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Current Imaging Strategies in Cardio-Oncology

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# PART II

# Clinical aspects of cardio-oncology

# Current imaging strategies in cardio-oncology

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## INTRODUCTION

The increasing number of cancer survivors is a reflection of the advancements that have been made in early detection, and treatment with chemotherapy, targeted therapies, immunotherapy and radiation (1). Cancer therapies can cause a range of cardiovascular adverse effects, including congestive heart failure, angina symptoms, acute coronary syndrome, stroke, arrhythmias, accelerated atherosclerosis, and peripheral arterial disease (2). Structural and functional changes of the cardiovascular endothelium owing to chemotherapeutic agents can lead to both short- and long-term sequelae that may impact long-term mortality and quality of life, even if the patient's malignancy is successfully treated. The presence of traditional cardiovascular risk factors is associated with increased risk of developing cardiovascular complications from cancer treatments. Cardiovascular imaging plays a crucial role in detecting both subclinical changes and symptomatic disease (3,4).

Although the frequency of screening for cardiotoxicity in patients undergoing active treatments and cancer survivors remains a topic of debate and ongoing research, screening and early diagnosis of cardiovascular complications of cancer treatments can potentially attenuate or prevent significant morbidity and mortality in cancer patients. Many different imaging modalities have been used for detection and monitoring of chemotherapeutic-related cardiotoxicity. Here, we highlight the important advantages and disadvantages, as well as the specific applications of transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (CMR), multigated cardiac blood pool imaging (MUGA), nuclear perfusion scans, positron emission tomography (PET), computed tomography (CT), and vascular ultrasound in cancer patients receiving chemotherapy and/or radiotherapy with potential short- and long-term cardiovascular toxicity. We also review the cardiotoxicity surveillance recommendations from the Children's Oncology Group, International Late Effects of Childhood Cancer Guidelines, as well as five different society-endorsed statements.

## IMAGING CLASSIFICATION OF CARDIOTOXICITY

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) define cancer therapeutic-related cardiac dysfunction (CTRCD) as a reduction in left ventricular ejection fraction (LVEF) of >10% to a value of <53% which should be confirmed

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on a follow-up study in 2–3 weeks (5). Table 2.1 lists the classifications of severity of left ventricular (LV) dysfunction, as well as the American College of Cardiology (ACC) and American Heart Association (AHA) stages of heart failure, which can also be applied to patients who develop cancer therapy-related cardiomyopathy.

While most of the guidelines on imaging for the detection of cardiotoxicity focus on LVEF assessment, other chemotherapeutic-related cardiac effects, including radiation-induced cardiac disease, coronary artery thrombosis, and vasospasm, will be mentioned here when appropriate. The cardio-oncologist now has access to a variety of multimodality imaging options to assess for cardiotoxicity, and it is critical to understand the strengths and weakness of each modality as well as the evidence to date regarding their indications (Table 2.2).

## Transthoracic echocardiography

TTE is the most commonly used method for evaluation of cardiac dysfunction from various causes. Echocardiography enables a comprehensive assessment of cardiac function, structure, valvular disease, and the pericardium. LVEF and right ventricular (RV) function are important parameters to assess when CTRCD is suspected, while pericardial and valve thickening are more common manifestations of radiation-induced cardiac disease. While chemotherapy-induced cardiotoxicity can affect the RV as well as the LV, changes in RV function is not known to be associated with worse outcomes. TTE also enables assessment of diastolic dysfunction; however, these changes have not been reliably predictive of cardiotoxicity (6).

TTE has tremendous advantages when compared to other imaging modalities because it is widely available, inexpensive, portable, and is not associated with radiation exposure. The main limitations include limited accuracy and reproducible measurements. LVEF measurement using 2D TTE biplane method (Figure 2.1) has a temporal variability/coefficient of variation of 7.4% (7), which is important to highlight because the measurement variability is close to the definition of cardiotoxicity (defined as a drop in LVEF of 10% or more (5)). Measurement variability is the result of a number of factors including poor acoustic windows and body habitus which can affect the quality of the

images as well as the geometric assumptions used to estimate 3D volumes from 2D images. Some of these limitations are minimized with 3D echocardiography measurements (Figure 2.2), which are not reliant on geometric assumptions. For example, LVEF assessment with 3D echocardiography has a temporal variability/coefficient of variation of 4.0% (7). Recognizing this, the ASE encourages use of 3D echocardiography whenever possible (5).

Echocardiography-based deformation imaging (also known as strain imaging), has become an essential tool for cardiotoxicity surveillance. While reduction in LVEF correlates with clinical cardiotoxicity, changes in strain are more sensitive, appear prior to LVEF reduction, and are suggestive of subclinical cardiotoxicity. Global longitudinal strain (GLS) is a measure of the average change in length of the left ventricular in the longitudinal direction in the apical four-, three-, and two-chamber views. GLS has been found to be the best predictor of cardiotoxicity due to anthracycline use (Figure 2.3). A fall in GLS between 10% and 15% is associated with development of both symptomatic and asymptomatic cardiotoxicity (8,9). A reduction of 15% from baseline is considered abnormal and suggestive of cardiac injury (10). A longitudinal strain <19% at the completion of anthracycline therapy has been associated with late development of cardiotoxicity (11). Although LV radial and circumferential strain are often measured, global radial and circumferential strain have not been correlated with cardiotoxicity. The European Society of Cardiology (ESC) and ASE recommend performing GLS measurements at the time of LVEF assessment (5,10). It is important to highlight that there are significant variations in normal strain values between vendors and tracking algorithms, therefore using the same software and vendor for follow-up studies is important (5).

## Multigated cardiac blood pool imaging

MUGA is a nuclear-based imaging modality that uses a radiotracer to tag red blood cells which are counted as they flow through the heart allowing for an highly accurate assessment of cardiac function. MUGA was the first imaging study used for LVEF assessment as a way to define and track cardiotoxicity (Figure 2.4). The initial recommendations for anthracycline-induced cardiotoxicity monitoring were based on

Table 2.1 Different classification schemes for cardiac toxicity and heart failure

| Classification system | Severity | | | | |
|---|---|---|---|---|---|
| | Low | | Intermediate | | High |
| **Oncology derived** | | | | | |
| LV systolic dysfunction (CTCAE, version 4.03) | – | – | Symptomatic as a result of a drop in EF; responsive to intervention | Refractory or poorly controlled HF owing to EF drop; intervention such as LVAD, vasopressor support, or heart transplantation indicated | Death |
| Heart failure (CTCAE, version 4.03) | Asymptomatic with abnormal biomarkers or imaging | Symptoms with mild to moderate activity or exertion | Severe with symptoms at rest or with minimal activity or exertion; intervention indicated | Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support) | Death |
| Decreased ejection fraction (CTCAE, version 4.03) | – | Resting EF 40–50%; 10–19% drop from baseline | Resting EF 20–39%; >20% drop from baseline | Resting EF <20% | – |
| Cardiac Review and Evaluation Committee | Any of 4 criteria confirms cardiac dysfunction: cardiomyopathy, reduced LVEF (global or more severe in the septum); symptoms of HF; signs associated with HF (S3 gallop and/or tachycardia); and decrease in LVEF from baseline ≥5% to <55% with accompanying signs or symptoms of HF or decline in LVEF ≥10% to <55% without accompanying signs of symptoms of HF | | | | – |
| **Cardiology derived** | | | | | |
| Heart failure stage (ACC/AHA) | Stage A, at risk (e.g., patients receiving cardiotoxic medications but without structural heart disease or symptoms) | Stage B, structural heart disease (hypertrophy, low EF, valve disease) | Stage C, structural heart disease with prior or current symptoms | Stage D, refractory HF requiring specialized interventions | – |
| NYHA symptom classification | Grade I, no limitations of activity | | Grade II, mild limitation of activity; grade III, marked limitation of activity | Grade IV, confined to bed or chair | – |

*Source:* Adapted from Khouri MG et al. *Circulation.* 2012;126:2749–63.
*Abbreviations*: CTCAE, Common Terminology Criteria for Adverse Events; EF, ejection fraction; HF, heart failure; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.

