The role and clinical effectiveness of multimodality imaging in the management of cardiac complications of cancer and cancer therapy

Raymond R. Russell, MD, PhD, FASNC,[a] Jonathan Alexander, MD,[b] Diwakar Jain, MD,[c] Indu G. Poornima, MD,[d] Ajay V. Srivastava, MD,[e] Eugene Storozynsky, MD, PhD,[f] and Ronald G. Schwartz, MD, MS[f,g]

[a] Rhode Island Cardiovascular Institute, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, Providence, RI
[b] Cardiology Division, Western Connecticut Medical Center at Danbury Hospital, Danbury, CT
[c] Section of Cardiovascular Medicine, New York Medical College and Westchester Medical Center, Valhalla, NY
[d] Division of Cardiology, Allegheny Health Network, Pittsburgh, PA
[e] Division of Cardiovascular Medicine, Scripps Clinic, La Jolla, CA
[f] Cardiology Division, Department of Medicine, University of Rochester Medical Center, Rochester, NY
[g] Nuclear Medicine Division, Department of Imaging Sciences, University of Rochester Medical Center, Rochester, NY

Received Apr 13, 2016; accepted Apr 13, 2016
doi:10.1007/s12350-016-0538-8

With the increasing number of individuals living with a current or prior diagnosis of cancer, it is important for the cardiovascular specialist to recognize the various complications of cancer and its therapy on the cardiovascular system. This is true not only for established cancer therapies, such as anthracyclines, that have well established cardiovascular toxicities, but also for the new targeted therapies that can have ''off target'' effects in the heart and vessels. The purpose of this informational statement is to provide cardiologists, cardiac imaging specialists, cardio-oncologists, and oncologists an understanding of how multimodality imaging may be used in the diagnosis and management of the cardiovascular complications of cancer therapy. In addition, this document is meant to provide useful general information concerning the cardiovascular complications of cancer and cancer therapy as well as established recommendations for the monitoring of specific cardiotoxic therapies.

Key Words: Multimodality imaging • cancer therapy • cardiac complications • cardio-oncology

Reprint requests: Raymond Russell, MD, PhD, FASNC, Rhode Island Cardiovascular Institute, Rhode Island Hospital, The Warren Alpert Medical School of Brown University, 593 Eddy Street, APC 737, Providence, RI, 02903; *raymond.russell@lifespan.org*

J Nucl Cardiol
1071-3581/$34.00

Published online: 01 June 2016

Abbreviations	
CHF	Congestive heart failure
ERNA	Equilibrium radionuclide angiocardiography
ESVI	End-systolic volume index
FDG F-18	Fluorodeoxyglucose
GBPS	Gated blood pool SPECT
LVEF	Left ventricular ejection fraction
*m*IBG	Metaiodobenzylguanidine
MUGA	Multi-gated acquisition scan
PET	Positron emission tomography
TKIs	Tyrosine kinase inhibitors

INTRODUCTION

The National Cancer Institute has estimated 14.5 million people were living with a cancer history in the United States in 2014, and it is anticipated this number will increase to 19 million people in the next 10 years.[1] Many factors contribute to the increased survival of patients with cancer, including the earlier detection of cancer at stages when there is a greater chance of successful treatment, improved staging of many malignancies with F-18 fluorodeoxyglucose (FDG) molecular imaging, and the use of immunotherapy and novel, molecularly targeted agents. However, these newer agents, as well as the well-established chemotherapeutic agents, such as anthracyclines, trastuzumab, cyclophosphamide, and 5-fluorouracil, can increase the risk of cardiovascular morbidity and mortality. Heart failure is known to have a prognosis worse than many cancers, and anthracycline-induced cardiomyopathy is associated with a much poorer prognosis than ischemic or idiopathic cardiomyopathy.[2] Importantly, cardiac monitoring techniques employing cardiac biomarkers, endomyocardial biopsy, and radionuclide angiocardiography improve the natural history of anthracycline-induced heart failure substantially. Despite the known association between the use of these agents and the development of cardiotoxicity, a minority of patients with cancer manifesting evidence of cardiotoxicity are referred to a cardiologist or placed on appropriate cardiac therapy.[3] The care of cancer patients is further challenged by a high degree of variability in the monitoring and management of the potential cardiac complications of anti-cancer therapies by physicians,[4] and a lack of implementation of standardized guidelines in general practice that further undermines efforts to prevent and limit heart failure complicating cancer chemotherapy.

Thus, a need exists for oncologists and cardiologists to understand the unique cardiovascular complications associated with cancer radiotherapy and chemotherapy. The field of cardio-oncology has emerged to support patient-centered cardiovascular health of individuals with cancer,[5] many of whom have pre-existing cardiac conditions. A patient-centered approach that balances the needs for cancer therapy with a structured, evidence-based approach for reducing cardiac complications is the goal of cardio-oncology. This multi-disciplinary, patient-centered team approach requires coordination of care by oncologists, cardiologists, and cardiovascular imaging specialists. Many cancer survivors face dual risks of recurrent and secondary malignancies as well as cardiovascular diseases.[6-9] The median age at the time of cancer diagnosis has increased over the past 30 years so that older patients—already at greater risk of having cardiovascular disease—will also undergo potentially cardiotoxic treatment for their cancer.[10] Childhood survivors of cancer have a prolonged cancer-free survival but are at risk for late cardiovascular disease due to their prior cancer treatment.[11]

This informational statement was therefore developed to achieve several goals. First, this statement provides general cardiologists, nuclear cardiologists, cardio-oncologists, heart failure cardiologists, and oncologists an understanding of the cardiovascular complications of cancer and cancer therapy. Second, it reviews published information concerning the proven clinical effectiveness of nuclear cardiology techniques that have been the evidence-based gold standard for reducing the incidence and severity of heart failure associated with radiation and chemotherapy, while improving its treatability over the past three decades. This statement also addresses the ongoing challenges of the field of cardio-oncology to move beyond descriptive diagnostics of newer cardiac monitoring techniques to establish an evidence base of patient-centered effectiveness in their implementation.

CARDIAC COMPLICATIONS OF CANCER THERAPY

Several cancer therapy agents have adverse cardiovascular effects and can result in treatment-related cardiotoxicity. This risk of cardiotoxicity is substantially higher in patients with a prior history of cardiac disease. Serious and potentially life-threatening cardiopulmonary complications of chemotherapy include coronary vasospasm, angina, myocardial infarction, dysrhythmias, hypertension, left ventricular (LV) dysfunction and congestive heart failure (CHF), pericardial effusion, and pulmonary fibrosis.[12,13] Close monitoring of left ventricular ejection fraction (LVEF) and modification or discontinuation of therapy and initiation of appropriate medical interventions for LV dysfunction at the appearance of subclinical LV dysfunction has ameliorated

substantially the natural history of cardiotoxicity of several cancer therapy agents.[14-21]

Although anthracycline agents and trastuzumab are most widely known for cardiotoxicity, an increasing number of cancer therapy agents have the potential for causing cardiotoxicity. With increasing rates of long-term remission and cure, and longer survival of cancer patients, adverse cardiovascular effects and late onset CHF have become significant concerns in the management of cancer survivors.[18] An exhaustive review of the various cancer therapies with associated cardiac toxicities is beyond the scope of this informational statement. Appendix Table 1 summarizes the cardiovascular effects of various cancer therapies, and a more complete discussion of those therapies in which cardiovascular imaging may be beneficial is presented in the informational statement. Readers are referred to a general overview of cardiovascular toxicities in the review by Yeh and Bickford.[22]

ANTHRACYCLINES

Anthracyclines are highly effective, broad-spectrum anti-neoplastic agents, but cardiotoxicity is a major limitation of their administration. Anthracyclines inhibit tumor DNA and RNA synthesis by intercalating between base pairs and inhibiting the activity of topoisomerase IIα, which prevents DNA repair. While cardiac myocytes do not express this isoform of topoisomerase, they do express topoisomerase IIβ, which is believed to play a role in the development of cardiotoxicity.[23] Oxidative injury due to free radical formation and peroxidation of membrane lipids, altered calcium handling by sarcoplasmic reticulum, and impaired protein synthesis are among some of the mechanisms proposed for anthracycline cardiotoxicity.[24] Anthracyclines cause progressive myocyte loss due to apoptosis and necrosis and adverse LV remodeling. Acute cardiotoxicity can occur during or soon after initiation of therapy and is associated with non-specific repolarization changes on the electrocardiogram, dysrhythmias, a myopericarditis-like picture with troponin elevation, and LV dysfunction.[25] These changes are generally transient and generally resolve spontaneously but can be progressive and life-threatening.[26]

Chronic cardiotoxicity is more common than acute cardiotoxicity and presents as LV systolic dysfunction, which is insidious in onset and asymptomatic in the early stages but can progress to cause a dilated cardiomyopathy and overt CHF. Chronic cardiotoxicity is further classified as type 1 or early onset and type 2 or late onset. Type 1 cardiotoxicity occurs within the first year of completion of chemotherapy, while type 2 cardiotoxicity occurs after the first year and can be observed as late as 10 or 20 years after completion of therapy.[17] A recent study in adults treated with anthracyclines suggests that the majority of patients develop cardiotoxicity within the first year after receiving the agent.[27] The total lifetime cumulative dose of anthracycline is the most important determinant of anthracycline cardiotoxicity.[28,29] Because the use of greater anthracycline dose intensity protocols is now possible with protection of marrow reserves by colony stimulating factors and bone marrow transplantation, the risk of cardiotoxicity is increased. There are other clinical factors that have been shown to increase the risk of developing left ventricular dysfunction (Appendix Table 2). In addition to those clinical factors, iron overload due to transfusions, nutrition, and mutations of genes involved in iron handling may also warrant earlier and more frequent evaluations of LVEF based on data of enhanced doxorubicin cardiotoxicity in iron-loaded rodents.[28-30]

Asymptomatic LV dysfunction characteristically precedes symptomatic CHF.[14,16,19,20] Prompt discontinuation of further anthracycline therapy based on technique-specific, baseline LVEF-specific guidelines for serial changes in LVEF can prevent progression of LV dysfunction to overt CHF. This approach is pivotal to the current strategies for the prevention of CHF in patients undergoing anthracycline therapy. Increases in end-systolic volume index may offer additional discrimination value in patients at risk for CHF before the onset of predetermined LVEF criteria of cardiotoxicity. Chronic anthracycline cardiotoxicity can also present as a restrictive cardiomyopathy with diastolic dysfunction and heart failure particularly in patients undergoing mediastinal irradiation. Prior to a widespread use of serial LV function monitoring, the incidence of CHF with doxorubicin was 4% to 7% in patients receiving 400 to 550 $mg \cdot m^{-2}$, 18% in those receiving 551 to 700 $mg \cdot m^{-2}$, and 30% or higher at doses over 701 $mg \cdot m^{-2}$.[12,19] Because the various anthracycline agents have different cardiotoxicities, it is important to convert the cumulative dose of other anthracyclines to the equivalent doxorubicin dose to aid in determining the frequency of monitoring (Appendix Table 3).

There is a large inter-individual variation in susceptibility to doxorubicin cardiotoxicity and CHF, with some patients developing CHF at relatively low doses, whereas others may tolerate relatively higher doses with no apparent change in LV function.[19,20] These variations in susceptibility are likely related, in part, to polymorphisms in genes related to the metabolism of anthracyclines;[31] however, the exact cellular, biochemical, molecular, and genetic mechanisms of cardiotoxicity associated with anthracycline are not fully understood. Use of radiation therapy, high-dose

cyclophosphamide, trastuzumab, and other tyrosine kinase inhibitors (TKIs) and taxanes also potentiate the cardiotoxicity and risk of heart failure of anthracyclines.[30,32]

Histological changes of anthracycline cardiotoxicity can be observed using endomyocardial biopsy. Billingham et al showed a linear progression of histopathological myocardial changes with increasing cumulative dosages of anthracycline therapy.[15] Although endomyocardial biopsy was used initially for monitoring anthracycline cardiotoxicity, its invasive nature limits its use in routine clinical practice. Significant inter-individual variation in the susceptibility to anthracycline cardiotoxicity makes it impractical to choose an arbitrary dose ceiling, which would prevent any CHF, whereas such a dose ceiling would deny the benefit of therapy to those who can safely tolerate higher doses without developing cardiotoxicity. Therefore, an approach of serial radionuclide LVEF monitoring during the course of anthracycline therapy and discontinuing further therapy at the appearance of subclinical LV dysfunction remains the most effective means for preventing overt clinical congestive heart failure. As discussed below, several traditional and novel candidate methods to detect anthracycline-induced cardiotoxicity and prevent HF at an earlier stage are being investigated.

TRASTUZUMAB

Trastuzumab (Herceptin) is another cancer therapeutic agent with a well-defined and predictable risk of cardiotoxicity. This agent is used in patients with HER2/neu overexpressing breast cancers. The cardiotoxicity of trastuzumab is quite different from anthracyclines, in that LV dysfunction is often reversible upon discontinuation of therapy. Furthermore, the cardiac dysfunction caused by trastuzumab is non-dose cumulative and is not associated with cardiomyocyte ultrastructural changes.[33] In addition, there are fewer defined clinical risk factors that can be used to identify those patients at increased risk for developing trastuzumab-associated LV dysfunction (Appendix Table 2). Preclinical studies have demonstrated an important cardioprotective and proangiogenic role for the HER2/neu receptor in the myocardium, which may explain, in part, the cardiotoxic effects of trastuzumab,[34,35] which blocks HER2/neu receptor activation.

Ewer et al reported in 38 patients with HER2/neu-positive breast cancer referred for trastuzumab-induced cardiotoxicity a decline in the mean LVEF from 61% to 43%, which improved to 56% upon discontinuation of trastuzumab. Interestingly, re-introduction of trastuzumab after the recovery of LVEF does not necessarily result in recurrence of LV dysfunction.[33] The effect of trastuzumab on patients with prior cardiac disease remains unclear, and it is recommended that such patients be very closely monitored.[32,36] Algorithms for monitoring of LVEF during adjuvant trastuzumab therapy have been published by Panjrath and Jain,[36] the Canadian Trastuzumab Working Group (Appendix Table 5),[32] and the European Society of Medical Oncologists.[37]

RADIATION THERAPY

Multiple studies have documented a significant increase in the incidence of cardiovascular disease in long-term cancer survivors, including increased need for CABG and coronary interventions.[38,39] Stress-induced myocardial perfusion defects have been reported after radiation treatment of left-sided breast cancer.[40,41] In a prospective study of more than 130 patients treated with radiotherapy at Duke University for breast cancer, 50% demonstrated new myocardial perfusion abnormalities, and the incidence depended on the volume of the heart being irradiated. In addition, Correa et al demonstrated a higher incidence of stress-perfusion defects in patients receiving left-sided versus right-sided radiation for breast cancer.[42] Also, anthracycline use, older age, and prior CAD are all risk factors for radiation-induced cardiovascular toxicity. Similar asymptomatic perfusion defects have been reported in patients with esophageal and lung cancer who underwent radiation treatment, and the majority of defects were noted in the inferior wall.[43] However, the long-term consequence of these asymptomatic perfusion abnormalities is not clear. Murine studies have shown evidence of coronary microvascular damage 20 weeks after chest radiation. This damage, however, did not translate into any functional change in LV systolic function.[44,45] The clinical presentation of coronary artery disease following radiotherapy is typically 10 years after completion of treatment.[46-48] The role of cardiac imaging in the diagnosis and management of radiation therapy-induced cardiotoxicity has been reviewed by an expert panel.[49]

5-FLUOROURACIL

Cardiotoxicity has been reported in up to 2.3% of patients receiving the antimetabolite 5-fluorouracil (5-FU).[50] Coronary vasospasm caused by 5-FU is associated with ischemia, chest pain, ECG repolarization changes, myocardial infarction, and death.[51-53] A prospective study of 100 consecutive patients without a history of cardiac disease or abnormal ECG prior to receiving 5-FU showed that eight patients developed chest pain, ECG changes, and one patient developed cardiogenic shock within 18 to 30 hours of the initiation

of the high-dose 5-FU infusion.[54] It is more likely to occur in those patients with coronary artery disease, prior radiation therapy, or concomitant use of cisplatin, which by itself can predispose to ischemia.[55] These adverse effects were not associated with biomarker release, and the symptoms resolved with discontinuation of the 5-fluorouracil.[54] Capecitabine, which is a prodrug that is metabolized to 5-FU, has similar cardiotoxic effects.[56]

TYROSINE KINASE INHIBITORS

Other agents that can potentially cause effects on myocardial perfusion include the newer TKIs, such as bevacizumab, sunitinib, and sorafenib. These agents inhibit the vascular endothelial growth factor (VEGF) signaling pathway thereby inhibiting angiogenesis.[57,58] The most common cardiovascular complication associated with these drugs is hypertension, which is believed to be mediated by decreased nitric oxide signaling and increased endothelin-1 production and capillary rarefaction.[59] In addition, coronary microvascular dysfunction caused by loss of vascular pericytes has been reported in *in vivo* studies of sunitinib[60]; however, clinical coronary events or myocardial ischemia have not been reported.

