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ECHOCARDIOGRAPHY (G DWIVEDI, SECTION EDITOR)

The Role of Echocardiography in Cardio-oncology Patients: Contemporary Indications and Future Directions

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Abstract

Purpose of Review This review discusses the latest advances, guideline recommendations, and limitations of the use of echocardiography in evaluation of cancer therapeutics–related cardiac dysfunction (CTRCD) and highlights advances in cardio-oncology that have the potential to augment the echocardiographic assessment of CTRCD.

Recent Findings Cardio-oncology is a rapidly evolving field aimed at improving the quality of life of cancer patients by preventing and treating the adverse cardiovascular complications of cancer therapy. Cardiac imaging tools, in particular transthoracic echocardiography, play a pivotal role in the early detection and monitoring of CTRCD. Recent studies have indicated the potential benefit of a number of echocardiographic parameters in addition to left ventricular ejection fraction in the evaluation of CTRCD.

Summary We anticipate that echocardiography will continue to play a central role in the field of cardio-oncology over the coming years. The utility and predictive value of echocardiographic indices will continue to improve with advances in imaging technology and development of novel biomarkers to supplement imaging parameters. Ensuring equitable and easy access to cardio-oncology services, especially in remote and disadvantaged communities, remains an area of ongoing investigation and will undoubtedly be assisted with new innovations in image acquisition, transmission, and analysis. Lastly, machine learning is likely to revolutionise the evaluation of CTRCD in light of the rapid progress of artificial intelligence–driven automation for the analysis and interpretation of echocardiograms.

Keywords Cardio-oncology · Cancer · Chemotherapy · Echocardiography · Imaging

Introduction

The last 30 years have witnessed a significant reduction in cancer mortality due to advances in cancer detection and treatment, resulting in an increasing prevalence of cancer survivors. Currently, there are over 15 million cancer survivors in the USA and close to 30 million worldwide [1–3]. Despite remarkable advances in the treatment of cancer, adverse effects of cancer therapy can reduce patient survival and quality of life in the long-term. As a consequence, focus has

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now turned to the prevention, detection, and management of cancer treatment–related toxicities.

Cardiovascular disease is recognised as the second leading cause of morbidity and mortality among cancer survivors [4]. Cardiotoxicity can result from the direct toxic effects of chemotherapy, radiotherapy or immunotherapy, and has various manifestations. It can present with myocardial dysfunction and heart failure, coronary artery disease, Takotsubo's cardiomyopathy, valvular heart disease, arrhythmias including QT prolongation, arterial hypertension, thromboembolic disease, peripheral vascular disease, pulmonary hypertension, and pericardial disease [5••, 6]. Cancer therapy–related cardiomyopathy or heart failure is associated with a high risk of adverse outcomes including cardiac transplantation, requirement of left ventricular assist device therapies, and death [7]. Furthermore, cancer therapy in childhood can have enduring consequences on cardiac function and occur many years after the completion of treatment [8].

While adverse cardiovascular effects have been reported for a wide range of chemo- and immunotherapies, anthracyclines, trastuzumab, tyrosine kinase inhibitors, and vascular endothelial growth factor inhibitors are the main culprits [9]. Radiotherapy directed at the left chest or the mediastinum increases the risk of radiation-induced heart disease immediately or several years after exposure [10••]. Cardiotoxicity may occur due to a direct effect of cancer treatment on the structure and/or function of the myocardium or by the progression of pre-existing cardiovascular disease that is potentiated by the presence of traditional risk factors [9, 11]. Cancer itself can induce cardiac remodelling independent of therapy, implying that deranged baseline cardiac parameters might be worsened by subsequent therapy [12, 13].

With increasing cardiovascular disease risk being recognised among cancer survivors, the identification of at-risk patients, prevention of cardiotoxicity, and early detection and prompt treatment of cancer therapy–related cardiovascular complications are now essential components of modern cardio-oncology/onco-cardiology practices. Cardiac imaging, particularly transthoracic echocardiography (Fig. 1), plays an invaluable role in the detection and management of cardiotoxicity. While other imaging modalities also have a role in cardio-oncology (Table 1), echocardiography is by far the most easily accessible, widely used, safe, and cost-effective. In this review, we discuss the contemporary role of echocardiography in cardio-oncology and discuss the most recent major developments in this field, ongoing research, and future prospects. Guideline recommendations pertinent to cardiovascular imaging in cardio-oncology are discussed along with associated evidence and limitations.

Echocardiography Parameters in Cardio-oncology

Left Ventricular Systolic Function

Left ventricular (LV) ejection fraction (EF) has been used as a marker of cardiotoxicity for the past three decades. A prospective cohort study of breast cancer patients receiving doxorubicin, trastuzumab, or both found a mean decline in LVEF of 2.8 to 3.8% at 3 years of follow-up [20•]. An LVEF of ≥ 55% is accepted as the normal reference range [14••, 19••]. The European Society of Cardiology defines cancer therapeutics–related cardiac dysfunction (CTRCD) as a decrease in LVEF of more than 10 percentage points to a value below 53% on echocardiography [14••] or below 50% on nuclear cardiac imaging with a multigated acquisition scan, confirmed on repeat imaging 2 to 3 weeks later [5••]. The method of choice for quantification of LV volume and LVEF is the modified biplane Simpson's technique by two-dimensional (2D) echocardiography. Three-dimensional (3D) echocardiography has been shown to be more accurate than 2D echocardiography in the measurement of LV volumes [21, 22] and is the preferred technique for monitoring LV function and detecting CTRCD [14••, 15•]. The measurement of LVEF by 3D echocardiography is more accurate than that

