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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Advances in Multimodality Imaging in Cardio-Oncology

JACC State-of-the-Art Review

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ABSTRACT

The population of patients with cancer is rapidly expanding, and the diagnosis and monitoring of cardiovascular complications greatly rely on imaging. Numerous advances in the field of cardio-oncology and imaging have occurred in recent years. This review presents updated and practical approaches for multimodality cardiovascular imaging in the cardio-oncology patient and provides recommendations for imaging to detect the myriad of adverse cardiovascular effects associated with antineoplastic therapy, such as cardiomyopathy, atherosclerosis, vascular toxicity, myocarditis, valve disease, and cardiac masses. Uniquely, we address the role of cardiovascular imaging in patients with pre-existing cardiomyopathy, pregnant patients, long-term survivors, and populations with limited resources. We also address future avenues of investigation and opportunities for artificial intelligence applications in cardio-oncology imaging. This review provides a uniform practical approach to cardiovascular imaging for patients with cancer.
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HIGHLIGHTS

- Echocardiography is the first-line imaging modality to assess cardiac function in patients with cancer before, during, and after cardiotoxic treatment.
- Cardiac magnetic resonance imaging can provide accurate assessment of myocardial structure and left ventricular function, and can facilitate diagnosis of myocarditis related to chemotherapy.
- Multimodality imaging can provide complementary information that may be helpful in evaluation of selected patients with cancer.

Cardio-oncology is a rapidly expanding field, as cardiovascular disease (CVD) and cancer remain the leading causes of mortality worldwide. Both CVD and cancer survivorship have improved, and the need to address the cardiovascular (CV) morbidity associated with cancer treatments is growing.

CV imaging continues to be a mainstay diagnostic component in cardio-oncology. Since the 2014 ASE/EACVI expert consensus statement,[1] there have been significant advances in the use of specific imaging techniques for cardiotoxicity screening and surveillance, as reflected by several imaging societies, in parallel with the development of newer antineoplastic therapies.[2-4]

In the present review, we offer an integrated perspective on behalf of the American College of Cardiology Cardio-Oncology and Cardiovascular Imaging Leadership Councils. This review has also been endorsed by the International Cardio-Oncology Society. As the practice of cardio-oncology is growing in academic and community centers around the world, it is crucial to provide updated guidance to inform best practices. This review addresses advancements in cardiac imaging and their applications, presenting multimodality imaging approaches for the surveillance and assessment of a range of CV toxicities, such as left ventricular (LV) dysfunction, vascular toxicity, myocarditis, atherosclerotic cardiovascular disease (ASCVD), valvular disease, and cardiac masses (**Central Illustration**).

MODALITIES OF IMAGING

Toxic effects of antineoplastic therapies or cancer itself can affect all CV structures. The primary CV imaging modalities including specific techniques, strengths, and weaknesses are detailed in **Table 1**. Echocardiography remains the first-line imaging modality for screening, diagnosis, and surveillance, with advanced imaging modalities, including cardiac magnetic resonance (CMR) imaging, nuclear imaging, and cardiac computed tomography (CCT), being useful to identify the etiology and extent of LV dysfunction, cardiac masses, and vascular toxicity.

MYOCARDIAL TOXICITY

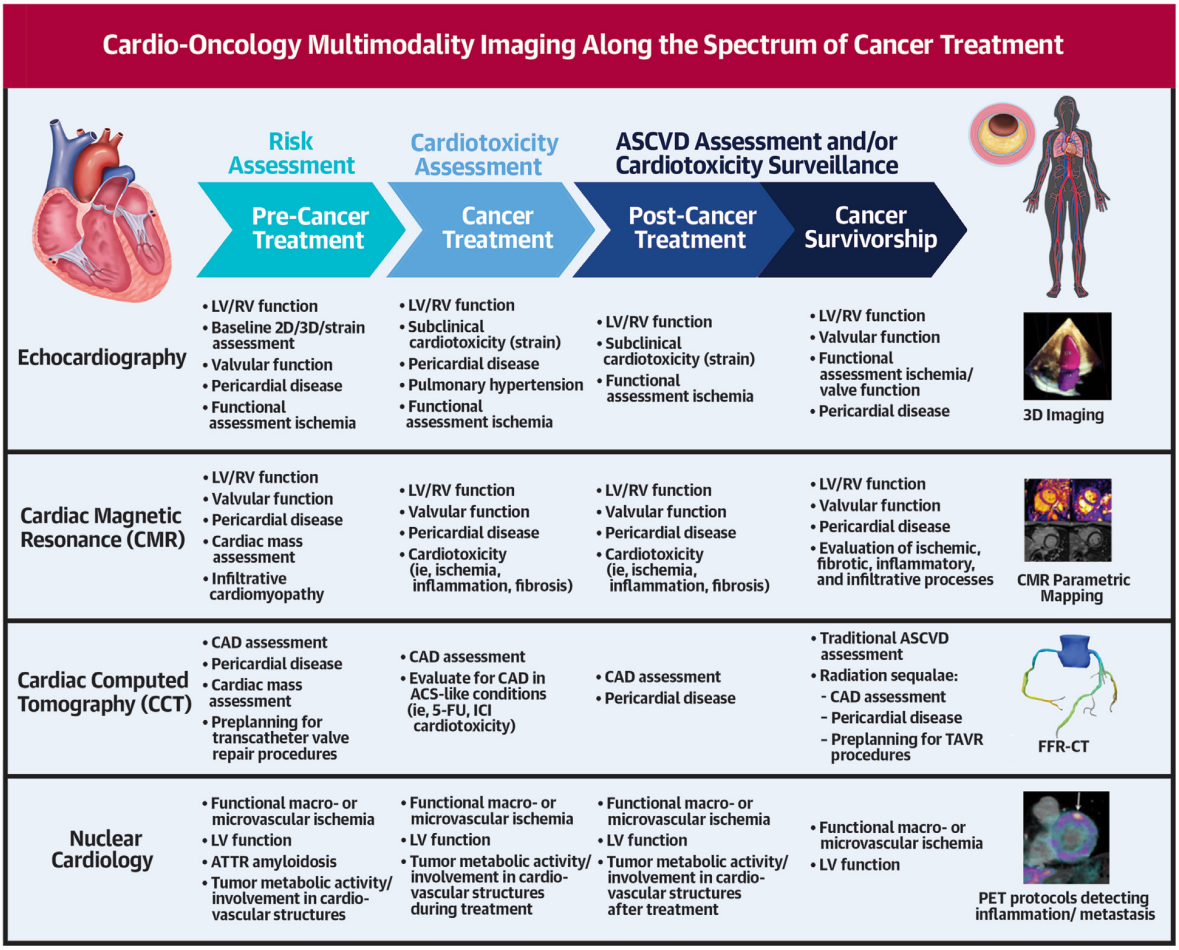
The most widely recognized myocardial toxicity readout is a decline in the left ventricular ejection fraction (LVEF) with or without symptomatic heart failure (HF). For the purposes of this review, we will use the term cancer treatment-related cardiac dysfunction (CTRCD) to denote this effect and cardiotoxicity for all other CV toxic effects. While the current paradigm relies heavily on the assessment of CTRCD by measurement of LVEF with 2-dimensional (2D) echocardiography, it is important to recognize that there may be over-reliance on LVEF, which is load dependent and can be a late marker of cardiotoxicity. The field is evolving to a more integrated approach to include complementary imaging techniques and biomarkers. **Table 2** describes the definition of CTRCD, from the perspective of imaging interpretation, proposed as a consensus by our Councils. The imaging definition of CTRCD presented in this document complements the clinical categories of cardiotoxicity recently described by the International Cardio-Oncology Society.[5] In patients receiving cancer therapeutics associated with CTRCD, cardiac imaging provides timely detection of cardiac dysfunction, allowing for early commencement of cardioprotective medications, and in many cases safe continuation of cancer therapy.