**Table 2.2** Imaging modalities currently used to evaluate cardiotoxicity

| Modality | Pros | Cons |
|---|---|---|
| MUGA | Reproducibility<br>Accuracy | Involves radiation<br>Not able to evaluate other cardiac structures |
| CMR | Accuracy<br>Can evaluate other cardiac structures<br>Can evaluate myocardial perfusion, viability and fibrosis | Not easily available at all centers<br>Higher costs |
| TTE (2D/3D) | Easy accessibility<br>Portability<br>No radiation<br>Can evaluate other cardiac structures and pulmonary hypertension<br>Can use speckle tracking to evaluate for subclinical markers like myocardial deformation | Not as accurate in evaluating LVEF when compared to MUGA and CMR and can miss small changes in LV contractility (use of contrast is recommended in 2D images if two contiguous segments are not well visualized in apical views) |

*Abbreviations:* MUGA, multigated blood pool acquisition; CMR, cardiac magnetic resonance imaging; TTE, transthoracic echocardiogram; 2D, 2-dimensional imaging; 3D, 3-dimensional imaging; LVEF, left ventricular ejection fraction.

LVEF assessment by MUGA (12). Compared to echocardiography, MUGA-derived cardiac functional assessment is more accurate with less measurement variability (13); however, it does not assess valvular or pericardial disease, and it provides limited information about RV function. In addition, it is both more costly than echocardiography and exposes the patient to radiation which can become significant if multiple follow-up studies are needed. In light of these limitations and concerns, MUGA is less commonly used as the first-line study than echocardiography. It remains a good option for highly accurate LVEF assessment when echocardiography is suboptimal or the LVEF measurement is uncertain.

## Cardiac magnetic resonance imaging

CMR is a newer and powerful imaging modality that manipulates magnetic fields to generate high resolution cardiac images. CMR is recognized by the ACC as a potential method for cardiotoxicity screening, and it is considered a gold standard study for assessment of LV function (14). CMR can assess both systolic and diastolic myocardial function, myocardial structure, and provide assessment of valve function. Using various sequencing methods, CMR can be adapted to provide virtually any information including pericardial thickness, myocardial fibrosis/scar, and evidence of infiltrative disease. It provides tissue characterization for cardiac masses

as well. It does not expose the patient to any radiation. Compared to echocardiography, images are higher resolution and more reproducible; therefore, when discontinuation of chemotherapy is being considered due to cardiotoxicity, CMR should be used to verify the LVEF (5).

While CMR is considered a very safe test, deposits of gadolinium, which is the main contrast used in CMR, have recently been noted in the brains of patients undergoing multiple CMR studies. This has raised some concern and has prompted an Food and Drug Administration (FDA). Drug Safety warning (15). The potential effects of gadolinium retention are currently being monitored and the FDA has expressed that based on current knowledge, the benefits of magnetic resonance imaging (MRI) continue to outweigh any potential harm. In patients with kidney dysfunction and a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m$^2$, gadolinium is contraindicated due to risk of a progressive condition called nephrogenic systemic fibrosis. Despite its breadth and accuracy, CMR use is limited for multiple reasons. It is expensive and not available in many centers. It requires long exam times with significant patient cooperation and long periods of breath-holding. In patients with pacemaker/defibrillator or breast implants, image quality can be limited by artifact.

CMR is well-recognized as a reliable study for evaluation of cardiotoxicity, and many types of
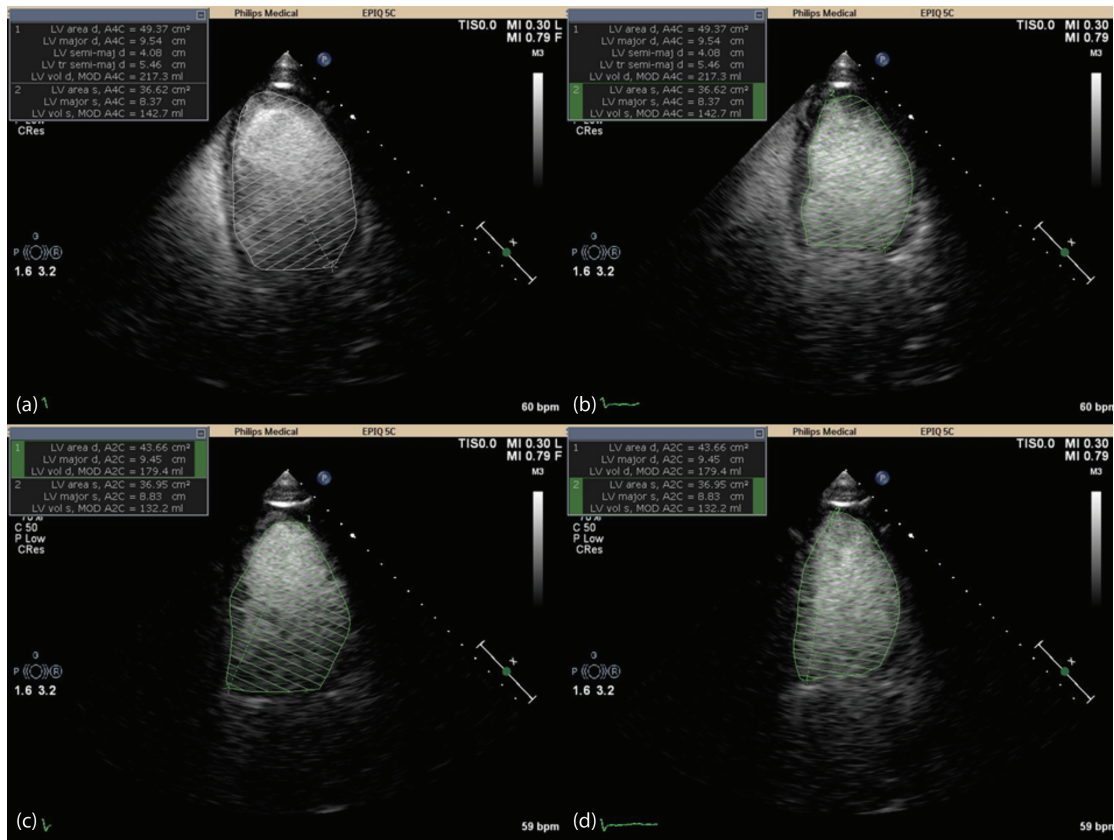
**Figure 2.1** Example of contrast echocardiography in a 72-year-old male with a history of metastatic fibrosarcoma who underwent a total cumulative dosing of 446 mg/m$^2$ of doxorubicin, olaratumab, and stereotactic body radiation therapy to the right middle lung lobe for a total dose of 50 Gy, with anthracycline and radiation associated cardiomyopathy. The LV endocardium is opacified with injection of perfluten lipid microspheres (Definity, Lantheus, Billerica, MA) allowing for more accurate assessment of LV function and to evaluate for thrombus. Biplanar quantification of LVEF, using modified Simpson's rule, was estimated at 30%. Panel (a): Apical four-chamber view in end-diastole. Panel (b): Apical four-chamber view in end-systole. Panel (c): Apical two-chamber view in end-diastole. Panel (d): Apical two-chamber view in end-systole. (MOD: method of disks.)

