Role of Cardiovascular Magnetic Resonance imaging in Cardio-Oncology

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Funding: CM is directly and indirectly supported by the University College London Hospitals (UCLH) and Barts NIHR Biomedical Research Centres

Conflicts of Interest: Nothing to Disclose

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Abstract

Advances in cancer therapy have led to significantly longer cancer-free survival times over the last 40 years. Improved survivorship coupled with increasing recognition of an expanding range of adverse cardiovascular effects of many established and novel cancer therapies has highlighted the impact of cardiovascular disease in this population. This has led to the emergence of dedicated cardio-oncology services that can provide pre-treatment risk stratification, surveillance, diagnosis and monitoring of cardiotoxicity during cancer therapies, and late effects screening following completion of treatment. Cardiovascular imaging and the development of imaging biomarkers that can accurately and reliably detect pre-clinical disease and enhance our understanding of the underlying pathophysiology of cancer treatment related cardiotoxicity are becoming increasing important. Multi-parametric cardiovascular magnetic resonance (CMR) is able to assess cardiac structure, function as well as providing myocardial tissue characterisation and can be used to address a variety of important clinical questions in the emerging field of cardio-oncology. In this review we discuss the current and potential future applications of CMR in the investigation and management of cancer patients.

Key words: Cardiovascular magnetic resonance; cardio-oncology; cancer; left ventricular dysfunction; cardiotoxicity

Introduction

Advances in cancer therapy have led to a doubling of survival over the last 40 years with half of cancer patients living for 10 or more years after diagnosis (1). These improved survival rates coupled with the wide range of adverse effects associated with novel cancer therapies (Figure 1) and an ageing population with higher baseline cardiovascular morbidity has resulted in increasing burden of cancer treatment related cardiotoxicity (2). Compared to controls adult cancer survivors have an elevated risk of cardiovascular disease (CVD) in the years after diagnosis, which seems to depend on the cancer subtype and therapy regime, and the development of CVD portends a worse prognosis (3-5). Close collaboration between cardiologists and oncologists is essential to provide patient-centred care, that is increasingly delivered through dedicated cardio-oncology services, with the aim of improving both cardiovascular and cancer outcomes (6). Central to cardio-oncology is the availability of multi-modality cardiac imaging. Multi-parametric cardiovascular magnetic resonance (CMR) has a prominent role within European Society of Cardiology (ESC) guidelines for the assessment of cardiovascular disease and is playing an increasingly important role in the field of cardio-oncology (7, 8).

Role of Imaging and CMR in patients with cancer

Cardio-oncology patient assessment can be broadly divided into a) pre-treatment risk stratification, b) surveillance, diagnosis and monitoring of cardiotoxicity during cancer therapies, c) late effects screening following completion of treatment, and d) assessment and monitoring of cardiac masses and infiltration. Imaging biomarkers that can accurately and reliably predict or detect pre-clinical disease and enhance our understanding of the underlying pathophysiology are increasingly required to support cardio-oncology care.

The choice of imaging modality in cardio-oncology is often dictated by local availability and expertise, however given the spectrum of cardiotoxicity encountered, should employ the most appropriate tool required for the clinical question. The ESC has set out several core principles for imaging in the context of screening and detection of cardiotoxicity during cancer treatment (9). These include using the same imaging modality throughout the screening and follow-up process, employing a modality with high reproducibility and sensitivity for detecting early

disease, minimising radiation and using a test that can offer information beyond ejection fraction quantification. CMR is well placed to address all these principles, and can also provide tissue characterisation and stress perfusion imaging to increase the scope of clinical information available from a single scan (8). CMR is therefore increasing in prominence across international cardiology and oncology guidelines (Supplemental Table 1) and has broad applications in cardio-oncology (Figure 2) (8-16).

Risk stratification prior to initiation of cancer therapy

The growing burden of pre-existing cardiovascular disease in cancer patients together with the range of cardiotoxicities reported across the array of therapeutic options available mean that risk stratification prior to initiation of treatment is vital for delivery of personalised cancer therapy. Risk stratification involves evaluation of prior cardiac history and risk factors, a comprehensive understanding of prior and planned cancer therapy, and measurement of baseline biomarkers including cardiac imaging (2).

For the majority of cardiotoxic therapies a baseline assessment of cardiac function is required prior to treatment initiation. Echocardiography is generally the first line approach both at baseline and for comparison during serial surveillance imaging (2, 9-11). Baseline detection of subclinical or symptomatic cardiac dysfunction may directly impact both choice of chemotherapeutic agent, the initiation of cardioprotective treatment where appropriate and the timing of interval surveillance imaging (2, 10).

CMR is recommended for baseline risk assessment in patients with poor quality echocardiographic images and for assessment in those with complex pre-existing heart disease or where vasodilator stress may be useful (9-12, 15). CMR has a high diagnostic accuracy for the detection of functionally-significant coronary artery disease and a normal perfusion scan is associated with low rates of subsequent cardiovascular events (17, 18).

Surveillance for Cardiotoxicity

Cancer treatment-related cardiac dysfunction (CTCRD)

Cancer treatment-related cardiac dysfunction (CTRCD) is a long established adverse effect of anthracyclines where progressive dose-related left ventricular (LV) dysfunction can develop, ultimately resulting in heart failure (19). Patients with traditional cardiovascular risk factors such as advancing age, hypertension and pre-existing LV dysfunction are at particular risk (20). More recently, other cancer therapies including trastuzumab, tyrosine kinase inhibitors and immunotherapy have also been associated with LV dysfunction. LV ejection fraction (LVEF) is the most widespread biomarker used for surveillance and early detection of declines in LVEF (98% of CTCRD is detectable in the first 12 months) enables prompt treatment with increased chance of recovery (21).

Current ESC guidelines define CTRCD as an absolute reduction in LVEF of >10% or to a value of less than <50%, with a relative reduction in global longitudinal strain (GLS) of >15% considered an early marker of cardiotoxicity (9). These should lead clinicians to consider initiation of cardioprotective medications and/or review of cancer therapy. Alternative cut-offs have however been proposed in guidelines from other societies (2, 10-12, 16), and the role of blood biomarkers for surveillance screening is increasingly recognised (22).

Measurement of left ventricular ejection fraction

Historically LVEF was assessed using multi-uptake gated acquisition (MUGA) scans due to widespread availability and good intra- and inter-observer reproducibility (23). When compared to CMR however, MUGA has been shown to lead to misclassification of CTRCD in up to 35% of patients (24) and this coupled with the need for ionising radiation and the lack of incremental information regarding other cardiac structures and functional parameters has meant that echocardiography has now replaced MUGA as the guideline-recommended first line imaging modality for surveillance (2, 9-12, 16). 2 dimensional (2D) echocardiography, although widely available and cheap is limited by geometric assumptions and LVEF quantification in patients with poor acoustic windows (such as following mastectomy) may not be accurate (9, 11, 15, 25).

Alongside accuracy (the relationship of the measurement to the true value), precision (measurement variation between tests in the absence of change: test-retest reproducibility) is essential for serial surveillance screening. This is both to ensure early detection and treatment of emerging cardiotoxicity, but also to prevent inappropriate cessation of cancer therapies due to false detection of pathology due to measurement error. Test-retest variability of echocardiographic biplane LVEF assessment in chemotherapy recipients with breast cancer can be as high as 10% questioning its ability to detect the 10% change required to diagnose CTRCD (26). 3D echocardiography reduces temporal variability (~6%) but remains highly dependent on acoustic windows, and therefore may only be feasible in two-thirds of patients post chemotherapy (26, 27). The temporal variability of CMR-derived LVEF is low (2.4 -7.3%) (28) and recent work has demonstrated that it has the highest reproducibility compared to 2D echocardiogram derived LVEF (or strain measured by either modality) for serial imaging in patients with CTRCD (29, 30). Extrapolating from this data, the superior precision of CMR-LVEF when compared to 2D echo-LVEF would also reduce the sample size from n=19 to n=12 for detection of a 10% change in LV systolic function; important for study design of cardioprotective medications.

All measurements of LVEF do however need to be interpreted in the context of changes in LV volumes related to loading conditions, and this is particularly important for cancer patients where these can change significantly between scans on serial surveillance imaging. 20% of patients meeting criteria for CTRCD on surveillance screening (based on a decline in LVEF) were shown to have isolated reductions in LV end diastolic volume (LVEDV) potentially due to intra-vascular volume depletion (31).

