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CARDIAC COMPLICATIONS OF CHEMOTHERAPY: ROLE OF IMAGING

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Opinion Statement

New advances in cancer diagnosis and treatment have increased survival rates in patients with cancer. In parallel with the increase in the number of cancer survivors is an increasing prevalence of cardiac complications from cancer treatment. Chemotherapy-induced cardiac dysfunction is a major contributor to adverse morbidity and mortality rates in cancer patients. Evidence suggests that both clinical symptoms and the traditional left ventricular ejection fraction (LVEF) may lack sensitivity as measures of cardiotoxicity. The early identification of subclinical LV dysfunction is becoming increasingly important, as this may allow cancer patients and their physicians to make informed decisions about therapeutic options. The features of echocardiography make it a useful tool in the diagnosis and monitoring of cardiotoxicity. This review will examine the role of cardiac imaging in detecting cardiotoxicity, focusing primarily on the conventional and more recent echocardiographic approaches for assessing subclinical cardiotoxicity.

Keywords

Echocardiography; Chemotherapy; Cardiotoxicity; Anthracyclines; Imaging

Introduction

Cancer is a significant public health problem in the United States and worldwide, with current statistics indicating 1 in 3 women and 1 in 2 men in the United States developing cancer in his or her lifetime [1]. Cancer therapy has undergone significant advancements over the last decades. While anthracyclines, antimetabolites, alkylating agents, and antimicrotubule agents are routinely used in chemotherapy, the recent discovery of new

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Compliance with Ethics Guidelines

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.

Conflict of Interest

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classes of treatments such as monoclonal antibodies and tyrosine kinase inhibitors has expanded the arsenal of cancer treatments available for use in the clinical setting. Novel diagnostic tools in combination with new therapies, more intensive treatment regimens, and better supportive care have increased overall life expectancy in cancer patients. In the United States alone, an estimated 13.7 million patients with a history of cancer were alive on January 1, 2012, and this number is estimated to increase to nearly 18 million by 2022 [2]. With the overall increase in the survival rates of cancer patients, however, there is a parallel increase in adverse cardiac effects from their cancer treatments [3–5] that may potentially counter any gains in life expectancy. A number of factors may contribute to this growing number of adverse cardiac effects, including increased length of survival, a larger number of cancer survivors who are older (and have more traditional cardiovascular risk factors) [1], increased incidence of more aggressive cancers requiring more aggressive therapy [5], and the recent introduction of a number of new classes of treatment agents with cardiotoxic effects [3, 6, 7].

Cardiac toxicity of chemotherapy agents

Cardiac toxicity is a recognized adverse event of chemotherapy use and encompasses a range of cardiac problems, including cardiac dysfunction (heart failure), myocardial ischemia or infarction, hypertension, thromboembolism, and arrhythmias [6]. The incidence of cardiotoxicity, particularly heart failure, depends upon a number of different factors relating to the chemotherapy used (i.e., type of drug, dose administered during each cycle, cumulative dose, schedule of administration, route of administration, combination of other cardiotoxic drugs, or association with radiotherapy) and patient-related factors (i.e., pre-existing heart disease, history of hypertension, and age > 65 years) [8]. Recent data suggest that as a result of their treatment, adult survivors of childhood cancer are 15 times as likely to have heart failure and 10 times as likely to have coronary artery disease as their siblings [9], and close to half of the adult patients exposed to anthracyclines will show some measure of cardiac dysfunction 10 to 20 years post-treatment with chemotherapy, with approximately 5% going on to develop overt heart failure [4, 10]. Radiation therapy, which is also frequently used in the treatment of cancer, has cardiotoxic effects and can potentially compound the cardiotoxicity of chemotherapeutic agents. The cardiotoxic effects of radiation therapy are pleomorphic and will not be discussed in this review (for a recent expert consensus, see [11]).

The anthracyclines are among the most common cardiotoxic chemotherapeutic agents and have been widely recognized since the 1960s as a contributor to heart failure. The vast majority of research on cancer treatment and cardiotoxicity has been on anthracycline-induced cardiotoxicity, which is related in part to the widespread use of anthracyclines due to their effective anti-neoplastic properties, particularly for aggressive cancers. More recently, hormonal therapy (including tamoxifen and the aromatase inhibitors) and a number of other chemotherapeutic agents, such as the taxanes and tyrosine kinase inhibitors, have been administered in cancer patients. There is particular interest in trastuzumab (a monoclonal antibody and tyrosine kinase inhibitor), as it appears to exacerbate the cardiac dysfunction seen with anthracyclines when used in combination. Tyrosine kinase inhibitors

such as sunitinib have been shown to cause LV dysfunction. It is likely, however, that newer tyrosine kinase inhibitors may also prove to be cardiotoxic.

