher increase in early gadolinium enhancement was present between baseline and day 3 after first cycle of therapy and had an area under the curve of 0.75 to discriminate subsequent cardiotoxicity. High-sensitive troponin T was not elevated in any of the patients after the first cycle of therapy and had an area under the curve of 0.75 to discriminate subsequent cardiotoxicity.35 These changes may be attributable to either an increase in extracellular distribution volume or enhanced water exchange between the compartments because of early myocardial injury.

None of the treated animals without events or the control group had an increase in SI. All animals with events had histopathologic evidence of myocellular vacuolization attributed to intracellular edema without myocardial fibrosis or necrosis.

Three preliminary human studies (Appendix Table I in the online-only Data Supplement) have assessed the use of myocardial edema imaging during cancer therapy. Using T2-weighted sequences (short tau inversion recovery) in 28 patients with breast cancer, Smith et al illustrated that a significant increase in SI on day 3 of therapy was seen among patients who had a drop in LVEF at 1 year. Two other studies (n=29 and 21, respectively) by Grover et al using short tau inversion recovery imaging in patients with breast cancer receiving anthracycline and trastuzumab showed an increase in myocardial SI compared with skeletal muscle of >1.9 at 3 months after start of therapy in 58% and 52% of patients, respectively. The latter of the 2 studies identified cardiotoxicity in 43% of patients at 12 months. However, neither study reported whether the increase in SI at 3 months predicted subsequent cardiotoxicity.

An ongoing trial of T1 and T2 mapping in 50 patients with lymphoma receiving anthracyclines will compare T2 values at the completion of chemotherapy (=3 months) between those who have preserved and reduced LVEF at 1 year.37 This study will also examine the relationship of T1 and T2 values to various biomarkers and myocardial mechanics and diastolic parameters by echocardiography. Another ongoing study will also assess the ability of T1 signal at 3 months to predict LV function changes at 24 months in anthracycline-treated patients.36

Detection of Cardiotoxicity During or Early After Cancer Therapy

Ventricular Volumes, Systolic Function, Mass, and Strain
In a recent study of patients with hematologic or breast malignancy treated with anthracyclines, CMR was performed before, at 1, 3, and 6 months into treatment.29 By 6 months, the LV end-systolic volume increased significantly with a concomitant drop in LVEF (Table 1). These changes were seen as early as 1 month into therapy. By 6 months, 26% of patients who had EF >50% at baseline experienced cardiotoxicity (EF <50%). In a previous publication, the same group

![Figure 2. Early gadolinium enhancement in a patient with breast cancer receiving adjuvant trastuzumab therapy referred with concern of cardiotoxicity. Left ventricular ejection fraction by cardiac MRI was 54%. Signal intensity measurements (mean/SD) in the myocardium and skeletal muscle precontrast (left) and postcontrast (right) illustrated. Calculated early gadolinium enhancement ratio was 16.3 (abnormal), suggestive of capillary leak/inflammation.](image-url)
demonstrated a significant increase in LV end-systolic volume and a decrease in LVEF between a baseline and 4-month CMR in 40 patients with hematologic or breast malignancy treated with anthracyclines (Table 1). Likewise, another small study of multiple malignancies detected a significant reduction in LVEF for the whole group by day 28 (Table 1) with an EF <55% in 27% of anthracycline-treated patients (Table 1). These findings are consistent among CMR-based studies, with other preliminary work by Grover et al (Appendix Table I in the online-only Data Supplement) emphasizing increase in LV volumes and reduction of LVEF and right ventricular EF as early as 1 month into therapy and persisting up to 12 months with cardiotoxicity identified in a subgroup. An ongoing observational study is examining serial CMR versus multiple gated acquisition–based LVEF for the detection of cardiotoxicity, its association with biomarkers, and prognosis in 50 trastuzumab-treated women with breast cancer. Currently, only 1 study of 10 adult patients receiving anthracyclines for hematologic malignancy illustrated reduced circumferential