In addition to hypertension, TKIs may also cause LV dysfunction. Eleven percent of patients receiving sunitinib had clinical manifestations of CHF or a decrease in their LVEF of at least 20% to an LVEF <50%.[58] While the development of LV dysfunction has not been reported with other TKIs, the potential for cardiotoxicity exists for many in this class of agents because the pathways that are targeted by these compounds are important not only in malignant cells but also in cardiac myocytes and endothelial cells.[61]

Another tyrosine kinase target, particularly for chronic myelogenous leukemia, is BCR-Abl kinase. Several TKIs have been developed against this target, including imatinib, dasatinib, erlotinib, and nilotinib. Each of these agents has specific cardiovascular effects, including pulmonary hypertension and thromboembolism. A unique aspect of this group of TKIs is the fact that unlike most other chemotherapies, these agents are given chronically to suppress chronic myelogenous leukemia rather than given for a finite period of time.

TAXANES

Taxanes, used to treat breast, lung, and ovarian cancer, can produce ischemia, arrhythmias and CHF. Up to 5% of patients receiving docetaxel have been reported to experience myocardial ischemia.[62] Taxanes can impair normal microtubular transport systems in cardiomyocytes, which has been shown to impair the storage of free fatty acids (FFA) in the cytosolic lipid pool and reducing mitochondrial FFA uptake for beta oxidation.[63]

INTERLEUKIN-2 THERAPY

High-dose interleukin-2 therapy is an effective treatment for renal cell carcinoma and malignant melanoma; however, its use can be limited because of the morbidity associated with the capillary leak syndrome caused by the agent.[64] The hemodynamic manifestations associated with the use of this agent include hypotension and tachycardia (both supraventricular and ventricular), resulting in myocardial ischemia because of supply/demand mismatch. Early studies of this agent demonstrated an incidence of myocardial infarction of 2% to 4%,[65] although subsequent studies have indicated much lower rates of myocardial infarction. It is important to note that this decrease in the incidence of myocardial infarction is due, in part, to screening of candidates for myocardial ischemia with stress testing.[66]

IMMUNE THERAPY

An important role of the cardio-oncologist is to provide cardiac risk assessment prior to the initiation of therapy and is highlighted by case reports for the novel monoclonal antibody, ipilimumab, which is used to treat metastatic melanoma. The antibody is directed against the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) receptor, which allows proliferation of effector T-lymphocytes thereby promoting immune-mediated tumor destruction. Unfortunately, this immune modulatory action also causes a variety of immune-mediated diseases, including thyroiditis.[67] In the setting of the thyroid storm that may occur, patients can develop atrial fibrillation with rapid ventricular rates.[68] It is therefore important to consider the potential for the development of demand ischemia from rapid atrial fibrillation and the need for further cardiovascular risk assessment.

Current Use of Cardiac Radionuclide Imaging Before, During, and After Cancer Therapy

ASSESSMENT OF LV FUNCTION

Cardiologists and oncologists are challenged to optimize the cardiovascular safety of chemotherapy and radiation therapy while maintaining a high degree of efficacy. The quest for therapeutic cancer cure is challenged by the risk of cardiotoxicity and clinical

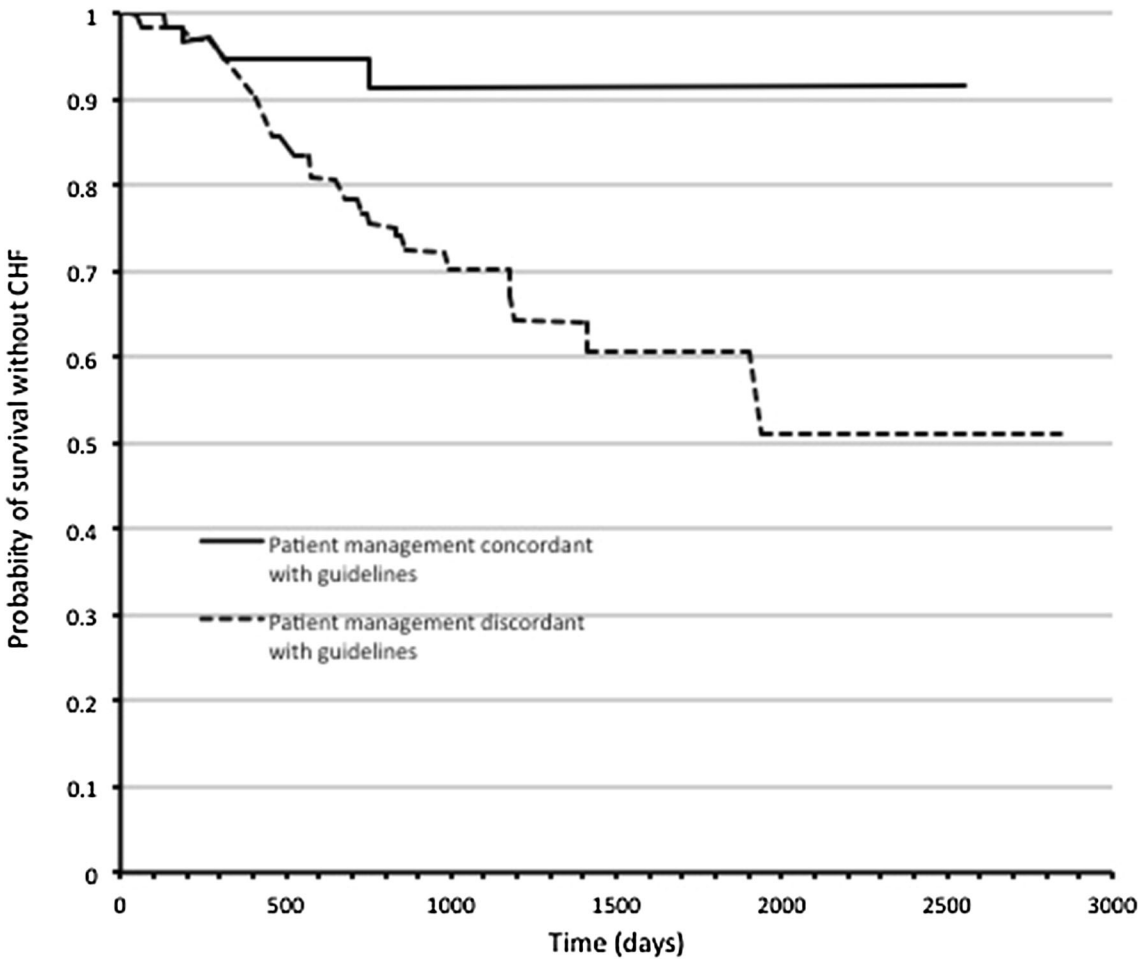

Figure 1. Effect of adherence to anthracycline treatment recommendations based on changes in LVEF. Utilizing recommendations published by Schwartz et al,[20] there was a significant decrease in the development of clinical congestive heart failure in patients treated with anthracyclines.

heart failure. Based on the use of quantitative radionuclide LVEF obtained prior to or before 100 $mg \cdot m^{-2}$ doxorubicin, strategies for management of anthracycline therapy that differ for normal and abnormal baseline LVEF were created and evaluated for effectiveness. High-risk patients managed concordant with guidelines experienced a 2.86% incidence of subsequent clinical congestive HF, whereas patients who were managed with serial quantitative ERNA who were not managed concordant with guidelines experienced a 20.8% incidence of HF (Figure 1).[13,20]

EQUILIBRIUM RADIONUCLIDE ANGIOCARDIOGRAPHY

Alexander and colleagues pioneered the concept of predicting doxorubicin-induced CHF by monitoring change in resting LVEF using equilibrium radionuclide angiocardiography (ERNA).[13,14,16,19,20] Patients who progressed to overt CHF had a decline in LVEF below the lower limit of normal, prior to the onset of CHF.[14,16,19] From a compiled registry of 1487 patients undergoing anthracycline therapy over seven years, approximately 20% of the patients were deemed to be at high risk for the development of CHF[20] based upon either high total cumulative dose of doxorubicin (>450 $mg \cdot m^{-2}$), decline in LVEF by at least 10 EF units to ≤LVEF 50%, or an abnormal baseline LVEF (<50%). Fifteen percent of these high-risk patients did develop CHF within one year of completion of treatment. The total cumulative doxorubicin doses that precipitated CHF (75 to 1095 $mg \cdot m^{-2}$) and the doses that did not cause CHF (30 to 880 $mg \cdot m^{-2}$) varied widely. CHF was noted mostly in patients with normal baseline LVEF that declined by at least 10% to a value of ≤50%, which was the largest subgroup studied.

Recommendations for monitoring patients receiving doxorubicin therapy and avoiding CHF were developed

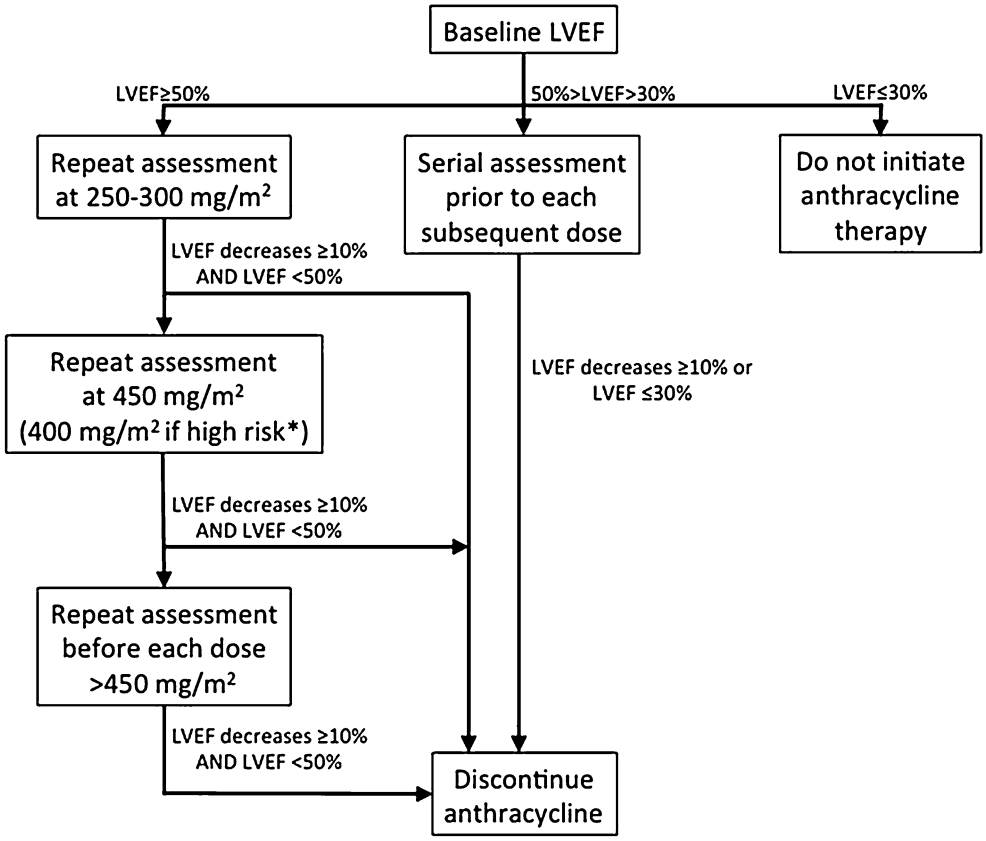

Figure 2. Original recommendations for altering anthracycline treatment based on serial assessment of LVEF with equilibrium radionuclide angiography.[20] *Risk factors included known heart disease, radiation exposure, treatment with cyclophosphamide, and electrocardiographic abnormalities.

based on the analysis of these data[20] in the context of a robust literature demonstrating accuracy, reproducibility of the methodology, and higher inter-study variability of LVEF in patients with normal compared to those with abnormal baseline LVEF.[69] These guidelines employing a strategy of precise radionuclide monitoring and recommendations for discontinuing chemotherapy based on initial pre-treatment LVEF are summarized in Figure 2 and continue to guide anthracycline therapy in the current era. The guidelines recommend a baseline ERNA measurement of LVEF prior to or before 100 mg·m^{-2} doxorubicin or equivalent anthracycline. For patients with a normal baseline LVEF, the next two measurements are performed at cumulative doses of 250-300 and 400-450 mg·m^{-2}. Discontinuation of doxorubicin with normal pre-chemotherapy baseline LVEF is recommended if LVEF decreases ≥10% (absolute EF units) from baseline and reaches an LVEF ≤50%. For patients with abnormal baseline LVEF <50%, serial studies are recommended after each dose of doxorubicin. Discontinuation of doxorubicin in patients with abnormal pre-chemotherapy baseline LVEF is recommended if LVEF decreases ≥10% (absolute EF units) from baseline or reaches LVEF ≤30%.[13,20]

Management concordant with these guidelines resulted in a greater than seven-fold reduction in the incidence of overt CHF[20] (Figure 1). Serial monitoring of LVEF is associated with a low incidence and relatively benign course of CHF. Similar results were observed by Mitani et al.[19] Thus, serial ERNA performed by specific guidelines during doxorubicin therapy and using established, standardized protocols for ERNA acquisition recommended by the American Society of Nuclear Cardiology[70] reliably monitors cardiotoxicity and identifies patients who safely tolerate high cumulative doses of doxorubicin. ERNA has the advantage of lower inter-observer variability (<5%),[71] high accuracy, and reproducibility than other modalities.[72-75] This strategy of LVEF monitoring and recommended treatment endpoints reflects fundamental understanding of the differences in day to day reproducibility of patients with normal vs. abnormal baseline LVEF, as delineated by Wackers et al who first demonstrated higher intrinsic day to day variability of

LVEF in the normal range of EF, analogous to the greater heart rate variability seen in healthy patients compared to patients with reduced EF who have a less variable EF and heart rate, probably reflecting a higher level of activation of the sympathetic nervous system.[69] Specifically, the mean variability of absolute ejection fraction for repeat studies in normal patients was significantly greater than in abnormal patients (5.4 ± 4.4 vs $2.1 \pm 2.0\%$, $P < .01$). This differential variability should be considered in interpreting sequential changes in LVEF.