As the different types of chemotherapeutic agents inflict cardiomyocyte damage via different mechanisms, these agents cannot be viewed collectively as a single class, and there is a move underway to classify cardiotoxicity based on the mechanism of toxicity of the individual agent rather than the more traditional approach of early or delayed chronic cardiotoxicity. Type I toxicity results from the use of agents such as anthracyclines or mitoxantrone, which causes a cumulative dose-dependent form of cardiotoxicity. Cellular damage due to defective mitochondrial biogenesis and reactive oxygen species formation [12] may be exacerbated by pre-existing cardiac dysfunction and individual genetic factors resulting in cardiac dysfunction. As this type of cardiotoxicity arises from cellular damage that results in cell death, there is minimal potential for replacement via regeneration, and hence this form of damage is irreversible, even though overall cardiac function may be preserved and compensatory function optimized through anti-remodeling pharmacologic and/or mechanical intervention [13]. On the other hand, type II toxicity results from agents such as the tyrosine kinase inhibitor trastuzumab and other small-molecule kinase inhibitors. These agents do not cause the type of cellular and progressive cardiac damage seen in type I toxicity, but have the potential to cause cardiac dysfunction [14] through transient impairment of the contractile elements within the cell. Recovery of cardiac function is frequently seen after cessation of treatment with the agent [15].

Importance of early detection of cardiotoxicity

Anthracycline-induced cardiomyopathy carries a worse prognosis than many other forms of cardiomyopathies and has less than a 50% rate of 2-year survival free of transplantation, although other studies cite lower mortality rates [16]. Once symptoms of heart failure manifest, the response to medical therapy is frequently refractory and the prognosis generally poor [17]. In theory, the early detection of chemotherapy-induced cardiotoxicity is of great interest, as this allows modification of dose and/or administration rate and schedule, use of anthracycline analogs of comparable efficacy and less cardiotoxicity whenever possible, or alteration of cancer therapy drug combinations in order to reduce cardiotoxicity without discontinuation of life-saving anti-neoplastic therapy [18]. Emerging evidence suggests that certain interventions, such as the initiation of enalapril or carvedilol early in the course of the disease, may slow the progression of left ventricular dysfunction and potentially lower the incidence of heart failure and death [19]. Although these findings are encouraging, it is still not known whether these results can be generalized to a larger population of patients or to those treated with lower doses of anthracyclines. While there are defined recommendations, such as those from the American College of Cardiology, for the initiation of ACE inhibitors for patients with stage A heart failure (defined as patients who are at high risk for developing HF but have no structural disorder of the heart) and other cardiovascular risk factors (hypertension or diabetes) and the addition of β -blockers to patients with stage B heart failure (defined as patients with a structural disorder of the heart but who have never developed symptoms of heart failure), it is not current practice to commence these medications in patients who have received cardiotoxic chemotherapy but have LVEF within normal limits and are asymptomatic [20].

Currently, a number of challenges exist in the identification of patients at risk of cardiotoxicity who may be suitable for cardioprotection. Firstly, there is significant variation in each individual's sensitivity to chemotherapy, with histopathologically confirmed anthracycline-induced cardiotoxicity reported in patients treated with low doses of anthracyclines (less than one-third of what is considered conventional maximum cumulative dose), while high doses have been tolerated by others. This unspecific nature and predictability of myocardial damage makes it difficult to define general recommendations regarding the monitoring of patients receiving chemotherapy treatment [8, 21]. Secondly, current clinical practice is limited to serial noninvasive surveillance for signs of early (subclinical) reduction of LV systolic function (using LVEF) [22], where any decreases in LVEF are assumed to be due to the chemotherapeutic agent(s) and any lack of change interpreted as evidence of absence of cardiotoxicity, even though none of these assumptions are necessarily accurate [23]. Thirdly, current measures of cardiotoxicity defined by decreases in LVEF may become apparent only at a late stage when the heart muscle has been significantly damaged exceeding its ability to compensate [23, 24]. Hence, based on current available measures, a significant drop in LVEF would signify advanced disease, potentially too late for any meaningful alterations in clinical management. Despite a number of attempts to unify approaches to manage these patients, there continues to be considerable debate over the assessment of cardiac function prior to, during, and after anticancer therapy [25, 26].