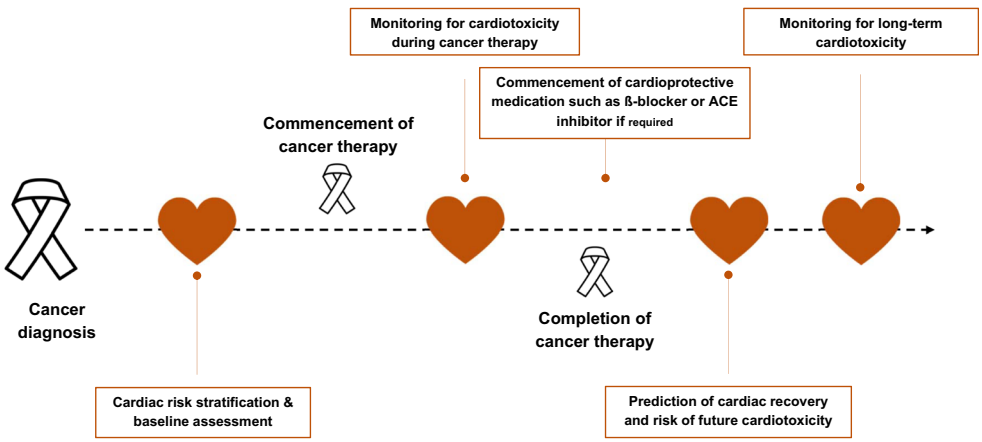

Fig. 1 Role of echocardiography in cardio-oncology. The figure illustrates the typically journey of a cancer patient undergoing treatment. The utility of echocardiography in the management of the cardiac sequelae of cancer therapy is illustrated by the heart icons and briefly summarised in the corresponding text boxes.

Table 1 Benefits and limitations of the various cardiac imaging modalities used in cardio-oncology

Imaging modality	Benefits	Limitations
Echocardiography	Availability, ease of use, cost-effectiveness, and reproducibility. No radiation exposure. Safe in patients with concomitant renal disease. Allows evaluation of cardiac structure (heart chambers, valves, and pericardium) and haemodynamic function (stroke volume, LV filling pressure, and pulmonary artery pressure) [14••, 15•, 16].	
Cardiac MRI	Reference standard for EF measurement [17]. Allows evaluation of the pericardium and detection of scarring and myocardial fibrosis [5••]. Allows assessment of tissue characterisation, evaluation of cardiac masses, and identification of infiltrative diseases [5••]. No radiation exposure.	Expensive. Limited availability. Use dependent on patient compliance while in scanner.
Multigated acquisition scintigraphy	Longest established method for quantifying LVEF in cancer patients. Robust method to assess LVEF in patients with atrial fibrillation. Superior to 2D echocardiography; values obtained have better correlation with other 3D imaging modalities such as 3D echocardiography and cardiac MRI [14••, 18].	Radiation exposure. Limited ability to assess cardiac structure and haemodynamics [19••]. Inability to measure strain.
Coronary CTA	Useful in patients with chest pain and prior chest irradiation to assess coronary artery disease.	Radiation exposure. Not used routinely to assess LVEF.

EF, ejection fraction; *LVEF*, left ventricular ejection fraction; *MRI*, magnetic resonance imaging; *CTA*, computed tomography angiography

obtained by the biplane method, with an error of less than 5% (compared to a more than 10% variation by the biplane method) [23•]. Despite its greater accuracy, studies demonstrating an improvement in the diagnosis of cardiotoxicity by means of 3D echocardiography are lacking. Furthermore, 3D echocardiography is not as widely available as 2D echocardiography [22]. The use of myocardial contrast agents are recommended to better delineate the endocardial border when two contiguous LV segments are not well visualised on non-contrast apical images [14••]. Of note, the minimum detectable difference for EF by contrast echocardiography appears to be 4 percentage points [24]. Calculation of LVEF could also be combined with assessment of the wall motion score index, which is based on a 16-segment model of the LV [25]. LVEF remains one of the most widely accepted indices for assessing CTRCD [14••, 15•].

Global Longitudinal Strain

Left ventricular ejection fraction is dependent on haemodynamic conditions and is not as sensitive to minor changes as measurements of myocardial deformation. Myocardial deformation (strain) can be measured using Doppler tissue imaging or 2D speckle tracking echocardiography (STE). Global longitudinal strain (GLS) via 2D STE is the optimal parameter of deformation for the early detection of subclinical LV dysfunction [22, 26–30]. The GLS calculates the systolic deformation of the myocardium and reflects its contractile function [31]. It has been shown to be a good predictor of subclinical LV dysfunction and CTRCD, as a worsening in GLS often occurs before a significant reduction in 2D LVEF [20•, 26, 32•, 33–35]. It is recommended that the measurements during chemotherapy should be compared with the baseline value [14••]. A relative percentage reduction of GLS of 15% from baseline is likely to be abnormal, a percentage reduction of GLS of < 8% from baseline is not considered to be meaningful [14••]. A GLS decrease of > 15% has been shown to have a sensitivity of 73.3–92.5% and a specificity of 78.5–83% for detecting subsequent cardiotoxicity defined by a greater than 10% decline in LVEF [35–37]. GLS has been shown to have good intra and inter-observer reproducibility [37, 38] and correlates with cumulative anthracycline dose ≥ 250 mg/m^2 and radiotherapy [38]. GLS thus remains a valuable indicator of subclinical LV dysfunction and its use in the early detection of cardiotoxicity is recommended [5••, 14••].