Only very limited data are available for the use of exercise ERNA in patients undergoing anthracycline therapy.[76] From a logistical standpoint, a substantial proportion of patients undergoing cancer therapy are not able to perform adequate exercise due to anemia, deconditioning, and uncontrolled variations in exercise tolerance. For these reasons, the use of exercise ERNA remains limited for evaluation of cancer patients.

Most of the studies for radionuclide monitoring cardiotoxicity of cancer chemotherapy have been carried out using planar ERNA. However, ECG-gated SPECT ERNA offers advantages over the conventional planar ERNA in monitoring cardiotoxicity and risk of CHF during the course of cancer therapy.[50] The accuracy of gated blood pool SPECT (GBPS) for the calculation of LVEF has been well validated,[50,77-80] although standardized methods of measurement must be utilized to maintain minimal variability and high precision.[81] SPECT ERNA allows wall motion and phase analyses in addition to right and left ventricular EF, and left and right ventricular end-systolic and end-diastolic volumes to be obtained.[50] LVEF by SPECT ERNA appears to be approximately 5% higher than planar ERNA due to the ability to exclude the atrial blood pool.[13,77] These additional parameters, particularly end-systolic volume index (ESVI) may provide additional parameters to quantify the risk of CHF in patients receiving cancer chemotherapy.[13] SPECT ERNA using high-sensitivity cadmium zinc telluride (CZT) cameras offers low-dose (10 mCi, 2.5 mSv), rapid imaging (10 min) with similar accuracy and improved reproducibility (Figure 3).[82]

ERNA quantification of the diastolic filling parameters, peak filling rate (PFR) and time to peak filling rate (TPFR), have been considered in patients receiving anthracyclines, but not investigated thoroughly as measures to enhance prediction of heart failure.[83,84] The incremental value, however, of these additional parameters over and above conventional LVEF monitoring in predicting and preventing CHF in cancer populations remains unknown and requires prospective evaluation.[85]

Proven Clinical Effectiveness of Radionuclide Angiocardiography vs Radiation Risk

The theoretical cancer risk of diagnostic radiation has frequently been cited as a reason to use alternative methods to assess LV performance. In the best interest of patient care, this rationale should be evaluated critically given the value of proven clinical effectiveness of ERNA to avoid clinical CHF and the absence of data of low-dose (<100 mSv) to very low-dose (<10 mSv) exposure on human health. No credible report of cancer resulting from low-dose radiation exposure of nuclear cardiology studies exists. Radiation exposure of an ERNA study with high-efficiency CZT SPECT technology (10 mCi) is equivalent to natural background radiation of 3 to 6 months, and traditional planar ERNA studies (20 mCi) provide an exposure of an estimated 6 to 12 months of natural background radiation. The incidence of naturally occurring cancers far exceed theoretical radiation-induced cancer rates, which are lower than background radiation risks associated with frequent hypothetical exposure to annual diagnostic radionuclide procedures (Figure 4).[86] Thus, proven clinical benefits of appropriate testing far outweigh the theoretical risk of cancer of clinically employed low-dose radiation, or potential alterations in DNA reported for cardiac studies.[87] Because SPECT MPI has recently been reported to result in a variable activation of the DNA damage response pathways, continued care should be taken to reduce radiation exposure to both the patients and operators.[88]

ECHOCARDIOGRAPHY

Echocardiography is often used to monitor LVEF and regional function in clinical cardiology. Advantages of echocardiography include its wide availability, lack of radiation exposure, and lower imaging cost. Disadvantages include increased variability of quantitative LVEF measurements, common use of visual estimations of EF and regional function, and acoustic artifact limiting window size. The variability of measured LVEF with two-dimensional echocardiography is between 5% to 10%,[72,89] which can cause failure to detect serial alterations of LVEF less than the 10% threshold required for prediction of HF using the published ERNA guidelines.[20] Echocardiography is perhaps more suited for use in pediatric patient population,[17] where smaller patient size permits effective use of higher frequency transducers, with better image quality and less acoustic artifact than in adults. The use of contrast echocardiography represents an important opportunity for further investigation,[90] although its

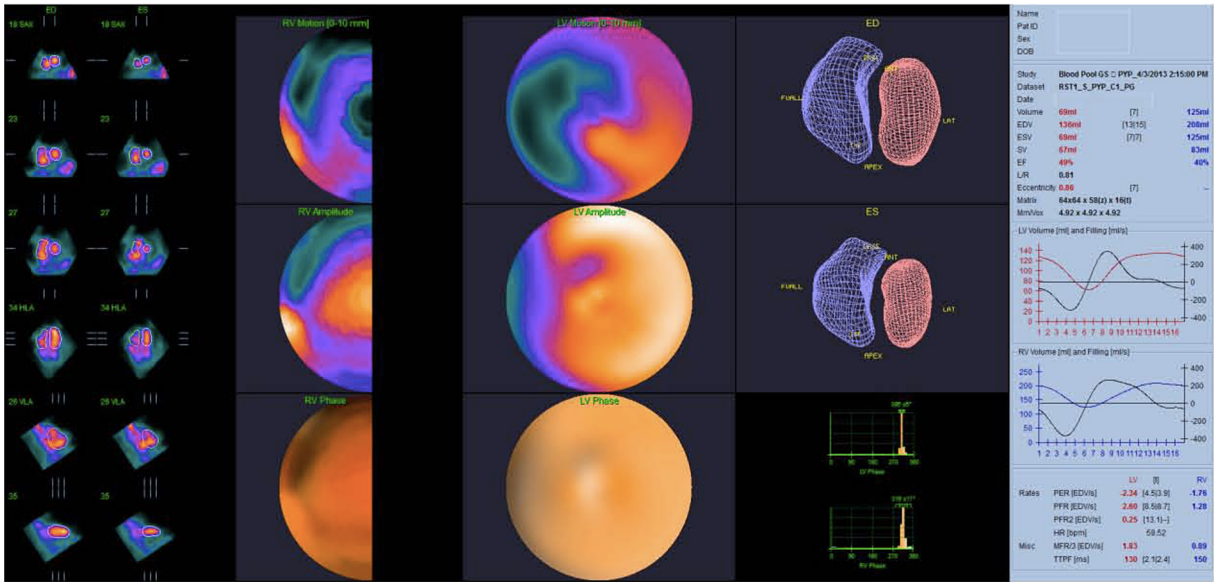

Figure 3. Representative example of high-efficiency CZT (Cadmium Zinc Telluride) ECG-gated SPECT equilibrium radionuclide angiocardiography (ERNA) from a 37-year-old woman with estrogen receptor/progesterone receptor/HER2/neu-positive pT1cN0MX infiltrating ductal carcinoma of the right breast status post-bilateral mastectomy undergoing treatment with trastuzumab and tamoxifen. Limited echocardiographic imaging due to acoustic artifact suggesting a decline in LVEF by serial echocardiography led to referral for ERNA. The study demonstrates normal LV volume indices and slightly reduced calculated EF (49%). The right ventricular size is normal and the calculated RVEF (40%) is slightly reduced with mild diffuse dysfunction. The LVEF returned to normal (65%) following completion of a full course of trastuzumab.

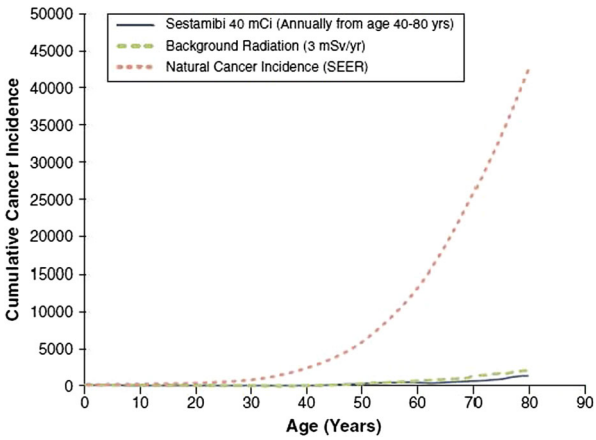

Figure 4. Estimated cumulative cancer incidence (expressed as cases per 100,000 women) based on background exposure, an annual exposure to 40 mCi of Tc-99 m sestamibi and the natural cancer incidence based on Surveillance, Epidemiology, and End Results (SEER) excess absolute risk model[84].

use was reported to not improve accuracy or reproducibility of LVEF measurements by six different echocardiographic techniques reported by the Cleveland Clinic investigators.[72] Of the six echocardiographic methods of LVEF measurement studied, the Cleveland Clinic investigators found only 3D echocardiography had sufficiently reproducible measurements (± 4.9%) to permit detection on serial studies of a change of LVEF of 10%.

It has been reported that echocardiographic evidence of LV diastolic dysfunction precedes resting systolic dysfunction.[75,91-93] These parameters include prolonged isovolumic relaxation period, reduction in peak flow velocity, and the ratio of early peak flow velocity/atrial peak flow velocity, as well as reduction in the deceleration rate of the early peak flow velocity. Stoddard et al reported prolongation of isovolumic relaxation time (IVRT) by Doppler echocardiography to predict doxorubicin-induced systolic dysfunction in a study of 26 patients.[93] Doxorubicin-induced decline of EF by greater than 10% to ≤55% was noted in 9 of 26 patients. IVRT was prolonged from 66 ± 18 to 84 ± 24 ms after a cumulative doxorubicin dose of 100 to 120 mg·m^{-2}. A greater than 37% increase in IVRT was 78% sensitive and 88% specific for predicting the ultimate development of doxorubicin-induced systolic dysfunction.[93] In a study of 20 patients receiving a mean cumulative dose of doxorubicin of 211 ± 82 mg·m^{-2}, pulsed tissue Doppler imaging was reported to show mitral annulus IVRT <80 ms in four patients who had LVEF <50% appeared to outperform both standard Doppler IVRT and basal segment

measurements, and a finding the authors reported could be of interest to predict later impairment of LV function.[75] However, it is generally believed that echocardiographic diastolic measures are more complex than systolic measures to obtain and interpret. Furthermore, reproducibility of echocardiographic measures of diastolic function has been problematic, and multiple diastolic measurements have had varying levels of success in identifying early cardiac toxicity.[91,94] The value of echocardiographic LVEF measurements for prediction of CHF in cancer patients receiving radiation, and chemotherapy may benefit from the development of echocardiography specific LVEF guidelines within the context of accuracy and reproducibility of the technique in both normal and abnormal LVEF ranges, as well as assessment of endpoints of therapy based on echocardiographic LVEF.[89] Recently, an Expert Consensus Statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging stated that the method of choice for quantification of LV volumes and calculation of LVEF is the modified biplane Simpson's technique (method of disks) by two-dimension echocardiography.[95]

MYOCARDIAL STRAIN IMAGING FOR DETECTION OF CARDIOTOXICITY

Thavendiranathan et al have reviewed the use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy.[96] The review reports on a meta-analysis of echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy in 3 studies. All studies of early myocardial changes with chemotherapy demonstrate alterations of myocardial deformation precede significant changes in echocardiographic LVEF. Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure of early change. A 10% to 15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in echocardiographic LVEF or heart failure.[97] In subsequent studies, a decrease in GLS to <19% was associated with later development of LV systolic dysfunction.[98] In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal echocardiographic LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. The specificity of longitudinal strain assessment in patients receiving chemotherapy may be reduced by obesity, valvular heart disease, infiltrative disease, LV hypertrophy, myocardial infarction, age, and gender. Whether strain-based approaches could be reliably implemented in multiple centers in a standardized fashion to obtain consistent values and to help predict cardiotoxicity and outcomes requires study. Furthermore, the use of vendor-neutral methods to measure strain and their ability to predict cardiotoxicity also need to be explored for this technique to be more widely and consistently applied. Finally, the prognostic significance of strain abnormalities in survivors of cancer and for those receiving radiation therapy has to be understood along with whether intervention would change the natural course of the cardiac disease.[72]

BIOMARKERS

High-sensitivity troponin elevation following anthracycline chemotherapy is predictive of larger and more sustained declines in LVEF compared to those without troponin elevation.[99] Other studies have not shown consistent correlation between troponin elevation and administration of anthracycline or trastuzumab.[100,101] While the emergence of ultrasensitive assays of picomolar concentrations of troponin may add important diagnostic and potential incremental prognostic value to the assessment of cancer treatment-induced cardiotoxicity and risk of CHF, the high-sensitivity cardiac troponin assays are only beginning to be used in the United States. An increase in pro-BNP (brain-type natriuretic peptide) has been reported early after anthracycline administration; however, elevated pro-BNP does not appear to be predictive of future LV dysfunction. The role of biomarkers is being currently evaluated in the multicenter NIH funded PREDICT study (ClinicalTrials.gov identifier NCT01032278). Measurements of biomarkers, alone or in combination with echocardiographic strain and strain rate imaging analyses, have been reported to identify pre-symptomatic anthracycline cardiotoxicity in a small series of patients.[98,102] The investigators suggested Doppler-based myocardial strain imaging should be used for cardiac function monitoring during chemotherapy, although this pilot study did not address issues of CHF prediction directly.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance (CMR) imaging is recognized by the ACC/AHA as a method to screen for chemotherapy-related cardiotoxicity.[103] Key advantages

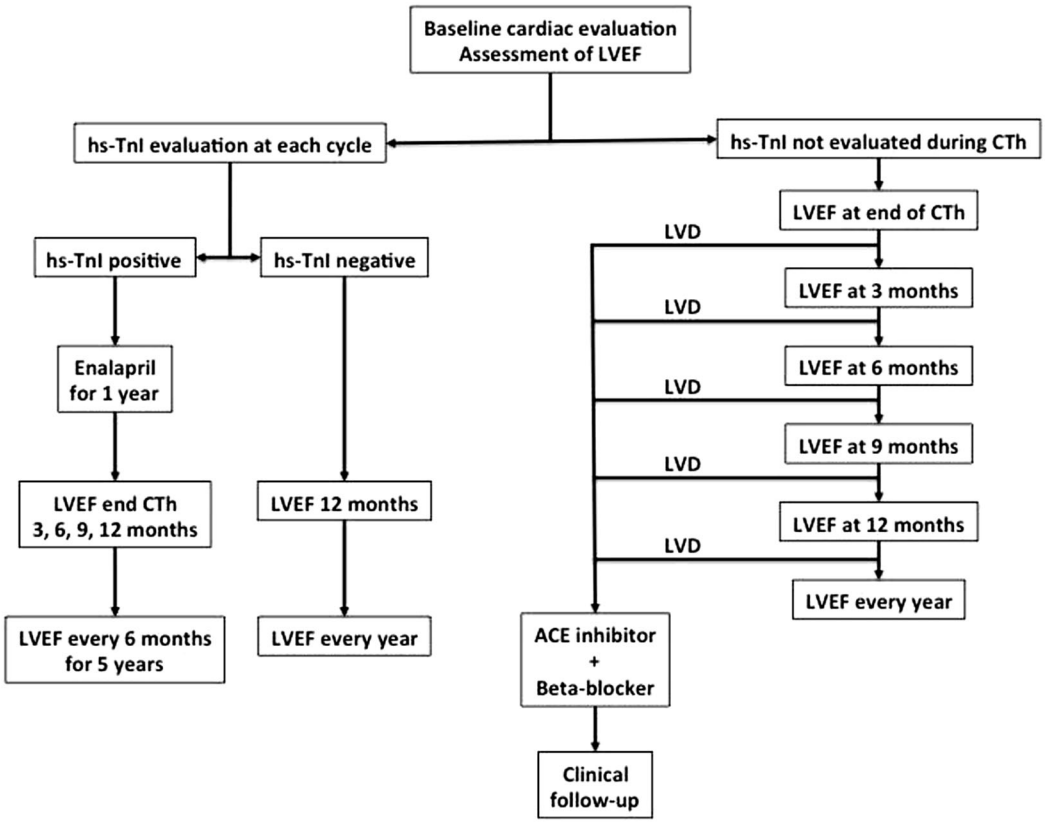

Figure 5. Recommendations from the European Society of Medical Oncologists for altering anthracycline chemotherapy (CTH) based on serial assessment of LVEF using either echocardiography or equilibrium radionuclide angiography in conjunction with assessment of high-sensitivity troponin I (hs-TnI) (37). LVD: left ventricular dysfunction defined by the National Cancer Institute as (1) a decrease in LVEF that was either global or more severe in the septum; (2) symptoms of congestive heart failure; (3) associated signs of CHF, including an S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% (by echocardiography) with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% (by echocardiography) without accompanying signs or symptoms.