The phenomenon of anthracycline-related cardiomyopathy has been known and documented since the 1970s. Subsequently, additional targeted cancer therapies have been associated predominantly with CTRCD (**Table 3**). With the advent of immune-oncologic therapies, myocarditis is also recognized as a cardiotoxic clinical syndrome that may or may not be associated with decreased LVEF.[6] It is important to note that CTRCD may occur with new cancer therapies, and that the rapid evolution of

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
3D = 3-dimensional
ASCVD = atherosclerotic cardiovascular disease
AI = artificial intelligence
CAC = coronary artery calcium
CAD = coronary artery disease
CAR = chimeric antigen receptor
CMR = cardiac magnetic resonance imaging
CRS = cytokine release syndrome
CT = computed tomography
CTA = computed tomographic angiography
CTRCD = cancer treatment-related cardiac dysfunction
CV = cardiovascular
CVD = cardiovascular disease
FDG = fluorodeoxyglucose
GLS = global longitudinal strain
ICI = immune checkpoint inhibitor
LGE = late gadolinium enhancement
LV = left ventricular
LVEF = left ventricular ejection fraction
MUGA = multigated acquisition scan
PET = positron emission tomography
RT = radiation therapy
RV = right ventricular
TTE = transthoracic echocardiography

CENTRAL ILLUSTRATION Role of Multimodality Imaging in Cardio-Oncology Patients



Baldassarre LA, et al. J Am Coll Cardiol. 2022;80(16):1560–1578.

This figure illustrates the role of cardiovascular imaging throughout the spectrum of cancer diagnosis and survivorship. The role of cardiovascular imaging begins before potentially cardiotoxic antineoplastic therapy for screening and risk assessment and continues for cardiotoxicity surveillance during treatment and survivorship. 2D = 2-dimensional; 3D = 3-dimensional; 5-FU = 5-fluorouracil; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; ATTR = transthyretin amyloidosis; CAD = coronary artery disease; CCT = cardiac computed tomography; CMR = cardiac magnetic resonance; FFR = fractional flow reserve; ICI = immune checkpoint inhibitor; LV = left ventricle; PET = positron emission tomography; RV = right ventricle; TAVR = transcatheter aortic valve replacement. Created in biorender.

antineoplastic agents is likely to require the continued review of reported associations and updates in recommendations.

BASELINE ASSESSMENT AND SURVEILLANCE IN ASYMPTOMATIC PATIENTS UNDERGOING CANCER TREATMENT ASSOCIATED WITH CTRCD. Baseline assessment of LV function, to detect unrecognized cardiac dysfunction (present in 3% of the Framingham cohort, higher in men and older individuals, likely higher in patients with cancer), serves as a safety check before cardiotoxic drug initiation and should be performed in all patients planned to undergo potentially cardiotoxic therapy.[7] Initial baseline assessment should be obtained ideally within the 3 months preceding treatment initiation.

A complete echocardiographic protocol with Doppler examination allows the assessment of LV and RV systolic function, LV diastolic function, and valvular and pericardial structures. An accurate and reproducible assessment of LVEF is important for

longitudinal detection of CTRCD, as detailed in **Table 2**. The use of ultrasound enhancing agents to improve endocardial borders is recommended if visualization is suboptimal. Quantitative assessment of LVEF is essential with 3-dimensional (3D) volumetric assessment being preferred owing to higher accuracy and reproducibility, followed by the 2D volumetric Simpson method.[8-10]

LV peak systolic longitudinal deformation global longitudinal strain (GLS)[11] is a more sensitive and reproducible measure of LV systolic function than LVEF and may detect subclinical cardiac dysfunction before the detection of abnormal LVEF.[11] Before cancer treatment, GLS has demonstrated its value as a screening tool for risk stratification.[12,13] Normal strain values may vary according to age, CV risk factors, and equipment; in practice, most providers recognize GLS $>-16\%$ as abnormal, GLS $<-18\%$ as normal, and GLS -16% to -18% as borderline.[11] We recommend LV GLS to be measured on all patients who otherwise require an echocardiogram at baseline before initiating cardiotoxic antineoplastic therapy.

LVEF and strain are used for the detection of CTRCD during and after cardiotoxic treatment. Both the absolute GLS value and the change in GLS over the course of antineoplastic therapy have been used to recognize subclinical CTRCD.[14] The recent SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) trial demonstrated that treatment with angiotensin-converting enzyme inhibitors and beta-blockers in patients with a variety of cancers (predominantly patients with breast cancer) receiving cardiotoxic therapy based on decreased LV GLS results in a smaller decrease in LVEF than if treated after the LVEF had already decreased.[15]

Given intervendor variability in normal strain value, using the same vendor for follow-up GLS assessment is important for meaningful comparison and early detection of CTRCD in multiple cancers and treatments.[1,14] Typically, a reduction in GLS by $\geq 15\%$ from baseline is considered to be suggestive of subclinical cardiotoxicity and/or future LV dysfunction. Therefore it is important that a relative change in GLS compared with the previous measurement be reported.[11]

While echocardiography remains the first-line investigation for the detection of antineoplastic therapy associated cardiomyopathy due to availability and portability, there is a complementary role for other imaging modalities for etiologic diagnosis. These may become first-line imaging choices in patients with inadequate echocardiographic windows.

Compared with 2D echocardiography, CMR has higher reproducibility for LVEF assessment, which is particularly advantageous in patients in whom high-accuracy serial imaging of cardiac function is required, such as in clinical trials. CMR is considered to be the criterion standard for LVEF assessment, as has been demonstrated in a cohort of female cancer patients following trastuzumab and doxorubicin therapy as well as in a cohort of adult survivors of childhood cancer who received prior anthracycline or chest radiation.[16] CMR may be considered for patients with low normal or decreased LVEF on echocardiogram—or discrepant LVEF assessments on serial imaging—to confirm LV dysfunction and explore its etiology before initiation of potentially cardiotoxic antineoplastic therapy.[17] Multigated acquisition (MUGA) was historically used in the assessment of LV systolic function, but given its limitation as outlined in **Table 1**, MUGA is not a first-line imaging choice for baseline and surveillance assessment.[18] However, MUGA can be considered in selected scenarios such as in patients with suboptimal echocardiographic windows, in patients with CMR incompatible implanted devices (such as patients after mastectomy with tissue expanders), and in centers without access to CMR.

The same modality that allows LVEF evaluation before initiation of antineoplastic therapy should be ideally used for serial surveillance.[19] In addition, abbreviated protocols limited to acquiring only LVEF and GLS can be applied for follow-up imaging with both echocardiography and CMR.

Table 3 describes the recommended imaging surveillance while undergoing antineoplastic therapy. After the completion of therapy, long-term surveillance of cardiac function is advised for any patient that has received a cardiotoxic drug, but the exact frequency requires additional studies. Yearly or biannual imaging follow-up after the completion of therapy is reasonable, especially in high-risk patients (CV risk factors, high doses, or combined cardiotoxic therapies), and the interval can be decreased if cardiac dysfunction is noted. In low-risk patients in whom cardiac function remains stable, increasing the interval for long-term imaging surveillance can be considered as deemed appropriate by the patient's physician, although some continued long-term follow up with continued CV risk assessment is recommended. In addition, in metastatic disease and with long-term treatment, frequency of imaging surveillance can be decreased.

Right ventricular (RV) function has not traditionally been incorporated into the definition of CTRCD.