Evaluation of cardiac function by imaging techniques in patients treated with chemotherapy

Guidelines currently exist for monitoring chemotherapy-induced cardiotoxicity in children treated with anthracyclines [27], but no defined guidelines have yet been delineated for the adult population. The American Heart Association recommends close monitoring of cardiac function in adults during anthracycline therapy but does not specify the methods that should be used to assess for cardiotoxicity, follow-up duration, frequency of testing, or thresholds that should be used [20, 27].

The current gold standard for the detection of anthracycline-induced cardiomyopathy is endomyocardial biopsy [28], which involves a right ventricular biopsy via the internal jugular vein, followed by examination of tissue by microscopy. While this approach provides accurate information on anthracycline-induced microscopic changes in heart muscle [29], the technique is limited by its availability, invasive nature, quality of the sample biopsied, and heterogeneity of the myocardial injury [30]. Thus endomyocardial biopsy is unsuitable as a first-line method for cardiotoxicity detection or serial monitoring.

Various imaging modalities such as cardiac magnetic resonance (CMR) imaging, radionuclide angiocardigraphy, and echocardiography are currently available in the clinical setting for detection of cardiac dysfunction. However, the optimal imaging modality for the detection and monitoring for cardiac toxicity must have certain features. In addition to having adequate sensitivity for the detection of subclinical cardiac damage, the imaging modality for detection of chemotherapy cardiotoxicity should also be safe for repeated use without adverse risk to the patient, and should be widely available and cost-effective. To

date, echocardiography has been the most suitable imaging modality clinically available for monitoring for cardiotoxicity. It is a noninvasive technique that can be performed at the bedside and does not expose patients to ionizing radiation. Furthermore, echocardiography provides additional information on valvular and diastolic function.

Echocardiographic measures of cardiac function

LVEF

Current noninvasive methods for detecting cardiotoxicity are based primarily on the detection of a decrement in the left ventricular ejection fraction (LVEF). LVEF is a commonly accepted measure of cardiac systolic function and an accepted indicator of prognosis in patients with heart failure [31]. Classically, cardiotoxicity due to chemotherapy is defined by a decline in LVEF, but because LVEF in healthy individuals can span a broad range, changes in LVEF indicative of LV damage can be appropriately identified only when comparisons are made between baseline and follow-up studies. Although a marked drop in LVEF during or after treatment with chemotherapy has been associated with symptomatic heart failure [32–34], there has been considerable confusion as to what degree of decrease in LVEF constitutes cardiotoxicity. This was highlighted in a recent systematic review of 7 clinical trials by the Cardiac Review and Evaluation Committee, which reported a mix of different LVEF thresholds used to define a significant decline [35]. Studies have relied on varying definitions for cardiotoxicity, including a decrease in LVEF from normal baseline to values below 50%, LVEF decrease of more than 20% from baseline but remaining above the lower limits of normal, LVEF decrease below 45%, reduction of LVEF >5% to LVEF <55% with symptoms of heart failure, or asymptomatic reduction of LVEF of >10% to LVEF <55% [36–38].

Despite the widespread use and acceptance of LVEF as a measure of cardiotoxicity, there is increasing evidence indicating that LVEF is not a sensitive measure of cardiomyocyte injury. In a study involving 158 patients receiving Adriamycin, LVEF did not appear to correlate with cardiac biopsy grades of myocardial damage [30]. In particular, patients were observed whose ejection fraction by nuclear angiography or echocardiography remained within the normal range despite definite evidence of cardiotoxicity on biopsy. These results support the hypothesis that changes in LVEF occur only late in the pathological process after compensatory mechanisms such as cardiac contractile reserve and other compensatory pathways are exhausted.

Nonetheless, pretreatment LVEF is generally accepted as a predictor of subsequent cardiotoxicity, at least in the adult population. A large study involving 1,664 breast cancer patients with baseline LVEF greater than 50% who were treated with anthracyclines or anthracyclines and trastuzumab highlighted that the absolute value of pretreatment LVEF was predictive of later occurrence of heart failure [37]. In contrast, the results of a retrospective review of all echocardiograms and related clinical decisions for 356 children who were followed for anthracycline cardiotoxicity suggested that the predictive value of pretreatment LVEF may not be as significant in the pediatric population. This apparent discrepancy may be due to the fact that adults may manifest subclinical LV dysfunction before treatment more frequently than children.

