Published in final edited form as:

Curr Probl Cancer. 2018 July ; 42(4): 386–396. doi:10.1016/j.crrproblcancer.2018.05.005.

Advanced imaging modalities to detect cardiotoxicity

Magid Awadalla^a, Malek Z.O. Hassan^a, Raza M. Alvi^a, and Tomas G. Neilan^{a,b,*}

^aCardiac MR PET CT Program, Massachusetts General Hospital, Boston, MA

^bCardio-oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, MA

Abstract

Recent advances in cancer treatments have significantly improved survival rates, reemphasizing the focus on reducing the potential complications associated with some therapies. Cardiovascular disease associated with chemotherapies is a major cause of morbidity and mortality in cancer survivors. Early detection of cardiotoxicity improves cardiac outcomes among cancer patients. The review will focus on imaging modalities used to assess cardiotoxicity - the cardiovascular consequences of chemotherapies. The review will discuss the benefits and limitations associated with each technique, as well as the guidelines available to help identify at risk patients. We will discuss novel techniques that may help detect earlier signs of cardiotoxicity, directing management that may improve clinical outcomes. Published by Elsevier Inc.

Keywords

Cardiotoxicity; Chemotherapy; Cardiac magnetic resonance; Echocardiography; Computed tomography; Radionuclide imaging; Ejection fraction

Introduction

Due to the improvement in cancer survival, an increasing number of patients may develop treatment-associated cardiac disease, broadly termed as cardiotoxicity. Standard current methods for detection of cardiotoxicity primarily involve serial measurement of the left ventricular ejection fraction (LVEF), a parameter that when reduced is a late manifestation in the cardiotoxic paradigm and when the possibility for reversibility declines. Early detection of cardiotoxicity may be important as clinical outcomes can be improved with the early initiation of cardioprotective medications. The past decade has seen rapid advances in imaging modalities such as cardiac magnetic resonance (CMR) and echocardiography. Advances in both echo and CMR allow the early detection of myocardial mechanical changes such as global longitudinal strain that occur prior to the onset of left ventricular (LV) dysfunction, while the main strengths of CMR are improved spatial resolution and complementary tissue characterization.

*Correspondence to: Tomas G Neilan, MD, MPH, Harvard Medical School, Cardio-Oncology Program, Cardiac MR PET CT Program, Massachusetts General Hospital, 165 Cambridge Street, Suite 400, Boston, MA 02114. tneilan@mgh.harvard.edu (T.G. Neilan).

This comprehensive review will discuss the current as well as emerging advanced imaging modalities available to detect cardiotoxicity and how these may shape the future guidelines for its early detection.

Definitions

Cardiotoxicity related to cancer therapy is a broad term and includes any functional or structural heart injury related to cancer treatment.^{1–4} Cardiotoxicity may occur secondary to the cancer, chemotherapy, or radiotherapy.⁵ The injury to the heart most commonly involves the myocardium leading to heart failure but can also involve the pericardium, valves, or coronary arteries progressing to pericardial disease, valvular disease, and coronary artery disease.^{6,7} The current standard definition for cardiotoxicity is defined by the Cardiac Review and Evaluation Committee (CREC) on trastuzumab-associated cardiotoxicity and the ESMO Clinical Practice Guidelines.⁸

Specifically, cardiotoxicity after chemotherapy is defined as a decrease in LVEF of $\geq 5\%$ to $< 55\%$ in the presence of symptoms of Heart Failure (HF) or an asymptomatic decrease in LVEF by $\geq 10\%$ to less than 55% . There are multiple factors involved in the development of cardiotoxicity and the definition of cardiotoxicity beyond the general and Cardiac Review and Evaluation Committee definition above varies widely; as a result, the estimated incidence varies significantly from $<1\%$ to nearly 50% when comparing over 40 different studies.⁹

Cardiotoxic chemotherapies—There are several cancer treatments that have been associated with the potential for cardiotoxicity. Some examples include anthracyclines, 5-fluorouracil, cyclophosphamide, tyrosine kinase inhibitors, vascular endothelial growth factor, immune checkpoint inhibitors, HER-2 antagonists and radiation therapy.^{2,6,8,10–15} Most of the data that exists relates to the cardiotoxicity that occurs with anthracyclines and trastuzumab (Herceptin, a HER-2 antagonist), and these will be the primary focus for the remainder of this article.