changes following anthracycline and trastuzumab treatment have been reported. Change in CMR-derived LV mass has been shown to predict cardiovascular events in patients with anthracycline cardiomyopathy (16). CMR can detect myocardial edema owing to acute inflammation after anthracycline administration as well as an increase in extracellular volume which may correlate with myocardial fibrosis (17,18). Patients with breast cancer and trastuzumab-induced cardiomyopathy have been shown to have mid-myocardial hyperenhancement (19) (Figure 2.5). In contrast, late gadolinium enhancement (LGE), which is associated with fibrosis/scar, is rare in anthracycline cardiotoxicity (16) and is largely helpful in excluding other etiologies of cardiomyopathy including prior myocardial infarction or amyloidosis.

## Nuclear perfusion imaging

Nuclear perfusion imaging is used to assess for coronary artery flow obstruction in patients with symptoms or signs of ischemia. It does also provide an assessment of LV function; however, this is not the test of choice for LVEF assessment due to low reliability compared to echocardiography. Therefore, in patients with suspected cardiotoxicity—as defined by a change in LVEF—this test is not routinely
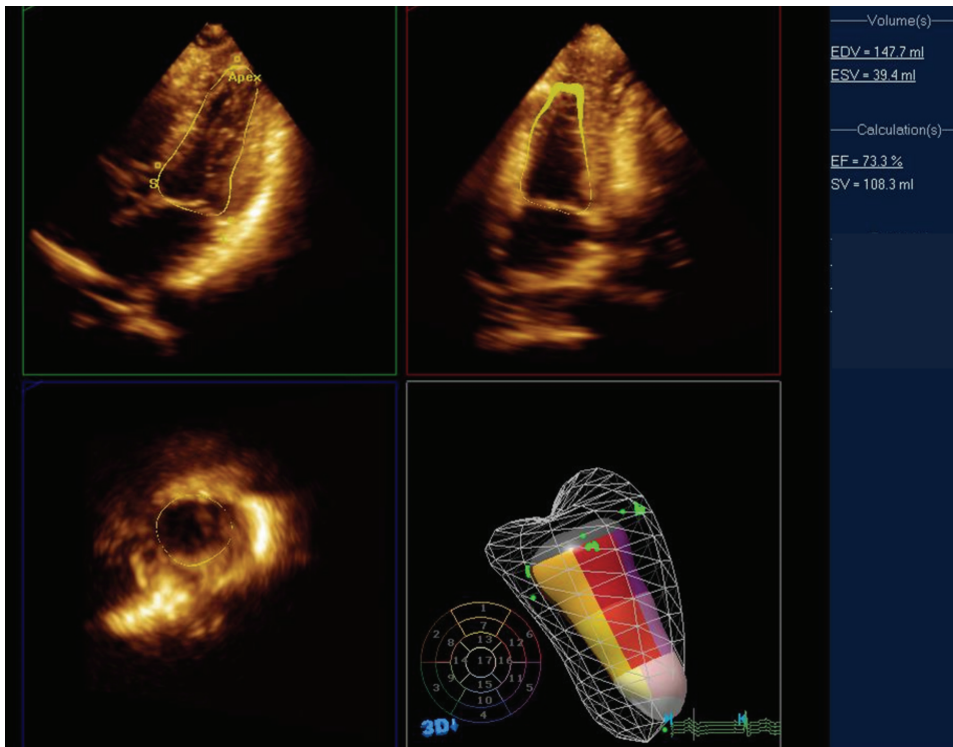
Figure 2.2 Example of 3D volumetric transthoracic echocardiographic assessment of left ventricular ejection fraction. (EDV: end-diastolic volume; ESV: end systolic volume; EF: ejection fraction; SV: stroke volume.)

performed. With chemotherapeutic agents associated with vascular thrombosis and vasospasm such as 5-flourouracil, tyrosine kinase inhibitors (TKI), and vascular endothelial growth factor (VEGF) inhibitors TKIs, perfusion imaging can be helpful to evaluate for cardiac ischemia in patients with cardiac symptoms. Screening with nuclear perfusion imaging in the asymptomatic patient prior to or during chemotherapy has not been well studied and is not generally recommended. One key exception is screening for coronary artery disease (CAD) in patients who have received prior chest or breast radiation. Patients with chest and/or breast radiation are at particularly high risk of CAD and have an estimated incidence of radiation-induced heart disease 5–10 years after treatment of 10%–30% (20). Based on one study, the prevalence of CAD based on coronary CT angiography in Hodgkin's lymphoma survivors was up to 39% with a significant percentage of high risk lesions (left main or proximal left anterior descending artery) (21). The EACI and ASE recommend screening with a stress test all high-risk patients (including those who received anterior or left-sided chest radiation) 5–10 years postradiation treatment (22).