include accuracy and reproducibility of LV and RV volumes and EF, the ability to visualize preclinical myocardial changes prior to the onset of LV dysfunction, increased T2-weighted images associated with tissue edema resulting from acute myocardial inflammation, and injury as seen in myocarditis.[104] A characteristic pattern of mid myocardial hyper-enhancement has been reported in breast cancer patients receiving trastuzumab who experienced LV dysfunction.[105] An experimental rodent study of early detection of doxorubicin cardiotoxicity correlated signal intensity of gadolinium-enhancement with the dose-related degree of myocardial vacuolization and decline in LVEF.[106] A new superparamagnetic iron oxide probe conjugated to recombinant human annexin has demonstrated diffuse myocardial signal loss in rats treated with doxorubicin, suggestive of apoptosis by CMR. CMR detection of anthracycline cardiotoxicity appears to hold promise for further clinical investigation. Effects of the intense magnetic fields with clinical CMR on DNA structure in human blood cells have been reported very recently, and assessment of the safety of CMR, particularly serial studies within 30 days, have been questioned.[87]

CONSIDERATIONS IN CHILDREN

Children appear to be more susceptible than adults to the cardiotoxic effects of anthracycline therapy, although there is considerable variation in the individual susceptibility to these side effects.[13,15,17,18,21,102,104] Children with Hodgkin's disease have been reported to

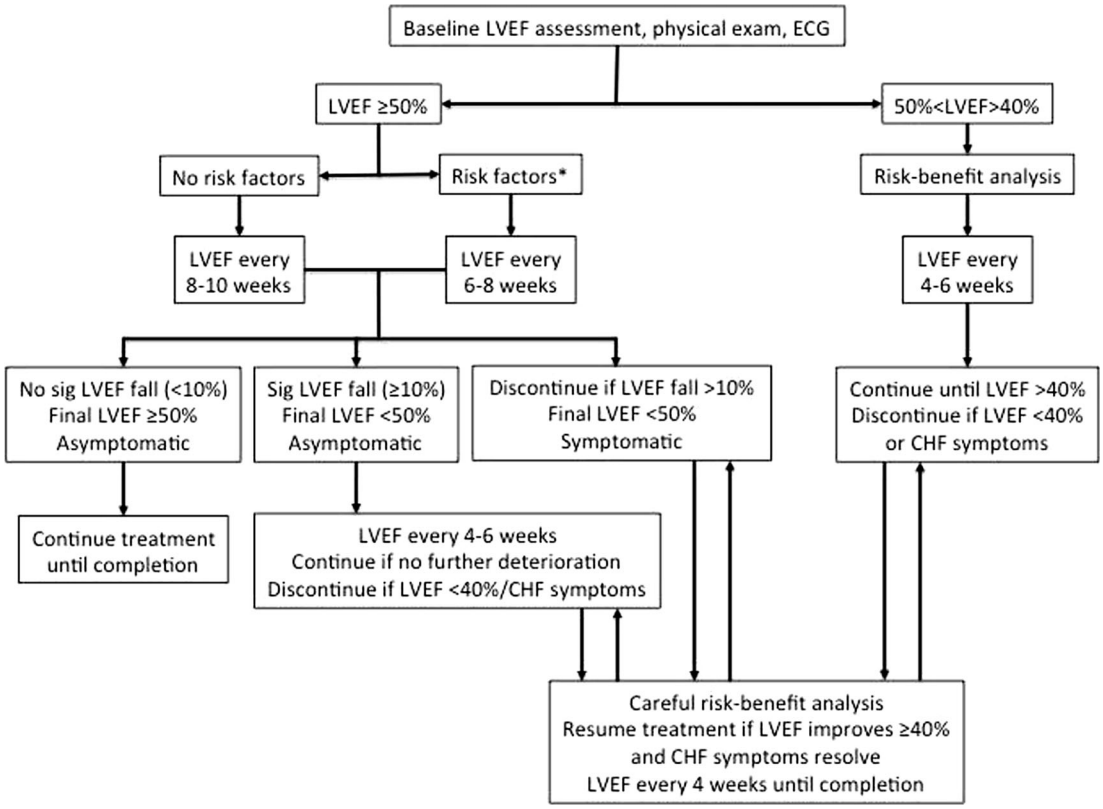

Figure 6. Recommendations from Panjrath and Jain for the management of trastuzumab therapy based on serial assessment of LVEF.[36] *Risk factors include age ≥65 years, hypertension, and history of heart disease.

manifest cardiotoxicity early after treatment and at low cumulative doses of doxorubicin. The potentially long latency and high cumulative incidence of chronic cardiac dysfunction associated with cancer treatment indicates the need for long-term monitoring of asymptomatic children. Because of this concern for the late cardiac manifestations of anthracycline-based chemotherapy, specific recommendations for serial assessment of LV function have been published by the Children's Oncology Group that take into account the age at which the patient received chemotherapy, with or without radiation therapy, and the cumulative dose of anthracycline (Appendix Table 4). ERNA was reported to be more sensitive than echocardiography in detecting early impairment of LV function and was recommended for baseline and serial assessment of LV function in children with Hodgkin's disease treated with doxorubicin.[107] This recent report supports the observation of the complementary nature of ERNA and echocardiography and the recommendations of the Children's Cancer Study Group for monitoring with both techniques.[21]

Current Protocols for the Assessment of LVEF

As noted above, several protocols have been proposed for monitoring patients receiving cardiotoxic agents, starting with the guidelines published by Schwartz et al in 1987.[13,20] These protocols, summarized in Appendix Table 5 and Figures 2, 5, 6, and 7, have been developed by different groups for specific therapies utilizing anthracyclines and/or trastuzumab. While there are differences in the frequency of assessment of LVEF between the various protocols, they share the key feature that the frequency of serial assessments is based on the baseline LVEF and whether there is a decrease in LVEF following therapy. It is important to note that the protocol developed by Schwartz et al is based on outcome data utilizing radionuclide angiography measurements of LVEF.[13,20] Only one protocol, proposed by the European Society of Medical Oncologists, incorporates the use of biomarkers in the monitoring of chemotherapy-induced cardiotoxicity.[37]

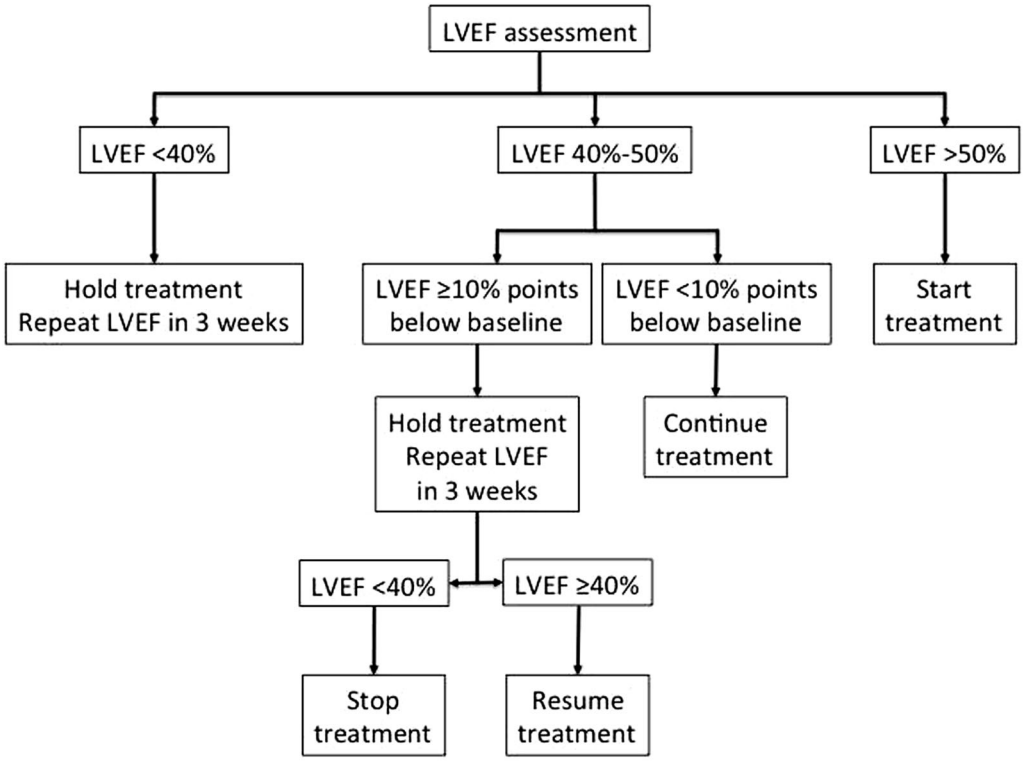

Figure 7. Recommendations from the European Society of Medical Oncologists for altering trastuzumab therapy based on serial assessment of LVEF[37].

RECOMMENDATIONS FOR CLINICAL AND COST EFFECTIVENESS OF MULTIMODALITY LVEF MONITORING IN TREATED CANCER PATIENTS (SEE APPENDIX TABLE 6)

As discussed above, utilizing a multimodality strategy of monitoring LVEF using methods that are highly reproducible (planar ERNA, gated SPECT ERNA, cardiac MR, or noncontrast 3D echo), to guide therapy results in a significant improvement in outcome with a lower development of clinical heart failure. This strategy requires initial assessment of LVEF prior to a patient receiving anthracycline chemotherapy in order to establish accurate information to direct a rational patient-centered monitoring follow-up strategy. Without this baseline LVEF assessment, it is impossible to differentiate whether a subsequent abnormal LVEF is due to cancer therapy versus pre-existing LV dysfunction. For patients with normal baseline LVEF, follow-up planar ERNA, SPECT ERNA, CMR, or echocardiography at 250 to 300 $mg \cdot m^{-2}$ are recommended. Repeat study at 400 $mg \cdot m^{-2}$ doxorubicin total cumulative dose is advised. Repeat measurement of LVEF prior to addition of radiation, cyclophosphamide, or trastuzumab should be performed. Any perceived decline of LVEF by ≥10 EF units should warrant consideration of the risk benefit of additional anthracycline therapy. Any technically limited study should be confirmed by a complimentary high-accuracy LVEF assessment.

Treatment strategies rely on appropriate and aggressive heart failure therapy with ACE inhibitor and beta-blocker therapy utilizing carvedilol, which can help stabilize, or even improve, LV systolic function.[108] The importance of early detection of anthracycline cardiotoxicity is essential as it has been shown that postponing the initiation of CHF therapy more than 6 months decreases the response rate to CHF therapy from 64% to 0%.[109] Given the high cost associated with the treatment of heart failure, estimated to be more than $20,000 per patient per year in direct costs,[110] monitoring and treatment strategies based on serial noninvasive measurements of LVEF can be cost effective in preventing heart failure and instituting heart failure therapy early when there are greater chances for improving function.

In summary, serial monitoring of LVEF by accurate and precise radionuclide imaging employing specific end points for recommendation to consider stopping therapy remains the most reliable technique

for the prevention of CHF related to anthracycline therapy. Treatment and monitoring strategies are needed to minimize or eliminate the late onset LV dysfunction and CHF. Gated SPECT ERNA appears very promising for its high degree of accuracy and reproducibility, quantitative tracking of RV, and LVEF and LV volume indices. Newer high-speed solid-state digital gamma cameras whose use in clinical practice continues to grow provide an opportunity to perform SPECT ERNA studies using lower dose of radiotracer, which is particularly appealing in pediatric patient population. Echocardiography is widely available and used but can be limited by inadequate acoustic windows and geometric assumptions and variance of LVEF of >5% in the calculation of LVEF. Therefore, use of noncontrast 3D echocardiography for measurement of the LVEF has sufficient accuracy to warrant a role in assisting the monitoring of patients with normal or abnormal baseline LVEF follow-up studies receiving anthracycline-based chemotherapy (Appendix Table 6). CMR may offer an alternative to the assessment of cardiac dysfunction associated with chemotherapy; however, this may be offset by its limited availability, high costs, limited patient tolerance, and acceptance.

EVALUATION OF MYOCARDIAL PERFUSION IMAGING IN PATIENTS UNDERGOING CHEMOTHERAPY OR RADIATION TREATMENT FOR CANCER

Several chemotherapeutic agents are associated with impairment of myocardial perfusion in preclinical and human studies. In addition, many patients with cancer have traditional cardiac risk factors or known coronary artery disease that may put them at greater risk for cardiac complications of their cancer therapy. Use of stress MPI should be supported by appropriate use criteria based on underlying cardiovascular risk and symptoms, although special consideration of myocardial perfusion imaging may be beneficial in identifying provocable ischemia and subsequent ischemic risk in those patients who are being considered for chemotherapy that may induce significant hemodynamic stress (interleukin-2 therapy), may cause vasospasm (5-FU or capecitabine), or may have antiangiogenic properties (trastuzumab, sunitinib, or bevacizumab). Unfortunately, the data regarding use of myocardial perfusion imaging (MPI) using SPECT or positron emission tomography (PET) in the evaluation of patients prior to or after treatment for cancer are scant. Although positive exercise stress tests have documented effort-induced ischemia during 5-FU infusion, there are currently no studies using exercise stress testing or MPI prospectively, to screen patients prior to administration of 5-FU.[111] Based on case reports, however, the 5-FU-induced cardiac symptoms are typically not associated with perfusion abnormalities consistent with the pathophysiology of coronary vasospasm.[112]

The majority of studies using MPI in patients being treated for malignancies pertain to evaluation after radiation treatment for thoracic or breast cancers. Although no guidelines currently exist to mandate screening for heart disease after radiation treatment, the National Cancer Collaborative Network recommends screening with a stress test between five to ten years after completion of treatment.[113] There is a firmer recommendation by the Children's Oncology Group to monitor LVEF five years after completion of treatment and to consider further ischemic evaluation if there is deterioration of LV function.[114] With the increasing availability of cardiac PET imaging, measurement of coronary flow reserve may be useful in early detection of radiation-induced coronary damage, although there are no reported data in this area. It is also important to note that significant improvements in delivery of radiation to the chest, such as image-guided therapy, three-dimensional treatment planning, reduced dose, respiratory gating, and fraction size, have also potentially reduced the cardiac risk.[115,116]

As discussed earlier in this informational statement, small molecular weight TKIs, such as bevacizumab and sunitinib, which inhibit angiogenesis can have cardiovascular side effects. Such side effects could alter coronary flow reserve, or potentially the resting blood flow to the myocardium.[60,61] Therefore, future evaluation of patients receiving antiangiogenic therapies may benefit from quantitative analysis of myocardial blood flow and coronary flow reserve to determine if there is a component of microvascular dropout responsible for LV dysfunction.[117]

In summary, abnormalities in myocardial perfusion can occur after chemotherapy and/or radiotherapy. Presently, there are few studies to support screening for CAD in this group of patients. However, recognizing chemo-radiotherapy as a risk factor for CAD is key while performing MPI in this patient population. Prospective studies to discern the role of MPI especially with coronary flow reserve assessment are warranted for early identification of myocardial vascular effects of chemotherapy and radiation treatment.

