Circulation

AHA SCIENTIFIC STATEMENT

Cardiovascular Imaging in Contemporary Cardio-Oncology: A Scientific Statement From the American Heart Association

Daniel Addison, MD, Chair; Tomas G. Neilan, MD, MPH, Vice Chair; Ana Barac, MD, PhD, FAHA; Marielle Scherrer-Crosbie, MD, PhD, FAHA; Tochi M. Okwuosa, DO, FAHA; Juan C. Plana, MD; Kerryn W. Reding, PhD, MPH, FAHA; Viviany R. Taqueti, MD, MPH; Eric H. Yang, MD, FAHA; Vlad G. Zaha, MD, PhD, FAHA; on behalf of the American Heart Association Council on Cardiovascular Radiology and Intervention; Cardio-Oncology Committee of the Council on Clinical Cardiology and Council on Genomic and Precision Medicine; and Council on Cardiovascular and Stroke Nursing

ABSTRACT: Advances in cancer therapeutics have led to dramatic improvements in survival, now inclusive of nearly 20 million patients and rising. However, cardiovascular toxicities associated with specific cancer therapeutics adversely affect the outcomes of patients with cancer. Advances in cardiovascular imaging have solidified the critical role for robust methods for detecting, monitoring, and prognosticating cardiac risk among patients with cancer. However, decentralized evaluations have led to a lack of consensus on the optimal uses of imaging in contemporary cancer treatment (eg, immunotherapy, targeted, or biological therapy) settings. Similarly, available isolated preclinical and clinical studies have provided incomplete insights into the effectiveness of multiple modalities for cardiovascular imaging in cancer care. The aims of this scientific statement are to define the current state of evidence for cardiovascular imaging in the cancer treatment and survivorship settings and to propose novel methodological approaches to inform the optimal application of cardiovascular imaging in future clinical trials and registries. We also propose an evidence-based integrated approach to the use of cardiovascular imaging in routine clinical settings. This scientific statement summarizes and clarifies available evidence while providing guidance on the optimal uses of multimodality cardiovascular imaging in the era of emerging anticancer therapies.

Key Words: AHA Scientific Statements ■ amyloidosis ■ cardiac magnetic resonance imaging ■ cardio-oncology ■ echocardiography ■ immunotherapy

Cardiotoxicity is a recognized limitation of a growing number of cancer therapies. Over the past decade, there has been a marked increase in the number, types, and targets of cancer therapies, with nearly 100 new US Food and Drug Administration drug approvals since 2010 alone.[1] The incidence of cardiotoxicity with cancer therapies varies widely, depending on the definitions, type of study, and study populations, and ranges from minimal with some cancer therapies to a common occurrence with others. Our understanding of the potential cardiotoxicities associated with both novel and established cancer therapies has grown but needs to improve further. Concurrently, there have been remarkable advances in the availability and capability of cardiovascular imaging techniques, and these advances in cardiovascular imaging have opened new avenues for the understanding, diagnosis, and management of cardiovascular diseases in populations with cancer and without cancer. Yet, uniformity in the use and application of contemporary cardiac imaging has not been optimal. In addition, traditional approaches for characterizing cardiotoxicity have focused on the measurement of the left ventricular ejection fraction (LVEF).[2] Increasingly, however, the manifestations of CVD among oncological patients receiving novel and more established anticancer therapies are recognized to extend well beyond reduction of the LVEF.[3–7] Therefore, there is a clear need for consensus on the optimal use and application of a growing spectrum of cardiac imaging modalities among patients receiving contemporary anticancer therapies.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001174

Circulation is available at www.ahajournals.org/journal/circ

In this American Heart Association scientific statement, we update and define best practices for the use of cardiac imaging in the patient with cancer who is receiving therapy. We specifically consider the role and use of (1) echocardiography, (2) cardiovascular magnetic resonance (CMR), (3) cardiovascular computed tomography (CCT), (4) cardiac single-photon emission computerized tomography (SPECT), and (5) cardiovascular positron emission tomography (PET). We also aim to provide consensus practical guidance on the appropriate application across increasingly common clinical cardio-oncology scenarios (eg, myocarditis, heart failure, arrhythmias).

CURRENT DEFINITIONS OF CARDIOTOXICITY

Cancer therapies can lead to a wide array of cardiovascular complications. Heart failure resulting as a complication of anthracycline therapy was first recognized in the late 1970s[8] and remained, for many years, a synonym for cardiotoxicity. The evolution of targeted cancer therapeutics has increased the awareness of different cardiovascular effects of cancer therapies and pointed to the need for improved cardiovascular toxicity definitions.

The International Cardio-Oncology Society consensus statement[9] provides a summary of changes in criteria to diagnose cardiovascular toxicities over time with suggestions for standardized definitions across cardiology and oncology clinical documents. Particularly relevant are the Common Terminology Criteria for Adverse Events,[10] used to capture toxicities in all oncology trials because they provide key data for cardiac safety monitoring in clinical practice.

We summarize here the definitions of the most common cardiovascular toxicities, including cardiomyopathy/heart failure, myocarditis, vascular toxicities, hypertension, and arrhythmias/QT prolongation, generally aligning with the International Cardio-Oncology Society harmonization framework.[9]

Cancer Therapy–Related Cardiac Dysfunction

This term was coined to describe symptomatic heart failure and asymptomatic decreases in the LVEF occurring in patients receiving anthracyclines or trastuzumab.[2] The definition of symptomatic heart failure in contemporary heart failure guidelines includes "the clinical syndrome with symptoms or signs caused by a structural or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of pulmonary or systemic congestion"[11,12] and should be followed in patients treated with potentially cardiotoxic cancer therapeutics. The diagnosis of asymptomatic cancer therapy–related cardiac dysfunction (CTRCD) is based on an LVEF change from baseline and has been most commonly defined as an absolute decrease of >10 percentage points to LVEF <53%.[13,14] More recently, a decline in global longitudinal strain and elevations of cardiac biomarkers have additionally been incorporated into the diagnosis of asymptomatic CTRCD.[9]

Myocarditis

Myocarditis has emerged as the most relevant cardiovascular toxicity of the immune checkpoint inhibitors (ICIs) and is considered a part of immune-related adverse events resulting from overactivation of T lymphocytes with inflammatory response.[3,4] The diagnosis of myocarditis relies on a combination of criteria, including clinical findings (chest pain), electrocardiographic abnormalities, elevations in cardiac troponin, abnormalities in cardiovascular imaging (in particular CMR demonstrating inflammation), and endomyocardial biopsy findings.[15] The proposed International Cardio-Oncology Society Consensus criteria include either a histopathological diagnosis (confirming the presence of inflammatory cell infiltrate with myocyte loss) or a clinical diagnosis based on a significant elevation of cardiac troponin with 1 major criterion (CMR evidence of myocarditis) or with 2 minor criteria (clinical syndrome, ventricular arrhythmia, decline in cardiac function, overlap syndrome, or suggestive CMR findings not meeting the full criteria for myocarditis).

