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STATE-OF-THE-ART PAPERS

Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

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The literature exploring the utility of advanced echocardiographic techniques (such as deformation imaging) in the diagnosis and prognostication of patients receiving potentially cardiotoxic cancer therapy has involved relatively small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy for 3 clinically-relevant scenarios. The systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the EMBASE (1974 to November 2013) and MEDLINE (1946 to November 2013) databases. All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant change in left ventricular ejection fraction (LVEF). Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10% to 15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or heart failure. In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. Thus, this systematic review confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy. (J Am Coll Cardiol 2014;63:2751–68) © 2014 by the American College of Cardiology Foundation

The mortality rate among patients with cancer has decreased over the past 20 to 30 years (1,2). However, cardiac toxicity (cardiotoxicity) from cancer therapy has become a leading cause of morbidity and mortality in survivors (3,4). In patients who develop heart failure (HF) from cancer therapy, the mortality rate is as high as 60% by 2 years (5). Therefore, contemporary management of patients with cancer should include careful consideration of potential cardiotoxicity during therapy, with a focus on early detection and intervention (6).

Historically, several definitions of cardiotoxicity have been proposed (7). The most commonly used definition is a ≥5% reduction in symptomatic patients (or ≥10% reduction in asymptomatic patients) in the left ventricular ejection fraction (LVEF) from baseline to an LVEF <55% (8). Early detection of cardiotoxicity has predominantly relied upon serial cardiac imaging to identify a reduction in left ventricular (LV) function without signs or symptoms of heart failure (stage B HF) (9). The use of LVEF has important limitations. First, the measurement of LVEF is subject to technique-related variability, which can be higher than the thresholds used to define cardiotoxicity (8,10). Second, the reduction in LVEF is often a late phenomenon, with failure to recover systolic function in up to 58% of patients despite intervention (11–15). Hence, there has been a growing interest in markers of early myocardial changes (i.e.,

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Abbreviations and Acronyms

2D = 2-dimensional
3D = 3-dimensional
echo = echocardiography
GCS = global circumferential strain
GLS = global longitudinal strain
GRS = global radial strain
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
RT = radiotherapy
SR = strain rate
STE = speckle tracking echocardiography
TDI = tissue Doppler imaging

changes with normal LVEF) that may predict the development of subsequent LVEF reduction or the progression to HF, so that preventive strategies with established cardioprotective medications such as beta-blockers, angiotensin-converting enzyme inhibitors, or dexrazoxane could be implemented.

Myocardial deformation can now be readily measured during routine echocardiography, and its value in detecting subclinical ventricular dysfunction, as well as its prognostic value, has been demonstrated in several clinical scenarios (16). A growing body of literature supports the use of myocardial deformation parameters to detect early myocardial injury and to forecast ventricular dysfunction (cardiotoxicity) in patients receiving cancer therapy. This systematic review seeks to summarize the existing data for the following clinically relevant scenarios: 1) detection of early myocardial changes; 2) prediction of subsequent cardiotoxicity; and 3) detection of late consequences of therapy (>1 year post-treatment).

Methods

Search strategy. The search method adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews (17). An EMBASE (1974 to November 7, 2013) and MEDLINE (1946 to November 7, 2013) search was performed by an experienced information specialist using the terms "antineoplastic agents," "radiotherapy," "cardiac toxicity," "echocardiography," and their variations as key words in the OVID search engine without language or species limitations (Fig. 1). References of all selected papers and reviews were screened to identify additional studies.

Inclusion and exclusion criteria. Any prospective or retrospective study of at least 10 patients that used echocardiographic (echo)-based myocardial deformation parameters as the primary method to detect cardiotoxicity during or after cancer therapy was included. In order to be included in this systematic review, studies had to provide data on changes in deformation parameters and LVEF during therapy. Studies that did not provide data on the type of chemotherapy or the timing of imaging were excluded.

Myocardial deformation. Echocardiographic measures of LV strain have become a robust method to measure myocardial deformation (16,18). Strain is a dimensionless index reflecting the total *deformation* of the ventricular myocardium during a cardiac cycle as a percentage of its initial length (reported as percentage). Strain rate (SR) is the *rate of*