Table 2. Published CMR Studies of Edema Imaging

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Cancer</th>
<th>n</th>
<th>Age/Sex</th>
<th>Treatment</th>
<th>Imaging Timing</th>
<th>Findings</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Lightfoot et al</td>
<td>Postcontrast, myocardial Gd-SI</td>
<td>No malignancy</td>
<td>40 rats</td>
<td>N/A, 100% male</td>
<td>Control (n=7), weekly doxo 1.5 mg/kg (n=19) and 2.5 mg/kg (n=14)</td>
<td>Pre, 2, 4, 7, and 10 wk post doxo initiation</td>
<td>In animals experiencing adverse cardiovascular events* (16/33 treated animals), Gd-SI increased compared with baseline at time of event</td>
<td>An increase in Gd-SI &gt;2.9 at midterm from baseline predicted subsequent CV events*</td>
</tr>
<tr>
<td>Oberholzer et al</td>
<td>TIRM</td>
<td>Multiple</td>
<td>7</td>
<td>N/A</td>
<td>Anth</td>
<td>Immediately post anth</td>
<td>2/7 had myocardial edema</td>
<td>...</td>
</tr>
<tr>
<td>Cottin et al</td>
<td>T1 and T2 relaxation times of ex vivo hearts (0.47-T magnet)</td>
<td>No malignancy</td>
<td>23 rats</td>
<td>N/A, 100% male</td>
<td>Control (n=10), low dose doxo 1 mg/kg intraperitoneal for 10 d (n=13; early injury model)</td>
<td>7 d post completion of treatment</td>
<td>Increased LV T1 and T2 values with doxorubicin. Correlations between T1 and T2 values and percent water content r=0.46 to 0.75. No change in LV performance for early injury model</td>
<td>...</td>
</tr>
<tr>
<td>Thompson et al</td>
<td>T1 and T2 relaxation times of ex vivo hearts (0.47-T magnet)</td>
<td>No malignancy</td>
<td>22 rats</td>
<td>4 wk, 100% male</td>
<td>Control (n=11), doxo (n=11) 1 mg/kg 7 wk, then 2 mg/kg 8–9 wk subcutaneous(chronic model)</td>
<td>At 16, 17, 18, or 19 wk</td>
<td>Increased LV T1 values with doxo 65±30 vs control 62±30 ms and higher in more advanced disease. No difference in T2 values 45.8±2.6 vs 47.5±3.6 ms. Myocardial water content not increased</td>
<td>...</td>
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</table>

*Anth indicates anthracycline; Doxo, doxorubicin; Gd-SI, gadolinium signal intensity; LV, left ventricular; N/A, not available; and TIRM, turbo inversion recovery magnitude sequence.

*Deterioration of LV ejection fraction or unanticipated death.
strain at 3 months after therapy using a feature-tracking algorithm (Figure 4) but in the context of reduced LVEF.30

Late Gadolinium Enhancement

Late gadolinium enhancement (LGE) imaging allows detection of myocardial fibrosis and scar and is widely used with good diagnostic and prognostic value in cardiovascular diseases.42 However, the limited data on the incidence, pattern, and prognostic significance of LGE in patients receiving cancer therapy are conflicting (Figure 5). Two retrospective and 1 prospective studies from the same group have illustrated the presence of LGE in the context of established cardiomyopathy in patients with breast cancer during5,43 and at end of therapy13 with anthracyclines and trastuzumab (Table 3). The pattern of LGE was subepicardial or myocarditis-like, and the incidence ranged between 94% and 100%. More recently, in 10 patients with non-Hodgkin lymphoma, new or progressive midmyocardial LGE was seen in 30% of patients 3 months after completion of therapy, some in the context of preserved LVEF.30 The potential prognostic value of LGE was shown in 2 retrospective studies5,43 where ≈40% of patients with LGE during therapy either had no improvement or further decline in LVEF at 6 months despite stopping trastuzumab and treatment with angiotensin converting enzyme (ACE) inhibitors and β-blockers. Unfortunately, neither of these studies adjusted for other covariates.5,43 Likewise, a preliminary report by Jordan et al (Appendix Table I in the online-only Data Supplement) of 51 patients with breast or hematologic malignancy receiving anthracyclines and decreasing LVEF described a diffuse pattern of signal enhancement on LGE images in all patients at 6 months into therapy reflecting either diffuse fibrosis or edema.