The historical cost of CMR coupled with reduced availability compared to echocardiography have limited its clinical application for surveillance screening outside of specific patients where echocardiography is not feasible. However the superior precision of CMR for serial screening may enable reduced frequency of surveillance, with cost effectiveness data demonstrating feasibility for surveillance in childhood cancer survivors (32). Evidence for use of rapid focussed CMR protocols without contrast and targeted to monitoring for CTRCD are increasingly being used, which provide cheaper, more cost effective and tolerable screening for high risk patients undergoing intensive monitoring (Figure 3) (33). Recent implementation

of machine learning algorithms for automated analysis of LVEF from CMR images will likely improve inter-observer precision further, and have been shown to reduce image analysis time from an average of 13 to 0.07 minutes (34). Together these developments improve the feasibility of CMR playing an increasingly prominent role for surveillance for CTRCD, particularly for high risk patients or in those for whom echocardiography may be challenging.

Myocardial strain

LVEF is a relatively late marker of myocardial dysfunction and correlates poorly with biopsy graded myocardial injury (35). Given that LVEF may be normal despite significant myocardial injury early in CTRCD, alternative more sensitive imaging biomarkers are needed to enable earlier diagnosis and treatment.

Reductions in myocardial deformation (including GLS) precede declines in LVEF and are recommended by multiple guidelines for inclusion into echocardiographic surveillance for CTRCD (9-11, 36). A relative reduction of >15% in echo-derived peak GLS is suggestive of cardiotoxicity, and the recently-completed Strain Surveillance of Chemotherapy for improving Cardiovascular Outcomes (SUCCOUR) trial is assessing the impact of a GLS-guided (as compared to LVEF-guided) approach for surveillance of cardiotoxicity on hard clinical outcomes (37).

Measurement of myocardial deformation using CMR previously employed a variety of techniques including tagging, displacement encoding with stimulated echoes (DENSE) and strain-encoded (SENC) imaging (38). These however require dedicated sequence acquisition with additional post processing and have never been used at scale clinically. The development of fast strain encoded CMR imaging (fast-SENC) enables real-time acquisition of myocardial strain within a single heartbeat and is being promoted for detection of cardiotoxicity using commercial MyoStrain analysis software (39, 40).

Recently the use of CMR strain derived from standard cine images using feature tracking (FT) software has been shown to add significant incremental prognostic value in combination with LVEF and late gadolinium enhancement (LGE) in both ischaemic and non-ischaemic

cardiomyopathies (41). Reductions in both global longitudinal and circumferential FT-derived strain, which correlate with subclinical declines in LVEF, have been demonstrated in patients receiving cardiotoxic cancer therapies (42, 43). Although assessing myocardial deformation using FT-CMR is clearly feasible in this setting, temporal variability is greater than for echo-derived GLS, and evidence that FT-CMR directed clinical management improves CTRCD outcomes is currently lacking (29, 30).

The role of other CMR measures as early biomarkers and to provide pathophysiological insights into CTRCD

Tissue characterisation

The underlying pathophysiology of anthracycline-related CTRCD is generally recognised to be secondary to myocyte apoptosis and atrophy, with a smaller contribution from myocardial fibrosis, although early myocardial oedema may play a role both in this and human epidermal growth factor (HER) 2 therapy related LV dysfunction (44, 45). Tissue characterisation using CMR enables interrogation of many of these processes including myocardial oedema and inflammation using T2-weighted imaging and T1 and T2 parametric mapping, diffuse fibrosis using T1 and extracellular volume fraction (ECV) measurement, and focal fibrosis and scar quantification with late gadolinium enhancement (LGE) imaging. Pre and post contrast T1 mapping are used together with haematocrit to estimate myocardial ECV fraction, which has been validated for measurement of fibrosis against histological collagen volume fraction (46-48).

Surveillance CMR during anthracycline treatment has shown that parametric mapping varies by timing of imaging during therapy, although ECV is generally elevated on completion of treatment in patients with CTRCD (example shown in Figure 4) (49, 50). Elevated T2 values compared with controls have been demonstrated early after initiating cancer therapy (<3 months) (51) and a recent porcine study found increases in T2 relaxation time prior to any detectable changes in T1, ECV or myocardial function following administration of doxorubicin, and that this correlated with histological findings of intracardiomyocyte oedema (52). Importantly, in animals where doxorubicin was stopped when T2 values increased, there were no subsequent changes in T1, ECV or LVEF. In contrast, in animals where doxorubicin

was continued, LVEF then declined and T1 and ECV increased, with supportive histological findings of interstitial fibrosis. T2 mapping therefore may provide a marker of cardiotoxicity at a stage where myocardial damage is reversible, and hence offers significant promise to the field. Conflicting results with reduced T1 values (but no changes in T2 or ECV) 48 hours post chemotherapy in patients who later developed cardiotoxicity were found by another group (53). Further work is required to understand these findings, and it is likely that the increases in ECV are due both to diffuse interstitial fibrosis and myocyte atrophy.

In studies of the late effects of anthracyclines, patients treated with anthracyclines 82 months previously were found to have higher ECV values than matched controls (54) and this was independent of underlying cancer or cardiovascular conditions (55). These findings have not however been replicated in scans in lower risk patients receiving contemporary doses of anthracyclines with and without trastuzumab (56, 57). While LGE offers prognostic information in a variety of cardiovascular diseases, it is not commonly found in cardiomyopathy related to anthracyclines or HER2 therapy where histology has shown diffuse interstitial rather than focal fibrosis (53, 54, 58-60).

Tissue characterisation using T1, T2 and ECV mapping may therefore proffer additional early biomarkers of cardiotoxicity and offer insights into the underlying pathophysiology. A lack of outcome data for the techniques in this setting, alongside a lack of standardisation of T1 mapping methods, and overlap between healthy and disease states mean that they are not included in current guidelines for screening for CTRCD in cancer patients (50, 61).

LV mass and myocyte atrophy

LV mass, measured by CMR, falls following administration of anthracyclines and provides an additional biomarker of cardiotoxicity (62). Indexed LV mass has an inverse relationship with anthracycline dose and is independently associated with adverse cardiovascular events in this patient group (63). The cellular basis for the reduction in LV mass (myocyte atrophy versus myocyte loss) has been studied using CMR in patients before, during and after anthracycline therapy using measures of ECV, LV mass and intracellular water lifetime (τ_{ic}; a marker of cardiomyocyte size) (64). The fall in LV mass during treatment was shown to be at least 40%

due to reductions in cardiomyocyte size, although these were partially offset by increases in ECV. Similar findings have been reported in experimental studies with animals showing myocyte atrophy to be related to LV mass reduction during anthracycline treatment (65).

Other adverse cardiovascular effects of cancer therapy

Myocarditis

Alongside CTRCD, cancer therapies are associated with other adverse cardiovascular effects. Several classes of cancer drugs are associated with acute myocarditis, with greatest attention currently focussed on immune checkpoint inhibitors (ICI). ICIs have changed the landscape of many cancers, however adverse effects are common (66, 67). Fulminant myocarditis has been reported in 1.16% of patients' early (median 34 days) in the course of therapy with ICIs, with major adverse cardiac events (MACE) in almost half (68).

Multiple clinical guidelines support the use of CMR for diagnosis of myocarditis in the general cardiology setting, with current Lake-Louise guidelines including both T2 weighted imaging (for oedema) and T1, ECV and LGE imaging (for fibrosis) in the diagnostic criteria (69, 70). CMR is likely to have value in the investigation of cancer patients with suspected myocarditis (example Figure 5), however CMR findings in ICI mediated myocarditis are less predictable. The largest international registry of 103 patients with ICI-associated myocarditis found that most patients had a normal LVEF (61%), 42% had LGE and 28% had evidence of oedema on T2-weighted imaging. The CMR findings were commonly discordant with histology, and tissue characterisation (LGE and T2 weighted imaging) was not associated with MACE (71). Despite this, CMR imaging including T1 and T2 parametric mapping and LGE has been recommended where ICI myocarditis is suspected, to help inform clinical decision-making including whether to stop immunotherapy, the need for endomyocardial biopsy and to guide administration of high dose steroids (10, 12, 71).

