

Multimodality Cardiac Imaging in the Era of Emerging Cancer Therapies

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Recently, the field of oncology has witnessed a surge of new therapeutic agents that have collectively led to improved rates of progression-free and overall survival for many cancers.¹ However, these advances have also led to increased morbidity attributable to treatment-related side effects, in particular, cardiac toxicities. Cancer therapeutics may negatively affect the heart in a host of ways, whether it is through direct tissue damage or indirectly by exacerbating cardiovascular risk factors.^{2–6} Given that cardiovascular disease is the most common cause of death among cancer survivors, increased recognition and understanding of these cardiovascular toxicities is paramount to successful management of this ever increasing survivorship population.^{1,5,7,8} Cardiac imaging has been essential to elucidating mechanisms for a growing number of cardiotoxicities, and its role in toxicity surveillance and management continues to evolve.^{9–12}

Approaching this review from the perspective of treatment-related cardiovascular toxicities, we examine evolving applications of imaging in contemporary cardio-oncology with specific focus on the more novel and emerging anticancer therapies. In doing so, we will examine broad categories of cancer therapeutics, highlight specific agents that have been implicated in cardiotoxicity, and discuss optimal cardiac imaging modalities for each class.³ We will also consider amyloidosis, in light of recent interest. Guideline-driven recommendations and position paper statements pertaining to cardiac imaging will be highlighted wherever possible.¹² We recognize that cardiac imaging position

statements are largely unavailable for certain drug categories, particularly for more novel agents. In these instances, primary literature and specific clinical cases pertaining to cardiac imaging applications for each cardiotoxicity will be reviewed.

Prominent cardiotoxicities as related to cancer therapies are detailed below:

1. Systolic dysfunction and heart failure
2. Coronary artery disease and myocardial ischemia
3. Myocarditis
4. Amyloidosis
5. Pericardial disease
6. Peripheral vascular disease and vascular dysfunction

Cancer Treatment–Related Systolic Dysfunction and Heart Failure

Multiple cancer therapeutic agents are associated with myocardial dysfunction and heart failure including anthracyclines, biologic agents, proteasome inhibitors, radiation therapy, and certain tyrosine kinase inhibitors. Anthracyclines remain among the most commonly used traditional chemotherapies and have been well implicated as a cause of heart failure.¹³ This toxicity is thought to be mediated by topoisomerase- β , which in turn activates oxidative phosphorylation and other apoptotic pathways.¹⁴ Heart failure symptoms typically manifest within the first year of exposure and follow a dose-response relationship. Toxicity often presents when the dose exceeds 350 mg/m².¹⁵ Additionally, patients with traditional cardiovascular risk factors, older age, prior systolic dysfunction, prior high-dose radiotherapy (≥ 30 Gy), or exposure to prior cardiotoxic therapies are at a higher risk of toxicity.¹⁶ The mortality associated with anthracycline cardiotoxicity ranges between 30% and 70%.¹⁶ Multiple imaging modalities have been employed to study anthracycline cardiac toxicity, and this continues to evolve (Figure 1A and 1B).

Biologic agents such as trastuzumab and pertuzumab are monoclonal antibodies that target HER2/neu receptors and are primarily used for the treatment of breast cancer. The cytotoxicity produced by these agents is attributable to activation of the PI3K (phosphatidylyl 3-kinase)/Akt (protein kinase B)/mTOR (mammalian target of rapamycin)/Ras/MAPK

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(mitogen-activated protein kinase) pathways.¹⁹ Cardiac side effect is primarily limited to left ventricular (LV) dysfunction and is thought to be reversible upon drug discontinuation.²⁰ LV dysfunction is not dose dependent but is related to traditional cardiovascular risk factors and prior anthracycline use.^{20,21}

Proteasome inhibitors such as bortezomib and carfilzomib cause disruption of normal protein homeostasis and have revolutionized the treatment of multiple myeloma. While beneficial in their pro-apoptotic effects on cancer cells, proteasome inhibitors are also associated with various, albeit largely reversible, cardiotoxic effects. Four percent to 7% of patients treated with bortezomib and carfilzomib will develop heart failure with more recent studies reporting an incidence of grade 3 or 4 heart failure upwards of 20%. Case series data demonstrate that patients with proteasome cardiotoxicity can have moderate-to-severe global LV hypokinesia with ejection fraction ranging between 20% and 50%.²² These agents are also linked to hypertension, pulmonary hypertension, and diastolic dysfunction.^{23,24}

Targeted therapies comprise a broad range of agents, including small-molecule tyrosine kinase inhibitors (TKIs), which modulate signal transduction, gene expression, angiogenesis, and apoptosis pathways in a variety of malignancies. TKIs each have their own mechanism of action, and their

associated cardiac side effect profile is heterogeneous. For example, sunitinib is linked to hypertension and heart failure, the latter on the order of 10%.^{25,26} Ibrutinib has been associated with rare cases of heart failure, atrial and ventricular arrhythmias, and sudden cardiac death.^{27,28} Sorafenib, dasatinib, and pazopanib are other members of the TKI class that have prominent cardiotoxic profiles and are discussed elsewhere.

Radiotherapy-associated cardiovascular disease is a major cause of morbidity and mortality in cancer survivors. The mechanism of toxicity predominantly originates from endothelial damage with a subsequent inflammatory response driving neointimal proliferation, fibrosis, and atherosclerosis.^{29,30} Radiotherapy-associated diastolic dysfunction and cardiac remodeling results in subsequent fibrosis and heart failure with preserved ejection fraction. This has been well demonstrated in the Hodgkin lymphoma cohort^{31,32} as well as in the breast cancer population, with associated reduced functional capacity and survival.^{33,34} Associated risk factors for radiotherapy-induced cardiac dysfunction include radiation dose over 30 Gy or any radiation exposure with concomitant anthracycline treatment, younger age of exposure, location of radiation, and preexisting cardiovascular disease.