In contrast, a recent study of anthracycline-treated patients did not identify LGE in any patient with imaging performed at baseline, 1, 3, and 6 months, despite a significant drop in LVEF over the 6-month period (Table 3).29 An ongoing clinical trial will compare LGE with later LVEF changes in 90 trastuzumab-treated women with and without LV dysfunction at 6 months into therapy.45

Arterial Stiffness

In patients with cardiovascular risk factors and advanced age, increased thoracic aortic stiffness has been associated
with adverse cardiovascular events.\textsuperscript{46} Two studies (Table 4) have examined the impact of anthracycline therapy on aortic stiffness measured by CMR.\textsuperscript{29,33} In patients receiving anthracyclines for breast or hematologic malignancies, a significant increase in pulse wave velocity and decrease in ascending aortic distensibility was seen between baseline and 4 and 6 months.\textsuperscript{29,33} In both studies, the whole population had a reduction in LVEF. These studies demonstrate that the early consequences of anthracycline therapy extend beyond the cardiac system.\textsuperscript{36}

Currently, the same group is assessing multiple CMR markers including arterial stiffness at baseline, 3, and 24 months of therapy in adults receiving anthracyclines alone or in combination with paclitaxel or trastuzumab.\textsuperscript{36} Another ongoing study will be assessing aortic stiffness changes in 25 patients with cancer being treated with anthracyclines.\textsuperscript{47} In addition, this study will measure aortic stiffness in 60 childhood cancer survivors 1 to 15 years postanthracycline therapy.\textsuperscript{37}

Detection of Late Cardiotoxicity From Cancer Therapy
As the number of childhood and adult cancer survivors increase, methods to identify late cardiotoxicity of cancer therapy have become important. Thus far, detection has primarily relied on the measurement of LVEF using multiple gated acquisition or echocardiography.
**Ventricular Function and Mass**

Because CMR is considered a gold standard for the measurement of LVEF and mass, studies comparing CMR to other imaging modalities against an independent reference standard to detect late cardiotoxicity are unavailable. However, CMR identified a higher prevalence of cardiomyopathy (EF <50%) in 114 asymptomatic adult survivors of childhood cancers treated with anthracyclines in comparison to 2-dimensional and 3-dimensional echocardiography (Table 1). In a smaller study of 28 anthracycline-treated childhood cancer survivors, LV dysfunction (EF <55%) was present in 54% of patients and right ventricular dysfunction in another subgroup. Recently, in 62 childhood cancer survivors exposed to anthracyclines, LV and right ventricular dysfunction (EF <55%) was reported in 79% and 80%, respectively, using CMR; 90% had LV end-systolic volume and 29% had LV end-diastolic volume >2 SD above the reference values. The higher proportion of LV dysfunction in the latter study is likely at least partially attributed to a nontypical approach of endocardial contouring resulting in higher volumes and lower EF. LV mass by CMR as a marker of late cardiotoxicity was examined in several studies (Table 1). LV mass >2 SD below the mean of normative CMR data has been reported in 48% of childhood cancer survivors (Table 1). The prognostic value of this finding was illustrated in 91 adult patients with reduced LVEF at a median of 88 months post-anthracycline therapy. During a median follow-up of 27 months, LV mass index was an independent predictor of a composite of cardiovascular death, appropriate implantable cardioverter defibrillator therapy, and admission for HF (hazard ratio, 0.89) despite medical therapy. An LV mass index of <57 g/m² had a sensitivity of 100% and specificity of 85% to predict adverse outcomes. Interestingly, the study by Ylänen et al showed that LV mass was not lower compared with normal values in childhood cancer survivors who received anthracyclines. This discrepancy may be because of the difference in time from therapy to imaging between studies and the approach to ventricular contouring.

