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Multimodality imaging for cardiotoxicity: state of the art and future perspectives

Jessica Artico, MD[1,2], Aderonke Abiodun, MBChB[1,2], Hunain Shiwani BMBS, FRCR[1,2], Hibba Kurdi MBBS, BSc[1,2], Daniel Chen, BMed, FRACP[1,3,4], Sara Tyebally, MBBS, BSc[1], James C. Moon, MD[1,2], Mark Westwood, MBBS, PhD[1], Charlotte H. Manisty, MBBS, PhD[1,2]

Address

[1]Cardiology Department, Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom

Email: jessica.artico@nhs.net; c.manisty@ucl.ac.uk

[2] Institute of Cardiovascular Sciences, University College London, London, United Kingdom

[3] Cardio-Oncology Service, University College London Hospital, London, United Kingdom

[4] Hatter Cardiovascular Institute, UCL, 67 Chenies Mews, London, United Kingdom

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Correspondence
Dr Jessica Artico and Dr Charlotte Mainsty
Cardiology Department,
Barts Heart Centre,
St Bartholomew's Hospital,
London, United Kingdom
jessica.artico@nhs.net, c.manisty@ucl.ac.uk

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Abstract

Modern cancer therapies have significantly improved survival leading to a growing population of cancer survivors. Similarly, both conventional and newer treatments are associated with a spectrum of cardiovascular disorders with potential long term sequelae. Prompt detection and treatment of these complications is therefore pivotal to enable healthy survivorship and reduce cardiovascular morbidity. Advanced multimodality imaging is a valuable tool for stratifying patient risk, identifying cardiovascular toxicity during and after therapy, and predicting recovery.

This review summarises the potential cardiotoxic complications of anti-cancer therapies and the multimodality approaches available in each case with special focus on newer techniques and the added value of biomarkers ultimately leading to earlier diagnosis and better prognostication.

Keywords: Cardiotoxicity, Chemotherapy, Cardio-Oncology, Cardiovascular Magnetic Resonance, Imaging, Multimodality.

Introduction

Over recent decades, remarkable progress has been made in the development of new therapies for cancer, leading to increased cancer survival. However, alongside these advances, many anticancer therapies bear a collateral effect of potential cardiovascular toxicity,[1,2] with a risk of both acute effects occurring during treatment, and long-term adverse cardiovascular events occurring many years after cancer remission. Cumulative effects and complex interaction between genetic background and environmental factors may also contribute in this setting as also described in other phenotypes of cardiac dysfunction[3, 4–6].

To maximise the life-prolonging effect of anticancer treatment and to avoid significant cardiovascular side effects, a close dialogue and collaboration between oncologist and cardiologist is essential in this setting. Indeed, it enables prompt recognition of cardiac toxicity, reconsideration of types of cancer therapy and/or guides decision-making related to initiation of cardioprotective medications. Overall, accurate cardiac evaluation of patients undergoing cancer therapy is required throughout the cancer patient pathway including 1) baseline risk stratification pre-treatment 2) surveillance for cardiotoxicity during treatment 3) investigation and monitoring of incident cardiotoxicity during treatment and 4) screening for the late sequelae after completion of treatment.

Modern cancer treatment regimens can lead to various forms of cardiotoxicity including left ventricular systolic dysfunction, myocarditis, coronary artery disease, valvular and pericardial disease. A multimodality imaging approach is essential to aid diagnosis and subsequent treatment of these complications (Figure 1). Improved pre-treatment cardiovascular assessment enables risk stratification to help guide choice of cancer therapies (for example avoidance of high dose anthracycline regimes, dose modification or administration of alternative preparations including liposomal doxorubicin), alongside providing a baseline for subsequent comparison during surveillance interval imaging during treatment. Similarly for

patients where coronary toxicities are common, baseline ischaemia or coronary imaging may be valuable in those at highest baseline risk.

Echocardiography is generally the first line cardiac imaging investigation used for cardiovascular assessment throughout the patient journey in cancer patients, due to widespread availability, low cost, high patient tolerability and lack of ionising radiation and hence is recommended in all current cardiology and oncology guidelines.[7–9] Cardiovascular magnetic resonance (CMR) has a growing role in cardio oncology [10,11] due to its great spatial resolution and tissue characterization, and it is increasingly being used both for surveillance screening and for assessment of myocarditis, pericardial and ischaemic heart disease. Although currently limited by availability, scan duration and costs, emerging faster and more cost-effective protocols may pave the way for more widespread use of CMR in cancer patients. Cardiac computed tomography angiography (CCTA) and nuclear imaging techniques enable timely non-invasive assessment of functional and anatomical components of coronary artery disease, and associated radiation doses are reducing with recent technical advances[12,13]. Alongside non-invasive cardiovascular imaging, serum biomarkers including troponin and N-type natriuretic peptide (NT-proBNP) play a complimentary role to facilitate early detection of cardiotoxicity.

This review will describe the role of advanced multimodality imaging and complementary biomarkers (Figure 2) and their future perspectives in the different potential toxicities derived from cancer therapies.