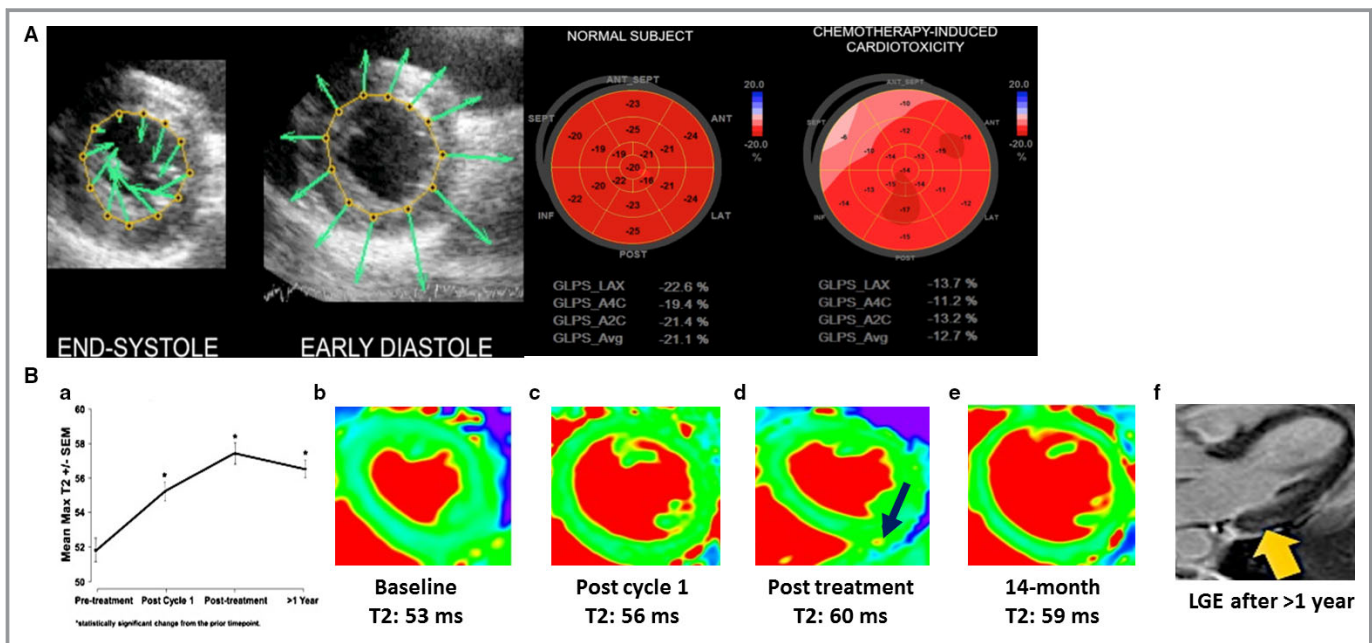


Figure 1. **A**, (Left) Velocity vector imaging tracking endomyocardial border throughout the cardiac cycle. (Right) Bull's-eye plot of average peak systolic global longitudinal strain in a normal subject compared with that of a patient with chemotherapy-induced cardiotoxicity. Adapted from Mele et al¹⁷ under the Creative Commons Attribution Non-Commercial-NoDerivs (CC-BY-NC-ND) license. **B**, Objective increase in myocardial T2 mapping values (a marker of inflammation/edema) after cardiotoxic anthracycline therapy exposure (A through E), even before cardiac fibrosis (F; yellow arrow, LGE) and clinical heart failure (with left ventricular ejection fraction decline) development among breast cancer patients via use of T2 mapping. Note: maximum T2 plateaus and actually declines after cancer therapy cessation (A, D, and E; black arrow in D, high T2). Adapted with permission from Lustberg et al.¹⁸ Copyright ©2019, Wolters Kluwer Health, Inc. LGE indicates late gadolinium enhancement.

Table 1. Existing Cardiac Imaging Recommendations Based on Prior Data

Anti-Cancer Agent	Monitoring Guidelines	Organization/Society Recommending
Anthracyclines	Echo	
	Recommended for those with symptoms of heart failure (E,B,1)*	ASCO ⁹
	Recommended for surveillance of those undergoing treatment, frequency based on clinical discretion (E,B,2)	ASCO ⁹
	Recommended to perform in asymptomatic patients 6 to 12 mo after completion of therapy in those felt to be at a higher risk for CTRCD (E,B,2)	ASCO ⁹
	LVEF measurement at baseline and during [†] treatment (2D/3D) and GLS with treatment or risk factor modification at LVEF ≥60%, 50%–59%, 40%–49%, and <40%	Liu et al ³⁷
	LVEF at baseline and at end of treatment. Regular LVEF monitoring if cumulative dose exceeds 240 mg/m ² . Recommendation based on use of 2D echocardiogram and GLS	SEOM, ¹⁰ ESC ¹²
	Measurement of LVEF at baseline, every 3 mo during chemotherapy, at the end of treatment (within 1 mo), every 3 mo during the first year after chemotherapy, every 6 mo during the following 4 y, and yearly afterward	Cardinale et al ¹⁵
CMR	Recommended instead of echo only if echo unavailable or not technically feasible (E,B,2)	ASCO ⁹
	Recommendation to perform in asymptomatic patients 6 to 12 mo after completion of therapy in those felt to be at a higher risk for CTRCD and not a good candidate for echocardiogram (E,B,2)	ASCO ⁹
	Utility of CMR over LVEF monitoring in terms of myocardial fibrosis and inflammation quantification	Jordan et al ³⁸
	Multigated angiocardigraphy (MUGA)	
Trastuzumab	Recommended instead of echo only if echo unavailable or not technically feasible and CMR unavailable (E,B,2)	ASCO ⁹
	Recommended to perform in asymptomatic patients 6 to 12 mo after completion of therapy in those felt to be at a higher risk for CTRCD and not a good candidate for echocardiogram and CMR unavailable (E,B,2)	ASCO ¹⁵
	LVEF >50% at baseline 1. Measurement at 250 to 300 mg/m ² 2. Measurement at 450 mg/m ² 3. Measurement before each dose above 450 mg/m ² 4. Discontinue therapy if LVEF decreases by ≥10% from baseline and <50%	ASNC ³⁹
	LVEF <50% at baseline 1. Do not treat if LVEF is <30% 2. Serial measurement before each dose 3. Discontinue therapy if LVEF decreases by ≥10% from baseline or LVEF ≤30%	ASNC ³⁹
	Echo	
Recommended for surveillance of metastatic breast cancer patients receiving trastuzumab indefinitely (E,C,2)	ASCO ⁹	
Recommended: 1. Baseline evaluation of LVEF 2. Repeat measurement of LVEF for the next 3 cycles while on treatment 3. Weekly echo if a significant drop in LVEF and withhold treatment. The caveat to this recommendation is that ASCO does not endorse holding treatment unless deemed clinically necessary by oncologist (E, evidence quality: insufficient) 4. Every 6 mo for the immediate 2-y period after completing the regimen	SEOM ¹⁰ ASCO ¹⁵ Manufacturer ^{40,41}	
Transthoracic echocardiograms that includes comprehensive 2D, 3D, and strain imaging. 1. Baseline 2. After starting HER2 targeted therapy every 6 weeks for 2 assessments 3. Every 3 mo during the study 4. Asymptomatic absolute decline in LVEF of ≥10% points from baseline or to ≤35%, HER2 targeted therapy hold with a confirmatory echocardiogram at 2 to 4 weeks 5. Repeat echo at the end of treatment and 6 mo after end of treatment	SAFE-HEaRt study ^{42,43}	

Continued

Table 1. Continued

Anti-Cancer Agent	Monitoring Guidelines	Organization/Society Recommending
Checkpoint inhibitors	<ol style="list-style-type: none"> Echo recommended upon signs/symptoms of myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis Additional testing guided by cardiology may include stress testing, cardiac MRI, and cardiac catheterization 	ASCO ⁴⁴
Tyrosine kinase inhibitors	Echo	
	<ol style="list-style-type: none"> Recommended baseline echo with follow-up at 1 mo and every 3 mo while on therapy with VEGF or VEGF receptor inhibitors Recommended stress echo in risk stratifying patients with intermediate or high pretest probability of CAD who are to undergo tyrosine kinase inhibitor therapy, particularly sorafenib and sunitinib 	ASE/EACVI ⁴⁵
Radiation therapy	Echo	
	Baseline and repeated echo after radiation therapy involving the heart are recommended for the diagnosis and follow-up of valvular heart disease	ASE/EACVI ⁴⁵
	<ol style="list-style-type: none"> Annual echocardiogram if symptomatic valvular disease Screening echocardiogram 10 y after radiation therapy and every 5 y thereafter in asymptomatic patients 	
	Cardiac MRI	
	Recommended in those with suboptimal echocardiography or discrepant results	ESC ¹²
	Coronary CT angiography/calcium artery calcium score	
	Reasonable to perform ≥ 5 y post radiotherapy, and further workup (eg, coronary angiography, functional testing) is indicated for risk stratification if there is concern for severe ischemic heart disease	SCAI ⁴⁶
SPECT	ASE ⁴⁵	
	<ol style="list-style-type: none"> Reasonable to screen for CAD with a functional noninvasive stress test 5–10 y after radiation exposure in asymptomatic individuals deemed a high risk for radiation induced heart disease Repeat stress testing can be planned every 5 y if the first exam does not show inducible ischemia 	
Prior exposure (not currently on therapy)	Echo	
	Recommended for those with symptoms of heart failure (E,B,1)	ASCO ⁹
	CMR	
	Recommended instead of echo only if echo unavailable or not technically feasible (E,B,2)	ASCO ¹⁶
Potential cardiotoxic therapy	Echo	
	LVEF measurement at baseline and during [§] treatment (2D/3D) and GLS with treatment or risk factor modification at LVEF $\geq 60\%$, 50%–59%, 40%–49%, and $<40\%$	Liu et al ³⁷

ASCO indicates American Society of Clinical Oncology; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CTRCD, cancer therapeutics-related cardiac dysfunction; EACVI, European Association of Cardiovascular Imaging; ESC, European Society of Cardiology; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; SCAI, Society for Cardiovascular Angiography and Interventions; MRI, magnetic resonance imaging; SEOM, Spanish Society of Medical Oncology; SPECT, single-photon emission computed tomography; VEGF, vascular endothelial growth factor.