The prognostic value and the timing of serial measurements of LVEF during treatment to detect and monitor chemotherapy-induced cardiotoxicity remain controversial. A number of relatively small studies of patients receiving anthracyclines correlated declines of LVEF of more than 15% [39], or 4% [40] during treatment, to subsequent development of heart failure, but conflicted with findings from a larger prospective study of 120 patients with breast cancer who were followed for 3 years after treatment with epirubicin. In the larger study, even though the absolute values of LVEF before and immediately after treatment were lower in patients who later developed congestive heart failure, there was no clear association between the percentage decrease in LVEF observed during treatment and subsequent development of symptomatic heart failure within the 3-year follow-up period [33]. The value of LVEF after anthracyclines treatment in the prediction of subsequent cardiotoxicity is more established. In a study involving 850 patients treated with anthracyclines and trastuzumab, 12.5% of patients with LVEF of 50–54%, 3.8% of patients with LVEF of 55–64%, and 0.9% of patients with LVEF >65% developed symptomatic heart failure over a follow-up period of 3 years [37]. The limitation of this parameter is that it is measured after anthracyclines treatment, when the oncology treatment cannot be easily modified and when cardioprotection may not be successful in reversing the LV dysfunction [19]. One of the key challenges in monitoring for chemotherapy-induced cardiotoxicity is reflected in the population of patients whose LVEF remains within the “normal” range despite a decline. For these reasons, there is particular interest in finding other echocardiographic parameters that may be of use in detecting subclinical myocardial dysfunction preceding a drop in LVEF to the abnormal range.

New improvements in LVEF measurements

Contrast Echocardiography

Accurate measurement of LVEF requires sufficient visualization of the endocardial border to enable manual tracing of the end-systolic and end-diastolic volumes from which ejection fraction is calculated. Hence, one disadvantage of echocardiography is that the accuracy of LVEF measurement is dependent on the quality of the images obtained and subject to measurement variability. The use of contrast agents has been reported to convert 74% of non-diagnostic studies into diagnostic studies by improving endocardial visualization [41], reducing intra-observer and inter-observer variability [42], and improving reproducibility. Furthermore, use of contrast not only improves poor baseline image quality, but it can enhance image alignment and help avoid off-axis scanning, thus improving accuracy of measurement for optimal quality images [43, 44]. Despite several multicenter and single-center trials demonstrating the usefulness of contrast in clinical practice, there are still no clear indications in chemotherapy guidelines or general American Society of Echocardiography and European Association of Echocardiography guidelines for the use of contrast to assess for chemotherapy cardiotoxicity [44]. Therefore, the use of contrast in the context of assessing for cardiotoxicity should be in accordance with the guidelines for the use of contrast in 2D echocardiographic imaging, where contrast is indicated if 2 or more segments are not well visualized.

Three-dimensional echocardiography

The lack of accuracy in measures such as LVEF using two-dimensional echocardiography stems from a number of limitations, including the use of mathematical models or geometrical assumptions and ventricular foreshortening. These limitations can be overcome using three-dimensional (3D) echocardiography. Several studies have demonstrated the superiority of 3D imaging to the more routinely used 2D images. Three-dimensional imaging has the advantage of reduced analysis time, higher reproducibility, and lower inter-observer variability [45, 46]. Contrast has also been used to enhance 3D echocardiographic images, particularly in patients with poor images, and to enhance assessment of regional wall motion, although results thus far have been inconsistent. In an early study, improvement in the accuracy and reproducibility of 3D LV volume measurements with contrast reached levels similar to those noted in patients with optimal imaging quality [47], although a more recent study found that contrast 3D echocardiography appeared to have greater variability than both 2D echocardiography with and without contrast and 3D echocardiography without contrast [48]. Nevertheless, contrast 3D may have the best correlation to MRI measurements [49]. A recent study of 56 female patients treated with chemotherapy who were assessed for cardiotoxicity at 4 points over a 1-year follow-up period demonstrated that LVEF measured using 3D acquisition without contrast injection had significantly lower variability (4.9%) compared to the 2D measures (approximately 10%) [58].