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is more common in patients with cancer and is associated with numerous chemotherapy agents including fluoropyrimidines, ICIs and tyrosine kinase inhibitors (72, 73). The exact pathophysiological mechanisms underlying these cardiotoxic effects are incompletely understood, however CMR remains important for diagnosis where the combination of apical regional wall motion abnormalities, regional elevations in T1 and T2 values and absent LGE are highly suggestive of Takotsubo cardiomyopathy and can help avoid invasive biopsy and/or coronary angiography (74).

Coronary artery disease/myocardial ischaemia

Several different cancer treatments agents are known to cause myocardial ischaemia and increase the risk of coronary events. In the short term fluoropyrimidines, platinum based compounds, tyrosine kinase and VEGF inhibitors and ICIs can lead to acute myocardial ischaemia and infarction through coronary vasospasm, endothelial damage and arterial thrombosis (9, 75, 76). Prior mediastinal radiotherapy can lead to accelerated atherosclerosis and a four to seven fold increased risk of coronary artery disease compared to the general population and may present 15-20 years after treatment (9).

Adenosine stress myocardial perfusion imaging using CMR is well validated for assessment of both acute and chronic ischaemic heart disease (77, 78) and the development of perfusion mapping techniques allows for direct quantification of myocardial perfusion reserve and diagnosis of microvascular disease (17, 79). Although specific evidence for stress perfusion CMR in the cancer setting is lacking, it is recommended both for baseline risk-stratification in high risk patients prior to administration of agents associated with coronary events or major cancer surgery (example Figure 6), and for assessment of patients presenting with chest pain and cardiotoxicity during treatment (10, 14). Use of stress imaging for late effects screening in survivors treated with radiotherapy (particularly mantle field) has been recommended but is not widely implemented (13).

Pericardial disease

Pericardial disease is common in patients with cancer due to malignant infiltration, inflammation from pericarditis and in the longer term from development of pericardial

constriction (9, 80). Pericarditis can also occur after use of cancer drugs including anthracyclines, cytarabine, ICI and bleomycin, and can develop any time after mediastinal radiotherapy, with a cumulative incidence of 2–5% (9). Pericardial constriction may develop in 4-20% of patients following high dose radiotherapy and can present years after initial treatment, and is also associated with graft-versus-host disease following allogenic stem cell transplantation (example Figure 7) (14).

Assessment of pericardial disease by CMR incorporates anatomical information (dark-blood T1 weighted imaging with and without fat suppression), together with functional assessment (bright blood cine imaging, real time cine imaging during respiration, myocardial tagging) and tissue characterisation (LGE imaging and parametric mapping) (81). Tagging techniques can reveal adherence of the visceral and parietal pericardium and flattening of the interventricular septum with inspiration on real-time free-breathing cine imaging providing evidence of interventricular dependence, a marker of constrictive physiology (CMR has been reported as having a sensitivity of 88% and specificity of 100% for detection of constrictive pericarditis) (82). Tissue characterisation also has utility for assessing pericardial disease in cancer patients with acute pericarditis and T1 mapping of effusions may help to discriminate between the aetiology (transudate, exudate or haemorrhagic fluid) (46).

Valvular heart disease and aortopathy

Valvular heart disease and aortopathy are recognised complications of mediastinal radiotherapy and may affect up to 10% of patients, although with modern treatment regimens this number has reduced significantly (Figure 8) (9). Echocardiography is the first line investigation for patients with suspected valve disease but CMR can provide complimentary information, particularly if echocardiographic measurements are discrepant or inadequate (83). CMR allows assessment of valve morphology, measurement of LV and RV volumes and function as well as quantification of valvular flows and velocities via phase contrast methods. Phase contrast CMR has also been used for assessment of vascular remodelling during cancer treatment, with evidence suggesting that anthracyclines increase aortic stiffness by an equivalent to 15 years of ageing (84).

CMR in specific cancer patient groups

Infiltrative Cardiomyopathy

Two infiltrative cardiomyopathies are commonly recognised in patients with malignancies: cardiac amyloidosis and iron overload.

Amyloidosis with AL amyloid deposition can occur in patients with myeloma or other haematological malignancies, and cardiac involvement may be the first presentation with symptoms of a restrictive cardiomyopathy. Characteristic CMR findings include LV wall thickening, abnormal gadolinium kinetics and subendocardial or transmural LGE (Figure 9) (85). Amyloid deposition also leads to expansion of the interstitial space leading to significantly elevated T1 and ECV values which can be used to differentiate it from other restrictive cardiomyopathies but also act as powerful prognostic markers (86). Typical CMR findings may enable clinicians to forgo the need for endomyocardial biopsy, should tissue diagnosis for amyloid typing be available from other sources.

Iron overload cardiomyopathy occurs as a consequence of frequent blood transfusions in haematological malignancies, resulting in myocardial iron deposition and progressive decline in LV systolic function, which can reverse with chelation therapy (87, 88). Myocardial iron loading leads to signal dephasing with shortening of T2* and T1 values on CMR, therefore serial CMR imaging with parametric mapping can be used to monitor iron loading and guide chelation therapy in patients with haematological conditions at risk of iron loading (89).

Cardiac masses and tumours

Comprehensive assessment of cardiac masses requires information regarding anatomy and relationship to adjacent structures, function (including obstruction or occlusion of cardiovascular structures) and tissue characterisation including vascularity. CMR therefore is ideally placed for non-invasive interrogation of masses although tissue diagnosis is generally required for definitive diagnosis of suspected malignant masses. CMR protocols usually involve dark and bright blood anatomical imaging, followed by cine imaging to evaluate functional significance, tissue characterisation using T1 imaging (with and without fat

saturation) and T2 weighted sequences, rest perfusion as well as early and late gadolinium enhanced imaging to help differentiate the aetiology. Malignant masses are often large, cross tissue planes, have heterogeneous signal intensity and due to increased vascularity will often demonstrate uptake on first pass perfusion and LGE imaging (example Figure 10). Cardiac thrombi are usually easily identifiable on early gadolinium imaging and are commonly seen in cancer patients with in-dwelling central venous catheters. Previous reviews have provided detailed assessment on the characterisation of cardiac masses (90, 91).

Future directions

Early identification of cardiotoxicity is vital and enables institution of early preventative therapy and modification of anticancer treatment regimes. Validation of other CMR biomarkers to identify cardiotoxicity and improve our understanding of the underlying pathophysiology are important areas of active research, although evidence of a relationship with outcomes is needed.

CMR can provide non-invasive assessment of cardiac metabolism and energetics, and may therefore offer additional insights into cardiotoxicity. Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) can be used to assess the myocardial phospocreatinine/adenosine triphosphate ratio as a marker of myocardial energetic status which is impaired in patients with heart failure risk factors such as diabetes (92). Animal models of anthracycline toxicity utilising ^{31}P-MRS have demonstrated alterations in energetics which precede contractile dysfunction possibly due to direct mitochondrial injury (93, 94). Hyperpolarised 13^{C} magnetic resonance imaging (MRI) is an emerging technique that affords assessment of metabolism within a tissue and has shown promise in pre-clinical studies assessing treatment response in breast cancer (95). Recent work has demonstrated the ability of hyperpolarised MRI to detect physiological and pathological changes of cardiac metabolism in vivo (96). Diffusion tensor imaging can detect changes in the myocardial microstructure and may present further opportunities to evaluate early cancer therapy related cardiotoxicity (97). Currently, these techniques are limited to a few centres worldwide with specific expertise but may offer the opportunity to