Importance of early detection of cardiotoxicity

Over the last decade, it has become clear that the early detection of cardiac dysfunction, cardiotoxicity or cardiac injury, and the institution of appropriate cardiovascular care can improve outcomes.⁶ Cardinale et al. studied the clinical response to heart failure in a group of 200 patients with anthracycline-induced cardiotoxicity and a resultant reduction in LVEF $\geq 45\%$.⁶ LVEF was assessed at regular intervals by echocardiography following the initiation of optimal heart failure medication including enalapril and carvedilol. Depending on the level of recovery of the LVEF, the patients were designated as complete recovery (LVEF recovery to $\geq 50\%$), partial recovery (increase by $\geq 10\%$ to LVEF $< 50\%$), or nonresponders (increase by $<10\%$ to LVEF $< 50\%$). Complete response was noted in 40% of patients, partial response in nearly 15% and nonresponse in 45% . The most critical determinant of LVEF response was the length of time from diagnosis and/or initiation of heart failure therapy. Specifically, for every doubling in time to diagnosis of cardiotoxicity and/or initiating heart failure therapy, there was a fourfold decrease in the chance of complete recovery. Patients initiated on therapy within 2 months had over 60% chance of complete

recovery of LVEF. In contrast, no LVEF recovery was seen in patients with a time to initiating heart failure treatment of > 6 months. This study highlights the importance of early identification of cardiac dysfunction, the narrow window of time for initiation of effective therapy that can improve outcomes and the potential benefit of detecting reversible cardiac injury that may even precede asymptomatic systolic dysfunction.

Current imaging guidelines

The recent American Society of Clinical Oncology (ASCO) guidelines have recommended measurement of the LVEF by echocardiography for screening of patients prior to, and, for many, after commencing cardiotoxic chemotherapeutic agents. CMR imaging or multigated acquisition (MUGA) scans are the alternative modalities of choice should echocardiography not be available or technically feasible with preference given to CMR.¹⁶ The recommendation for subsequent surveillance imaging and measurement of the LVEF is based on chemotherapy dose and baseline cardiovascular risk factors. For instance, higher doses of doxorubicin (250 mg/m² or more), high dose radiotherapy (30 Gy or more), or the combination of lower-dose anthracycline (less than 250 mg/m² of doxorubicin) with lower dose radiotherapy (less than 30 Gy) warrants subsequent measurement of the LVEF as compared to lower risk individuals who receive a lower dose.^{5,17,18} In the case of trastuzumab, the manufacturers recommend a baseline evaluation of LVEF, followed by repeat measurement of LVEF every 3 months (4 cycles) while on treatment (4 weekly if a significant drop in LVEF with treatment withheld), and every 6 months for the immediate 2-year period after completing the regimen.¹⁹

Imaging modalities for cardiotoxicity screening

Echocardiography—Two-dimensional (2D) echocardiography is the most common imaging modality for evaluation of patients in preparation for, during, and after potentially cardiotoxic therapy.¹⁶ This is because of its wide availability, reproducibility, versatility, lack of radiation exposure, and safety in patients with concomitant renal disease. Echocardiography allows evaluation of left and right ventricular dimensions, volumes, and function as well as valvular, pericardial, large vessel pathology, and additional components particularly important in assessment of radiation-induced cardiotoxicity.^{20,21} Echocardiography has limitations, most notable is the temporal variability in LVEF which approaches 8%–10% in 2D echocardiography.²² This variability can be improved through the use of contrast, especially in patients with inadequate acoustic windows.²³ Three-dimensional (3D) echocardiography also improves accuracy and reproducibility,²⁴ but may not readily be available in all laboratories.

For some patients receiving anthracyclines, a decline in systolic function may occur, but the LVEF may remain within the normal range despite documented toxicity.^{25–27} As a result, significant research has focused on the development of additive echocardiographic parameters for the detection of subclinical myocardial dysfunction. Diastolic dysfunction typically precedes systolic dysfunction and the role of echocardiographic measures of diastolic function has been tested after chemotherapy; however, the results are inconsistent and therefore diastolic measures are not routinely recommended for this indication.^{28,29}

Stress echo—Exercise and pharmacologic stress testing may also be useful to unmask subclinical abnormalities of LV function induced by chemotherapeutic agents.³⁰ In a study involving nearly 40 patients receiving doxorubicin, an abnormal LVEF at rest within 1 month of having chemotherapy was reported to have a sensitivity of over 50% and a specificity of 75% for detecting patients at moderate or high risk of developing congestive cardiac failure even though a follow-up time frame was not clearly outlined. With the addition of exercise, sensitivity increased to nearly 90% but specificity decreased to 40%.³¹ In a study of young adults with acute lymphoblastic leukemia treated with anthracyclines, nearly half the subjects demonstrated a normal Ejection Fraction (EF) at rest but reduced LVEF during stress.³² Studies using dobutamine stress echocardiography have yielded conflicting results in the detection of chemotherapy cardiotoxicity. High dose dobutamine stress echocardiography revealed an alteration of the fractional shortening and the transmitral E/A ratio in over 25 asymptomatic patients treated with high-dose anthracyclines.³³ In contrast, other studies did not report any incremental value of the technique for early detection of cardiotoxicity.^{34,35} The lack of any conclusive data, the semi-invasive nature of the test, and repeatability means stress echocardiography limits the utility of this approach for the detection of chemotherapy-induced cardiotoxicity.