LV Diastolic Function

An assessment of LV diastolic function, including grading of diastolic function and an estimate of LV filling pressures, may be performed in addition to the assessment of LV systolic function. Monitoring of LV diastolic function on the basis of the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′) at baseline or 3 months after commencement of trastuzumab did not predict LVEF decline [39]. Furthermore, diastolic dysfunction was present in only one in five asymptomatic survivors of differentiated thyroid cancer at a median follow-up of 17 years [40]. On the other hand, diastolic dysfunction preceded systolic dysfunction by an average of 73 days in breast cancer patients with normal baseline diastolic function treated with various chemotherapeutic regimens [41]. The E/e′ ratio was able to detect

early decline in LV function more accurately than LVEF in breast cancer patients treated by multiple chemotherapy protocols [22]. While traditional parameters of diastolic dysfunction (mitral inflow analysis and left atrial volume/function) did not change in patients undergoing radiotherapy for left-sided breast cancer, indices of diastolic strain (E-Sr and A-Sr) declined 6 weeks after the radiation exposure [42]. A greater reduction in both traditional diastolic parameters and diastolic strain parameters was observed in the group with more than 10% reduction in GLS, suggesting that these parameters, especially diastolic strain, might be an early predictor of cardiotoxicity [42]. Further support for the usefulness of diastolic dysfunction comes from a recent meta-analysis of four studies by Nagiub and colleagues that demonstrated the usefulness of some diastolic parameters (mitral E, lateral E′, and mitral E/A) in predicting doxorubicin-induced cardiotoxicity [43]. Although abnormal diastolic parameters may reflect subclinical LV dysfunction and precede systolic dysfunction [28], their prognostic value and clinical significance in the context of CTRCD remains uncertain at present [14••].

Right Ventricular Function

In addition to the changes in LV function, alterations in right ventricular (RV) systolic and diastolic function might reflect early signs of anthracycline-induced cardiotoxicity [44]. This is plausible given that deformation mechanics of both the left and right ventricles follow similar temporal pattern and degree of impairment during trastuzumab therapy. A RV GLS decline of 14.8% was shown to predict cardiotoxicity with 66.7% sensitivity and 70.8% specificity. Compared to LV GLS, RV GLS appears to be less sensitive and specific [37]. A reduction in RV free wall strain and RV GLS was observed 6 months post-chemoradiotherapy for non-small cell lung cancer but the implications of these parameters are limited by the short follow-up period and unclear association with LVEF [45]. The clinical significance of measuring RV function on echocardiography therefore remains to be validated.

Other Echocardiographic Indices

Other parameters of cardiac function measured during echocardiography, including LV torsion [46], longitudinal peak systolic strain [47], circumferential strain [48], intraventricular pressure gradient [49], left atrial volume [3, 50], cyclic variation of integrated backscatter [51], and ventricular-arterial coupling [48] have been found to be altered in patients undergoing chemotherapy or radiotherapy. However, the association between a change in these parameters and a reduction in LVEF, or their long-term prognostic value, has not been established and their clinical significance is uncertain. Narayan et al. demonstrated that in breast cancer patients receiving doxorubicin, trastuzumab, or both, changes in radial strain at 4 to 6 months were significantly associated with LVEF at 2 years ($p = 0.02$) [20•]. An early worsening in circumferential strain was significantly associated with a LVEF decline of ~ 2% at 1 year ($p < 0.001$) and approached statistical significance at 2 years ($p = 0.09$) [20•]. Similar to strain, a 0.1/s worsening of longitudinal strain rate 6 months after commencement of cancer therapy was associated with CTRCD at 12 months, defined by a decrease in LVEF by ≥ 10% to less than 50% [48]. A decrease in relative wall thickness and early increases in E/a and measures of end-systolic stress were significantly associated with LVEF declines at 1 year ($p < 0.05$) but not 2 years [20•]. Finally, LV segmental wall motion abnormality was shown to be a predictor of cardiotoxicity along with GLS in one report [52]. Prolongation of LV electromechanical delay might be another useful early predictor of cardiotoxicity as elongation of the time interval from QRS onset on electrocardiography to the beginning and peak of trans-aortic flow on pulsed-waved Doppler echocardiography occurs before changes in LVEF and GLS [53]. Despite these promising findings, none of the above indices have been shown to be clinically useful at present [14••, 54, 55].