*Evidence-based Y/N=E/N, level of evidence high/intermediate/low=A/B/C, strength of recommendation strong/moderate/weak=1/2/3.

†During treatment frequency not defined.

Echocardiography and Treatment-Related Myocardial Dysfunction

Because of its wide accessibility, low cost, and negligible side effect profile, echocardiography is the cornerstone of myocardial dysfunction assessment. Echo is the most common modality used to monitor patients who are on traditional chemotherapeutic regimens such as anthracyclines, given the strong causal relationship between these agents and cardiomyopathy. Guidelines recommend using echocardiography in clinical scenarios of

heart failure presentation, surveillance during therapy, and follow-up until 1 year after treatment completion.⁹ Specific echo guidelines regarding monitoring anthracyclines have been proposed by multiple organizations and are detailed in Table 1. The 2014 expert consensus statement by the American Society of Echocardiography³⁵ recognized echocardiographic strain as a valuable modality when following patients receiving cardiotoxic therapies since reduction in myocardial strain, particularly global longitudinal strain (GLS), has been shown to be predictive of future

myocardial dysfunction³⁶ (Figure 1A). Hence, there has been introduction of strain imaging in certain monitoring guidelines.¹⁰

Echo is important for assessing myocardial dysfunction related to biologic agents such as trastuzumab and pertuzumab. The largest study of echocardiographic monitoring of vascular endothelial growth factor inhibitors, including biologic agents, comprised of 40 individuals who were followed via a 2-dimensional speckle tracking echocardiography protocol with baseline echocardiography and repeat 2-dimensional speckle tracking echocardiography at 1, 3, and 6 months.⁴⁷ Trastuzumab has been extensively studied, and monitoring guidelines are summarized well in a recent review by Jerusalem et al⁴⁸ and detailed in Table 1, including the protocol of ongoing SAFE-HEaRT (Cardiac Safety Study in Patients With HER2 + Breast Cancer) trial.^{42,43}

Echo also has a central role in the surveillance of suspected TKI cardiotoxicity as reflected by the US Food and Drug Administration's prescription to discontinue certain agents when a decline in LV ejection fraction is noted.²⁶ Derangement in GLS is known to precede LV dysfunction in patients who had received a variety of TKIs, suggestive of a class effect.^{47,49} Professional societies have published recommendations summarized in Table 1 regarding baseline echocardiography and screening intervals in patients receiving TKI therapy.^{12,35}

Though no established guidelines exist, echocardiography is also important in evaluating suspected proteasome-induced cardiac toxicity. Gavazzoni et al observed that mean systolic and diastolic pressure increased and echo parameters (namely, E and E') used to assess diastolic function worsened in patients treated with carfilzomib.⁵⁰ As with other cardiotoxicities, GLS with speckle tracking echocardiography can be employed to detect subclinical LV dysfunction, particularly with carfilzomib.⁵¹ Echo remains the initial imaging modality of choice when assessing radiation-induced myocardial function and valvular disease. Radiotherapy-associated diastolic dysfunction is commonly attributable to adverse cardiac remodeling. Echo can assess diastolic dysfunction patterns via tissue Doppler and strain imaging. Imaging surveillance recommendations from professional societies for this patient population are noted in Table 1.

Cardiac Magnetic Resonance Imaging and Treatment-Related Myocardial Dysfunction

Cardiac magnetic resonance imaging (CMR) is the gold standard for evaluation of chamber quantification and function. In patients in whom echo-derived LV function is equivocal, in question, or marginally decreased, CMR can be a useful arbiter in the decision to withhold or continue therapy. CMR is an important adjunctive diagnostic tool when the etiology of a new cardiomyopathy is in question or in prognostication.

Increasingly, CMR has been recognized as a valuable tool for following patients on anthracycline therapy given not only its

accurate assessment of LV function but also its ability to detect fibrotic (late gadolinium enhancement [LGE] and T1 mapping) and inflammatory patterns (T2 mapping), which may help in early diagnosis and prognostication of anthracycline-induced cardiomyopathy^{52,53} (Figure 1B). Currently, additional prospective studies testing the potential of CMR-derived indices (ie, T1/T2) to detect meaningful toxicity before clinical presentation are under way. CMR has been used to study the diastolic pattern, fibrosis, and myocardial strain after treatment with trastuzumab therapy.^{54,55} CMR usage continues to increase among this population, as reflected by its role in high-profile trials, like MANTICORE 101-Breast (Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research) and others.⁵⁶

CMR is a valuable tool for soft tissue characterization and its role in the evaluation of patients with suspected proteasome-induced myocardial dysfunction continues to evolve. Much of the information regarding CMR findings in this population is based on case report level data.^{22,50,51,57,58} Typical CMR findings include mild-moderate LV dilation, global hypokinesis, and subendocardial to midwall myocardial linear or circumferential stripes of delayed myocardial enhancement consistent with fibrosis. T2 mapping may show hyperintense signals consistent with myocardial edema. These findings are relatively nonspecific and can be seen in other nonischemic cardiomyopathies. Other cases series, however, showed that these CMR findings, in particular the LGE findings, are not universal in patients with suspected proteasome-induced heart failure.²²

CMR is important for assessing radiotherapy-associated myocardial dysfunction and fibrosis burden, particularly when the etiology of heart failure is unclear. CMR provides accurate volumetric and mass information in addition to tissue characterization via T1 mapping and fibrosis imaging (Figure 2). Emerging CMR technologies also have strain packages that do not necessitate speckle tracking requirements.

In patients treated with TKIs who developed LV dysfunction without a clear ischemic etiology, the role of CMR is less clear. Available smaller observational-level data do not demonstrate characteristic CMR resting perfusion defects or LGE patterns.^{60,61} Clinical data regarding the use of parametric mapping for tissue characterization in this subgroup are lacking. This is of particular interest given increasing data describing change in myocardial and vascular character with various TKIs. Further validated studies are needed to elucidate the role of CMR in evaluating suspected TKI-induced myocardial dysfunction.

Nuclear Imaging and Treatment-Related Myocardial Dysfunction

Historically, a multigated angiocardigraphy (MUGA) scan was one of the most common modalities employed for measuring LV ejection fraction.^{9,15,39} However, MUGA has been largely

supplanted by more advanced imaging modalities such as 3-dimensional echo, and CMR. That is mainly because MUGA scan provides limited information,⁶² is less accurate,⁶³ and has a higher radiation exposure (8 mSv in MUGA versus 0 in CMR/3-dimensional echo)^{64,65} to patients compared with the aforementioned modalities. Specific single-photon emission computed tomography tracers have been developed for assessing left ventricular function in patients with suspected anthracycline-induced cardiomyopathy, but clinical use of these agents is not widespread.⁶⁶

Fludeoxyglucose (FDG) positron emission tomography (PET) has a role in assessing myocardial dysfunction, particularly in those who have received prior radiation treatment. Radiotherapy-associated cardiomyopathy may manifest not only with fibrosis but also with elevated plasma levels of brain natriuretic peptide.⁶⁷ These patients with elevated brain natriuretic peptide may demonstrate abnormal FDG accumulation on PET imaging along irradiated regions (Figure 3).^{67–69} This clinical utility suggests that cardiac PET may have an adjunctive role in assessing cardiotoxicity in this patient population.