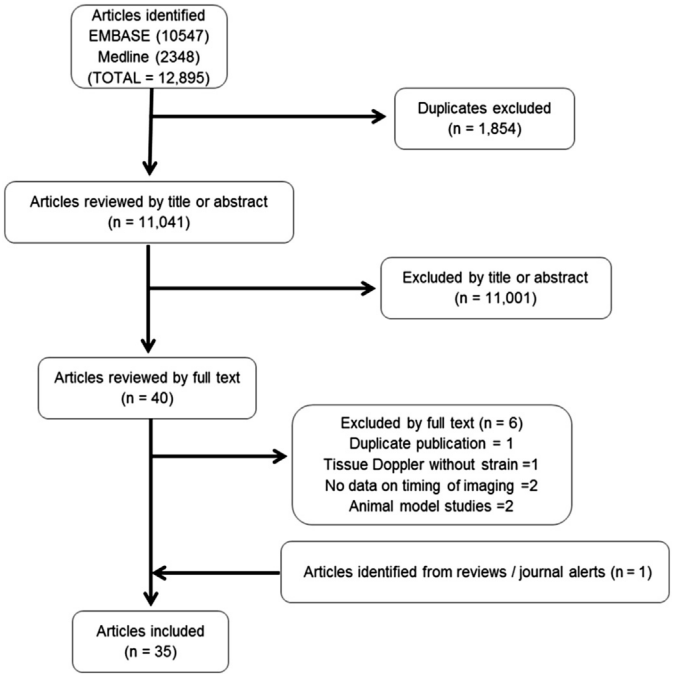

Figure 1 Literature Search Flow Diagram

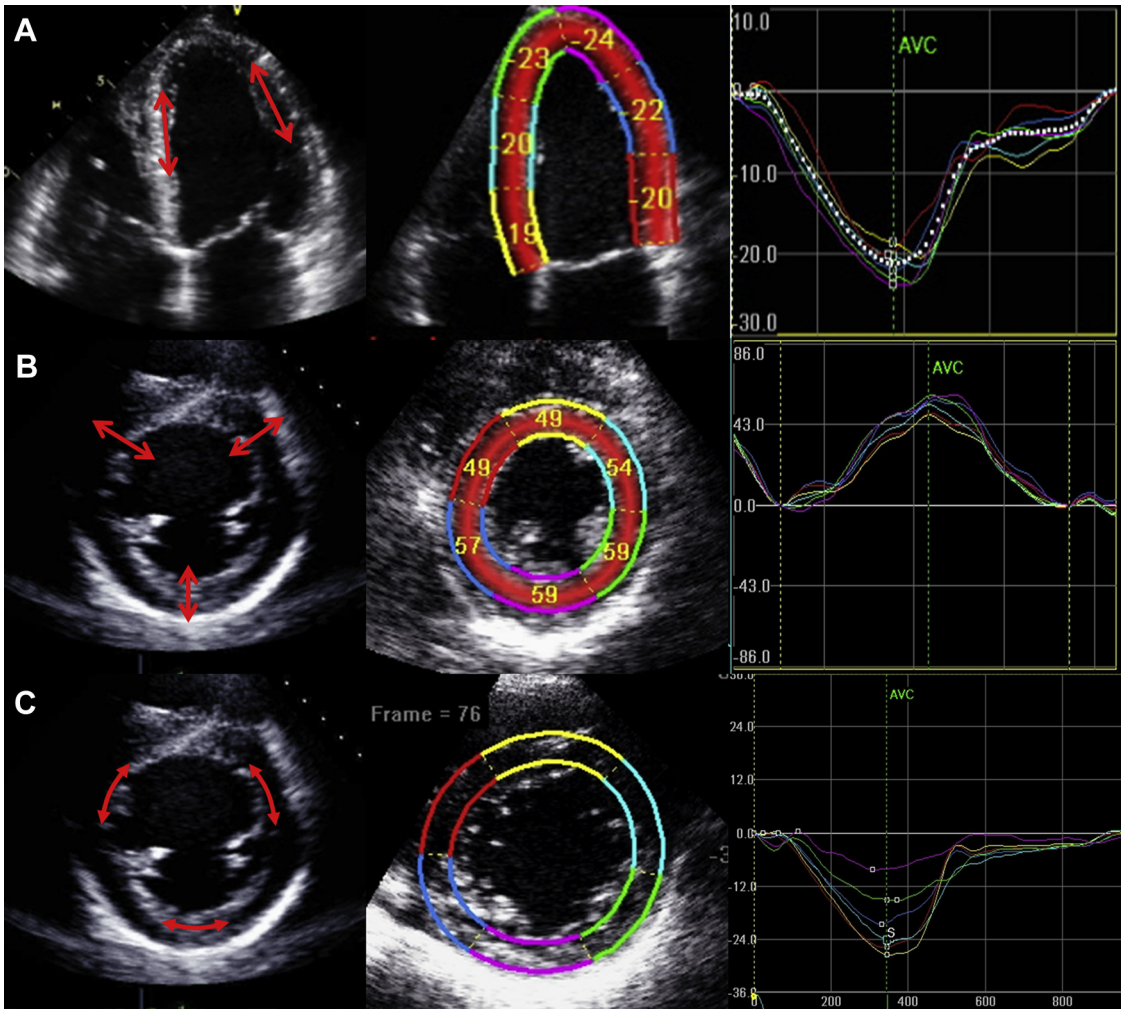

Figure 2 **Speckle Tracking Echocardiography-Based Peak Systolic Strain Measurements in a Patient With Breast Cancer Prior to Initiation of Cytotoxic Chemotherapy**

(A) Global longitudinal strain (GLS), **(B)** global radial strain (GRS), and **(C)** global circumferential strain (GCS). The **left panels** show the direction (**arrows** demonstrate the direction) in which various strain parameters are being measured. The **middle panels** demonstrate the segmental strain values (except for circumferential strain). The **right panels** illustrate the regional strain curves. Circumferential strain curves in the **bottom right panel** highlight the segmental variability in measurements, illustrating the challenges with this specific strain measurement. Reported normal value for GLS is −19.7% (95% confidence interval [CI]: −20.4% to −18.9%), for GRS 47.3% (95% CI: 43.6% to 51.0%), and GCS −23.3% (95% CI: −24.6% to −22.1%) (68). AVC = aortic valve closure.

deformation or stretch (reported as s^{-1}) (18). Both strain and SR can be measured in the longitudinal, radial, and circumferential directions (Fig. 2) (16,18). A key advantage of strain or SR measurement is its ability to differentiate active versus passive movement within a myocardial segment, allowing for the analysis of regional myocardial deformation independent of the translational motion of the heart. Although neither LV strain nor SR are load independent, peak systolic SR correlates well to load-independent indexes of contractility and, hence, provides valuable information about intrinsic contractile function (18,19). LV torsion is a measure of the maximum instantaneous difference in the rotation of the base of the heart in comparison to the apex (20). This is then followed by untwisting contributing to ventricular filling. Peak systolic twisting velocity measures the peak positive rate of torsional deformation during the ejection phase, whereas peak diastolic untwisting velocity measures the peak negative rate of torsional deformation during early diastole (18,20,21). Currently myocardial deformation can be measured using tissue Doppler imaging (TDI) (Fig. 3) and 2- and 3-dimensional speckle tracking echocardiography (STE) (Fig. 2) (18).

Outcomes. Outcomes of interest were absolute and percentage reductions in myocardial deformation parameters during or after therapy and performance of these parameters in predicting subsequent cardiotoxicity (defined in the preceding text).

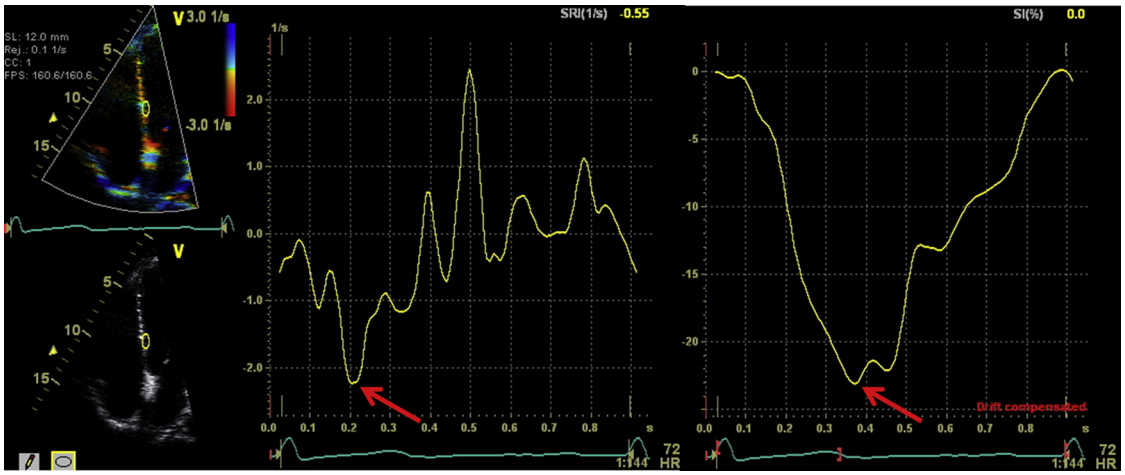

Figure 3 Tissue Doppler-Based Strain Assessment

(Left) Tissue Doppler image of the interventricular septum and the region of interest **(yellow oval)** from where the strain and strain rate values were obtained. **(Middle)** Longitudinal strain rate curve; and **(right)** longitudinal strain of the basal interventricular septum. The **arrows** illustrate the points on the curve where the peak systolic longitudinal strain rate and longitudinal strain would be recorded.

Data extraction. All relevant data were extracted using a standard data form by one reviewer (P.T.) and verified by a second reviewer (F.P.). All discrepancies were mutually reviewed and resolved by consensus. Multiple authors were contacted for clarification of data in various publications. We excluded 2 studies without data on timing of echocardiography, as we were unable to make contact with the authors for this additional data (22,23). The following data were extracted: year of publication, number of patients, cancer type, age, sex, chemotherapy used and doses, type and timing of imaging, changes in deformation parameters, and prognostic data.