Arrhythmias

Atrial fibrillation, ventricular arrhythmias, and other significant arrhythmias have been increasingly recognized as serious toxicities seen with a growing number of anticancer therapies.[6,7] Appreciation of the true burden and impact of these events has been limited. Here, for uniformity, we define cardiotoxic arrhythmias as any significant arrhythmia seen during or within 6 months after anticancer treatment.[16,17]

Vascular Toxicities

Vascular toxicities are a heterogeneous group of pathophysiological processes that include disease of arterial and venous circulation such as atherosclerosis, vasospasm, thrombosis, and stroke (eg, with radiotherapy, 5-fluorouracil, ICI treatment).[9]

Hypertension

Defined as an elevated systolic/diastolic blood pressure >130/80 mm Hg, hypertension has emerged as a well-recognized, on-target side effect of cancer therapeutics, such as targeted therapies that inhibit Bruton tyrosine kinase and vascular endothelial growth factor signaling pathways.[9,17]

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001174

EVIDENCE OF IMAGING PARAMETERS AS MARKERS OF CARDIOTOXICITY

In cardio-oncology, imaging markers provide a way to detect toxicity before the development of irreversible organ damage and, if abnormal, lead to a pathway of care that allows patients with cancer to continue their treatment safely without a cardiac event or cardiac sequelae. Parameters such as LVEF, strain, and T1/T2 mapping represent a feasible and promising opportunity to objectively measure and evaluate an indicator of biological processes, pathogenic processes, or responses to a therapeutic intervention. These markers are objective, generally reproducible, widely available, and increasingly well studied, making them optimal tools for clinical practice while informing the strength of suggested practices and the early initiation of cardioprotective therapies such as β-blockers and angiotensin-converting enzyme inhibitors.[18] This is supported by several clinical trials wherein a change precedes new or recurrent cardiovascular events.[19–21] For example, among 136 patients with cancer, elevation in some parametric mapping markers (T1/T2) after immune checkpoint therapy predicted future or recurrent major cardiovascular events.[22] Reduced strain predicted heart failure among anthracycline- and human epidermal growth factor receptor 2-positive (HER2)–treated patients.[19,20] Similarly, increased left atrial volume and ventricular fibrosis were predictors of future atrial fibrillation in tyrosine kinase inhibitor (here ibrutinib)–treated patients.[23,24] Within this scientific statement and when referenced, imaging markers are considered measures that can be quantified and reflect dynamic cardiovascular pathophysiology in a patient. These markers may also be applied before, during, and after treatment for the early identification of late side effects in cancer survivors (Figure 1).

USE AND ROLE OF ECHOCARDIOGRAPHY IN CARDIO-ONCOLOGY

Echocardiography is the first-line imaging test to evaluate cardiac function in cardio-oncology patients treated with therapies that can induce CTRCD. The evidence supporting the proposed uses and consensus described here has been obtained mostly from studies done with anthracyclines and HER2-targeting therapies.

Both LVEF and peak systolic global longitudinal strain are used in the clinical decision pathways. Right ventricular function should also be obtained (Supplemental Table 1) because it has shown prognostic value but has not been used independently to direct clinical decisions. Three-dimensional acquisition is preferred to obtain a 3-dimensional LVEF. Although there is some flexibility in prior recommendations to perform an imaging study in patients with low cardiovascular risk,[25] most clinical societies recommend obtaining an echocardiogram before the initiation of a cardiotoxic cancer therapy.[2,9]

Baseline LVEF remains a powerful predictor of subsequent heart failure in patients treated with anthracyclines, and patients with LVEF at the lower limits of normal are also at risk of increased heart failure.[26] Pre-chemotherapy strain is associated with subsequent heart failure and may be most useful in stratifying patients who have low-normal LVEFs.[27] In patients with an abnormal LVEF at baseline, efforts are made to find less cardiotoxic alternative cancer treatments; however, the extent of the LVEF abnormality is important in order to weigh against the benefit of the cancer treatment. Anthracyclines are usually not prescribed if the LVEF is <30% and are prescribed on a case-by-case base, with intensive surveillance, if the LVEF is between 30% and 50%. Small prospective studies have reported the relative safety of trastuzumab[28] and sunitinib[29] in patients with mildly impaired LVEF. Given the available evidence, we suggest baseline assessment for pediatric patients and for adult patients with at least 1 cardiac risk factor (eg, age >50 years). We also suggest baseline LVEF assessment in all patients initiating anthracycline and HER2 therapies.

We suggest repeating echocardiography at a dose of ≥250 mg/m^2 doxorubicin equivalent in patients at higher risk of CTRCD, and at more frequent intervals (depending on the cardiovascular profile of the patient) in patients treated with HER2-targeting therapies (Table 1 and Supplemental Figure 1). In patients treated with MEK inhibitors or vascular endothelial growth factor inhibitors, most of the observed myocardial effect occurs during treatment, and echocardiographic follow-up during treatment may be useful, especially in high-risk patients. An echocardiogram in the year after the end of anthracycline or HER2 antibodies treatment is also suggested (Supplemental Figure 2).

The definition of CTRCD is debated and relies on the magnitude of the decrease in LVEF and, in some statements, the associated changes in strain and blood biomarkers.[2] Although the recent SUCCOUR trial (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) did not show an advantage of strain-guided cardioprotective therapy compared with LVEF-guided therapy in patients treated with anthracyclines, the end point was 2-dimensional LVEF as opposed to a clinical end point.[20] It is also plausible that strain has the most benefit in patients with low-normal LVEF. A clinical application of strain in these patients has been proposed, with an absolute value of <16% or a decrease of >15%, even with LVEF above the lower limit of normal (eg, LVEF <53%), raising the issue of abnormal function and justifying closer surveillance and possible cardioprotection.[30]

In patients treated with ICIs, there is no requirement to routinely obtain an echocardiogram. If symptoms of