Several preliminary studies (Appendix Table I in the online-only Data Supplement) have shown results consistent with the published literature. A study by Kotwinski et al of patients with breast cancer (n=164) receiving anthracycline and trastuzumab therapy imaged 15.1 to 23.7 months postinitiation of therapy illustrated a cardiotoxicity (absolute decline of ≥5%) rate of >20% with CMR. In 18 asymptomatic childhood cancer survivors treated with anthracyclines >10 years previously, Hughes et al demonstrated LVEF <50% in 18%. Also, the LV mass index was low for the entire group. These patients all suffered cardiotoxicity at some point before the CMR study.

**Late Gadolinium Enhancement**

The pattern of LGE described in anthracycline-treated patients with remote cancer includes midmyocardial, right ventricular insertion point, and epicardial. The incidence of LGE in this setting seems to be low (8%), at an intermediate (20 months) period post-therapy, even in the presence of established cardiomyopathy (Table 3). LGE was not identified in a recent study of 62 childhood cancer survivors treated with anthracyclines and imaged 7.8 years later. In the only published prognostic study, the presence of LGE in patients with established anthracycline cardiomyopathy was not an independent predictor of adverse cardiovascular outcomes, although the incidence of this finding was low. Recent preliminary data are concordant with these observations (Appendix Table I in the online-only Data Supplement); studies by Hughes et al and Miller et al of survivors of anthracycline-treated childhood cancer did not identify LGE despite a subgroup of patients...
having LV dysfunction, and similarly, survivors of breast cancer did not have LGE at 15 to 24 months after anthracycline or trastuzumab therapy in a study by Kotwinski et al.

Diffuse Myocardial Fibrosis

Although LGE can identify focal areas of myocardial fibrosis, pathological myocardial fibrosis due to cancer therapy tends to be diffuse and may be missed due to the nature of image acquisition and predominantly qualitative analysis. Estimation of the extracellular volume fraction (ECV) with techniques such as pre- and postcontrast T1 mapping may be better able to illustrate the diffuse nature of myocardial injury (Figure 6). In a rat model of chronic adriamycin toxicity, rats with histological evidence of chronic cardiotoxicity showed higher native T1 values compared with controls without an increase in myocardial water content or CMR-based T2 values. Similarly, ECV has been recently correlated with anthracycline dose, functional capacity, LV dysfunction, and markers of adverse ventricular remodeling in pediatric and adult patients well after completion of anthracycline-based chemotherapy (Table 5). Preliminary studies (Appendix Table I in the online-only Data Supplement) are also concordant with these findings.

Monitoring Response to Cardioprotective Therapy With CMR

Accurate sequential monitoring of LV function, morphology, or myocardial tissue changes with CMR can be used in clinical trials of prophylactic cardioprotective medications in patients receiving cancer therapy or in monitoring the response to cardiac therapy in patients with established cardiomyopathy. A recent randomized controlled study of β-blockers and ACE inhibitors in 90 patients with hematologic malignancies receiving anthracyclines illustrated a 3.4% drop of LVEF in the control group and no change in the treatment group at 6 months using CMR. Several ongoing therapy trials have chosen CMR-based parameters as the primary efficacy end point. The current Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE)-101 randomized placebo-controlled trial of an ACE inhibitor or β-blocker in 159 women with breast cancer receiving trastuzumab is using CMR-based change in end-diastolic volume at 12 months as the primary end point.