Cancer Treatment–Related Atherosclerosis and Myocardial Ischemia

A number of oncologic agents have been associated with myocardial ischemia, thrombosis, and coronary artery disease, including traditional chemotherapy drugs, TKIs, hormonal agents, and radiation therapy. Cisplatin is a traditional chemotherapeutic alkylating agent that is employed in the treatment of a variety of solid-tumor malignancies and is associated with a 1% to 12% incidence of myocardial infarction. Bleomycin is an antitumor antibiotic that interferes with DNA crosslinking and is associated with a 1% to 3% incidence of coronary vasospasm and myocardial infarction. 5-Fluorouracil is associated with 1% to 19% incidence of vasospasm, myocardial infarction, and Takotsubo cardiomyopathy.⁴⁶ A number of TKIs are associated with cardiac ischemia attributable to the modulation of cardiovascular homeostatic pathways. Sorafenib is a multi-target TKI that is associated with cardiac ischemia (3%) and hypertension (10%–17%).⁷⁰ Pazopanib is associated with a variety of cardiac toxicities including ischemia, hypertension, LV dysfunction, and QT prolongation.⁷¹

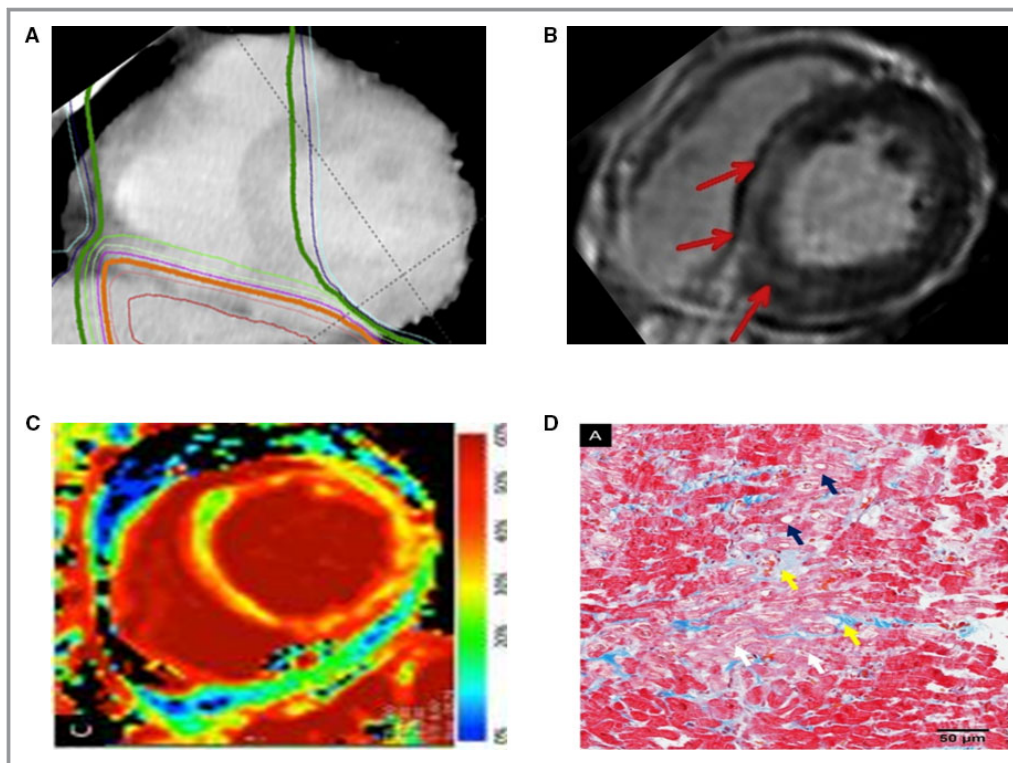


Figure 2. Correlation between radiotherapy (A) and discrete myocardial fibrosis (LGE, red arrows; B). Cardiac magnetic resonance imaging-detectable diffuse fibrosis (ECV; C) corresponding to biopsy-proven fibrosis (D), after esophageal cancer radiotherapy. Specifically, histopathologically, interstitial fibrosis (yellow arrow) and myocardial degeneration such as irregular arrangement (white arrow) or vacuolar changes (blue arrow) are seen. Adapted with permission from Mukai-Yatagai et al.⁵⁹ Copyright ©2018, Elsevier. ECV indicates extracellular volume; LGE, late gadolinium enhancement.

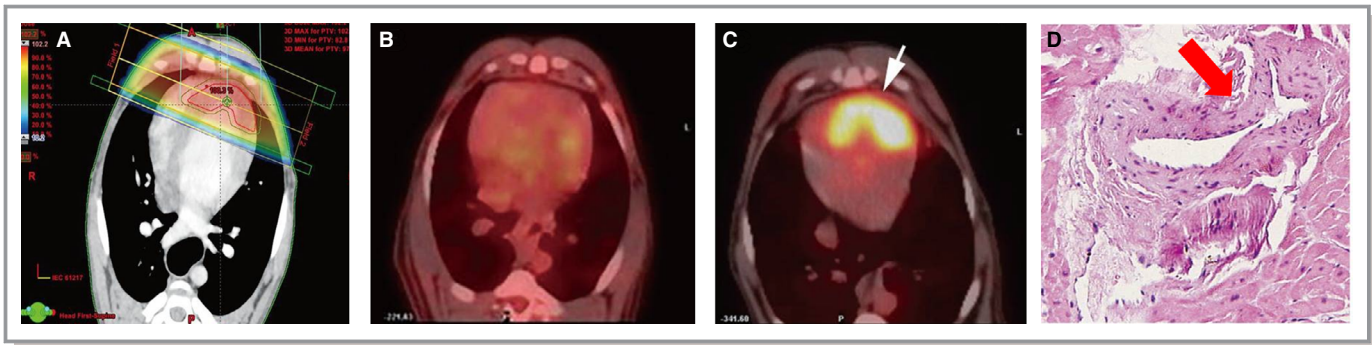


Figure 3. Within the radiation field (A), change in positron emission tomography (PET)-measured myocardial metabolic activity from before (B) to 3 months after (C, white arrow) radiotherapy treatment, with corresponding fibrosis (D, red arrow) observed on histopathological examination following local heart irradiation in beagles. Echocardiographic parameters remained unchanged. Adapted from Yan et al⁶⁹ under the Creative Commons Attribution Non-Commercial (CC-BY-NC) License.

Selective estrogen receptor modulators (ie, tamoxifen) and aromatase inhibitors (anastrozole, letrozole, and exemestane) work to counteract growth in certain subtypes of hormonally responsive breast cancers and in turn reduce recurrence and improve disease-free survival.^{72,73} However, these agents have notable cardiac side effects. Tamoxifen is associated with higher rates of stroke and pulmonary embolism when compared with placebo.⁷⁴ Pooled data analyses from large trials demonstrate a modest increase in myocardial infarction, angina, and heart failure with aromatase inhibitors when compared with tamoxifen.⁷⁵

Androgen deprivation therapy (ie, leuprolide, goserelin, flutaminde, and abiraterone) is the mainstay of treatment of metastatic prostate cancer. They are collectively associated with hyperinsulinemia, hypertension, peripheral artery disease, and hypercholesterolemia. Data are conflicting about the direct impact of these agents on cardiovascular mortality with more recent meta-analyses demonstrating a modestly increased risk of myocardial infarction, stroke, and nonfatal cardiovascular disease, predominantly in men who had preexisting cardiovascular disease or cardiac risk factors.^{76–80}

Radiotherapy leads to endothelial damage with a subsequent inflammatory response driving atherosclerosis and subsequent clinically relevant ischemic events.^{29,30} As studied in the Hodgkin lymphoma and breast cancer survivor populations, those who have received radiation treatment have an elevated relative risk of developing coronary artery disease (2.2 and 1.27, respectively) when compared with the general population.^{33,81} The risk of coronary artery disease significantly increases with time since radiotherapy. In addition, these patients suffer worse long-term outcomes after cardiac surgery.⁸² A major concern in this population is the lack of traditional symptoms on presentation for obstructive coronary disease, which is attributable to radiation nerve damage to the chest wall.

Clonal hematopoiesis of indeterminate significance (CHIP) refers to somatic mutations that occur within hematopoietic

stem cells and is associated with increased cardiovascular risk, including myocardial infarction, and decreased overall survival.^{83,84} Interestingly, an increased prevalence of CHIP has been noted in patients who have received prior cancer treatment, particularly radiotherapy.⁸⁵ Though a mechanistic link between CHIP and cardiac mortality has yet to be definitively established, it is plausible that CHIP alleles confer cardiovascular risk via atherosclerosis mechanisms.^{83,84} The optimal management strategies require further investigation.