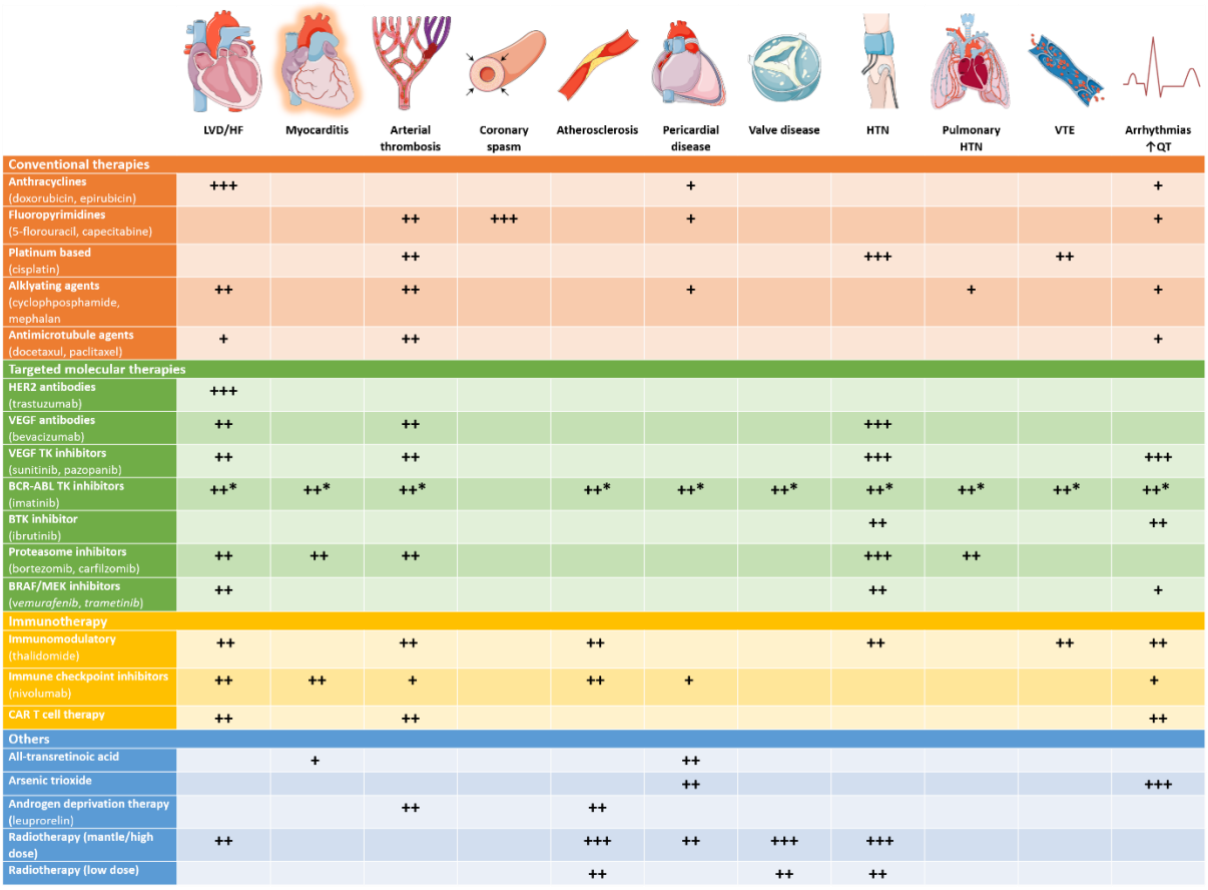
further our understanding of the alterations of myocardial metabolism or structure in early chemotherapy related cardiotoxicity.

Conclusion

Survival from cancer continues to improve as newer targeted chemotherapeutic agents emerge. In tandem the role of the cardio-oncologist continues to expand with the recognition of cardiotoxicities related to anticancer agents and the fact that cardiovascular events are a leading cause of death in cancer survivors (98, 99). The role of the cardio-oncology team is to identify and prevent the development of cardiotoxicity, initiating appropriate treatment and instituting surveillance for secondary prevention. Central to cardio-oncology is a growing need for a range of non-invasive biomarkers (both blood and imaging) that are accurate, precise and reproducible in order to provide personalised risk stratification that will allow early intervention to improve morbidity and mortality. Multi-parametric CMR affords reproducible assessment of cardiac structure and function as well as providing tissue characterisation which can be used for diagnosis and surveillance as well as furthering our understanding of the underlying pathophysiology of CTRCD. CMR plays an increasing role in cardio-oncology in both clinical and research settings but further efforts are needed to determine if and how CMR biomarkers can be used to impact on prognosis in patients with cancer.

Figures

Figure 1: Types of cancer therapy and potential cardiotoxic effects.



	LVD/HF	Myocarditis	Arterial thrombosis	Coronary spasm	Atherosclerosis	Pericardial disease	Valve disease	HTN	Pulmonary HTN	VTE	Arrhythmias ↑QT
Conventional therapies											
Anthracyclines (doxorubicin, epirubicin)	+++					+					+
Fluoropyrimidines (5-florouracil, capecitabine)			++	+++		+					+
Platinum based (cisplatin)			++					+++		++	
Alklyating agents (cyclophposphamide, mephalan	++		++			+			+		+
Antimicrotubule agents (docetaxul, paclitaxel)	+		++								+
Targeted molecular therapies											
HER2 antibodies (trastuzumab)	+++										
VEGF antibodies (bevacizumab)	++		++					+++			
VEGF TK inhibitors (sunitinib, pazopanib)	++		++					+++			+++
BCR-ABL TK inhibitors (imatinib)	++*	++*	++*		++*	++*	++*	++*	++*	++*	++*
BTK inhibitor (ibrutinib)								++			++
Proteasome inhibitors (bortezomib, carfilzomib)	++	++	++					+++	++		
BRAF/MEK inhibitors (*vemurafenib, trametinib*)	++							++			+
Immunotherapy											
Immunomodulatory (thalidomide)	++		++		++			++		++	++
Immune checkpoint inhibitors (nivolumab)	++	++	+		++	+					+
CAR T cell therapy	++		++								++
Others											
All-transretinoic acid		+				++					
Arsenic trioxide						++					+++
Androgen deprivation therapy (leuprorelin)			++		++						
Radiotherapy (mantle/high dose)	++				+++	++	+++	+++			
Radiotherapy (low dose)					++		++	++			

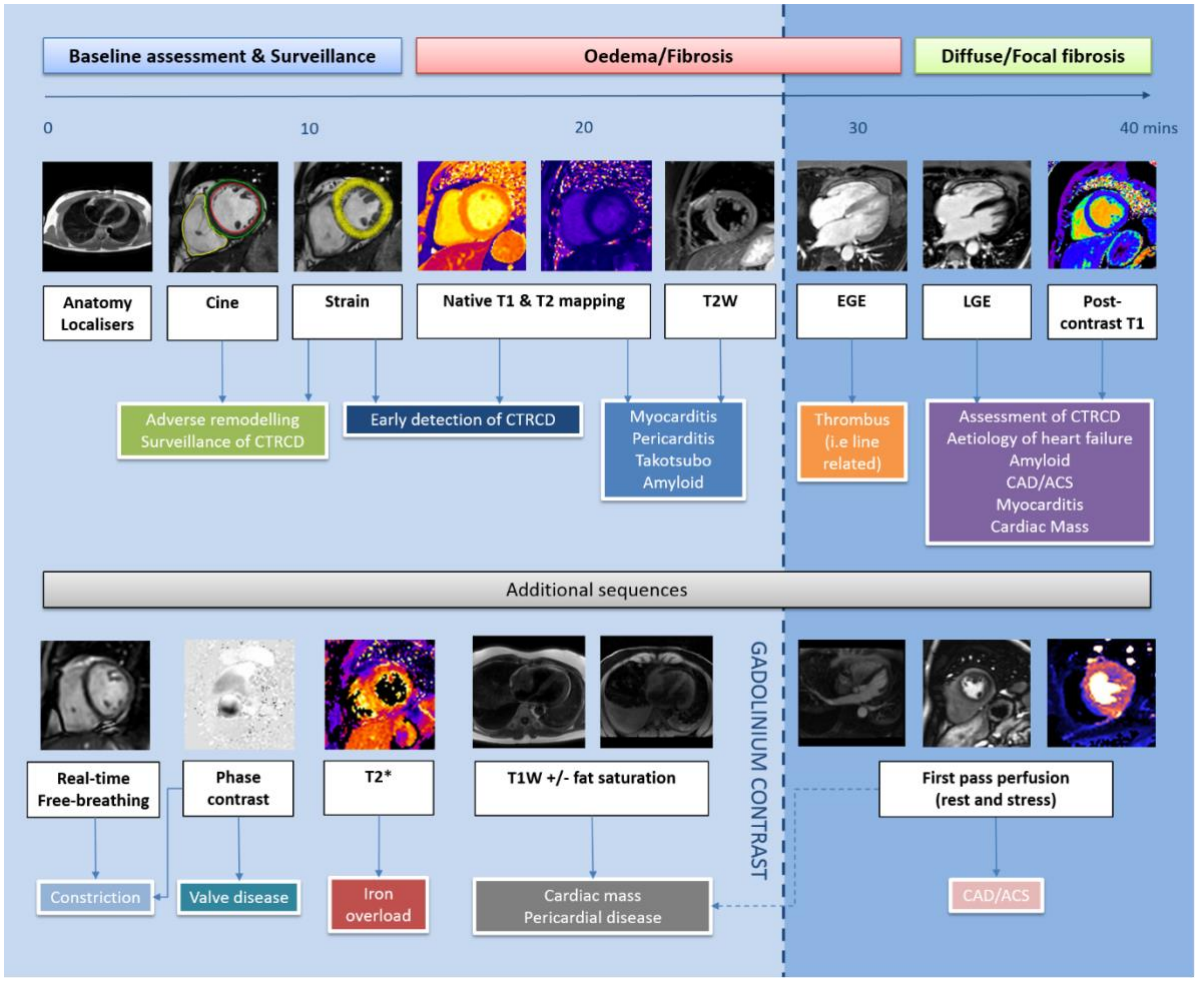
Images from Servier® Medical Art (http://smart.servier.com)