Table 5. Published CMR Studies of Diffuse Fibrosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Cancer</th>
<th>n</th>
<th>Age/Sex</th>
<th>Treatment</th>
<th>Imaging Timing</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tham et al</td>
<td>T1 mapping and ECV</td>
<td>Multiple pediatric</td>
<td>30</td>
<td>7–19 y, 50% female</td>
<td>Anth, radiotherapy 17%</td>
<td>7.6±4.5 y postchemo</td>
<td>ECV correlated with Anth dose (r=0.40), peak VO₂ max (r=−0.52), LV mass/volume ratio (r=−0.64), and wall thickness/height ratio (r=−0.72)</td>
</tr>
<tr>
<td>Neilan et al</td>
<td>T1 mapping and ECV</td>
<td>Multiple</td>
<td>42</td>
<td>53±17 y, 50% women</td>
<td>Anth, radiotherapy 29%</td>
<td>89±40 mo postchemo</td>
<td>ECV elevated in patients compared with controls (0.36±0.03 vs 0.29±0.02), ECV correlated with left atrial volume index (r=0.65) and echocardiography measured medial E' (r=−0.63), lateral E' annular velocities (r=−0.64), E/E' (0.61)</td>
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</table>

Anth indicates anthracycline; CMR, cardiac MRI; ECV, extracellular volume quantification; and LV, left ventricular.
outcome. The randomized placebo-controlled Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) trial of angiotensin receptor blocker or β-blocker in 120 women with breast cancer receiving epirubicin-containing chemotherapy and trastuzumab as indicated will be using a change in LVEF by CMR as the primary end point.

**Conclusions**

The best approach for the care of patients at risk of cardiotoxicity from cancer therapy remains to be determined. Options include treating every patient with cardioprotective therapy to avoid cardiotoxicity or to selectively treat those identified as having early toxicity through surveillance. For the latter approach, cardiovascular imaging will play an important role. CMR’s excellent reproducibility for LVEF, volume, and mass measurement, and its specific applications for tissue characterization make it an attractive technique for detection of subclinical and overt cardiotoxicity.

Based on published and preliminary CMR work, the detection of myocardial inflammation and edema may reflect the earliest changes of cardiotoxicity from cancer therapy with potential to predict subsequent ventricular dysfunction. Myocardial strain changes may be seen once the tissue-level changes reach a certain threshold. LV end-systolic volume increase also seems to be an early marker of cardiotoxicity and requires further investigation. Although the frequency and pattern of LGE during therapy is unclear, it may identify patients at a reduced propensity toward recovery of ventricular function. Assessment of change in arterial stiffness may provide an understanding of the early systemic vascular effects of cancer therapy, but its prognostic implications need to be clarified.

In patients with remote cancer therapy, CMR can accurately measure LVEF and mass as a marker of cardiotoxicity. Although the prevalence of LGE well after anthracycline therapy seems to be low, diffuse fibrosis detected using T1 mapping and ECV quantification may be methods of recognizing late subclinical cardiotoxicity. The prognostic significance and cardiac treatment implications of these findings are unknown. However, ECV measures may identify patients who may benefit from close cardiac follow-up.

Overall, CMR will likely allow accurate identification of subclinical or established cardiotoxicity from cancer therapy. Potential clinical uses of specific CMR techniques based on the current evidence are summarized in Table 6. As a result of cost and availability issues, CMR may be a component of an overall imaging process rather than the obligatory, entry diagnostic, or screening test of choice for patients. It remains to be determined if the higher cost of CMR is sufficiently compensated by the ability to identify a higher risk group and provide targeted cardiac therapy. The potential for preemptive reduction of HF and allowing completion of cancer therapy may translate into a favorable cost–benefit analysis.

**Future Directions**

The application of CMR for surveillance of cardiotoxicity is immature. It seems that cardioprophylaxis is possible, but the most cost-effective means of delivery and monitoring is obscure. Fundamental questions remain unresolved regarding the timing of appropriate follow-up and the use of markers other than LVEF. In our opinion, early functional changes are likely more easily assessed by echo-based myocardial strain, although confirmatory studies by CMR may be valuable. Use of unique tissue characterization capabilities of CMR (eg, inflammation and edema) will be dependent on acceptance of T2 and T1 mapping and ECV quantification. New CMR methods, such as diffusion tensor imaging, need to be explored in the identification of cardiac toxicity. Also, with increasing availability of positron emission tomography–MRI systems, focus on myocardial metabolic changes due to cancer therapy should become a focus of investigation.