Results

Detection of early myocardial changes during cancer chemotherapy. Thirteen peer-reviewed publications, involving approximately 384 patients treated with anthracycline-containing regimens, assessed various echo-based myocardial deformation parameters to detect early myocardial changes without providing data on prognosis (24–36). These were single-center cohort studies that primarily focused on breast and hematological malignancies. The mean age ranged from 49 to 70 years (56% to 100% female) in the adult studies, and from 9 to 15 years (23% to 48% female) in the pediatric studies. Earlier work used TDI-based strain, whereas the more contemporary studies have generally used 2-dimensional (2D) STE (Table 1). Despite heterogeneity in the data with respect to patient age, types of cancer, strain techniques, and timing of follow-up, the studies all uniformly demonstrate that changes in myocardial deformation occur earlier than a change in LVEF and at anthracycline doses lower than what was historically thought to be cardiotoxic (e.g., 200 mg/m^2 of epirubicin). The degree of change in myocardial deformation parameters amongst the studies has depended on the technique used (2D STE vs TDI) and the type of strain measured.

2D-BASED STRAIN. In the absence of a reduction in LVEF, a 2D STE–measured reduction in peak systolic global longitudinal strain (GLS) between 9% and 19% seems to be common either during or immediately after anthracycline therapy (Table 1). Although a reduction in peak systolic global radial strain (GRS) of 6% to 17% (34,37–40) or peak systolic global circumferential strain (GCS) of 11% to 16.7% (38,40,41) may also indicate early myocardial changes, these changes have been less consistent (30,34,41,42). An important limitation of both GRS and GCS is the lower reproducibility of these measurements, which makes the identification of changes from pre- to post-chemotherapy more challenging. Similarly, SR measurements using STE have important technical limitations. Although rotational myocardial deformation and early diastolic SR are potential markers of early myocardial changes (30,33,42), neither of these parameters are currently sufficiently feasible and reliable for routine clinical application.

TDI-BASED STRAIN. When using TDI-based strain, longitudinal SR of the basal interventricular septum consistently demonstrates a reduction (ranging from 9% to 20%) between pre-therapy and low doses of anthracyclines (e.g., 200 mg/m^2 of epirubicin). In contrast, changes in longitudinal strain (LS) have not been a reliable measure of early injury, especially when measurements are obtained only from the basal interventricular septum (25,28,29). However, when multiple septal segments or all 18 myocardial segments are

used, reductions in LS of 15% and 17% were seen after first dose of anthracycline (26) and 6 cycles of liposomal doxorubicin (27), respectively. Radial strain parameters are known to be variable. However, a fall in radial SR of 13% to 28% (26,27,35,43) or radial strain of 24% to 35% of the mid inferior-lateral walls also seems to detect early myocardial changes, although the latter has not been consistent (43).

Changes in strain values appear to be regional, although the segmental variation has been inconsistent among studies (31,34). Unfortunately, although biopsy changes have been documented with early injury, the clinical application of biopsy is neither relevant nor feasible, so whether the changes in myocardial deformation truly represent cardiac injury cannot be proven. However, several studies have shown a positive association between higher doses of anthracycline (30–32) or serum markers such as reactive oxygen species levels and troponins (25,28,29,36,40,41) and larger reductions in strain or SR measurements, suggesting that there is biological plausibility for these findings.

Prognostic value of myocardial deformation parameters to detect cardiotoxicity. Although the early detection of myocardial changes appears to be conceptually important, the real value of these changes lie in their ability to prognosticate clinically-relevant outcomes such as subsequent LVEF reduction or the development of HF. The prognostic value has been evaluated in 8 studies (Table 2) involving approximately 452 patients (age range from 47 to 51 years, 58% to 100% women) (37–44). Published studies have either been single-center (37–39,42,44) or multicenter (40,41) cohort studies and, other than the 3 recent studies (37–39), all have only included patients with breast cancer. Most (40–44) have included patients with human epidermal receptor 2 overexpressing breast cancers, with all patients receiving trastuzumab and the majority receiving anthracyclines. However, important differences between studies (Table 2) include differences in duration of follow-up (6 months vs. 12 to 15 months), treatment regimens (proportion receiving anthracycline and radiotherapy, cumulative epirubicin dose, and use of taxanes), the definition of the "baseline" echo (pre- vs. post-anthracyclines), and the number of apical views used to measure strain (all 3 views versus the basal and mid segments of just 2 views). The definition of cardiotoxicity was, however, similar between the studies and the incidence of cardiotoxicity ranged between 13% and 32%, likely relating to differences in baseline cardiac risk factors, treatment regimens, and duration of follow-up.

An early fall in GLS by STE between 10% and 15% predicts subsequent cardiotoxicity (including both asymptomatic and symptomatic LV dysfunction) (37,39–42,44) (Fig. 4, Online Videos 1, 2, and 3). The 95% confidence interval for the optimal GLS cutoff extends from 8.3% to 14.6% (42). The reported sensitivity and specificity of GLS to predict cardiotoxicity (Table 3) is likely optimistic, given the small sample sizes and few cardiotoxicity events. In patients where a relative change in GLS was unavailable, absolute levels of GLS $>-19\%$ and -20.5% early during therapy have been associated with cardiotoxicity (40,42). In contrast, GRS was not predictive of cardiotoxicity in the 2 larger studies (40,42), whereas GCS was not predictive in any studies. However, a combined parameter of GLS and LV twist (GLS $\times$ LV twist) appears to be the best predictor of subsequent cardiotoxicity, with test characteristics superior to even GLS (Table 3) (39). This latter parameter provides a combined assessment of LV subendocardial function (GLS) and subepicardial function (LV twist), potentially providing a more sensitive measure of early myocardial changes, although this needs confirmation in other studies. A summary of myocardial strain and SR cutoff values to predict cardiotoxicity from the preceding studies is provided in Table 3.

Detection of late subclinical consequences of cancer therapy. After chemotherapy regimens are completed, there are limited recommendations as to appropriate follow-up (Online Table A). However, specifically with anthracyclines, cardiotoxicity can be first detected several years after therapy (45,46). Hence, there has been a growing interest in detecting subclinical cardiotoxicity in survivors using myocardial deformation parameters with the hope of identifying high-risk patients and providing targeted therapy with cardioprotective medications to ultimately prevent further LV remodeling and progression to HF syndrome.

There are 9 published case-control studies that have used various myocardial deformation parameters to detect late subclinical cardiac injury, consisting of approximately 436 patients (median age 12.7 years, 30% to 100% women) (21,47–54), but none have provided data on prediction of subsequent cardiac events (Table 4). The only study in adult breast cancer survivors (49) showed a 7.7% reduction in GLS in patients compared with controls when imaged between 3.1 and 4.2 years post-therapy, with lower GLS values with adjuvant trastuzumab use. All other studies have been in survivors of various pediatric cancers treated with anthracyclines (21,47,48,50–54). The time between completion of therapy to cardiac imaging ranged from 8 months to 29.2 years. All studies have compared findings in patients with controls, with none comparing identified abnormalities to pre-therapy imaging. Therefore, it is unknown whether some of these patients had pre-therapy ventricular dysfunction. Two studies using TDI-based strain (48,52) have demonstrated a reduction in LS and longitudinal SR of the interventricular septum, LV lateral wall, and right ventricular free wall. Despite a difference in cumulative anthracycline doses between the studies (<300 mg/m^2 vs. >350 mg/m^2), both illustrated reductions in strain values, emphasizing that myocardial injury can occur at lower anthracycline doses as well. This variability in doses may also explain variations in the incidence of LV dysfunction of between 5% and 16%. Both studies have shown that anthracyclines can also affect right ventricular function, a concept that has not been adequately explored.