CARDIAC COMPLICATIONS OF MALIGNANCIES

Malignancies can affect the heart in a variety of ways, either through infiltration of the heart by primary tumors or secondary metastatic infiltration of the myocardium and other cardiac structures. More commonly, the cardiac manifestation of a malignancy is the development of a pericardial effusion. Below is a summary of cardiac malignancies and their associated complications that may be evaluated using nuclear cardiology techniques.

CARDIAC NEOPLASMS

Primary cardiac neoplasms are rare and are often difficult to diagnose, with an overall cumulative prevalence of up to 0.3%.[118,119] Despite such a low prevalence, cardiac neoplasms have generated significant interest due to the varied clinical presentations. Advances over the last decade in echocardiography, computed tomography (CT), CMR, and PET[120] have greatly facilitated earlier diagnosis and therapy.[121] Cardiac neoplasms can be classified into primary and secondary neoplasms. Primary cardiac neoplasms can be further divided into benign and malignant neoplasms. Greater than 75% of diagnosed primary cardiac neoplasms are benign, of which myxomas are the most common. Of the primary malignant cardiac neoplasms, angiosarcomas are the most common.[122] Secondary cardiac neoplasms are overall much more prevalent (approximately 30 to 40 times more common) and are usually a result of metastatic disease or direct invasion from chest tumors. The clinical presentation of cardiac neoplasms is often dictated by their anatomic location and therefore can have varied symptoms based on systemic, cardiac, embolic, or local mass-effect factors.

Primary Benign Cardiac Neoplasms

Myxoma is the most common type of primary neoplasm and accounts for almost 50% of all primary cardiac neoplasms.[118,119] Myxomas are usually diagnosed in young to middle-aged adults, with a greater female preponderance. A meta-analysis showed that 83% of cardiac myxomas arise in the left atrium, 12.7% occur in the right atrium, and 1.3% of cardiac myxomas are bilateral. In some cases, there can be ventricular involvement. Recurrence can occur despite resection and, therefore, patients should be monitored after surgical resection. The detection of myxomas in extracardiac locations should strongly raise the suspicion of a distinct familial disease, known as ''Carney complex.'' The presence of multiple intracardiac tumors should also raise the possibility of Carney syndrome.

Lipoma is the second most common primary cardiac neoplasm and is usually found incidentally on imaging of the chest or heart. They are usually seen as masses protruding into any of the cardiac chambers. Lipomas usually occur as single, well-encapsulated masses, though multiple lesions can occur. Most cardiac lipomas are asymptomatic but can produce a variety of symptoms depending on the size and location. Large lipomas may cause compression of the heart and result in pericardial effusion.

Papillary fibroelastoma is a benign tumor affecting the cardiac valves and is distinct from Lambl excrescence and accounts for the majority of cardiac valvular neoplasms. Most patients are asymptomatic, although varying presenting symptoms have been reported and include transient ischemic attacks, stroke, endocarditis, cerebral embolism, and myocardial infarction. The aortic valve is the most common site of origin, although it can originate on any valve.

Rhabdomyomas are the most common cardiac neoplasms during infancy and childhood. A majority of the cases of cardiac rhabdomyomas occur in patients younger than one year of age. These neoplasms typically occur in the ventricles, although up to a third of cases can involve either atrium. Most cardiac rhabdomyomas spontaneously regress by age 5, and conservative clinical management is the mainstay in the majority of cases. Cardiac fibroma is the second most common primary cardiac neoplasm seen in infants and children.

Hemangiomas and lymphangiomas are primary benign vascular tumors of the heart. Hemangiomas are more common than lymphangiomas and can occur at any age. Cardiac hemangioma can occasionally be associated with hemangioma in other sites, such as the gastrointestinal tract or the skin. Hemangiomas can further be distinguished based on the size of their vascular channels into capillary, cavernous, or venous hemangiomas.

Malignant cardiac neoplasms

Sarcomas account for the majority of primary malignant cardiac neoplasms followed by primary cardiac lymphomas. Secondary malignant cardiac neoplasms usually result from primary lung or breast neoplasms, or Hodgkin's lymphoma. The most common primary sarcomas of the heart include angiosarcomas, leiomyosarcomas, rhabdomyosarcomas, and undifferentiated sarcomas. Cardiac angiosarcomas typically occur in middle-aged adults. Patients typically present with advanced metastatic disease, and symptoms include shortness of breath, chest pain, and constitutional symptoms. Patients can also exhibit signs of superior

vena cava syndrome, cardiac tamponade, or evidence of CHF. Cardiac angiosarcomas metastasize to most organ systems and are typically associated with a poor prognosis of less than 1 year.[123]

Primary cardiac lymphomas are rare but can occur in both immunocompetent and immunocompromised individuals. Due to the association with HIV infection and an increasing population of living solid-organ transplant recipients, there is an increasing incidence of cardiac lymphomas. Often extracardiac involvement is present. Clinical presentation varies from isolated cardiac symptoms to constitutional symptoms, and pericardial effusion is present in a significant percentage of patients. Primary cardiac lymphomas are similar to other lymphomas and are sensitive to chemotherapy. Despite this, overall prognosis is still poor and more than 50% of the patients die within 2 to 3 months of initial diagnosis.[123]

CARDIAC AMYLOIDOSIS

In amyloidosis, there is extracellular deposition of proteins that have a unique structure (fibrils in a β-pleated sheet configuration). Fibrils are composed of low molecular weight subunits of a variety of normal serum proteins. While there are various types of amyloidosis, for the purpose of this review, we will focus on immunoglobulin light chain AL amyloidosis. AL is a systemic disorder that can affect any organ, including the heart. Amyloid protein deposition into the myocardial interstitium is a well-recognized cause of a progressive restrictive or infiltrative cardiomyopathy and carries a grave prognosis. The median age at diagnosis is 60-65 years with a male predominance. Most patients with AL cardiac amyloid often develop significant heart failure with poor survival beyond 2 years of symptom onset unless treated with heart transplantation and concomitant bone marrow transplantation.[124] AL amyloidosis can also occur in patients with other plasma cell disorders such as multiple myeloma, plasma cell malignancies, or Waldenstrom's macroglobulinemia.

Clinical manifestations in a given patient are determined by the extent of amyloid involvement of a particular organ system, but patients often experience multi-system symptoms due to the deposition of amyloid fibrils in more than one system. AL amyloidosis is usually suspected in a patient presenting with any one of the following: unexplained generalized edema, proteinuria in a non-diabetic, CHF with no obvious etiology, increased cardiac biomarkers in the absence of primary heart disease, carpal tunnel syndrome, or macroglossia.[125,126]

PERICARDIAL EFFUSION

Patients with cancer may develop pericardial effusions because of the presence of metastatic disease in the pericardium, radiation therapy, chemotherapeutic agents (cyclophosphamide), or immunotherapy. In patients undergoing ERNA for LVEF assessment, pericardial effusions are suspected when a photopenic ''halo'' appearance is seen around the heart.

USE OF NUCLEAR CARDIOLOGY TECHNIQUES IN THE DETECTION OF BENIGN AND MALIGNANT CARDIAC TUMORS

SPECT Imaging

The first report of tumor detection by radioisotope techniques was using planar thallium- and technetium-based imaging.[127-129] While Tc-99m tetrofosmin and sestamibi have been used to detect lung, breast, and other tumors, there have not been reports of using these isotopes to detect cardiac tumors because of the background myocardial uptake of perfusion tracers, although perfusion defects have been reported at the sites of intracardiac tumors.[130,131] Not uncommonly, extracardiac radiotracer uptake is noted in planar projections of myocardial perfusion SPECT scans performed with thallium or technetium-based isotopes.[132] Often this uptake is noted in breast and lung tumors, mediastinal, neck, or axillary lymph nodes, where these could represent a malignancy. In a retrospective study by Williams et al,[132] noncardiac findings were identified by surveying 12,526 reports of dual-isotope myocardial perfusion imaging studies.[131] Of these, 48% were suggestive of malignancy, and foci in the breast or lung were more likely to be confirmed as representing cancer. Benign tumors such as thymoma may also be identified through mediastinal uptake on cardiac SPECT MPI. Hence, examination of the rotating planar images may be very useful in the detection of extracardiac tumors.

PET Imaging

Whole-body PET using FDG is considered the gold standard for the detection of malignancies associated with high rates of anaerobic glycolytic metabolism, especially for the evaluation of metastases.[133] PET imaging with FDG is clearly able to differentiate hypermetabolic lesions that are likely malignant from areas of low FDG uptake that may represent normal tissue or benign tumors.[134,135] In the case of cardiac tumors, the data on the use of the FDG-PET imaging are primarily in the form of case reports; the majority of

which are in patients with angiosarcomas or secondary metastases to the heart.[136-139]

Metastases to the heart and pericardium are incidentally discovered on autopsies in 10 to 12% of all malignancies.[140,141] Primary tumors most likely to have cardiac metastasis found at autopsy include pleural mesotheliomas (48.4%), melanomas (27.8%), lung adenocarcinomas (21%), and undifferentiated carcinomas (19.5%). On the other hand, primary cardiac tumors are rare with an overall incidence of 0.001% to 0.028% in autopsy studies, of which 20% to 25% are malignant.[118] The most common primary cardiac malignancy is angiosarcoma, and there are multiple case reports of the use of FDG-PET imaging in the diagnosis and staging of these tumors.

Unlike echocardiography, CT and MRI, which can define tumors structurally and anatomically, the greatest utility of FDG-PET imaging comes from its ability to differentiate benign from malignant tumors, as well as to identify areas of distant metastases or local extension that can change management strategies.[142,143] Rahbar et al studied the differences in FDG uptake between benign and malignant primary and secondary cardiac tumors and found that a standardized uptake value (SUV) of greater than 3.5 is suggestive of the presence of a malignant tumor.[144] In this retrospective study, FDG-PET imaging had a sensitivity and specificity of 100% and 86%, respectively, in identifying the cardiac malignancy. Furthermore, FDG-PET was more sensitive than CT/MRI in detecting distant metastases that can change treatment options in patients with cardiac malignancy from surgical removal to palliative therapy. Hence, the authors propose that when MRI/CT findings are inconclusive with respect to the malignant nature of an intracardiac tumor—and in those with confirmed intracardiac malignancies—FDG-PET can be helpful in diagnostic and prognostic assessment. It is important to remember for cancer FDG imaging, it is essential to suppress myocardial glucose uptake maximally in order to identify accurately areas of increased FDG uptake as being related to the malignancy. Correlating the areas of increased FDG uptake with the CT or MRI images also helps improve identification of malignant cardiac tumors.

Potential Future Uses of Nuclear Cardiology in the Care of Patients with Cancer

Although the focus of this informational statement has been on the proven clinical effectiveness of a patient-centered approach to cardiac imaging to identify cardiotoxicity and manage risk of CHF, nuclear cardiac imaging holds the prospect for unique methods of diagnosis not provided by other modalities. This strength comes from the ability to identify molecular targets using radiolabeled tracers. The identification of such targets requires an understanding of the basic cellular and molecular mechanisms of cancer pathogenesis that can affect the heart and of the agents used to treat malignancies. As summarized below, there already exist several areas of active investigation for the application of radiotracer-based techniques to evaluate the cardiac complications in patients with cancer.

Early detection of anthracycline-induced cardiotoxicity

Because of the relatively irreversible nature of systolic dysfunction in patients with anthracycline-induced cardiotoxicity, it is essential that methods are established to identify those individuals at risk for anthracycline-induced cardiotoxicity and to identify the development of cardiotoxicity prior to a decrease in the LVEF. As discussed above, echocardiographic strain analysis and biomarker monitoring offer some promise in detecting preclinical decreases in function;[98] however, several novel SPECT techniques have also been evaluated.[74] These novel techniques include sympathetic neuronal imaging with ^{123}I-*m*IBG,[145-148] ^{111}In-antimyosin, a specific marker of myocyte injury and necrosis,[148,149] and ^{99m}Tc-annexin V, a marker for apoptosis and programmed cell death.[150,151]

Apoptosis imaging

The mechanism responsible for chronic LV dysfunction caused by anthracyclines involves activation of apoptotic pathways through the production of reactive oxygen species.[23] This increase in myocyte apoptosis can be detected in early stages of cardiotoxicity by annexin V imaging. Animal models of anthracycline cardiotoxicity have demonstrated the ability to detect increased rates of apoptosis using Tc-99m-labeled annexin V[150] and identify evidence of myocyte loss prior to the development of LV dysfunction as determined echocardiographically.[152] Because imaging with radiolabled annexin V is a direct reflection of the underlying process responsible for anthracycline-induced cardiotoxicity, namely apoptosis, this technique could potentially represent a method to not only identify cardiotoxicity prior to the development of overt systolic dysfunction but also provide a method to monitor therapies directed at reducing the apoptotic process.[152,153] While annexin V imaging has been performed in heart transplant recipients to detect apoptosis,[154] it remains unclear whether annexin V will play an important clinical role in monitoring anthracycline-induced CHF.[150,151]

Caspase 3, an enzyme involved in the terminal step of the apoptotic pathway, has recently been studied as a potential target for the detection of anthracycline-induced cardiotoxicity. Using ^{18}F-CP18, an F-18-labeled synthetic substrate for caspase 3, Su et al evaluated caspase 3 activity, apoptosis, and changes in LV function in a mouse model of anthracycline-induced cardiotoxicity. This study demonstrated a linear relationship between ^{18}F-CP18 uptake and quantitative assessments of myocyte apoptosis based on TUNEL staining and was associated with decreased LV function.[155] Further studies are required to determine if increased ^{18}F-CP18 uptake precedes the decline in LVEF and whether the agent is effective in humans.

Antimyosin Imaging

Prior to the onset of apoptosis in chronic anthracycline cardiotoxicity, and in the setting of acute anthracycline cardiotoxicity, direct myocyte damage can occur with associated release of troponin T and brain natriuretic peptide.[156-158] Because sarcolemmal disruption and cardiac myocyte damage in the setting of myocardial infarction can be evaluated based on binding of radiolabeled antimyosin antibodies to intracellular myosin, researchers have also evaluated the use of this radiotracer for detecting anthracycline-induced cardiotoxicity. In initial studies, the intensity of antimyosin antibody uptake is directly proportional to the cumulative dose of anthracycline[159] and the severity of myocyte damage.[160]

Studies using ^{111}In-antimyosin antibodies demonstrated intense uptake of the radiotracer in breast cancer patients who had received high cumulative doses (500 mg·m^{-2}) of doxorubicin and had a decrease in their LVEF,[161] although the researchers did not determine the degree of antimyosin antibody uptake prior to anthracycline administration. In subsequent studies, antimyosin scintigraphy was shown to detect evidence of myocyte damage at doses of doxorubicin between 240 and 300 mg·m^{-2} when there was no evidence of LV dysfunction.[148] At doses in the range of 420 to 600 mg·m^{-2}, there was even greater uptake of ^{111}In-antimyosin antibody that was associated with decreases in LVEF. Importantly, patients with intense uptake of antimyosin antibodies at the intermediate doses of doxorubicin were more likely to develop LV dysfunction at subsequent higher doses of the chemotherapeutic drug.[149] However, the lack of specificity for predicting subsequent CHF and lack of ongoing availability of ^{111}In-antimyosin antibody in the United States suggest an unlikely role for it in the foreseeable future.