TABLE 1 Summary of Imaging Modalities

Echocardiography[1,96-99]

Technique

- 2D echocardiography and Doppler—structural and functional assessment, including LV and RV (size, function, and EF), valvular disease, pericardial disease, pulmonary hypertension, cardiac tumor, thrombus
- 3D—LV and RV EF, valve assessment, visualization of tumor
- Strain—GLS (2D and 3D) may identify subclinical cardiotoxicity or LV dysfunction from other causes; the pattern of strain imaging may suggest presence of cardiac amyloidosis, regional wall motion abnormalities, constrictive pericarditis
- Ultrasound enhancing agents—improve LV assessment when imaging difficult, and improve characterization (including perfusion) of cardiac masses (thrombus or tumors)
- Stress echocardiography (exercise/dobutamine)—risk stratification for CAD in patients with cancer
- TEE—2D and 3D evaluation of cardiac masses, valves, and endocarditis in immunocompromised patients

Strengths

- First-line imaging test. Easily accessible, can occur at the bedside
- Offers information regarding numerous aspects of cardiac structure and function
- Offers quantitative assessment for serial surveillance

Limitations

- Operator experience important, with potential for subjectivity in interpretation; interobserver variability with LV assessment
- Strain assessments need to be performed on the same vendor machine and ideally by the same sonographer
- Imaging windows may be difficult in those with lung disease, obesity, mastectomy, or breast implants

Cardiac MRI[1,100,101]

Technique

- Cine/steady-state free precession imaging—structural and functional assessment, including LV and RV EF, valvular and pericardial disease assessment, cardiac tumor, and thrombus anatomic assessment
- LV mass and volumes—markers for cardiotoxicity via CMR
- T1 mapping—assessment for myocardial fibrosis and infiltrative processes such as cardiac amyloid
- T2 mapping—assessment for the presence of edema or inflammation
- LGE—inflammation, fibrosis, infiltrative process
- Strain techniques (including tissue tracking, HARP, DENSE, fast-SENC)—evaluate for subclinical cardiotoxicity and other causes of abnormal GLS
- Stress CMR—evaluation for CAD or microvascular disease, radiation-induced heart disease

Strengths

- Superior image quality and resolution, cross-sectional imaging
- Ability to tissue-characterize the LV and pericardium (for presence of scar, inflammation, or infiltrative process) and masses (combination morphology, location, T1, T2, and LGE may help to differentiate different types of masses)

Limitations

- Cost and access; CMR is less readily available than echocardiography
- Gadolinium cannot be administered in severe renal impairment (risk of nephrogenic systemic fibrosis)
- Movement and arrhythmia may limit image quality
- Scan time is prolonged; patients undergoing treatment for cancer may not be able to participate in extended breath holds; may be intolerable for those with significant claustrophobia
- CMR may be contraindicated in those with metal devices/prostheses; older cardiac devices may contraindicate CMR, and newer cardiac devices may result in artifacts and reduced image quality despite being CMR conditional

Cardiac CT[37,102-104]

Technique

- Coronary CTA—to exclude or identify and assess severity of CAD in the evaluation of chest pain or LV dysfunction
- Coronary CTA with FFR—evaluation of coronary stenosis and congenital anomalous coronary for functional significance
- CTA with myocardial late iodine enhancement—may evaluate for inflammation, fibrosis, infiltrative process in those who are unable to undergo CMR
- CAC score—risk stratification for asymptomatic patients with cancer or survivors with ASCVD risk factors to guide use of statins
- Assessment of cardiac masses, pericardial disease, and valvular function/disease, and transcatheter valve intervention preplanning

Strengths

- Rapid and readily available
- Coronary CTA can offer definitive evaluation of CAD with high negative predictive value
- Noninvasive high-resolution anatomic evaluation and direct visualization of CAD; may identify subclinical CAD that may result in early treatment with statin and intensive risk factor modification
- May identify and characterize high-risk plaque features
- CAC detected on nongated CT chest scans performed in cancer patients may identify previously unknown CAD or subclinical ASCVD; potential role in patients undergoing radiation therapy (long-term follow-up)

Limitations

- Involves radiation exposure
- Iodinated contrast may limit use in more advanced renal insufficiency that does not yet require dialysis, and those with contrast allergy require premedication
- Assessment of severity of coronary lesions may be limited by the presence of significant calcification, which may be present in the more elderly, renal insufficiency or prior radiation therapy
- Tachycardia and inability to perform breath hold may limit image quality

Continued on the next page

TABLE 1 Continued

Nuclear Imaging[1,105-107]

Technique

- Stress SPECT/PET—to exclude or identify the presence of exercise/pharmacologic induced ischemia
- MUGA—assessment of LV EF
- FDG PET/CT—may identify metastasis, cardiac tumor, or inflammation (such as in cardiac sarcoidosis)
- Technetium pyrophosphate scan—diagnosis of cardiac transthyretin amyloid

Strengths

- SPECT and MUGA are readily available with good access
- PET offers superior accuracy for ischemia assessment in those who are obese
- SPECT and PET scans may offer CAC score with scout CT, which may identify nonobstructive CAD for risk factor management, especially when ischemia is absent according to perfusion imaging
- MUGA measure of EF is highly reproducible

Limitations

- Exposure to radiation
- Aside from EF, MUGA does not provide information about other cardiac structures; other LV characteristics according to MRI and echocardiography have been shown to have utility in identifying cardiotoxicity
- SPECT may be susceptible to attenuation artifacts in the obese, false positives, and may miss balanced ischemia
- Availability of PET may be limited to larger medical centers

2D = 2-dimensional; 3D = 3-dimensional; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CAD = coronary artery disease; CMR = cardiac magnetic resonance imaging; CT = computed tomography; CTA = computed tomographic angiography; EF = ejection fraction; FDG = fluorodeoxyglucose; FFR = fractional flow reserve; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LV = left ventricular; MUGA = multigated acquisition scan; PET = positron emission tomography; RV = right ventricular; SPECT = single-photon emission computed tomography; TEE = transesophageal echocardiography.

However, emerging evidence suggests that RV abnormalities are prognostically significant in patients undergoing anthracycline and trastuzumab therapy[20]; however, it remains to be seen whether it can be extrapolated to other cardiotoxic antineoplastic therapy. RV assessment by means of echocardiography routinely includes RV dimensions or areas, RV S′, tricuspid annular plane systolic excursion, and pulmonary artery systolic pressure. RV deformation analysis is currently still being investigated for detecting subclinical RV dysfunction.

Several studies have shown progressive impairment of diastolic function in patients treated with anthracyclines. Although it may precede systolic dysfunction, the prognostic value of diastolic dysfunction is modest.[21]

PRESENTATION WITH HF SYMPTOMS DURING CANCER TREATMENT. Echocardiography is a first-line imaging modality that complements electrocardiography (ECG) and cardiac blood biomarkers in patients with any new or worsening CV symptoms, such as symptoms of HF, arrhythmia, or hemodynamic instability, given its widespread availability (**Central Illustration**). A complete 2D study including LV GLS and 3D LVEF, including Doppler examination for diastology assessment, should be performed as described in the baseline protocol. CMR is often helpful to establish the etiology of symptomatic HF, and therefore may be used as a complement to echocardiography or as the first line of imaging depending on the clinical setting.[22] CMR harnesses multiparametric tissue characterization and perfusion to identify the etiology of cardiomyopathy, differentiating ischemic from toxic, inflammatory, infiltrative, restrictive, or constrictive causes.[23]

INFILTRATIVE CARDIOMYOPATHY. Infiltrative cardiomyopathy with light-chain amyloid may develop in patients with multiple myeloma or may progress from monoclonal gammopathy of undetermined significance. The prevalence of cardiac amyloidosis due to wild-type transthyretin amyloid is also higher than previously thought, especially in elderly patients in whom cancer prevalence is high.[24] In patients with suspected cardiac amyloidosis, echocardiography with LV GLS, CMR, and nuclear imaging complement the diagnostic workup, with endomyocardial biopsy being required if diagnostic uncertainty remains.

TABLE 2 American College of Cardiology Cardio-Oncology and Imaging Councils Definition of Cancer Treatment–Related Cardiac Dysfunction for Imagers

Definition	
Definite:	Reduction in LVEF by ≥10% to a value of <50%[a] Refer to cardiology/cardio-oncology, start cardioprotective meds, and consider closer monitoring.
Possible:	Reduction in LVEF by ≥10% to a value of 50%-55%, or Reduction in LVEF by <10 percentage points to a value of <50%, or Relative reduction in GLS of ≥15% without significant reduction in LVEF Refer to cardiology/cardio-oncology, consider cardioprotective meds and closer monitoring with risk-benefit discussions with ongoing cancer treatments.
Comments	
	LVEF should be measured primarily by means of 3D volumetric echocardiography. If this is not available or is not diagnostic, CMR assessment of LVEF should be considered. If CMR is not available, Simpson biplane 2D assessment of LVEF should be undertaken. Finally, if diagnostic echocardiography or CMR is not available, MUGA should be considered for LVEF assessment.