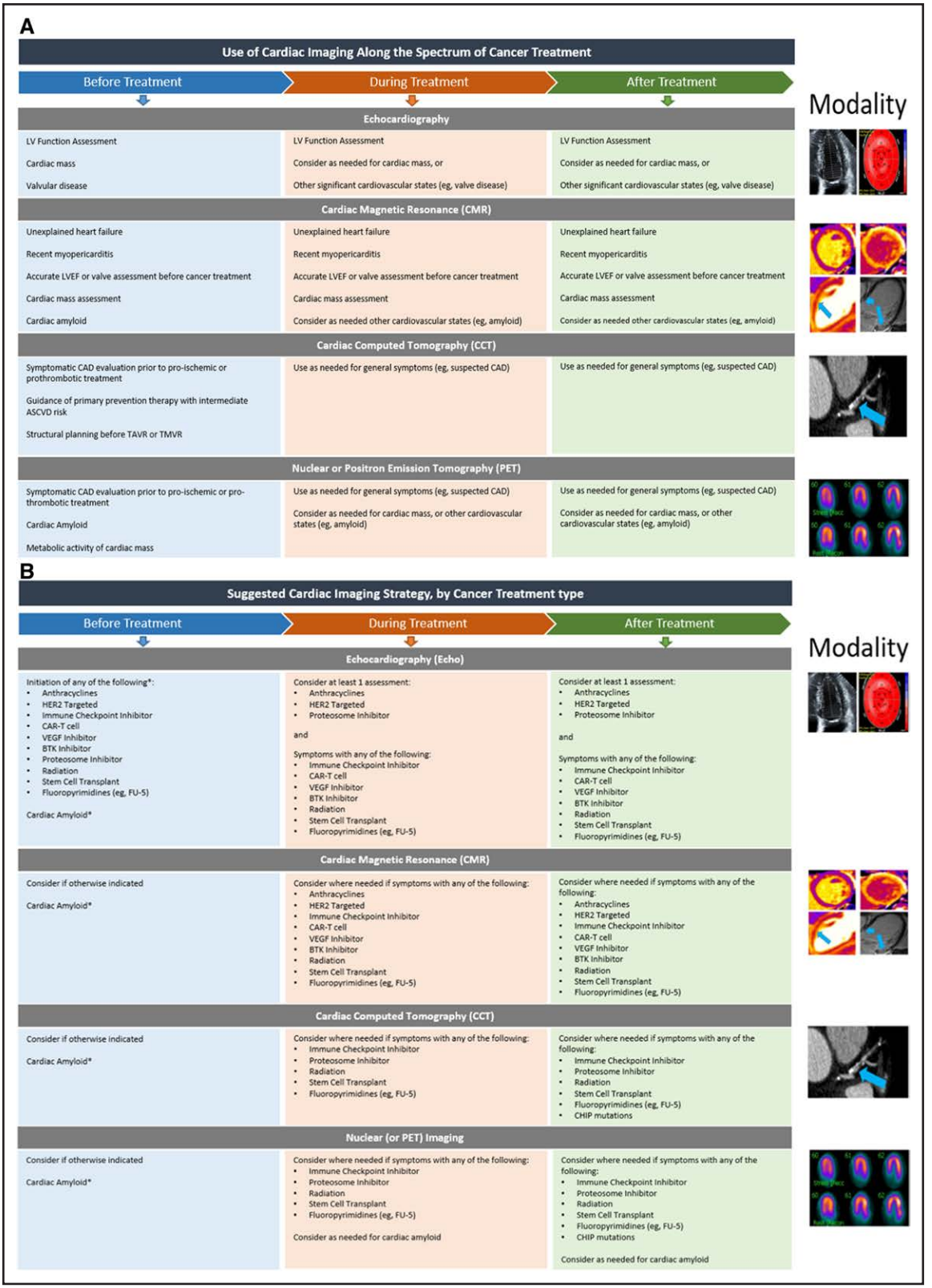

Figure 1. Suggested management strategy for uses of multimodal cardiac imaging along the spectrum of cancer care (A) and by type of cancer therapy used (B) before, during, and after cancer treatment.

ASCVD indicates atherosclerotic cardiovascular disease; BTK, Bruton tyrosine kinase; CAD, coronary artery disease; CAR-T, chimeric T-cell antigen therapy; HER2, human epidermal growth factor receptor-2; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; TAVR, transcatheter aortic valve replacement; TMVR, transcatheter mitral valve repair; and VEGF, vascular endothelial growth factor. *As needed.

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001174

Table 1. Summary of Existing Evidence for Baseline Imaging, by Common Toxicities Seen With Cancer Treatments

	Best clinical use				
Cancer therapy type	Echocardiography	CMR	CCT	Nuclear*†	Best practices
Anthracyclines	+++	++	–	–	In patients with ≥1 cardiac risk factors, pretreatment echocardiogram (or CMR) is suggested. Consider repeat echocardiography (or CMR) during treatment. Consider posttreatment screening echocardiography (or CMR) every 2–5 y.
HER2-targeted agents	+++	++	–	–	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider repeat echocardiography (or CMR) during treatment. Consider posttreatment screening echocardiography (or CMR) every 2–5 y.
ICI	+++	+++	++	++	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider repeat echocardiography (or CMR) in those with suspected cardiotoxicity.
CAR-T	+++	++	+	–	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment screening echocardiography (or CMR) within 12 mo.
BTK inhibitors	+++	++	–	–	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.
VEGF	++	+	+	+	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.
Stem cell transplantation	+++	+	+	+	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity. Consider posttreatment CCT (or nuclear stress, CMR, or cardiac PET) in those with suspected ACS.
Radiation	+++	+	++	++	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity. Consider posttreatment CCT (or nuclear stress, CMR, or cardiac PET) in those with suspected ACS.
Second- and third-generation BCR-ABL and other TKIs	++	+	–	–	Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.
MEK and RAF inhibitors	++	+	–	–	Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.
Fluoropyrimidines	++	+	++	+	Consider posttreatment CCT (or nuclear stress, CMR, or cardiac PET) in those with suspected ACS.
Proteasome inhibitors	++	++	–	–	Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.
Other (eg, IL-2 inhibitors)‡	++	+	+	+	In patients with ≥1 cardiac risk factors, pretreatment echocardiography (or CMR) is suggested. Consider posttreatment echocardiography (or CMR) in those with suspected cardiotoxicity.

ACS indicates acute coronary syndrome; BCR-ABL, breakpoint cluster region-Abelson murine leukemia; BTK, Bruton tyrosine kinase; CAR-T, chimeric T-cell antigen therapy; CCT, cardiac computed tomography; CCTA, cardiac computed tomography angiography; CMR, cardiovascular magnetic resonance; HER2, human epidermal growth factor receptor-2; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; MEK, mitogen-activated protein kinase kinase; PET, positron emission tomography; RAF, rapidly accelerated fibrosarcoma; TKI, tyrosine kinase inhibitor; and VEGF, vascular endothelial growth factor.

*Cardiac mass or as needed for other emerging cancer drug classes.

†Among ICI-treated patients, nuclear ischemic imaging for those with suspected clinical coronary artery disease.

‡Multigated acquisition scan may be used in cases in which left ventricular ejection fraction estimation is needed and echocardiography, CMR, and CCTA are not available.

+/– Refers to strength of evidence (ie, +++ implies strong evidence; ++, moderate evidence; and +, less evidence).

heart failure are noted or a diagnosis of myocarditis is suspected, an echocardiogram is warranted (Supplemental Table 2).[9,15] Although LVEF is normal in up to half of cases of myocarditis,[4] global longitudinal strain may differentiate between patients who will and those who will not develop major cardiac adverse events.[31] The role of echocardiography has not been fully elucidated in patients treated with chimeric antigen receptor T-cell therapy, in whom most episodes of heart failure appear reversible and are associated with cytokine release syndrome.[5] However, LVEF is most often decreased when an echocardiogram is performed during the episode.[33]

USE AND ROLE OF CMR IMAGING IN CARDIO-ONCOLOGY

CMR imaging has been established as the reference standard for the measurement of cardiac chamber volumes, myocardial mass, and contractile function. For screening and monitoring of cardiac function in patients with cancer