Cardiac Computed Tomography and Treatment-Related Atherosclerosis and Myocardial Ischemia

Although traditional ischemic evaluations include nuclear or echocardiographic modalities, cardiac computed tomography (CT)—including coronary artery calcium scanning and CT coronary angiography—has become more prominent because of its excellent diagnostic and prognostic information via anatomic evaluation of atherosclerosis. Coronary artery calcium scanning is a non-contrast-enhanced CT image acquisition of the coronary arteries to assess atherosclerotic plaque burden and in turn has shown to have important prognostic value for future adverse cardiac events in asymptomatic individuals.⁸⁶ Coronary CT angiography offers a non-invasive alternative to left heart catheterization with comparable diagnostic accuracy and important prognostication in patients who present with stable chest pain.⁸⁷ While coronary CT angiography adds further radiation exposure, the typical dose ranges from 2 to 5 mSv, with improved technology resulting in <1 mSv. As traditional therapies such as 5-fluorouracil, certain TKI agents, and radiotherapy have all been associated with myocardial ischemia, coronary CT angiography is an excellent modality to exclude clinically significant coronary artery disease in such patients who are undergoing an ischemic evaluation (Figure 4). This is a particularly appealing alternative where invasive angiography may be

untenable given elevated bleeding risks commonly noted in this population. In the aforementioned CHIP population, Jaiswal et al⁸⁴ showed that these patients had a 3-fold higher risk of having high coronary artery calcium score (>615 Agatston units). Given the increased cardiovascular mortality risk noted with these patients, coronary artery calcium scoring may have a role in primary prevention paradigms in this population. This is an exploratory application in this respect and for the cardio-oncology population as a whole, and represents an exciting area for future study.

Cardiac PET and Treatment-Related Atherosclerosis and Myocardial Ischemia

Cardiac PET offers not only accurate assessments of myocardial function and ischemia. This is particularly useful in assessing ischemic events in those receiving vasospastic chemotherapy like 5-fluorouracil.⁸⁹ However, there are no guideline recommendations regarding FDG-PET in this population, outside of established methodologies for ischemic evaluations and cardiac viability assessments. Additional applications are demonstrated in animal literature, where PET is being studied as a noninvasive method to detect alterations in cardiac metabolism that potentially predates overt cardiotoxicity.⁹⁰ In human subjects, similar observations have been made in case-level data where aberrations in cardiac PET imaging had preceded clinical coronary events in a patient treated with a TKI.⁹¹ It remains to be seen how these findings can be applied to routine clinical practice and population-wide screening schemas in this population.

Other Imaging Modalities and Treatment-Related Atherosclerosis and Myocardial Ischemia

Stress echocardiography has an established role in ischemic evaluations in the cardio-oncology population.³⁵ In line with that of the general population, it can be used for the detection and prognostication of stable coronary artery disease or in the evaluation of those with intermediate pretest probability for CAD. This should particularly be considered if the patient is undergoing treatment with regimens associated with ischemia including 5-fluorouracil, bevacizumab, sorafenib, and sunitinib.³⁵ Stress echocardiography may also be useful in the evaluation of subclinical LV dysfunction and the evaluation of contractile reserve in patients with treatment-related cardiac dysfunction. Regarding the use of single-photon emission computed tomography, there are no guideline recommendations outside of established methodologies for ischemic evaluations. CMR can also provide quantitative myocardial perfusion mapping to directly quantify regional myocardial perfusion reserve and detect prior myocardial infarction using LGE when an ischemic insult is suspected⁹² (Figure 5).

Immunotherapy-Related Myocarditis

Immunotherapies, such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cell transfer therapy, amplify T-cell-mediated immune responses against cancer cells and represent an exciting evolution in oncologic therapeutics. Many tumors express inhibitory cellular membrane ligands that effectively act as cloaking mechanisms to avoid host immune detection. Blockade of these ligands and/or the corresponding receptors on host cells with monoclonal antibodies activate the



Figure 4. (Left) Cardiac computed tomography (CT) with 3-dimensional reconstruction rendering allowing for (right) omniplane visualization of coronary artery plaque and calcification. Adapted with permission from Layoun et al.⁸⁸ Copyright © 2019, Springer Science Business Media, LLC, part of Springer Nature.

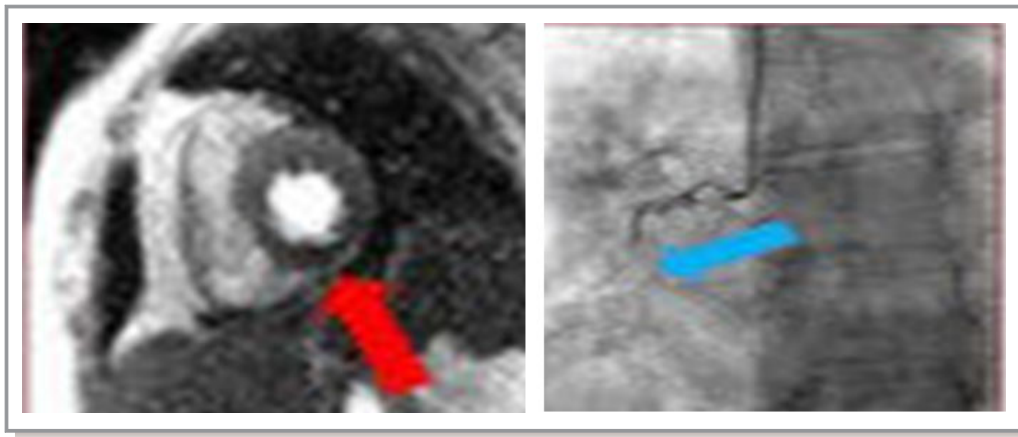


Figure 5. Cardiac magnetic resonance imaging scan of short-axis plane of left ventricle in a breast cancer survivor showing inferior wall perfusion defect consistent with prior myocardial infarction (left) with corresponding occlusion of the right coronary artery (right). Adapted from Vasu et al⁹³ under the Creative Commons Attribution (CC-BY) license.

immune system to recognize and target cancer cells.⁹⁴ ICIs have led to progression-free survival in a variety of metastatic disease states but are associated with various cardiac side effects, most notably myocarditis.^{95,96} Initial clinical trial data indicated that the prevalence of severe myocarditis was rare (0.06%), with a higher occurrence (0.27%) reported in patients receiving multiple ICIs.^{97–99} Yet more recent data suggest that the prevalence may in fact be higher on the order of 1% to 2%.¹⁰⁰ A recent consensus statement by Bonaca et al¹⁰¹ elaborated on the definition of myocarditis in relation with ICI and further evaluation with multiple imaging modalities, which are detailed in Table 2.

Chimeric antigen receptor T-cell therapy is a technique wherein a patient's T cell is genetically modified *ex vivo* with a fusion protein receptor that is specific for a tumor antigen. Once reinfused back into the patient, engagement of this receptor with a tumor antigen results in activation of the T cell against the tumor cell.¹⁰⁶ Clinical trials demonstrated an array of toxicities with these agents, including cytokine release syndrome, neurotoxicity, and prolonged cytopenias. Cardiac-related events such as arrhythmias and cardiomyopathies have ranged from 29% to 30%, including rare reports of cardiac arrest.^{107–112} Single-center data suggest that many of these toxicities are associated with cytokine release syndrome and resolve within 6 months of follow-up.¹¹³ The pathophysiology of these toxicities—whether mediated directly by the chimeric antigen receptor T-cell product itself, indirectly by a cytokine-mediated process, or an alternative mechanism—is not well understood.