[a]LVEF lower limit of normal (LLN) may differ according to modality and laboratory. If LVEF < LLN, cardioprotective therapy should be started. Serial biomarkers (troponin and N-terminal pro–B-type natriuretic peptide) and clinical symptoms of heart failure can help guide management.

LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

TABLE 3 Multimodality Imaging During and After Treatment With Cancer Therapeutics Mostly Associated With Cardiomyopathy and Heart Failure

		Cardiac Function Screening/Surveillance[a]		
Class/Cancer Therapeutic	**Cardiotoxicity Profile**	**Baseline**	**During Treatment**	**Survivorship**
Anthracyclines (doxorubicin, epirubicin, idarubicin, daunorubicin, mitoxantrone)	Cardiomyopathy and heart failure during or within 1 year of therapy; late effects relatively rare[108]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	Follow-up assessment after cumulative dose of >250 mg/m^2 doxorubicin-equivalent and after every 50 mg/m^2 thereafter	LVEF assessment at the end of therapy and then 6-12 months following the completion of anthracycline therapy
HER2-targeted monoclonal antibodies (trastuzumab, pertuzumab, trastuzumab emtansine [T-DM1], trastuzumab-deruxtecan)	Cardiomyopathy and heart failure during the therapy; late effects relatively rare[109]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	Follow-up assessment during treatment typically every 3 months (frequency may vary depending on the agent and treatment duration)[a]	As needed[110]
Proteasome inhibitors (carfilzomib, bortezomib)	Cardiomyopathy and heart failure during the therapy[111]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	If patients experience any concerning CV symptoms or develop evidence of heart failure	As needed
MEK inhibitors (trametinib, selumetinib, cobimetinib, binimetinib) (MEK inhibitor is used typically in combination with BRAF inhibitor)	Cardiomyopathy and heart failure during the therapy[112]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	1 month after the initiation and then every 2-3 months while on therapy[113]	As needed
Selected VEGF inhibitors (sunitinib, pazopanib)	Cardiomyopathy/heart failure, hypertension, atherosclerotic disease typically during the therapy[114]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	Reassess LVEF at cycle 1, possibly cycle 3; yield of ongoing surveillance likely very low beyond cycle 3 in asymptomatic patients[75]	As needed
Osimertinib (EGFR-TKI)	Cardiomyopathy/heart failure, atrial fibrillation, QT prolongation during the therapy[115]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	Follow-up assessment during treatment typically every 3 months in patients with CV risk factors[116]	As needed[115]
Ibrutinib (Bruton TKI)	Atrial fibrillation, ventricular arrhythmia, hypertension, cardiomyopathy/heart failure during the therapy	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	In patients with symptoms suggestive of CV event or heart failure, or patients with arrhythmia (atrial fibrillation or ventricular arrhythmia); use of imaging in these instances follows the standard cardiac imaging recommendations	As needed[117]
Immune checkpoint inhibitors (ICIs)	Myocarditis, cardiomyopathy/heart failure, arrhythmia typically early during the therapy; late effects not yet well known[56]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	Immunomodulatory effects of ICIs may persist even after cessation of therapy. If patient has any concerning symptoms, should consider cardiac imaging like during the treatment phase.	As needed
CAR T-cell therapy	Heart failure, mostly associated with cytokine release syndrome (CRS)[68]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	With grade ≥2 CRS or if develop symptoms	As needed
Mitomycin	Heart failure[118]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	If symptoms	As needed
Aflibercept	Heart failure[119]	LV and RV systolic/diastolic function + GLS assessment (first-line: echocardiography; second CMR, third MUGA)	If symptoms	As needed

For symptomatic patients, see Figure 1. [a]After the completion of therapy, long-term surveillance of cardiac function is advised for any patient having received a cardiotoxic drug, but the exact frequency requires additional studies. Yearly or biannual imaging follow-up after the completion of therapy is reasonable, especially in high-risk patients (CV risk factors, high doses, or combined cardiotoxic therapies), and the interval can be decreased if cardiac dysfunction is noted. In low-risk patients in whom cardiac function remains stable, increasing the interval for long-term imaging surveillance can be considered as deemed appropriate by the patient's physician, although some continued long-term follow-up with continued CV risk assessment is recommended. In metastatic disease and with long-term treatment, frequency of imaging surveillance can be decreased.

CAR = chimeric antigen receptor; CV = cardiovascular; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; other abbreviations as in Tables 1 and 2.

Abnormal pattern of LV GLS where GLS in the basal and midsegments of the LV is more severely impaired compared with the strain values in the apical segments (apical sparing) has been shown to significantly enhance the ability of echocardiography to accurately identify cardiac amyloidosis.[25] On CMR, abnormal native T1 signal, difficulty in nulling the postcontrast myocardium, and the presence of late gadolinium enhancement (LGE) have been described.[26] However, neither echocardiography nor CMR can distinguish the amyloid type, whereas nuclear imaging can. Imaging with ^{99m}Tc-pyrophosphate and ^{99m}3,3-diphosphono-1,2-propanodicarboxylic acid is useful for identifying transthyretin amyloidosis in the majority of patients, and even recent abbreviated protocols have demonstrated 98% sensitivity and 96% specificity.[27] N-[methyl-11C]2-(49-methylaminophenyl)-6-droxybenzothiazole (11C-Pittsburgh B compound) and florbetapir are newer agents that can specifically bind to cardiac amyloid. Importantly, if a monoclonal protein is detected along with a positive nuclear scan, cardiac or other tissue confirmation of amyloid type is mandatory, because nuclear imaging may also be positive in light-chain amyloidosis.

TAKOTSUBO CARDIOMYOPATHY. Malignancy is associated with an increased risk of stress cardiomyopathy, or takotsubo cardiomyopathy, which is characterized by acute and usually reversible LV systolic dysfunction in the absence of obstructive coronary artery disease, commonly triggered by acute emotional or physical stress.[28] Long-term mortality is higher among patients with stress cardiomyopathy and malignancy, and several potential triggers may include an underlying chronic inflammatory state, the physical stress of cancer surgery, systemic antineoplastic therapy, radiation treatment, increased risk for severe infections, and the emotional turmoil of a cancer diagnosis.[28] Symptoms can mimic myocardial infarction, pulmonary embolism, cerebrovascular disorders, or antineoplastic therapy-induced cardiotoxicity. Therefore, it is essential to rule out an ischemic etiology, leveraging coronary computed tomographic angiography (CTA) or invasive angiography when indicated.