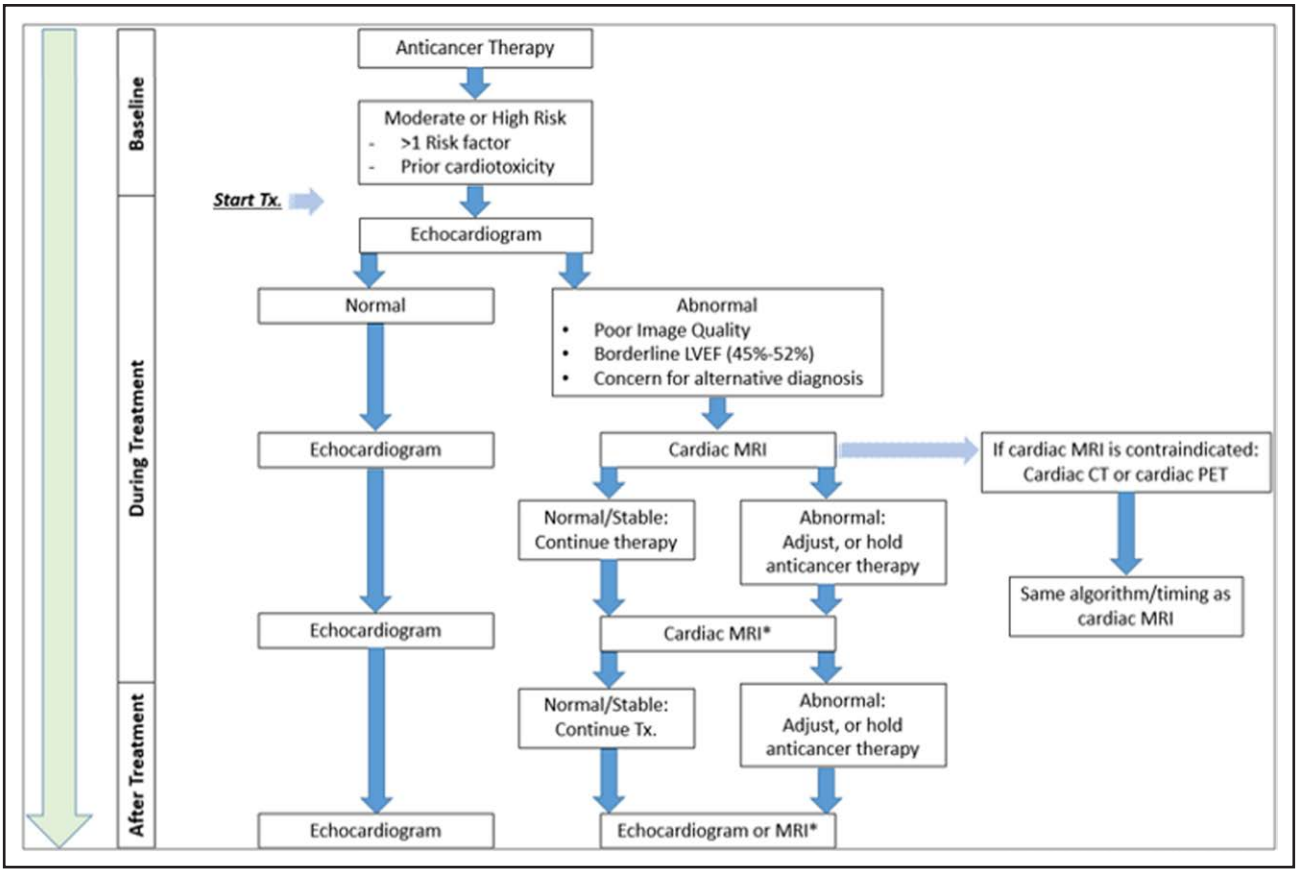

Figure 2. Suggested algorithm for monitoring left ventricular function before, during, and after cancer therapy for function monitoring.*

CT indicates computed tomography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PET, positron emission tomography; and Tx, treatment. Risk factors include (but are not limited to) age >50 years, hypertension, diabetes, cardiac arrhythmia, and prior heart failure. *Additional imaging during treatment should be tailored to the patient's cardiotoxic risk profile and treatment. All patients initiating anthracycline and HER2 therapies should have a baseline LVEF assessment as part of risk stratification.

treated with cardiotoxic chemotherapy, CMR has been suggested as a second-line modality after echocardiography, usually reserved for cases with difficult sonographic windows or cases in which there is a borderline or abnormal LVEF (Figures 2 and 3).[25,34] However, additional CMR data, including multiparametric tissue characteristics and deformation, myocardial blood flow, and arterial stiffness data, likely improve the cardiovascular assessment in selected groups of oncological patients. CMR use in cardio-oncology has been the subject of numerous small-scale studies and reviews over the past decade. Therefore, in this section, we provide a brief summary of updated evidence for the role of CMR in the evaluation of oncological patients before, during, and after cancer therapy, as well as an outline for developments that may affect cardio-oncological applications in the future.

Beyond the accurate measurement of ventricular volumes, myocardial mass, and systolic function, the measurements of LV and left atrial deformation (strain) are useful indicators in patients with heart failure with preserved ejection fraction[35–37] (Supplemental Table 3). Several studies have investigated the role of strain in assessing subclinical cardiotoxicity.[21,38–41,43] Multiparametric T1/T2 mapping has also repeatedly been shown to have both prognostic and diagnostic value for cardiotoxicity.[22,23,41,44–50] This is notable because clinical CMR-derived native T1 and extracellular volume fraction capture fibrotic change seen in preclinical models with various anticancer agents.[22,23,45–47] In addition, arterial stiffness has been identified as a marker of vascular toxicity in childhood- and adult-cancer survivors.[51–53] Yet, beyond structure and function assessments and clarifications of echocardiographic findings, CMR should be applied principally to patients with confounding disease presentations or when high-risk conditions are present (eg, suspected myocarditis, heart failure of unclear origin, and scar burden assessment in cardiotoxicity of uncertain origin, or with ventricular arrhythmias) until additional studies are available; Table 2 and Supplemental Figure 3.[49] Similarly, CMR should be considered for the evaluation of the pericardium through hemodynamic assessment of mitral/tricuspid inflow variation, interventricular dependence, and pericardial thickness and identification of pericardial inflammation through edema and fibrosis imaging. The further introduction of machine learning in the CMR