Table 1 Summary of Studies That Have Used Advanced Myocardial Mechanics to Illustrate Early Myocardial Injury During Cancer Chemotherapy

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Pre-Echo	Post-Echo	Vendor, Reproducibility
Stoodley et al. 2013 (32)*	STE	Breast	78	52 ± 10	98.7	Doxorubicin 81%, epirubicin 19%	Pre- and 1-week post-anthracycline, then at 6 and 12 months	GLS −18.6 ± 2.4%	GLS −17.0 ± 2.2% (post-anthracycline)	GE, interobserver GLS COV 9.0%, intraobserver 9.9%
Stoodley et al. 2013 (33)*	STE	Breast	52	49 ± 9	100	Doxorubicin 77% epirubicin in 23%	Pre- and 1-week post-anthracycline	e-SR 1.0 ± 0.2/s	e-SR 0.9 ± 0.2/s	GE, interobserver and intraobserver as mean difference (SD) for early 0.08 (0.12/s) and 0.01 (0.05/s) and late diastolic SR 0.06 (0.12/s) and 0.01 (0.08/s), GLS −1.73 (1.0%) and −0.86 (0.59%)
Zhang et al. 2012 (36)	TDI	Breast	60	54 ± 12	100	Epirubicin	Pre-treatment and at 7 days (post reaching 100, 200, 300, and 400 mg/m^2)	LSR −1.69 ± 0.64/s	LSR −1.35 ± 0.36/s (at 200 mg/m^2)	Philips, interobserver and intraobserver of LSR as percentage of mean of 2 repeated measures: 10 ± 4% and 11± 3%.
Motoki et al. 2012 (30)	STE	NHL, AML, ALL	25	58 ± 11	56	Anthracyclines	Pre-treatment and at 1 and 3 months	No values provided	Reduced torsion, twisting and untwisting rate, and GLS by 1 month	GE, interobserver and intraobserver variability as bias ±1.96 (SD) for LV torsion were −0.26° (1.59) and −0.21° (1.39).
Stoodley et al. 2011 (34)*	STE	Breast	52	49 ± 9	100	Doxorubicin and epirubicin	Pre- and 1-week post-anthracycline	GLS −17.8 ± 2.1% GRS 40.5 ± 11.4%	GLS −16.3 ± 2.0% GRS 34.3 ± 11.4%	GE, mean (SD) interobserver and intraobserver for GLS −1.73 (1.0%) and −0.86 (0.59%). GRS 5.0 (7.8%) and 3.4 (12.4%). GCS 1.48 (1.24%) and 1.62 (1.10%)
Cadeddu et al. 2010 (25)	TDI	Multiple	49	56 ± 13	76	Epirubicin	Pre-treatment and at 7 days (post 100, 200, 300, and 400 mg/m^2)	LSR −1.78 ± 0.24/s	LSR −1.41 ± 0.31/s (by 200 mg/m^2)	Toshiba, no data

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Table 1 Continued

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Pre-Echo	Post-Echo	Vendor, Reproducibility
Wildiers et al. 2008 (35)†	TDI	Breast	16	Median 69 (range 65–74)	100	Liposomal doxorubicin	Pre-treatment, before 4th cycle, after 6th cycle	RS 50 ± 12% RSR 4.6 ± 1.2/s	RS 33 ± 8% RSR 3.3 ± 1.0/s after 6th cycle	GE, no data
Mantovani et al. 2008 (28)‡	TDI	Multiple	31	59 ± 14	74	Epirubicin	Pre-treatment, at 7 days post 100, 200, 300, and 400 mg/m^2, and at 3, 6, 12, and 18 months	LSR −1.79 ± 0.06/s	LSR −1.45 ± 0.15/s (at 200 mg/m^2)	Toshiba, no data
Jurcut et al. 2008 (27)†	TDI	Breast	16	69.8 ± 3.1	100	Liposomal doxorubicin	Pre-treatment and within 7–14 days after 3rd and 6th cycles	RS 50.1 ± 11.6% RSR 4.57 ± 1.18/s GLS −22.7 ± 2.8%	RS 37.7 ± 10.2% RSR 3.64 ± 1.52/s (after 3 cycles) GLS −18.8 ± 2.8% (after 6 cycles)	GE, mean relative intraobserver variability was 8.3% of strain and 9.1% for strain rate
Mercuro et al. 2007 (29)‡	TDI	Multiple	16	56 ± 3	81	Epirubicin	Pre-therapy and after 200, 300, and 400 mg/m^2	LSR −1.82 ± 0.57/s	LSR −1.45 ± 0.44/s (after 200 mg/m^2)	Toshiba, no data
Poterucha et al. 2012 (31)	STE	Various pediatric	19, 19 controls	15.3 ± 3	37	Doxorubicin (89%), idarubicin (32%), danorubicin (5%)	Before and 4 and 8 months after starting anthracycline	GLS −19.9 ± 2.1%	GLS −18.1 ± 2.5% (by 4 months)	GE, GLS, COV interobserver 7.2%, intraobserver 10%
Al-Biltagi et al. 2012 (24)	STE	ALL	25, 30 controls	9 ± 2.6	48	Doxorubicin	Pre-treatment and within 1 week of starting	GLS −18.7 ± 4.5%	GLS −15.1 ± 2.5%	GE, no data
Ganame et al. 2007 (26)	TDI	Multiple	13	10.7 ± 3.8	23	Danorubicin, doxorubicin, idarubicin	Before first dose, then after 1st, 2nd, and 3rd doses	LS −27 ± 5% LSR −2.2 ± 0.4% RS 74 ± 14% RSR 5.4 ± 0.9/s	LS −23 ± 7% LSR −2.0 ± 0.4% RS 56 ± 11% RSR 4.6 ± 0.8/s (after first dose)	GE, mean difference (95% CI): intra/interobserver LS 2.67 (3.69%)/5.14 (3.73%), LSR 0.13 (0.13/s)/0.44 (0.41/s), RS 2.03 (2.81%)/6.44 (8.98%), RSR 0.44 (0.36/s)/0.50 (0.33/s)

Studies in adult patients are presented first, followed by studies in pediatric patients. Details in Online Table A. The word global was used for all STE-based strain as multiple segments were used; for TDI strain, unless multiple segments were used, the character G is removed to illustrate that this is not "global" strain. *‡Study from same group with likely overlap in the patients. †Study of the same patients. Please see Online Table B for further study details.

ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukemia; CI = confidence interval; COV = coefficient of variance; e-SR = early diastolic strain rate; GCS = global circumferential strain; GCSR = global circumferential strain rate; GE = General Electric; GLS = global longitudinal strain; GLSR = global longitudinal strain rate; GRS = global radial strain; GRSR = global radial strain rate; IVS = interventricular septum; LS = longitudinal strain; LSR = longitudinal strain rate; NHL = non-Hodgkin's lymphoma; RS = radial strain; RSR = radial strain rate; SAX = short axis; SR = strain rate; STE = speckle-tracking echocardiography; TDI = tissue Doppler imaging.