Sympathetic Imaging

The progression of anthracycline cardiotoxicity leading to CHF is associated with global myocardial adrenergic derangement.[145] Research has focused on the ability of neuronal imaging using the norepinephrine analog, ^{123}I-metaiodobenzylguanidine (*m*IBG), to detect anthracycline-induced cardiotoxicity. Changes in the uptake and retention of *m*IBG have been shown to provide important prognostic information in patients with heart failure that is incremental to LVEF.[162] Not unexpectedly, in patients who have demonstrated anthracycline-induced cardiomyopathy, there is a higher *m*IBG washout rate associated with lower LVEF.[163] Furthermore, the presence of a preserved *m*IBG washout rate in patients with evidence of cardiotoxicity, as demonstrated by a significant decrease in LVEF, may identify patients that can tolerate further anthracycline-based chemotherapy.[163] Such findings in a limited number of patients must be evaluated in larger cohorts of patients receiving anthracycline chemotherapy.

While risk stratification of patients with established anthracycline-induced LV dysfunction is important, what is of even greater value is the identification of subclinical cardiotoxicity prior to the development of LV systolic dysfunction. Based on the hypothesis that anthracyclines can cause either direct sympathetic neuronal damage or changes in neuronal function,[164] several preclinical studies have evaluated changes in cardiac sympathetic neuronal function caused by this class of chemotherapeutic agents. In a rat model of cardiotoxicity in which animals received weekly injections of 2 mg·kg^{-1} of doxorubicin (the equivalent of approximately 75 mg·m^{-2}), abnormalities in cardiac *m*IBG accumulation were observed one week prior to a decline in LVEF.[165] This change in *m*IBG uptake preceding changes in LV function was confirmed in subsequent studies that also demonstrated a greater impact on subendocardial sympathetic innervation compared to subepicardial innervation.[165] It must be kept in mind that in this study, as in the majority of animal studies, the doses and scheduling of anthracycline treatment are higher and more frequent, respectively, than what are used in clinical practice. Therefore, future animal studies of anthracycline-induced cardiotoxicity should attempt to simulate the clinical scenario more closely.

In patients receiving anthracycline-based chemotherapy, a similar decrease in *m*IBG retention, as indicated by

a decrease in the heart/mediastinal ratio, has been reported prior to a decrease in LVEF or fractional shortening.[146,166] These changes in *m*IBG retention, however, may only occur at higher doses (420-600 $mg \cdot m^{-2}$) of anthracyclines.[148] Interestingly, it has also been reported in a small study of patients for whom these abnormalities in neuronal function may persist up to ten years, despite normalization of LV function.[167]

These studies suggest that cardiac sympathetic neuronal imaging using *m*IBG may identify subclinical anthracycline-induced cardiotoxicity prior to the development of overt LV systolic dysfunction and aid in determining prognosis in those individuals who have declines in LVEF following treatment with anthracycline-based chemotherapy. In addition to SPECT-based *m*IBG, PET-based radiopharmaceuticals, such as ^{18}F-6-fluorodopamine, ^{11}C-hydroxyephedrine, and ^{11}C-epineiphrine may also hold promise for the evaluation of anthracycline-induced cardiotoxicity. Larger trials will be required to establish the value of cardiac sympathetic imaging in patients receiving anthracyclines.

Use of Radiolabeled Trastuzumab in the Assessment of Cardiotoxicity

As noted above, radiolabeled antibodies have been used to identify cardiac myocyte damage caused by anthracycline-based chemotherapy, but radiolabeled antibodies may be used to detect a variety of epitopes that may be important in assessing the impact of chemotherapy on the cardiovascular system. One such example is the use of ^{111}In-trastuzumab imaging. Trastuzumab is the humanized monoclonal antibody used to treat HER2/neu receptor-positive breast cancer. If this therapeutic antibody is labeled with ^{111}In and injected in tracer quantities, it will bind to HER2/neu receptors on the cell surface. These receptors are present not only on breast cancer cells, but also on normal endothelial cells and cardiac myocytes.

In a study of 20 patients with breast cancer who were injected with ^{111}In-trastuzumab prior to receiving adjuvant or neoadjuvant trastuzumab therapy, 7 had uptake of the radiotracer and 6 of these individuals subsequently developed trastuzumab-associated heart failure.[168] In contrast, another study was unable to demonstrate any relationship between cardiac uptake of radiolabeled trastuzumab and subsequent development of LV dysfunction, although that study did not perform the trastuzumab-based imaging prior to the start of trastuzumab therapy.[169] A subsequent study performed to determine if heart failure, either caused by anthracycline therapy or from a non-chemotherapy-related cause, was associated with increased uptake of radiolabeled trastuzumab did not reveal any relationship between the development of heart failure, regardless of etiology, and cardiac ^{111}In-trastuzumab uptake.[170] The discrepant results of the trastuzumab studies may be ascribed to a variety of factors, including small numbers of patients in each study, differences in the relationship between when patients underwent imaging and when they received trastuzumab therapy, and a continued incomplete understanding of the mechanisms responsible for trastuzumab-induced cardiotoxicity. Therefore, further studies are needed to determine if radiolabeled trastuzumab may be used in the evaluation of cardiotoxicity.

Assessment of cardiac metabolic alterations

As discussed above, FDG can be used to identify hypermetabolic primary and secondary cardiac tumors; however, it may be possible to evaluate fundamental changes in myocardial metabolism in response to chemotherapy. Specifically, taxanes, which inhibit microtubule synthesis, have been shown to alter fatty acid metabolism, and ^{123}I-BMIPP and ^{123}I-IPPA scintigraphy have been reported to monitor this biochemical perturbation in mitochondrial free fatty acid oxidation without impairing myocardial perfusion.[63] Taxanes in combination with carboplatin are reported to exert a more profound depression on myocardial free fatty acid metabolism and myocardial contractile dysfunction than doxorubicin alone. The incremental value of reduced ^{123}I-BMIPP or ^{123}I-IPPA metabolism on prediction of chemotherapy-induced CHF remains undefined and further research is required to determine if assessment of myocardial fatty acid metabolism using these agents might be used to detect cardiotoxicity.

Evaluating Cardiac Amyloid

Although once an underdiagnosed condition, there has been an increasing awareness of the contribution of cardiac amyloid to cardiac morbidity and mortality. While senile and mutational transthyretin amyloidosis (ATTR amyloidosis) are the most common causes of cardiac amyloidosis, the deposition of misfolded light chain proteins in the myocardium in patients with multiple myeloma can cause AL amyloid. Previously, the identification of cardiac involvement with AL

amyloid was associated with a very poor prognosis,[126] but the development of aggressive but effective chemotherapeutic regimens has improved survival and underscores the need to identify cardiac involvement at an early stage. While imaging with ^{99m}Tc-labeled pyrophosphate (PYP) has been shown to identify cardiac involvement with ATTR amyloid,[171] PYP does not bind to AL amyloid with the same affinity and therefore cannot be used to detect cardiac light chain depositions. However, advances in the development of PET-based radiotracers for the detection of neurofibrillatory plaques in patients with Alzheimer disease may provide a basis for the detection of cardiac AL amyloid in patients at an early stage prior to the development of clinical signs of cardiac involvement.[172]

'Pittsburgh compound B (PiB) is a ^{11}C-labeled PET tracer that binds to amyloid fibrils, increasing the retention of the compound in the brains of patients with Alzheimer's disease. Enhanced retention of PiB has been demonstrated in patients with both AL and ATTR amyloid compared to healthy individuals.[173] A second PET-based radiotracer that binds to neurofibrillatory plaques, ^{18}F-florbetapir, has also shown promise in detecting cardiac amyloid.[174] In both of these studies, patients had verified cardiac amyloid and thickened left ventricles. It remains to be determined if these compounds may be used to detect cardiac involvement with AL amyloid at an early, subclinical stage. In addition, although there is some preliminary evidence that there is even greater retention of ^{18}F-florbetapir in the setting of AL amyloid compared to ATTR amyloid,[174] further studies are required to determine if this agent can differentiate the two forms of cardiac amyloid. FDA approval of ^{18}F-florbetapir for neurologic application provides opportunity for investigation of its value in the identification of cardiac AL amyloid associated with plasma cell dyscrasias such as lymphoma, multiple myeloma, and Waldenstrom macroglobulinemia.\]

CONCLUSIONS

The current era offers great promise for the development of safer and more potent chemotherapeutic agents and numerous methods to optimize detection of cardiotoxicity and LV dysfunction that predict risk of CHF with continued therapy. In our quest to prevent cardiotoxicity, the challenge for the field of cardio-oncology is two-fold: to develop therapeutic approaches with less cardiotoxicity and to develop optimally predictive methods that minimize cardiotoxicity until safer agents are available. This challenge will require us to understand better the cellular, biochemical, and genomic mechanism of cardiotoxicity in order to prevent heart failure while optimizing chemotherapeutic benefit. To advance the field of cardio-oncology, a number of novel diagnostic approaches have been recommended that will require thoughtful prospective evaluation with assessment of the clinical value on HF reduction of technique-specific endpoints of therapy. The role of myocardial strain imaging appears promising and requires rigorous evidence-based proof of effectiveness and value for detecting cardiotoxicity and preventing clinical HF compared to highly accurate modalities of LV volume and EF monitoring with planar and SPECT ERNA and CMR.

Additional radiotracers will likely emerge based on an understanding of the mechanisms of action of novel, molecularly targeted agents. Further studies will be necessary to establish the performance characteristics of these newer techniques based on specific toxicity endpoints and to determine the added value that they bring to patient care. Techniques that provide direct imaging of amyloid imaging with ^{99m}Tc-PYP and ^{18}F-florbetapir show great promise for the early detection of this important cause of heart failure in cancer patients.

In summary, cardio-oncology is a multi-disciplinary field that requires very specialized knowledge from oncology and cardiology, including an understanding of the role of noninvasive imaging in the evaluation and management of the cardiovascular complications from cancer and its therapy. This review of ongoing evidence of the accuracy, reproducibility, and proven clinical effectiveness of patient-centered monitoring of cardiotoxicity, and HF risk in cancer patients has led to the current recommendations for a rational approach to multimodality imaging, as summarized in Appendix Table 6. In the best interests of patient care and advancing the field of cardio-oncology, it is critical that technique-specific, evidence-based guidelines be established to help improve and standardize the use of all noninvasive cardiac testing and the ensuing treatment decisions to optimize the cardiovascular health and care of patients with cancer.

APPENDIX

See Tables 1, 2, 3, 4, 5, and 6

Table 1. Chemotherapeutic agents and their associated cardiovascular toxicities

	CHF	QT prolongation	Arrhythmias	Bradycardia	Atrial fibrillation	Hypertension	Hypotension	Myocardial ischemia	Myo/ pericarditis	Thrombosis/ embolism	Endocardial fibrosis	Hyperlipidemia
Alkylating Agents												
Busulfan									×		×	
Cisplatin	×					×				×*		
Cyclosphasphamide	×*		×						×			
Ifosfamide	×*											
Mitomycin	×											
Angiogenesis inhibitors												
Lenalidomide				×						×*		
Pamolidomide										×*		
Thalidomide				×						×*		
Anthracyclines												
Daunorubicin	×								×			
Doxorubicin	×*								×			
Epirubicin	×								×			
Idarubicin	×*								×			
Mitoxantrone	×								×			
Antiandrogen therapy												
Abiraterone												×
Degarelix												×
Enzalutamide												×
Antiestrogen therapy												
Anastrozole												×
Letrozole												×
Tamoxifen		×								×*		
Antimetabolites												
5-florouracil								×*	×			
Capecitabine								×*				
Cytarabine	×								×			
Methotrexate			×									
Fludarabine	×								×			
Antimicrotubule agents												
Docetaxel	×*							×				
Etoposide							×					
Paclitaxel	×	×		×*				×				
Teniposide												
Vinblastine								×				
Vinocristine								×				

Table 1 continued

	CHF	QT prolongation	Arrhythmias	Bradycardia	Atrial fibrillation	Hypertension	Hypotension	Myocardial ischemia	Myo/ pericarditis	Thrombosis/ embolism	Endocardial fibrosis	Hyperlipidemia
Histone deacetylase inhibitors												
Romidepsin		×										
Vorinostat		×*								×		
Monoclonal antibodies												
Bevacizumab						×*		×				
Ipilimumab					×							
Rituximab			×				×					
Trastuzamab	×*											
Proteosome inhibitors												
Bortezomib	×							×				
Carfilzomib	×											
Tyrosine kinase inhibitors												
Dasatinib		×										
Erlotinib								×		×		
Imatinib	×					×						
Lapatinib		×*										
Nilotinib		×*										
Ponatinib						×				×		
Sorafenib						×*		×				
Sunitinib	×*					×*						
Miscellaneous												
Arsenic trioxide		×*										
Bleomycin									×			
Interferon						×	×*	×				
Interleukin-2			×				×*	×				
Tretinoin	×						×					

*CHF includes either left ventricular dysfunction or clinical congestive heart failure. Complications with a reported incidence of at least 5% are presented with an asterisk

Table 2. Risk factors for developing left ventricular dysfunction with anthracycline or trastuzumab treatment

Anthracyclines	Trastuzumab
Age >65 or <5 years	Age >60 years
Hypertension	Prior anthracycline treatment
Female gender	
Mediastinal radiation	
Pre-existing cardiac disease	
Treatment with other cardiotoxic agents	
Cumulative doxorubicin dose >450 mg·m^{-2}	
Larger individual anthracycline doses	

Table 3. Isotoxic dose conversions for anthracycline agents

Agent	Multiplication factor to derive equivalent doxorubicin dose
Daunorubicin	1.00
Epirubicin	0.67
Idarubicin	5.00
Mitoxantrone	4.00

Based on data from Children's Oncology Group. "Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer." October 2013; version 4. Available at http://www.survivorshipguidelines.org

Table 4. Recommendations for monitoring of LVEF in survivors of childhood cancer

Age at treatment	Chest radiation	Total anthracycline dose	Recommended frequency of LVEF assessment
<1 year	Yes	Any	Every year
	No	<200 mg·m^{-2}	Every 2 years
		≥200 mg·m^{-2}	Every year
1 to 4 years	Yes	Any	Every year
	No	<100 mg·m^{-2}	Every 5 years
		≥100 to <300 mg·m^{-2}	Every 2 years
		≥300 mg·m^{-2}	Every year
≥5 years	Yes	<300 mg·m^{-2}	Every 2 years
		≥300 mg·m^{-2}	Every year
	No	<200 mg·m^{-2}	Every 5 years
		≥200 to <300 mg·m^{-2}	Every 2 years
		≥300 mg·m^{-2}	Every year

Based on data from Children's Oncology Group "Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer." October 2013; version 4. Available at http://www.survivorshipguidelines.org

Table 5. Recommendations for trastuzumab therapy by the Canadian Trastuzumab Working Group[32]

