Cardiovascular Imaging in Cardio-Oncology

The Role of Echocardiography and Cardiac MRI in Modern Cardio-Oncology

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KEYWORDS

• Cardio-oncology • Advanced imaging • Echocardiography • Cardiac MRI • Immunotherapy toxicity

KEY POINTS

- Echocardiography, the first-line imaging modality for cancer therapy-related cardiotoxicity (CTRCT) screening, should be obtained with signs or symptoms of cardiac involvement in patients with history of cardiotoxic cancer therapy.
- Echocardiographic strain imaging can detect subclinical cardiac dysfunction and is a promising tool for the prediction and prognostication of CTRCT.
- Cardiac MRI (CMR) should be obtained if echocardiography is insufficient or suboptimal, highly accurate volume assessments are needed, or myocarditis is suspected.
- Parametric T1 and T2 mapping should be included, when possible, in the CMR evaluation of cancer patients.
- CTRCT surveillance varies based on patient risk and cancer therapy. Baseline echocardiography should be obtained before therapy initiation in all intermediate and high-risk patients and considered in low-risk patients.

INTRODUCTION

The constant evolution of cancer treatment has led to improved outcomes in numerous malignancies.[1] With improved cancer survivorship and the introduction of novel therapies such as biologic agents and immunotherapeutics, the prevalence of systemic toxicities, in particular cardiotoxicity, has grown.[2] Because cardiovascular (CV) disease remains the leading noncancer cause of death in cancer survivors, cardio-oncology strives to understand and improve CV health in patients with cancer.[3,4]

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CV imaging is crucial in recognizing, understanding, monitoring, and treating cancer treatment-related cardiotoxicities (CTRCT).[5] Structural and functional imaging modalities provide important information in the management of pathologic cardio-oncologic conditions. Echocardiography continues to be highly used for assessment of cardiac structure and function due to its low cost, accessibility, and effectiveness. Newer echocardiographic applications, such as strain imaging, are increasingly used in evaluation of CTRCT, especially to detect subclinical disease.[6,7] Similarly, cardiac magnetic resonance (CMR) has become a crucial imaging modality in cardio-oncology. Although less accessible, CMR offers accurate functional and structural assessment because of excellent reproducibility, high signal-to-noise ratio in addition to fine tissue characterization that is particularly helpful when echocardiography is insufficient or suboptimal.[6,8] This review will discuss current evidence for use of echocardiography and CMR in cardio-oncology and practical clinical uses for each.

Traditional 2D Echocardiography

Due to availability, low cost, short acquisition time, and safety, echocardiography is the first-line imaging modality for CTRCT screening by all published cardio-oncology guidelines and expert consensus statements.[5] **Fig. 1** illustrates the relative utility of echocardiography considering various parameters. Although left ventricular ejection fraction (LVEF) as measured by the Simpson biplane method is the most cited parameter in strict definitions of cardiotoxicity (definitions range from reduction in LVEF by 5%–10% to absolute LVEF of less than 50%–55%),[9] LVEF assessment via 2D echocardiography lacks the sensitivity and reproducibility for primary CTRCT screening.[10] Thus, newer echocardiographic applications such as strain imaging, 3D echocardiography, and contrast echocardiography have growing roles in screening for CTRCT.

Echocardiographic strain imaging

Myocardial strain, or deformation, is the measure of percent change in the length of a myocardial segment during a given timeframe. This parameter is helpful in quantifying myocardial function directly rather than indirectly via 2D LVEF with the Simpson biplane method. Speckle-tracking echocardiography (STE) is the preferred method of strain imaging. STE tracks the artifactual "speckles" created by reflected and scattered ultrasound beams through cardiac tissue. Strain can be calculated for the 3 major orientations of myocardial fibers (longitudinal, radial, and circumferential) and as global longitudinal strain (GLS), which uses data from multiple cardiac segments. All of these show promise in the early detection of CTRCT before changes in LVEF occur.[7,11] A decrease in GLS of less than or equal to 15% from baseline is considered abnormal and has been most extensively studied.[12]

Several studies have assessed the prognostic value of GLS in the early prediction of CTRCT before LVEF changes. A 2019 systematic review[13] evaluated 21 such studies of patients treated with anthracyclines with or without trastuzumab for a variety of cancers. Summary odds ratios (ORs) for the prediction of CTRCT based on threshold GLS values and percent change of GLS after treatment initiation were 12.27 and 15.82, respectively. Since the publication of this systematic review, newer studies have shown similar findings,[14–18] some incorporating several biomarkers for additional predictive value with mixed utility.[19–21] GLS has been studied in pediatric populations as well. Although less robust, the studies use strain-imaging to evaluate subclinical cardiac dysfunction in varying follow-up periods after anthracycline therapy or radiation.[22–27] As in adults, GLS in pediatric patients detects myocardial dysfunction before changes in LVEF. Future studies in all populations should focus on both early and long-term predictive value of strain imaging with and without biomarkers for the development of CTRCT.

Echocardiography in anthracyclines

Anthracyclines are antitumor antibiotics that play a major role in the treatment of a wide range of cancers. Both antitumor action and cardiotoxicity are thought to be due to activation of apoptotic pathways triggered by a combination of 3 separate mechanisms: direct DNA damage via intercalation into DNA strands, transcription interference via inhibition of topoisomerase enzymes, and DNA and cellular damage via generation of free radicals.[28,29] Cardiotoxicity manifests primarily in the form of myocardial dysfunction, usually within 1 year[30] of therapy initiation, and it can progress to irreversible heart failure, characterized by diffuse fibrosis.[31] Risk factors for cardiotoxicity include cumulative anthracycline exposure, age greater than 65 years or less than 18 years, female sex, preexisting cardiac risk factors, kidney disease, and exposure to other cardiotoxic therapies.[32] Patients can be categorized into low, intermediate, and high risk for cardiotoxicity based on these risk factors (**Table 1**). Echocardiography is the primary screening tool for anthracycline cardiotoxicity, with GLS emerging as the most sensitive measure of early myocardial dysfunction.[13]

Value of Echocardiography and Cardiac MRI	Echocardiography	Cardiac MRI
Cost Efficiency	●●●◐	●●●○
Availability	●●●◐	●●◐○
Reproducibility	●●◐○	●●●◐
Radiation Safety	●●●●	●●●●
Patient Tolerability	●●●◐	●●◐○
Pericardial Disease	●●○○	●●●○
Tissue Characterization	●●○○	●●●●
Mass/Tumor Characterization	●●○○	●●●●
Inflammation	●○○○	●●●●
Perfusion/Ischemia	●○○○	●●●○
Myocardial Mass	●●◐○	●●●●
Volume	●●●○	●●●●
Functional Assessment	●●●○	●●●●
Valvular Disease	●●●●	●●●○

Fig. 1. Comparison of value of echocardiography and CMR. One filled in black circle represents minimal value, 2 represents limited value, 3 represents good value, and 4 represents gold standard.

Echocardiography in Her2/Neu therapy

Trastuzumab is a monoclonal antibody used mostly in the treatment of HER2-positive breast cancer that targets HER2/neu receptors, epidermal growth factor receptor tyrosine kinases (TKs) important in cell proliferation. Cardiotoxicity is the major adverse effect attributed to trastuzumab, primarily manifesting as potentially severe, reversible left ventricular (LV) dysfunction while on therapy[33] as well as right ventricular (RV) dysfunction.[34] Myocardial dysfunction has been reported in up to 30% of patients[19] with a 3% risk of severe cardiotoxicity.[35] Women treated with both anthracyclines and trastuzumab are at higher risk of cardiotoxicity than those treated with either alone.[36] Toxicity is thought to be due to inhibition of cardioprotective mechanisms (sarcomere maintenance, proapoptotic molecule scavenging) initiated by neuregulin-1-mediated activation of HER2. Subsequent oxidative stress and upregulation of angiotensin II is thought to further promote toxicity.[33] As with anthracyclines, GLS detects subclinical myocardial dysfunction before LVEF changes and should be implemented in any echocardiographic assessment of patients treated with trastuzumab.[13,18]

Echocardiography in targeted therapies and immunotherapy

Although anthracyclines and trastuzumab represent the classic culprits of CTRCT, emerging therapies also cause cardiotoxicities that can be assessed via echocardiography and strain imaging. These include targeted therapies (eg, proteasome inhibitors [PIs], vascular endothelial growth factor inhibitors [VEGF-Is], tyrosine kinase inhibitors [TKIs]) and immunotherapies (eg, immune checkpoint inhibitors [ICIs], chimeric antigen receptor T cell [CAR-T] therapy).