Table 2 Summary of Studies That Have Used Early Changes in Advanced Myocardial Mechanics to Predict Subsequent Cardiotoxicity

Study First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Pre-Echo	Post-Echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Mornos et al. 2013 (39)	STE	Breast lymphoma, ALL, AML, osteosarcoma	74 & 37 controls	51 ± 11	58	Anthracyclines	Pre, post, and 6, 12, 24, and 52 weeks	GLS -21·2 ± 2·5% GRS 47·8 ± 5.3%	GLS -19·0 ± 2·4% GRS 41·1 ± 5·4% (6 weeks)	13	ΔGLS 2.8% (13·1% relative), sensitivity 79% and specificity 73% at 6 weeks for toxicity at 24 −52 weeks	GE, intraobserver ICC for GLS 0.95, interobserver 0.91
Negishi et al. 2013 (42)	STE	Breast	81	50 ± 11	100	Trastuzumab, doxorubicin 46%, RT 62%	Pre-trastuzumab, and 6 and 12 months later	GLS -20.7 ± 2.6% GLSR −1.17 ± 0.24/s GLSR-E 1.36 ± 0.28/s	GLS −18.3 ± 2.1% GLSR −1.00 ± 0.15/s GLSR-E 1.20 ± 0.28/s (at 6 months in patients who later had toxicity)	30	GLS change ≥11% between pre-treatment and 6 months, sensitivity 65%, spec 95% or absolute GLS >−20.5 at 6 months, sensitivity 96%, spec 66% for toxicity at 12 months	GE, intraobserver ICC (95% CI) for GLS 0.85 (0.54%–0.96%), GLSR 0.91 (0.70–0.98/s), GLSR-E 0.90 (0.66–0.97/s). Interobserver 0.71 (0.23%–0.92%), 0.85 (0.28–0.97/s), 0.87 (0.56–0.97/s)
Baratta et al. 2013 (37)	STE	Breast	36	47 ± 16	58	Doxorubicin 58% trastuzumab 22%	Pre- and 2,3,4, and 6 months after start of therapy	GLS −20.3 ± 2.7% GRS 53.1 ± 4%	GLS −18.9 ± 2.5% (3 months) GRS 50 ± 3.9% (4 months)	19.4	GLS fall ≥15% at 3 months, sensitivity 86%, spec 86%. GRS fall ≥10% at 4 months, sensitivity 86% spec 69%	GE, mean (SD) absolute difference inter/intraobserver GLS 0.6 (1.4%)/0.2 (1.1%), GRS 3.4 (7.1%)/3.2 (6.6%)
Sawaya et al. 2012 (40)	STE	Breast	81	50 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 60%	Pre-anthracycline and at 3, 6, 9, 12, and 15 months	GLS −21 ± 2% GRS 53 ± 15% GCS −18 ± 4%	GLS −19 ± 2% GRS 50 ± 17% GCS −16 ± 4% At 3 months	32	Absolute GLS < −19% at 3 months, sensitivity 74%, spec 73% for subsequent toxicity	GE, same variability as in previous study (41)
Sawaya et al. 2011 (41)	STE	Breast	43	49 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 11.6%	Pre-anthracycline and at 3 and 6 months	GLS −20.5 ± 2.2% GCS 18 ± 4%	GLS −19.3 ± 2.4% GCS 15 ± 4%	21	GLS fall >10% at 3 months, sensitivity 78%, spec 79% for toxicity at 6 months	GE, intraobserver as absolute mean error (SD) GLS −0.14 (1.1%), interobserver 0.5 (1.5%)

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Table 2 Continued

Study First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Pre-Echo	Post-Echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Fallah-Rad et al. 2011 (44)	STE	Breast	42	47 ± 9	100	Epirubicin, doxorubicin, trastuzumab, RT 98%	Pre-anthracycline, Pre-trastuzumab and at 3, 6, 9, and 12 months	GLS −19.8 ± 1.8% GRS 41.4 ± 15.2%	GLS −16.4 ± 1.1% GRS 34.5 ± 15.2% (3 months into trastuzumab)	24	Absolute GLS fall of 2.0%, sensitivity 79%, spec 82%. Absolute GRS fall of 0.8%, sensitivity 86%, spec 81% for subsequent toxicity	GE, intraobserver as ICC (COV) GLS 0.94 (3.5%), GRS 0.91 (3.2%). Interobserver 0.90 (5.2%), 0.82 (5.4%)
Hare et al. 2009 (43)	TDI and STE	Breast	35	51 ± 8	100	Doxorubicin, epirubicin, trastuzumab, RT 77%	Pre- and/or post-anthracycline and at 3-month intervals	STE GLSR −1.30 ± 0.21/s STE RSR 2.02 ± 0.61/s	STE GLSR −1.24 ± 0.18/s (by 3 months) STE RSR 1.75 ± 0.41/s (by 6–9 months)	14	A >1 SD drop in GLSR (toxicity at mean follow-up of 22 ± 6 months)	GE, intra/interobserver as ICC for 2D GLS 0.94/0.91, GLSR 0.94/0.91, GRS 0.86/0.50, GRSR 0.83/0.65
Mavinkurve-Groothuis et al. 2013 (38)	STE	ALL	60, 60 controls	6 (2.2–15.4)	38	Anthracycline, RT 100%	Pre-anthracycline, 10 weeks, and 12 months	GLS −18.2 ± 3.1% GLSR −1.44 ± 0.3/s GRS 66.8 ± 1% GCS −19.4 ± 4.3	GLS −16.7 ± 5.2% GLSR −1.20 ± 0.4/s GRS 55.2 ± 16% GCS −16.9 ± 3.1% (by 12 months)	0	Strain values were not predictive of decrease in LV fractional shortening	GE, no data

Studies in adult patients are presented first followed by studies in pediatric patients. Details are in Online Table B. Please see Online Table C for further study details.

4CH = 4-chamber; GLSR-E = early diastolic global longitudinal strain rate; ICC = intraclass correlation coefficient; LV = left ventricular; RT = radiotherapy; other abbreviations as in Table 1.

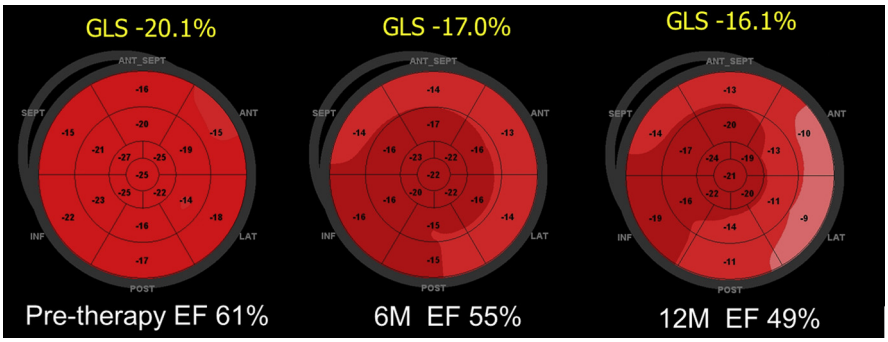

Figure 4 The Utility of Early Strain Changes to Predict Subsequent Cardiotoxicity

The images demonstrate a "bull's eye" plot of strain values for each of the 17 myocardial segments. A patient receiving cytotoxic chemotherapy had normal baseline strain and left ventricular (LV) ejection fraction (EF) **(left)**. Six months into therapy, the LVEF dropped by 6% but did not meet criteria for cardiotoxicity. However, the peak systolic global longitudinal strain (GLS) fell by 15.4% (a significant change based on the literature). Then, by 12 months there was a clinically significant fall in LVEF meeting the criteria for cardiotoxicity. See Online Videos 1, 2, and 3 for 4-chamber movie images demonstrating the changes in function. LVEF was calculated using the Biplane Simpson's method. 6M = 6 months; 12M = 12 months.