## Positron emission tomography

PET is a nuclear-based imaging technique that uses a biologically active molecule to detect metabolic activity in various tissues. One important application of PET within cardiology is for assessment of myocardial viability. The use of PET imaging for the detection of cardiotoxicity is not well studied. One small study of six female cancer patients undergoing doxorubicin treatment received a PET scan with carbon-11 acetate before and during chemotherapy. In this study, there was no change in the metabolism or blood flow associated with treatment (23). PET using fludeoxyglucose (a glucose analog) may show changes in glucose utilization preceding cardiotoxicity in patients receiving anthracyclines; however, further studies are needed to evaluate the significance of these changes (24).
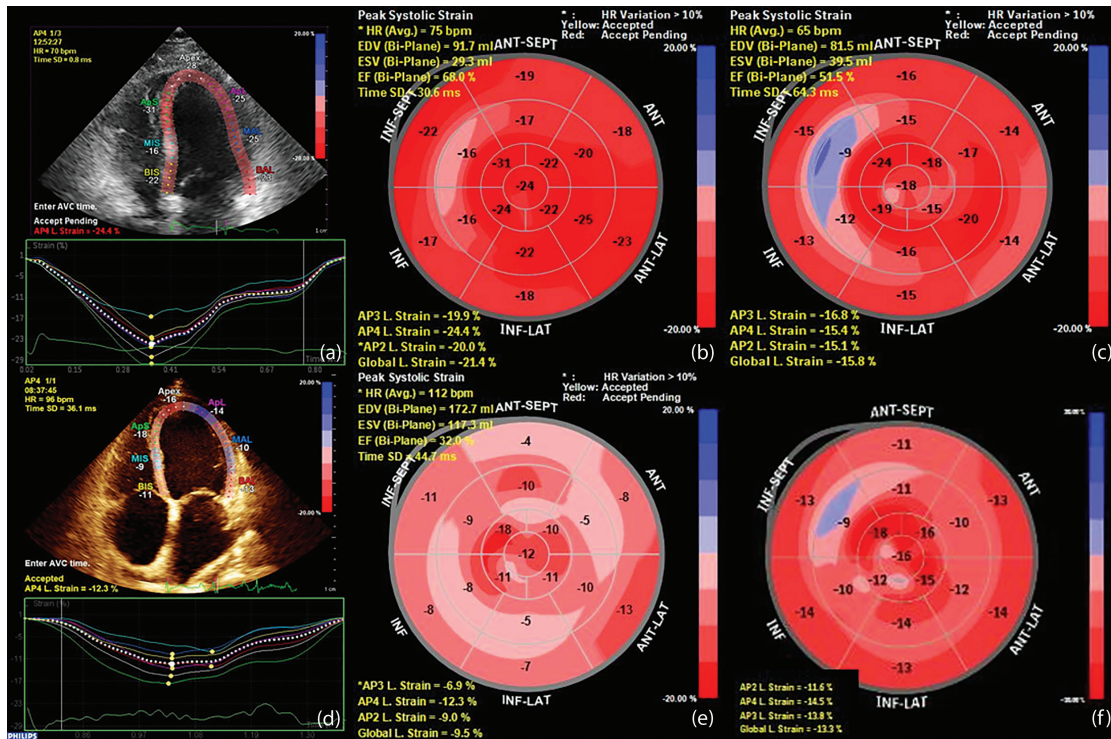
**Figure 2.3** Serial transthoracic echocardiographic imaging with speckle tracking of the patient from Figure 2.1: 72-year-old male with a history of metastatic fibrosarcoma who underwent a total cumulative dosing of 446 mg/m$^2$ of doxorubicin, olaratumab, and stereotactic body radiation therapy to the right middle lung lobe for a total dose of 50 Gy. Panel (a): Speckle tracking in the apical four-chamber view 3 months into treatment, demonstrating normal LVEF quantification of 68% and normal LV strain values in all wall segments. Longitudinal strain curves are noted below imaging. Panel (b): Representative polar map of study done in Panel (a), displaying peak longitudinal strain values using the two-chamber, three-chamber, and four-chamber TTE views with a normal global longitudinal strain (GLS) value of −21.4%. Panel (c): Polar map of LV strain analysis performed 3 months later, showing a decrease in LV function to 52% and a decrease in GLS value to −15.8%. Panel (d): Speckle tracking of four-chamber view of TTE performed 8 months after completion of doxorubicin treatment demonstrates a significant worsening from baseline of strain curves with an LVEF of 21%. Panel (e): Polar map of LV strain value of study done in Panel (d), with a GLS value of −9.5%. Panel (f): Polar map of LV strain performed on TTE study done 5 months later on medical therapy shows a mild improvement in LVEF to 30% and mild improvement in GLS value of −13.3%. (Aps: apical septum; MIS: midseptum; BIS: basal septum; ApL: apical lateral; MAL: mid-anterolateral; BAL: basal anterolateral.)

## Cardiac computed tomography

CT scanners obtain high-spatial resolution images providing accurate assessment of LVEF, valve structure, and the pericardium. CT scans are also able to identify the risk and presence of CAD by quantifying coronary calcification and visualizing the coronary artery lumen. Although the accuracy of CT is comparable to echocardiography, CT is not used as first line imaging for assessing cardiac function and structure for cardiotoxicity detection. Coronary CT angiography may have a role in patients who develop symptoms on particular chemotherapeutic agents that are linked to coronary ischemia/thrombosis, such as 5-fluorouracil, capecitabine, paclitaxel, cisplatin, or VEGF inhibitors (2–3), as cancer patients may be too high risk to undergo invasive coronary angiography.

An important limitation of CT that makes it less appealing for routine use is that it requires high radiation doses (22). Other limitations include the need for iodinated contrast, breath-holding, and poor image quality with elevated heart rates. Coronary artery and valvar disease assessment can
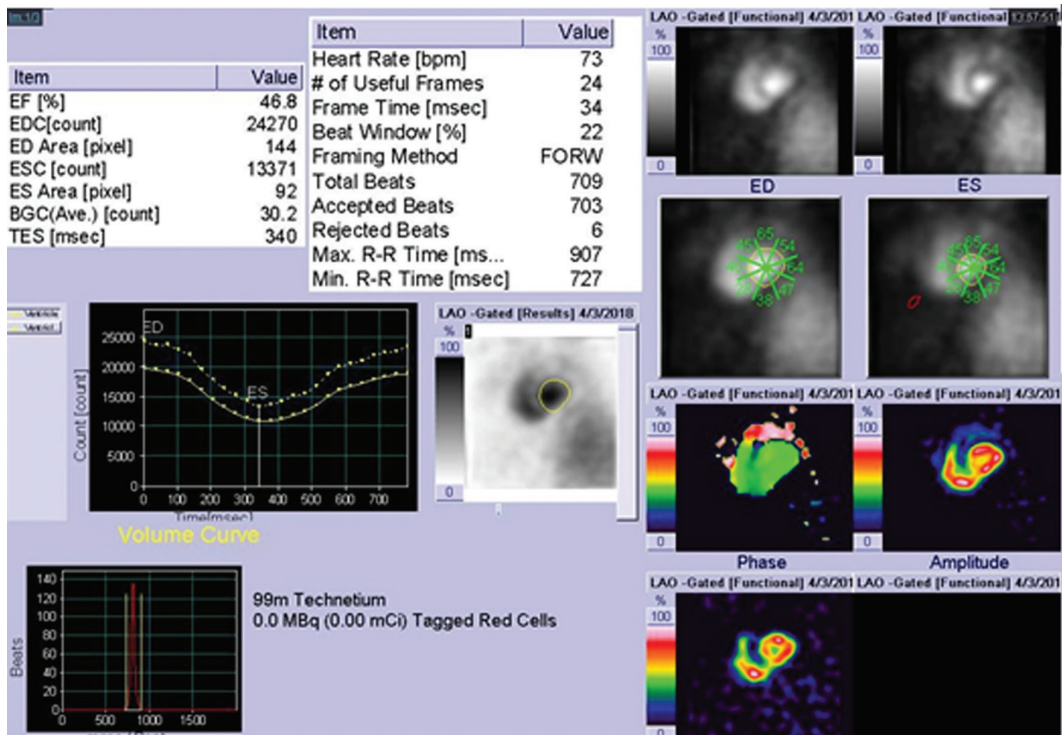
**Figure 2.4** Example of multigated acquisition (MUGA) scan in a 32-year-old male with a history of presumed methamphetamine induced cardiomyopathy, diabetes, and obesity with newly diagnosed acute lymphoblastic leukemia undergoing anthracycline treatments. A pretreatment echocardiogram demonstrated suboptimal imaging, even with contrast administration, with an estimated LVEF of 36%. MUGA demonstrated an LVEF of 46.8%. (EF: ejection fraction; EDC: end diastolic count; ESC: end systolic count; TES: time to end of systole; LAO: left anterior oblique.)

also be limited by the presence of calcium blooming, which can overestimate the severity of coronary vessel stenosis (28).