Echocardiography in proteasome inhibitors

Proteasome inhibitors (PI), such as bortezomib and carfilzomib, are used in the treatment of multiple myeloma and are known to cause cardiotoxicity in the form of myocardial dysfunction and heart failure.[37] Proposed mechanisms include interference of production of nitric oxide in the endothelium leading to vasoconstriction and

Table 1
Low, intermediate, and high-risk features for development of CTRCT. A patient should be grouped with their highest individual risk factor

	Risk Factor Categories for CTRCT
Low Risk	• Age 18–50 y • Cumulative dose <200 mg/m2 doxorubicin (or equivalent) • No preexisting or new CVD risk factors[a] • Cumulative RT dose <30 Gy without chest involvement
Intermediate Risk	• Age 50–65 y • Cumulative dose 200–400 mg/m2 doxorubicin (or equivalent) • 1–2 preexisting or new CVD risk factors[a] • Cumulative RT dose >30 Gy without chest involvement • Single-agent targeted therapy or immunotherapy
High Risk	• Age <18 or >65 y • Cumulative dose >400 mg/m2 doxorubicin (or equivalent) • Any RT involving the chest • Any combination of cardiotoxic cancer therapies, even within same class • >2 preexisting or new CVD risk factors[a] • Underlying CVD (CAD, HF, PAD, and so forth) • History of CTRCT

Abbreviations: CAD, coronary artery disease; CTRCT, cancer therapy-related cardiotoxicity; CVD, cardiovascular disease; Gy, Gray unit(s); HF, heart failure; PAD, peripheral artery disease; RT, radiation therapy.
[a] CVD risk factors include, but are not limited to, hypertension, insulin resistance, diabetes mellitus, smoking, obesity, and dyslipidemia.

inhibition of the ubiquitin-proteasome system leading to protein misfolding and cell death. Cardiomyocytes are particularly vulnerable to this second mechanism because they are nonproliferative and express elevated proteasome levels.[38] Meta-analyses of carfilzomib and bortezomib showed ORs of 2.03 and 1.74, respectively, for the development of cardiotoxicity and a cumulative incidence of cardiotoxicity in nearly 10% of those on carfilzomib.[39,40] PI use is associated with decreased GLS without change in LVEF, indicating subclinical cardiac dysfunction[41] and early detection of CTRCT,[38] but the amount of published data is minimal.

Echocardiography in vascular endothelial growth factor inhibitors

VEGF-Is are used to treat a variety of malignancies by inhibiting tumor angiogenesis. Numerous VEGF-Is are cardiotoxic, causing hypertension and myocardial dysfunction.[42] Hypertension is thought to be driven via inhibition of endothelial nitric oxide production. The myocardial dysfunction is less well understood but thought to include a multitude of effects leading to inhibition of cardioprotective cellular mechanisms, coronary microvasculature destabilization, and decreased density of myocardial capillaries.[43] Although LVEF effects have been inconsistent, STE monitoring in patients receiving various VEGF-Is showed significant decrease in GLS from baseline both during treatment[44] and up to 6 months following treatment.[45,46]

Echocardiography in tyrosine kinase inhibitors

TKIs are a diverse group of agents that target TK molecules in various cellular functions. By targeting specific pathways, TKIs can be tailored for specific types of malignancies. Because TKs are so widely used in cellular biology, there is much cross-reactivity with other TKs leading to "off target" effects, including cardiotoxicity in the form of cardiomyopathy and heart failure.[47,48] Sunitinib and pazopanib, VEGF-Is acting via the TKI mechanism, are associated with myocardial dysfunction and demonstrate significant decrease in GLS.[45] Newer generation Bcr-abl-targeting TKIs cause significantly lower GLS compared with first generation, but the absolute value difference is minimal with no comparison to baseline, limiting the clinical relevance of this finding.[49] Another subset of TKIs, B-Raf proto-oncogene (BRAF), and mitogen-activated protein kinase kinase (MEK) inhibitors, are used in the treatment of melanoma and are known to be cardiotoxic, most commonly in the form of LVEF reduction (seen in 13% of patients[50]) and hypertension. Combination BRAF/MEK therapy poses higher risk for LVEF reduction, hypertension, and thromboembolic phenomena compared with BRAF therapy

alone.[51,52] In TKI CTRCT, heart failure tends to present in the first 6 months of therapy. However, no published studies address predictive value of GLS or other parameters.

Echocardiography in immunotherapies

Immunotherapies such as ICIs and CAR-T therapy are used in a wide range of cancers. ICIs work by targeting molecules that inhibit immune destruction by T-cells. Not surprisingly, this general approach can lead to unintended inflammatory cascade throughout the body, including cardiac manifestations[53] such as myocarditis, pericarditis, arrhythmia, cardiomyopathy, or myocardial ischemia. The most apparent risk factor for ICI-cardiotoxicity is combination therapy with another cardiotoxic agent (including another ICI).[54] With increasing recognition of the immune phenomena associated with immunotherapy, retrospective studies estimate myocarditis occurs in up to 1% of patients taking ICIs.[55–57] In patients that develop ICI myocarditis, GLS is reduced even if LVEF is not and is associated with future major adverse cardiac events (MACE).[58] There is evidence of STE-detected RV dysfunction that correlates with duration of ICI use, suggesting a role in CTRCT monitoring.[59]

In contrast to ICIs, CAR-T therapy works by using T cells that have been harvested from the host, reprogramming them to target tumor cells, and reintroducing them into the host. CAR-T cardiotoxicity manifests primarily as arrhythmia, cardiomyopathy, or ischemic events. LVEF reduction has been demonstrated in 5% to 10% of patients on CAR-T therapy.[60–62] To our knowledge, there are no published studies evaluating strain imaging in patients receiving CAR-T therapy. Thus, the rate of cardiac toxicity is likely underestimated.

Echocardiography in radiation therapy

Radiation has long been used as a cancer therapy. Cardiotoxicity arises from direct cellular damage of the myocardium and endothelial tissue of the heart and vasculature within the field of radiation. Cardiotoxicity can manifest as hypertension, coronary artery disease (CAD), valvular disease, pericarditis, myocarditis, cardiomyopathy, or arrhythmia.[63] Cardiotoxicity risk is increased in patients with total exposure of greater than 15 Gy and increases with increasing doses.[64] Strain imaging, GLS mostly, has been used to evaluate CTRCT following radiotherapy (RT) to the chest. Numerous studies show subclinical cardiac dysfunction after initiation of chest RT (in the absence of other cardiotoxic therapies) for the treatment of breast cancer in both acute and follow-up periods of up to 3 years.[65–71] Higher radiation doses[66–68,70,71] and left-sided breast radiation[67,68] are associated with larger decreases in GLS. The apical region[72] and subendocardial region of the heart receiving the most radiation[65] have demonstrated earlier detection of strain reduction, suggesting higher sensitivity for the detection of CTRCT by assessing these regions.

