

## Cancer Therapy–Related Cardiac Dysfunction and Heart Failure

### Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging

Michelle W. Bloom, MD; Carine E. Hamo, MD; Daniela Cardinale, MD, PhD;  
Bonnie Ky, MD, MSCE; Anju Nohria, MD; Lea Baer, MD; Hal Skopicki, MD, PhD;  
Daniel J. Lenihan, MD; Mihai Gheorghiade, MD Alexander R. Lyon, MD, PhD;  
Javed Butler, MD MPH MBA

**Abstract**—Advances in cancer therapy have resulted in significant improvement in long-term survival for many types of cancer but have also resulted in untoward side effects associated with treatment. One such complication that has become increasingly recognized is the development of cardiomyopathy and heart failure. Whether a previously healthy person from a cardiovascular perspective develops cancer therapy–related cardiac dysfunction or a high-risk cardiovascular patient requires cancer therapy, the team of oncologists and cardiologists must be better equipped with an evidence-based approach to care for these patients across the spectrum. Although the toxicities associated with various cancer therapies are well recognized, limitations to our understanding of the appropriate course of action remain. In this first of a 2-part review, we discuss the epidemiologic, pathophysiologic, risk factors, and imaging aspects of cancer therapy–related cardiac dysfunction and heart failure. In a subsequent second part, we discuss the prevention and treatment aspects, concluding with a section on evidence gap and future directions. We focus on adult patients in all stages of cancer therapy from pretreatment surveillance, to ongoing therapy, and long-term follow-up. (*Circ Heart Fail.* 2016;9:e002661. DOI: 10.1161/CIRCHEARTFAILURE.115.002661.)

**Key Words:** anthracyclines ■ cardiomyopathies ■ cardiotoxicity ■ chemotherapy ■ heart failure  
■ trastuzumab ■ ventricular dysfunction, left

Early detection and treatment has transformed cancer from a uniformly fatal disease to one that in many cases is a chronic condition. Improved survival, however, is often accompanied by treatment-related complications, including adverse effects of cancer therapies on the heart. In the long term, the risk of death from cardiovascular causes exceeds that of tumor recurrence for many forms of cancer.<sup>1,2</sup> Patnaik et al<sup>3</sup> found that cardiovascular disease (CVD) was the leading cause of death among older female breast cancer survivors without an initial diagnosis of CVD. Risk of toxicity was increased in patients with advanced age, multiple comorbid conditions, and in those requiring prolonged or intensive treatment. Cancer therapies including cytotoxic chemotherapy, molecular targeted therapies, and mediastinal irradiation have been linked to myocyte damage, left ventricular dysfunction (LVD), heart failure (HF), thrombogenesis, pericardial

pathology, hypertension, ischemia, conduction and rhythm disturbances, and vasospasm.<sup>4,5</sup> HF as a result of cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy.<sup>6</sup> In part 1 of this 2-part review, we describe the definitions, pathophysiology, risk factors, and imaging aspects relevant to cancer therapy–related cardiac dysfunction.

### Definitions

Several definitions of cancer therapy–related cardiac dysfunction have been proposed, making development of uniformly accepted recommendations for diagnosis, surveillance, and treatment challenging. The National Cancer Institute broadly defines cardiotoxicity as toxicity that affects the heart<sup>7</sup> and proposes the Common Terminology Criteria for Adverse Events that defines LVD and HF based on severity into grades

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From the Cardiology Division (M.W.B., C.E.H., H.S., J.B.) and Oncology Division (L.B.), Stony Brook University, NY; Oncology Division, European Institute of Oncology, Milan, Italy (D.C.); Cardiology Division, University of Pennsylvania, Philadelphia (B.K.); Cardiology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (A.N.); Cardiology Division, Vanderbilt University, Nashville, TN (D.J.L.); Cardiovascular Division, Center for Cardiovascular Innovation, Northwestern Feinberg School of Medicine, Chicago, IL (M.G.); and Cardiovascular Division, NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital and Imperial College London, London, United Kingdom (A.R.L.).