Myocardial strain imaging—Earlier myocardial damage may be detected using strain imaging.^{36,37} Cardiac strain is a technique that objectively quantifies myocardial mechanical function and more sensitively detects cardiac systolic function beyond EF.^{37,38} Using this technique, myocardial deformation or strain can be quantified in all three dimensions (longitudinal, radial, and circumferential) through the quantification of the temporal displacement between neighboring reflections. The American College of Cardiology and/or American Heart Association defines four stages (A-D) of heart failure. Stage A = at high risk for heart failure, but without structural heart disease or symptoms, Stage B = structural heart disease but without signs or symptoms of heart failure, Stage C = structural heart disease with prior or current symptoms of heart failure, and Stage D = refractory heart failure.³⁹ Currently, cardiotoxicity in patients receiving chemotherapy is typically diagnosed in Stage B to C. Myocardial strain imaging offers the potential to diagnose cardiotoxicity much earlier, technically in Stage A, which would likely result in much better clinical outcomes for patients, and reduced healthcare costs. There is substantial reproducible data to support the use of echocardiographic myocardial strain imaging in detecting subclinical left ventricular dysfunction in patients undergoing potentially cardiotoxic chemotherapy.^{36–38,40} Studies of early myocardial changes with chemotherapy show that changes in strain precede declines in LVEF; specifically, a 10%–15% early reduction in global longitudinal strain using speckle tracking strain has been shown to predict the development of subsequent toxicity, a finding replicated in subsequent studies.⁴¹ Due to the consistency of the published data, the American Society of Echocardiography published an expert consensus¹⁷ which incorporates strain imaging into the management of patients receiving drugs with the potential for either Type I cardiotoxicity (ie anthracyclines) or Type II cardiotoxicity (ie trastuzumab). In both cases, echocardiography with strain imaging is recommended at baseline. For drugs with the potential for Type I toxicity, echocardiographic imaging, including strain, is recommended at completion of therapy and 6 months later.

For drugs with the potential for Type II toxicity, echocardiography with strain imaging is recommended every 3 months during therapy. In both cases, a relative decline in global longitudinal strain $> 15\%$ is defined as indicative of subclinical left ventricular dysfunction and should prompt cardiology consultation, as well as potential initiation of cardioprotective drugs,^{42,43} and chemotherapy dosing modifications. Limitations exist in this approach, which are worth discussing. Specifically, as the case with 2D echo, acoustic windows may also be a limitation for measuring myocardial strain, as adequate tracking of endocardial borders are required for accurate measurements. Furthermore, strain analysis is typically performed off-line, also there are differences in the software used, and again requires significant laboratory experience.

Radionuclide imaging

Multiple gated acquisition: The ASCO guidelines 2016 recommend the use of MUGA to assess LVEF if such a measurement is not feasible by echocardiography and CMR. MUGA has previously been the most widely used imaging modality for the evaluation of LVEF; this use is principally due to its availability, accuracy, and reproducibility.⁵ MUGA uses technetium-99 m (99mTc) labeled red blood cells to assess cardiac function. This modality is more accurate, reproducible and associated with a lower inter and intraobserver variability than 2D echocardiography.⁴⁴ MUGA has also correlated well with other 3D imaging tools, such as CMR, but individual left ventricular volumes and LVEF values still differ significantly across the techniques, which suggests that choosing a single technique may provide the best option for serial monitoring of LVEF.⁴⁵ Limitations include a radiation exposure of approximately 5–10 millisieverts, which is most significant in the pediatric population given increased concern for radiation exposure, and its inability to assess cardiac structure.⁴⁶

SPECT: Single-photon electron computed tomography (SPECT) was one of principle methods for cardiotoxicity screening until the recent ASCO guidelines. The previous guidelines, which remained for nearly 3 decades, were based on the single largest study, which monitored the heart during anthracyclines using serial SPECT over a 7-year period, and involved nearly 1500 patients. Using this method of screening, 19% of patients were shown to be at a high risk of cardiotoxicity (defined as LVEF $< 50\%$, a drop in LVEF by 10% , cumulative doxorubicin dose $> 450 \text{ mg/m}^2$), findings which have been replicated in a more recent study of a similar cohort that showed a similar proportion (16%) of patients receiving doxorubicin were deemed at risk (defined as patients with normal LVEF at baseline $> 50\%$ who had a $> 10\%$ fall in LVEF to a level $< 50\%$ during therapy) at some point during their therapy.⁴⁷ Those who developed clinical heart failure had a greater absolute drop in LVEF compared to those who did not (mean drop in LVEF $23\% \pm 14\%$ vs $12\% \pm 10\%$).⁴⁸ Although monitoring resting LVEF by SPECT is helpful in detecting early anthracycline cardiotoxicity, it still has a low sensitivity (53%) as compared to myocardial tissue biopsy³¹ and is associated with additional radiation.

Positron emission tomography—Positron emission tomography (PET) is the gold standard technique to assess myocardial metabolism and perfusion due to its high spatial and

temporal resolution and high diagnostic sensibility and accuracy. There have been limited clinical studies applying cardiac PET to monitor for anthracycline cardiotoxicity.

In patients receiving anthracyclines, there was no early or late change in uptake of carbon-11 acetate, a tracer that is a marker for both myocardial blood flow and an indicator of oxidative metabolism through the Tricarboxylic Acid (TCA) cycle.⁴⁹ However, a study in rats demonstrated decreased myocardial uptake of a β -adrenergic antagonist [3H] CGP12177 in the septum and free wall 3 weeks after treatment with anthracyclines.⁵⁰ It is unclear whether β -receptor density is a good surrogate marker to predict anthracycline cardiotoxicity in humans, and further larger studies are required to develop this field.