3D Echocardiography

3D echocardiography is a modality that has emerging potential in cardio-oncology. Although not as ubiquitous as 2D echocardiography, it offers superior capability in the assessment of LVEF,[4,73] providing values that agree with CMR.[74] Compared with 2D echocardiography, 3D echocardiography offers more reproducible LVEF,[10] faster and earlier strain assessment,[75,76] and more detailed structural and anatomic characteristics of cardiac masses.

Echocardiography and Cardiac Masses

Echocardiography plays a pivotal role in the detection and diagnosis of cardiac masses. Although rare, neoplastic cardiac masses carry significant morbidity and mortality.[77] Benign cardiac tumors are more common than malignant ones. Metastatic cardiac tumors, seen in 10% to 12% of patients with a known primary cancer,[78] are more common than primary cardiac malignancy. 2D echocardiography can delineate cardiac masses and certain characteristics (size, shape, mobility, relative density, associated effusions) quite well for initial evaluation (**Fig. 2**, Panel A). However, there is limited ability to distinguish right-sided masses, left atrial (LA) appendage masses, extracardiac masses, tissue characteristics, and type of mass.[79] 3D echocardiography better evaluates size and anatomic associations of cardiac masses, adding benefit in surgical planning.[76] Perfusion contrast with 2D echocardiography enhances diagnostic utility and has sensitivity and specificity of 93% to 100% in differentiating thrombi versus benign tumor versus malignant tumor.[80–82] Transesophageal echocardiography (TEE) has shown high diagnostic accuracy[82] with better anatomic resolution of right-sided and posterior structures,[83] but it is an invasive procedure associated with risks including those of sedation and expense.

Echocardiography in Tamponade and Pericardiocentesis

Pericardial effusions can be due to infection, autoimmune inflammation, direct effect of malignancy, adverse effect of cancer therapy (radiation-induced pericardial disease, ICI inflammation, volume overload), postsurgical, or idiopathic.

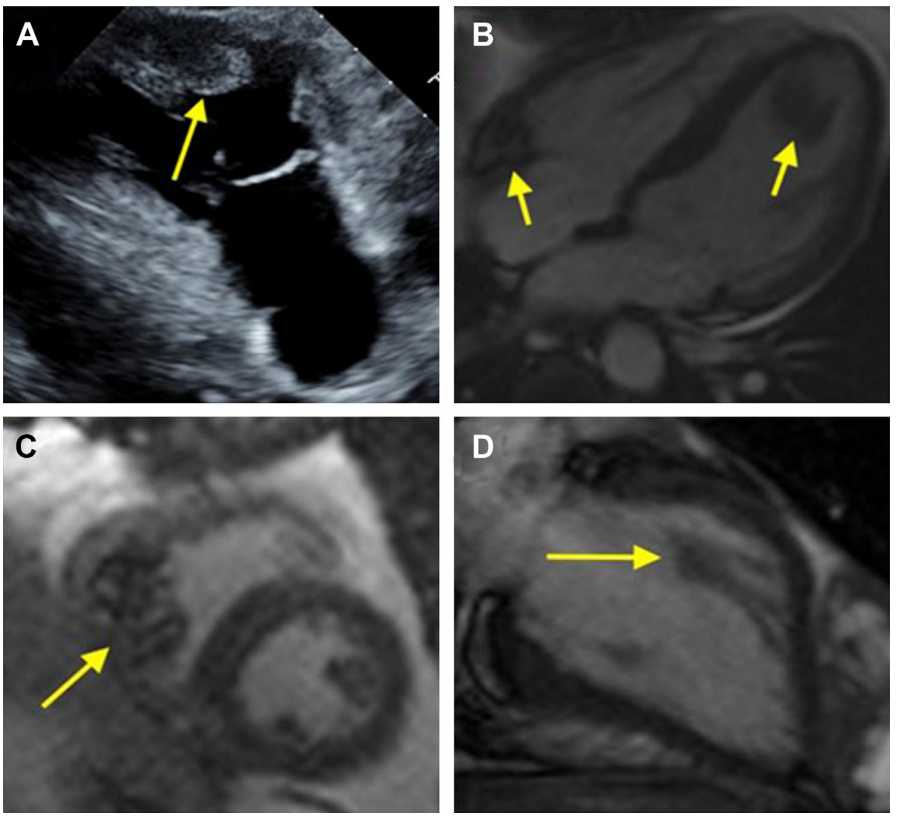

Fig. 2. (*A*) Mass identified in the RV outflow tract on echocardiography. Suspected to be a metastatic lesion from an unknown primary source. (*B*) Two masses identified on CMR (horizontal long axis view). The LV mass is a metastatic melanoma. The RA mass is a thrombus. (*C*) One RV mass on CMR (short axis view), diagnosed as metastatic melanoma with surrounding thrombus. (*D*) One LV mass identified on CMR (vertical long axis view), diagnosed as a poorly differentiated synovial sarcoma.

Pericardial effusions are readily identified on traditional 2D echocardiography, although may require multiple views if the effusion is loculated. If posterior, TEE may be required to adequately view the effusion. Pericardiocentesis, drainage of a pericardial effusion, is generally indicated for asymptomatic and large effusions, hemodynamically significant effusions (ie, impending or active tamponade), or fluid biopsy to aid diagnosis. Although overt tamponade implies active hemodynamic consequences such as hypotension, tachycardia, dyspnea, or pulsus paradoxus from compression of the heart, effusions at high risk for developing tamponade cannot be readily identified on physical examination alone. Echocardiography, viewed as the gold-standard for diagnosis, can identify signs of compression before the presence of symptoms. These include RA or RV collapse during diastole, abnormal septal motion indicating interventricular dependence, dilated inferior vena cava without inspiratory collapse, swinging heart, or decreased mitral early filling velocity on doppler.[84] Echocardiography-guided pericardiocentesis, which has been used for decades, is safe and effective in patients with cancer and should be used before surgical drainage when possible.[85–87]

Echocardiography in Cardiac Amyloidosis

Cardiac amyloidosis is a group of conditions that result in the infiltration and expansion of myocardial extracellular space with amyloid protein deposits. Although various proteins can misfold and deposit, amyloid from transthyretin (ATTR) and amyloid from immunoglobulin light chains (AL) account for 95% of cases. Cardiac amyloidosis usually manifests clinically as heart failure (preserved ejection fraction more often than reduced ejection fraction), restrictive cardiomyopathy, and dysrhythmias. Typical 2D echocardiographic findings include ventricular wall hypertrophy (concentric

more common in AL, asymmetric more common in ATTR), diastolic and/or systolic dysfunction, restrictive LV filling, biatrial enlargement, valvular thickening, and a "sparkling" texture of the myocardium.[9,88] Two-dimensional STE often reveals a characteristic pattern of reduced GLS with apical sparing, due to segmental differences in total amyloid mass distribution,[89] with a reported sensitivity of 93% and specificity of 82% for cardiac amyloidosis when compared with LV hypertrophy controls.[90] The combination of GLS values with apical sparing and serum T-troponin offers better sensitivity and specificity.[91] One recent study[92] found a GLS/Ejection Fraction (EF) ratio greater than 4.1 to be a strong predictor of cardiac amyloidosis, with an OR of 35.57. Although echocardiography is the universal initial imaging modality when suspicious for cardiac amyloidosis, it cannot reliably distinguish between amyloidosis and other causes of hypertrophy. Thus, echocardiography alone is not sufficient for diagnosis.