**Disclosures**

None.

**References**


Cardiac MRI in the Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy: A Systematic Review
Paaladinesh Thavendiranathan, Bernd J. Wintersperger, Scott D. Flamm and Thomas H. Marwick

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SUPPLEMENTARY MATERIAL
**Supplementary Table A:** Preliminary studies (abstracts) using CMR for the detection of early cardiac injury or subsequent cardiotoxicity either during or late after treatment presented at major conferences between 2009-2013.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>MRI method</th>
<th>Cancer Type</th>
<th>N</th>
<th>Age / Gender</th>
<th>Treatment</th>
<th>Timing of Imaging</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes, 2009</td>
<td>CMR LVEF, mass, and LGE</td>
<td>Childhood cancer survivors with history of cardiotoxicity</td>
<td>18</td>
<td>Median age ~20, (11 females)</td>
<td>Anth</td>
<td>16 years (median) years post therapy</td>
<td>78% had elevated LVESV, 28% had elevated LVEDV, median LVEF 55%, 18% had LVEF &lt; 50%. LV mass indexed reduced for whole group. No LGE.</td>
</tr>
<tr>
<td>Smith, 2009</td>
<td>CMR cine images for LV mass and function, T2 weighted STIR</td>
<td>Breast cancer</td>
<td>28</td>
<td>-</td>
<td>Anth</td>
<td>Before therapy, 3 days post 1st cycle, and 1 year post.</td>
<td>Significant reduction in EF seen in 50% (from 75.5% to 70.4% at 1 year). In these patients on day 3 LV mass and STIR signal intensity increased significantly compared to pre therapy.</td>
</tr>
<tr>
<td>Miller, 2012</td>
<td>LVEF, pre and post contrast T1 mapping (ΔR1), LGE, circumferential strain</td>
<td>Acute myelogenous leukemia</td>
<td>15</td>
<td>49 ± 17yrs, 47% female</td>
<td>Anth 74-362mg/m²</td>
<td>Mean 7yrs post AML diagnosis</td>
<td>Correlation between cumulative Anth dose and EDV (r=0.43) and ESV (r=0.43). Also correlation between ΔR1 and E/A ratio (r=0.58), EDV (r=0.44), and ESV (r=0.44). No LGE.</td>
</tr>
<tr>
<td>Grover, 2012**</td>
<td>LV function and volumes by SSFP, STIR for edema imaging, and LGE (toxicity defined as decrease in EF by 10% or below lower limits of normal)</td>
<td>Breast cancer</td>
<td>29</td>
<td>-</td>
<td>Anth</td>
<td>Baseline, 1 and 3 months following commencement of Anth</td>
<td>↑LVESVi at 1 month and 3 months, ↑LVEDVi at 3 months. Decrease in GLS by echo at 3 months but not at 1 month. HsTp increased at 3 months but not at 1 month. T2 signal intensity increased in 58% at 3 months. No LGE.</td>
</tr>
<tr>
<td>Kotwinski, 2013⁵</td>
<td>Cardiac MR based LV function using SSFP, and LGE imaging</td>
<td>Breast Cancer</td>
<td>164</td>
<td>-</td>
<td>Anth ± TZM, Epi 300-450mg/m²</td>
<td>Pre therapy and Baseline, 1 and 3 months post therapy</td>
<td>20.7% with subclinical toxicity (defined an absolute EF fall ≥5% without symptoms). No LGE in any (119 patients imaged).</td>
</tr>
<tr>