PET and myocardial fibrosis: Recent animal studies involving mice, showed an increase in myocardial Fludeoxyglucose (FDG) uptake by PET in mice treated with sunitinib (a tyrosine kinase inhibitor), compared to untreated mice.^{13,51} This FDG uptake precisely correlated with myocardial fibrosis on tissue analysis.¹³ This same group showed that an endothelin receptor antagonist (macitentan) prevents deregulation of myocardial metabolism and cardiac fibrosis and restores the diastolic function impaired by sunitinib.¹³ This clinically significant correlation and potential improvement in outcomes has brought a lot of interest in PET imaging for cardiotoxicity screening particularly in patients taking sunitinib, however this needs to be proven first in human populations.

Computed tomography

Computed tomography (CT) assessment of the heart for cardiotoxicity is principally useful following radiation therapy. While CT may be utilized for cardiac functional assessment, it is primarily useful for evaluating pericardial or coronary artery disease related to cancer, chemotherapy or radiation therapy.⁵² It can also be complementary or an attractive alternative to CMR in the assessment of cardiac masses especially when there are contraindications to CMR. Cardiac CT can offer detailed cross-sectional anatomical imaging of the chest and, when intravenous contrast is used, a detailed differentiation of the cardiac cavities and vessels from surrounding tissues is possible.⁵³ By synchronizing the acquisition or reconstruction of the images to the electrocardiogram, motion-free, and phase-consistent images of the heart can be obtained, which are important for the robust depiction of the coronary arteries and functional analysis. Advantages of cardiac CT in comparison with other imaging modalities include high-spatial resolution, short exam times, and high sensitivity for calcified tissues. In specific, CT is a reliable noninvasive technique for imaging the coronary arteries.⁵³ There are 2 main types of cardiac CT, coronary calcium scoring and coronary CT angiography (CCTA). Coronary calcium scoring does not use x-ray contrast, and images are taken of the heart to look for the presence of calcium deposits in the coronary arteries, and are mainly used to assess asymptomatic patients with low or intermediate risk of CAD for detection of calcifying plaque.⁵³ CCTA allows for further quantification of total and noncalcifying coronary plaque burden and stenosis gradation.⁵⁴

Radiation therapy is associated with an increased risk of developing coronary artery disease. CCTA reported a seven fold increase in coronary artery abnormalities in asymptomatic patients receiving mediastinal radiotherapy for Hodgkin's lymphoma.⁵⁵ This increase

mainly involved disease of the arteries exposed to the most radiation in the anterior aspect of the mediastinum including the left main and the left anterior descending. Radiation triggers an inflammatory process in the arterial wall that results in arterial wall thickening and morphologically resembles spontaneous atherosclerosis.⁵⁶ Due to this process, vascular CT angiography may be used to evaluate carotid, subclavian and aortic diseases related to radiation therapy.⁵⁷ Of particular interest is the screening before any cardiac surgery for porcelain aorta, a finding noted in patients 10–20 years after radiotherapy.⁵⁸

CT can also assess the pericardial space for effusions and pericardial thickening related to pericarditis that can occur due to the cancer or associated therapies.

Cardiac magnetic resonance

CMR is the gold standard for detecting cardiotoxicity due to its accuracy, reproducibility, and ability to detect subtle changes in cardiac function that may be predictive of cardiotoxicity.^{5,16} CMR uses magnetic fields and radiofrequency pulses to produce both still and moving images of the heart. This imaging modality is free of radiation, and is particularly useful in imaging obese patients in whom echocardiography yields suboptimal images. CMR is also useful for evaluating the pericardium, and several techniques can be used with CMR to help identify various indicators of cardiotoxicity. Different sequences are available with complementary strengths.

Cine imaging is used to evaluate the cardiac structure and morphology, phase-contrast imaging is used to assess valvular function, and tissue characterization allows measurement of edema and fibrosis.^{59–62} Late gadolinium enhancement is used to detect focal myocardial fibrosis or scar tissue, however this is a rare finding in patients postanthracycline therapy in particular.⁵⁹ Limitations of magnetic resonance imaging include inability to perform in patients with implanted cardiac devices, claustrophobia, availability, and higher costs than echo and MUGA.