The remaining 6 pediatric studies have used STE-based strain, but with significant heterogeneity with respect to the types of cancers, time of imaging, cumulative anthracycline dose, and the type of strain measurements. However, in anthracycline-treated survivors, a reduction was reported in most strain and SR parameters, ranging from 6.6%

Table 3 Early Predictors of Cardiotoxicity

Studies/First Author (Ref. #)	Sensitivity	Specificity	PPV	NPV
Fallah-Rad et al. (44)*				
2% absolute (10.1% relative) decrease in LS	79%	82%	60%	92%
0.8% decrease in RS	86%	81%	60%	95%
Sawaya et al. (41)†				
10% decrease in GLS	78%	79%	50%	93%
Elevated hsTnI	67%	82%	50%	90%
10% decrease in GLS and elevated hsTnI	55%	97%	83%	89%
10% decrease in GLS or elevated hsTnI	89%	65%	40%	97%
Sawaya et al. (40)†				
GLS <19%	74%	73%	53%	87%
hsTnI >30 pg/ml	48%	73%	44%	77%
LS <19% and usTnI >30 pg/ml	35%	93%	67%	77%
LS <19% or usTnI >30 pg/ml	87%	53%	43%	91%
Negishi et al. (42)‡				
11% reduction in global GLS	65%	95%	—	—
3.6% reduction in global GLSR early diastole	82%	67%	—	—
6.4% reduction in global GLSR	73%	67%	—	—
Absolute GLS at 6 months <−20.5%	96%	66%	—	—
Mornos et al. (39)§				
71% × ° reduction in GLS × LV twist	90%	82%	—	—
2.77% absolute (~13% relative) reduction in GLS	79%	73%	—	—
1.75° absolute reduction in apical rotation	70%	78%	—	—
Baratta et al. (37)‖				
≥15% decrease in GLS	86%	86%	—	—
≥10% decrease in GRS	86%	69%	—	—
≥15% decrease in GLS AND ≥10% decrease in GRS	71%	97%	—	—

*Difference between patients with cardiomyopathy versus without cardiomyopathy at 3 months after trastuzumab initiation following AC therapy. †Difference between baseline and after completion of AC therapy at 3 months, before trastuzumab initiation. ‡Difference between baseline and at 6 months after trastuzumab initiation (± AC therapy) in patients with cardiomyopathy. §Difference between pre-anthracyclines and 6 weeks into anthracycline therapy. ‖Difference between pre-anthracyclines and 3 months into anthracycline therapy for GLS, 4 months for GRS, and 4 months for the combined change.

GLS = global longitudinal strain; hsTnI = high-sensitivity troponin I; NPV = negative predictive value; PPV = positive predictive value; RS = radial strain; usTnI = ultrasensitive troponin I; other abbreviations as in Tables 1 and 2.

to 29.6% compared with controls (21,47,50,51,53,54). Possible reasons for this variation could include differences in follow-up duration, maximal dose of anthracyclines, and radiotherapy, and inclusion of patients with overt LV systolic dysfunction. There appears to be a discrepancy amongst studies with respect to the value of longitudinal deformation parameters in survivors, although radial and circumferential strain appear to be consistently abnormal. Similar to studies during therapy, the change in mechanics is regional, with the interventricular septum being the most consistently affected (47,51,53).

Rotational deformation parameters have also been assessed in survivors by the same group in 3 publications (21,53,54). Although there were differences in types of cancers, all of the included patients received similar anthracycline doses and were imaged at similar time points post-therapy. At a segmental level, the apical rather than basal rotational deformation appears to be consistently affected. Furthermore, a reduction in left ventricular peak torsion has been described (21). In layer-specific strain analysis, the changes in rotational parameters seem to vary across myocardial layers (53). With 3-dimensional (3D) echocardiography, global 3D systolic strain, twist, and torsion are reported to be reduced compared with controls (54).

Detection of myocardial injury from radiotherapy. There is limited literature on the detection of early myocardial changes from radiotherapy (RT) (Table 5), with data on approximately 232 patients (age 48 to 51 years, 40% to 100% of women). Two studies (55,56) in patients with breast cancer illustrated a relative fall in GLS of 9.8% to 10.2% and GLSR of 12.8% immediately after RT when compared with pre-therapy using TDI-based strain. The mean LV specific dose in these 2 studies ranged from 6.7 to 9.0 Gy. The strain drop was only seen in women with left-sided breast cancer (and not in those with right-sided cancer) and was only limited to the anterior LV myocardial segments, which received the highest radiation doses. Patients in both studies also received anthracycline and some received trastuzumab, making it difficult to differentiate the effect of RT from chemotherapy. This is important as the effects of RT and chemotherapy are likely additive (57). In patients with Hodgkin's lymphoma treated with RT with or without doxorubicin 22 years previously, the reduction in STE-based GLS was highest in patients who had RT with doxorubicin (21%) and less in those who only had RT (14%), compared with controls. In 2 older studies (58,59), in patients with various cancers, a reduction in longitudinal systolic and diastolic strain was only present after 50 Gy of thoracic RT in patients not exposed to chemotherapy. However, the impact of radiation on measures of myocardial deformation has not been consistent with 3 other studies, which focused primarily on the toxicity of chemotherapy, not identifying an interaction between radiotherapy and strain (32,43,49). However, none of these latter studies provided data on radiation dose or the side of radiotherapy, both of which are important in the development of cardiac injury.

Discussion

There are several key messages in this review. Reductions in echocardiographic measures of myocardial deformation parameters are a sign of subclinical myocardial changes from cancer therapy and occur prior to any change in LVEF as assessed by conventional 2D echocardiography. Importantly, early reduction in myocardial deformation appears to forecast the development of subsequent cardiotoxicity, with STE measured GLS being the most consistent parameter. The thresholds of change in GLS to predict cardiotoxicity have ranged from 10% to 15% using STE. These thresholds generally have better negative predictive value than positive predictive value, probably reflecting the low prevalence of cardiotoxicity in the patients studied. Unfortunately, in survivors, although deformation parameters appear to detect subclinical myocardial changes, the value of these changes in predicting subsequent LV dysfunction or heart failure is unknown. Finally, RT also affects myocardial deformation, with changes occurring predominantly in those receiving therapy to the left chest and to myocardial segments receiving the highest radiation doses.