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001174

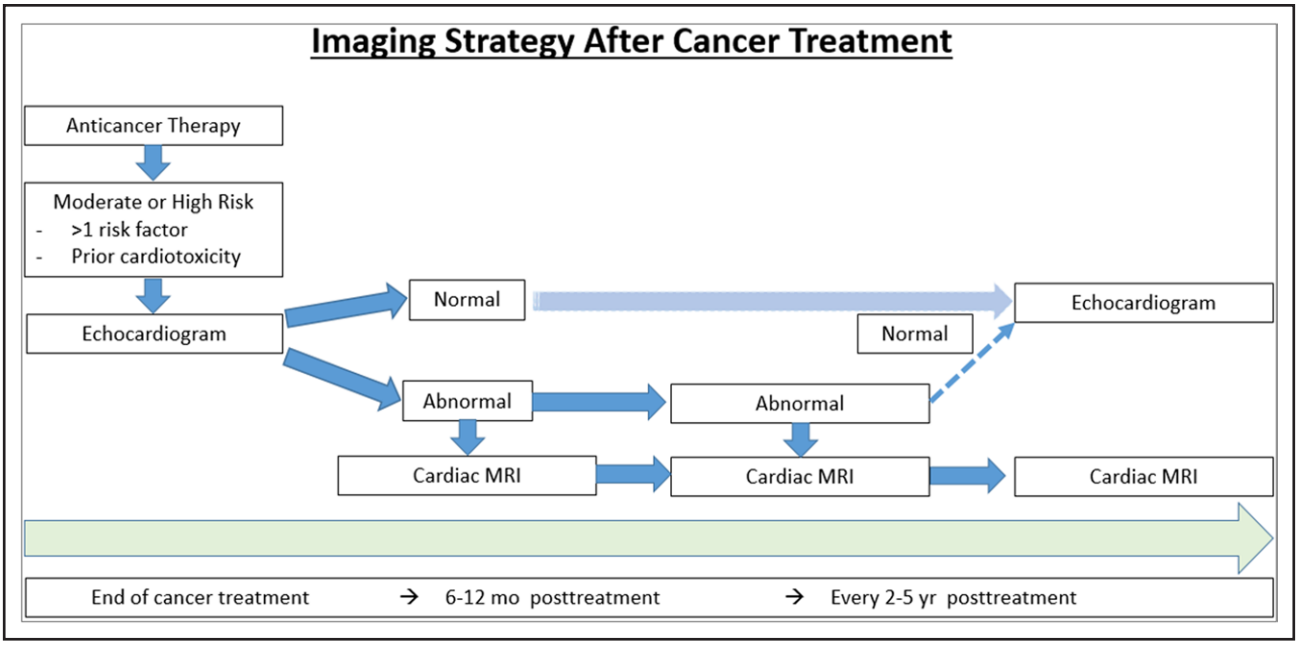

Figure 3. Suggested algorithm for monitoring left ventricular function in the patient (first) seen after cancer therapy completion. MRI indicates magnetic resonance imaging. Risk factors include (but are not limited to) age >50 years, hypertension, diabetes, cardiac arrhythmia, and prior heart failure. *Baseline echocardiography in those treated with potentially cardiotoxic cancer therapy (Table 1).

technology will open new directions toward a potential more accessible infrastructure at lower costs with rapid protocols, prognostic implications, and unprecedented early mechanistic diagnosis capability of cardiac dysfunction in patients with cancer. With time, this may make CMR even more ubiquitous in the cardio-oncology setting.

In summary, although additional studies are ongoing, the role of CMR in cardio-oncology continues to rapidly grow. The comprehensive data provided by this imaging modality may allow the use of CMR in patients who have complex differentials, such as toxic versus ischemic versus inflammatory cardiomyopathy (eg, ICI cardiotoxicity), which otherwise would potentially need a sequential combination of multiple imaging and invasive studies.

USE AND ROLE OF CARDIAC COMPUTED TOMOGRAPHY IN CARDIO-ONCOLOGY

CCT angiography (CCTA) is a standard test for the diagnosis of atherosclerotic cardiovascular disease (ASCVD), the assessment of cardiac masses, and the imaging of the pericardium.[54–56] As a result of improvements in technology, high temporal resolution, and reduced radiation exposure compared with some traditional cardiac imaging methods (ie, SPECT), CCTA is applied in various outpatient and inpatient settings to evaluate cardiac sources of chest pain. For cardio-oncology patients at high bleeding risk, CCTA provides a noninvasive option to assess for either coronary artery disease or cardiac pathology in symptomatic patients when the risk of using invasive methods (ie, coronary angiography) outweighs the benefits.[57] In addition, for the majority of patients with cancer, the accuracy of standard risk predictors—defined in this case by ASCVD risk—is largely unknown, given the myriad effects of cancer biology and cardiotoxic treatments with varying cardiovascular risk profiles.[58] Coronary artery calcium scoring has been used to re–risk-stratify ASCVD risk in intermediate-risk and long-term cancer survivorship cohorts (Supplemental Figure 4).[59] Although more definitive trials are needed, this may provide more precise risk assessment in various cancer populations, in whom the burden of nontraditional risk factors (eg, radiation) is increased (Table 1). Rudimentary coronary artery calcium visualization can already be achieved with computed tomography (CT) imaging, even with standard chest CT imaging already used for cancer staging and surveillance purposes.[60] Available literature suggests that statin is underused in incidentally diagnosed coronary artery calcium in patients with cancer.[61] In addition, ASCVD progression can be potentially monitored and studied in hybrid imaging protocols evaluating for cancer treatment response or cancer recurrence in prognostically favorable malignancies. A recent expert consensus statement also advocates for using preexisting CT imaging to evaluate for subclinical ASCVD and to implement primary or secondary prevention measures according to the overall trajectory of the prognosis of the patient with cancer if there is benefit in reducing long-term cardiovascular risk.[62]

For patients with significant valvular disease, CCTA is already standard of care in assessing cardiac anatomy and preplanning for transcatheter structural valvular disease interventions and extracardiac vascular anatomy.[54] This may be applicable in patients with cancer who require valvular intervention before high-risk cancer treatment (ie, severe aortic stenosis or mitral regurgitation, before

Table 2. Suggested Cardiac Imaging Modalities, by Cardiac Disease Presentation

	Suggested use					
Clinical manifestation	Echocardiography	CMR	CCT	SPECT	PET	Other (MUGA)
Heart failure	+++	++	+	++	+	+
ACS	+++	++	+++	+++	+++	–
Atrial fibrillation, SVTs	+++	+	+	–	–	–
Ventricular arrhythmia	+++	+++	+	–	–	–
Myocarditis	+++	+++	+	–	+	–
Pericarditis	+++	++	+	–	–	–
Valvular	+++	+	+	–	–	–
Peripheral vascular disease	–	+	+*	–	–	–
Pulmonary hypertension	+++	+	–	–	–	–
Cardiac amyloidosis	+++	+++	–	+++†	–	–
Cardiac mass	+++	+++	++	–	+	–
Preoperative evaluation	+++	+	++	++	+	+

ACS indicates acute coronary syndromes; CCT, cardiac computed tomography; CMR, cardiovascular magnetic resonance; MUGA, multigated radionuclide acquisition; PET, positron emission tomography; SPECT, single-photon emission computed tomography; and SVT, supraventricular tachycardia.

*If coverage is extended to include noncardiac vasculature (eg, aorta).

†For 99mTechnetium-pyrophosphate (PYP) scanning.

+/– Refers to strength of evidence (ie, +++ implies strong evidence; ++, moderate evidence; and +, less evidence).

cancer-related surgery, or before systemic treatments with potential for hemodynamic instability) or in addressing the long-term effects of chemoradiation in cancer survivors with radiation-induced valvulopathy. Although additional investigations are ongoing, several radiation cardiotoxicity studies have demonstrated growing utility for the capture of cardiac injury after radiotherapy.[63,64]

There are cancer agents that can cause unique mimickers of acute coronary syndrome—fluoropyridines and ICIs—for which invasive diagnostic workup may raise concerns about higher risk for complications in patients with cancer with multiple comorbidities or active hematologic derangements (ie, thrombocytopenia, anemia, neutropenia).[62] Coronary CT imaging provides a noninvasive alternative and has an extremely high negative predictive value for higher-risk patients; however, this accuracy can be negatively affected by higher heart rates, arrhythmias, or severe coronary calcifications, resulting in bloom artifact. CCTA may provide anatomic evaluation of the pericardium through assessment for effusions in the acute or subacute phase or calcifications in the chronic phase. CCTA can also provide LVEF assessment (with ECG-triggered image acquisition during systole and diastole) in patients with suboptimal imaging or contraindications to other first-line imaging modalities.[65] Other common applications include the ability to visualize intracardiac tumors or masses and to image the pericardium, with simultaneous noninvasive coronary angiography in the event that surgical intervention is warranted (Supplemental Table 4).