Cancer therapeutics related cardiac dysfunction (CTRCD)

Cancer therapeutics related cardiac dysfunction (CTRCD) is the commonest form of cardiotoxicity and is defined as a decline in left ejection fraction (LVEF) of greater than 10 percentage points to a value of less than 50%[8]. The potential for anthracycline chemotherapy to cause heart failure has been recognised for almost five decades, however other cancer drug

classes including HER2 targeted therapies including trastuzumab, VEGF inhibitors, proteasome inhibitors, small molecule tyrosine kinase inhibitors and immunotherapy can also lead to LV dysfunction[14]. Given the potential for cardiotoxicity with these drugs, current guidelines recommend baseline cardiovascular assessment including quantification of ejection fraction, and then subsequent interval surveillance imaging based on the risk both of cardiotoxicity from the drugs administered, and the patient's individual risk [15–21] . Guidelines recommend using the same imaging modality throughout treatment for serial left ventricular function assessments[9], and echocardiography is typically the first line test currently, however other modalities may be used particularly where echocardiography is challenging, or results are inconsistent. The inability to detect subtle declines in LV function has the potential to delay the initiation of cardioprotective medications and lead to the development of irreversible cardiomyopathy. Similarly, over-diagnosis of CTRCD may lead to inappropriate cessation of first line cancer therapies.

Echocardiography

The calculation of LVEF using echocardiography by volumetric assessment using Simpson's Biplane is currently the recommended first line imaging modality for assessment of the left ventricular systolic function in patients at baseline and during surveillance, Figure 3. Good acoustic windows are crucial for accurate measurements, and this may be challenging especially in post mastectomy patients, in patients with breast reconstructions and in patients post radiotherapy[22].

Surveillance for CTRCD requires serial imaging for detection of small changes in LVEF between scans. 2D echocardiography is known to have high test-retest variability (10-11% on previous studies[23,2425]), and although improved by the use of transpulmonary contrast

administration, more precise methods may be required in order to aid accurate clinical decision making regarding the continuation or cessation of cancer treatment.

3-Dimensional echocardiography

Ventricular volumes and LVEF obtained by 3D have been shown excellent correlation with those obtained by MRI[26–28] (considered the gold standard modality for measurement) and this has also been shown to be the case in breast cancer patients on trastuzumab at baseline, 6 months and 12 months after treatment initiation (r=0.87 at baseline, r=0.91 at 12 months)[29]. Thavendiranathan et al demonstrated in 56 stable breast cancer patients on chemotherapy that non contrast 3D echocardiography using semi-automated quantification methods had superior test-retest variability (6%) and superior inter and intra observer variability[30] when compared to contrast 3DE, contrast enhanced 2DE and non-contrast 2DE. 3DE is therefore the preferred technique of choice for monitoring LV function and detecting CTRCD in cancer patients[8,31]. Limitations of 3DE are poor temporal and spatial resolution, dependence on high quality 2D imaging, and dependence on further operator training and due to cost, there is limited access in many institutions.

Global longitudinal strain measurement

Whilst LVEF is an important marker in the assessment of global left ventricular systolic function, LVEF can be preserved in patients with impaired systolic function as it does not reflect intrinsic myocardial contractility. Strain is a measure of myocardial deformation and reported as a percentage change in length or thickness of the LV myocardium in relation to its original length or thickness. Strain can be measured in circumferential, radial or longitudinal planes however it is global longitudinal strain (GLS) that has the highest body of clinical evidence and it has been shown to be a superior predictor of all-cause mortality to LVEF[32]. Multiple studies have validated the use of the GLS index as a biomarker of subclinical left ventricular dysfunction secondary to cancer treatment[33,34,28], with prospective data from 81

breast cancer patients receiving trastuzumab with or without anthracyclines, an 11% reduction in GLS at 6 months compared to baseline was significantly associated with a subsequent change in LVEF of >10% at 12 months[35]. Further studies have also corroborated these findings in the breast cancer setting[36,37] and also in paediatric populations treated with anthracyclines[38]. Looking at strain by feasibility, 3D EF and 3D strain showed a potential superiority, but also suboptimal feasibility compared to standard echocardiography in diagnosing subclinical ANT cardiotoxicity in breast cancer patients, while 2D GLS is superior to standard echo and presents a good feasibility[39].

Therefore, current international guidelines recommend measurement of GLS in all patients undergoing screening for CTRCD[15–21], using a reduction in GLS of >15% to be significant[8].

The use of change in GLS to guide initiation of cardioprotective medications in patients receiving anthracyclines has been assessed prospectively against a cohort receiving standard care (cardioprotective medications started following an absolute reduction in LVEF >10%) in the international multicentre SUCCOUR study. Whilst the use of cardioprotective therapy was higher in the GLS arm, there was no significant difference in LVEF between both groups at 1 year follow up[40].

Further long-term randomised trials are required to ascertain whether GLS predicts persistent long term LVEF changes. Disadvantages of GLS include reliance on high quality 2D imaging, inability to calculate values in the presence of varying heart rates or arrhythmia, and due to the presence of multiple vendors, results are not transferable across differing software packages. GLS is also subject to loading conditions which may vary significantly at different stages of treatment.

Contrast echocardiography

The use of transpulmonary contrast agents during echocardiography improves endocardial definition, and hence reproducibility of LVEF measurement[41–45]. ASE EAE consensus guidelines recommend the use of contrast agents when two contiguous LV segments cannot be visualised on apical windows on non-contrast images[46,47]. In cancer patients requiring frequent cardiac imaging for CTRCD surveillance, contrast echo is advantageous to non-contrast 2D echo due to superior reproducibility[48] – particularly in patients with suboptimal non-contrast echocardiographic imaging. Additionally contrast echocardiography is advantageous in cancer patients as it improves the definition of intracavity structures such as ventricular thrombi which may occur in the context of CTRCD typically appearing hypointense due to lack of vascularity[49]. Contrast echocardiography does however require intravenous cannulation which can be problematic for some patients during chemotherapy, particularly for breast cancer patients where lymphoedema may reduce access sites requires. However, it has been shown to be feasible in a large study with breast cancer patients undergoing imaging surveillance[50]. Additionally, it is quick and relatively cheap compared to using other imaging modalities. Large studies have shown that contrast is safe in acute and stable patients and is not associated with excess adverse events,[33,34] although anaphylaxis can rarely occur.