Cardiovascular complications of cancer therapy. Many of the chemotherapeutic agents in use today can have associated cardiovascular side effects, the most common of which are cardiomyopathy and HF (45,60). Amongst the various medications, the anthracycline class of drugs (e.g., doxorubicin and epirubicin) and the human epidermal growth factor receptor type 2 (HER 2) monoclonal antibody, trastuzumab, have been most commonly implicated and best studied. A recent meta-analysis of 55 published randomized controlled trials showed that the use of anthracycline-based versus nonanthracycline-based regimens were associated with a significantly increased risk of both clinical (odds ratio: 5.43) and subclinical (odds ratio: 6.25) cardiotoxicity (61). Despite this toxicity, anthracyclines remain the cornerstone of treatment in many malignancies, including lymphomas, leukemias, and sarcomas, and are still widely used in both advanced and early-stage breast cancer (60). Combined therapy generally increases the incidence of cardiotoxicity (62). This has been best demonstrated in women with HER 2–positive breast cancers treated with anthracycline followed by trastuzumab, in whom the incidence of cardiotoxicity has been reported to be as high as 41.9% in older women during long-term follow-up (46). Two types of cardiomyopathy have been defined to distinguish anthracycline-induced myocardial damage (type I) from trastuzumab-induced myocardial dysfunction (type II). Type I cardiomyopathy is related to the cumulative dose, is largely irreversible, and results from free radical formation and mitochondrial dysfunction ultimately leading to myofibrillar disarray and necrosis (63). In contrast, type II cardiomyopathy is not dose-related, may be reversible, and results in no apparent ultrastructural changes (63).

Detection of cardiotoxicity. The current recommendations for pre-treatment cardiac evaluation and monitoring of

Table 4 Summary of Studies That Have Used Advanced Myocardial Mechanics Parameters to Demonstrate Subclinical Myocardial Injury in Patients Who Previously Received Cancer Chemotherapy

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Control Strain	Patients Strain	Vendor, Reproducibility
Ho et al. 2010 (49)	STE	Breast	70, 50 controls	54 ± 8	100	Anthracycline, ± trastuzumab, RT 80%	Mean 4.2 ± 1.8 yrs post-anthracycline or 3.1± 1.9 yrs post-trastuzumab	GLS −19.6 ± 1.8%	GLS −18.1 ± 2.2%	GE, intraobserver/interobserver as ICC (COV) GLS 0.97 (3.1%)/0.95 (4.8%), GRS 0.97 (2.9%)/0.97 (5.0%)
Yu et al. 2013 (54)*†	3D STE	Multiple pediatric	53, 38 controls	18.6 ± 5.1	30	Anthracyclines	Median of 7.2 yrs (2.4–16.4 yrs) post	3D LV global strain 44.6 ± 7.8%	3D LV global strain 35.4 ± 7.5%	Toshiba, intra/interobserver as COV 3D strain 7.3%/8.2%
Yu et al. 2013 (53)*†	STE -	Multiple pediatric	32, 28 controls	19.3 ± 5.4	34	Anthracyclines	Median of 6.9 years (2.2–14.4 yrs) post	Versus control GRS reduced at multiple levels and layers between 11.6%–20.6%. Transmural GCS gradient by 9.9%–19.2%. Apical transmural rotation gradient by 41.3%‡		Toshiba, Interobserver and intraobserver reported as COV for all parameters. Intraobserver ranged from 2.49%–6.29%, and interobserver from 2.86%–13.35%
Yagci-Kupeli et al. 2012 (52)	TDI	Multiple pediatric	19, 17 controls	Median age 14	32	Doxorubicin, danorubicin, or epirubicin, RT 10.5%	Median of 67 months (range 8–142 months) post	LS and LSR were significantly lower in the basal RV, LV septal, lateral, and inferior walls. No values.		GE, no data

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Table 4 Continued

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Control Strain	Patients Strain	Vendor, Reproducibility
Cheung et al. 2011 (21)	STE	ALL (childhood survivors)	36, 20 controls	15.6 ± 5.5	47	Doxorubicin or danorubicin	Median of 7 yrs (3.1–24.3 yrs) post	Peak LV torsion 11.8 ± 4.5° Systolic twisting velocity 91.0 ± 22.3°/s Diastolic untwisting velocity −109.6 ± 33.4°/s	Peak LV torsion 8.0 ± 4.1° Systolic twisting velocity 68.1 ± 20.3°/s Diastolic untwisting velocity −90.1 ± 34.3°/s	GE, intra/interobserver as mean (SD) difference for LV torsion 0.9° (5.0)/4.0° (7.1), peak systolic twisting velocity 0.0°/s (9.5)/−2.1°/s (10.8), peak diastolic untwisting velocity −1.7°/s (11.2)/−2.0 °/s (14.4)
Cheung et al. 2010 (47)	STE	ALL	45, 44 controls	15.3 ± 5.8	38	Doxorubicin or danorubicin RT 0%	Median 6.3 yrs (2.7–19.8 yrs) post	LS −19.0 ± 2.2% CS −17.4 ± 4.3% RS 50.0 ± 16.4% CSR 1.06 ± 0.28/s	LS −17.6 ± 3.0% CS −14.5 ± 2.9% RS 40.1 ± 15.6% CSR 0.90 ± 0.21/s	GE, no data
Mavinkurve-Groothuis et al. 2010 (50)	STE	Multiple pediatric	111, 107 controls	20 (5.6-37.4)	49	Doxorubicin, danorubicin, RT 6.3%	Median of 13.2 yrs (5.0–29.2 yrs post)	GLS −21.2 ± 1.6% GLSR −1.40 ± 0.08/s GRS 57 ± 5% GRSR 3.43 ± 0.36/s GCS −22.6 ± 2.1% GCSR −1.83 ± 0.17/s	GLS −19.8 ± 2.6% GLSR −1.22 ± 0.19/s GRS 49 ± 12% GRSR 1.75 ± 0.35/s GCS −15.9 ± 6.7% GCSR −1.48 ± 0.42/s	GE, no data

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Table 4 Continued

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Treatment	Echo Timing	Control Strain	Patients Strain	Vendor, Reproducibility
Park et al. 2009 (51)	STE –V V I	Multiple pediatric	14, 14 controls	6 to 17	50	Anthracyclines	>3 yrs post-therapy	Longitudinal peak systolic strain rate −1.89 ± 0.63/s Diastolic strain 2.96 ± 1.26% (septum only)	Longitudinal peak systolic strain rate −1.66 ± 0.27/s Diastolic strain 2.38 ± 0.77%	Siemens, intraobserver as mean absolute difference (95% CI) GLS 0.99 (4.08%), GLSR 0.13 (0.53/s), diastolic strain rate 0.18 (0.72/s)
Ganame et al. 2007 (48)	TDI	Pediatric, ALL, lymphoma, solid tumor, or AML	56, 32 controls	12.7 (4–28)	61	Doxorubicin, danorubicin, or idarubicin	Median 5.2 yrs (2.0–15.2 yrs) post	Basal RV LS −40 ± 16%	Basal RV strain −33 ± 13% Reduced RS and RSR by ~15%–20% (no numbers)	GE, intra/interobserver as absolute mean difference (95% CI) LS 2.56 (3.72%)/3.48 (3.89%), LSR 0.11 (0.12/s)/0.41 (0.42/s), RS 2.79 (2.91%)/6.03 (8.57%), RSR 0.52 (0.47/s), 0.53 (0.59/s)

Studies in adult patients are presented first followed by studies in pediatric patients. Details in Online Table D. *Study from same group with likely overlap in the patients. †Due to the large amount of data only summary changes are provided.
GPI = global performance index (global 3-dimensional strain × torsion/systolic dyssynchrony index); V V I = vector velocity imaging; other abbreviations as in Tables 1 and 2.