Despite the advantages of 3D echocardiography and the use of contrast injections in poorly echogenic patients, the question remains as to whether LVEF is the most sensitive measure of cardiotoxicity. As an example, unlike more sensitive myocardial deformation indices, LVEF measured using 3D echocardiography did not decrease in 35 women undergoing treatment with trastuzumab for breast cancer [50], although this discrepancy may be due to significant interpretive variation [23]. Furthermore, as noted previously, in order for an appreciable drop in LVEF to occur, the myocardium must have undergone sufficient damage; thus there is a need for more sensitive measures of left ventricular function that are able to reflect subclinical cardiotoxicity [23, 24].

Diastolic parameters and chemotherapy cardiotoxicity

Diastolic parameters have been demonstrated to be a more sensitive alternative to LVEF for detection of subtle cardiac dysfunction in several myocardial pathologies, particularly in ischemia [51]. A number of small studies in the 1980s and 1990s revealed abnormalities in diastolic indices following treatment with anthracyclines [52–57]. More recent studies have also reported changes in diastolic parameters such as E/A ratio, Tei index, E/e' , and myocardial performance index compared to normal controls in adults following anthracycline treatment and in survivors of pediatric malignancy treated with anthracyclines [32, 58]. However, these changes in diastolic parameters were still mostly within the normal range and were poorly correlated between resting diastolic abnormalities post-anthracycline treatment and reduction in LV systolic function [59]. Two other recent studies, (one of 68 patients with different malignancies treated with epirubicin [60] and the other comprising 20 breast cancer patients who were treated with anthracyclines [61]) demonstrated early

changes in LV diastolic function. The value of diastolic abnormalities in predicting the development of left ventricular systolic dysfunction at 3 months was suggested in three small studies [55, 59, 61]. However, none of these studies demonstrated conclusively the prognostic value of diastolic parameters in the prediction of late cardiotoxicity. Thus the value of diastolic parameters in diagnosing cardiotoxicity remains controversial.

Stress echo and detection of chemotherapy-induced cardiotoxicity

Exercise and pharmacologic stress-testing may be useful to unmask subclinical abnormalities of LV function induced by chemotherapeutic agents. Interestingly, although exercise capacity is a predictor of prognosis in cancer patients [62], studies examining the benefits of stress-testing in the setting of chemotherapy-induced cardiotoxicity are small and few in number. One such study examined 37 patients who received doxorubicin and were found to have abnormal LVEF at rest within 1 month of undergoing chemotherapy. Based on this study, routine echocardiography was reported to have a sensitivity of 53% and a specificity of 75% for detecting patients at moderate or high risk of developing congestive cardiac failure, even though a follow-up time frame was not clearly outlined. With the addition of exercise, sensitivity increased to 89% but specificity decreased to 41% [63]. Another study demonstrated that 10 of 23 young adults with acute lymphoblastic leukemia treated with anthracyclines before the onset of puberty and followed for a median of 21 years after remission demonstrated normal EF at rest but reduced LVEF during stress [64]. One challenge associated with exercise stress-testing, however, pertains to difficulty in achieving maximal exercise for patients receiving chemotherapy.

There are also conflicting results regarding the effectiveness of dobutamine stress echocardiography in the detection of chemotherapy cardiotoxicity. A very subtle alteration of myocardial contractile reserve during low-dose dobutamine stress echocardiography 7 months after completion of a third cycle of high-dose chemotherapeutic regimen was described in 17% of 49 breast cancer patients to be predictive for developing a significant decline in LVEF 18 months after cessation of high-dose chemotherapy [65]. High-dose dobutamine stress echocardiography also revealed an alteration of the fractional shortening and transmitral E/A ratio in 26 asymptomatic patients treated with high-dose anthracyclines [66]. Conversely, other studies reported no incremental value of this technique for early detection of cardiotoxicity [67, 68]. The lack of any conclusive data, the semi-invasive nature of the test, and the limited repeatability suggest that stress echocardiograms most likely will not be routinely used to monitor for cardiotoxicity.