One possible application of CT scanning is risk stratification in cancer patients undergoing chemotherapy with potential cardiotoxicity. PET-CT scans, which are routinely performed for cancer staging, can also potentially provide quantitative coronary artery calcium burden for patients. In contrast to LVEF and valve assessment, CT calcium scores can be obtained without using high radiation exposure and without contrast use. Calcium scores assessed on CT imaging have been shown to predict CAD in patients without clinical cardiovascular disease. The association of high coronary artery calcium scores has been reported in small studies of Hodgkin's lymphoma and breast cancer survivors treated with chemoradiation (25–27). Patients with elevated calcium scores undergoing cardiotoxic chemotherapy should undergo aggressive primary prevention with initiation of statin therapy if tolerated, as they may be at risk of downstream cardiac events (29). In cancer survivors who have undergone mediastinal radiation, cardiac CT can also provide an all-encompassing visualization of cardiac and vascular sequelae, including evaluating for radiation induced aortic, pericardial, valvular, myocardial, and CAD (Figure 2.6).

## Carotid ultrasound

Carotid duplex is a noninvasive, relatively inexpensive, and readily available modality to assess extracranial circulation that is not reliant on ionizing radiation. Despite advances in magnetic resonance angiogram and CT angiography, due to other limiting factors (i.e., availability, cost, radiation, iodinated contrast exposure, claustrophobia), these studies may be difficult to perform
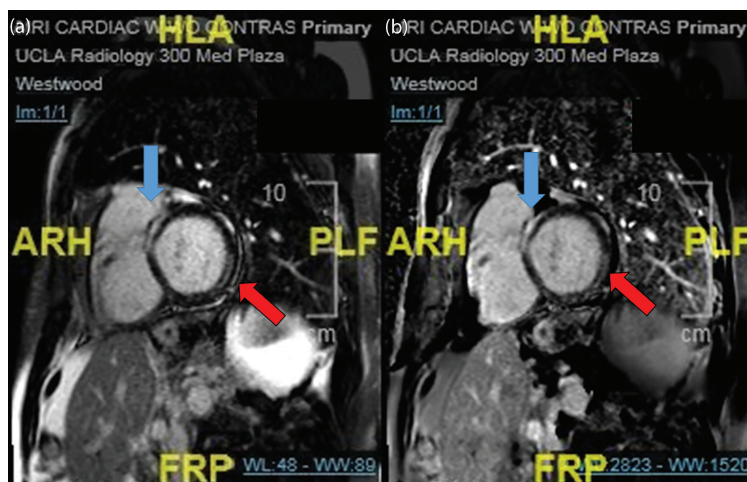
Figure 2.5 Example of cardiac magnetic resonance of patient from Figure 2.1, with anthracycline and radiation associated cardiomyopathy. The view shown is a short axis view of the left ventricle across the mitral valve, with myocardial abnormal delayed enhancement of the basal to mid-interventricular septum (blue arrows) and basal inferolateral wall (red arrows), consistent with a nonischemic pattern. Invasive coronary angiography did not reveal any macrovascular disease. Left ventricular systolic function was severely depressed at 23%. Panel (a): Magnitude only inversion recovery (MAG) images. Panel (b): Phase sensitive inversion recovery (PSIR) images.
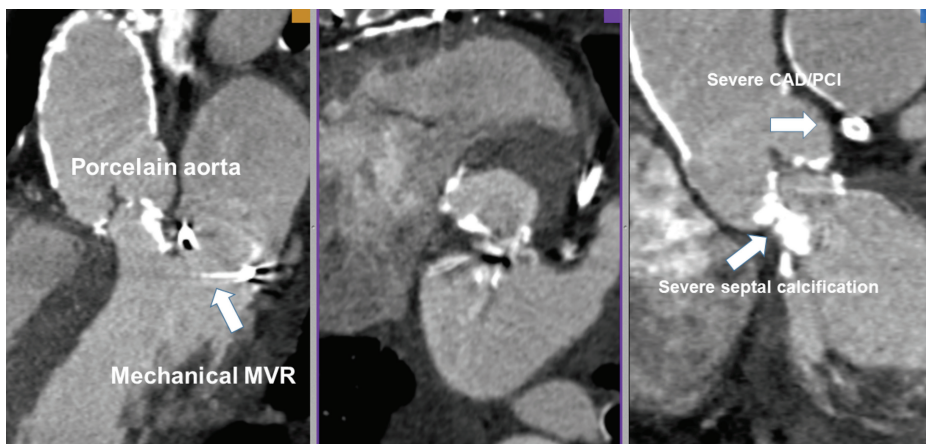


Figure 2.6 Example of cardiac computed tomography angiography (CCTA) in visualizing extent of chemoradiation induced cardiovascular sequelae. Multiplanar reconstructions from a pretranscatheter aortic valve replacement CCTA for a 57-year-old female, who had Hodgkin's lymphoma at the age of 16 who underwent chemotherapy and mediastinal radiation. She presented with severe aortic stenosis, having already had a mechanical mitral valve replacement 3 years prior. A heavily calcified (porcelain) aorta is seen, along with evidence of prior coronary stent placement from radiation induced CAD, along with severe septal calcification. (MVR: mechanical valve replacement; CAD: coronary artery disease; PCI: percutaneous coronary intervention.)

serially (30). For asymptomatic patients with elevated risk for carotid artery disease based on the type of cancer treatment (such as those receiving mediastinal and/or neck radiation), it may be reasonable to obtain serial carotid ultrasounds for monitoring. However, in patients with signs and symptoms of cardiovascular disease, especially treated with high-risk agents such as nilotinib or ponatinib, carotid ultrasound and MR/CT angiography may be considered for further identification

of baseline, and accelerated development of atherosclerotic disease with treatments (2).

Measurement of carotid intima-media thickness (CIMT), with B-mode ultrasound is a noninvasive, sensitive, and reproducible technique for identifying and qualifying atherosclerotic burden and cardiovascular risk. CIMT measurements should be limited to the far wall of the common carotid artery, and should be supplemented by a thorough scan of the extracranial carotid arteries for the presence of carotid plaque, which increases the sensitivity for identifying subclinical vascular disease. Carotid plaque is defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall, or as a focal region with CIMT greater than 1.5 mm that protrudes into the lumen, that is distinct from the adjacent boundary. The presence of carotid plaque and CIMT greater than, or equal to 75th percentile for the patient's age, sex, and race, are indicative of increased cardiovascular risk (31). CIMT measurement has been used to identify patients receiving head and neck radiation who are at high cardiovascular risk (32) and may ultimately lead to more effective prevention and improvement in cardiovascular outcomes.