Abbreviations: BTK, bruton tyrosine kinase; CAR, chimeric antigen receptor; HER2, human epidermal growth factor 2; HF, heart failure; HTN, hypertension; LVD, left ventricular dysfunction; MEK, MAPK/ERK kinase; TK, tyrosine kinase; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism

+++, treatment associated with >10% risk of side effect, ++ estimated risk of between 1 to 10%, + estimated risk <1%

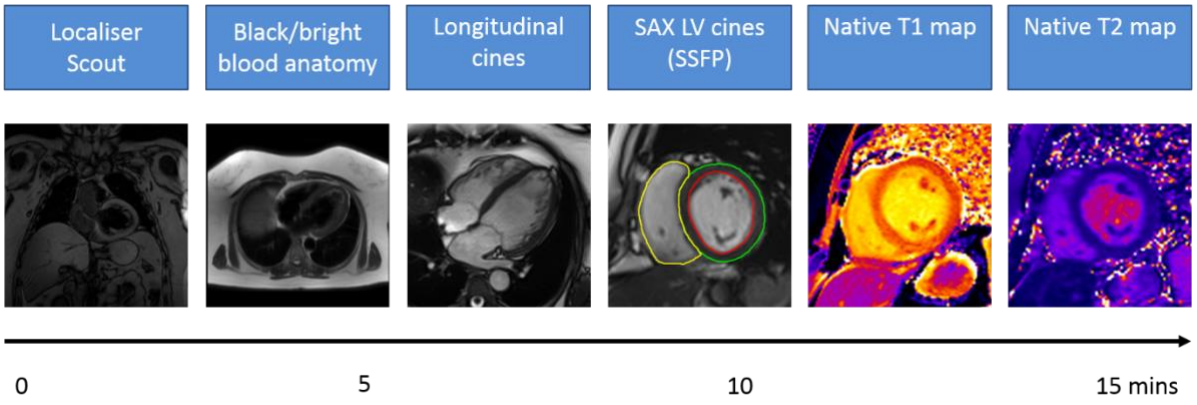
*varies by drug

Figure 2: Clinical CMR protocol outlining the potential value of individual sequences for the assessment of cancer patients.



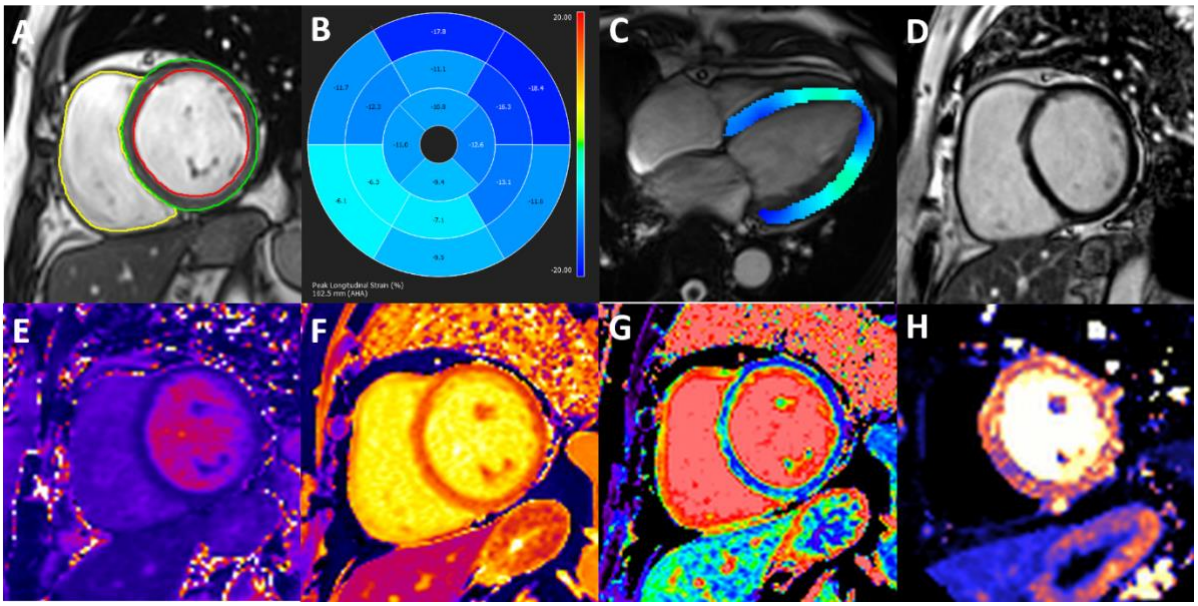
Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CTRCD, cancer treatment-related cardiac dysfunction; EGE, early gadolinium enhancement; FB, free-breathing; LGE, late gadolinium enhancement; T1W, T1 weighted; T2W, T2 weighted.

Figure 3: Abbreviated (non-contrast) protocol for surveillance for cancer treatment-related cardiac dysfunction



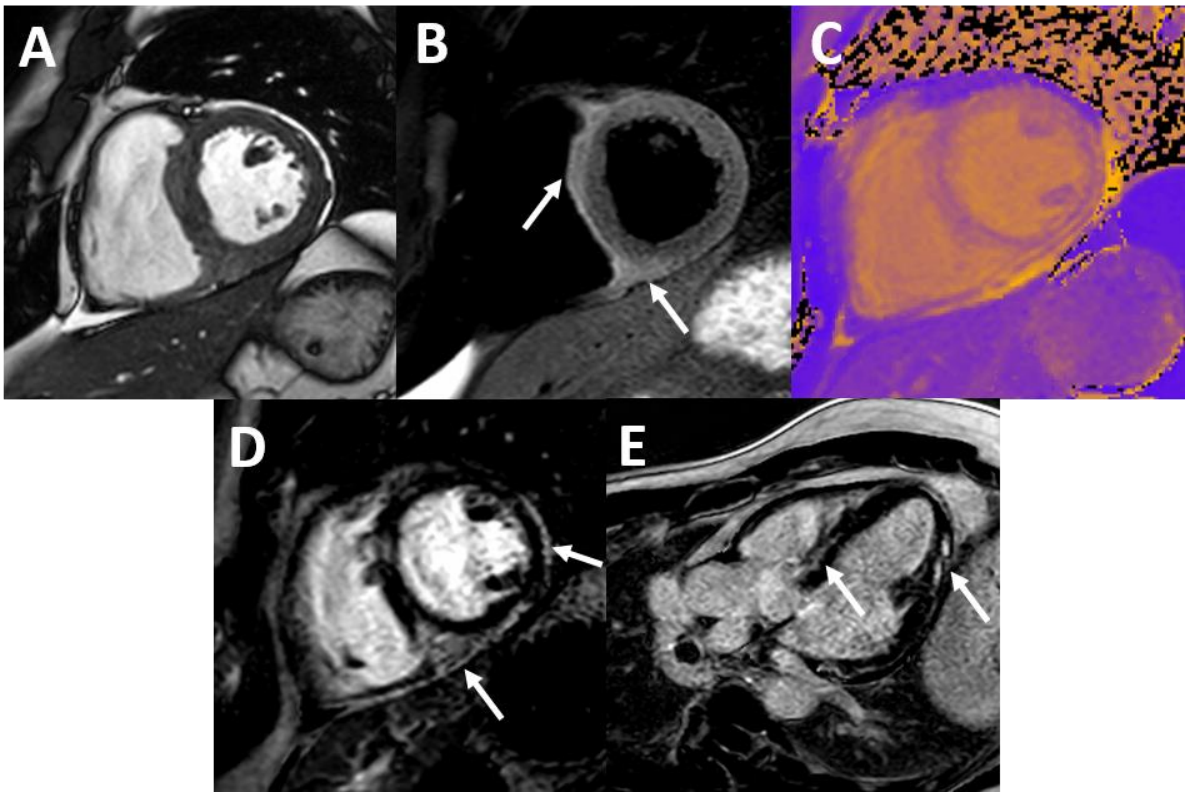
Abbreviations: SSFP, steady state free precession.