Strain and strain rate

Myocardial deformation (strain) and deformation rate (strain rate) offer a more sensitive approach than LVEF to measuring cardiotoxicity. These measures can provide a multidimensional evaluation of myocardial mechanics (longitudinal, radial, and circumferential function) and have the added advantage of being able to detect subtle wall motion abnormalities of regional function that do not decrease global LV ejection fraction [24, 69–72]. There is now an emerging body of work in animal models and in humans demonstrating that strain and strain rates are more sensitive measures than LVEF for

detecting early LV dysfunction in subjects treated with anthracyclines alone or in combination with other treatments such as trastuzumab and taxanes [50, 73–75]. To date, a total of 15 peer-reviewed studies report the use of strain, strain rate, and torsion in the detection of subclinical cardiotoxicity in patients treated for cancer. There are studies describing early abnormalities affecting all of the components of strain and strain rate that precede decrease in LVEF, identified both by tissue Doppler imaging (TDI) and speckle tracking (11 studies) during or soon after treatment (Table 1). While some of the studies report decreases in radial and circumferential strain, most studies now report the longitudinal strain exclusively due to the significant variability seen with the other types of strain, particularly with radial strain. Torsion analysis was also used as an alternative to strain in the early detection of subclinical anthracycline cardiotoxicity in 25 patients 1 and 3 months post-chemotherapy, where significant deteriorations in torsion, twisting rate, and untwisting rate were demonstrated 1 month after chemotherapy even though left ventricular dimensions and LVEF did not show any significant change [76]. The long-term effects of anthracyclines have also been identified using strain and strain rate (presently 5 studies), reporting long-term changes in deformation indices following treatment, with mean follow-up periods post-treatment ranging from 4 to 22 years (see Table 1).

There are limited data on the prognostic value of deformation indices. In a mouse model of doxorubicin cardiotoxicity, strain rate predicted the development of late cardiac dysfunction and mortality [77]. The largest human study thus far involved 81 women with breast cancer who were treated with anthracyclines, followed by trastuzumab and Taxol. In this study, a decrease in peak global longitudinal strain from baseline after treatment with anthracyclines as opposed to LVEF and parameters of diastolic function predicted subsequent cardiotoxicity within the 12-month follow-up period with a sensitivity of 74% and a specificity of 73%. [*78] The value of longitudinal strain (and strain rate) was recently confirmed in another study of 81 patients [79]. Other studies also report early decreases in 2D global longitudinal, global, or regional circumferential strain and radial strain in patients treated by anthracyclines, with or without taxanes, and trastuzumab [*75, 78, 80–82].

While a number of small and medium-sized studies report abnormalities of both strain and strain rate in the absence of LVEF changes or before changes in LVEF occur, 2D strain measurements may be less variable than strain rate. Whether strain rate adds significant incremental value to strain measurements is an area that requires further studies. Additionally, of the three major types of strain that can be measured – the longitudinal, radial, and circumferential components – the longitudinal strain appears to be the most reproducible, while the radial strain appears to show the greatest variability. Larger studies with longer follow-up are warranted to definitively demonstrate whether deformation indices can predict the development of cardiotoxicity [*75, 78] and to determine if guided interventions may be of some value.

Nuclear scans

The multiple-gated acquisition (MUGA) scan, a nuclear medicine technique, is commonly used for the detection of cardiac dysfunction following treatment with anthracyclines, as this type of imaging is able to detect the presence of cardiac dysfunction in a highly reproducible

manner [83, 84]. Despite its slightly higher reproducibility and lower variability compared to 2D echocardiography [85], MUGA utilizes the measure of LVEF which, as outlined previously, may not be an accurate measure of subclinical cardiotoxicity. This imaging method is also disadvantaged by the need for radioactivity. Given that each MUGA scan on average delivers a dose of 800 mBecquerels (or 5–12 mSv, which corresponds to 2–3 years of radiation from natural sources), it is not ideal for frequent monitoring due to cumulative radiation exposure [86]. Furthermore, a MUGA scan is not able to provide an assessment of wall thickness with valvular disease which may contribute to LV dysfunction in certain cohorts.

Cardiac Magnetic Resonance

Other modalities such as cardiac magnetic resonance (CMR) imaging may be useful in detecting cardiotoxicity and may be effective in supplementing the information gained from echocardiography or may provide additional insight where echocardiography is limited. CMR is currently considered the gold standard for assessment of LV function [87] and is recognized by the American College of Cardiology (ACC)/American Heart Association (AHA) as a method to diagnose cardiac dysfunction [88]. It has the unique advantage of being able to detect myocardial edema – which may be seen in acute myocardial injury – and fibrosis with the presence of late gadolinium enhancement, and hence may be sensitive enough to detect subclinical myocardial changes prior to the onset of LV dysfunction. To date, the cardiac findings detected on CMR imaging in patients who have been treated with chemotherapy have been from small pilot studies [89]. A recent study comprising 13 patients with normal LV function treated with anthracycline demonstrated no correlation between anthracycline dose and myocardial fibrosis (although there was a relationship with increased LV volume [90]), while a case-control study of 42 patients treated with anthracyclines demonstrated that increased extracellular volume correlated with myocardial fibrosis [91]. The increase in extracellular volume, therefore, may be a noninvasive estimate of diffuse fibrosis. A recent study involving 53 patients treated with anthracyclines demonstrated changes in LV end-systolic volumes, LV strain, pulse wave velocity, and LVEF by CMR within 6 months of receiving low to moderate doses of anthracyclines, but no significant new changes in late gadolinium enhancement indicative of focal scar tissue [92].