Practical Use of Echocardiography in Everyday Clinical Practice

Each institution and case will have varying protocols for which views and data are obtained on echocardiogram. The following has been suggested for comprehensive initial echocardiographic assessment in screening for CTRCT: 2D LVEF via Simpson biplane method or 3D LVEF, 2D or 3D GLS, 2D or 3D LV systolic volume, RV function markers (such as tricuspid annular plane systolic excursion, RV fractional area change, RV ejection fraction [RVEF], RV free wall strain), velocity of tricuspid regurgitation.[9] Suggested echocardiographic surveillance protocols for patients on anthracycline therapy and trastuzumab therapy can be found in **Fig. 3** and **Fig. 4**, respectively. Suggested echocardiographic surveillance protocols for patients on radiation therapy, targeted therapy, or immunotherapy can be found in **Table 2**. Recommendations for targeted therapies and immunotherapy are less defined due to the relative dearth of data in novel agents. Individual risk assessment and joint decision making is paramount in developing a patient-centered screening plan. Regardless of therapy, baseline echocardiography before initiation of therapy should be obtained in all intermediate and high-risk patients and can be considered in low-risk patients. Additionally, any time there are signs or symptoms of cardiotoxicity, echocardiography should be obtained, and referral to a cardio-oncologist should be considered.

Cardiac MRI

Cardiac MRI and left ventricular ejection fraction

Although CMR is not deployed for routine screening in cardio-oncology, it offers superior imaging in tissue characterization, volume assessments, spatial resolution, and potentially strain imaging. **Fig. 1** illustrates the relative utility of CMR in various parameters. CMR can investigate most adverse cardiac effects from cancer therapies and allows the specific assessment of RV and LV function, ventricular and atrial volumes, ventricular and LA deformation, myocardial mass, pericardial disease, fibrosis, infiltrative tissue, edema, and inflammation.[9,93] Measurement of LVEF is considered the gold standard due to excellent accuracy and precision.[6,94] CMR is used for LVEF measurement when there are poor echocardiographic windows or echocardiography is equivocal or unreliable. Given the poor agreement of 2D echocardiography with CMR-derived LVEF, CMR should be used any time highly accurate LVEF quantification is needed, especially if 3D echocardiography is not available.[5,95]

Cardiac MRI strain imaging

Similar to echocardiography, CMR-derived LVEF lacks the sensitivity to detect early myocardial dysfunction in CTRCT. Cardiac deformation quantification via strain imaging techniques is available in some clinical CMR laboratories and is useful in detection of subclinical myocardial dysfunction. Techniques include CMR reference tagging, phase velocity mapping, displacement encoding with stimulated echoes, strain encoded (SENC) imaging (**Fig. 5**), and feature tracking (FT). CMR reference tagging is the most validated and considered gold standard for CMR strain imaging; however, CMR-FT is gaining traction due to ease of clinical use.[93,96,97] Analogous to STE but with better resolution,[98] CMR-FT is a postacquisition processing method that can be applied to images obtained for LVEF assessment, requiring no additional scanner time.[96] CMR-FT shows good reproducibility in global strain measurements, provided the same software package is used.[99,100] The potential for early detection and prognostication in CTRCT by CMR strain has been demonstrated in patients receiving various cardiotoxic chemotherapies,[101,102] and is discussed further below. CMR-FT has even shown promise in evaluation of LA strain, which, along with MRI measured LA volume, could represent an important marker for potential development of atrial arrhythmias and clot formation.[98,103]

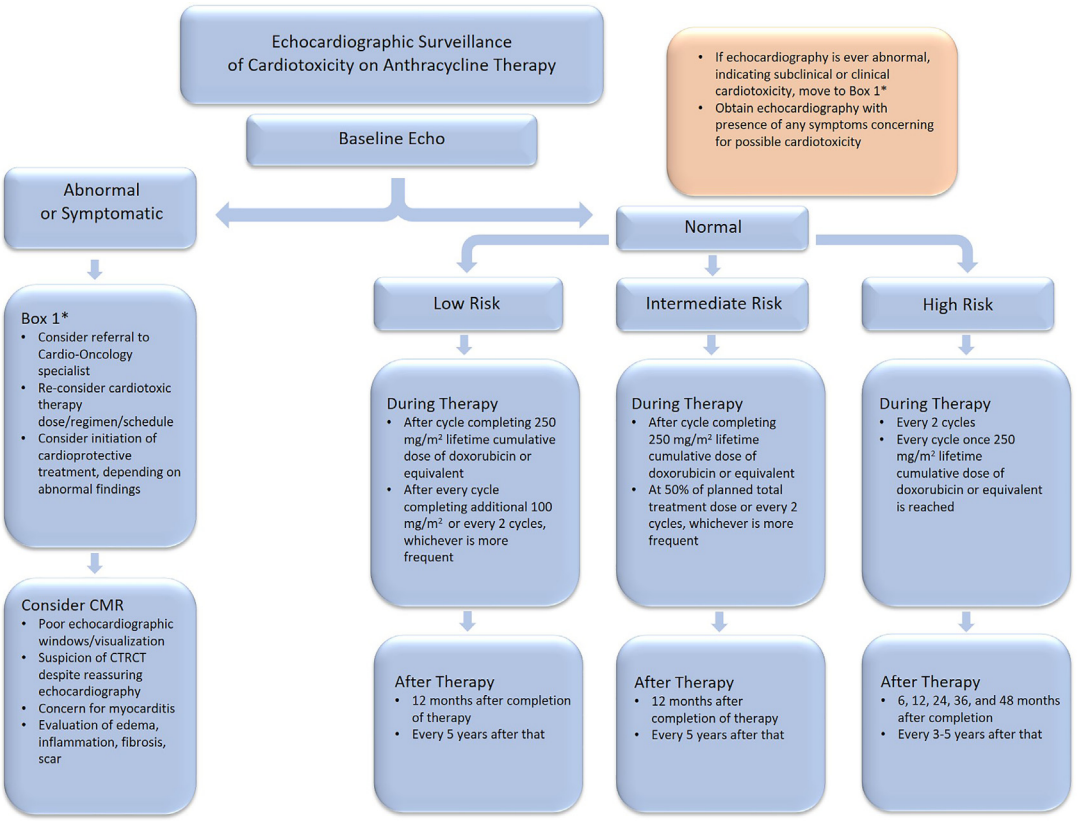

Fig. 3. Suggested echocardiographic surveillance protocol of cardiotoxicity in patients on anthracycline therapy. Low risk features include age 18 to 50 years, cumulative dose less than 200 mg/m^2 doxorubicin (or equivalent), no preexisting or new CVD risk factors. Intermediate features include age 50 to 65 years, cumulative dose 200 to 400 mg/m^2 doxorubicin (or equivalent), 1 to 2 preexisting or new CVD risk factors. High-risk features include age less than 18 or greater than 65 years, cumulative dose greater than 400 mg/m^2 doxorubicin (or equivalent), any combination of cardiotoxic cancer therapies, underlying CVD, history of CTRCT. CAD, coronary artery disease; CMR, cardiovascular magnetic resonance imaging; CTRCT, cancer therapy-related cardiotoxicity; CVD, cardiovascular disease; Echo, echocardiography; mo, month.

Cardiac MRI T1 and T2 mapping

T1-weighted imaging (**Fig. 6**) reflects the inherent intracellular and extracellular makeup of tissue. Unitless values of intensity (compared with a reference "region of interest" within the same image) are assigned to each pixel but are only comparable within the same image. T1 is lengthened (brightened) by water, edema, and inflammation; it is shortened (darkened) by iron, fat, and contrast.[104] T1 mapping is a relatively new CMR application that allows for creation of color maps, where each colored pixel represents a quantified, parametric, tissue-specific T1 value of the corresponding voxel that is comparable across images.[105] This allows sensitive detection of subtle T1 changes within the myocardium, often representing early stages of disease. T1 mapping reliably distinguishes regional and diffuse fibrosis (scar),[106] edema,[107] and infarction.[108] It has shown promise in detecting numerous cardiac disease states.[98,109,110] Late gadolinium enhancement (LGE; see **Fig. 6**), conversely, only visualizes regional fibrosis well.[98] T1 mapping solves this limitation while providing a contrast-free alternative for fibrosis detection. T1 mapping is primarily used for evaluation of the LV, but there are sequences that can evaluate fibrosis of the LA, with possible application in cancer therapies causing atrial arrhythmias.[111] Contrast T1 imaging is useful, however, in quantifying extracellular volume (ECV), which correlates histologically[112] with the excess collagen deposition of fibrosis.