Figure 4: Anthracycline-induced cardiomyopathy.



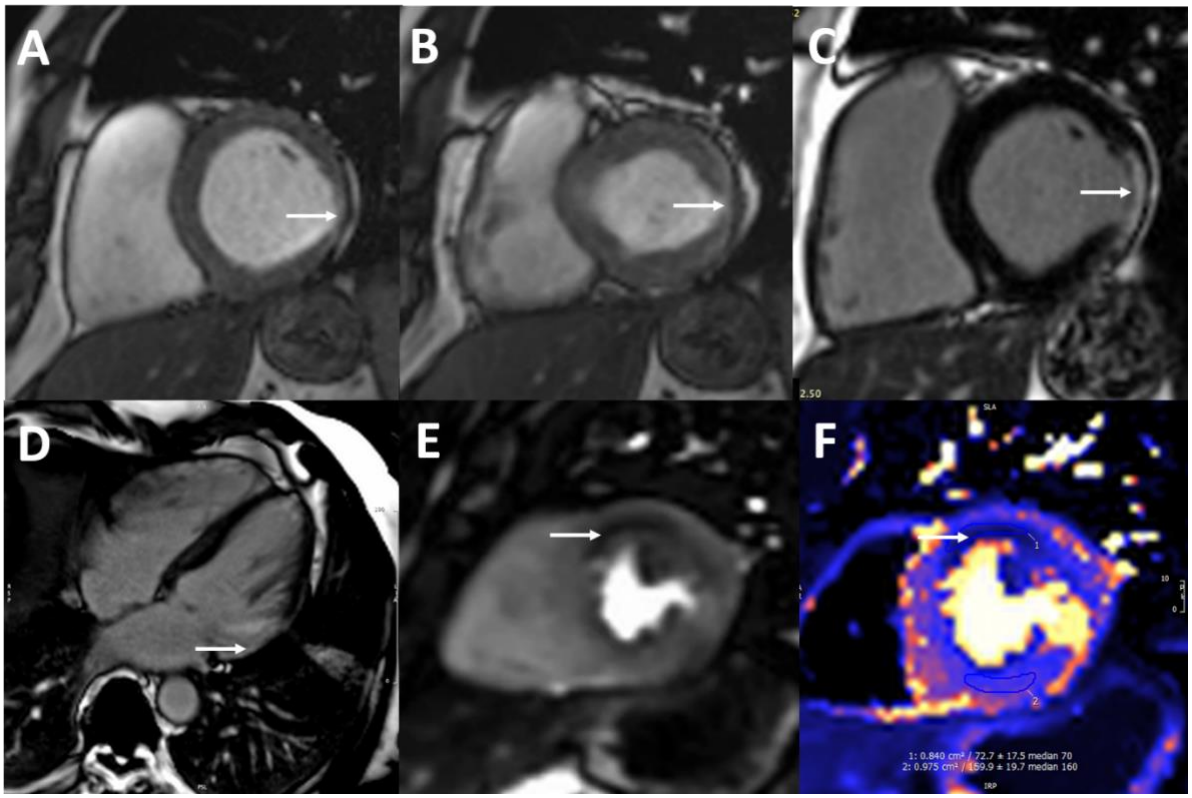
Imaging in a patient with severe LV dysfunction 6 months post treatment for diffuse large B cell lymphoma with R-CHOP (including anthracycline) chemotherapy. (A) Cine imaging shows mild LV dilatation (101mL/m^2), global hypokinesia and moderately impaired systolic function (LVEF 42%). (B&C) Reduced global longitudinal strain (GLS -8.3%) with low indexed LV mass (37g/m^2). LGE imaging (D) with normal T2 values on mapping (42ms) (E) suggestive of no active inflammation, and elevated septal T1 at 1365ms (3T, normal range 1110-1210ms) and ECV of 30% suggestive of mild diffuse myocardial fibrosis (F&G). Normal first pass stress perfusion (H). Findings consistent with anthracycline-related cardiomyopathy.

Figure 5: Chemotherapy-related myocarditis



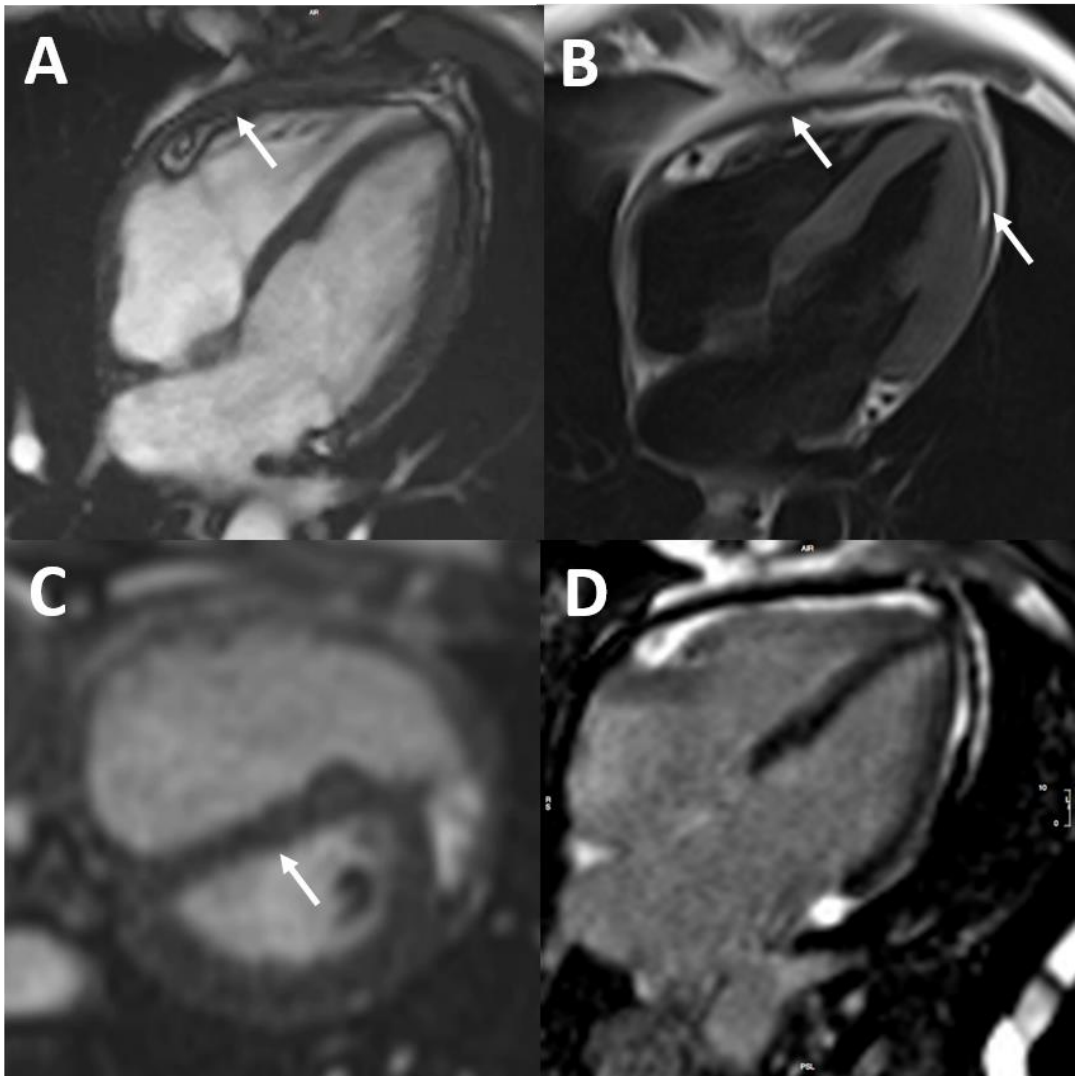
Images from a 36 year old male with chest pain and troponin elevation after commencing all trans-retinoic acid (ATRA) and arsenic trioxide chemotherapy for acute promyelocytic leukaemia. Coronary angiography was normal and CMR was requested to evaluate the cause of the troponin rise. (A) Cine imaging showed subtle thickening of the interventricular septum (15mm) with minimal pericardial fluid. (B) Global myocardial oedema was seen on T2 weighted imaging (myocardial:skeletal muscle signal intensity 3.2) with increased signal intensity in the septum and inferior wall (arrows). (C) High native T1 value at 1146ms (1.5T normal range 930-1000ms) and subepicardial hyperenhancement in the inferior/inferoseptum and lateral wall and mid-myocardial hyperenhancement in the septum on LGE imaging (D&E) (arrows).