CMR

CMR has shown to have the highest reproducibility for measurement of LV volumes and ejection fraction for serial imaging in patients with CTRCD compared to other imaging modalities including echocardiography. [41 42,43] CMR is not dependent on acoustic windows, uses no radiation and also has other inherent features including tissue characterisation making it an ideal imaging tool for the evaluation of cardio-oncology patients.

Myocardial strain can also be calculated from CMR images – both using dedicated sequences (tagging, SPAMM, SENC) and from standard cine imaging where feature tracking (FT) software can derive global and regional longitudinal, circumferential and radial strain. [53,54]. Reductions in FT-derived markers of strain have been demonstrated to correlate with subclinical declines in LVEF in patients receiving cardiotoxic cancer treatments, and have been shown to be impaired late after anthracycline chemotherapy in adult survivors of non-Hodgkin lymphoma, providing a possible future early biomarker of CTRCD [55].

Using dedicated fast strain-encoded CMR imaging (fast-SENC) sequences, real-time myocardial strain can be acquired within a single heartbeat and commercial MyoStrain analysis software calculates the percentage of left ventricular myocardial segments with strain ≤−17%, and thereby provides a measure of cardiac function[56,57]. Emerging data suggests that fast-SENC imaging may provide an accurate and sensitive tool for prediction of those at risk of developing cardiotoxicity[58] alongside early detection.

Tissue characterization

CMR has the unique ability to provide tissue characterization, which may offer additional insights into the underlying pathophysiology of cardiotoxicity alongside potentially providing additional prognostic information. Late gadolinium enhancement, the most widely used tissue characterization tool, is able to detect focal fibrosis and myocardial injury and has been consistently shown to provide prognostic information in many cardiovascular diseases including ischaemic heart disease and cardiomyopathy. For common presentations of CTRCD (including secondary to anthracyclines or HER2 targetted therapies) however, LGE is not commonly seen and focal fibrosis is not a feature[59–61].

Parametric mapping techniques are however able to interrogate and measure other pathophysiological myocardial processes that may be present in CTRCD, including diffuse fibrosis (using T1 mapping and extracellular volume fraction (ECV) measurement) and

myocardial oedema (using T1 and T2 parametric mapping). Myocardial tissue abnormalities such as intracellular and interstitial oedema and fibrosis may precede the reduction in myocardial strain or LVEF [62,63] in CTRCD.

Diffuse myocardial fibrosis, measured by T1 mapping and ECV, seems to be a late feature of anthracycline-induced cardiotoxicity and to be associated with impaired diastolic function, independently of underlying cancer or cardiovascular conditions [59,64]. In cancer survivors, an increase in ECV is likely a marker of interstitial fibrosis and has been associated with higher anthracycline doses and lower exercise capacity [65], being ECV generally elevated on completion of treatment in patients with CTRCD [66]. T1 mapping may vary by timing of imaging during anthracycline therapy. In fact, another study performed in the early stages after anthracycline administration (48 h post-chemotherapy) demonstrated reduced T1 values, with no changes in T2 or ECV, in patients who later developed cardiotoxicity [60].

Other studies using multiparametric mapping found elevated T2 values early after initiating anthracycline therapy, suggesting that myocardial oedema may appear early after initiating cancer therapy (<3 months) [67]. A translational porcine study, demonstrated, after administration of doxorubicin, the presence of raised T2 levels prior to any detectable changes in T1, ECV, or myocardial function and that this correlated with histological findings of intracardiomyocyte oedema [68]. Furthermore, it showed that, continuing administration of doxorubicin, LVEF declined and T1 and ECV increased while, if the drug was stopped when T2 values increased, there were no subsequent changes in T1, ECV, or LVEF. These findings are still based on small numbers and need confirmation by broader studies but propose a pathophysiological pathway for anthracycline cardiotoxicity whereby early (reversible) myocardial oedema is followed by diffuse myocardial fibrosis. They also suggest a starting point for the creation of possible future imaging biomarkers able to detect

CTRCD at a very early stage and promptly reconsider oncology treatment and/or cardioprotective treatment.

Cardiac CT

The role of cardiac CT for assessing for cancer treatment related cardiac dysfunction is limited, with echocardiography and cardiac MRI providing the mainstay of assessment and surveillance in cardio-oncology patients. However, in select cases, where other non-invasive methods are inadequate, cardiac CT may be used in the quantification of LV and RV function with retrospective gating [69]. This is not standard practice due to the cumulative radiation doses and contrast usage required for serial cardiotoxicity screening.

Nuclear

A wide variety of nuclear medicine techniques may be employed in monitoring the effects of cardiotoxicity in cardio-oncology patients including multi-gated radionuclide angiography (MUGA), single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Although previously MUGA was the technique most commonly used for cardiotoxicity surveillance, its use has been significantly reduced in contemporary times. Whilst nuclear medicine techniques have high reproducibility in assessing LVEF, they are limited by their lack of assessment of other cardiac structures, their high radiation dose and the limited availability compared to echocardiography [70].