Role of Echocardiography

Risk Stratification and Baseline Assessment

The prevalence and mortality related to cardiovascular disease is higher in cancer survivors compared to non-cancer survivors [56]. Accurate risk stratification is crucial to identifying those patients at high risk of developing cardiotoxicity who are likely to benefit the most from a cardio-oncology referral. Patient and treatment characteristics considered high risk for the development of cardiotoxicity are summarised in Table 2. Echocardiography plays a central role in risk stratification and baseline assessment of patients undergoing cancer treatment. Evaluation of echocardiographic parameters such as LVEF and GLS alongside biomarkers such as troponin prior to commencement of therapies is recommended [5••, 14••, 15•, 16••, 19••].

A meta-analysis of the clinical utility of baseline cardiac assessment found such assessments to have low yield. Only 4.4% (95% CI 3.0–6.0%) of patients with early-stage breast cancer undergoing adjuvant anthracycline-based chemotherapy had abnormal baseline LVEF by echocardiography and only 7 out of 20 patients with abnormal baseline LVEF (35%) had their chemotherapy regimen changed [67•]. Likewise, a finding of LVEF < 50% led to a change from planned anthracycline-based chemotherapy to non-anthracycline-based chemotherapy in only one-third of breast cancer patients [68]. Despite these sub-optimal results, baseline echocardiographic evaluation of cardiac function and risk

Table 2 Factors that increase the risk of cancer therapeutics–related cardiovascular dysfunction

Cancer therapy–related risk factors [16, 57–61]	Patient-related risk factors [16, 62–66]
1. High-dose anthracycline e.g. doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2 2. High-dose radiotherapy e.g. radiotherapy ≥ 30 Gy with the heart in the treatment field 3. Lower-dose anthracycline in combination with lower-dose radiotherapy 4. Lower-dose anthracycline or trastuzumab alone in the presence of multiple (≥ 2) cardiovascular risk factors such as smoking, hypertension, diabetes mellitus, dyslipidaemia, and/or obesity 5. Treatment with lower-dose anthracycline (doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2) followed by trastuzumab 6. Autologous bone marrow transplantation.	1. Older age at treatment (≥ 60) 2. Moderate or severe valvular heart disease 3. Hypertension 4. History of myocardial infarction 5. Compromised cardiac function e.g. LVEF 50–55%

LVEF, left ventricular ejection fraction

assessment for CTRCD is currently recommended for all patients commencing potentially cardiotoxic therapy because a baseline assessment allows identification of changes in cardiac function during and after therapy.

A follow-up schedule should be discussed between the cardiologist and oncologist based on a patient's baseline risk, type and dose of the cancer therapeutic agent, and logistical factors [69]. Optimisation of cardiovascular risk factors and pre-existing cardiac dysfunction identified on baseline echocardiography maybe helpful in reducing the risk of cardiotoxicity. This includes management of hypertension, diabetes mellitus, dyslipidemia, pre-existing heart failure, and other cardiac conditions as well as encouraging smoking cessation, weight loss, and physical activity [5••, 15•, 16••, 19••]. Despite the benefits of early screening for patients at high risk of CTRCD, awareness about the necessity of screening cancer patients undergoing radiotherapy was found to be low among the thirty-six centres of the European Heart Rhythm Association Electrophysiology Research Network [70]. Therefore, improving awareness about the risk of cardiotoxicity in patients undergoing cancer therapy might be beneficial in centres that do not have dedicated cardio-oncology specialists.

Monitoring During and After Cancer Therapy

Periodic assessment of cardiac function during and after treatment is recommended, especially in symptomatic patients [5••, 14••, 15•, 16••, 19••]. In a cohort of HER2+ breast cancer patients, Kim and colleagues demonstrated that regardless of the baseline LVEF, a decline in LVEF of ≥ 5% within 3 months of starting adjuvant trastuzumab was associated with CTRCD at a median follow-up of 4.5 years [71]. Low-risk patients receiving anthracyclines at cumulative doses of < 240 g/m^2 may be followed-up with repeat measurements at the completion of therapy and 6 months later [5••, 14••, 57, 72]. Once this dose is exceeded, re-evaluation before each subsequent cycle, corresponding to each additional 50 mg/m^2, is recommended [14••]. Patients receiving trastuzumab who have had previous anthracycline exposure or radiotherapy in the region of the heart should have repeat measurements every 3 months during therapy and once after completion of therapy [5••, 14••], although evidence for this approach seems limited at present [73]. Increased echocardiographic screening of patients with asymptomatic declines in EF did not influence treatment decisions in patients receive trastuzumab [74], highlighting the uncertain benefit of increased surveillance during treatment. The development of signs and symptoms of heart failure, any abnormality on imaging, or a rise in troponin warrants further evaluation with a repeat echocardiogram within 2 weeks and a cardiology consultation [14••, 32•, 75, 76].

An echocardiogram is recommended between 6 and 12 months after completion of cancer treatment in asymptomatic individuals considered at high risk of cardiotoxicity (Table 2) [14••, 16]. If there is no evidence of cardiac dysfunction on imaging at that time, further imaging surveillance should be guided by patient circumstances and clinical judgement. Any abnormality on imaging or the development of signs and symptoms of heart failure should prompt further evaluation and a cardiology consultation. In patients who receive high doses of chest irradiation (> 30 Gy), surveillance transthoracic echocardiography should be considered 10 to 15 years after the initial treatment and continued at 5-yearly intervals thereafter [5••, 10••]. This is more likely to be beneficial in patients with pre-existing cardiovascular risk factors [10••].