Myocardial T1 mapping: Myocardial T1 mapping is a technique, which uses T1 relaxation times to calculate the volume of distribution (Vd) of gadolinium-based contrast agents (GBCAs) in the myocardium, a measure that is increased in the presence of diffuse myocardial fibrosis.^{61–63} The relaxation properties change when GBCAs are used and often T1 maps are acquired pre and post contrast injection. The differences between these two values are corrected for patients' hematocrit, and allow quantification of the extracellular volume fraction (ECV).^{59–62,64,65} Several CMR-based clinical investigations have leveraged T1 measurements and mapping to study myocardial remodeling in cancer patients and survivors. In a study of childhood cancer survivors, an increased ECV was positively correlated with higher anthracycline doses.⁶⁶

The ECV was also associated with decreased mass/volume ratio, a reflection of wall thinning and a lower peak VO2 max. In a study of 42 adults, mean age of 55 years, with clinical heart failure, imaged late (median time interval of 84 months) following anthracycline therapy, there was an association between an increased ECV and diastolic dysfunction as well as increased left atrial volumes.⁵⁹ A study involving 37 cancer patients yet to receive therapy, 37 on anthracycline therapy, 17 receiving nonanthracycline

chemotherapy and 230 control participants, showed that native T1 and ECV was elevated in the anthracycline-treated group, whilst no difference was found between the nonanthracycline survivors and pretreatment group, suggesting that these imaging biomarkers of fibrosis are directly associated to prior receipt of anthracyclines and independent of underlying cancer diagnosis.⁶⁷ Larger-scale studies in patients receiving cardiotoxic chemotherapeutic agents are still needed to determine whether there is a threshold for myocardial T1 or Vd beyond which there is increased risk for developing LV dysfunction, and correlated with cumulative doses of chemotherapeutic agents to help identify those at higher and lower risk of developing CIC.

Myocardial edema: CMR also has the unique ability to detect myocardial edema, which may be seen in acute myocardial injury. Acute myocardial injury and inflammation causes an increased signal in the myocardium on T2 weighted (T2W) images which can be seen in myocarditis and infarction.^{68,69} In an animal study where mice underwent serial imaging pre and post anthracyclines, mice treated with anthracyclines had an early increase in myocardial edema and a related sub-acute increase in myocardial fibrosis, both of which were found to be predictive of late animal mortality.⁶⁰ However, T2W imaging in CIC has not been widely evaluated and further research is required in this field to determine whether myocardial edema is of value in identifying high-risk patients prior to receiving chemotherapy and also monitoring of CIC.

Myocardial strain: Novel CMR strain techniques using feature tracking measuring global longitudinal, radial and circumferential strain have been studied in small retrospective case-control studies. In one study, all strain parameters were shown to be lower in patients with cardiotoxicity as compared to normal controls.⁷⁰ Further larger prospective studies are required to study early strain patterns during initiation of chemotherapy, and followed up with serial CMRs at different time points of treatment. This may help identify those at higher risk of CIC and allow earlier intervention that can potentially improve clinical outcomes.

Cellular size and mass: Novel CMR indices assessing radiation, chemotherapy-induced cardiomyocyte injury and atrophy are currently being studied. These include quantification of the intracellular lifetime of water (tau), a measure proportional to cardiomyocyte diameter and determination of the total cardiomyocyte LV mass.⁷¹ However, while promising, these techniques are limited to specialized centers and data applying these techniques are pending.

Vascular dysfunction: In addition to the potential development of cardiac dysfunction, many cancer therapies may be associated with the development of vascular dysfunction. Recently, Chaosuwanakit et al. demonstrated that pulse wave velocity measured during CMR, was increased in participants receiving cancer therapy.⁷² This increase in pulse wave velocity was associated with a three fold in the risk of a future cardiovascular event. The increase in aortic stiffening was not dose-dependent, suggesting that there may be thresholds of susceptibility to vascular dysfunction, and further research may be useful in identifying these susceptibilities.

Risks of gadolinium: The US Food and Drug Administration currently warns against the use of GBCAs in patients with renal failure due to the risk of nephrogenic systemic fibrosis, a potentially fatal multiorgan system fibrosing disease associated with GBCAs. This risk can be avoided with patient screening and administration of a contrast agent only to patients with a glomerular filtration rate of over 30 mL per minute per 1.73 m², and avoidance in those with acute renal insufficiency related to hepatorenal syndrome or perioperative liver transplantation.^{73,74}

Additionally, there is also recent concern regarding the retention of gadolinium and its long-term and cumulative effects on the body and brain.⁷⁵ This is currently being investigated.

Conclusion

As cancer therapy improves, survivors will have a longer lifespan and some may face unanticipated cardiac sequelae from cancer treatment. Performing serial advanced noninvasive imaging modalities to detect earlier signs of CIC can facilitate mitigation of these potential side effects. There are strengths and weaknesses to each modality approach (Table 1)—echocardiography, nuclear imaging, CT, and CMR; therefore, the future of surveillance for CIC is likely to involve an algorithm which includes one or more imaging modality to risk stratify prior to and after commencing cancer therapy, with subsequent tailoring to the patient based on both the risk assessment and type of cancer therapy. The use of these advanced imaging modalities has shifted the previous reliance on LVEF for determining which patients are at risk for developing cardiotoxicity, and has allowed for earlier detection prior to potentially irreversible damage. This approach may lead to an improvement in clinical cardiovascular outcomes.