Complimentary Role of Biomarkers

LV dysfunction or CTRCD is the most widely studied end point of cardiotoxicity in trials looking at imaging modalities and complementary biomarkers. Troponin and brain natriuretic peptide (BNP) are the most common both in mainstream cardiology and in current data on cardiac toxicity.

Most data to date have been obtained from studies of patients receiving anthracycline therapy [71,72]. The relationship between elevated troponin and early LV dysfunction via

echocardiography (2D, Simpson's biplane), in patients receiving chemotherapy has been previously demonstrated by Cardinale et al [73–75]. Not only were they able to demonstrate this positive correlation but also were able to use the troponin values to predict those less likely to recover from chemotherapy (trastuzumab) induced cardio-toxicity despite optimal heart failure management [75].

The largest study of trastuzumab induced cardiotoxicity is the HERA trial by Zardavas et al [76], which observed that an elevated cardiac troponin post-anthracycline treatment but before trastuzumab (baseline pre trastuzumab) predicted which women developed future trastuzumab-induced cardiotoxicity, whereas troponin surveillance during trastuzumab was not sensitive[77]. Other studies demonstrated that troponin did not precede the development of CTRCD[75]. This indicates that although troponin is a sensitive marker of cardio-toxicity in the active treatment phase and immediately post treatment, it may be less sensitive as a marker of sub-clinical cardiotoxicity in the post treatment surveillance phase.

NPs have a variety of roles in detecting cardio-toxicity and surveillance. They have been shown to be useful in acute cardio-toxicity related to anthracycline therapy [78] and as a screening tool for cancer patients receiving therapy [79 80 81], supporting a combined biomarker and imaging approach in the surveillance of cardiotoxicity. However, there still remains some disparity, with some studies unable to demonstrate a statistically significant relationship between NPs and cardio-toxicity[82]. This can in part be explained by differences in study set up including timing of serum sampling and follow up, different unmatched study cohorts with different treatment therapies and variable cut offs for BNP.

Inflammation is a common pathway underlying cancer processes and cardiovascular disease and therefore markers of inflammation are considered important biomarkers of cardiotoxicity [83]. The most studied marker is C-reactive protein (CRP); an acute phase reactant produced by

liver cells due to stimulation by interleukin-6 which is in turn produced by macrophages and T cells [84].

Elevated levels of CRP have been linked to reduced LV function in an array of CV disease including myocardial infarction and heart failure [85]. A study of 54 patients receiving trastuzumab showed that increased levels of CRP was detected a median of 78 days before cardiotoxicity became evident as defined by a decrease in LV function on echocardiography [86]. However, other studies have failed to demonstrate similar results, which again may be due to other confounding factors and variation in study design, cancer diagnosis and treatment options [87,88].

Ischaemic Heart Disease and vascular disease

Several anti-cancer treatments are known to cause atherosclerosis, coronary vasospasm and arterial thrombosis, eventually leading to acute myocardial infarction or ischaemia. They include platinum-based compounds, fluoropyrimidines, immune checkpoint inhibitors (ICIs), vascular endothelial growth factor receptor (VEGF) inhibitors and as a late sequala of radiotherapy.[89–91,92].

Currently, the assessment for ischaemic heart disease in the context of patients undergoing cardio-oncology treatments is mainly indicated for: 1. baseline risk stratification prior to administration of cancer treatments associated with coronary event 2. Risk stratification pre major cancer surgery 3. Investigation of acute cardiotoxic events 4. Late effects screening

Echocardiography

Resting and stress echocardiography plays an important role in the investigation of these patients. Specifically, stress echocardiography using either exercise or pharmacological stressors such as dobutamine is established for detection of functionally significant epicardial coronary artery disease. Additionally, stress echocardiography is a useful method for

assessing myocardial viability, LV contractile reserve (LVCR) and ischaemia. It therefore could potentially be used to aid baseline risk stratification in patients with an intermediate or high pre-test probability prior to undergoing treatments which may induce coronary events[8] as well as being beneficial in guiding decisions on revascularisation in patients who develop acute cardiotoxic events.

CMR

CMR, and especially stress CMR, has a significant role for the detection of acute and chronic ischaemia,[93] providing an assessment of myocardial viability via LGE imaging, functional perfusion abnormalities using stress first pass perfusion imaging, alongside the gold standard measurement of ventricular function.[94,95]. Importantly, thanks to its' unique ability for tissue characterization, it is able to investigate and diagnose coronary mimics, such as myocarditis or tako-tsubo cardiomyopathy – both relatively common causes of acute cardiotoxic events.

In the setting of cancer patients, CMR is currently also used both for baseline risk-stratification in high-risk patients prior to major cancer surgery or treatments generally associated with coronary events, and during treatment for the assessment of patients presenting with chest pain [96,97].

Cardiac CT

Coronary CT has excellent sensitivity and a high negative predictive rate for detection of coronary artery disease [98]. It may therefore be used as a negative predictive tool in excluding CAD in patients due to receive chemotherapy or radiation. Additionally, Fractional Flow Reserve as calculated by CT (FFRCT) is able to predict which patients are likely to have low cardiac event rates [99]. Cardio-oncology patients may have platelet or clotting abnormalities secondary to their disease or cancer treatment, thereby making them high-risk candidates for invasive coronary angiography (ICA). CCTA can be used as an alternative in this patient group with study showing high correlation with angiographic findings [100]. Guidance by the

European Society of Cardiology (ESC) suggests that patients undergoing therapies potentially linked to IHD should be screened with an appropriate imaging modality, including cardiac CT. With regards to radiation-induced CAD, as the development occurs >5 years post-RT, a screening at this point is reasonable. However, cardiac CT is currently not recommended as a routine surveillance tool [96].