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommend that cardiac magnetic resonance imaging (MRI) be used as an additional tool in situations where discontinuation or change of chemotherapy regimens due to CTRCD is being considered, imaging is difficult and cannot be enhanced by contrast, and accurate tissue characterisation is required [14••]. A multigated acquisition scan is often used as an adjunct rather than a substitute for echocardiography. However, cardiac MRI or a multigated acquisition scan can be used if echocardiography is not technically feasible or available.

Echocardiography and Biomarkers

According to the European Society for Medical Oncology (ESMO) guidelines, cardiac monitoring during cancer therapy can be performed by two pathways. The first involves cardiac imaging exclusively while the second involves a combination of serum troponin and cardiac imaging after baseline cardiac evaluation and echocardiography [19••]. In the former, an echocardiogram is performed at baseline, 3, 6, and 9 months during treatment and then at 12 and 18 months after the initiation of anthracycline treatment [19••]. In the latter, serum troponin is assessed following each cycle of chemotherapy [19••]. Troponin negative patients are recommended to have annual echocardiograms. While levels of troponin I and troponin T have been shown to increase during chemotherapy, the association between this rise and changes in cardiac function is not evident [77, 78] and the positive predictive value of troponin T above 0.008 ng/mL is low (54.5%) [79]. For example, elevations in troponin I did not reflect adverse cardiac function following haematopoietic stem cell transplantation [80]. Due to low quality of evidence, troponins should be used with caution in monitoring for cardiotoxicity. The precise monitoring protocol adopted should take into account the limitations of monitoring, clinical judgement of healthcare providers, and patient circumstances [16].

Primary Prevention and Treatment of Cardiotoxicity

Prophylactic use of beta blockers such as carvedilol prior to initiation of anthracycline-based chemotherapy has been associated with a reduced incidence of cardiotoxicity and diastolic dysfunction, and a lower rise in troponin I. However, no effects were observed on asymptomatic LVEF decrease, brain natriuretic peptide levels, or all-cause mortality [81, 82••]. The ACE inhibitor lisinopril appears to be as effective as carvedilol in reducing the incidence of cardiotoxicity and treatment interruptions in breast cancer patients treated with trastuzumab [83]. However, neither protective therapy affected patients' quality of life 12 months after completion of chemotherapy [83]. Detection of CTRCD as soon as it develops is key to good cardiovascular outcomes [84], and echocardiography plays a central role in the treatment algorithm for CTRCD (Table 3). If LV dysfunction is confirmed on imaging during monitoring, alteration or discontinuation of the treatment regimen, initiation of cardioprotective agents such as ACE inhibitors and beta blockers, and a follow-up schedule should be determined. Early initiation of heart failure treatment is likely to be beneficial in patients with LV dysfunction due to cardiotoxicity [85].

Limitations of Echocardiography

Echocardiography has many advantages over other imaging modalities and plays a central role in cardio-oncology (Table 4). However, issues of reproducibility and lack of standardisation of measurement conventions remain an issue [86]. A study investigating the reproducibility of echocardiographic parameters between two academic core laboratories found evidence of only borderline acceptability in LVEF and 4-chamber GLS calculations between the laboratories [87]. As a consequence, it is recommended that the same system and software from the same vendor be used for longitudinal follow-up and that the sonographers and physicians have adequate training to reduce both intra- and interobserver and test-retest variability [14••, 88–90].

A prospective, longitudinal cohort study of breast cancer patients undergoing treatment with doxorubicin, trastuzumab, or both, and followed up for a median time of 2 years, demonstrated the limitation of some echocardiographic parameters in predicting long term cardiac function [20•]. Alterations in LVEF, longitudinal strain, circumferential strain, circumferential end-systolic stress, and effective arterial elastance at 4 to 6 months post-therapy were associated with worse dyspnoea at 1 year [20•]. Increase in effective arterial elastance and a decrease in LV end-diastolic volume at 4 to 6 months were also associated with an increase in heart failure score at 1 year [20•]. However, no significant associations between LVEF or other echocardiographic indices and heart failure symptoms persisted at 2 years post treatment [20•].

The utility of GLS as an early marker of cardiotoxicity has also been questioned. A prospective study of cardio-oncology patients in Israel found that 75% of patients that had a relative reduction in their GLS of ≥ 10% did not have a subsequent decrease in LVEF at the follow-up echocardiography assessment [91]. This study was observational in nature and had a number of limitations including a small sample size, heterogenous population of cancer patients undergoing different treatment regimens, and considerable variability in the length of the follow-up period, making interpretation of the results difficult. Trivedi and colleagues showed that decreases in GLS persist for up to 1 year after radiotherapy without any concomitant decline in LVEF [92]. Further well-designed studies are therefore required to confirm the utility of GLS in monitoring for subclinical cardiotoxicity during and after cancer therapies.