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Correspondence to Javed Butler, MD, MPH, MBA, Cardiology Division, Stony Brook University, Health Sciences Center, T-16, Room 080 SUNY at Stony Brook, NY 11794. E-mail: javed.butler@stonybrookmedicine.edu

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1 to 5. Grade 1 is defined as asymptomatic elevations in biomarkers or abnormalities on imaging. Grades 2 and 3 consist of symptoms with mild and moderate exertions. Grade 4 includes severe, life threatening symptoms requiring hemodynamic support, and grade 5 involves death.<sup>8</sup> The Food and Drug Administration defines anthracycline cardiotoxicity as >20% decrease in left ventricular ejection fraction (LVEF) when baseline LVEF is normal, or >10% decrease when baseline LVEF is not normal.<sup>9</sup>

The Cardiac Review and Evaluation Committee supervising trastuzumab trials defines cardiotoxicity as a decrease in LVEF that is either global or more severe in the septum and decline in LVEF of at least 5% to <55% with accompanying signs or symptoms of HF, or a decline of at least 10% to <55% without HF signs or symptoms.<sup>10</sup> Several trials have specified toxicity with different parameters making estimation of the prevalence of cardiac toxicity difficult. In the Herceptin Adjuvant (HERA) trial, definitions of asymptomatic LVEF reductions were different and included decrease by  $\geq 10\%$  from baseline to an LVEF <50%, and HF as above accompanied by symptoms.<sup>11</sup> The Breast Cancer International Research Group (BCIRG) used >10% reduction from baseline LVEF assessment to define asymptomatic LVD.<sup>12</sup> An expert consensus published by the American Society of Echocardiography and European Association of Cardiovascular Imaging, comprised several well-respected cardiologists and oncologists within the field of cardio-oncology, defines cancer therapeutics–related cardiac dysfunction as a decrease in the LVEF of >10%, to a value <53% confirmed by repeat imaging. Further characterization is based on the presence or absence of symptoms.<sup>13</sup> These definitions include arbitrary cutoffs without taking into account baseline risk and are not guided by clinical outcomes. In addition, LVEF-based definition has limitations including variable reproducibility, and the fact that many patients with HF have preserved LVEF. A more comprehensive definition for diagnosis of cancer therapy–related cardiotoxicity should take into account other imaging and biomarker based abnormalities as well.

### Classification

Several attempts have been made to classify cardiotoxicity. Ewer and Lippman<sup>14</sup> proposed cardiotoxicity based on the type and extent of structural abnormalities and degree of reversibility. Type I is irreversible and dose related with myocyte injury, whereas type II includes reversibility with cessation of treatment, lack of dose-relationship, and absence of ultrastructural abnormalities. Although intuitive, with anthracyclines as an example of type I and trastuzumab of type II cardiotoxicity, subsequent studies have raised concerns. This classification does not reflect the reality that anthracyclines and trastuzumab are rarely administered as sole agents and are usually shortly preceded or followed with drugs belonging to other classes. Hence, it is likely that the final cardiotoxic effect results from a synergic/combined action. Although anthracyclines and trastuzumab are different in their mechanisms of cardiotoxicity, early recognition and initiation of neurohormonal antagonists may reverse LVD in both cases.<sup>15,16</sup> Trastuzumab cardiotoxicity may be associated with troponin elevation and is not always reversible.<sup>15</sup> Therefore, it is more appropriate to

understand the biological mechanisms of cardiotoxicity and the clinical features at different stages of presentation.