Novel quantitative CMR techniques – approaches such as gadolinium-based contrast in T1-mapping – have successfully identified subtle myocardial abnormalities, such as diffuse fibrosis, not visible on delayed hyperenhancement imaging [93, 94]. The degree of diffuse fibrosis measured by cardiac MRI was shown to correlate with LV remodeling in childhood cancer survivors after anthracycline chemotherapy [89, 95]. A more recent study of 91 patients with reduced LVEF post-anthracycline therapy demonstrated an inverse relationship between anthracycline dose and LV mass. In this study, reduced LV mass and greater anthracycline dose were associated with increased rates of major adverse cardiovascular events within a median follow-up period of 88 months [91]. It is evident that further research and larger-scale studies in patients receiving cardiotoxic chemotherapeutic agents are still needed to define the validity and value of these findings in terms of monitoring for cardiotoxicity in the clinical setting. Furthermore, the routine use of CMR for monitoring

cardiotoxicity must be balanced against the limitations of the patient tolerability, cost, and availability of this imaging modality.

Conclusion

The developments in cancer therapy and subsequent rise in number of cancer survivors have resulted in increased rates of cardiac complications. Diagnostic tools are needed to allow for the early detection of cardiotoxicity in order for appropriate management decisions to be made. Echocardiography has a major role to play in this emerging area, with increasing evidence demonstrating that novel echocardiographic techniques can be successfully used for the assessment of cardiac function pretreatment and early in the course of chemotherapy. LVEF is currently used as a prognostic tool, and its value may be improved by the use of 3D echocardiography and contrast injections when visualization is poor. Evidence is accumulating that strain and strain rate are valuable tools for the early detection of LV dysfunction. However, there are still inherent challenges and pitfalls associated with these novel techniques, including the need for extensive experience prior to routine clinical application. Importantly, the optimal timing and number of follow-up imaging studies is still unknown and may depend upon consideration of multiple factors such as treatment regimen, the presence of cardiovascular risk factors, pretreatment, and any early changes in cardiac function during treatment. Finally, larger studies are needed to better understand what defines cardiotoxicity and to evaluate the prognostic role of imaging parameters in order to better inform current clinical practice and guidelines.