T2-weighted imaging (see **Fig. 6**), like T1, is reflective of the intracellular and extracellular makeup of tissue. T2 time is increased by free water and most helpful in distinguishing edema and

Table 2
Suggested echocardiographic and CMR surveillance protocols of cardiotoxicity for patients undergoing targeted therapy, immunotherapy, or radiation therapy

Suggested Clinical Imaging Surveillance Protocols for CTRCT in Various Cancer Therapies

Class	Echocardiography	Cardiac MRI
All classes	• Consider baseline for all intermediate and high risk patients before initiation of therapy • Any time there are signs or symptoms concerning for possible CTRCT	• Consider with abnormal echo or poor visualization • Consider if clinical suspicion for CTRCT persists despite normal/equivocal echo • Unexplained CVD
PI	• Periodically if history of other cardiotoxic cancer therapy, personal CVD or risk factors, or specifically taking carfilzomib	• Consider with abnormal echo or poor windows/ visualization • Unexplained CVD
VEGF-I and TKI (including BRAF, MEK, and VEGF inhibitors with TKI mechanism)	• High risk patients on TKI: consider screening Echo every 1–3 mo during therapy • Intermediate risk patients on TKI: consider every 6–12 mo during therapy • Intermediate or greater risk of CAD before initiation of TKI: consider stress echo • All patients on VEGF-I, high risk in particular: consider echo every 3–6 mo during therapy • High-risk patients on combination BRAF/MEK therapy: consider echo every 1–3 mo during therapy • Low or intermediate risk patients on BRAF or BRAF/MEK therapy: consider echo at 6 mo, then every 6–12 mo while on therapy	• Low threshold to move to CMR after echo • With any cardiac symptoms, suspicious elevation in troponin, or ECG change • Consider if concern for ischemic cardiotoxicity • Unexplained CVD
Immunotherapies (ex. ICIs, CAR-T cell therapies, allogeneic stem transplantation)	• High risk or taking other cardiotoxic therapy (including 2nd ICI): serial echo reasonable • In high risk patients, first echo should be obtained within 1-2 months after initiation of therapy • If LV function abnormal prior to initiation of ICI, every 3-6 months for duration of therapy • Consider anytime screening ECG or serum biomarkers are abnormal	• Low threshold to move to CMR after echo • With any cardiac symptoms, suspicious elevation in troponin, or ECG change • Consider if concern for ischemic cardiotoxicity • Unexplained CVD

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Table 2
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Suggested Clinical Imaging Surveillance Protocols for CTRCT in Various Cancer Therapies

Class	Echocardiography	Cardiac MRI
RT	• High-risk patients: 1–2 y after completion of therapy and every 5–10 y following • Intermediate risk or lower: every 5–10 y after therapy completion	• If concern for radiation-induced myocardial or pericardial disease despite normal or equivocal echo • Unexplained CVD

Abbreviations: BRAF, B-Raf proto-oncogene; CAD, coronary artery disease; CAR-T, chimeric antigen T-cell therapy; CMR, cardiovascular magnetic resonance imaging; CTRCT, cancer therapy-related cardiotoxicity; CVD, cardiovascular disease; ECG, electrocardiogram; Echo, echocardiography; ICI, immune checkpoint inhibitor; LV, left ventricular; MEK, mitogen-activated protein kinase kinase; mo, month; RV, right ventricular; TKI, tyrosine kinase inhibitor; VEGF-I, vascular endothelial growth factor inhibitor; y, year.

inflammation, proving to be comparable to Lake Louise criteria for diagnosis of myocarditis.[113] T2 mapping can now be created, just as T1 mapping can,[104] with good reproducibility.[114] However, it has not been as thoroughly studied in CTRCT as has T1 mapping.

Cardiac MRI in anthracyclines

Anthracycline cardiotoxicity is characterized by myocardial dysfunction that in its most severe presentation manifests as heart failure with reduced ejection.[28] Although CMR is more sensitive and accurate in LVEF assessment than echocardiography,

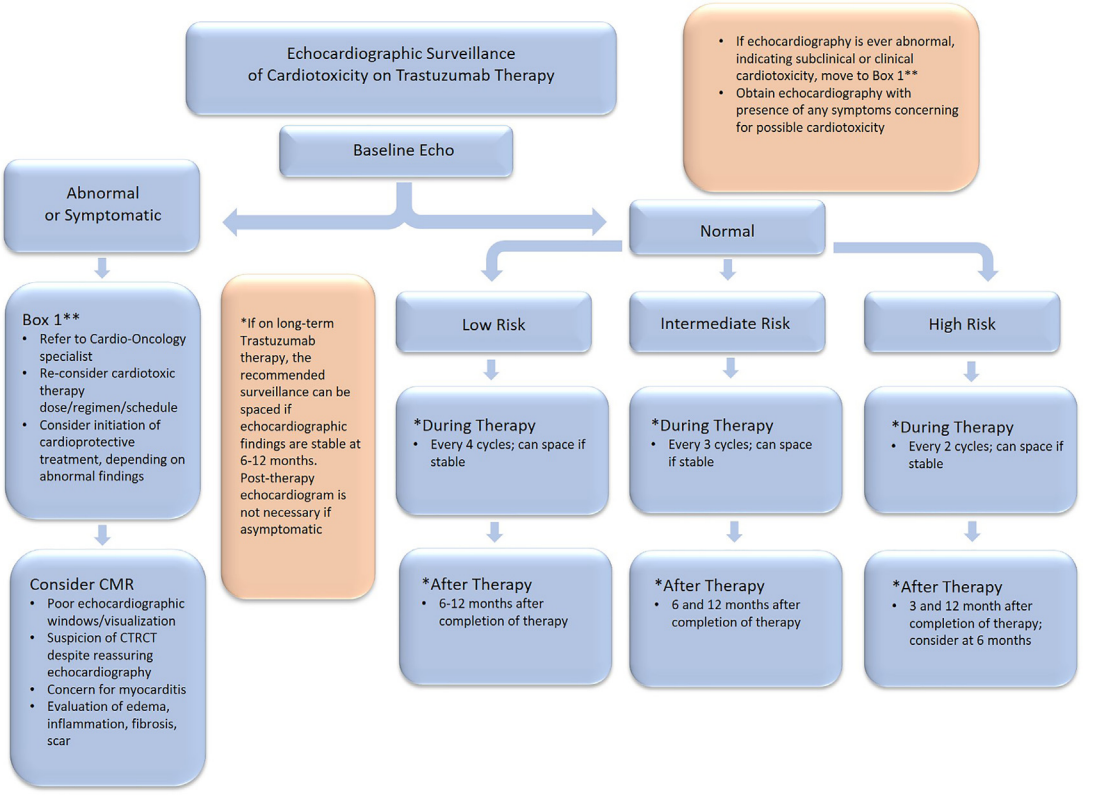

Fig. 4. Suggested echocardiographic surveillance protocol of cardiotoxicity in patients on trastuzumab therapy. Low risk features include age 18 to 50 years, no preexisting or new CVD risk factors. Intermediate features include age 50 to 65 years, 1 to 2 preexisting or new CVD risk factors. High-risk features include age less than 18 or greater than 65 years, any combination of cardiotoxic cancer therapies, underlying CVD, history of CTRCT. CAD, coronary artery disease; CMR, cardiovascular magnetic resonance imaging; CTRCT, cancer therapy-related cardiotoxicity; CVD, cardiovascular disease; Echo, echocardiography; mo, month.