## Pathophysiology and Epidemiology

### Anthracyclines

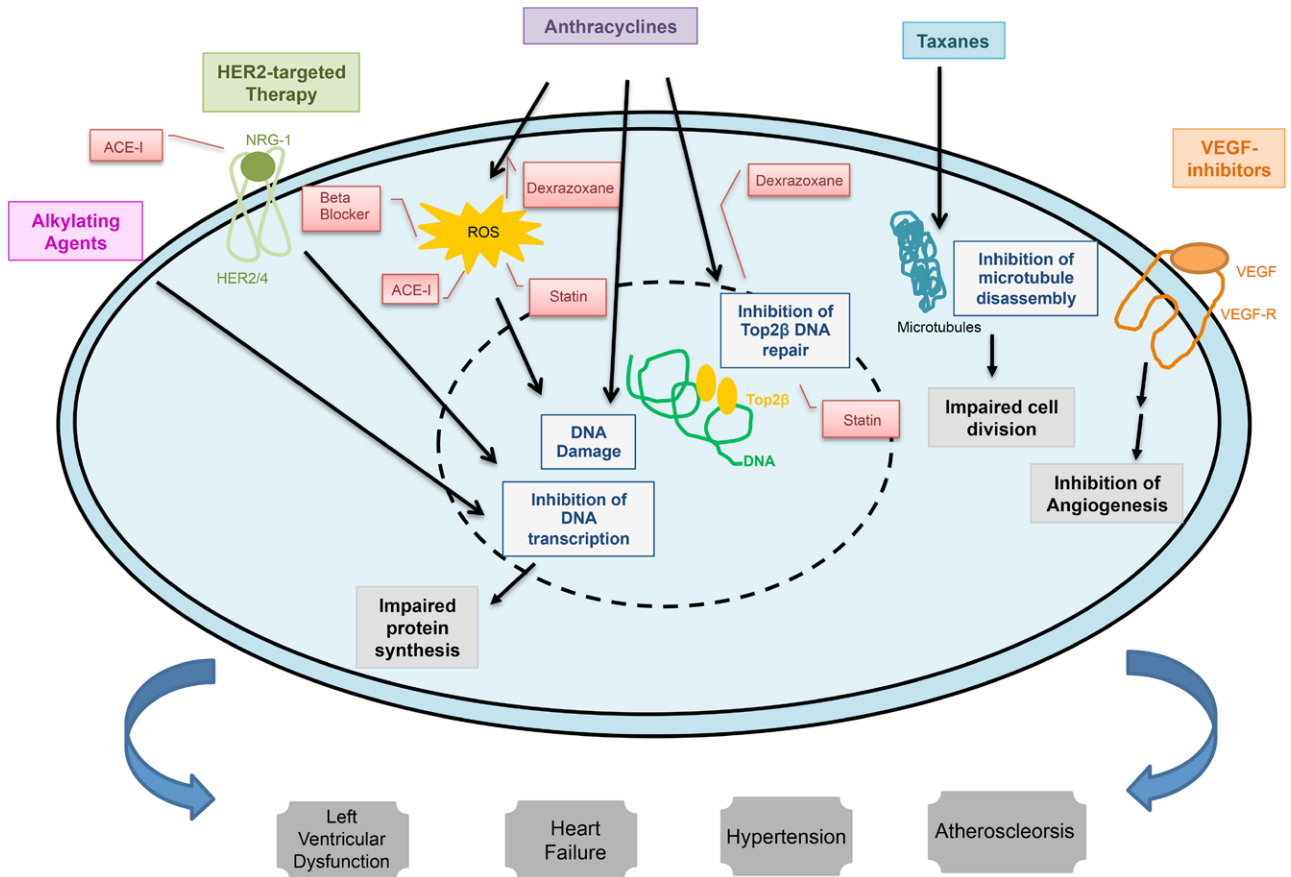
Anthracyclines (eg, doxorubicin, daunorubicin, epirubicin, and idarubicin) are a class of highly effective chemotherapy agents used for the treatment of many solid and hematologic cancers.<sup>17</sup> In breast cancer, doxorubicin and epirubicin are used in both the neoadjuvant (before definitive surgery) and adjuvant (following definitive surgery) setting, as well as in metastatic patients. The mechanisms of action of anthracyclines include intercalation into nuclear DNA to impair protein synthesis, production of reactive oxygen species, and inhibition of topoisomerase II to inhibit DNA repair. Topoisomerase, an enzyme involved in DNA transcription and replication, is a known target of anthracyclines.<sup>18</sup> There are 2 isozymes of topoisomerase, Top 2- $\alpha$ , expressed in rapidly dividing cells, and Top 2- $\beta$ , expressed in quiescent cells such as cardiac myocytes.<sup>19</sup> The cardiac toxicity of anthracyclines is thought to be mediated through the binding of these agents to DNA and Top 2- $\beta$  in cardiac myocytes, resulting in a complex formation that ultimately culminates in cell death (Figure).<sup>20</sup> Older studies suggest an association between cumulative dosing and cardiotoxicity, with diastolic dysfunction reported at doses of 200 mg/m<sup>2</sup> of doxorubicin and systolic dysfunction at 400 to 600 mg/m<sup>2</sup>.<sup>21</sup> This has been challenged in recent literature suggests that LVD can occur at any dose as evidenced in 18.9% of patients receiving a doxorubicin dose of 240 mg/m<sup>2</sup> in combination with cyclophosphamide.<sup>22</sup> Factors increasing the risk of anthracycline toxicity include the presence of other CVD risk factors, associated therapies like mediastinal irradiation, and concomitant therapy with agents such as cyclophosphamide, paclitaxel, and trastuzumab.<sup>23</sup> Anthracycline toxicity may be acute, sub-acute, or chronic. Acute toxicity is uncommon ( $\approx 1\%$ ) and generally reversible, whereas early-onset chronic progressive toxicity (1.6–2.1%) developing during treatment and late-onset chronic progressive types (1.6–5%) are more likely to be irreversible.<sup>24</sup> This classification has been challenged as possible evolution of one phenomenon being clinically identified at various stages.<sup>16</sup>