Future Directions

Validation of Echocardiography Findings

While there are numerous proposed echocardiographic parameters for early subclinical cardiotoxicity, their use in the clinic has not been validated. The MEDIRAD EARLY

Table 3 Current guidelines for the role of echocardiography in the management of CTRCD. Recommendations are in accordance with the ASCO, ESC, CCS, and ESMO guidelines as indicated

	Signs	Recommendation	Organisation
	Anthracycline-induced toxicity		
1.	Decline in LVEF ≥ 10 to < 50%	Repeat assessment of LVEF [5••]. Commence ACE inhibitor (or ARB) and ß-blocker to prevent further LV dysfunction [5••].	ESC
3.	Symptomatic LV dysfunction (LVEF < 40%)	Cease chemotherapy and commence appropriate heart failure therapy with ACE inhibitor (or ARBs) and ß-blockers [19••].	ESMO
4.	LVEF is > 40% but < 50%	Reassess cardiac function in 3 weeks. If this is confirmed, cease chemotherapy and commence appropriate heart failure therapy and more frequent follow-up [19••].	ESMO
5.	Symptomatic heart failure without a decline in LVEF	Chemotherapy can be continued [19••].	ESMO
6.	Asymptomatic decline in LVEF to < 40% or an LVEF reduction of ≥ 15% from baseline to < 50%	Withhold cancer therapy, commence heart failure therapy, and discuss with the cardio-oncology team [19••].	ESMO
7.	Asymptomatic decline in LVEF to < 50% but greater than 40%	Cancer therapy can be continued. Commence ACE inhibitor (or ARB) and ß-blocker plus more frequent echocardiography and clinical review [19••].	ESMO
8.	Troponin positive patients	Start ACE inhibitor to prevent decline in LVEF and do an echocardiogram at the end of the cancer therapy and 3-monthly thereafter [19••].	ESMO
	Trastuzumab-induced cardiotoxicity		
1.	Decline in LVEF to < 45% or by > 10% from baseline to a value between 45 and 49%	Withhold trastuzumab and repeat LVEF measurement in 3 weeks [5••, 15•, 16]. If the LVEF is restored to > 49%, trastuzumab may be reinitiated [5••, 15•, 16]. If the LVEF remains between 45 and 49%, trastuzumab may be continued but an ACE inhibitor should be initiated [5••, 15•, 16]. If the LVEF remains ≤ 44%, cease trastuzumab and commence ACE inhibitor and ß-blocker [5••, 15•, 16].	ASCO, CCS, ESC
2.	Symptomatic heart failure	Commence ACE inhibitor (or ARB) and ß-blocker [19••].	ESMO
3.	Asymptomatic decline in LVEF to < 40%	Commence ACE inhibitor (or ARB) and ß-blocker. ACE inhibitors alone are sufficient for asymptomatic patients, however in the setting of a previous myocardial infarction, ß-blocker may be added [19••].	ESMO
4.	Symptomatic heart failure with LVEF between 40 and 50%	Consider commencing ACE inhibitors [19••].	ESMO

ACE, angiotensin converting enzyme; *ARB*, angiotensin receptor blocker; *ASCO*, American Society of Clinical Oncology; *ASE*, American Society of Echocardiography; *CCS*, Canadian Cardiovascular Society; *CTRCD*, cancer chemotherapeutics–related cardiac dysfunction; *ESC*, European Society of Cardiology; *ESMO*, European Society of Medical Oncology

HEART study currently underway across five centres in Europe aims to identify and validate novel cardiac imaging and circulating biomarkers of radiation-induced cardiovascular changes arising within the first 2 years of breast cancer radiotherapy in women with unilateral breast cancer (NCT03297346) [93]. The parameters being investigated are reproduced in Table 5. Preliminary results are expected to be published later this year and are likely to aid risk stratification approaches and inform primary and secondary preventive measures [93]. The SUCCOUR trial currently in progress across twenty-three international sites is a 3-year prospective randomised controlled trial investigating the benefit of using GLS as a marker of cardiotoxicity compared to the traditional measure of LVEF. Analysis of preliminary data have shown that of 40 patients randomised to the GLS-guided arm, 15 were started on cardioprotective therapy, whereas only 4 of 46 patients in the EF-guided arm were started on the same cardioprotective regimen. The trial will help elucidate the role of GLS in the detection and subsequent treatment of cardiotoxicity [94].

There is a paucity of strategies for predicting risk and detecting CTRCD early in paediatric populations. A large multicentre observational study investigating the genomic, biomarker, and imaging parameters that can be used as predictors of risk or aid in the early diagnosis of cardiotoxicity is underway (NCT01805778). Indices of early cardiac remodelling such as the LV wall thickness Z-score and the LV thickness-to-dimension ratio are being investigated as predictors of subsequent global dysfunction in paediatric cancer patients receiving anthracycline treatment. The results of this study are

Table 4 A summary of recommendations for the diagnosis, monitoring, treatment, and follow-up of CTRCD. The type and strength of evidence behind the recommendation is created by ASCO using the GuideLines Into Decision Support (GLIDES) methodology. The strength of each recommendation is rated as strong, medium, or weak based on the evidence of a true net effect, consistency of results, concerns about study quality and the extent of agreement among panellists [16]