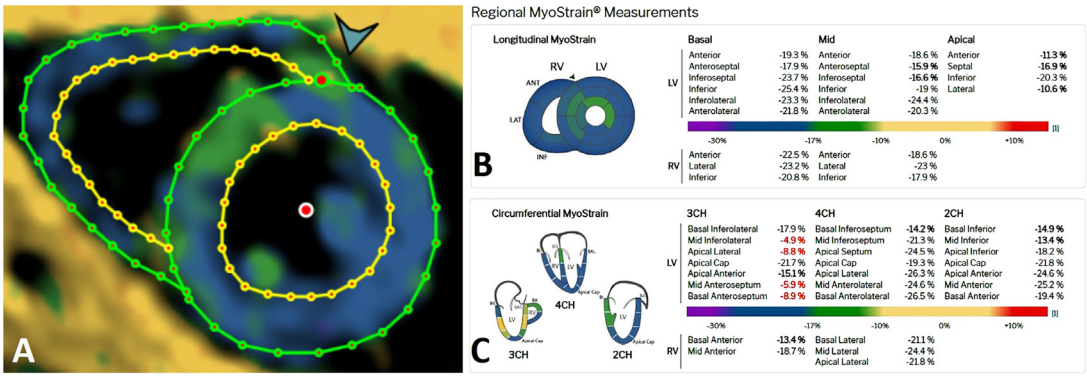

Fig. 5. (*A*) Representative screenshot of CMR (SENC) image in short axis view with overlying endocardial (yellow) and epicardial (green) borders. (*B*) MyoStrain LV and RV longitudinal strain with corresponding heat map, and absolute values of each individual segment. (*C*) MyoStrain LV and RV circumferential strain with corresponding heat map, and absolute values of each individual segment. CMR, cardiovascular magnetic resonance imaging; LV, left ventricular; RV, right ventricular; SENC, strain encoded.

it is not sensitive enough for CTRCT screening.[109] CMR strain imaging, while not as extensively studied or as readily available as echocardiographic strain imaging, shows a similar promise in early detection and prediction of CTRCT[96] via both systolic[115–119] and diastolic[120] measurements. Because anthracycline CTRCT is characterized by diffuse fibrosis,[31] LGE is seen in just 6% of patients.[121] Numerous studies have demonstrated that T1 mapping and ECV quantification detect fibrosis after anthracycline therapy, representing an avenue for early diagnosis of CTRCT.[118,122–125] One prospective study[118] showed elevated T1 and T2 mapping values in patients on anthracycline therapy compared with controls 3 months after therapy initiation but only elevated T1 more than 12 months after therapy initiation. This suggests that initial edema/inflammation eventually progresses to fibrosis. The authors created criteria for detection of cardiotoxicity in these patients, which led to diagnostic accuracy of 84% for detection of CTRCT, outperforming both GLS and troponin alone. More studies are needed to elucidate ideal threshold values for optimum diagnostic and prognostic ability. Published data on T2 mapping in anthracyclines, although minimal, shows early edema and inflammation[118,126] after administration, indicating early signs of CTRCT, with excellent sensitivity.[127] There is encouraging data for the utility of T2 mapping in CTRCT in various animal models,[128–130] but human studies remain relatively sparse. Other CMR-derived measurements have been studied in anthracycline use. LA enlargement has been associated with increasing anthracycline doses, potentially offering a marker of diastolic dysfunction.[131] Decrease in myocardial mass after anthracycline therapy has been repeatedly demonstrated,[95,121,132,133] which is associated with increased risk of MACE[121] and HF symptoms.[133]

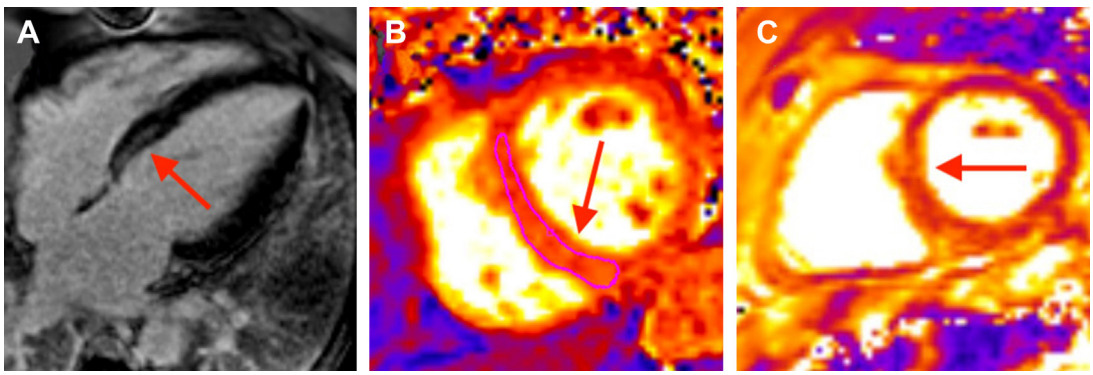

Fig. 6. Representative images of (*A*) late gadolinium enhancement, and elevated (*B*) myocardial native T1, and (*C*) myocardial native T2 in a patient with suspected targeted cancer therapy (TKI) cardiotoxicity, as visualized by cardiac magnetic resonance imaging. Red arrows in panels (*B*) and (*C*) indicate areas of elevated T1 and T2, respectively; the pink outline in panel (*B*) denotes a region of interest (ROI) in the septum.

Cardiac MRI in HER2/Neu therapy

CMR strain parameters have shown promising ability to predict the development of CTRCT in patients on trastuzumab therapy. One prospective study demonstrated that a 15% relative decrease in tagged-CMR GLS, tagged-CMR global circumferential strain (GCS), and CMR-FT correspond to increased odds of CTRCT of 47%, 50%, and 87%, respectively.[134] Multiple other studies have shown a decrease in various CMR-measured strain parameters, often with persistence up to 12 months. Recovery by 18 months is frequently seen, highlighting the reversibility of trastuzumab cardiotoxicity.[135–137] Diastolic function has been assessed with both strain and LV diastolic filling rates, but these data are inconsistent.[137,138] CMR evaluation of LGE highlights a key difference in the pathogenesis of trastuzumab from anthracyclines. Although LGE is uncommon in anthracycline cardiotoxicity due to diffuse fibrosis, LV lateral wall LGE enhancement is seen in 94% to 100%[139,140] of patients treated with trastuzumab who had reduced LVEF. This parallels the knowledge that trastuzumab cardiotoxicity primarily affects the LV. There is CMR evidence to add to echocardiographic evidence[34] that RV myocardial dysfunction is also seen, although more subtle than LV dysfunction.[141] Animal studies show increased T1 and T2 values in subjects receiving trastuzumab with eventual recovery.[142–144] Human data show similar findings,[145] but clinical utility in early detection and prediction of CTRCT is limited due to temporal variability.[101,146]

Cardiac MRI in proteasome inhibitors

Case reports represent the bulk of literature covering the heterogeneous CMR findings in PI cardiotoxicity. Fibrosis indicated by LGE is the most common finding, seen mostly at the basal and inferior portions of the septum.[147–149] Conversely, 2 patients receiving both carfilzomib and bortezomib developed significant but reversible LVEF reduction with wall motion abnormalities without LGE.[37] The only prospective study we are aware of studied 11 patients with CV risk factors but no preexisting CV disease for up to 6 months after bortezomib therapy with echocardiography and CMR. All imaging parameters, including echocardiographic GLS and CMR LGE, were normal.[150] More data is needed for proper understanding of CMR findings in PI-associated CTRCT.