Echocardiography is usually the first test of choice, and the most common contractile abnormality of the LV in takotsubo cardiomyopathy is apical akinesis with hyperkinesis of the basal segments. Other less common patterns of combined akinesis of the mid-LV and apex, isolated akinesis of the mid-LV, isolated basal akinesis, and biventricular involvement have been noted.[29] CMR can be a helpful additional test to distinguish among other potential etiologies of cardiomyopathy, such as myocarditis. Typical CMR features include myocardial edema with a transmural midventricular to apical regional distribution pattern matching the areas of LV dysfunction,[30] and most of the patients do not exhibit any significant LGE.[31]

VASCULAR TOXICITY

BASELINE RISK: SCREENING FOR ASYMPTOMATIC ATHEROSCLEROSIS. Treatments associated with increased risk of atherosclerosis and metabolic and vascular effects are summarized in **Table 4**. Coronary artery calcium (CAC) scoring has a prominent and well validated role in the ASCVD risk assessment in the asymptomatic patient and can assist in more accurate risk stratification on top of traditional risk models across different ethnic groups and both sexes.[32] However, what warrants further investigation is its prognostic role in patients with cancer, and its relationship to cancer biology and antineoplastic treatments, which can alter the progression of ASCVD and influence future CV events and mortality.[33,34] In addition, the accuracy of CAC scoring and risk prediction in studies and registries, such as the Multi-Ethnic Study of Atherosclerosis (MESA), may not have the same accuracy in patients with a history of cancer and certain treatments associated with vascular toxicity (ie, radiation therapy [RT], immunotherapy, targeted therapies).[35]

Standard serial computed tomographic (CT) imaging performed for staging/treatment planning purposes provides an opportunity for surveillance of the evolution of ASCVD and can lead to decisions of early aggressive CV risk factor modification in prognostically favorable malignancies.[36] CAC assessment may have limitations in non-ECG-gated imaging protocols, but methods to provide reasonable quantitative estimates have been described.[37] The early recognition of increased ASCVD risk is especially important, because lipid-lowering medications such as statins are generally underused in patients with cancer.[38] Well established treatments such as RT can promote accelerated ASCVD.[39,40] Early detection and treatment of subclinical atherosclerosis in cancer survivors is recommended.[41,42] Novel and increasingly used treatments, particularly immune checkpoint inhibitors (ICIs), may have proatherosclerotic effects and have been associated with higher CV events.[43,44] Therefore, the need for a structured approach for ASCVD imaging in the cancer patient is critical to provide insight into strategies to attenuate both short- and long-term CV events, and possibly reveal mechanisms of cardiotoxicity and ASCVD unique to certain cancer disease states and treatments. Therefore, a review of

TABLE 4 Cardiotoxicity of Treatments Associated With Atherosclerosis

Class	Agent	CV Toxicity: As Defined by Atherosclerotic, Vascular, or Metabolic Associations
Tyrosine kinase inhibitors (TKIs)	Imatinib (1st gen)	N/A (possible metabolic benefit)
	Nilotinib (2nd gen)	HTN, ischemic events[120]
	Dasatinib (2nd gen)	Pulmonary arterial hypertension
	Bosutinib (2nd gen)	N/A[121]
	Ponatinib (3rd gen)	PAD, other ischemic events[122]
Other TKIs?	Sorafenib/pazopanib/axitinib	Sorafenib/sunitinib associated with arrhythmia/heart failure/ACS[123]
	Sunitinib	Sorafenib/sunitinib associated with arrhythmia/heart failure/ACS
	Regorafenib	Associated with HTN[124]
Immune checkpoint inhibitors	Ipilimumab Nivolumab Pembrolizumab Cemiplimab[43] Atezolizumab Curvalumab Avelumab	For the class: myocarditis/pericarditis, cardiomyopathy, arrhythmias predominate; initial reports included only small numbers of ischemic/atherosclerotic events (also vasculitis), but more recent 3× higher risk of atherosclerotic events (6.55/100 patient-years at 2 years)[125]
BRAF inhibitor/MEK inhibitor (combo) compared with BRAFi monotherapy	Vemurafenib and cobimetanib Dabrafenib and trametinib Encorafenib and nimetinib	For the class: main CV risk is PE, cardiomyopathy, HTN, AF, and QTc prolongation[112]
Radiation therapy (RT)		Highly prevalent (up to 85% follow radiotherapy), often years after therapy (ASCVD, valvular, pericardial) but some early events (arrhythmias, heart failure); risk further increased among those with 2 or more RT and chemotherapy[40]
Antimetabolites	5-Fluorouracil	Associated with coronary vasospasm which may lead to angina and/or MI (even in absence of underlying CAD)[126]
	Capecitabine ("oral 5-FU")	Associated with coronary vasospasm[126]
	Gemcitabine	Associated with MI; mechanism of MI doesn't appear to be atherosclerotic in nature
	Pentostatin	Rare heart failure/ischemia[127]
	Cladribine	Rare heart failure/ischemia[128]
Microtubule agents	Paclitaxel (taxane)	No strong association with atherosclerotic heart disease; case reports of myocardial ischemia/infarction[129]
	Docetaxel (taxane)	No strong association with atherosclerotic heart disease; case reports of MI/infarction[129]
	Vinblastine (vinca alkaloids)[130,131]	Vinca alkaloids (especially vinblastine): rare MI/infarction—mechanism via vasospasm?
	Ixabepilone	In combination with capecitabine, higher MI/ventricular dysfunction compared with capecitabine alone
Alkylating agents	Cisplatin	Long-term survivors associated with increased risk of dyslipidemia, HTN, obesity, and metabolic syndrome (ie, risk factors for atherosclerosis); also, MI/ischemic cardiomyopathy reported[132]
Bleomycin	Bleomycin	Rare reports of CAD/MI/infarction after bleomycin (rarely, pericarditis)[133]
Monoclonal antibodies	Bevacizumab	Associated with arterial ischemic events[134]
	Rituximab	Arrhythmias/angina in <1% of infusions; no atherosclerosis association[135]
Interferon alpha	Interferon-alfa	Associated with MI/infarction (especially among patients with previous CAD; also, arrhythmias and cardiomyopathy[136]
Interleukin-2	IL-2	Associated with MI/infarction (especially among patients with previous CAD; also, arrhythmias and cardiomyopathy[137]
Topoisomerase inhibitor	Etoposide	Associated with MI/vasospastic angina in case reports[138]
Androgen deprivation therapy for prostate cancer or aromatase inhibitors for breast cancer	Anastrozole, letrozole, exemestane GnRH agonists, GnRH antagonists, enzalutamide, and abiraterone acetate	Hypertension, hyperlipidemia, metabolic syndrome, atherosclerosis, heart failure

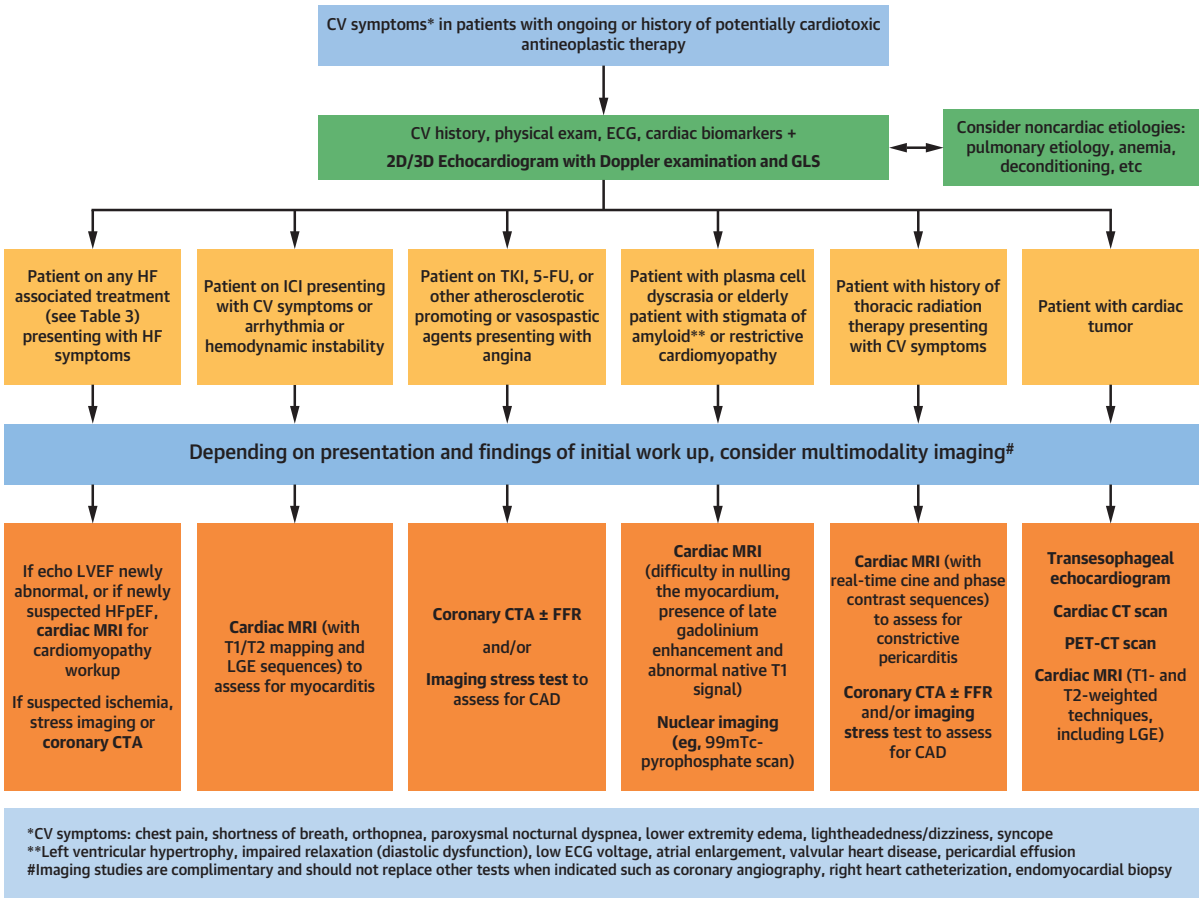
Many of the CV events are rare and the exact incidences difficult to accurately determine.