References

1. Ong DS, Scherrer-Crosbie M, Coelho-Filho O, Francis SA, Neilan TG. Imaging methods for detection of chemotherapy-associated cardiotoxicity and dysfunction. *Expert Rev Cardiovasc Ther*. 2014 4;12:487–497. [PubMed: 24650314]
2. Neilan T, Asnani A, Tripathy D, Scherrer-Crosbie M. Prevention and management of anthracycline cardiotoxicity. [cited 2018 Jan 10]; Available from: <https://www.uptodate.com/contents/prevention-and-management-of-anthracycline-cardiotoxicity>.
3. Wang DY, Okoye GD, Neilan TG, Johnson DB, Moslehi JJ. Cardiovascular toxicities associated with cancer immunotherapies. *Curr Cardiol Rep*. 2017 3;19:21. [PubMed: 28220466]
4. Meyersohn NNM, Pursnani A, Neilan TG. Detection of cardiac toxicity due to cancer treatment: role of cardiac MRI. *Curr Treat Options Cardiovasc Med*, 2015 8;17:396. [PubMed: 26134969]
5. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*, 2016 9 21;37:2768–2801. [PubMed: 27567406]
6. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*, 2010 1 19;55:213–220. [PubMed: 20117401]
7. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA*, 1991 9 25;266:1672–1677 [PubMed: 1886191]
8. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol Off J Am Soc Clin Oncol*, 2002 3 1;20:1215–1221

9. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013 4;49:1374–1403. [PubMed: 23485231]
10. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018 4 24;71:1755–1764. [PubMed: 29567210]
11. Chu TF, Rupnick mA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet Lond Engl*. 2007 12 15;370:2011–2019.
12. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys*. 2010 3 1;76:656–665. [PubMed: 20159360]
13. Sourdon J, Lager F, Viel T, et al. Cardiac metabolic deregulation induced by the tyrosine kinase receptor inhibitor sunitinib is rescued by endothelin receptor antagonism. *Theranostics*. 2017;7:2757–2774. [PubMed: 28824714]
14. Addison D, Lawler PR, Emami H, et al. Incidental Statin use and the risk of stroke or transient ischemic attack after radiotherapy for head and neck cancer. *J Stroke*. 2018 1;20:71–79. [PubMed: 29402065]
15. Addison D, Seidelmann SB, Janjua SA, et al. Human Papillomavirus status and the risk of cerebrovascular events following radiation therapy for head and neck cancer. *J Am Heart Assoc*. 2017 8 30;6:1–9.
16. Armenian SH, Lacchetti C, Lenihan D. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary. *J Oncol Pract*. 2017 4;13:270–275 [PubMed: 27922796]
17. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2014 9;27:911–939.
18. Avelar E, Strickland CR, Rosito G. Role of Imaging in cardio-oncology. *Curr Treat Options Cardiovasc Med*. 2017 6;19:46. [PubMed: 28474324]
19. Highlights of prescribing information [Internet]. [cited 2018 Jan 2]. Available from: https://www.gene.com/download/pdf/herceptin_prescribing.pdf.
20. Daher IN, Kim C, Saleh RR, Plana JC, Yusuf SW, Banchs J. Prevalence of abnormal echocardiographic findings in cancer patients: a retrospective evaluation of echocardiography for identifying cardiac abnormalities in cancer patients. *Echocardiography*. 2011 11;28:1061–1067. [PubMed: 21854439]
21. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*. 2012 9 1;5:596–603. [PubMed: 22744937]
22. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol*. 2013 1 8;61:77–84. [PubMed: 23199515]
23. Hoffmann R, von Bardeleben S, ten Cate F, et al. Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. *Eur Heart J*. 2005 3;26:607–616. [PubMed: 15618026]
24. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol*. 2004 8 18;44:878–886. [PubMed: 15312875]
25. Dodos F, Halbsguth T, Erdmann E, Hoppe UC. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. *Clin Res Cardiol Off J Ger Card Soc*. 2008 5;97:318–326.
26. Cottin Y, Touzery C, Coudert B, et al. Impairment of diastolic function during short-term anthracycline chemotherapy. *Br Heart J*. 1995 1;73:61–64. [PubMed: 7888264]