USE AND ROLE OF CARDIAC NUCLEAR IMAGING IN CARDIO-ONCOLOGY

Multigated acquisition scan, also known as equilibrium radionucleotide angiography, is a blood pool nuclear scan that was established in the 1970s and was adopted as a go-to modality for serial evaluation of the LVEF in patients with cardiotoxicity at a time when cardio-oncology was focused primarily on anthracyclines.[66] Although this modality allowed a more accurate estimation of the LVEF at a time when alternatives were limited, the role of multigated acquisition in the current spectrum of imaging modalities is decreased by the use of less toxic protocols, including contrast-enhanced echocardiography, CCTA, and CMR.[67] Thus, multigated acquisition should be reserved for patients needing LVEF estimation when CMR, CCTA, or quality echocardiography imaging is not available.

Imaging Myocardial Ischemia

Nuclear cardiovascular functional imaging techniques based on SPECT and PET have an established role in cardiovascular medicine in the detection of abnormal myocardial perfusion and for ischemia risk stratification.[68] Quantitative myocardial perfusion with PET is becoming more accessible with the growth in the number of scanners.[69,70] Combined with anatomic imaging (ie, coronary CT angiography), SPECT myocardial perfusion imaging has been shown to have prognostic value for long-term cardiovascular events.[71]

The vascular toxicities of multiple lines of cancer treatment have been recognized.[72] Although to date nuclear cardiology modalities have not been systematically investigated in patients treated with vasculotoxic therapies, they are used before high-risk procedures according to general guidelines.[73] The same general guidelines apply currently for the diagnosis of myocardial ischemia during cancer therapy. Considering the progressive cardiovascular risk in long-term cancer survivors, because of the exposure to high-risk oncological therapies, nuclear cardiac imaging is considered for long-term surveillance. A lower threshold for ischemia evaluation should be considered when significant coronary disease is suspected.[25]

Metabolic Tracers

Nuclear imaging has reached an established role in oncology, where it is used not only in diagnosis but also as a guiding tool for therapy. Serial staging scans offer the opportunity to investigate cardiovascular effects without additional administration of radioactive tracers.

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001174

Alone, SPECT can be limited,[74] but with ^{123}iodine-labeled metaiodobenzylguanidine, a norepinephrine analog radiotracer, it has been demonstrated to detect anthracycline-treated cardiotoxicity even before more severe cardiac damage.[75] SPECT imaging based on indium-111–labeled anti-myosin antibody, a marker of myocardial cell necrosis, also captures anthracycline-induced injury in various cancer populations, as similarly seen with anti-myosin–based imaging.[75,76] 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) is the most widely used tracer allowing the identification of tumors based on differences in metabolic activity relative to the surrounding tissues (Supplemental Table 5).[77] FDG has been used in cardiovascular imaging primarily for the evaluation of myocardial viability and inflammation (eg, sarcoidosis) by the application of specific nutritional preparation protocols that rely on myocardial metabolic flexibility to enhance or decrease myocardial glucose uptake. More recently, FDG-PET has been evaluated for vascular inflammatory changes due to immunotherapy, with potential long-term consequences for atherosclerosis progression.[60,78]

Clinical Applications

Beyond traditional application for the evaluation of suspected ischemia, recent advances in SPECT relevant to cardio-oncology include the development of high-resolution cadmium-zinc-telluride detectors and stress-first imaging protocols with reduced radiation doses for evaluation of suspected myocardial ischemia.[78a] Similarly, recent data have established the use of Tc-99 pyrophosphate bone imaging for improved noninvasive diagnostic accuracy and evaluation of cardiac transthyretin amyloidosis.[78b] Advances in PET allow for enhanced diagnostic accuracy over cardiac SPECT and should be considered where practically available. This includes the evaluation of coronary blood flow and coronary flow reserve for quantification of myocardial ischemia (eg, coronary microvascular dysfunction), and (FDG-PET) imaging for evaluation of myocardial viability postinfarction or cardiac inflammation in infiltrative cardiomyopathies.[78a,78c]

FDG-PET is well established for the assessment of tumor burden and response to therapy (Supplemental Figure 5 and Supplemental Table 6). In cardio-oncology, PET remains an active area of study. In a study of chimeric antigen receptor T-cell therapy–treated patients with non-Hodgkin lymphoma, the degree of cytokine release syndrome toxicities (including cardiac) correlated with FDG-PET–derived tumor burden. In ICI-treated patients, FDG-PET activity did not differentiate myocarditis outcomes (FDG-PET/CT imaging for the diagnosis of ICI-associated myocarditis). However, novel tracers such as ^{8}Ga-DOTATOC and ^{68}Ga-FAPI may hold promise as evidenced by a recent series in which uptake was strongly associated with histological disease.[79,80] Yet, whether PET can be routinely used in the cardiotoxic management setting remains to be seen.

In suspected cardiac amyloidosis, 99m-technetium-pyrophosphate SPECT imaging has greatly accelerated the diagnosis and treatment initiation.[78b,79]

USE OF CARDIAC IMAGING IN PEDIATRIC CANCER POPULATIONS

More than 15 000 children are diagnosed with cancer every year in the United States alone.[81] Similar to adults, improved diagnosis and treatment strategies have led to a dramatic increase in survival.[1] However, >50% of children with cancer receive known cardiotoxic therapies (eg, anthracyclines, checkpoint inhibitors), and cardiotoxicity remains a key limitation to long-term outcomes in this population.[82] Although significant overlap in the imaging strategies among this population is present, increased emphasis on the minimization of radiation (and contrast) exposure is of high(er) importance.[83,84] Furthermore, compared with adults, pediatric echocardiography evaluations should generally include a more segmental approach (eg, information on the relationship between the cardiac anatomy and surrounding extracardiac structures). CMR is useful to assess for myocardial cardiotoxic changes (eg, cardiac inflammation or fibrosis) in addition to delineation of congenital or tumor anatomy. This is exemplified by prospective data demonstrating a correlation between CMR and biomarker change shortly after anthracycline administration in children.[83,84] Echocardiography also has shown efficacy in detecting post–cancer treatment change.[85] For CCTA and PET imaging, fast acquisition protocols should be considered to reduce radiation.[86] However, additional pediatric-focused imaging studies are needed.