### Alkylating Agents

Alkylating agents (eg, cyclophosphamide, ifosfamide, and melphalan) inhibit DNA transcription, thereby affecting protein synthesis.<sup>25</sup> Agents such as cyclophosphamide have been associated with development of LVD in 7% to 28% of patients and may be dose related ( $\geq 150$  mg/kg and 1.5 g/m<sup>2</sup> per day), occurring shortly after initial administration.<sup>26</sup> LVD has also been observed with ifosfamide at doses that exceed 12.5 g/m<sup>2</sup>.<sup>27</sup>

### Microtubular Polymerization Inhibitors

Taxanes (eg, paclitaxel and docetaxel) bind to and inhibit disassembly of microtubules, interrupting cell division.<sup>28</sup> Taxanes interfere with the metabolism and excretion of anthracyclines and may potentiate LVD risk, particularly with high-dose anthracycline use. HF incidence with these agents is relatively low, with a reported 1.6% versus 0.7% incidence in patients



**Figure.** Pathophysiology of cardiac toxicity from various chemotherapeutics and role of preventative therapies. Alkylating agents inhibit DNA transcription, impairing protein synthesis. Human epidermal receptor 2 (HER2/ErbB)-targeted therapy inhibits the activation of HER2 resulting in the inhibition of a signal transduction pathway that ultimately impairs DNA transcription. Anthracyclines intercalate into DNA, impairing protein synthesis, generate reactive oxygen species (ROS) resulting in DNA damage as well as inhibit topoisomerase II-beta (Top2B), impairing DNA repair. Taxanes impair microtubule function needed for cell division. Vascular endothelial growth factor (VEGF)-inhibitors blocks the activation of kinases resulting in the downstream inhibition of angiogenesis. Dexrazoxane, an iron-chelating agent, may decrease the formation of ROS through prevention of anthracycline–iron complex formation as well as inhibit the formation of Top2B-DNA cleavage complexes, which impair DNA repair.  $\beta$ -Blockers, statins, and angiotensin converting enzyme inhibitors (ACE-I), through antioxidant properties, may inhibit the production of ROS. ACE-Is may decrease angiotensin-induced blockade of the neuregulin-1 (NRG-1)/ErbB pathway. Statins have also been shown to inhibit Top2B-mediated DNA damage. The various cellular effects of these chemotherapy agents may ultimately result in cardiovascular manifestations in the form of left ventricular dysfunction, heart failure, hypertension, and atherosclerosis.

with anthracycline-containing versus anthracycline-sparing regimens.<sup>12</sup> Slower infusion or increasing intervals between paclitaxel and doxorubicin may attenuate toxicity.<sup>29</sup> Newer adjuvant protocols and formulations might decrease the likelihood of toxicity.<sup>30</sup>