## Ankle-brachial index

Ankle-brachial index (ABI) is a simple test, which provides an accurate and rapid way for detecting the presence and severity of lower extremity arterial disease. The ABI is defined as the ratio of the systolic blood pressure in the upper arm compared to the ankle. Brachial and dorsalis pedis arterial systolic pressures are measured by applying an appropriately sized blood pressure cuff and using a continuous wave Doppler probe to record the arterial signal. Values below 0.9 are indicative of peripheral arterial disease (30). ABI can be performed at baseline and annually in asymptomatic patients at risk for peripheral artery disease such as patients receiving abdominal and/or pelvic radiation. In symptomatic patients, especially treated with high-risk agents such as nilotinib or ponatinib, direct visualization with arterial ultrasonography or CT/MR angiography may be indicated (2).

## Venous duplex ultrasound

Deep vein thrombosis is a common problem in cancer patients. Compression venous ultrasound is considered the imaging modality of choice for the diagnosis of deep vein thrombosis. Using a high resolution linear array transducer, the deep venous system is usually examined from the level of the inguinal ligament at the common femoral vein to the tibioperoneal trunk. The large veins should be examined in the transverse plane with and without compression every 2–3 cm. Lack of coaptation of the vein wall is consistent with presence of venous thrombosis (30). Venous duplex should be considered in symptomatic cancer patients for detection of thromboembolic disease (2).

## IMAGING CARDIOTOXICITY SURVEILLANCE GUIDELINES

A number of society-driven consensus statements (Table 2.3) have been published to outline cardiotoxicity surveillance strategies based on the known time course of LV dysfunction with particular cancer treatments. Data on optimal surveillance continues to be limited due to the relative lack of long-term, wide scale studies examining the effects of potentially cardiotoxic treatments; also confounding this are the ongoing dynamic treatment strategies of malignancies, and development of new chemotherapeutic agents with unknown long-term complications. Nonetheless, these statements can act as a guide for short- and long-term cardiotoxicity surveillance and treatment of cancer patients and survivors.

## Children's Oncology Group

The online Children's Oncology Group (COG) Long-Term Follow-Up (LTFU) Guidelines, which were last modified in 2018 (at the time of this writing), provides guidance to healthcare professionals regarding surveillance for organ toxicities related to chemoradiation treatments in the pediatric/young adult population (33). The authors deemed patients at high risk for cardiotoxicity if they received a total cumulative dosing of doxorubicin equivalent of ≥250 mg/m$^2$ in patients. Chest radiation ≥35 Gy, in the absence of anthracycline therapy, was also considered a major risk factor for cardiotoxicity. The LTFU guidelines recommend echocardiography as an imaging modality of choice with assessment of ventricular function at baseline, at entry into long-term follow-up, then periodically based on radiation dose, and

Table 2.3 Recommendations for surveillance for cardiac dysfunction according to major societies

| Society | Modality of choice | Frequency of LVEF assessment |
|---|---|---|
| American Society of Clinical Oncology (ASCO) | 1. Echocardiography; MUGA or MRI if echocardiography is not available, with MRI preferred over MUGA | Frequency of surveillance should be determined by the provider based on patient's clinical characteristics |
| | 2. Strain imaging and biomarkers (BNP, troponin) could be considered in conjunction with routine echocardiography | Repeat assessment at 6–12 months after therapy in patients considered at high risk |
| American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) | 1. Echocardiography, ideally incorporating 3-dimensional imaging and global longitudinal strain | Baseline, end of, and 6 months after therapy associated with type I cardiotoxicity (i.e., anthracyclines) |
| | 2. Consider measuring high-sensitivity troponin in conjunction with imaging | Baseline, every 3 months during therapy associated with type II cardiotoxicity (ie trastuzumab) |
| European Society for Medical Oncology (ESMO) | 1. Echocardiography or MUGA | Baseline, every 3, 6, 9, 12, and 18 months after initiation of treatment |
| | | For patients with metastatic disease, obtain baseline measurement and only repeat if patient develops symptoms of HF |
| | 2. May consider MRI as an alternative | Assessment 4 and 10 years after anthracycline therapy if treated <15 years of age, or >15 years with cumulative dose of >240 mg/m$^2$ doxorubicin |
| European Society of Cardiology (ESC) | 1. Echocardiography including 3-dimensional assessment of LVEF and global longitudinal strain | Baseline, every 3 months during therapy (i.e., anthracyclines or trastuzumab) and once after completion |
| | 2. MUGA and MRI may be considered as alterantives | Repeat assessment in 2–3 weeks for any suspected cancer treatment related cardiac dysfunction |
| Canadian Cardiovascular Society (CCS) | 1. Echocardiography including 3-dimensional imaging and strain, MUGA and MRI as alternatives | No specific recommendation |
| | 2. Consider concomitant measurement of biomarkers (BNP, troponin) | |
| Trastuzumab Labeling | 1. Echocardiography or MUGA | Baseline (immediately preceding initiation of trastuzumab), every 3 months during or upon completion of therapy, and at every 6 months for at least 2 years following completion of therapy |

*Source:* Adapted from Florido R et al. *J Am Heart Assoc.* 2017;6:e006915.
*Abbreviations:* MUGA, multigated acquisition; MRI, magnetic resonance imaging; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

cumulative anthracycline dose. In addition, for patients who have received ≥40 Gy of neck radiation, carotid ultrasound is recommended 10 years after treatment to screen for carotid artery disease.

## International Late Effects of Childhood Cancer Guidelines

In 2015, the International Late Effects of Childhood Cancer Guideline Harmonization Group attempted to unify different societal consensus statements (North American Children's Oncology Group, Dutch Childhood Oncology Group, UK Children's Cancer and Leukaemia Group, Scottish Intercollegiate Guidelines Network) owing to discordant statements ranging from cutoff doses of anthracyclines deemed to be high risk for developing cardiotoxicity, surveillance imaging modality of choice, as well as frequency of screening in the pediatric/young adult population (34). The total anthracycline cumulative dose considered high risk for developing cardiomyopathy was ≥250 mg/m$^2$ or a radiation dose of ≥35 Gy chest radiation, or a combination of both treatments with a moderate to high dose of anthracycline (≥100 mg/m$^2$) and moderate to high dose chest radiation (≥15 Gy). Echocardiography was considered to be the surveillance modality of choice for LV systolic function, but radionuclide angiography and CMR was also reasonable in patients where echocardiography was not technically feasible or optimal. For patients deemed low to high risk, cardiomyopathy surveillance was recommended to begin no later than 2 years after the completion of cardiotoxic therapy, with repeat imaging at 5 years after diagnosis and continued every 5 years afterwards. However, the authors felt that more frequent and life-long cardiomyopathy surveillance was also reasonable for survivors with anthracycline exposure.

## European Society of Medical Oncology

Published in 2012, the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines were the product of a multidisciplinary working group that provide guidance on cardiotoxicity surveillance, and a review of known cardiotoxic chemotherapeutics (35). LVEF assessment with echocardiography was regarded as mandatory for baseline cardiac function prior to treatment with potentially cardiotoxic chemotherapy. They also advocated for MUGA and CMR as alternative imaging modalities summarizing their advantages and disadvantages. For echocardiographic protocol, they advised image acquisition by 2D or 3D if available, and assessment of diastolic function and LV volume. At the time this document was written, a "high risk" cumulative dose cutoff of doxorubicin was >500 mg/m$^2$, which was subsequently lowered in later consensus statements/guidelines from other societies.