Table 5 Summary of Studies That Used Advanced Myocardial Mechanics to Detect Early Myocardial Injury From Radiation Therapy

First Author, Year (Ref. #)	Method	Cancer	n	Age, yrs	Women, %	Cancer Side	Treatment	Echo Timing	Strain Pre	Strain Post	Vendor, Reproducibility
Erven et al. 2013 (55)	TDI	Breast	75	—	100	51 left, 24 right	Doxorubicin or epirubicin, RT (50 Gy) mean heart and LV doses 9 ± 4 Gy for left-sided cancer and 4 ± 4 Gy and 1 ± 0.4 Gy for right-sided	Before RT, immediately after 50 Gy, and at 8 and 14 months	GLS −19.4 ± 2.4% Strain rate −1.4 ± 0.26/s	GLS −17.5 ± 1.9% (immediately post), lowest at 8 months −16.6 ± 1.4% Strain rate −1.22 ± 0.15/s immediately post	GE, no data
Erven et al. 2011 (56)	TDI	Breast	30	—	100	20 left 10 right	Epirubicin, RT (50 Gy) mean LV dose was 6.7 ± 6 Gy for left-sided RT and 0.6 ± 0.1 Gy for right-sided RT	Before RT, immediately after 50Gy, and at 2 months	GLS −19.5 ± 2.1%	GLS −17.6 ± 1.5%, left side RT patients immediately post	GE, no data
Tsai et al. 2011 (57)	STE	Hodgkin's	47, 20 controls	51 ± 9	66	—	RT (mean 41 Gy) with (n = 27) and without doxorubicin (n = 20).	22 ± 2 yrs post	Controls: GLS −20.4 ± 1.7%	Patients: GLS −16.1 ± 1.9 in RT with doxorubicin, 17.5 ± 1.7 RT no doxorubicin	GE, intraobserver and interobserver Cronbach α were 0.98 and 0.97
Chang et al. 2009 (58)	TDI	Lung, breast	40	48.7 ± 3.2	40	—	RT only (30–60 Gy)	1–2 days pre-RT, and after weeks 3 (30 Gy), 4 (40 Gy), 5 (50 Gy), or 6 (60 Gy)	Strain reduced at 50 and 60 Gy vs. those imaged pre-therapy. At 60 Gy, reduction in systolic strain ranged from 27.4%–39.5%, and diastolic strain from 31.8%–37.9%.		Philips, no data
Wang et al. 2006 (59)	TDI	Lung, esophageal, thymic, lymphoma	40	48 ± 3.2	55	—	RT only (26–60 Gy).	1–3 days before RT and after 2.5–3 weeks (26–30 Gy) or 5–6 weeks (50–60 Gy)	Strain reduced at 50–60 Gy vs. those pre-therapy. Systolic strain rate reduction ranged from 30.3%–42.5% and diastolic strain rate between 32.9%–44.0%.		Philips, no data

Please see Online Table E for further study details.
Abbreviations as in Tables 1 and 2.

patients receiving cancer therapy are not specific and vary among the different guidelines by cardiovascular and oncology societies. A summary of the core recommendations from the major guidelines is summarized in Online Table A (60,64–67). The European Society for Medical Oncology has provided the most comprehensive recommendations for monitoring during and after chemotherapy, based on clinical risk factors and cumulative dose (64). The American Society of Echocardiography, in collaboration with the European Association of Cardiovascular Imaging have created an Expert Consensus Document on the evaluation of adult patients during and after cancer therapy that will soon be published. Although several imaging modalities such as cardiac magnetic resonance imaging or multigated acquisition scans can be employed in the evaluation of cardiotoxicity, the benefit of echocardiography comes from its versatility, lower cost, ability to assess more than ventricular function, and avoidance of repeated radiation exposure.

Diastolic function has also been explored as a marker of early cardiotoxicity in several studies, but the best diastolic parameter to follow is not clear. Also, no echocardiography studies to date have demonstrated that an early subclinical drop in LVEF or changes in diastolic parameters can predict subsequent cardiotoxicity. Furthermore, although controversial, several studies show that systolic strain changes occur prior to or in the absence of changes in traditional diastolic parameters (21,28,29,41,47,49,56,57). The strength of echo-measured myocardial deformation parameters therefore includes the ability to more readily detect regional abnormalities in LV function along with improved measurement reproducibility due to the semiautomated nature of the measurements, and the ability to forecast subsequent LV dysfunction. The reproducibility data for strain measurements presented in each study are summarized in Tables 1, 2, 4, and 5.

Tissue Doppler and STE-based strain have been used to detect early myocardial changes in patients receiving chemotherapy. With TDI, interventricular septal longitudinal SR appears to be most consistently reduced during therapy. However, the most clinically relevant data on predicting cardiotoxicity have been based on STE-based strain. Also, TDI-based strain analysis requires data acquisition for each myocardial segment with careful attention to frame rates as well as alignment of the walls with the Doppler beam (18). The measurements of strain and SR can be noisy, and significant expertise is required for proper interpretation (18). This makes clinical application more challenging as compared with STE-based strain, which can be obtained at lower frame rates using standard 2D images and has a more streamlined post-processing (18). In addition to easily measuring GLS from all 18 myocardial segments, STE allows measurement of radial and circumferential strain in multiple segments, as well as rotational parameters. Also, the reproducibility of STE-based strain analysis is superior to TDI-based analysis (18).

Normal ranges for GLS defined in a recent meta-analysis (mean GLS −19.7%; 95% confidence interval: −20.4% to −18.9%) (68) underpin the use of a normal cutoff exceeding −19%. However, because of baseline variability in strain values between different patients, within-patient change may be a more reliable parameter compared with a population-derived absolute cut-off value. The threshold for change in GLS to predict cardiotoxicity is not clear, although between 10% and 15% appears to have the best specificity. The observer variability of the GLS measurements based on the summarized studies is within the suggested threshold to predict cardiotoxicity.

Future directions. Much remains to be understood about the role of cardiovascular imaging in the identification and management of cardiotoxicity from cancer chemotherapy. Whether strain-based approaches could be reliably implemented in multiple centers, including nonacademic settings, needs to be studied. The ability of strain changes to predict subsequent cardiotoxicity needs to be examined in larger multicenter studies and in cancers other than breast cancer, where treatment with potentially cardiotoxic regimens is provided. Whether strain measurements are required at multiple time-points or a single selected time-point has to be determined. An approach that uses strain as the primary marker of cardiotoxicity to initiate cardioprotective therapy needs to be compared with a traditional LVEF-based approach. The long-term effect of strain changes that occur during therapy needs to be understood. The use of vendor-neutral methods to measure strain and their ability to predict cardiotoxicity also need to be explored for this technique to be more widely applied. Finally, the prognostic significance of strain abnormalities in survivors of cancer and those receiving radiation therapy has to be understood along with whether intervention would change the natural course of the cardiac disease.

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Key Words: chemotherapy ■ cardiotoxicity ■ tissue Doppler ■ speckle tracking echocardiography.

APPENDIX

For supplemental tables and videos, please see the online version of this article.