USE AND ROLE OF CARDIAC IMAGING TO REDUCE DISPARITIES IN CARDIO-ONCOLOGY

Numerous studies have demonstrated disproportionately higher cancer-specific and overall mortality rates among Black patients. For example, Surveillance, Epidemiology, and End Results program data show higher general cancer mortality rates among Black individuals (169 per 100 000) compared with other racial and ethnic groups in the United States (150 per 100 000 for White individuals).[87] Overall, there are limited data documenting disparities in cardiovascular outcomes among Black patients with cancer and across various cancer subtypes. In a retrospective study of 59 Black and 157 White patients, Black patients with breast cancer had higher rates of cardiotoxicity resulting in incomplete HER2-targeted therapy compared with White patients (odds ratio, 4.61 [95% CI, 1.70–13.07]).[88] Similarly, a study of 120 Black patients with breast cancer found 3-times-higher rates of cardiotoxicity compared with historical controls.[89] In a large retrospective study of 6493 survivors of several childhood cancers, Black race

and ethnicity were associated with a higher prevalence of cardiotoxicity (relative risk, 1.68; P=0.03).[90] Furthermore, in a retrospective study, women and Black individuals had a 3-fold increase in ICI-related cardiac events.[91]

Although there have been limited data documenting race- and sex-based disparities in cardiovascular imaging studies, the data for racial disparities in cardiovascular imaging among patients with cancer are sparse. A study of Medicare claims data from 5 centers found decreased used of transthoracic echocardiography among Black women compared with women of other races (relative risk, 0.92 [95% CI, 0.88–0.95]; P<0.001).[92] This finding is particularly relevant in the cardio-oncology population in whom serial imaging is relevant for prompt diagnosis of cardiotoxicity associated with cancer therapy. In particular, imaging with speckle tracking echocardiography is an important prognosticator among patients with cancer and cardiovascular disease.[93] Thus, a potential role of imaging in this population is to provide the backbone for objective assessment of cardiotoxicity. Such objective assessments are necessary for successful studies and clinical trials assessing disparities in cardio-oncology care and outcomes (Figure 4). This assertion is supported by prior studies suggesting that underdiagnosis might be a contributing factor to disparities in imaging.[94] The reasons for underdiagnosis are unclear, although other studies have cited poor access to care as a major contributor to disparities. Yet, a recent study of 149 patients (68 Black, 41 White, 33 Hispanic) from a safety net hospital who had undergone HER2-targeted therapy or anthracyclines for breast cancer found no statistical difference in the percentage of patients who had surveillance imaging to monitor for a reduction in LVEF.[95] These patients had been referred to a cardio-oncology clinic for cardiovascular care, suggesting a referral pattern with meticulous serial imaging and biomarker follow-up assessments that might benefit disparities in care.

Overall, more prospective studies are needed to determine the most effective use of imaging in diverse populations. At the outset, along with the need for more oncology clinical trials focused on cardiovascular outcomes,[96] there is a need to include diverse populations comprising people of underrepresented racial and ethnic groups in these trials.[97] Cardio-oncology specialists with expertise in cardiovascular imaging should be an intrinsic part of the expert panel of advisors on such oncological clinical trials to better inform serial and follow-up imaging based on cardiotoxicity risks anticancer therapies. The specialists should insist on outcomes in racial and ethnic disparities in cardiovascular imaging to be of core interest.

INTEGRATED CLINICAL PRACTICE APPROACH

Contemporary approaches to cardiovascular imaging in cardio-oncology are based on integration of cardiovascular imaging into oncological and cardiovascular clinical care at the time of diagnosis and during and after cancer treatment. This is a major shift from the historical practice, which focused largely on LVEF assessment before treatment with select cancer (chemo)therapeutics as a single assurance of cardiac safety. Table 1 provides strong suggestions for the use of cardiac imaging with common and emerging anticancer therapies. As with Figure 1, this scientific statement is meant to guide care, and multiple considerations will be needed over the coming decade to address the wave of additional cancer therapeutics and cardiotoxicities in this dynamic field.

EVIDENCE GAPS AND FUTURE RESEARCH DIRECTIONS

It is evident that LVEF is not sensitive enough either to predict later heart failure or to detect complications such as ICI-associated myocarditis or targeted therapy–associated arrhythmias (Supplemental Table 5).[4] The use of myocardial strain, tissue characterization, and blood biomarkers has added to the definitions of cardiotoxicity (Supplemental Figure 6).[9] Another key challenge has been the rapid growth of cancer therapeutics such as oral tyrosine kinase inhibitors that are presenting with subclinical metabolic and vascular effects for which we lack adequate imaging (bio) markers for early diagnosis or monitoring of progression.[98] To this end, additional prospective studies testing the benefits/risks of specific imaging-based strategies (eg, echocardiography versus CMR) for the care and management of patients with cancer are needed. Last, education is crucial. Recent population-based studies have shown that cardiovascular imaging among patients with breast cancer may not be done in the patients most at risk of cardiotoxicity,[99] thus raising concerns about its ability to identify patients in need and to improve cardiovascular outcomes. Supplemental Table 7 provides common areas wherein additional research is needed to further inform care.

At the same time, we have seen major progress with increased awareness of cardio-oncology and advanced collaboration across cardiovascular and oncology professionals, investigators, and professional societies in the research and development of clinical practice guidance and educational and training activities.[25,100] Continued implementation of cardiovascular imaging in definitions of cardiovascular toxicities,[9] including severity grading criteria and diagnostic evaluation standards, will provide a path for inclusion of cardiovascular imaging in oncology clinical trials and postmarketing surveillance studies and, ultimately, the development of integrated approach to clinical care.

CONCLUSIONS

Cancer survival continues to improve. Given this trend and the knowledge that cardiovascular disease is the most common cause of death among cancer survivors, there is a critical need to identify and treat patients with