Nuclear

Non-invasive measurement of myocardial perfusion with nuclear medicine techniques are a viable option in the cardio-oncology patient population who are likely to experience premature ischaemic heart disease [101]. SPECT Myocardial Perfusion Imaging (MPI) is still one of the most available and most widely used techniques for the assessment of significant coronary artery disease[102]. Its widespread use in evaluating coronary artery disease has also been validated in cancer patient population[103]. SPECT can be used to evaluate an individual prior to treatment and determine the level of myocardial ischemia, does not require exercise and is not limited by a post-treatment morbid status. PET MPI whilst previously used only to assess tumour burden, can now be used in the setting of cardiotoxicity. PET MPI is able to measure the myocardial perfusion reserve (MPR) allowing for more absolution quantification of myocardial blood flow[104]. However, it has only been used experimentally for the assessment of chemotherapy or radiation induced heart toxicity and is not currently used in mainstream clinical practice[105] .

Complimentary Role of Biomarkers

Although troponin assessment is widely used for detection of acute coronary events in the general population, its use in cancer patients is complicated by the relatively high prevalence of small troponin elevations occurring during cancer treatment. [106,107]. A study by Ky et al investigated the use of multiple biomarkers known to be associated with CV disease and found that a rise in absolute troponin levels to be associated with increased risk of

cardiotoxicity [108]. This pattern has also been seen in other cardio-oncology toxicity trials, including in those receiving anthracycline therapy [77,109]. Other groups have suggested that using baseline troponin with incremental values is a better predictor of cardio-toxicity than absolute numbers[110]. The problem in translating this into clinical practice is that the studies use end points of myocardial injury that encompass a wide range of cardiovascular disease.

Myocarditis

Several anti-cancer treatments are known to cause myocarditis [111] including proteasome inhibitors, tyrosine-kinase inhibitors, chimeric antigen receptor T-cell (CART) therapy, and most importantly immune checkpoint inhibitors (ICIs) and. Fulminant myocarditis has been detected in 1.16% of patients taking ICI, with presentation a median of 34 days after initiating ICIs, and major adverse cardiac events, including cardiogenic shock, complete heart block and life threatening arrhythmias, were reported in almost half of the patients with ICI myocarditis [112].

Echocardiography

Abnormal findings may include depressed left ventricular function, the presence of regional wall motion abnormalities and presence of a pericardial effusion. It is important to note that preserved ventricular function does not exclude this diagnosis and in one small study with 35 patients with confirmed ICI myocarditis the LV systolic function was preserved in 51%[113]. There is some evidence to suggest that GLS has a stronger role in this condition and in one study involving 101 patients with ICI myocarditis, GLS was lower compared to controls in both those with preserved (60%) and reduced LVEF and more importantly a low GLS was significantly associated with MACE irrespective of LVEF[114].

CMR

CMR is a well-recognised imaging technique for patients with myocarditis. In fact, the Lake Louise criteria [115], which include T2-weighted STIR imaging, T1 and T2 mapping imaging, as well as LGE, are widely used for diagnosis and monitoring of myocarditis, as well as for its prognostication. A recent international study on patients with ICI-associated myocarditis (figure 4) who underwent CMR described very heterogeneous cardiac findings in this subset of patients, which seem to have different characteristics than the classic lymphocytic, post-viral myocarditis [116]. Similar to echocardiographic findings, 61% of patients had a preserved LVEF, however myocardial oedema was only present in almost one-third of patients. LGE was present in nearly half patients and the pattern of LGE was very variable and included diffuse, subepicardial, midmyocardial, and subendocardial/transmural. Most notably, LGE was present in only 22% of patients when scanned within 4 days of admission but visible in 72% of patients if the CMR was performed on or after day 4 of admission, suggesting that timing of CMR has a pivotal role for the detection of ICI-associated myocarditis. The use of CMR for diagnostic of ICI-induced myocarditis may enable avoidance of invasive endocardial biopsy in patients where clear Lake Louise criteria are fulfilled, however normal CMR findings do not rule out myocarditis where other clinical or biochemical abnormalities are detected.

Cardiac CT

Standard Cardiac CT imaging is poor for detection of myocarditis, however dual energy CT (DECT) can enable quantification of myocardial extracellular volume (ECV) and therefore may be a useful alternative when CMR is not available ,[117] and also for ruling out coronary events.

Nuclear Medicine

FDG PET/CT provides metabolic evidence of inflammation with areas of increased myocardial FDG uptake, and showed close spatial correlation with CMR for the assessment of myocardial inflammation in myocarditis[118]. In this context, imaging PET/CT, might be beneficial in the diagnostic work-up of myocarditis following anticancer therapy, [119],[120]although evidence supporting PET/CT specifically in the domain of cardiotoxicity is lacking.

Complimentary Role of Biomarkers

In patients receiving ICI therapy troponin has been shown to be effective in guiding response to therapy and in those who develop myocarditis, not only is troponin useful for the diagnosis but also for monitoring safe discharge [75,113]. Similarly, troponin was found to be important in those receiving CAR-T cell treatment, being elevated in 94% of patients in a study looking at CV abnormalities [121]. There is no data from studies describing other biomarkers including NPs in myocarditis, however, CRP is also of particular interest as a biomarker of cardiotoxicity in those receiving CAR-T cell therapy as it is important for early detection of cytokine storm syndrome as a consequence of the therapy.