Cardiac MRI in tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors

There is scant published data on CMR findings in VEGF-Is and TKIs, mostly in the form of case reports. Many overlap as they involve TKIs that inhibit VEGF pathways. One prospective study evaluated cardiotoxicity of 90 patients in phase I trials of a VEGF-I monoclonal antibody, VEGF-I TKI, or a kinesin inhibitor.[151] Out of 90 patients, 10 developed cardiotoxicity. Of these 10 patients, 2 were taking the VEGF-I TKI and 6 were taking the VEGF-I monoclonal antibody. The only patient with a reduced EF was taking the VEGF-I TKI. None of the 10 patients had LGE on CMR. One case report of sunitinib-induced cardiomyopathy included CMR evaluation that showed no LGE or resting perfusion defects.[152] We are not aware of any published data pertaining to CMR strain, T1 mapping, or T2 mapping in relation to cardiotoxicity of TKIs or VEGF-Is. Because of the propensity of some TKIs to invoke atrial arrhythmias, such as ibrutinib, LA evaluation with LGE, T1 and T2 mapping, and CMR strain could be beneficial and warrants further study. Hypertension and vascular effects of therapies that inhibit VEGF pathways make CAD and myocardial ischemia an important adverse effect to monitor for. Along with stress and perfusion imaging, CMR offers techniques with the ability to quantify myocardial viability.[6,98]

Cardiac MRI in immunotherapy

CMR is the gold-standard noninvasive diagnostic tool for myocarditis, the most important cardiotoxic effect of immunotherapy. The Lake Louise Criteria (LLC), introduced in 2009 for the diagnosis of non-ICI myocarditis, require clinical suspicion of myocarditis plus 2 of the following: regional or global myocardial increase in T2-weighted images, increased global myocardial early T1 gadolinium enhancement, or $\geq$ 1 focal lesion with nonischemic regional LGE.[153] The emergence of T1 and T2 mapping and ECV quantification has outdated the original criteria, leading some groups to use modified LLC to incorporate these parameters to increase diagnostic accuracy.[55,154,155] One study found 100% of ICI myocarditis cases met original LLC or had abnormal T1 or T2 imaging.[155] A meta-analysis of non-ICI myocarditis patients found native T1 and T2 mapping and ECV provide comparable diagnostic performance to LLC with native T1 having higher sensitivity than LLC for non-ICI myocarditis. It is important to note the underlying inflammatory mechanisms of ICI myocarditis are not necessarily comparable to non-ICI myocarditis. Additionally, diagnostic specificity is challenging in ICI myocarditis due to inherent heterogeneity, stemming from varying levels of inflammation in varying cardiac structures.[156] This heterogeneity is reflected in the literature in both clinical presentations and imaging findings.[157–159]

Reduced LVEF on CMR is not a sensitive finding for ICI myocarditis, reported in just 39%

to 50% of patients.[155,158–160] Strain imaging via CMR-FT has demonstrated significant reduction of LV-GLS in all ICI myocarditis patients, with even larger reduction in those with reduced LVEF.[158] Although LA strain has demonstrated additional prognostic value when combined with LV strain and LLC[161] in non-ICI myocarditis, this was not seen in ICI myocarditis. In ICI myocarditis, LGE has been reported in 48% to 80% of patients.[56,157–159] LGE occurs in noncoronary distributions, but location varies by case.[159] Presence of LGE is an independent predictor of mortality in ICI myocarditis[158] but has not been associated with MACE.[159] Interestingly, in one study,[159] LGE was seen in 21.6% of patients when CMR was obtained before day 4 of admission and 72% when obtained on or after that. Thus, LGE prognostic value might differ depending on the timing of CMR acquisition.

Qualitative T1 and T2 lack adequate sensitivity compared with quantitative mapping.[155,158,162] A retrospective[155] study that evaluated T1 and T2 mapping in patients with ICI myocarditis found elevated values compared with controls in 78% and 43% of the patients, respectively. Elevated T1 values were independently associated with MACE and lower MACE-free survival. No patients with normal T1 values had MACE, suggesting a clinically important negative predictive value. Although abnormal T2-mapping has been associated with MACE in non-ICI myocarditis,[163] this is not reflected in ICI myocarditis.[155,159] Increased ECV is also associated with MACE and death in non-ICI myocarditis,[164,165] although no published data addresses this in ICI myocarditis.

Cardiac MRI in radiation therapy

Cardiotoxicity from RT has a wide spectrum of manifestations, all stemming from direct macrovascular and microvascular damage. Literature surrounding radiation can be difficult to interpret, as most studies involve patients who, in addition to RT, have received anthracyclines and/or trastuzumab. Radiation cardiotoxicity can lead to reduction in LVEF detectable by CMR. This is seen transiently at 6 months with resolution at 2 years,[166] and, in survivors, many years after therapy.[167] LA volume assessment reveals an association between LA size and radiation dose, suggesting a possible early marker of diastolic dysfunction.[131] CMR strain imaging for the detection of subclinical cardiac dysfunction in patients who received radiation is not as well studied. In one study, there is a transient decrease in CMR-derived strain at 6 and 12 months that recovers by 24 months.[166] Other studies in humans and rats have similar findings, but it is unclear if there is a correlation between GLS reduction and radiation dose.[168,169] Fibrosis indicated by LGE has been well-documented following RT; however, studies are vastly heterogeneous, reporting LGE incidence of 0% to 100%.[168,170–173] Multiple studies demonstrate LGE presence in areas that received the highest radiation doses.[170,172,173] Studies of T1 mapping post-RT are sparse and inconsistent. Some show elevated T1 mapping values in areas of higher radiation,[172,174] whereas others found either no elevation of T1 values[168] or no correlation with radiation dose.[171] There is minimal published data on T2 mapping post-RT.

CMR offers sensitive and detailed structural and tissue characterization of pericardial toxicity and its associated hemodynamic consequences. LGE of the pericardium indicates active pericarditis, whereas chronic constrictive pericarditis will not enhance. CMR tagging can identify pericardial adhesions. Real-time cine imaging during respiration can reveal hemodynamic consequences of constrictive pericarditis, such as ventricular interdependence. Real-time phase contrast imaging can be useful in detecting effects of respiration on flow through the mitral and tricuspid valves.[6,63,104] CMR can also be helpful in evaluation of valvular pathologic conditions induced by radiation toxicity, generally not seen for 10 to 20 years after therapy. CMR is particularly useful in visualizing the pulmonary valve, which can be challenging via echocardiography. CAD and ischemic heart disease secondary to radiation therapy are also assessable by CMR via perfusion imaging and coronary artery visualization.[6,63,98,104] CMR can even play a role in prevention of cardiotoxicity. Through various techniques under investigation, CMR shows promise in preparatory and real-time imaging to improve safety and precision of RT[175] and radiosurgery,[176] reducing total radiation exposure.