Echocardiography and Immunotherapy-Related Myocarditis

Echo has an important role in the assessment of cardiac function with guidelines recommending a screening echo when

the suspicion of ICI cardiotoxicity arises.⁴⁴ Aside from standard echocardiographic parameters, there has been recent work on the use of GLS in assessing LV function in patients treated with ICIs. Awadalla et al¹⁰² assessed GLS in patients treated with ICI who developed myocarditis and showed that GLS is reduced with both preserved and reduced ejection fraction. They also noted that lower GLS is associated with subsequent major adverse cardiac events in those with ICI-related myocarditis. Waheed et al¹⁰³ similarly demonstrated a decrease in GLS in patients treated with ICIs who developed myocarditis despite the LV ejection fraction remaining unchanged. These studies support observations noted in other cardiomyopathies that strain, particularly GLS, can be used to detect LV dysfunction despite a normal ejection fraction assessment.

Cardiac Magnetic Resonance Imaging and Immunotherapy-Related Myocarditis

The end result of many immunotherapies is to elicit an inflammatory response against a target tumor site. Yet off-target actions may also produce systemic and cardiac inflammatory injury and subsequent fibrosis.⁴⁴ In this sense, CMR is a powerful tool in the diagnosis of ICI cardiotoxicity, as it allows for assessment of myocardial edema, inflammatory injury, and fibrosis. Although there are no guideline-driven CMR recommendations specifically pertaining to ICI-related myocarditis, generally speaking, CMR is the noninvasive test of choice for the assessment of myocarditis.¹¹⁴ Condition-specific protocols include contrast-enhanced T1-weighted, noncontrast T2-weighted, and more advanced quantitative tissue characterization using parametric (T1 and T2) mapping sequences. Inflammatory processes tend to cause cell injury and permeability of cellular membranes, in turn leading to global and regional edema (Figure 6A). T2 reflects the free-

Table 2. Recommended Modality Without Specific Guidelines*

Therapeutic Agent	Imaging Modality	Source
Immune checkpoint inhibitors	Echo	
	Consider echo with strain imaging when suspicion of ICI toxicity exists: <i>Definite myocarditis:</i> New wall motion abnormality on echo not explained by another diagnosis (ie, acute coronary syndrome, stress-induced cardiomyopathy, sepsis) and <i>all</i> of the following: (1) clinical syndrome consistent with myocarditis, (2) elevated biomarker of cardiac myonecrosis, (3) ECG evidence of myopericarditis, (4) negative angiography or other testing to exclude obstructive coronary disease <i>Probable myocarditis:</i> New wall motion abnormality on echo with a clinical syndrome consistent with myocarditis not otherwise explained by another diagnosis and <i>either:</i> (1) elevated biomarker of cardiac myonecrosis or (2) ECG evidence of myopericarditis <i>Possible myocarditis:</i> New wall motion abnormality on echo <i>one</i> of the following: (1) clinical syndrome consistent with myocarditis not explained by alternate diagnosis, (2) ECG evidence of myopericarditis	Bonaca et al ¹⁰¹ Adawalla et al ¹⁰² Waheed et al ¹⁰³
	CMR	
	Consider CMR when suspicion for ICI-induced myocarditis exists: <i>Definite myocarditis:</i> CMR diagnostic of myocarditis, a clinical syndrome not explained by alternate diagnosis, and one of following: (1) elevated biomarker of cardiac myonecrosis or (2) ECG evidence of myopericarditis <i>Probable myocarditis:</i> CMR with findings diagnostic of myocarditis not explained by alternate clinical diagnosis with <i>any</i> of the following: (1) clinical syndrome consistent with myocarditis, (2) elevated biomarker of cardiac myonecrosis, or (3) ECG evidence of myopericarditis <i>Possible myocarditis:</i> Nonspecific CMR findings suggestive of myocarditis with one or more of the following: (1) clinical syndrome consistent with myocarditis not explained by alternate clinical diagnosis, (2) elevated biomarker of cardiac myonecrosis, (3) ECG evidence of myopericarditis	Mahmood et al ¹⁰⁰ Bonaca et al ¹⁰¹ Salem et al ¹⁰⁴
	18 FDG-PET	
	Scenario meeting criteria for <i>possible myocarditis</i> (see above) with PET showing patchy cardiac FDG uptake without another explanation	Bonaca et al ¹⁰¹
Tyrosine kinase inhibitors	Echo	
	In context of appropriate symptoms, screening echo test of choice to evaluate pulmonary pressures, right ventricular dysfunction or hypertrophy, septal deviation to the left to provide supporting evidence of pulmonary hypertension (Dasatinib use [†])	Moslehi et al ¹⁰⁵
	CMR	
	Consider CMR during evaluation of suspected TKI-related ischemia (sorafenib [†])	Sudasena et al ⁹²
	18 FDG-PET	
	Consider cardiac PET during evaluation of suspected TKI-related ischemia (sorafenib [†])	Sudasena et al ⁹² Toubert et al ⁹¹
Proteasome inhibitors	Echo	
	Consider echo with strain imaging when evaluating LV systolic and diastolic parameters for suspected proteasome inhibitor LV dysfunction	Gavazzoni et al ⁵⁰ Iannaccone et al ⁵¹
Radiation therapy	CMR	
	Consider T1-weighted mapping in the evaluation in suspected radiation induced myocardial fibrosis	Mukai-Yatagai et al ⁵⁹

18-FDG PET indicates 18-fluorodeoxyglucose positron emission tomography; CMR, cardiac magnetic resonance imaging; GLS, global longitudinal strain; ICI, immune checkpoint inhibitor; LVEF, left ventricular ejection fraction; TKI, tyrosine kinase inhibitor.

*Reflects emerging data that may show efficacy to additional applications of cardiac CT, MRI, and PET in broader applications.

[†]Recommendations apply only to specific agent, not class.

water content of the tissue, and thus inflammation and edema lead to elevated T2. LGE imaging can reveal high signal intensity, diffuse subepicardial or midwall distribution patterns; however, signal intensity on LGE images can be elevated with either edema or fibrosis. By combining information from T1, T2, and LGE imaging, CMR can identify myocarditis with sensitivity of 76% and specificity of 96% when compared with invasive histologic confirmation.^{115,116} These techniques have allowed

for a major step forward in the assessment of cardiotoxic injury, by providing a novel avenue to evaluate quantitative, rather than traditional subjective/qualitative, early cardiotoxic change. These observations extend beyond more traditional markers of cardiotoxicity as measured by echocardiography alone, including GLS. The ability of CMR to aid in myocyte-level tissue characterization offers a valuable tool, which may prove vital in the understanding, diagnosis, and management of ICI-