27. Cottin Y, L'huillier I, Casasnovas O, et al. Dobutamine stress echocardiography identifies anthracycline cardiotoxicity. *Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol*. 2000 9;1:180–183
28. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. *Heart Br Card Soc*. 2004 10;90:1214–1216.
29. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? *J Clin Oncol Off J Am Soc Clin Oncol*. 2008 3 10;26:1201–1203.
30. Tan TC, Scherrer-Crosbie M. Assessing the cardiac toxicity of chemotherapeutic agents: role of echocardiography. *Curr Cardiovasc Imaging Rep*. 2012 12 1;5:403–409. [PubMed: 23227272]
31. McKillop JH, Bristow MR, Goris ML, Billingham ME, Bockemuhl K. Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. *Am Heart J*. 1983 11;106:1048–1056. [PubMed: 6637763]
32. Jarfelt M, Kujacic V, Holmgren D, Bjarnason R, Lannering B. Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2007 11;49:835–840. [PubMed: 17610264]
33. Hamada H, Ohkubo T, Maeda M, Ogawa S. Evaluation of cardiac reserved function by high-dose dobutamine-stress echocardiography in asymptomatic anthracycline-treated survivors of childhood cancer. *Pediatr Int Off J Jpn Pediatr Soc*. 2006 6;48:313–320.
34. Bountiokos M, Doorduijn JK, Roelandt JRTC, et al. Repetitive dobutamine stress echocardiography for the prediction of anthracycline cardiotoxicity. *Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol*. 2003 12;4:300–305.
35. Lanzarini L, Bossi G, Laudisa ML, Klersy C, Arico M. Lack of clinically significant cardiac dysfunction during intermediate dobutamine doses in long-term childhood cancer survivors exposed to anthracyclines. *Am Heart J*. 2000 8;140:315–323. [PubMed: 10925349]
36. Thavendiranathan P, Poulin F, Lim K-D, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014 7 1;63:2751–2768. [PubMed: 24703918]
37. Januzzi JL, Chandrasekhar Y. Strain echocardiography: the new gold standard for imaging ventricular function? *J Am Coll Cardiol*. 2017 8 22;70:955–957. [PubMed: 28818205]
38. Santoro C, Arpino G, Esposito R, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. *Eur Heart J Cardiovasc Imaging*. 2017 5 1;18:930–936. [PubMed: 28379383]
39. Members C, Hunt SA, Baker DW, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation*. 2001 12 11;104:2996–3007. [PubMed: 11739319]
40. Jordan JH, Sukpraphrue B, Melendez GC, Jolly M-P, D'Agostino RB, Hundley WG. Early myocardial strain changes during potentially cardiotoxic chemotherapy may occur as a result of reductions in left ventricular end-diastolic volume: the need to interpret left ventricular strain with volumes. *Circulation*. 2017 6 20;135:2575–2577. [PubMed: 28630272]
41. Tang Q, Jiang Y, Xu Y, Xia H. Speckle tracking echocardiography predicts early subclinical anthracycline cardiotoxicity in patients with breast cancer. *J Clin Ultrasound JCU*. 2017 5;45:222–230. [PubMed: 27910996]
42. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006 12 5;114:2474–2481. [PubMed: 17101852]
43. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006 12 5;48:2258–2262. [PubMed: 17161256]
44. Urena PE, Lamas GA, Mitchell G, et al. Ejection fraction by radionuclide ventriculography and contrast left ventriculogram. A tale of two techniques. SAVE Investigators. Survival and ventricular enlargement. *J Am Coll Cardiol*. 1999 1;33:180–185. [PubMed: 9935027]

45. Mogelvang J, Stokholm KH, Saunamaki K, et al. Assessment of left ventricular volumes by magnetic resonance in comparison with radionuclide angiography, contrast angiography and echocardiography. *Eur Heart J.* 1992 12;13:1677–1683. [PubMed: 1289099]
46. Mettler FA, Huda W, Yoshizumi TT, Mahesh M Effective doses in radiology and diagnostic nuclear medicine: a catalog. *Radiology.* 2008 7;248:254–263. [PubMed: 18566177]
47. Mitani I, Jain D, Joska TM, Burtneess B, Zaret BL Doxorubicin cardiotoxicity: prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiology in the current era. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol.* 2003 4;10:132–139.
48. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiology. *Am J Med.* 1987 6;82:1109–1118. [PubMed: 3605130]
49. Nony P, Guastalla JP, Rebattu P, et al. In vivo measurement of myocardial oxidative metabolism and blood flow does not show changes in cancer patients undergoing doxorubicin therapy. *Cancer Chemother Pharmacol.* 2000;45:375–380. [PubMed: 10803920]
50. Kenk M, Thackeray JT, Thorn SL, et al. Alterations of pre- and postsynaptic noradrenergic signaling in a rat model of adriamycin-induced cardiotoxicity. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol.* 2010 4;17:254–263.
51. O'Farrell AC, Evans R, Silvola JMU, et al. A novel positron emission tomography (PET) approach to monitor cardiac metabolic pathway remodeling in response to sunitinib malate. *PloS One.* 2017;12:e0169964.
52. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. *Ann Intern Med.* 2011 3 15;154:413–420. [PubMed: 21403076]
53. Lancellotti P, Nkomo VT, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr.* 2013 9;26:1013–1032.
54. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2007 1 23;49:378–402. [PubMed: 17239724]
55. Kupeli S, Hazirolan T, Varan A, et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. *J Clin Oncol Off J Am Soc Clin Oncol.* 2010 2 20;28:1025–1030.
56. Aoki S, Hayashi N, Abe O, et al. Radiation induced arteritis: thickened wall with prominent enhancement on cranial MR images report of five cases and comparison with 18 cases of Moyamoya disease. *Radiology.* 2002 6;223:683–688. [PubMed: 12034935]
57. Rajiah P, CT and MRI in the evaluation of thoracic aortic diseases. *Int J Vasc Med.* 2013;2013
58. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol.* 2006 10 3;48:1475–1497 [PubMed: 17010819]
59. Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. *Am J Cardiol.* 2013 3 1;111:717–722 [PubMed: 23228924]