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy can be an adverse event related to cancer therapy and is associated with higher odds of in-hospital mortality and long-term mortality when compared with patients with takotsubo alone[122], [123.] Several chemotherapy agents have been associated with Takotsubo, including fluoropyrimidines, Immune checkpoint inhibitors and tyrosine kinase inhibitors[124].

Echocardiography

Echocardiogram is the first-line imaging modality. The wall motion abnormalities typically involve akinesia and ballooning of the mid-cavity and apex of the left ventricle with hyperkinesia of the base of the heart, with regional wall motion abnormalities extend beyond a single epicardial vascular distribution[125–127]. however, atypical forms of Takotsubo cardiomyopathy have also recently been described[128].

CMR

CMR provides a comprehensive assessment and has been increasingly used to diagnose this condition and to differentiate from acute coronary syndromes or from different types of cardiomyopathies[129]. Although late gadolinium enhancement is generally absent[129], myocardial oedema of the mid and apical segments can be seen on T2 weighted imaging, appearing as a high intensity signal with a diffuse or transmural distribution[130]. T1 and T2 mapping show a basal to apical gradient increase in values, [131], enable quantification and hence permit monitoring of Takotsubo cardiomyopathy (Figure 5). In addition, CMR can also help enable identification of thrombus in the ventricles not seen on echocardiography, and better assess the RV which is involved in 26% of patients[132].

Nuclear

123I-MIBG scintigraphy has been used to evaluate Takotsubo cardiomyopathy, showing decreased uptake of 123I-MIBG in the inferior wall and apex, corresponding to the akinetic areas of myocardial stunning. Interestingly, rest 99mTc-sestamibi images performed the following day for comparison show normal up-take in areas of decreased 123I-MIBG[133].

Pericardial Disease

Acute pericarditis disease and pericardial effusions may occur as a complication of a range of cancer treatments such as anthracyclines and cyclophosphamide and may also occur

following radiotherapy[134]. Pericardial disease can also represent a long-term consequence of radiation therapy to the chest – particularly where mantle field radiotherapy is used, causing pericardial thickening and constrictive physiology.

Echocardiography

Whilst echocardiography typically the first line imaging modality in suspected pericarditis, it is not uncommon for appearances to be normal. Echocardiography is however useful to assess the size, location and haemodynamic significance of pericardial effusions and to guide interventions such as pericardiocentesis. Constrictive pericarditis is an uncommon but important late sequela of radiotherapy and patients will typically present with right heart failure. 2D echocardiography is useful in the initial assessment in assessing pericardial thickening, respiratory ventricular interdependence, and Doppler inflow variation on the tricuspid and mitral valves.

CMR

CMR permits direct visualisation, functional assessment and tissue characterisation[14] of pericardial disease, and is superior to echocardiography in the diagnosis of pericardial thickening which may be present in acute pericarditis – particularly where dedicated T1 weighted fat imaging is performed. Pericardial fluid can be distinguished from the pericardial layers with cine SSFP imaging in which the pericardium has low signal intensity in contrast to the high signal intensity of pericardial fluid. As the whole pericardium can be visualised on CMR, the volume, distribution, presence of loculations and subsequent haemodynamic effect of pericardial effusions can be effectively assessed using CMR. Furthermore, characterisation of pericardial effusions is possible with CMR as pericardial T1 values have been shown to correlate with pericardial protein content. Pericardial protein content is inversely correlated with pericardial T1 values and therefore CMR has been shown to have a high diagnostic accuracy for transudative pericardial effusions at 1.5T (95% sensitivity, 81% specificity) and

the ability to help discriminate between transudative and exudative effusions and may negate the need for invasive pericardiocentesis in the case of a transudative pericardial effusion[135]. Guidelines recommend investigation with CMR to assess myocardial involvement using parametric mapping. Finally, following administration of intravenous gadolinium-based contrast agents, enhancement of the pericardium is strongly suggestive of an inflammatory pericardial process[136].

CMR may provide additional diagnostic assessment of pericardial constriction, with real time free breathing cine sequences allowing assessment of the effects of respiration on ventricular filling and the demonstration of ventricular interdependence which is key in the diagnosis of pericardial constriction[137]. Whilst there is an inability to detect pericardial calcification, pericardial thickening is present in around 82% of cases[138].Associated extracardiac features such as ascites, pleural effusions and dilated hepatic veins are also seen on CMR.

Cardiac CT

Cardiac CT is able to distinguish the pericardial layer from the surrounding pericardial fat. It can identify both pericardial thickening and pericardial calcification caused either by malignancy or secondary to treatment in the cardio-oncology patient. The ability to detect pericardial calcification helps to distinguish between constrictive and restrictive ventricular filling patterns, [139] and is essential for pre-procedural planning prior to pericardectomy. Similarly to CMR, it is also able to detect (figure 6) and quantify the volume of pericardial effusion and to in select cases distinguish between transudate and exudate [140].

Nuclear

Nuclear medicine techniques, particularly FDG-PET, may be used to identify neoplastic involvement of the pericardium [141]. It is also able to identify acute or chronic pericarditis and detect the burden of inflammatory tissue [142].