Figure 6: CMR imaging for risk stratification in a patient with coronary disease prior to 5-fluorouracil chemotherapy.



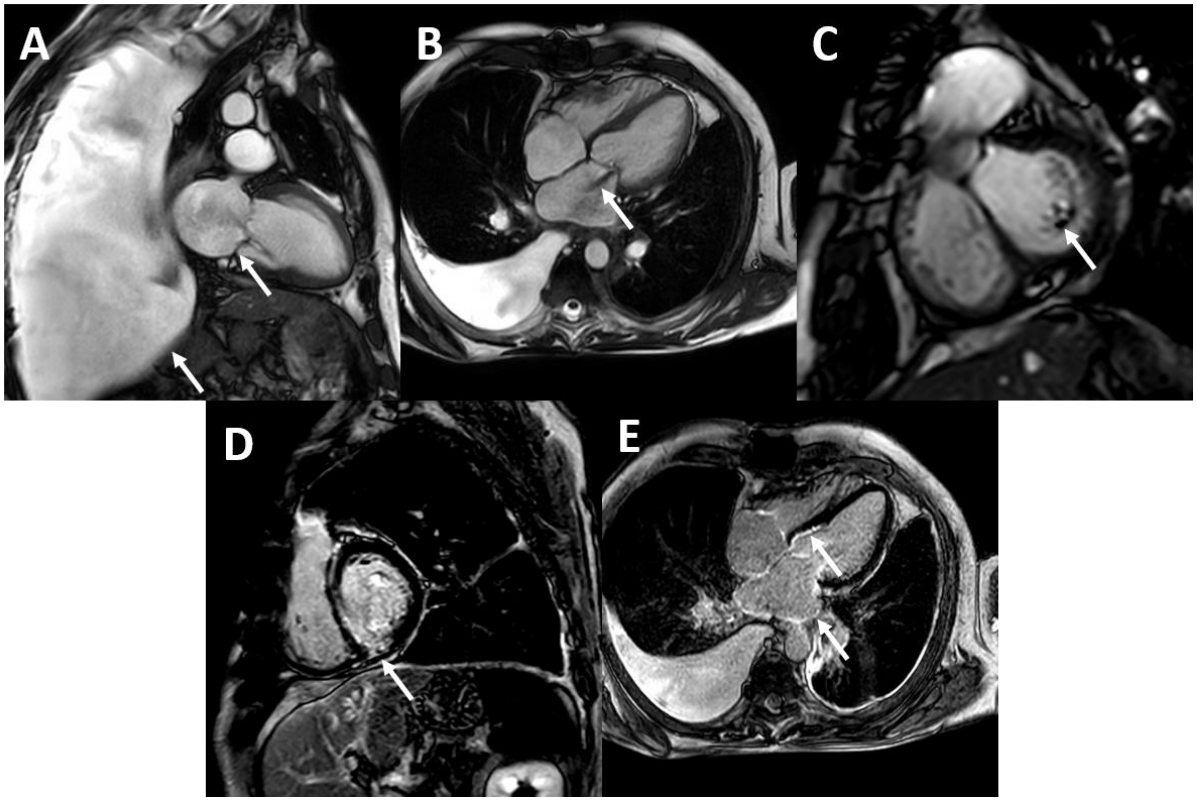
Images from 73 year old male with recurrent colorectal cancer following a recent coronary event with previous coronary artery bypass grafting. CMR was requested for risk stratification prior to 5-fluorouracil-based chemotherapy. (A&B) Cine images show thinned and akinetic basal lateral wall (arrows) with transmural LGE consistent with established circumflex infarction. (C&D) Marked perfusion defect in the basal anterior and anteroseptal segments (myocardial blood flow 0.72ml/g/min) on first pass perfusion imaging post adenosine with quantitative myocardial perfusion mapping (E&F). Patient underwent PCI to the LAD before completing chemotherapy without complications.

Figure 7: Pericardial constriction due to graft-versus-host disease (GvHD) following stem cell transplantation



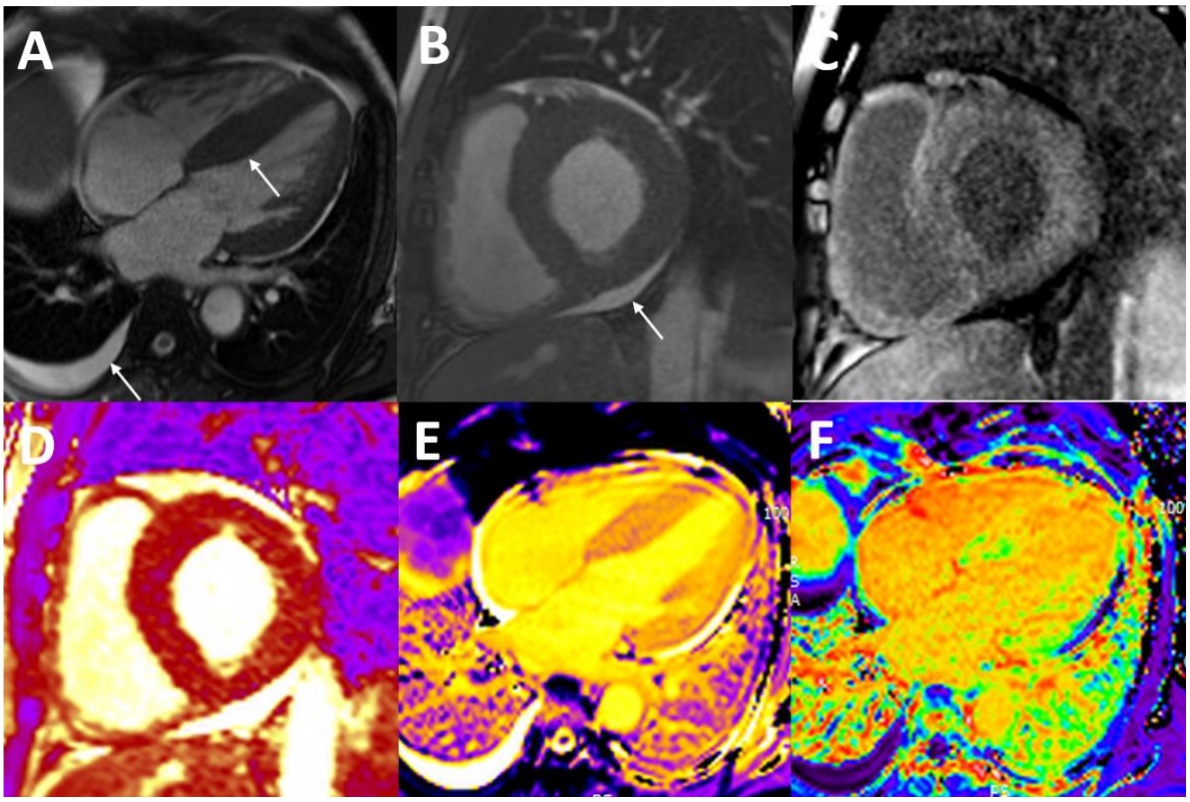
Imaging from a 40 year old female with shortness of breath and raised NTproBNP 18 months post myeloablative allogeneic stem cell transplantation for refractory acute myeloid leukaemia. She had known extra-cardiac chronic GvHD with scleroderma and oral involvement with echocardiography suggestive of constrictive physiology. (A&B) Cine and black blood imaging show circumferential pericardial thickening up to 7mm (arrows) with flattening of the interventricular septum with inspiration consistent with ventricular interdependence on real-time free breathing cine imaging (C) and no LGE.(D) Findings consistent with pericardial constriction secondary to GvHD.

Figure 8: CMR imaging late following mediastinal radiotherapy showing mitral valve and coronary artery disease.