60. Farhad H, Staziaki PV, Addison D, et al. Characterization of the Changes in cardiac structure and function in mice treated with anthracyclines using serial cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging*, 2016 12;9:1–20
61. Neilan TG, Coelho-Filho OR, Shah RV , et al. Myocardial extracellular volume fraction from T1 measurements in healthy volunteers and mice: relationship to aging and cardiac dimensions. *JACC Cardiovasc Imaging*, 2013 6;6:672–683. [PubMed: 23643283]
62. Neilan TG, Coelho-Filho OR, Danik SB, et al. CMR quantification of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. *JACC Cardiovasc imaging*. 2013 9;6:944–954.
63. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* . 2008 11 4;52:1574–1580. [PubMed: 19007595]
64. Neilan TG, Farhad H, Mayrhofer T, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. *JACC Cardiovasc imaging*. 2015 4;8:414–423.
65. Neilan TG, Bakker JP, Sharma B, et al. T1 measurements for detection of expansion of the myocardial extracellular volume in chronic obstructive pulmonary disease. *Can J Cardiol*. 2014 12;30:1668–1675. [PubMed: 25442461]
66. Tham EB , Haykowsky MJ , Chow K, et al. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson*, 2013 6 10;15:48
67. Jordan JH, Vasu S , Morgan TM, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. *Circ Cardiovasc Imaging*, 2016 8;9:1–19
68. Zagrosek A, Abdel-Aty H, Boye P, et al. Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. *JACC Cardiovasc Imaging*. 2009 2;2:131–138 [PubMed: 19356545]
69. Abdel-Aty H, Zagrosek A, Schulz-Menger J, et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. *Circulation*, 2004 5 25;109:2411–2416 [PubMed: 15123531]
70. Bogachkov A, Lin K , Freed BH, Markl M, Carr JC , Collins JD , Myocardial strain analysis with CMR in cardiotoxicity patients using deformation field analysis: comparison to healthy volunteers and heart transplant patients. *J Cardiovasc Magn Reson*, 2016 1 27;18:W30
71. Coelho-Filho OR, Shah R , Neilan TG, et al. Characterization of both myocardial extracellular volume expansion and myocyte hypertrophy by CMR in heart transplantation recipients without active rejection: implications for early cardiac remodeling. *J Cardiovasc Magn Reson*, 2015 2 3;17(Suppl 1) O75
72. Chaosuwanakit N, D'Agostino R, Hamilton CA, et al. Aortic stiffness increases upon receipt of anthracycline chemotherapy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010 1 1;28:166–172
73. Peak AS, Sheller A, Risk factors for developing gadolinium-induced nephrogenic systemic fibrosis. *Ann Pharmacother*, 2007 9;41:1481–1485. [PubMed: 17684032]
74. Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA, Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment—report of 33 cases. *Radiology* , 2009 2;250:371–377 [PubMed: 19188312]
75. Quattrocchi CC, van der Molen AJ. Gadolinium retention in the body and brain: is it time for an International Joint Research Effort? *Radiology*. 2017 1;282:12–16. [PubMed: 28005498]

Table 1

Cardiac imaging modalities available to detect cardiotoxicity, with advantages and limitations.

Modality	Advantages	Limitations
<i>Echocardiography</i>	<ul style="list-style-type: none"> • Noninvasive • No associated adverse events • Analysis of systolic and diastolic function • Analysis for valvular abnormalities • Tissue velocity imaging • Strain imaging (global longitudinal strain) for early detection of subclinical cardiotoxicity 	<ul style="list-style-type: none"> • Inter- and intraobserver variability • Interpretation dependent on image quality, which may be influenced by body habitus • Standard echo parameters have poor cellular correlation
<i>Cardiac magnetic resonance imaging</i>	<ul style="list-style-type: none"> • Accurate heart anatomical description • Absence of radiation exposure • Accurate and reproducible EF assessment • Early cellular detection of subclinical cardiotoxicity (ECV, Tau, cardiomyocyte mass, edema) • Accurate assessment of cardiac ischemia 	<ul style="list-style-type: none"> • Limited availability • High costs • Contraindicated in some patients with metallic devices • Unable to perform in patients with claustrophobia • Potential risk of nephrogenic systemic fibrosis in renal impairment • Potential gadolinium accumulation in brain
<i>Radionuclide Imaging: MUGA/SPECT</i>	<ul style="list-style-type: none"> • High sensitivity and specificity for EF assessment • Low inter- or intraobserver variability 	<ul style="list-style-type: none"> • Radiation exposure • Less information on diastolic function • Limited information on subclinical cardiotoxicity parameters
<i>Positron emission tomography</i>	<ul style="list-style-type: none"> • Myocardial metabolic and perfusion evaluation • Useful in diagnosis of metastatic lesions and monitor response to therapy 	<ul style="list-style-type: none"> • Limited availability • Unclear evidence of any information on subclinical cardiotoxicity parameters
<i>Computed tomography</i>	<ul style="list-style-type: none"> • Useful in evaluating cancer-associated masses, pericardial and coronary artery disease 	<ul style="list-style-type: none"> • Radiation exposure • Limited information on subclinical cardiotoxicity parameters