Complimentary Role of Biomarkers

There are no studies looking at the role of biomarkers in pericarditis. The presence of a positive troponin level would signify myocardial involvement

Valvular Heart Disease

Valvular heart disease may occur as a complication of cancer treatment most commonly as a direct consequence of radiotherapy, due to infective endocarditis related to the presence of indwelling catheters and also as secondary mitral regurgitation due to annular dilatation resulting from CTRCD.

Echocardiography

Resting transthoracic echocardiography is the first line imaging modality in patients with suspected valvular heart disease[143–145]. Radiotherapy typically affects the left sided heart valves with the aortic valve being most commonly affected and valvular dysfunction occurs insidiously over many years following treatment with a median onset of 22 years[146]. Spectrum of echocardiographic findings include leaflet fibrosis, retraction, thickening and calcification and lesions can be stenotic, regurgitant or mixed. Calcifications commonly extend to the subvalvular apparatus and aorto-mitral continuity.

Studies have shown that mild valvular disease is a common finding at 10 years post radiation exposure[147–149]. There is no consensus guideline on how frequently to monitor patients post radiotherapy but in one review it is suggested to perform the first study at 10 years following radiotherapy and at varying subsequent intervals depending on the findings shown[150].

In patients with poor transthoracic windows and suspected clinically important valve disease, transoesophageal echocardiography (TOE) is indicated, and may particularly be required where endocarditis is suspected in patients with neutropaenic sepsis secondary to cancer treatment.

Furthermore, Stress echocardiography (SE) plays an important role in the assessment of native valve lesions by providing a comprehensive assessment of the valve and ventricular function mainly during exercise but also with low dose pharmacological agents[151 143]. Stress echo in this context would be most useful in patients with radiation induced valve disease.

CMR

CMR can have a complementary role to echocardiography when there are poor acoustic windows or echocardiographic measurements are discrepant [152]. CMR, in fact, allows measurement of biventricular volumes and function, assessment of valve morphology as well as valvular flow and regurgitation quantification using phase contrast imaging methods [153].

Cardiac CT

Cardiac CT contributes to assessment of total aortic valve calcium burden in aortic stenosis and pre-procedural planning. It plays a particularly important role in the workup of patients undergoing a transcatheter aortic valve implantation (TAVI) [154]. For cardio-oncology patients who, as a result of treatment, may have secondary extra-cardiac complications related to treatment including mediastinal stenosis, cardiac CT is invaluable to surgical planning [155].

Nuclear

Nuclear medicine techniques have a limited role in the assessment of valvular heart disease. PET/CT is however able to identify endocarditis with reasonable sensitivity [156].

Complimentary Role of Biomarkers

There are no trials exploring the use of biomarkers and their association with cardiotoxicity in valve disease.

Future Perspective

The future of cardio-oncology lies in the early detection of cardio-toxicity and its prompt treatment, with the aim of minimising the burden of cardiovascular morbidity and mortality in cancer patients treated with cardiotoxic agents. This can be achieved through the appropriate use of multiple imaging modalities and complementary biomarkers in order to guide management. The main challenges ahead include the paucity of evidence from randomised controlled trials and the heterogenicity of imaging findings given the complex nature of oncology diagnosis and treatment regimens.

Future directions in this field include Phosphorus magnetic resonance spectroscopy (31P-MRS), which has been used in animal models to demonstrate alterations in energetics that precede contractile dysfunction[157]. Other promising avenues include hyperpolarised MRI which has been promising in detecting cardiac metabolism changes in vivo[158] and diffusion tensor imaging which can detect changes in myocardial micro-structure and therefore has potential to detect early changes associated with cardiotoxicity[159].

With regards to blood biomarkers, an increasing number of centres are evaluating the role of serum biomarkers combined with imaging biomarkers for the detection and surveillance of cardiac toxicity. Furthermore, interest in the discovery of newer biomarkers has peaked in recent years. Some Myeloperoxidase (MPO) produced and secreted by leucocytes has been shown to have a role in predicting adverse outcomes in acute coronary syndromes where troponin levels have not been elevated [160]. It has been shown to work synergistically with other cardiac biomarkers such as troponin to aide in the diagnosis of early cardiotoxicity [161]. Other novel biomarkers include microRNAs thought to be important in a range of inflammatory conditions but have yet to be used in cardio-oncology trials.

Conclusion

Our review highlights the important and varied roles that multimodality cardiac imaging has in the assessment suspected cardiotoxicity from oncology treatments. 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, to guide oncology treatment choice thereby minimising long term CV complications. Regardless of how effective these new techniques are, there is unlikely to be a one size fits all approach to detecting cardiotoxicity, rather a multi-disciplinary, multi-modality with complementary biomarkers approach. The rapid development of novel cancer therapies, each with its own spectrum of cardiotoxicities, demands an armamentarium of imaging and blood biomarkers able to detect and direct appropriate treatment to prevent cardiovascular morbidity and enable healthy cancer survivorship.

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Figure legends

Figure 1: The role of multimodality imaging in detecting various cardiotoxicities with their most common agents/therapies described

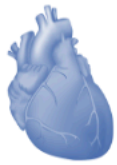
Figure 2: Flowchart of the potential role of multimodality imaging for cancer therapy induced cardiotoxicity

Figure 3: Transthoracic echocardiogram in a 61-year-old female pre and post treatment for breast cancer. A 61 year old female following 8 cycles of anticancer treatment for breast cancer consisting of 8 cycles of anthracyclines and HER2 targeted therapies. Pre-treatment echocardiogram in the apical 4 chamber view in diastole(a) and systole(b) showed preserved left ventricular ejection fraction of 61% on Simpson's Biplane (d) with a normal GLS of -21%(e). Post-treatment echocardiogram in the apical 4 chamber view in diastole(e) and systole(f) showed severely impaired left ventricular ejection fraction of 25% on Simpson's Biplane(g) with a markedly reduced GLS of -6.5%(h).