Potential Role of Stress Perfusion and Other Cardiac MRI Imaging Techniques

Numerous cancer therapies increase risk of vascular disease, as does malignancy itself. Contrast-enhanced myocardial stress perfusion has excellent diagnostic performance in the detection of ischemic disease.[177] However, screening via stress-perfusion CMR without symptoms does not provide additional benefit in cardiotoxicity diagnosis or management.[178] Pulse wave velocity, an MRI method of quantifying arterial stiffness, is elevated during and after breast cancer treatment with various anticancer therapies[179,180] and could represent a method of risk stratification. Four-dimensional flow MRI can provide flow and pressure parameters of the vasculature. Its role in risk

stratification is still under exploration.[181] Real-time CMR has shown benefit in enhancing precision of radiation targeting to reduce total radiation exposure[175,176] and increasing diagnostic yield of endomyocardial biopsy.[182]

Cardiac MRI and Cardiac Masses

The superior tissue characterization and spatial resolution of CMR makes it the preferred method of imaging for intracardiac and pericardial masses (see Fig. 2, Panels B-D). CMR is particularly helpful in confirmation and further characterization when echocardiography is not sufficient.[183] Balanced steady-state free precession (SSFP) is the primary method for detailed anatomic description. T1-weighted or T2-weighted double inversion recovery imaging with or without fat saturation is useful in tissue characterization of masses. Gadolinium enhancement is helpful in assessing tumor vascularity and associated myocardial fibrosis.[184] CMR performs well at distinguishing nontumors from tumors and benign tumors from malignant ones.[185,186] With a wider field of view, CMR can catch pericardial and extracardiac masses missed by echocardiography. Additionally, CMR outperforms echocardiography in predicting ultimate tumor diagnosis as confirmed by pathology. CMR has fewer false positives and can eliminate the need for biopsy by ruling out a mass seen on echocardiography.[183]

Cardiac MRI in Tamponade and Pericardiocentesis

Although echocardiography is generally sufficient to diagnose pericardial effusion and tamponade, CMR can offer further details in the assessment of pericardial disease. CMR can identify loculated or posterior effusions, pericardial thickening, and pericardial masses where echocardiography often cannot. As described above, CMR is certainly capable of detecting signs of tamponade[6,63,104]; however, it is generally unnecessary unless echocardiography is unavailable or CMR is to be obtained for another reason. One of the more helpful applications of CMR in pericardial disease is the ability to distinguish constrictive pericarditis (thickened pericardium, interventricular dependence) from restrictive cardiomyopathy (diastolic dysfunction, large but normally contoured atria, thickened myocardium, normal pericardium).[187,188] CMR does not play a role in percutaneous pericardiocentesis but can aid in planning for surgical drainage of a pericardial effusion.

Cardiac MRI in Cardiac Amyloidosis

CMR, with its fine tissue characterization, plays an important role in cardiac amyloidosis screening, diagnosis, and surveillance of disease burden. LGE is almost invariably seen in cardiac amyloidosis, with the typical patterns being diffuse subendocardial (representing earlier stages) and diffuse transmural (representing later stages). RV LGE is also seen in greater than 90% of patients. Transmural LGE is more common in ATTR than AL[189] and also carries prognostic value.[190] Native T1 values are markedly elevated in cardiac amyloid, and T1 mapping is particularly helpful when amyloid renal disease precludes the use of gadolinium.[162] ECV quantification is a valuable tool given the underlying pathologic mechanisms of amyloidosis.[191] ECV values are markedly elevated in cardiac amyloidosis, often indicating greater than 40% ECV. Serial measurement of ECV is reliable,[192] prognostic,[193] and indicates disease progression or response to therapy.[194–196] T2 mapping, of which there is little published data in regards to amyloid, shows higher values in amyloidosis compared with controls. However, there is little difference in AL and ATTR.[197] Although LGE, T1 mapping, and ECV all provide valuable roles in cardiac amyloidosis, a recent meta-analysis suggests that ECV provides the highest diagnostic and prognostic capability of the 3.[198] Regardless, all should be included in any cardiac amyloidosis evaluation.

Practical Use of Cardiac MRI in Everyday Clinical Practice

Guidelines do not recommend routine screening for CTRCT via CMR unless echocardiography is not feasible due to poor windows or CMR is needed for other indications.[5] Additionally, if echocardiography is normal or equivocal, but clinical suspicion for cardiotoxicity remains high, CMR should be obtained. CMR protocols for CTRCT evaluation differ between institutions and individual cases. Commonly used sequences include cine balanced SSFP, strain imaging through myocardial tagging or other methods, phase contrast flow, native T1 and T2 sequences with respective parametric mapping, postcontrast T1 ECV mapping, first pass arterial perfusion, inversion recovery, and 4D flow.[93,199] Suggested CMR surveillance protocols for patients on anthracyclines and trastuzumab can be found in Figs. 3 and 4, respectively. Suggested CMR surveillance protocols for patients on radiation therapy, targeted therapy, and immunotherapy can be found in Table 2. Again, individual risk assessment and joint decision-making is a crucial part in developing a patient-centered surveillance plan. Patients should be referred to a cardio-oncologist any time there are signs or symptoms of cardiotoxicity.

Future Directions and Ongoing Clinical Trials

Cardio-oncology has seen a boom in research during the past 10 years. The more we learn, the more our gaps in knowledge become evident. Strain imaging via echocardiography represents our best early imaging biomarker for CTRCT, and the addition of serum biomarkers can increase diagnostic and prognostic value. Most of the available data, however, are in observational studies of patients exposed to anthracyclines, trastuzumab, or radiation. More prospective studies with larger cohorts are needed in patients exposed to all groups of cardiotoxic cancer therapies, especially novel therapies. The LATER CARDS study will provide a large prospective dataset of echocardiographic findings and serum biomarkers in the understudied pediatric population.[200]

CMR, although offering better imaging sensitivity and specificity for most cardiac pathologic conditions, is more difficult to clinically implement and has not been as robustly studied as echocardiography. Future research should aim for larger, prospective studies evaluating traditional and emerging CMR protocols. Patients on targeted and immunotherapies are understudied compared with anthracyclines, trastuzumab, and radiation and should be a major focus of research as well. The CARTIER study is a prospective study of elderly patients on cardiotoxic chemotherapy who will receive serial CMR before each cycle of treatment and with follow-up after treatment completion.[127] The CareBest prospective study, currently underway, will enroll greater than 2000 patients with breast cancer and study various CMR parameters in a short CMR protocol[201]. Similarly, other CMR-based trials across various cancer drug-classes are underway, which should illuminate the role of trackable subclinical disease in the development of limiting CVD.

Machine learning is a growing research tool with much potential in cardio-oncology. It allows for identification of similar groups buried within the noise of highly heterogenous populations. Machine learning has been used to identify potentially cardioprotective variants in cardiac injury pathway genes among pediatric cancer survivors with anthracycline-induced CTRCT[202]. It has also been used to identify unique asymptomatic diastolic dysfunction phenotypes based on echocardiographic parameters, each with distinct long-term outcome risks.[203] It is natural to foresee the incredible value of machine learning to sift and organize the vast amount of hard data collected with echocardiography and CMR into clinically useful CTRCT prediction tools[6]. Some combination of serum biomarkers and echocardiographic strain parameters is the intuitive place to start given our current knowledge.

Finally, research should also focus on our ability to implement CTRCT screening protocols. Only 30% to 40% of patients receive optimal screening via echocardiography.[204] Implementing user-friendly guidelines and clinical tools, development of dedicated cardio-oncology programs and multidisciplinary clinics, improved patient and provider education of CTRCT, and development of quicker and cheaper imaging protocols could increase patient participation in CTRCT screening. Continued improvement of CTRCT screening protocols has the potential to positively impact survival and outcomes in the ever-growing population of patients with cancer.

CLINICS CARE POINTS

- When using echocardiography to measure LVEF, remember there is limited precision. Values can vary up to 10% between studies.
- A normal EF does not rule out the possibility of CTRCT.
- When interpreting deformation values, remember that threshold numbers and strict normal ranges have not been widely agreed upon. Relative change from baseline is a better datapoint to follow.
- Multidisciplinary clinics can minimize patient stress, enhance communication, and increase patient access to guideline and evidence-based screening/treatment.
- Echocardiography alone is not sufficient to diagnose myocarditis. CMR should be obtained anytime there is a question of myocarditis.
- Normal EF and lack of LGE do not rule out myocarditis.
- Although appropriate surveillance practices allow us to catch and treat CTRCT early, optimizing modifiable risk factors (diet, exercise, smoking, hypertension, and so forth) is equally important.
- Educating patients on signs and symptoms of CTRCT is important for patient empowerment and home monitoring of symptoms.
- Consult with an imaging or cardio-oncology specialist before obtaining echocardiography and/or CMR to ensure all needed parameters/sequences are acquired. This can prevent repeated scans and optimize available clinical data.

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