For patients receiving anthracycline and/or trastuzumab therapy, it was advised that cardiac function be assessed at baseline, 3, 6, and 9 months during treatments, and then at 12 months and 18 months after the initiation of treatment. The working group acknowledged that limited data were available for elderly patients and "increased vigilance" was recommended for patients ≥60 years old. For patients with metastatic disease, LVEF should be monitored at baseline and then "infrequently" in the absence of symptoms. For long-term cardiotoxicity surveillance, assessment of cardiac function was recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or at age >15 years with a cumulative dose of doxorubicin of >240 mg/m$^2$ or epirubicin >360 mg/m$^2$.

During cardiac monitoring, if an LVEF reduction of ≥15% from baseline with normal function (LVEF ≥50%) was noted, anthracyclines and/or trastuzumab could be continued. If LVEF declined to <50% during such treatments, the LVEF should be reassessed after 3 weeks. If the LVEF reduction was confirmed, it was advised to hold chemotherapy and initiate cardioprotective agents with frequent clinical and echocardiographic evaluation. If the LVEF decreased to <40%, it was advised that chemotherapy stop and alternatives be considered, along with initiation of treatment for LV dysfunction.

## American Society of Clinical Oncology

In 2016, the American Society of Clinical Oncology (ASCO) published their Clinical Practice Guideline in the Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers. An expert panel conducted a systematic review of 104 studies, which comprised of meta-analyses, randomized clinical trials, observational studies, and clinical

experience from 1996 to 2016 (36). This ASCO document is notable because the threshold considered high risk for cardiotoxicity was lowered to a doxorubicin cumulative dose of $\geq$250 mg/m$^2$ or an epirubicin cumulative dose of $\geq$600 mg/m$^2$. In addition, high-dose radiotherapy (RT) with a total dose of $\geq$30 Gy where the heart is in the treatment field, or a combination of anthracycline and chest RT at any dose was considered high risk for cardiotoxicity as well.

Echocardiography is the preferred diagnostic imaging modality for workup of cardiac dysfunction. CMR and MUGA can be considered if echocardiography is not available or technically feasible, with preference given to CMR. Although there are no specific recommendations of frequency of cardiovascular imaging during treatments, it was recommended that an echocardiogram be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk of cardiotoxicity.

## Canadian Cardiovascular Society

In their 2016 society guidelines, the Canadian Cardiovascular Society (CCS) recommended that patients who received potentially cardiotoxic cancer therapy undergo LVEF assessment before initiation of treatments (37). The same imaging modality should be used to determine LVEF before, during, and after completion of therapy. For those undergoing echocardiographic imaging, myocardial strain imaging be considered as a tool to assist in detecting subclinical cardiotoxicity. They determined that a relative percentage reduction in GLS of <8% was likely not clinically significant, whereas a relative reduction of >15% was likely to be abnormal. The CCS also preferred the use of 3D echocardiography whenever feasible and technically satisfactory (37). The intervals of imaging were not specified in this document.

## European Society of Cardiology

The ESC published an ESC Position Paper on cancer treatments and cardiovascular toxicity in 2016. The ESC Task Force determined echocardiography to be the method of choice in the detection of myocardial dysfunction before, during, and after cancer therapy (10). They advocated for 3D echocardiography if endocardial definition was optimal, and for performing 2D biplane Simpson method if 3D imaging was not available or was suboptimal.

The task force determined that any significant decrease in LVEF (>10%) to a value that does not drop below the lower limit of normal (defined as an LVEF of 50%), should undergo repeated LVEF assessment shortly after and over the duration of cancer treatment. If LVEF decreases >10% to a value below the lower limit of normal, medical treatment should be initiated. The ESC also recommended considering an LVEF assessment at baseline, every 3 months during treatment, and at the end of treatment with either anthracyclines or trastuzumab. While they supported long-term surveillance after cancer treatment, no specific frequency was recommended.

## American Society of Echocardiography/European Association of Cardiovascular Imaging

The ASE and European Association of Cardiovascular Imaging (EACVI) released a joint expert consensus statement in 2014, providing a proposed cardio-oncology echocardiography protocol (Table 2.4), and cardiotoxicity surveillance intervals based on the types of chemotherapeutic agents being used (5). The classifications of CTRCD were divided into "Type I" (associated with anthracycline use and permanent/irreversible myocardial damage if not treated) and "Type II" CTRCD (associated with trastuzumab and tyrosine kinase inhibitors, which is more reversible with discontinuation of therapy and/or initiation of treatment). Although this classification system is oversimplified and may not be applicable to a variety of other novel cancer treatments (i.e., targeted therapies, immunotherapy), the document focuses on more commonly used treatments with known cardiotoxic profiles. Further research efforts are needed to document short- and long-term cardiovascular outcomes for current and future cancer therapy agents in order to provide a more nuanced, accurate classification system for physicians to provide adequate imaging surveillance for cancer patients during and after their treatments.

For patients undergoing treatments associated with potential irreversible (Type I) cardiotoxicity, it is advised to obtain an LVEF assessment at baseline, at the end of treatment, and 6 months later for doxorubicin equivalent doses of <240 mg/m$^2$, along with serial biomarker assessments. For doses

**Table 2.4** ASE/EACVI recommended cardio-oncology echocardiogram protocol

- Standard transthoracic echocardiography
  - In accordance with ASE/EAE guidelines and IAC-Echo
- 2D strain imaging acquisition
  - Apical three-, four-, and two-chamber views
- Acquire ≥3 cardiac cycles
  - Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
    - Frame rate between 40 and 90 frames/sec or ≥40% of HR
  - Aortic VTI (aortic ejection time)
- 2D strain imaging analysis
  - Quantify segmental and global strain (GLS)
  - Display the segmental strain curves from apical views in a quad format
  - Display the global strain in a bull's-eye plot
- 2D strain imaging pitfalls
  - Ectopy
  - Breathing translation
- 3D imaging acquisition
  - Apical four-chamber full volume to assess LV volumes and LVEF calculation
  - Single and multiple beats optimizing spatial and temporal resolution
- Reporting
  - Timing of echocardiography with respect to the IV infusion (number of days before or after)
- Vital signs (BP, HR)
- 3D LVEF/2D biplane Simpson's method
- GLS (echocardiography machine, software, and version used)
- In the absence of GLS, measurement of medial and lateral s' and MAPSE
- RV: TAPSE, s', FAC

*Source:* Adapted from Plana JC et al. *J Am Soc Echocardiogr*. 2014;27:911–39.

*Abbreviations:* ASE/EACVI, American Society of Echocardiography/European Association of Cardiovascular Imaging; BP, blood pressure; FAC, fractional area change; HR, heart rate; IAC-Echo, Intersocietal Accreditation Commission Echocardiography; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; VTI, velocity-time integral.

that exceed 240 mg/m$^2$, LVEF assessment is advised prior to each additional 50 mg/m$^2$. In addition, the ASE/EACVI consensus statement prefers that 3D echocardiography be used for LVEF assessment; however, if this is not feasible, contrast echocardiography with GLS and troponin-I assessment can be considered. Cardiology consultation is advised for a reduction in LVEF to <53%, abnormal GLS value, and/or elevation in troponin levels. If abnormal LVEF values are seen during surveillance, CMR was advised for confirmation of LV dysfunction.