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Table 1

Clinical Studies using deformation indices in cancer treatments

Early	Population	Treatment	Timing of echo	Findings deformation	Decrease LVEF	Predictive value/correlations
Ganane <i>et al</i> [96]	13 children Multiple Ca	Dauno or doxo 30–75 mg/m ² × 3	Baseline and <2h after the first 3 doses	Decrease rad SR, S (in flat segment), long SR, S (septum) (1st dose), other segments and circ not done	2 nd dose	
Jurecut <i>et al</i> [97]	16 women >65 yo Breast Ca	Pegylated liposomal doxo 30mg/m ² × 6	Baseline, 7–14d after 3 rd and 6 th dose	Decrease rad SR, S (3 rd), long SR, S (6 th), circ not done	No decrease	
Hare <i>et al</i> [50]	35 women Breast Ca	Doxo 60mg/m ² × 4 epi 100mg/m ² × 3, 5 pts w prior treatment, cycloph, taxanes, trastu	1th	Decrease long SR (3m), radial SR (12m), no decrease S, circ not done	No decrease 2D and 3D	
Cadeddu <i>et al</i> [98]	49 adults, Multiple Ca 25 telmisartan, 24 placebo	Epi 100mg/m ² × 4, other?	Baseline and 7d after each dose (5 time points)	Long SR (decreased 2 dose, normalized after in telmisartan), no decrease S, circ and rad not done	No decrease	
Sawaya <i>et al</i> [75]	43 women Breast Ca	Doxo 60mg/m ² × 4 epi 100mg/m ² × 3, 10 pts w prior treatment, cycloph taxanes, trastu	Baseline before or after anthrac, 3m, 6m	Decrease long S (basal/mid), rad S, circ S (3m). Apex and SR not done	Decrease at 6m.	Long S 3m predicts LVEF decrease 6m
Fallah-Rad <i>et al</i> [80]	42 women Breast Ca	Doxo 60mg/m ² × 4 epi 100mg/m ² × 6, 5 pts w prior treatment, cycloph, taxanes, trastu (treatment duration 15m)	Baseline and every 3m (total of 12m)	Decrease long S, rad S starting at 3m only in pts who developed LVEF decrease and CHF symptoms (24%)	Decrease starting at 6m only in patients who developed symptoms (24%?)	Long S and rad S 3m are decreased in a majority of pts with LVEF decrease and symptoms and in few others
Stoodley <i>et al</i> [99]	52 women Breast Ca	Doxo (236±33 mg/m ²), epi (408±110 mg/m ²)	Baseline, 7d post anthrac	Decrease long S, rad S; no decrease circ S Regional: all but apex (long) sep, inf (rad), sep (circ)	Decrease	
Sawaya <i>et al</i> [78]	81 women Breast Ca	Doxo 60 mg/m ² × 4 or epi 100 mg/m ² × 4 then cycloph, taxanes, trastu (treatment duration 15 m)	Baseline and every 3m (total of 15m)	Decrease long S (basal/mid), rad S, circ S starting at 3m. Apex and SR not done	Decrease starting at 3 months	Long S 3m predicts subsequent LVEF decrease. Long S decreased in all pts with symptoms.
Poterucha <i>et al</i> [81]	19 children Multiple Ca, 19 controls	Doxo, dauno, ida 296±103 mg/m ²	Baseline, 4m, 8m (end treatment)	Decrease long S (4m) Rad, circ, SR not done	No decrease	Mid and apical long S 8m correlated with changes EF 8m
Moroki <i>et al</i> [76]	31 patients (25 analyzable), Multiple Ca	Anthrac 170±87 mg/m ²	Baseline, 1 m, 3m	Decrease long S, torsion, twisting and untwisting rate	No decrease	All correlated with anthrac dose
Late	Population	Treatment	Timing of echo	Findings deformation	Decrease LVEF	Predictive value/correlations

Early	Population	Treatment	Timing of echo	Findings deformation	Decrease LVEF	Predictive value/correlations
Ganane <i>et al</i> [73]	56 patients (4–28yo) Multiple Ca, 32 age-matched controls	Doxo, dauno, ida, median 240mg/m ² (90–300 mg/m ²)	Median 5.2y after treatment (2–15.2y)	Decreased long S and SR (4ch only) and rad S and SR (in flat segment only). Other segments and circ not done	Not decreased	
Cheung <i>et al</i> [100]	45 children AML (15±6y), 44 control	Doxo, dauno median 240 mg/m ² (120–470 mg/m ²), no radioth	Median 6.3y after treatment (2.7–19.8y)	Decrease long S not SR (4ch only), decrease rad S (SR not done), circ S, SR Regional: long bas, mid sept, rad: all segments, circ: all but lat	Decreased	
Ho <i>et al</i> [100]	70 women Breast Ca, 50 controls	Anthracc median 402 mg/m ² (312–580 mg/m ²), 80% cycloph, 51% taxanes, 27% trastu, 27% radioth	Mean 4.2±1.8y after anthrac	Decreased long S, no diff rad S, SR and circ not done	Not decreased	
Tsai <i>et al</i> [101]	47 patients With Hodgkin with radioth and with (27) or without (20) doxo, 20 controls	Doxo 309±92 mg/m ²	Mean 22±3y after treatment	Decreased long S, with diff between with and without doxo. Decreased circ S, rad not done.	Decreased no diff between with or without doxo	

Ca=cancer, AML=acute myeloblastic leukemia, radiother=radiotherapy, Doxo=doxorubicin, dauno=daunorubicin, ida=idarubicin, epi=epirubicin, cycloph=cyclophosphamide, trastu=trastuzumab, anthrac=anthracycines, long=longitudinal, rad=radial, circ=circumferential, S=strain rate, inf=inferior, lat=lateral, mid=midventricular, diff=diffrence, diast=diastolic, LVEF=left ventricular ejection fraction