ACS = acute coronary syndrome; AF = atrial fibrillation; HTN = hypertension; MI = myocardial infarction; N/A = not available; PAD = peripheral arterial disease; PE = pulmonary embolism; other abbreviations as in Tables 1 and 3.

pertinent history, laboratory findings, and imaging studies to assess CV risk (including assessment of cardiac function) are important at baseline before antineoplastic therapies. Dedicated CAC scoring can be considered in high-risk patients and treatments to help guide preventative medical therapy.

ISCHEMIC COMPLICATIONS OF CANCER THERAPY. Chemotherapy-associated ischemic complications due to related atherosclerotic lesions, such as myocardial infarction, stroke, and peripheral artery disease, are typically reported as CV adverse events. Most CV adverse events occur in patients with moderate to high

FIGURE 1 Imaging Algorithm in Patients With Cardiovascular Symptoms



This figure illustrates the stepwise algorithm to guide the selection of cardiovascular imaging in patients with cardiovascular symptoms while undergoing antineoplastic therapy. 2D = 2-dimensional; 3D = 3-dimensional; 5-FU = 5-fluorouracil; CAD = coronary artery disease; CT = computed tomography; CTA = computed tomographic angiography; CV = cardiovascular; ECG = electrocardiography; FFR = fractional flow reserve; GLS = global longitudinal strain; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; ICI = immune checkpoint inhibitor; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography; TKI = tyrosine kinase inhibitor.

ASCVD risk profiles.[45] In patients with cancer, in addition to the evaluation for obstructive coronary artery disease (CAD), exclusion of states mimicking acute coronary syndrome, such as coronary vasospasm (ie, fluoropyrimidine cardiotoxicity), myocarditis (ie, ICI associated), or takotsubo cardiomyopathy, may require anatomic or physiologic cardiac imaging (Figure 1). Coronary CTA is a particularly useful noninvasive method to exclude the presence of obstructive coronary artery disease in acute coronary syndrome-like states such as 5-fluorouracil-associated vasospasm, ICI myocarditis, and takotsubo cardiomyopathy in selected patients.[46] Fractional flow reserve CTA for functional assessment of moderate stenoses can enhance risk stratification in patients with cancer, and this strategy has also been shown to be cost-effective in the general population.[47,48] While not specifically tested in cardio-oncology patients, stress CMR may also be useful for the assessment of ischemia, and it has prognostic value.[49]

COMBINED MYOCARDIAL AND VASCULAR TOXICITY

RT-ASSOCIATED CV EFFECTS. Radiation therapy (RT) is used for more than 50% of cancers.[50] Classically, RT has been performed with photon radiation, and in the past decade, proton beam has been introduced as a new option. This newer method focuses

more on the tumor and affects less of the surrounding structures, such as the heart and blood vessels.

Radiation exposure of the heart is common in patients treated for lymphoma and left breast, lung, and esophageal cancer. Radiation therapy exposure of the heart can be associated with CAD, valvular heart disease, pericarditis and pericardial effusion, restrictive cardiomyopathy, myocardial fibrosis, conduction abnormalities, and dysautonomia. Radiation-induced injury can affect both the microvasculature and the macrovasculature, promote accelerated atherosclerosis, and induce fibrosis of the myocardium, pericardium, and valves. Acute inflammatory complications can occur early after RT exposure, such as pericarditis or pericardial effusion, and evolve with progressive fibrotic complications and accelerated atherosclerosis over years after RT. Risk factors for negative outcomes are high mean heart dose (>30 Gy), younger age at exposure, presence of CVD or CV risk factors, concomitant chemotherapy (primarily anthracyclines), and time from RT.[51] The understanding of these mechanisms and risk factors by physicians can lead to a tailored assessment and monitoring of these patients with the objective of early detection or prevention of radiation-induced heart disease.

Echocardiography, as described above, provides a comprehensive evaluation of the cardiac structures and contractile function, and other complementary modalities, such as cardiac CTA, CMR, or nuclear medicine can be applied (**Table 4**).

The 2013 consensus on multimodality imaging after radiotherapy suggested that after termination of radiotherapy, if the patient has a high risk of ASCVD, transthoracic echocardiography be performed after 5 years with or without stress echocardiography, and if the patient is at low or intermediate risk this should be done after 10 years in asymptomatic patients.[52,53] The Councils would recommend at least this interval of imaging evaluation, with a low threshold for a shorter interval and consideration of alternative contemporary testing for ischemia, such as coronary CTA, when deemed appropriate.[53]

Because of the high surgical risk of valvular interventions in RT patients, percutaneous techniques may be safer.[54] Cardiac CT is well established as a tool in anatomic pre-planning for transcatheter-based valvular interventions, including aortic valve replacement.[55] In addition, CT can also evaluate for other non-CV sequelae of radiation, including evaluating for the presence of a porcelain aorta, carotid artery disease, and radiation-associated pulmonary fibrosis, which may increase one's risks for worse outcomes with surgery.[42]

CANCER THERAPY-ASSOCIATED IMMUNE-RELATED ADVERSE EFFECTS. The incidence of fulminant ICI-induced myocarditis is relatively low, but lower-acuity disease is likely underestimated, because surveillance testing is not widely performed.[56] Although it is not common, it is associated with a high rate of major adverse CV events (up to 50%), including death.

Consensus guidance from the American Society for Clinical Oncology, the National Comprehensive Cancer Network, and the Society for Immunotherapy Cancer recommend baseline CV evaluation, including history, examination, ECG, and troponin assessment, especially in high-risk patients, such as those planning to undergo combination ICI therapy.[57,58] We suggest baseline assessment of cardiac function (in addition to baseline ECG and troponin) in all patients undergoing cardiotoxic therapy, including ICIs.[7] Specifically, comparative information is useful if any symptoms concerning for cardiotoxicity occur, because a lack of baseline may lead to unnecessary withholding of therapy. We recognize, however, that no data exist to support the prognostic value of this practical approach and that cost-effectiveness studies should also be considered.