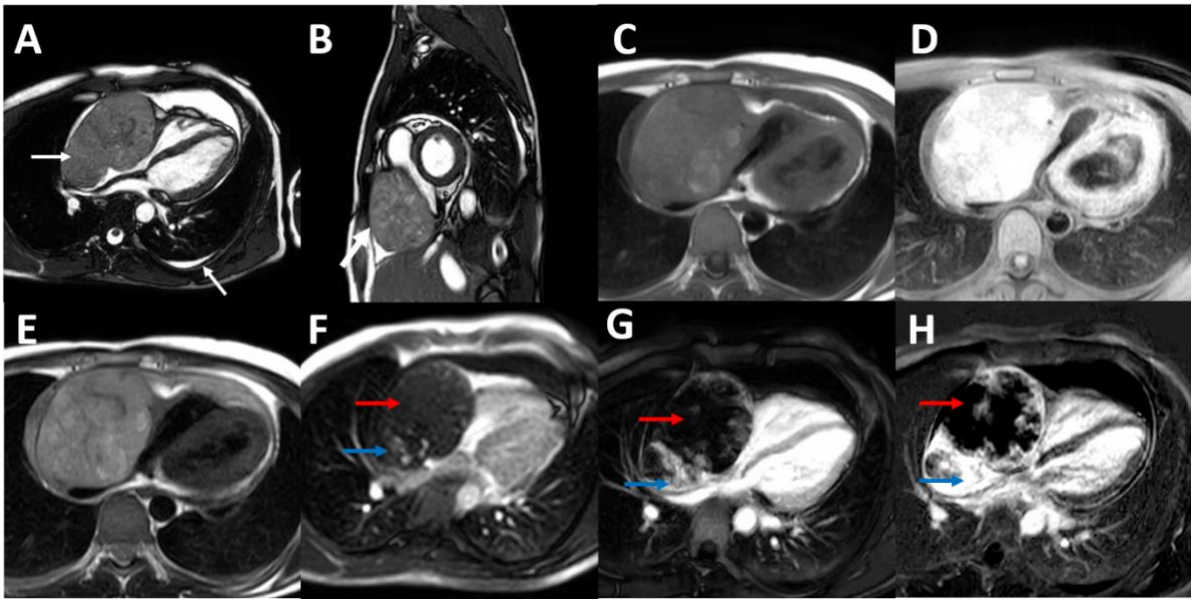
Images from a 54 year old male with exertional breathlessness 35 years post mantle field radiotherapy for Hodgkin's lymphoma. (A, B&C) Cine imaging shows thickened and restricted posterior mitral valve leaflet with severe mitral regurgitation and a right sided pleural effusion. (D&E) Subendocardial LGE in the basal inferior and inferoseptal segments consistent with a previous right coronary artery infarction alongside biatrial and papillary muscle scar.

Figure 9: AL amyloidosis in a patient with multiple myeloma.



Images from a 45 year old male with lambda light chain myeloma with shortness of breath and left ventricular hypertrophy on echocardiography. (A&B) Cine imaging shows biatrial enlargement, concentric hypertrophy (interventricular septum 18mm) with small pericardial and right sided pleural effusions (arrows). (C) Diffuse global LGE throughout both ventricles on phase sensitive inversion recovery (PSIR) imaging with dark blood pool indicating abnormal gadolinium kinetics. (D) Borderline elevated septal T2 values (51ms; normal range 40-48ms) with markedly elevated septal T1 at 1271ms (1.5T, MOLLI 5s3s3s; normal range 990-1050ms) and ECV 58% (E&F).

Figure 10: CMR assessment of a cardiac mass.



Images from a 58 year old male with chest pain and a cardiac mass on echocardiography. (A&B) Cine imaging shows a large mass infiltrating the right atrium and crossing tissue planes into the pericardium with left sided pleural effusion (white arrows). The mass has heterogeneous hyperintensity on T1 and T2 weighted imaging (C&E) with no T1 weighted fat suppression (D). Heterogeneous perfusion (F) with higher vascularity at the margins (blue arrows) and reduced vascularity at the core of the lesion (red arrows) on both early and late gadolinium enhancement (G&H). Tissue characteristics and invasion suggest a malignant mass with a necrotic core – most likely angiosarcoma (confirmed on subsequent histology).

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Supplemental Material

Supplemental Table 1: International societal recommendations for the use of CMR in cancer patients

Organisation	Title	Year	Type of document	Recommended use of CMR
HFA/EACVI/ESC (10)	Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies.	2020	Position statement	**Baseline assessment in patients with:** • poor quality echocardiographic images • complex pre-existing heart diseases • suspected angina - vasodilator stress CMR recommended **Serial monitoring in patients with:** • poor quality echocardiographic images or with measurement discrepancy **For assessment of known cardiotoxicity:** • To identify prior MI scar, diffuse fibrosis and intracellular or interstitial oedema which may facilitate our understanding of the pathogenesis of cardiotoxicity

				Myocarditis: • Evaluation of suspected ICI-mediated myocarditis **Pericardial diseases, myocardial infiltration and cardiac masses:** • Comprehensive evaluation of pericardial diseases, cardiac masses, infiltrative (amyloidosis) as well as storage diseases. • To assess response to treatment following systemic therapy, RT and/or surgery to cardiac tumours.
ESC (9)	ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines	2016	Position Paper	**Serial monitoring:** • To clarify function with borderline or contradictory results from other modalities. **For assessment of known cardiotoxicity:** • To identify cause of LV dysfunction

				• Evaluation of cardiac fibrosis, by LGE imaging, for prognosis • Evaluation of inflammation, oedema and diffuse fibrosis through T1 and T2 mapping techniques. **Pericardial diseases** • Evaluation of the pericardium, particularly in patients with prior chest irradiation. **Myocardial infiltration and cardiac masses:** • Comprehensive evaluation of cardiac masses and infiltrative conditions **Valvular heart disease:** • may be useful in those with suboptimal echocardiography or discrepant results
ASE/EACVI (11)	Expert consensus for multimodality	2014	Consensus recommendations	**Cardiotoxicity screening:**

	imaging evaluation of adult patients during and after cancer therapy			• Reference standard for LV and RV volumes and LVEF – especially if chemotherapy discontinuation is considered and/or evaluation using other modalities challenging **Cardiac masses and pericardial diseases:** • For cardiac tumours and pericardium • when constrictive pericarditis remains uncertain after echocardiography **Valvular heart disease:** • for serial monitoring of ventricular volumes and function in patients with significant valve regurgitation
ASE/EACVI (14)	Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults	2013	Expert Consensus	**Cardiotoxicity screening:** • Method of choice in patients with poor acoustic windows • For assessment of myocardial fibrosis **Pericardial disease:**

				• For assessment of constrictive pericarditis. **Valvular heart disease:** • in patients with inadequate echocardiographic quality or discrepant results **Coronary artery disease:** • For screening for obstructive CAD 5–10 years post-radiotherapy in high risk patients.
ESMO (12)	Management of cardiac disease in cancer patients throughout oncological treatment	2020	Consensus recommendations	**Cardiotoxicity Screening:** • Should be used for serial imaging of LV systolic function dependant on local availability and expertise. **Myocarditis:** • Evaluation of ICI-mediated myocarditis **Valvular heart disease:**

				• for assessment of valvular heart disease in those with suboptimal echocardiography or discrepant results
JACC (13)	Prevention, Diagnosis, and Management of Radiation-Associated Cardiac Disease	2019	Scientific statement	**Cardiotoxicity screening:** • As an adjunct to echocardiography in technically difficult subjects. • For assessment of ischemic/nonischemic myocardial fibrosis **Pericardial disease:** • To discriminate constrictive pericarditis versus restriction.
ASCO (15)	Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers	2017	Clinical Practice Guideline	**Cardiotoxicity screening:** • first-line when echocardiography is unavailable or not technically feasible

Abbreviations

ASCO – American Society of Clinical Oncology; ASE – American Society of Echocardiography; CAD – coronary artery disease; CMR – Cardiovascular Magnetic Resonance; DCM – Dilated Cardiomyopathy; EACVI - European Association of Cardiovascular Imaging; ESC –

European Society of Cardiology; ESMO – European Society for Medical Oncology; HCM – Hypertrophic Cardiomyopathy; HFA – Heart Failure Association; ICI – Immune checkpoint inhibitors; JACC – Journal OF American College of Cardiology; LGE – late gadolinium imaging; LV – left ventricle; LVEF – Left ventricular ejection fraction; MI – Myocardial infarction; RT – Radiotherapy