For patients who are receiving cancer treatments with potentially reversible (Type II) cardiotoxicity, such as trastuzumab, or following treatment associated with potentially irreversible cardiotoxicity, LVEF/GLS/troponin-I assessment is advised at baseline and every 3 months until treatment is finished. Long-term surveillance is not advised. As with the CCS guidelines, a GLS relative percentage decrease of <8% was unlikely to be clinically significant, where as a relative percentage decrease of >15% was concerning for subclinical cardiotoxicity.

Although the document now advocates for echocardiography as the first line imaging modality of choice for cardiotoxicity surveillance, it also does mention historical proposed surveillance intervals for anthracycline induced cardiotoxicity with MUGA imaging (12):

1. LVEF >50% at baseline
   a. Measurement at 250–300 mg/m$^2$
   b. Measurement at 450 mg/m$^2$
   c. Measurement before each dose above 450 mg/m$^2$
   d. Discontinue therapy if LVEF decreases by ≥10% from baseline and LVEF ≤50%

2. LVEF <50% at baseline
   a. Do not treat if LVEF is <30%
   b. Serial measurement before each dose
   c. Discontinue therapy if LVEF decreases by ≥10% from baseline or LVEF ≤30%

The document does not give recommendations for long term surveillance in cancer survivors.

In a separate document for patients undergoing radiotherapy, the ASE/EACVI Expert Consensus for Multi-Modality Imaging Evaluation of Cardiovascular Complications of Radiotherapy in Adults was released in 2013 (22). Patients at high risk for developing radiation-induced heart disease (RIHD) included the following risk factors:

- Anterior or left chest irradiation location, with one or more of the following risk factors:
  - High cumulative dose of radiation (>30 Gy)
  - Younger patients (<50 years)
  - High dose of radiation fractions (>2 Gy/day)
  - Presence and extent of tumor in or next of the heart
  - Lack of shielding
  - Concomitant chemotherapy (i.e., anthracyclines cause considerably higher risk)
  - Cardiovascular risk factors (i.e., diabetes mellitus, smoking, obesity, moderate hypertension, hypercholesteremia)
  - Preexisting cardiovascular disease.

Because of the complex and extensive effects of chest radiation exposure, including macro- and microvascular injury, valvular dysfunction, progressive myocardial fibrosis, and pericardial disease (38), the document discusses the indications of multiple imaging modalities, including echocardiography, CMR, cardiac computed tomography angiography (CTA), and functional stress testing for specific disease states related to RIHD. However, the frequency and imaging modality of choice in screening for subclinical/clinical RIHD is overall unclear; owing to the relative paucity of evidence, the authors recommend yearly targeted clinical history and physical exam of patients who have received chest radiation exposure. For asymptomatic patients, it was reasonable to perform screening echocardiography to evaluate for overall manifestations of RIHD 5 years after exposure in high-risk patients, and 10 years after exposure in other patients. In high-risk patients, functional noninvasive stress testing for CAD detection 5–10 years after exposure was reasonable, with reassessment every 5 years.

For other cardiovascular manifestations, including valvular disease, if a cardiac murmur is heard, then echocardiography is indicated with serial imaging as per cardiology guidelines; if neurological symptoms are noted, then carotid ultrasonography is indicated, although frequency of surveillance and when to initiate it for these specific disease states are not known. For suspected pericardial constriction from radiation, CMR was indicated. Workup for suspected angina/ischemia include echocardiography and functional noninvasive stress testing, or invasive testing depending on clinical assessment.

## American Society of Nuclear Cardiology

In 2016, the American Society of Nuclear Cardiology (ASNC) published an information statement reviewing the cardiotoxic effects of cancer treatments and a review specifically focused on applications of nuclear cardiology technologies (39). The statement refers to a variety of prior guidelines, including the ESMO Clinical Practice Guidelines and the COG Long Term Follow-Up Guidelines as previously discussed in recommendations on LVEF assessment during and after cancer treatment both in children and adults.

## Society of Cardiovascular Angiography and Interventions

In 2016, the Society of Cardiovascular Angiography and Interventions (SCAI) released an expert consensus statement, which provided recommendations on pharmacologic and interventional management of cancer patients with cardiotoxicity, and/or preexisting or acquired atherosclerotic cardiovascular disease (ASCVD) (2). In addition, it also gave expert opinion recommendations on patients receiving specific kinds of radiation therapy that may affect the extracardiac vasculature. Although data on long-term event rates are limited, ABIs and carotid ultrasonography was advised—every 5 years for the latter posttreatment—particularly in patients at elevated ASCVD risk and who received radiation therapy to the

neck area (i.e., lymphoma, head and neck cancers). Chemotherapy agents such as cisplatin, nilotinib, and ponatinib were considered to be high risk agents for arterial/venous thrombotic disease. The SCAI document advises consideration of noninvasive imaging modalities such as carotid ultrasound, as well as MRI for cerebrovascular disease and CT aortography for peripheral arterial disease assessment in patients who received agents such as nilotinib and ponatinib.

Similar to the ASE/EACVI expert consensus statements, SCAI recommends that patients who received RT undergo screening echocardiography every 5 years for high-risk patients, and every 10 years for patients with no RIHD risk factors. The document also advocated for consideration of cardiac CT angiography as an alternative to functional exercise stress testing every 5 years after RT, or an additional early evaluation at 2 years if RT was performed at >60 years of age, if the patient had known CAD, or had one or more cardiovascular risk factors.

## CONCLUSIONS

There have been many technological advances made in the field of echocardiography, including the advent of 3D imaging, and strain imaging which has allowed for more precise LVEF assessment and less dependence on imaging modalities that required radiation exposure (i.e., MUGA). Echocardiography has largely supplanted MUGA as the test of choice in cardiotoxicity surveillance owing to improvements in imaging quality, as well as being able to provide information on chamber size, valvular function, and the presence of pericardial disease without exposing the patient to ionizing radiation. CMR has now allowed for superior imaging with visualization of pericardial and valvular disease, and there is ongoing interest in developing techniques to assess for subclinical/clinical cardiotoxicity with patterns of gadolinium enhancement in the myocardium. Other advanced imaging modalities, such as cardiac CT angiography, may be useful in selected patients for assessment of atherosclerotic disease but have limited utility in this population. Arterial/venous ultrasounds remain useful in detecting thrombotic complications of cancer and their treatments, as well as sequelae of chemoradiation. However, the frequency and duration of clinical utilization, as well as cost

effectiveness of these imaging modalities, continues to remain a question and an area of ongoing research and interest. Further investigations are warranted in refining the definition of cardiotoxicity, and determining the ideal duration and method of surveillance with the armamentarium of advanced imaging modalities that are available—which will continue to evolve (40).

As cancer treatments continue to develop at a rapid pace, resulting in growing cancer survival rates, precise imaging modalities are critical in detecting preexisting and acquired cardiovascular disease with treatments. It is essential that cardio-oncologists be cognizant of the dynamic nature of multimodality imaging and society-endorsed cardiotoxicity surveillance recommendations for this unique population. In doing so, we can provide the most evidence-based care to cancer patients, ideally enable the continuation of critical cancer treatments, and prevent and/or minimize cardiovascular toxicity in the growing cancer survivor population.

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