<td>Kotwinski, 2013⁵</td>
<td>Early gadolinium relative enhancement (EGE) (cardiotoxicity defined as a drop in EF ≥ 5% at 19 mos post therapy)</td>
<td>Breast Cancer</td>
<td>51 (20% developed cardiotoxicity)</td>
<td>-</td>
<td>Anth with or without TZM</td>
<td>Pre therapy, day 3 post 1st cycle and median 19 mos post therapy</td>
<td>EGE increased significantly more (mean increase 23.8%) on day 3 in the patients with toxicity with an area under ROC curve of 0.75 to predict toxicity. No patients had positive high sensitivity Troponin T (hsTp) at end of first cycle. 78% of patients had positive hsTp at end of anth but this was a poor discriminator of cardiotoxicity (AUC 0.51).</td>
</tr>
<tr>
<td>Grover, 2013⁷</td>
<td>LVEF and volumes, STIR for edema, and LGE (LV dysfunction defined as decrease in EF by 10% or below lower limits of normal at 12 months)</td>
<td>Breast cancer</td>
<td>33 (only 21 had the 12 month study)</td>
<td>-</td>
<td>Anth and/or TZM</td>
<td>Baseline, 1, 3, and 12 months</td>
<td>↑LVESVi and RVESVi and ↓LVEF and RVEF between baseline and 12 mos. Changes were significant by 1 month into therapy. 43% had persistent LV dysfunction at 12 mos. 52% had ↑T2 signal by STIR at 3 months. One patient in the TZM group had LGE at 3 months. Echo myocardia changes were significant by 1 month into therapy. 43% had persistent LV dysfunction at 12 mos. 52% had ↑T2 signal by STIR at 3 months. One patient in the TZM group had LGE at 3 months. Echo myocardia *circumferential strain.</td>
</tr>
<tr>
<td>Toro-Salazar, 2013⁴</td>
<td>CMR LV volumes, function and mass, T1 mapping, and ECV calculation</td>
<td>Childhood cancer survivors with normal systolic function</td>
<td>27 (ECV measured in 13 ) vs controls</td>
<td>11.8-28.8yrs years</td>
<td>Anth (mean cumulative dose 363 ± 89mg/m²)</td>
<td>2.4 to 24 years post anth</td>
<td>Post contrast T1 values lower (455ms vs 487ms). Higher ECV with higher anth dose ±400mg/m2. Lower average circumferential strain.</td>
</tr>
<tr>
<td>Grover, 2013⁹</td>
<td>LV and RV volumes and EF (RV impairment = reduction in EF below 50% or absolute reduction of ≥5% from baseline)</td>
<td>Breast Cancer</td>
<td>33 (only 21 had 12 month study)</td>
<td>-</td>
<td>Anth and/or TZM</td>
<td>Baseline, 1, 3, and 12 months</td>
<td>23% had significant RV impairment at 3 months and 81% at 12 months. Echo based TAPSE also decreased at 3 months.</td>
</tr>
<tr>
<td>Jordan, 2013</td>
<td>LVEF, LGE-SI (signal intensity)</td>
<td>Breast and hematological cancer</td>
<td>51</td>
<td>52 ± 2yrs, 84% women</td>
<td>Anth or TZM</td>
<td>Baseline, 3 and 6 months after chemotherapy initiation</td>
<td>LVEF decreased from baseline 58 ± 6% to 54 ± 7% at 3 months to 53 ± 7% at 6 months. Mean LGE SI increased 14.0 ± 5.5 to 16.1 ± 7.6 to 15.6 ± 6.8. A diffuse pattern of LGE SI was seen at 6 months compared to baseline or 3 months</td>
</tr>
</tbody>
</table>