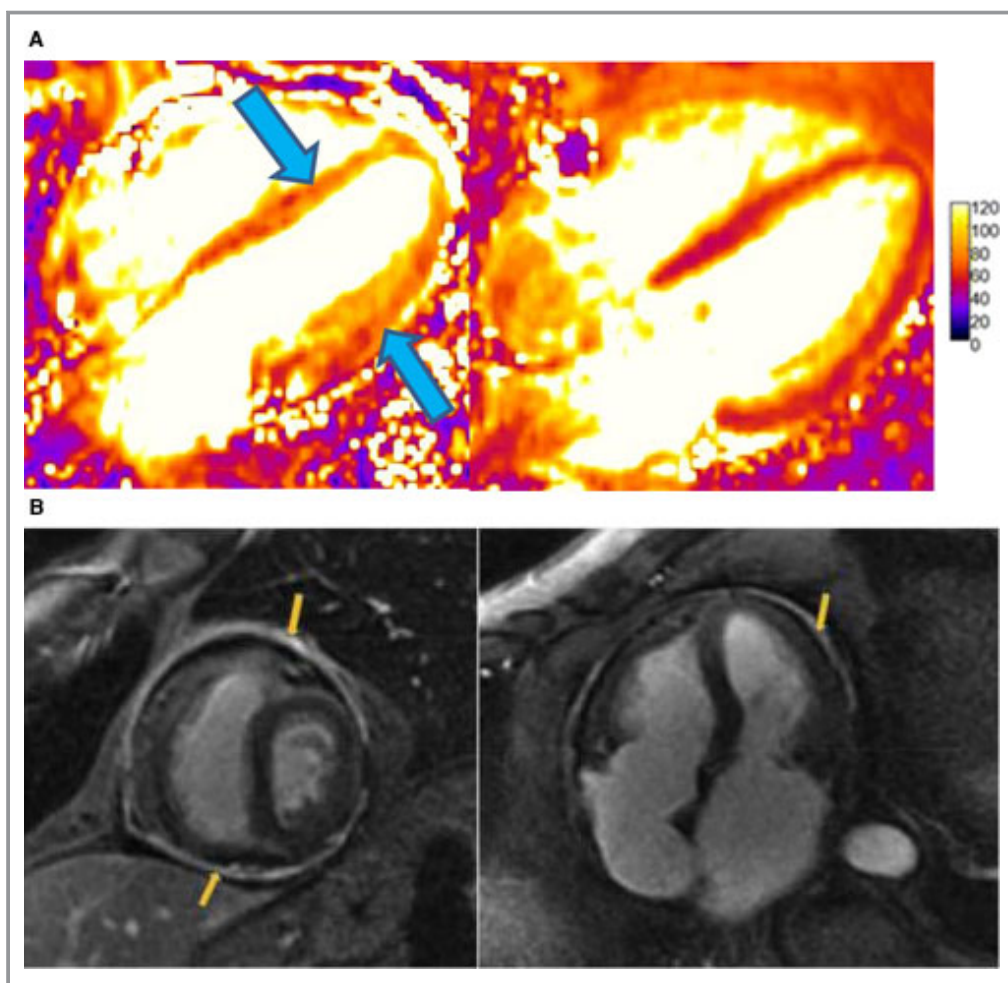


Figure 6. A, (Left) Cardiac MRI T2 maps at diagnosis of myocarditis in a patient treated with pembrolizumab showing global hypokinesia with moderate systolic dysfunction (LVEF, 41%) and diffusely elevated T2 signal (arrows). (Right) T2 maps after withdrawal of pembrolizumab and 1-month course of prednisone 1 mg/kg with resultant normalized systolic function (LVEF, 59%) and improved T2 signal. B, Cardiac magnetic resonance imaging scan late gadolinium enhancement (LGE) sequences showing thickened and enhanced pericardium in a patient with constrictive pericarditis following radiation therapy. Adapted with permission from Aldweib et al.¹²³ Copyright © 2018, Eureka Science (FZC). LVEF, left ventricular ejection fraction.

related myocarditis events. Moreover, this modality may assist in the serial assessment of potential steroid (or even nonsteroid) treatment(s) response over time. With limited numbers, Mahmood et al¹⁰⁰ showed there was no difference in cardiac events between those patients with and without LGE noted on their CMR who had been diagnosed with myocarditis. However, additional studies are needed to confirm the efficacy of parametric mapping after ICI or other immune-based therapy exposure.

Cardiac PET and Immunotherapy-Related Myocarditis

FDG-PET is widely used to assess tumor burden and response to therapy, and it has an established role in the diagnosis and

follow-up evaluation of certain inflammatory myopathies.¹¹⁷ However, there are no existing guidelines regarding the use of cardiac PET in evaluation of immunotherapy-related myocarditis. Nevertheless, the application of cardiac PET in patients receiving such agents is an active field of study. Wang et al¹¹⁸ noted that the degree of tumor burden assessed via PET in patients with non-Hodgkin lymphoma receiving chimeric antigen receptor T-cell transfer therapy correlated with the degree of cytokine release syndrome. They showed how PET could be used to assess myocarditis, pericardial effusions, and treatment response in a patient with diffuse large B-cell lymphoma with cardiac involvement. Others have shown that the development of cytokine release syndrome did not confound PET findings, a particular concern given the inflammatory milieu involved in this common side effect.¹¹⁹ As

murine and early human studies have shown, PET has the potential to visualize minuscule concentrations of tracers linked to T-cell populations and show promise in tracking T-cell clonal response.¹²⁰ Whether this can be applied to better assess patients with suspected chimeric antigen receptor T-cell therapy cardiotoxicity, including myocarditis, remains to be seen.

Pericardial Disease

Radiotherapy is the prototypical agent associated with pericarditis. Radiation can induce acute pericarditis early after treatment, which is usually self-limited. However, rare presentations of recurrent pericarditis have been noted and can result in constrictive physiology. Cancer survivors receiving chest radiotherapy have ≈ 13 times higher likelihood of requiring a pericardiectomy as compared with matched cohorts.¹²¹

Imaging Modalities and Treatment-Related Pericardial Disease

Echocardiography is the first-line modality in evaluation of pericardial disease, as it can assess for pericardial effusion in addition to providing valuable hemodynamic data indicative of tamponade or constrictive physiology. Cardiac CT may provide anatomic evaluation of the pericardium via the presence of a pericardial effusion in the acute phase or calcification in the chronic phase. CMR can be used to evaluate the pericardium via hemodynamic assessment through interventricular dependence and mitral/tricuspid inflow variation,¹²² in addition to pericardial inflammation through edema and fibrosis imaging¹²³ (Figure 6B).

Cardiac Amyloidosis

Cardiac amyloidosis is heterogeneous group of infiltrative cardiomyopathies typified by the deposition of extracellular amyloid protein resulting progressive heart failure, arrhythmias, and death. Incidence, prognosis, diagnostic evaluation, and treatment all depend on the subtype, chiefly among them being amyloid light chain (AL) and acquired transthyretin amyloidosis. A recent study conducted in the United Kingdom estimates that the incidence of AL amyloidosis is 8.0/100 000 per year, with greater than half of patients demonstrating cardiac involvement.^{124,125} The median survival for acquired transthyretin amyloidosis with cardiac involvement is 3 to 5 years, while median survival for AL amyloidosis with cardiac involvement is reportedly <12 months.^{126,127} Contemporary treatment regimens for AL and acquired transthyretin have led to improvements in

quality of life, decreased hospitalization, and extended overall survival.^{124,128} Thus, early identification and risk stratification of patients with cardiac amyloid infiltration is vital to reducing the death toll of this fatal disease.

While endomyocardial biopsy was traditionally used for diagnosis, advances in noninvasive imaging in echocardiography, nuclear medicine, and CMR have provided early and accurate detection in a previously underdiagnosed population. Echo findings include LV hypertrophy in the setting of a low to normal QRS amplitude on electrocardiography, systolic dysfunction, restrictive physiology, and pericardial effusion. Strain imaging may demonstrate a characteristic pattern of global dysfunction with relative apical sparing.¹²⁹ Technetium-labeled bone scintigraphy is a highly sensitive technique for the diagnosis acquired transthyretin cardiac amyloidosis, with myocardial tracer uptake showing a >99% sensitivity and 86% specificity (Figure 7).^{130,131} CMR is able to accurately diagnose cardiac amyloidosis through characteristic global subendocardial LGE and abnormal myocardial gadolinium kinetics.¹³² CMR also provides further incremental clinical value via prognostication and treatment response through T1 mapping.¹³³ As AL treatment regimens often include proteasome inhibitor agents such as bortezomib, which in turn are associated with LV dysfunction and heart failure, echo and CMR have an important role in evaluating treatment-related cardiac toxicity as detailed elsewhere.^{22,51,57,58}

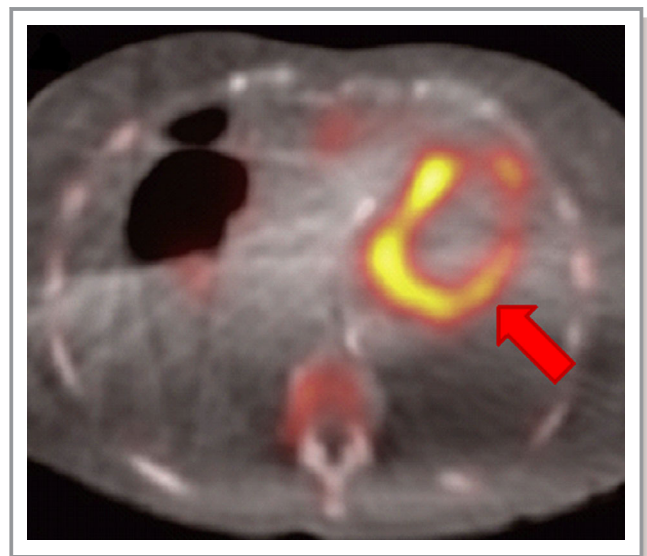


Figure 7. 88-year-old female with aortic stenosis and amyloid transthyretin cardiac amyloidosis by ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid scan; arrow points to regions of increased uptake. Adapted from Scully et al¹³¹ under the Creative Commons Attribution (CC-BY) license.