 Circulation. 2023;148:e00–e00. DOI: 10.1161/CIR.0000000000001174

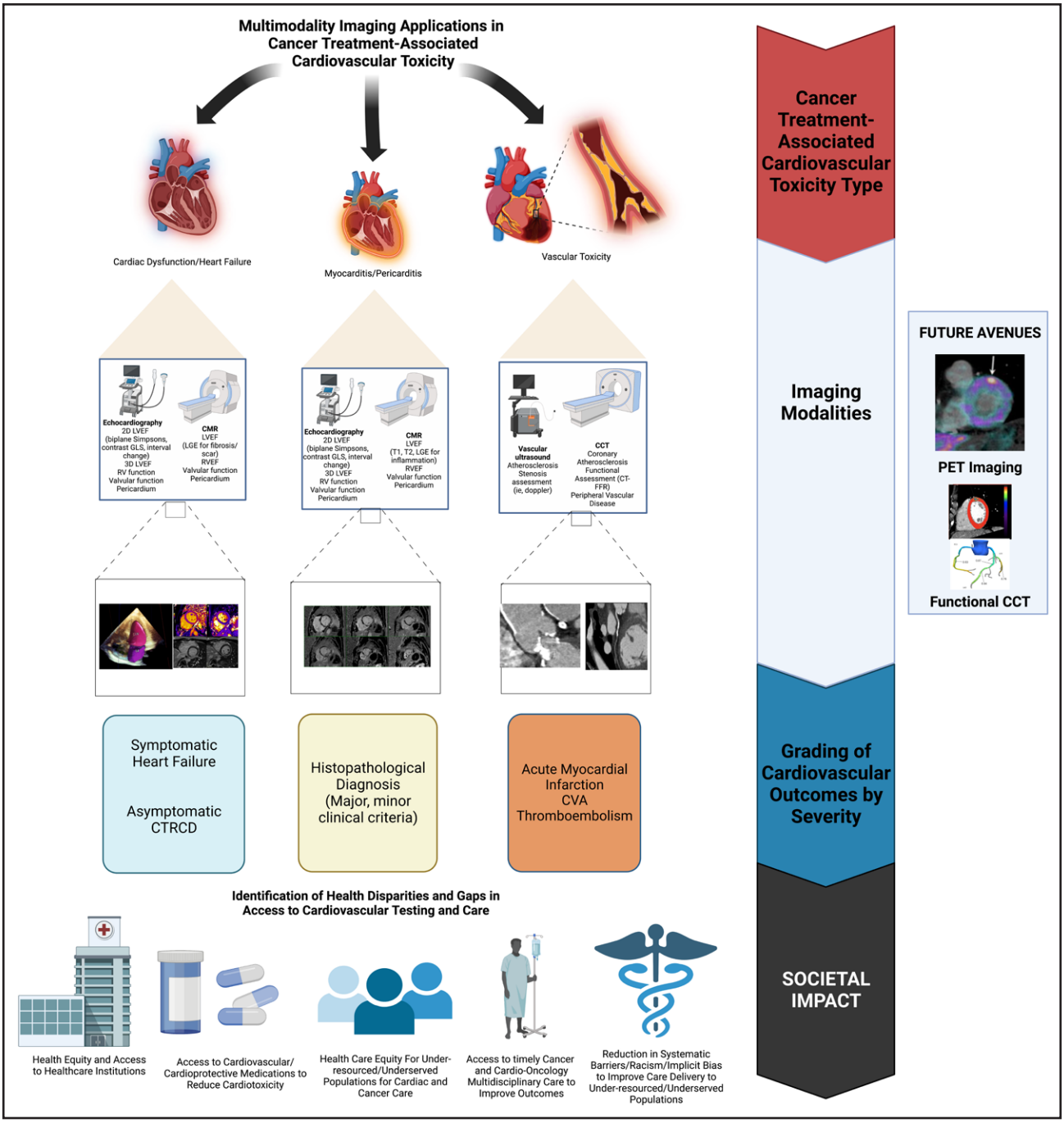

Figure 4. Summary of the uses of multimodality cardiac imaging in the cancer treatment setting.
2D indicates 2-dimensional; 3D, 3-dimensional; CCT, coronary computed tomography; CMR, cardiac magnetic resonance imaging; CT-FFR, computed tomography fractional flow reserve; CTRCD, cancer therapy–related cardiac dysfunction; CVA, cerebrovascular accident; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; PET, positron emission tomography; RV, right ventricular; RVEF, right ventricular ejection fraction; T1, longitudinal relaxation time; and T2, transverse relaxation time.

adverse cardiovascular outcomes related to prior and ongoing cancer therapies. Multimodality imaging will continue to play an essential role in the evaluation of treatment-related cardiac toxicities. Building on a rapidly growing body of evidence and the evolving novel applications of cardiac imaging in relation to treatment toxicity, we offer practical best practices for the use of imaging in the contemporary patient with cancer. Multimodality cardiac imaging will continue to be essential to meet the unmet needs and knowledge gaps within cardio-oncology.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a

Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on May 16, 2023, and the American Heart Association Executive Committee on June 21, 2023. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Addison D, Neilan TG, Barac A, Scherrer-Crosbie M, Okwuosa TM, Plana JC, Reding KW, Taqueti VR, Yang EH, Zaha VG; on behalf of the American Heart Association Council on Cardiovascular Radiology and Intervention; Cardio-Oncology Committee of the Council on Clinical Cardiology and Council on Genomic and Precision Medicine; and Council on Cardiovascular and Stroke Nursing. Cardiovascular imaging in contemporary cardio-oncology: a scientific statement from the American Heart Association. *Circulation.* 2023;148:e•••–e•••. doi: 10.1161/CIR.0000000000001174

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Acknowledgments

The authors acknowledge and thank the health care professionals, patients, and their families who supported the American Heart Association.

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Daniel Addison	Davis Heart and Lung Research Institute, The Ohio State University	NIH (K23-HL155890)†; American Heart Association–Robert Wood Johnson Foundation†; NIH (R01-HL170038)†	None	None	None	None	None	None
Tomas G. Neilan	Massachusetts General Hospital	National Institutes of Health/National Heart, Lung, and Blood Institute grants (R01HL130539, R01HL137562, K24HL150238, R01HL159187) NIH (R01HL170038)†; BMS (PI on study)†; AstraZeneca (PI on study)†	Dr Neilan is supported by a gift from A. Curt Greer and Pamela Kohlberg† and from Christina and Paul Kazilionis†, the Michael and Kathryn Park Endowed Chair in Cardiology†, and a Hassenfeld Scholar Award† TGN has received advisory fees from AbbVie†; C4 Therapeutics†; CardioRx†; H3-Biomedicine†; Genentech†; Roche†; Sanofi†; BMS†; and Intrinsic Imaging†. TGN has received grant funding from AstraZeneca† and BMS†.	None	None	None	None	None
Ana Barac	Inova Schar Heart and Vascular and Inova Schar Cancer Institute	None	None	None	None	None	None	None
Tochi M. Okwuosa	Rush University Medical Center	None	None	None	None	None	None	None
Juan C. Plana	Baylor College of Medicine	None	None	None	None	None	General Electric*	None
Kerryn W. Reding	University of Washington	None	None	None	None	None	None	None
Marielle Scherrer-Crosbie	Hospital of the University of Pennsylvania Perelman School of Medicine	National Institutes of Health/National Heart, Lung, and Blood Institute grant (R01HL130539)†	None	None	None	None	None	None
Viviany R. Taqueti	Brigham and Women's Hospital, Harvard Medical School	NIH/NHLBI (K23 HL135438, R01 HL173756)† (money paid directly to institution, no compensation to author)	None	None	None	None	Broadview Ventures†; Abbott*; Genetesis*	None

(*Continued*)

Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Eric H. Yang	University of California at Los Angeles, UCLA Cardiovascular Center	None	None	None	None	None	None	None
Vlad G. Zaha	University of Texas Southwestern Medical Center	Cancer Prevention Research Institute of Texas (CPRIT, RP180404)†	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Frank A. Flachskampf	Uppsala University, Institutionen for Medicinska Vetenskaper (Sweden)	None	None	None	None	None	None	None
Tobias Saam	Die Radiologie (Germany)	None	None	None	None	None	None	None
Samir Sarikouch	Hannover Medical School (Germany)	None	None	None	None	None	None	None
Richard A.P. Takx	University Medical Center Utrecht (Netherlands)	None	None	None	None	None	None	None
Hein Jan Verberne	Amsterdam UMC, AMC, University of Amsterdam (Netherlands)	None	None	None	None	None	None	None
David E. Winchester	Malcom Randall VA Medical Center	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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