	Recommendation	Organisation	Type	Strength
1.	Echocardiography is the standard imaging modality of choice for assessment of cardiac structure and function.	ASE/EACVI	Evidence-based	Strong
2.	If echocardiography is not available or technically feasible, a multigated acquisition scan or cardiac MRI can be used, with preference given to cardiac MRI.	ASCO, ASE/EACVI	Evidence-based	Moderate
3.	The same imaging modality and method should be utilised to determine LVEF before, during, and after completion of cancer therapy.	CCS, ASE/EACVI	Formal consensus	Moderate
4.	3D echocardiography is the preferred imaging technique in monitoring LV function and detecting CTRCD.	CCS, ASE/EACVI	Formal consensus	Moderate
5.	2D STE (GLS) and serum biomarkers, in particular troponin, are useful tools for detecting subclinical LV dysfunction but its significance is still unknown.	ESC, ASCO, CCS, ASE/EACVI, ESMO	Formal consensus	Moderate
6.	Evaluation of LVEF prior to commencement of potentially cardiotoxic cancer treatment is necessary. Periodic assessment during and post treatment is recommended especially in symptomatic patients.	ESC, ASCO, CCS, ASE/EACVI, ESMO	Formal consensus	Strong
7.	Baseline evaluation of LVEF, GLS, and troponin should be undertaken prior to initiation of agents associated with CTRCD.	ESC, ASCO, CCS, ASE/EACVI	Evidence-based	Moderate
8.	Serial assessments with cardiac imaging and/or serum biomarkers are recommended during treatment and post completion of therapy.	ESC, ASCO, CCS, ASE/EACVI, ESMO	Evidence-based	Moderate
9.	In patients who receive high doses of chest irradiation, screening with non-invasive imaging should be considered 10 to 15 years after the initial treatment.	ESC, ASE/EACVI	Evidence-based	Weak
10.	Significant changes in LVEF necessitate confirmation with repeat imaging within 2 to 3 weeks. A significant decline in LVEF warrants initiation of heart failure treatment (ACE inhibitors/ARBs and beta blockers).	ESC, ASCO, CCS, ESMO	Evidence-based	Strong
11.	The decision to withhold or discontinue cancer therapy should be made by the oncologist in close collaboration with a cardiologist after considering the risks and benefits of continuation of therapy.	ASCO	Informal consensus	Weak

ACE, angiotensin converting enzyme; *ARB*, angiotensin receptor blocker; *ASCO*, American Society of Clinical Oncology; *ASE*, American Society of Echocardiography; *CCS*, Canadian Cardiovascular Society; *CTRCD*, cancer chemotherapeutics–related cardiac dysfunction; *EACVI*, European Association of Cardiovascular Imaging; *ESC*, European Society of Cardiology; *ESMO*, European Society of Medical Oncology; *GLE*, global longitudinal strain; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; *MRI*, magnetic resonance imaging; *STE*, speckle tracking echocardiography

expected to aid in the identification of at-risk children with cancer who might benefit from cardioprotective therapies during cancer treatment, and provide a framework for closer surveillance after completion of cancer therapy [95]. Currently, the approach to detecting and monitoring of cardiotoxicity in paediatric populations undergoing cancer treatment is similar to that used in adult cancer patients [96].

Use of Echocardiography in Conjunction with Other Modalities

Electrocardiography

Other means of cardiac assessment have the potential to augment the usefulness and interpretation of echocardiography results. A retrospective study of adult survivors of paediatric cancers treated with anthracyclines showed a correlation between QTc prolongation and subsequent LV dysfunction. The QTc was longer in patients with LV dysfunction compared with patients who had normal echocardiograms (451 ± 32 ms vs. 423 ± 25 ms, $p < 0.001$). The mean time from QTc ≥ 450 ms to echocardiographic evidence of LV dysfunction was 1.8 ± 2.9 years [97]. QTc prolongation was also observed in a sample of ten breast cancer patients undergoing treatment with epirubicin and cyclophosphamide [98]. While these results suggest that ECG monitoring of the QT interval might be useful in patients undergoing therapy, the level of agreement between ECG abnormalities and echocardiographic evidence of cardiac dysfunction is currently low [99]. It is therefore unclear whether abnormal ECG patterns such as prolonged QTc or T wave changes [100] have long term prognostic utility.

Portable Wireless Devices

Use of wireless handheld devices capable of simultaneous collection of carotid arterial pulse waveform and phonocardiogram data was shown to be more accurate than 2D echocardiography and comparable with the gold-standard measure of MRI in the measurement of LVEF [101]. The study

Table 5 Cardiac imaging parameters and circulating biomarkers being investigated as predictors of early cardiotoxicity in the EARLY HEART study. Table modified from Walker et al. [93]

2D STE
• Global and segmental longitudinal strain and strain rate
• Global and segmental radial strain and strain rate
• LVEF using Simpson's biplane method
• E/A wave ratio: ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)
• E/Ea wave ratio: ratio of peak velocity blood flow from gravity in early diastole (the E wave) to early diastolic velocity of lateral mitral annulus (e′ lateral)
• Tricuspid annular plane systolic excursion
• Heart rate
• Cardiac output measured by multiplying heart rate by the stroke volume
Computed tomography coronary angiography
• Coronary artery calcium score, overall and per artery
• Presence and type of plaque (noncalcified, partly calcified, and calcified); overall and per segment or artery
• Presence and severity of luminal narrowing based on plaque; overall and per segment or artery
Magnetic resonance imaging
• RV end-diastolic and end-systolic volumes, LV end-diastolic and end-systolic volumes, LV mass
• LVEF, RVEF
• Presence and extent of myocardial infarction based on delayed enhancement
• Tissue characterisation based on pre- or postcontrast T1 mapping
• Presence of myocardial oedema based on T2 mapping
Circulating biomarkers
• Markers of cardiac injury: CRP, Troponin I, Troponin T, BNP, N-terminal-proBNP, beta2-microglobulin, Galectin 3
• Extracellular vesicles: CD14 (monocytes), CD31 (endothelial), CD41 (platelets), CD3 (lymphocytes), CD235a (erythrocytes); exosomes
• Cardiac miRNAs (miR-1, miR-24, miR-133a/b, miR-208a/b, miR-210); non-cardiovascular miR-122
• Circulating DNA methylation