	Asymptomatic decrease in LVEF from baseline		
	≤10 LVEF points	**10-15 LVEF points**	**≥15 LVEF points**
Within facility's normal limits	Continue trastuzumab	Continue trastuzumab	Hold trastuzumab and repeat LVEF assessment after 4 weeks
1-5 LVEF points below LLN	Continue trastuzumab[1]	Hold trastuzumab and repeat LVEF assessment after 4 weeks[1,2]	Hold trastuzumab and repeat LVEF assessment after 4 weeks[2,3]
≥6 LVEF points below LLN	Continue trastuzumab and repeat LVEF assessment after 4 weeks[3]	Hold trastuzumab and repeat LVEF assessment after 4 weeks[2,3]	Hold trastuzumab and repeat LVEF assessment after 4 weeks[2,3]

[1] Consider cardiac assessment and initiation of ACE inhibitor therapy
[2] After two holds of therapy, consider permanent discontinuation of trastuzumab therapy
[3] Initiate ACE inhibitor therapy and refer to cardiologist

Table 6. Evidence-based recommendations for clinical and cost effectiveness of multimodality LVEF monitoring in cancer patients treated with chemotherapy and/or radiation therapy obtain baseline radionuclide (ERNA or 'MUGA') LVEF (pre-therapy, or <100 mg·m^{-2} doxorubicin or equivalent)

Monitoring and treatment strategy for normal baseline LVEF (≥50% Planar ERNA; ≥55% SPECT ERNA)
Serial LVEF by ERNA, 3D echo without contrast, or CMR at 250 to 300 mg·m^{-2}
Repeat ERNA at 400 mg·m^{-2} doxorubicin or equivalent therapy
Repeat ERNA prior to addition of radiation, cyclophosphamide, or trastuzumab
Treatment endpoint (Normal Baseline LVEF):
Discontinue cancer therapy and initiate carvedilol and ACE inhibitor if the LVEF declines by ≥10 EF units OR declines to ≤30% Planar ERNA; ≤35% SPECT ERNA
Monitoring and treatment strategy for abnormal baseline LVEF (<50% Planar ERNA; <55% SPECT ERNA)
Serial LVEF by ERNA, 3D echo without contrast, or CMR shortly prior to each subsequent dose of cancer therapy
Repeat ERNA prior to addition of radiation, cyclophosphamide, or trastuzumab
Treatment endpoint (Abnormal Baseline LVEF):
Discontinue cancer therapy and initiate carvedilol and ACE inhibitor if the LVEF declines by ≥10 EF units OR declines to the lower limit of normal LVEF (≤30% Planar ERNA; ≤35% SPECT ERNA)

Modality selection is determined by published evidence-based level of accuracy and reproducibility of reported LVEF measurements.[13,16,20,93,174] Any technically limited study should be confirmed by a complimentary high-accuracy ERNA or CMR study

References

1. DeSantis CE, Lin CC, Mariotto AB, et al Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 2014;64:252-71.
2. Felker GM, Thompson RE, Hare JM, et al Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077-84.
3. Yoon GJ, Telli ML, Kao DP, Matsuda KY, Carlson RW, Witteles RM. Left ventricular dysfunction in patients receiving cardiotoxic cancer therapies are clinicians responding optimally? J Am Coll Cardiol 2010;56:1644-50.
4. Chavez-MacGregor M, Niu J, Zhang N, et al Cardiac monitoring during adjuvant trastuzumab-based chemotherapy among older patients with breast cancer. J Clin Oncol 2015;33:2176-83.
5. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: The need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst 2010;102:14-25.
6. Reulen RC, Winter DL, Frobisher C, et al Long-term cause-specific mortality among survivors of childhood cancer. JAMA 2010;304:172-9.
7. Colzani E, Liljegren A, Johansson AL, et al Prognosis of patients with breast cancer: Causes of death and effects of time since diagnosis, age, and tumor characteristics. J Clin Oncol 2011;29:4014-21.
8. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: A retrospective cohort study. Breast Cancer Res 2011;13:R64.
9. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, et al Overall survival and cause-specific mortality of patients with stage T1a, bN0M0 breast carcinoma. J Clin Oncol 2007;25:4952-60.
10. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist 2007;12:20-37.
11. Lipshultz SE, Adams MJ, Colan SD, et al Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: Pathophysiology, course, monitoring, management, prevention, and research directions: A scientific statement from the American Heart Association. Circulation 2013;128:1927-95.
12. Carver JR, Shapiro CL, Ng A, et al American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. J Clin Oncol 2007;25:3991-4008.
13. Schwartz RG, Jain D, Storozynsky E. Traditional and novel methods to assess and prevent chemotherapy-related cardiac dysfunction noninvasively. J Nucl Cardiol 2013;20:443-64.
14. Alexander J, Dainiak N, Berger HJ, et al Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278-83.
15. Billingham ME, Mason JW, Bristow MR, Daniels JR. Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 1978;62:865-72.
16. Choi BW, Berger HJ, Schwartz PE, et al Serial radionuclide assessment of doxorubicin cardiotoxicity in cancer patients with abnormal baseline resting left ventricular performance. Am Heart J 1983;106:638-43.
17. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991;324:808-15.
18. Lipshultz SE, Lipsitz SR, Sallan SE, Dalton VM, Mone SM, Gelber RD, et al Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23:2629-36.
19. Mitani I, Jain D, Joska TM, Burtness B, Zaret BL. Doxorubicin cardiotoxicity: Prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era. J Nucl Cardiol 2003;10:132-9.
20. Schwartz RG, McKenzie WB, Alexander J, et al Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy: Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987;82:1109-18.
21. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991;266:1672-7.
22. Yeh ETH, Tong AT, Lenihan DJ, et al Cardiovascular complications of cancer therapy: Diagnosis, pathogenesis, and management. Circulation 2004;109:3122-31.
23. Zhang S, Liu X, Bawa-Khalfe T, et al Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639-42.
24. Volkova M, Russell R. Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. Curr Cardiol Rev 2011;7:214-20.
25. Bristow MR, Thompson PD, Martin RP, Mason JW, Billingham ME, Harrison DC. Early anthracycline cardiotoxicity. Am J Med 1978;65:823-32.
26. Dazzi H, Kaufmann K, Follath F. Anthracycline-induced acute cardiotoxicity in adults treated for leukaemia. Analysis of the clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukaemia at the University Hospital of Zurich, Switzerland, between 1990 and 1996. Ann Oncol 2001;12:963-6.
27. Cardinale D, Colombo A, Bacchiani G, et al Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015;131:1981-8.
28. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. Cancer 2003;97:2869-79.
29. Von Hoff DD, Layard MW, Basa P, et al Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710-7.
30. Panjrath GS, Patel V, Valdiviezo CI, Narula N, Narula J, Jain D. Potentiation of Doxorubicin cardiotoxicity by iron loading in a rodent model. J Am Coll Cardiol 2007;49:2457-64.
31. Wojnowski L, Kulle B, Schirmer M, et al NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. Circulation 2005;112:3754-62.
32. Mackey JR, Clemons M, Cote MA, et al Cardiac management during adjuvant trastuzumab therapy: Recommendations of the Canadian Trastuzumab Working Group. Curr Oncol 2008;15:24-35.
33. Ewer MS, Vooletich MT, Durand JB, et al Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. J Clin Oncol 2005;23:7820-6.
34. Hedhli N, Dobrucki LW, Kalinowski A, et al Endothelial-derived neuregulin is an important mediator of ischaemia-induced angiogenesis and arteriogenesis. Cardiovasc Res 2012;93:516-24.
35. Hedhli N, Huang Q, Kalinowski A, et al Endothelium-derived neuregulin protects the heart against ischemic injury. Circulation 2011;123:2254-62. doi:10.1161/CIRCULATIONAHA.

36. Panjrath GS, Jain D. Trastuzumab-induced cardiac dysfunction. Nucl Med Commun 2007;28:69-73.
37. Curigliano G, Cardinale D, Suter T, et al Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23 Suppl 7:vii155-66.
38. Hooning MJ, Botma A, Aleman BM, et al Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst 2007;99:365-75.
39. McGale P, Darby SC, Hall P, et al Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. Radiother Oncol 2011;100:167-75.
40. Marks LB, Yu X, Prosnitz RG, et al The incidence and functional consequences of RT-associated cardiac perfusion defects. Int J Radiat Oncol Biol Phys 2005;63:214-23.
41. Seddon B, Cook A, Gothard L, Salmon E, Latus K, Underwood SR, et al Detection of defects in myocardial perfusion imaging in patients with early breast cancer treated with radiotherapy. Radiother Oncol 2002;64:53-63.
42. Correa CR, Litt HI, Hwang WT, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. J Clin Oncol 2007;25:3031-7.
43. Gayed IW, Liu HH, Wei X, et al Patterns of cardiac perfusion abnormalities after chemoradiotherapy in patients with lung cancer. J Thorac Oncol 2009;4:179-84.
44. Gabriels K, Hoving S, Seemann I, et al Local heart irradiation of ApoE(−/−) mice induces microvascular and endocardial damage and accelerates coronary atherosclerosis. Radiother Oncol 2012;105:358-64.
45. Seemann I, Gabriels K, Visser NL, et al Irradiation induced modest changes in murine cardiac function despite progressive structural damage to the myocardium and microvasculature. Radiother Oncol 2012;103:143-50.
46. Giordano SH, Kuo YF, Freeman JL, Buchholz TA, Hortobagyi GN, Goodwin JS. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005;97:419-24.
47. Patt DA, Goodwin JS, Kuo YF, et al Cardiac morbidity of adjuvant radiotherapy for breast cancer. J Clin Oncol 2005;23:7475-82.
48. Yu X, Prosnitz RR, Zhou S, et al Symptomatic cardiac events following radiation therapy for left-sided breast cancer: Possible association with radiation therapy-induced changes in regional perfusion. Clin Breast Cancer 2003;4:193-7.
49. 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 2013;26:1013-32.
50. Van Kriekinge SD, Berman DS, Germano G. Automatic quantification of left ventricular ejection fraction from gated blood pool SPECT. J Nucl Cardiol 1999;6:498-506.
51. Gradishar WJ, Vokes EE. 5-Fluorouracil cardiotoxicity: A critical review. Ann Oncol 1990;1:409-14.
52. de Forni M, Malet-Martino MC, Jaillais P, et al Cardiotoxicity of high-dose continuous infusion fluorouracil: A prospective clinical study. J Clin Oncol 1992;10:1795-801.
53. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: Revisited. Expert Opin Drug Saf 2009;8:191-202.
54. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994;28:374-8.
55. Berliner S, Rahima M, Sidi Y, Teplitsky Y, et al Acute coronary events following cisplatin-based chemotherapy. Cancer Invest 1990;8:583-6.
56. Frickhofen N, Beck FJ, Jung B, Fuhr HG, Andrasch H, Sigmund M. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol 2002;13:797-801.
57. Schmidinger M, Zielinski CC, Vogl UM, et al Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:5204-12.
58. Chu TF, Rupnick MA, Kerkela R, et al Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-9.
59. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: Basic mechanisms and potential cardioprotective therapies. J Am Heart Assoc 2014;3:e000665.
60. Chintalgattu V, Rees ML, Culver JC, et al Coronary microvascular pericytes are the cellular target of sunitinib malate-induced cardiotoxicity. Sci Transl Med 2013;5:187ra69.
61. Force T, Kolaja KL. Cardiotoxicity of kinase inhibitors: The prediction and translation of preclinical models to clinical outcomes. Nat Rev Drug Discov 2011;10:111-26.
62. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. J Clin Oncol 1991;9:1704-12.
63. Saito K, Takeda K, Imanaka-Yoshida K, Imai H, Sekine T, Kamikura Y. Assessment of fatty acid metabolism in taxan-induced myocardial damage with iodine-123 BMIPP SPECT: Comparative study with myocardial perfusion, left ventricular function, and histopathological findings. Ann Nucl Med 2003;17:481-8.
64. Schwartz RN, Stover L, Dutcher J. Managing toxicities of high-dose interleukin-2. Oncology (Williston Park) 2002;16:11-20.
65. Dutcher J, Atkins MB, Margolin K, et al Kidney cancer: The Cytokine Working Group experience (1986-2001): Part II. Management of IL-2 toxicity and studies with other cytokines. Med Oncol 2001;18:209-19.
66. Atkins MB, Lotze MT, Dutcher JP, et al High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105-16.
67. Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: A comprehensive retrospective review from a single institution. Endocr Relat Cancer 2014;21:371-81.
68. Yu C, Chopra IJ, Ha E. A novel melanoma therapy stirs up a storm: Ipilimumab-induced thyrotoxicosis. Endocrinol Diabetes Metab Case Rep 2015;2015:140092.
69. Wackers FJ, Berger HJ, Johnstone DE, et al Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: Validation of the technique and assessment of variability. Am J Cardiol 1979;43:1159-66.
70. Corbett JR, Akinboboye OO, Bacharach SL, et al Equilibrium radionuclide angiocardiography. J Nucl Cardiol 2006;13:e56-79.
71. Marshall RC, Berger HJ, Reduto LA, Gottschalk A, Zaret BL. Variability in sequential measures of left ventricular performance assessed with radionuclide angiocardiography. Am J Cardiol 1978;41:531-6.
72. 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;61:77-84.
73. Walker J, Bhullar N, Fallah-Rad N, et al Role of three-dimensional echocardiography in breast cancer: Comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol 2010;28:3429-36.