Figure 4: CMR in a patient receiving nivolumab for colorectal cancer. A 79-year-old female presenting in complete heart block 11 days post treatment with nivolumab for colorectal cancer recurrence. Late gadolinium enhancement sequences on cardiac magnetic resonance imaging (a, b) showed subepicardial enhancement in the anteroseptum as depicted by the white arrows. Corresponding quantitative T1(c) and T2(d) mapping values in a 1.5T scanner showed elevated T1 (1082ms, normal range: 970 to 1050 ms) T2 (53 ms, normal range: 40 to 51 ms) values.

Figure 5: Imaging modalities evaluating Tako-tsubo cardiomyopathy. Echo (panel a and b) and CMR cine imaging (panel c and d) demonstrate basal hyperkinesis with mid and apical akinesis resulting in apical ballooning. This is further demonstrated on LV ventriculogram (panel e) producing the typical 'octopus pot' shape which lends the syndrome its name. Tissue characterisation confirms prolongation of T1 (1059 to 1139 ms; normal range 970 to 1050) (panels f and g) and T2 (54 to 61ms; normal range 40 to 51ms) (panels h and i), most prominent in the mid to apical segments.

Figure 6: Contrast enhanced CT (non-gated) in a female patient with a previous history of osteosarcoma. A 55-year-old female presenting with worsening shortness of breath on a background of previous osterosarcoma in the left anterior chest treated with surgery, chemotherapy and radiotherapy 23 years ago. Contrast enhanced CT chest demonstrated a moderate sized global pericardial effusion as depicted by the white arrows.

Cardiotoxicity	Agents/Therapies	Imaging Modalities			
		Echocardiography	Cardiac MRI	Cardiac CT	Nuclear cardiology
Cardiac Dysfunction 	• Anthracyclines • HER2-targeted therapies • Alkylating agents • VEGF inhibitors • Multi-targeted kinase Inhibitors • Proteasome inhibitors • Immunomodulatory drugs • Combination RAF and MEK inhibitors • Androgen deprivation therapies • Immune checkpoint inhibitors • Radiotherapy	• 2D LVEF • 3D LVEF • GLS • Tissue doppler echo • RV Function • Contrast echo/ultrasound enhancing agents to enhance LV endocardial border definition • Stress echo for contractile reserve	• LVEF • LV and RV dimensions • Strain imaging • T1 mapping • T2 mapping	• Assessment of LV function if other non-invasive methods are inadequate • Quantitative assessment of RV function. • Assessment of RV morphology • Identifying cardiac decompensation (ie. pulmonary oedema)	• LVEF
Ischaemic Heart Disease 	• Fluoropyrimidines • Platinum based therapy • Alkylating agents • Antimicrotubule agents • VEGF inhibitors • Tyrosine Kinase Inhibitors • Proteasome inhibitors • Immune checkpoint inhibitors • CAR T cell therapy • Androgen deprivation therapies • Radiotherapy	• Regional wall motion abnormalities at rest • Stress echo for viability and ischaemic testing	• LVEF • Stress/perfusion imaging • Tissue characterisation for viability assessment • Regional wall motion abnormalities	• Assessment of coronary artery calcium score • Assessment of total coronary artery plaque burden, severity, composition and location • FFR CT to assess flow limiting coronary artery disease	• Stress/perfusion imaging • Assessment of viability
Myocarditis 	• Tyrosine Kinase Inhibitors • Proteasome inhibitors • Immune checkpoint inhibitors • CAR T cell therapy	• 2D LVEF • 3D LVEF • Regional wall motion abnormalities	• LVEF • Regional wall motion abnormalities • Tissue characterisation for assessment of myocardial inflammation	• Limited role	• Assessment of myocardial inflammation
Takotsubo 	• Fluoropyrimidines • Immune checkpoint inhibitors • Tyrosine kinase inhibitors	• 2D LVEF • 3D LVEF • Regional wall motion abnormalities (in most cases apex) • Identification of apical thrombus	• LVEF • Regional wall motion abnormalities (in most cases apex) • Tissue characterisation (basal to apical gradient at t1 and T2 mapping) • Identification of apical thrombus	• Limited role	• Limited role • Reduced uptake in inferior wall and apex
Pericardial Disease 	• Anthracyclines • Fluoropyrimidines • Alkylating agents • Tyrosine Kinase Inhibitors • Transretinoic acid • Arsenic trioxide • Radiotherapy	• Assessment of constrictive physiology • Assessment of pericardial thickness • Assessment of pericardial effusion	• Assessment of constrictive physiology • Assessment of pericardial thickness • Assessment of pericardial effusion	• Identification of pericardial calcification • Identification of pericardial thickening • Identification of pericardial effusion and differentiating between transudate and exudate	• Limited role • Assessment of pericardial inflammation
Valvular Heart Disease 	• Radiotherapy	• Assessment of valvular lesions and haemodynamic significance • Stress echo to assess symptoms and severity • 2D/3D TOE	• Assessment of valvular lesions • Assessment of haemodynamic significance through flow imaging sequences	• Assessment of aortic calcium score • Identification of valvular calcification • Surgical planning	• Limited role • Assessment of endocarditis (prosthetic valves)