The diagnosis of ICI-associated myocarditis is challenging with routine imaging such as echocardiography.[56] Reduced GLS according to echocardiography has been demonstrated at the time of diagnosis compared with baseline and compared with patients without myocarditis. In addition, reduced GLS has also demonstrated to be associated with worse outcomes in patients with myocarditis, suggesting the utility of GLS in both diagnosis and prognostication.[59]

For patients with abnormal baseline echocardiography, further evaluation of the cardiomyopathy by means of CMR is recommended. In patients on ICI therapy with concerning CV symptoms, further testing with serial troponin and CMR is recommended (**Figure 1**). The diagnosis of myocarditis on CMR is made using the updated Lake Louise criteria including multiparametric tissue characterization with T1 and T2 mapping and LGE sequences.[60,61] Importantly, T1 and T2 mapping parameters have been shown to have incremental value over LGE in detecting myocarditis and are recommended to be routinely used in the evaluation of these patients.[60] Interestingly, the use of LGE alone has limited sensitivity in diagnosis of ICI-associated myocarditis.[61] In addition, CMR strain may improve the detection of myocarditis in this patient population.[62] When access to CMR is limited, when the test is not diagnostic, and for severely ill patients who may not tolerate the CMR test, an endomyocardial biopsy may

be required for diagnosis. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging may also be considered in these scenarios when CMR cannot be obtained but may be difficult to implement in the acute setting and is not an established method for myocarditis evaluation in these patients.[63] Importantly, the evidence regarding the utility of FDG-PET imaging for the diagnosis of myocarditis is limited and primitive, and the results need to be interpreted with caution.

While there are no specific guideline-directed recommendations regarding long-term surveillance for patients after ICI-induced myocarditis, follow-up CMR at 3 to 6 months has been shown to be valuable prognostically in patients with acute myocarditis in general.[64] In certain situations, such as worsening clinical status or lack of improvement, repeated CMR at an earlier interval may be considered. In addition, recent data from patients evaluated longitudinally after ICI therapy indicate a 3-fold increase in the risk of atherosclerotic CV events and aortic atherosclerotic progression.[43] While at this time there are no specific imaging surveillance guidelines for atherosclerosis detection after ICI therapy, it is important to increase the awareness of this potential risk to promote early CV risk optimization and the application of well established tools such as CAC score evaluation in the longer term.

Chimeric antigen receptor (CAR) T-cell treatment is a personalized cellular immunotherapy, generated by harvesting, genetic engineering, expansion, and reinfusion of T cells expressing chimeric receptors against specific tumor antigens that attack malignant cells and provide ongoing immune surveillance for new neoplastic cells. CAR T-cell therapy has been used successfully on a growing number of malignancies.[65] During treatment, patients can develop a cytokine release syndrome (CRS) due to the widespread release of inflammatory cytokines and chemokines from activated immune cells.[66-68] CV manifestations, including hypotension, tachyarrhythmias, and LV dysfunction, can complicate the clinical course.[66-68] While there are no guidelines for baseline testing before CAR T-cell therapy, imaging studies with transthoracic echocardiography (TTE), and CMR as needed, should be considered.[69] Approximately, up to 10% to 15% of patients may develop cardiomyopathy in the context of high-grade CRS following CAR T-cell therapy.[68,69] Therefore, it is reasonable to consider repeated imaging for those who experience high-grade CRS. Although there is a lack of robust data, in patients with pre-existing CAD or multiple CV risk factors, an imaging stress test can be considered before CAR T-cell therapy to assess for occult obstructive CAD, because such patients may be at increased risk for major CV events in the setting of CRS-induced stress, including hypotension and tachycardia.[66] However, it is important to ensure that such work-up should not delay the necessary cancer therapy.

SPECIAL POPULATIONS

WITH PRE-EXISTING OR NEW CARDIOMYOPATHY: PERMISSIVE CARDIOTOXICITY. With the exception of small studies targeting the cardio-oncologic intersection, most clinical trials of cancer therapeutics exclude patients with pre-existing cardiomyopathy. This leaves uncertainty when treating patients who have cardiomyopathy preceding cancer therapies. For example, in patients undergoing anthracycline-based chemotherapy, low baseline LVEF has been associated with worsening cardiomyopathy during treatment. Based on this evidence, a cautionary approach has been suggested for patients with baseline LVEF <50%: LVEF should be reassessed before every anthracycline infusion and anthracycline should not be administered if LVEF at any point is ≤30%.[70] There is limited evidence available on management strategies for asymptomatic patients with mildly to moderately reduced LVEF (>30% and <50%). While conventional cardioprotective therapy in patients undergoing anthracycline-based therapy has shown marginal benefit, it is important to note that patients in these trials were younger, and had normal baseline LVEF and few CV risk factors. On the other hand, small retrospective studies have demonstrated a potential benefit of cardioprotective agents, particularly the off-label use of dexrazoxane from the beginning of anthracycline therapy in reducing the risk of cardiotoxicity in patients with pre-existing LV dysfunction.[71] Although more investigations are needed, in high-risk cancer patients without acceptable alternative antineoplastic therapy, this approach can be considered after carefully weighing the risks and benefits and with close monitoring of cardiotoxicity, while on guideline-directed CV medical management and therapy. In such scenarios, we recommend LVEF assessment (preferably by means of echocardiography) before each anthracycline infusion. If available, GLS should be measured each time as well. It is important to note that GLS may be abnormal at baseline (before the initiation of anthracycline) in patients with pre-existing cardiomyopathy. However, a serial comparison of their values can be helpful in promptly recognizing subclinical cardiotoxicity. Although it is not established, it is likely that the

TABLE 5 Special Considerations for LV Function Monitoring During Antineoplastic Therapy in Patients With Cardiomyopathy

Anthracyclines (doxorubicin, epirubicin, idarubicin, daunorubicin, mitoxantrone)	• LVEF <30%: do not use • LVEF 30%-49%: reassess LVEF and GLS before each dose
HER2-targeted monoclonal antibodies (trastuzumab, pertuzumab, trastuzumab emtansine [T-DM1], trastuzumab-deruxtecan)	LVEF 40%-49%: reassess LVEF every 6 weeks for 2 assessments then every 3 months
VEGF pathway inhibitor (sunitinib)	Reassess LVEF at cycle 1, possibly cycle 3; yield of ongoing surveillance likely very low beyond cycle 3 in asymptomatic patients
Proteasome inhibitor (carfilzomib)	• LVEF ≥40%: no clear benefit from serial echocardiographic surveillance, but optimization of risk factors is prudent • LVEF <40%: repeat echocardiography in 3 months after initiation of therapy

These decisions are made in a multidisciplinary shared decision-making manner, weighing risk and benefit of alternate noncardiotoxic medications. Cardioprotective therapy should be given to all patients with LVEF < lower limit of normal. Low threshold should be maintained to repeat echocardiography in case patient develops any CV symptoms or arrhythmia while undergoing potentially cardiotoxic antineoplastic therapy. Cardiotoxic antineoplastic therapy may also cause RV systolic dysfunction and therefore, it should also be monitored along with LV systolic function, especially in symptomatic patients.

Abbreviations as in Tables 1, 2, and 3.

incremental benefits of GLS in detecting subclinical cardiotoxicity are even higher in these high-risk patients with pre-existing cardiomyopathy.

Similarly, close monitoring of cardiac function with imaging can avoid interruption or early discontinuation of other treatments associated with CTRCD, a situation associated with less favorable oncologic outcomes and decreased overall survival.[72] Two small prospective trials investigating safety of using HER2-targeted therapy in patients with breast cancer and mild LV dysfunction demonstrated that in patients without clinical HF it is safe to continue HER2-targeted therapies while receiving cardioprotective cardiac medications and close cardiac monitoring.[73,74] Tyrosine kinase inhibitors, such as sunitinib, have been associated with CTRCD. In a multicenter prospective study of patients with renal cell carcinoma receiving sunitinib, incident CTRCD occurred in 10% of patients, a third of whom had a baseline LVEF <50%.[75] All recovered with a change in dose, dose schedule, or initiation of new antihypertensive treatment, demonstrating that continuation of sunitinib is possible with careful monitoring.[75]

The irreversible proteasome inhibitor carfilzomib has been associated with a risk of CV events, such as HF, with or without decreased LVEF.[76] So far, no apparent benefit from serial echocardiographic surveillance has been demonstrated.[77,78] However, especially in patients with LVEF <40%, repeated echocardiography should be considered in a few months after initiation of therapy or if symptoms develop. A summary of the surveillance strategies in patients with impaired LVEF is included in Table 5.