74. de Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, et al Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. J Nucl Med 2011;52:560-71.
75. Tassan-Mangina S, Codorean D, Metivier M, et al Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: Early and late alterations of left ventricular function during a prospective study. Eur J Echocardiogr 2006;7:141-6.
76. Palmeri ST, Bonow RO, Myers CE, et al Prospective evaluation of doxorubicin cardiotoxicity by rest and exercise radionuclide angiography. Am J Cardiol 1986;58:607-13.
77. Groch MW, DePuey EG, Belzberg AC, et al Planar imaging versus gated blood-pool SPECT for the assessment of ventricular performance: A multicenter study. J Nucl Med 2001;42:1773-9.
78. Adachi I, Akagi H, Umeda T, et al Gated blood pool SPECT improves reproducibility of right and left ventricular Fourier phase analysis in radionuclide angiography. Ann Nucl Med 2003;17:711-6.
79. Lefrak E, Pitha J, Rosenheim S, et al A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302-14.
80. Clements IP, Brinkmann B, Mullan BP, O'Connor MK, Breen JF. MCGregor CG. Operator-interactive method for simultaneous measurement of left and right ventricular volumes and ejection fraction by tomographic electrocardiography-gated blood pool radionuclide ventriculography. J Nucl Cardiol 2006;13:50-63.
81. Daou D, Harel F, Helal BO, et al Electrocardiographically gated blood-pool SPECT and left ventricular function: Comparative value of 3 methods for ejection fraction and volume estimation. J Nucl Med 2001;42:1043-9.
82. Jensen MM, Schmidt U, Huang C, Zerahn B. Gated tomographic radionuclide angiography using cadmium-zinc-telluride detector gamma camera; comparison to traditional gamma cameras. J Nucl Cardiol 2014;21:384-96.
83. Cottin Y, Touzery C, Coudert B, et al Impairment of diastolic function during short-term anthracycline chemotherapy. Br Heart J 1995;73:61-4.
84. Cottin Y, Touzery C, Dalloz F, et al Comparison of epirubicin and doxorubicin cardiotoxicity induced by low doses: Evolution of the diastolic and systolic parameters studied by radionuclide angiography. Clin Cardiol 1998;21:665-70.
85. Schwartz RG, Venci N. Can serial changes of diastolic dysfunction signal incremental risk of chemotherapy-induced heart failure missed by the timing of declining LV ejection fraction? J Nucl Cardiol 2015. doi:10.1007/s12350-015-0194-4.
86. Gerber TC, Gibbons RJ. Weighing the risks and benefits of cardiac imaging with ionizing radiation. JACC Cardiovasc Imaging 2010;3:528-35.
87. Fiechter M, Stehli J, Fuchs TA, Dougoud S, Gaemperli O, Kaufmann PA. Impact of cardiac magnetic resonance imaging on human lymphocyte DNA integrity. Eur Heart J 2013;34:2340-5.
88. Lee WH, Nguyen P, Hu S, et al Variable activation of the DNA damage response pathways in patients undergoing single-photon emission computed tomography myocardial perfusion imaging. Circ Cardiovasc Imaging 2015;8:e002851. doi: 10.1161/CIRCIMAGING.114.002851.
89. Mor-Avi V, Lang RM. Is echocardiography reliable for monitoring the adverse cardiac effects of chemotherapy? J Am Coll Cardiol 2013;61:85-7.
90. Mulvagh SL, Rakowski H, Vannan MA, et al American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr 2008;21:1179-201; quiz 281.
91. Banchs J, Jefferies JL, Plana JC, Hundley WG. Imaging for cardiotoxicity in cancer patients. Tex Heart Inst J 2011;38:268-9.
92. Marchandise B, Schroeder E, Bosly A, et al Early detection of doxorubicin cardiotoxicity: Interest of Doppler echocardiographic analysis of left ventricular filling dynamics. Am Heart J 1989;118:92-8.
93. Stoddard MF, Seeger J, Liddell NE, Hadley TJ, Sullivan DM, Kupersmith J. Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-induced systolic dysfunction in humans. J Am Coll Cardiol 1992;20:62-9.
94. Civelli M, Cardinale D, Martinoni A, et al Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. Int J Cardiol 2006;111:120-6.
95. 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 2014;27:911-39.
96. Thavendiranathan P, Poulin F, Lim KD, 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;63:2751-68.
97. Sawaya H, Sebag IA, Plana JC, et al Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011;107:1375-80.
98. 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;5:596-603.
99. Cardinale D, Sandri MT. Role of biomarkers in chemotherapy-induced cardiotoxicity. Prog Cardiovasc Dis 2010;53:121-9.
100. Dolci A, Dominici R, Cardinale D, Sandri MT, Panteghini M. Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: Systematic review of the literature and recommendations for use. Am J Clin Pathol 2008;130:688-95.
101. Fallah-Rad N, Walker JR, Wassef A, et al The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol 2011;57:2263-70.
102. Jurcut R, Wildiers H, Ganame J, et al Strain rate imaging detects early cardiac effects of pegylated liposomal Doxorubicin as adjuvant therapy in elderly patients with breast cancer. J Am Soc Echocardiogr 2008;21:1283-9.
103. 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;48:1475-97.
104. Zagrosek A, Abdel-Aty H, Boye P, Wassmuth R, Messroghli D, Utz W, et al Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. JACC Cardiovasc Imaging 2009;2:131-8.
105. Fallah-Rad N, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance

imaging in trastuzumab induced cardiomyopathy. J Cardiovasc Magn Reson 2008;10:5.
106. Lightfoot JC, D'Agostino RB Jr, Hamilton CA, et al Novel approach to early detection of doxorubicin cardiotoxicity by gadolinium-enhanced cardiovascular magnetic resonance imaging in an experimental model. Circ Cardiovasc Imaging 2010;3:550-8.
107. Corapcioglu F, Sarper N, Berk F, Sahin T, Zengin E, Demir H. Evaluation of anthracycline-induced early left ventricular dysfunction in children with cancer: A comparative study with echocardiography and multigated radionuclide angiography. Pediatr Hematol Oncol 2006;23:71-80.
108. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: A prospective, blinded, long-term observational study of outcome in 120 patients. Ann Oncol 2002;13:699-709.
109. Cardinale D, Colombo A, Lamantia G, et al Anthracycline-induced cardiomyopathy: Clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213-20.
110. Voigt J, John MS, Taylor A, Krucoff M, Reynolds MR, Gibson CM. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol 2014;37:312-21
111. Lestuzzi C, Vaccher E, Talamini R, et al Effort myocardial ischemia during chemotherapy with 5-fluorouracil: An underestimated risk. Ann Oncol 2014;25:1059-64.
112. El Fadl MHA, Bagai RK, Spiro TP, Daw HA. 5-Fluorouracil-induced cardiotoxicity during chemotherapy for adenocarcinoma of the small bowel. Gastrointest Cancer Res 2009;3:167-70
113. Heidenreich PA, Kapoor JR. Radiation induced heart disease: Systemic disorders in heart disease. Heart 2009;95:252-8.
114. Shankar SM, Marina N, Hudson MM, Hodgson DC, Adams MJ, Landier W, et al Monitoring for cardiovascular disease in survivors of childhood cancer: Report from the Cardiovascular Disease Task Force of the Children's Oncology Group. Pediatrics 2008;121:e387-96.
115. Campbell BA, Voss N, Pickles T, et al Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: A question of field size. J Clin Oncol 2008;26:5170-4.
116. Hughes S, Liong J, Miah A, et al A brief report on the safety study of induction chemotherapy followed by synchronous radiotherapy and cetuximab in stage III non-small cell lung cancer (NSCLC): SCRATCH study. J Thorac Oncol 2008;3:648-51.
117. Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. JACC Cardiovasc Imaging 2010;3:623-40.
118. Burke A. Primary malignant cardiac tumors. Semin Diagn Pathol 2008;25:39-46.
119. Burke A, Virmani R. Tumors of the heart and the great vessels. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology 1996.
120. von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: Current applications and future directions. Radiology 2006;238:405-22.
121. Meng Q, Lai H, Lima J, Tong W, Qian Y, Lai S. Echocardiographic and pathologic characteristics of primary cardiac tumors: A study of 149 cases. Int J Cardiol 2002;84:69-75.
122. Best AK, Dobson RL, Ahmad AR. Best cases from the AFIP: Cardiac angiosarcoma. Radiographics 2003;23 Spec No:S141-5.
123. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: Diagnosis and management. Lancet Oncol 2005;6:219-28.
124. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation 2005;112:2047-60.
125. Falk RH, Dubrey SW. Amyloid heart disease. Prog Cardiovasc Dis 2010;52:347-61.
126. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: A review. J Am Heart Assoc 2012;1:e000364.
127. Aktolun C, Bayhan H, Kir M. Clinical experience with Tc-99 m MIBI imaging in patients with malignant tumors. Preliminary results and comparison with Tl-201. Clin Nucl Med 1992;17:171-6.
128. Coleman RE. Single photon emission computed tomography and positron emission tomography in cancer imaging. Cancer 1991;67:1261-70.
129. Yigitbasi OG, Tutus A, Bozdemir K, Nardali M, Guney E. 201Tl imaging for differentiating between malignant and benign neck masses. Nucl Med Commun 1998;19:555-60.
130. Ruggiero NJ 2nd, Doherty JU, Ferrari VA, Hansen CL. Myocardial perfusion defect caused by intramyocardial lipoma. J Nucl Cardiol 2008;15:286-9.
131. Mansi L, Rambaldi PF, Cuccurullo V, et al Diagnostic and prognostic role of 99 mTc-Tetrofosmin in breast cancer. Q J Nucl Med 1997;41:239-50.
132. Williams KA, Hill KA, Sheridan CM. Noncardiac findings on dual-isotope myocardial perfusion SPECT. J Nucl Cardiol 2003;10:395-402.
133. Fletcher JW, Djulbegovic B, Soares HP, et al Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 2008;49:480-508.
134. Fischman AJ. Positron emission tomography in the clinical evaluation of metastatic cancer. J Clin Oncol 1996;14:691-6.
135. Weber WA, Avril N, Schwaiger M. Relevance of positron emission tomography (PET) in oncology. Strahlenther Onkol 1999;175:356-73.
136. Dhull VS, Sharma P, Mukherjee A, Jana M, Bal C, Kumar R. 18F-FDG PET-CT for evaluation of cardiac angiosarcoma: A case report and review of literature. Mol Imaging Radionucl Ther 2015;24:32-6.
137. Freudenberg LS, Rosenbaum SJ, Schulte-Herbruggen J, et al Diagnosis of a cardiac angiosarcoma by fluorine-18 fluorodeoxyglucose positron emission tomography. Eur Radiol 2002;12:S158-61.
138. Higashiyama S, Kawabe J, Hayashi T, et al Effectiveness of preoperative PET examination of huge angiosarcoma of the heart. Clin Nucl Med 2009;34:99-102.
139. Hori Y, Funabashi N, Miyauchi H, Nakagawa K, Shimura H, Miyazaki M, et al Angiosarcoma in the right atria demonstrated by fusion images of multislice computed tomography and positron emission tomography using F-18 Fluoro-Deoxyglucose. Int J Cardiol 2007;123:e15-7.
140. Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases. J Clin Pathol 2007;60:27-34.
141. Butany J, Leong SW, Carmichael K, Komeda M. A 30-year analysis of cardiac neoplasms at autopsy. Can J Cardiol 2005;21:675-80.
142. Nonaka A, Stugaard M, Ueda O, Hara H, Shimada T, Shiotani H. Fluorodeoxyglucose-positron emission tomography differentiating thrombus from tumor in the left ventricle. J Am Coll Cardiol 2009;53:894.

143. Tong AK, Mann KP, Schuster DM, Yan X. A rare presentation of myocardial plasmacytoma assessed by FDG PET/CT. Clin Nucl Med 2014;39:643-5.
144. Rahbar K, Seifarth H, Schafers M, et al Differentiation of malignant and benign cardiac tumors using 18F-FDG PET/CT. J Nucl Med 2012;53:856-63.
145. Carrio I. Cardiac neurotransmission imaging. J Nucl Med 2001;42:1062-76.
146. Olmos RAV, ten Bokkel Huinink WW, ten Hoeve RF, et al Assessment of anthracycline-related myocardial adrenergic derangement by [123I]metaiodobenzylguanidine scintigraphy. Eur J Cancer 1995;31A:26-31.
147. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (*m*IBG) parameters in patients with heart failure: A systematic review. Eur Heart J 2008;29:1147-59.
148. Carrio I, Estorch M, Berna L, Lopez-Pousa J, Tabernero J, Torres G. Indium-111-antimyosin and iodine-123-*m*IBG studies in early assessment of doxorubicin cardiotoxicity. J Nucl Med 1995;36:2044-9.
149. Carrio I, Lopez-Pousa A, Estorch M, Duncker D, Berna L, Torres G, et al Detection of doxorubicin cardiotoxicity in patients with sarcomas by indium-111-antimyosin monoclonal antibody studies. J Nucl Med 1993;34:1503-7.
150. Bennink RJ, van den Hoff MJ, van Hemert FJ, et al Annexin V imaging of acute doxorubicin cardiotoxicity (apoptosis) in rats. J Nucl Med 2004;45:842-8.
151. Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007;49:330-52.
152. Gabrielson KL, Mok GS, Nimmagadda S, et al Detection of dose response in chronic doxorubicin-mediated cell death with cardiac technetium 99 m annexin V single-photon emission computed tomography. Mol Imaging 2008;7:132-8.
153. Spallarossa P, Garibaldi S, Altieri P, Fabbi P, Manca V, Nasti S, et al Carvedilol prevents doxorubicin-induced free radical release and apoptosis in cardiomyocytes in vitro. J Mol Cell Cardiol 2004;37:837-46.
154. Narula J, Acio ER, Narula N, et al Annexin-V imaging for noninvasive detection of cardiac allograft rejection. Nat Med 2001;7:1347-52.
155. Su H, Gorodny N, Gomez LF, et al Noninvasive molecular imaging of apoptosis in a mouse model of anthracycline-induced cardiotoxicity. Circ Cardiovasc Imaging 2015;8:e001952.
156. Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, Sakurai M. Plasma levels of natriuretic peptides in relation to doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. Med Pediatr Oncol 2001;37:4-9.
157. Cardinale D, Sandri MT, Martinoni A, et al Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 2002;13:710-5.
158. Cardinale D, Sandri MT, Martinoni A, et al Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2000;36:517-22.
159. Carrio I, Estorch M, Berna L, Germá JR, Alonso C, Ojeda B, et al Assessment of anthracycline-induced myocardial damage by quantitative indium 111 myosin-specific monoclonal antibody studies. Eur J Nucl Med 1991;18:806-12.
160. Hiroe M, Ohta Y, Fujita N, Nagata M, Toyozaki T, Kusakabe K, et al Myocardial uptake of 111In monoclonal antimyosin Fab in detecting doxorubicin cardiotoxicity in rats. Morphological and hemodynamic findings. Circulation 1992;86:1965-72.
161. Estorch M, Carrio I, Berna L, Martínez-Duncker C, Alonso C, Germá JR, et al Indium-111-antimyosin scintigraphy after doxorubicin therapy in patients with advanced breast cancer. J Nucl Med 1990;31:1965-9.
162. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010;55:2212-21.
163. Olmos RAV, ten Bokkel Huinink WW, Greve JC, Hoefnagel CA. I-123 *m*IBG and serial radionuclide angiocardiography in doxorubicin-related cardiotoxicity. Clin Nucl Med 1992;17:163-7.
164. Takano H, Ozawa H, Kobayashi I, Hamaoka S, Nakajima A, Nakamura T, et al Atrophic nerve fibers in regions of reduced *m*IBG uptake in doxorubicin cardiomyopathy. J Nucl Med 1995;36:2060-1.
165. Wakasugi S, Fischman AJ, Babich JW. Metaiodobenzylguanidine: Evaluation of its potential as a tracer for monitoring doxorubicin cardiomyopathy. J Nucl Med 1993;34:1283-6.
166. Takeishi Y, Sukekawa H, Sakurai T, Saito H, Nishimura S, Shibu T, et al Noninvasive identification of anthracycline cardiotoxicity: Comparison of ^{123}I-*m*IBG and ^{123}I-BMIPP imaging. Ann Nucl Med 1994;8:177-82.
167. Nousiainen T, Vanninen E, Jantunen E, Remes J, Kuikka J, Hartikainen J. Anthracycline-induced cardiomyopathy: Long-term effects on myocardial cell integrity, cardiac adrenergic innervation and fatty acid uptake. Clin Physiol 2001;21:123-8.
168. Behr TM, Behe M, Wormann B. Trastuzumab and breast cancer. N Engl J Med 2001;345:995-6.
169. Perik PJ, Lub-De Hooge MN, Gietema JA, van der Graaf WT, de Korte MA, Jonkman S, et al Indium-111-labeled trastuzumab scintigraphy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2006;24:2276-82.
170. de Korte MA, de Vries EG, Lub-de Hooge MN, Jager PL, Gietema JA, van der Graaf WTA, et al 111 Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: A clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. Eur J Cancer 2007;43:2046-51.
171. Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013;6:195-201.
172. Merlini G, Narula J, Arbustini E. Molecular imaging of misfolded protein pathology for early clues to involvement of the heart. Eur J Nucl Med Mol Imaging 2014;41:1649-51.
173. Antoni G, Lubberink M, Estrada S, Axelsson J, Carlson K, Lindsjö L, et al In vivo visualization of amyloid deposits in the heart with 11C-PIB and PET. J Nucl Med 2013;54:213-20.
174. Dorbala S, Vangala D, Semer J, Strader C, Bruyere Jr JR, Di Carli MF, et al Imaging cardiac amyloidosis: A pilot study using (1)(8)F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging 2014;41:1652-62.