Peripheral Vascular Disease and Vascular Dysfunction

Vascular disease, namely venous thromboembolism and hypertension, is a pervasive side effect of a number of cancer therapies. Additional vascular complications include pulmonary hypertension, arterial thromboembolism, and vasospasm. Traditional therapies associated with vascular side effects include fluoropyrimidines, taxanes,¹³⁴ vinca alkaloids, platinum compounds, cyclophosphamide, anthracyclines,¹³⁵ and bleomycin,¹³⁶ among others.

Therapeutic agents specifically associated with systemic or pulmonary hypertension including androgen deprivation therapies, proteasome inhibitors, biologic agents, and various TKIs, particularly those that modulate the vascular endothelial growth factor pathway. Vascular endothelial growth factor stimulates endothelial cells to release nitric oxide and prostacyclin, causing vasodilation. Thus, inhibiting this pathway is thought to lead to hypertension. Though commonly classified as a biologic agent, bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor used in the treatment of a variety of malignancies including colon, lung, and renal cancer. Bevacizumab can lead to hypertension in roughly 35% of patients, which in turn, is thought to be responsible for downstream myocardial dysfunction.⁴⁷ Sunitinib, sorafenib, pazopanib, ibrutinib, and axitinib are a few prominent TKI agents associated with hypertension, with the former being the most well studied. Up to 80% of patients on sunitinib may experience systolic hypertension (median blood pressure of 160 mm Hg) by the end of the second cycle of treatment.¹³⁷ Dasatinib is a second-generation TKI commonly used in the treatment of chronic myelogenous leukemia and has been linked to pulmonary hypertension with a variably low incidence.¹⁰⁵ Dasatinib-induced pulmonary hypertension is thought to be partially reversible and, if confirmed, should be permanently discontinued.^{105,138}

Finally, radiation therapy causes acute and chronic vascular inflammatory effects resulting in a range of vascular dysfunction including premature atherosclerotic disease, venous stenosis and thrombosis, and dysautonomia, to name a few.^{139–143} The mechanisms of each of these side effects are summarized in an American Heart Association Statement by Campia et al.²

Imaging Modalities and Cancer Treatment–Related Vascular Disease

Vascular imaging is governed by the type of the pathology, availability, and local expertise rather than the specific chemotherapy used.^{2,12,144,145} Peripheral arterial and carotid imaging ranges from inexpensive modalities like duplex ultrasound to highly accurate but expensive modalities like magnetic resonance angiography and invasive angiography. Duplex ultrasound, CT

angiography and ventilation-perfusion scans have been widely used in the evaluation of venous thromboembolic events. Whenever therapy-induced pulmonary hypertension is suspected, echo is the first imaging test of choice.⁴⁷ Given that cancer treatment–related hypertension can lead to downstream myocardial dysfunction, an echocardiogram is also an important initial imaging test for this cohort as well.^{47,146} Phase contrast magnetic resonance angiography provides important information on vascular morphology and flow quantification.¹⁴⁷ A new technology that has been introduced in the space of magnetic resonance angiography is 4-dimensional flow. Four-dimensional flow magnetic resonance angiography provides 3-dimensional vascular morphology as well as dynamic quantitative flow information across the cardiac cycle.¹⁴⁷ This technology has added a new dimension in vascular imaging with the ability to derive parameters such as wall shear stress, pressure gradients, and turbulence. There are many potential uses¹⁴⁸ of this technique including evaluation of valvular disease in radiation-induced heart disease and ruling out renal vascular disease as a cause of secondary hypertension in setting of cancer therapy–related hypertension.

Future Perspective and Direction

Cancer survival continues to improve in the era of emerging anticancer therapies.¹⁴⁹ Given this trend and the fact that cardiovascular disease is the most common cause of death among cancer survivors, there is pressing need to identify and treat patients with adverse cardiovascular outcomes related to prior and ongoing cancer therapies. There remain a number of unmet needs in the cardio-oncology realm, including the role of primary prevention in cardiotoxicity, appropriate therapeutic response and surveillance in secondary prevention, and the optimal mode and timing of cardiac imaging in this population as a whole.

Multimodality cardiac imaging will continue to have an essential role in the evaluation of treatment-related cardiac toxicity. Our review offers a comprehensive summary of guideline-directed recommendations on this subject, where available. In areas where there is a paucity of data, we highlight primary literature detailing novel and evolving applications of cardiac imaging as related to treatment toxicity. With these data, along with our single-center experience, we offer our practical approach to multimodality imaging for evaluation of cardiotoxicity, as summarized in Table 3.

Echocardiography has served as the cornerstone of baseline and surveillance assessments, displacing MUGA in a whole host of diagnostic algorithms. Applications of strain imaging continue to expand, though more studies are needed to validate its use as a reliable method of detecting subclinical LV dysfunction, particularly with newer agents. CMR is unparalleled in a variety of applications including evaluation of chamber quantification, myocardial tissue characterization, and

Table 3. Practical Considerations in Multimodality Imaging for Evaluation of Cardiotoxicity

	Volume and Functional Assessment	Tissue/Mass Characterization	Myocarditis/ Inflammation	Valve Disease	Pericardial Disease	Coronary Disease/ Ischemia	Radiation Exposure	Reproducibility/ Accuracy	Cost	Availability
Cardiac MRI	+++	+++	+++	++	+++	++	None	+++	+	+
CT Coronary	++	+	–	+	++	+++	+	+++	++	+
PET/Nuclear	+++	++	+++	–	+	+++	+++	+++	++	++
Echo	+ / ++	++	–	+++	+ / ++	– / + (wall motion)	None	+	+++	+++

Adapted with modifications from Seraphim et al¹⁵⁰ under the Creative Commons Attribution (CC-BY) license. CT indicates computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

multidimensional quantitative vascular assessment. Although CMR had previously been confined primarily to academic centers, accessibility continues to improve given the ever decreasing costs of CMR, growing expertise, and expanded use in traditionally limited patient populations including those with pacemaker/defibrillator devices and severe renal dysfunction.^{151,152} Given this, we expect CMR to assume a broader role in cardiotoxicity diagnostic and surveillance imaging. More data are needed to drive standardization of CMR protocols in the evaluation of specific cardiac toxicities.

Previously mentioned animal studies and case reports demonstrate novel applications of cardiac PET beyond its traditional role of ischemia and viability assessments. For example, the use of cardiac PET in tracking specific T-cell clones in those treated with immunotherapy or who develop cardiac events with such agents holds promise. Given that the withdrawal of an anticancer agent may hold grave clinical consequences for patients, such dynamic imaging techniques could provide an additional tool to help clinicians avoid unwarranted discontinuation of therapy.

Coronary artery calcium scanning and coronary CT angiography applications continue to expand, particularly as newer gating techniques have allowed lower radiation exposure and high-fidelity imaging acquisition. As coronary CT angiography is the only modality mentioned above that allows for an accurate noninvasive anatomic assessment of coronary vasculature, it is uniquely positioned for evaluating patients with suspected ischemic insults from cardiotoxic agents, particularly where invasive angiography is undesirable.

Our review highlights the important and varied roles that cardiac imaging has in the assessment suspected cardiotoxicity in the oncologic population. Multimodality cardiac imaging will continue to be essential to filling unmet needs and knowledge gaps, and in turn, augment best practice recommendations in the management of the cardio-oncology patient.

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