BNP, B-type natriuretic peptide; *LVEF*, left ventricular ejection fraction; *RVEF*, right ventricular ejection fraction; *CRP*, C-reactive protein

population comprised of childhood cancer survivors, mostly acute lymphoblastic leukaemia and Hodgkin lymphoma, who had received a median cumulative anthracycline dose of 240 mg/m^2. The mean EF by the handheld platform (56.5%) did not differ substantially from that by cardiac MRI (56.8%). The correlation between LVEF values was stronger between the handheld platform and MRI ($R = 0.44$) compared to echocardiography and MRI ($R = 0.12$). By comparison, echocardiography had lower sensitivity and higher false negative rates compared with the MRI-determined LVEF cut-off of < 45%. The use of a handheld device was shown to be feasible, with a high sensitivity and low false-negative rate with cardiac MRI as the reference [101]. Once validated, this technology has the potential for use in preliminary screening without the lag-time between imaging and interpretation of results.

^{18}Fluorodeoxyglucose Positron Emission Tomography

^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), used to monitor tumour response to therapy, might also be used to monitor myocardial toxicity associated with cancer therapy [102]. Increased glucose metabolism in the RV wall was observed within 1 week of anthracycline or trastuzumab treatment [103]. In a study of 26 patients with Hodgkin's lymphoma undergoing doxorubicin treatment, a progressive increase in LV glucose uptake was observed on ^{18}FDG-PET over the course of doxorubicin treatment without any change in LVEF measured by echocardiography [104]. However, patients that had LV standardised glucose uptake values above the median also had significantly reduced LVEF compared to those patients with standardised glucose uptake values below the median. The difference between LVEF at the completion and beginning of treatment was inversely correlated with LV standardised uptake values at the end of treatment [104]. While these findings suggest that ^{18}FDG-PET might be a useful tool in early cardiac surveillance in conjunction with an echocardiogram following cancer therapy, the fact that the LVEF dropped below 53% in only 3 out of 26 (7%) subjects limits its predictive value. Furthermore, the feasibility of routine ^{18}FDG-PET is limited

by the requirement of two different protocols for preparation (oncological and cardiovascular) prior to the scan.

Artificial Intelligence and Machine Learning

Advances in machine learning in medicine provide an unparalleled opportunity to automate echocardiographic image acquisition and interpretation. A fully automated, scalable machine learning pipeline for view classification, image segmentation, measurement of cardiac structure and function, and disease detection has recently been explored [105]. Automation of echocardiography studies offers the prospect of early and cost-effective detection of cardiac dysfunction in asymptomatic individuals to monitor cardiotoxicity of cancer therapies and hence modify treatment approaches. Automation of image acquisition and interpretation could enable increased frequency of serial measurements, most of which could be done in primary care settings [105]. As a proof-of-concept, plots of strain trajectories for individual patients were generated using automated measurements of GLS by Zhang and colleagues [105]. As further validation, average longitudinal strain values in patients who received or did not receive doxorubicin-cyclophosphamide neoadjuvant therapy before receiving trastuzumab/pertuzumab were compared. Consistent with prior results, pre-treatment with anthracyclines resulted in lower median and nadir absolute strain values as determined by the automated algorithm for reporting these parameters [105]. Once validated, this "democratisation of healthcare" [106] offered by an automated approach to echocardiography has the potential to facilitate studies earlier in a disease course, more frequently, and in areas with poor access to specialist services [105].

Conclusion

Cardiovascular disease is one of the leading causes of morbidity and mortality in individuals undergoing cancer treatment and those who have survived the gauntlet of cancer therapy. Screening of patients at high risk of cardiotoxicity, early detection of cardiotoxicity during treatment, and monitoring for cardiovascular sequelae following completion of treatment are essential in reducing the burden of cardiovascular disease associated with cancer treatment and improving quality of life. Echocardiography is a vital tool in the armamentarium of cardio-oncologists given its widespread availability, relatively low cost, and acceptance among specialists. While parameters such as LVEF and GLS are extensively studied and form the backbone for evaluation of cardiotoxicity in cancer patients, their long-term prognostic value is not fully appreciated. Trials evaluating the validity of a range of echocardiographic parameters in addition to LVEF and GLS are currently underway and have the promise to elucidate the most useful echocardiographic indices for evaluating cardiotoxicity in the setting of cancer treatment. Combining the robustness of echocardiography with other novel approaches to detecting and monitoring cardiac dysfunction such as handheld devices and artificial intelligence/machine learning has the ability to revolutionise the field of cardio-oncology in the coming years.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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