PATIENTS RECEIVING ANTINEOPLASTIC TREATMENT AROUND PREGNANCY OR WITH PREGNANCY AFTER EXPOSURE. Pregnant patients with concurrent cancer diagnoses provide a unique management challenge because a balance must be found between therapies that affect their own survival and possible adverse effects to the fetus. One case series including 160 pregnant women treated with anthracyclines identified 3 infants with CTRCD.[79] Another case series showed no cardiac dysfunction in 81 children (ages 9.3-29.5 years) that were exposed to maternal anthracyclines.[80] When the LVEF of the pregnant patient is <20% during pregnancy, the European Society of Cardiology recommends a discussion about terminating the pregnancy.[81]

Pregnancy in cancer survivors presents its own challenges. A recent meta-analysis showed a 47-fold increased risk of pregnancy-related LV dysfunction or HF in women with a history of CTRCD compared with no history of CTRCD.[82] Predictors of HF included lower pre-pregnancy LVEF, younger age at cancer diagnosis, longer time from cancer treatment to first pregnancy, and higher cumulative anthracycline dose.[82]

Prepregnancy echocardiography is important for appropriate planning and informed decision making. In patients with cardiomyopathy, echocardiography should be repeated to assess the stability of LV function after neurohormonal therapy. Either exercise or dobutamine stress echocardiography should also be considered to assess LV contractile reserve, simulating the late phase of pregnancy. In the absence of a baseline evaluation, echocardiography should be performed during early pregnancy. It should then be repeated at 30 to 32 weeks of gestation (correlating with maximum volume expansion) or with any symptom development. Postpartum echocardiography should be repeated 1 month after delivery, or sooner if symptoms arise.[82,83]

LONG-TERM SURVIVORS OF PEDIATRIC CANCERS. Cancer childhood survivors are at a significantly higher risk of developing CVD compared with the general population, as well as compared with their siblings. Risk factors for developing cardiac events in this

population are previous treatment with anthracyclines and/or chest RT.[84] It is very important to follow these patients for late complications and consider CV imaging surveillance, along with addressing and focusing on aggressive lifestyle and risk factor modification.[85] The Children's Oncology Group (COG) long-term follow-up guidelines and International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) cardiomyopathy surveillance guideline recommend surveillance with TTE every 5 years or more frequently, depending on the determined risk for cardiotoxicity, based on cumulative anthracycline dose, RT dose received, and CV risk factors. Surveillance should begin no later than 2 years after the end of treatment in high-risk groups.[2]

CARDIAC TUMORS

Distinct imaging features of cardiac masses by modality and technique are topics that have been extensively covered in several comprehensive reviews.[86,87] The most important consideration is to establish whether the mass is an artifact, tumor, or a thrombus. This will affect management significantly, because a tumor requires tissue diagnosis in most cases whereas a thrombus prompts anticoagulation.[86,88] Cardiac masses are often incidentally discovered on TTE, ultrasound contrast can be utilized to assess for perfusion of cardiac masses, and transesophageal echocardiography has an important role in localizing the size and point of attachment of cardiac masses and can be especially useful when there has been a cardioembolic event related to certain tumor types, such as papillary fibroelastoma.[86] CMR has become the modality of choice for further evaluation of cardiac masses, given its good spatial resolution, less vulnerability to artifacts, and tissue characterization features.[88,89] CMR has been shown to have excellent accuracy to differentiate a tumor from a thrombus, and it is helpful to distinguish benign from malignant cardiac tumors. More recently, in a large cohort multicenter study, CMR diagnosis in patients with a suspected cardiac tumor has been shown to have incremental prognostic value to clinical risk factors.[90] CCT with iodinated contrast and PET with ^{18}F-FDG may help in differentiating benign masses from malignant cardiac tumors when CMR evaluation is not possible.[91] To assess cardiac involvement of neuroendocrine tumors, there is added utility in performing PET with ^{68}Ga-DOTA^{0}-Tyr^{3}-octreotide.[92] Further recommendations for multimodality imaging selection in cardiac mass evaluation are evolving in parallel with developments in oncologic imaging.[92]

VALUE-BASED HEALTH CARE AND CV IMAGING IN CARDIO-ONCOLOGY POPULATIONS WITH LIMITED RESOURCES

Value-based health care is increasingly critical to the provision of safe and equitable access to contemporary therapies for cancer. The costs of treatment can be magnified by the costs of surveillance for early detection of cardiotoxicity. There have been numerous studies to assess the role of imaging, but definitive cost-effectiveness studies looking at the optimal choice of modality and timing of biomarkers are still lacking.

Implementing value-based health care is especially important to increase access in areas of limited resources. Although awareness of the need for cardio-oncology care has increased worldwide, and several—mostly academic—centers have initiated such programs, there are several hospital settings (eg, governmental, group, and private practices), where access to such specialized care remains limited for a variety of reasons, including the availability of diagnostic technology, accessibility, and affordability. Another barrier is the predominant location of health care centers in major urban areas around the world, with a lack of even the most basic infrastructure in rural areas.

These limitations are shared by developing countries as well as industrialized nations. In most developing countries, the cost of specialized care such as cancer treatment and cardiotoxicity screening/surveillance imaging is an out-of-pocket expense that very often is unaffordable by the vast majority of people, especially when required multiple times throughout the cancer therapy and in survivorship. Recommendations for surveillance during the COVID-19 pandemic may be used as a guideline in centers with limited resources.[93]

Technologic advances have led to the development of portable ultrasound devices and artificial intelligence (AI) algorithms that can automatically track the endocardial border and calculate LVEF. While such echocardiograms may not provide a comprehensive assessment, it can be very helpful in resource-limited settings given that the operation of such a device does not require a high level of training, imaging acquisition can be performed relatively quickly, and it can help provide reliable and reproducible assessment of LVEF without an expert reader. The addition of cardiac-specific biomarkers such as cardiac troponin and B-type natriuretic peptide should be considered. In addition, AI-based deep-learning convolutional neural network algorithms for ECGs have demonstrated the ability to identify patients with LV systolic dysfunction and could serve as an

additional tool for screening and surveillance of cardiotoxicity.[94]

It is important to be aware that most of the patients in the resource-limited setting are not undergoing any screening or surveillance for cardiotoxicity. Therefore, the goal of such tools is to improve the degree of surveillance as a gatekeeper tool and reserve more comprehensive studies for selected high-risk patients or those with abnormal findings on the initial screening evaluations.

LIMITATIONS, KNOWLEDGE GAPS, AND FUTURE DIRECTIONS

While there have been several important advances in imaging as it relates to cardio-oncology, there remains an important need to overcome the limitations of imaging. Much of imaging is still limited by operator and interpreter variability, as well as access. Estimation of commonly used indices of cardiac function, including LVEF or LV strain, or even degree of coronary stenosis, is subject to interpreter variability. To overcome this, there is a need for careful oversight and quality control and quality assurance assessment before the adoption of any new imaging measure. Quality control and assurance measures should be performed at standardized intervals on a regular basis.

Moreover, the true clinical utility of many of the advanced imaging measures for the screening, diagnosis, and early detection of CV disease remains uncertain. There remains vigorous and healthy debate regarding the clinical role of measures such as GLS as a risk-guided approach to cardio-protection. The value of subclinical changes in cardiac function also remains to be determined.

There is a critically important question related to the access and costs of many imaging modalities, including CMR imaging with multiparametric mapping. The cost-effectiveness of surveillance imaging in survivorship is an area of active research as well, with data suggesting that there may be more cost-effective strategies than those currently recommended.[95]

The application of AI and machine learning strategies to phenotype the pathophysiologic perturbations with potentially cardiotoxic cancer therapy is an area of growth for the field. AI with deep learning may help to automate some of the tedious tasks, improve the accuracy and reproducibility, and enhance the efficiency across the spectrum of imaging modalities. More broadly, the use of AI may allow integration of clinical and laboratory parameters with multimodality imaging data to define individual phenotypes and better detect and predict the CV risk and potential treatment responses of cardio-oncology patients.

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