*Both studies by the same group presented at SCMR at 2 consecutive years. There is likely overlap in the patients.*; Doxo, doxorubicin, LVEF, left ventricular ejection fraction; SE, standard error; SD, standard deviation; Anth, anthracycline; mos, months; yrs, years; CM, cardiomyopathy; HF, heart failure; doxo, doxorubicin; TZM, trastuzumab; epi, epirubicin; hsTp, high sensitive troponin
**Supplementary Table B:** Ongoing clinical trials using CMR for the detection of early cardiac injury or subsequent cardiotoxicity either during or after treatment.

<table>
<thead>
<tr>
<th>Primary Investigator</th>
<th>MRI method</th>
<th>Cancer Type</th>
<th>N (design)</th>
<th>Age / Gender</th>
<th>Treatment</th>
<th>Timing of Imaging</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brezden-Masley¹¹</td>
<td>LVEF MRI vs MUGA</td>
<td>HER2+ Breast Cancer (stage I-IV)</td>
<td>50 (prospective observational)</td>
<td>&gt;18 yrs, 100% Female</td>
<td>Anth and trastuzumab</td>
<td>Baseline and Q 3 months</td>
<td>Compare CMR vs MUGA to detect cardiotoxicity. To examine associations between CMR based structure and function changes and biomarkers and long term outcomes.</td>
</tr>
<tr>
<td>Hundley¹²</td>
<td>LVEF, strain, T1 myocardial signal, aortic pulse wave velocity</td>
<td>Not specified</td>
<td>150 (prospective observational)</td>
<td>&gt;22 yrs, male or female</td>
<td>Anth ≥350mg/m2, or Anth ≥250mg/m2 followed by paclitaxel or trastuzumab</td>
<td>Baseline, 3 mos, 24 mos</td>
<td>Compare automated vs manual measurements of CMR parameters. To assess if changes in CMR parameters between baseline and 3 months will predict changes seen at 24 months.</td>
</tr>
<tr>
<td>Hare¹³</td>
<td>T1 and T2 mapping, EGE LVEF, strain and strain rate</td>
<td>Lymphoma</td>
<td>50 (prospective observational)</td>
<td>18-90yrs, male or female</td>
<td>Anth</td>
<td>Baseline, ~3 moths, 1 yr post start of Anth</td>
<td>Compare T2 times at complete of chemotherapy (3 mos) between those with and without LV dysfunction at 12 mos. Compare difference in fibrosis (T1) between those who had &gt; and &lt;10% increase in myocardial T2 signal. Relationship of biomarkers and CMR T2/T1 values, LVEF, myocardial strain/strain rate and/or diastolic parameters (latter 2 by echo)</td>
</tr>
<tr>
<td>Switsers¹⁴</td>
<td>LGE</td>
<td>HER2+ Breast Cancer</td>
<td>90 (prospective observational)</td>
<td>&gt;18yrs, 100% Female</td>
<td>Anth and trastuzumab</td>
<td>Baseline, 6 and 12 mos</td>
<td>Proportion of patients with LV dysfunction who have LGE versus those who did not have LV dysfunction. Recovery in LVEF with LGE positive versus negative</td>
</tr>
<tr>
<td>Salazar¹⁵</td>
<td>ECM remodelling</td>
<td>Childhood cancer survivors</td>
<td>80 (prospective observational)</td>
<td>9-35yrs, males and females</td>
<td>Anth</td>
<td>Not specified, but atleast 2 years post Ant</td>
<td>Not specified</td>
</tr>
<tr>
<td>Castellino¹⁶</td>
<td>Aortic stiffness</td>
<td>Childhood cancer survivors, children schedule for therapy</td>
<td>115 (60 survivors, 30 controls, 25 pts to receive therapy), (prospective observational)</td>
<td>16-40 years</td>
<td>Anth</td>
<td>1-15 years post therapy, timing during therapy not provided</td>
<td>To determine if aortic stiffness on myocardial strain is increased in childhood cancer survivors treated with anthracycline. To determine if aortic stiffness changes during treatment.</td>
</tr>
<tr>
<td>Azambuja¹⁷</td>
<td>LVEF, myocardial inflammation or injury, fibrosis</td>
<td>Breast Cancer Survivors</td>
<td>150 (cross-sectional)</td>
<td>18-90yrs, 100% female</td>
<td>Anth and non-anth therapy</td>
<td>~15 years post therapy</td>
<td>No specific CMR parameters or outcomes described</td>
</tr>
</tbody>
</table>

Please see table A for abbreviations
REFERENCES