#### HER2-Targeted Cancer Therapies

Overexpression of human epidermal growth factor receptor 2 (HER2/ERbB2) in breast cancer is a poor prognostic indicator, as these tumors tend to be more aggressive and associated with higher reoccurrence rates.<sup>31</sup> Trastuzumab, a humanized anti-HER2 monoclonal antibody targeting the extracellular domain of this oncoprotein, has been shown in both the metastatic<sup>32</sup> and the adjuvant<sup>33</sup> setting to dramatically change the survival in HER2 positive breast cancer. HER2/ERbB2 is expressed on myocytes and plays a protective role against myocardial stress.<sup>21</sup> The binding of cancer drugs to HER2 receptor may disrupt this cardioprotective pathway and result in cardiotoxicity. Trials with trastuzumab observed increased

incidence of LVD and its use with anthracyclines potentiate cardiotoxicity risk.<sup>10</sup> Previous trials in the adjuvant setting reported HF in 1.7% to 4.1% and LVD in 7.1% to 18.6% of patients receiving trastuzumab, although in practice, incidence may be higher.<sup>34</sup> Lapatanib, an oral tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor, is approved in the metastatic setting and pertuzumab, a monoclonal antibody that blocks the dimerization of HER2 with other HER2 receptors, is approved in both the neoadjuvant and metastatic setting in combination with trastuzumab and docetaxel.<sup>35</sup> Combination treatment using 2 anti-HER2 agents improves rates of pathologic complete responses in the neoadjuvant setting and survival in the metastatic settings, with comparable cardiotoxicity.<sup>36</sup> Trastuzumab emtansine is a HER2-targeted antibody drug conjugate combining trastuzumab with a cytotoxic agent DM1, reported a 2.7% incidence of LVD.<sup>37</sup> As the available treatments expand, new questions arise with respect to the development of cardiotoxicity.

### VEGF Inhibitors (Monoclonal Antibodies and Small Molecules, Eg, Tyrosine Kinase Inhibitors)

Vascular endothelial growth factor (VEGF) inhibitors exert their action by inhibiting VEGF-mediated angiogenesis through various mechanisms.<sup>38</sup> Small molecule tyrosine kinase inhibitors (sunitinib and sorafenib) are nonselective inhibitors of VEGF receptors, inhibiting up to 50 different kinases in addition to their intended target, thus, producing unwanted effects.<sup>39</sup> These agents have been linked to hypertension, ischemia, LVD, and HF.<sup>40</sup> Initial reports of sunitinib showed a 10% incidence of LVD but with recovery upon completion of therapy,<sup>41</sup> and a 1.5% to 4.1% incident of HF.<sup>42</sup> The real world experience is in fact worse, with  $\approx$ 14% of patients experiencing a >10% decline in ejection fraction.<sup>43</sup> Bevacizumab is a monoclonal antibody that targets VEGF and is associated with a 5-fold increase in HF risk.<sup>44</sup>

### Radiotherapy

Radiation-induced heart disease is well recognized and may manifest years after exposure. Radiotherapy is associated with macrovascular, microvascular, and endothelial injury; valvular dysfunction; atherosclerosis; fibrosis; and pericardial disease. LVD and HF can occur as acute radiation myocarditis<sup>45</sup> but more commonly develops as a long-term consequence of fibrosis leading to ventricular dysfunction or restrictive cardiomyopathy.<sup>45</sup> The presence of other CVD risk factors, concomitant anthracycline use, and anterior or left chest irradiation all increase risk. Mediastinal irradiation increases CVD and HF risk even 40 years after initial exposure.<sup>46</sup> In a recent study of patients receiving radiation, there was a linear increase in coronary events with radiation dose. Events occurred 5 years after initial exposure and continued through the third decade following exposure.<sup>47</sup>

### Risk Factors

Identification of patients at risk is difficult though important. Patient-related risk factors include those with preexisting cardiac risk factors such as hypertension, diabetes mellitus, smoking, previous LVD or HF, coronary disease, increasing age, female gender, and postmenopausal status.<sup>48</sup> Genetic polymorphisms may predispose to cardiotoxicity at lower anthracycline dose,<sup>49</sup> suggesting that genetic variation might modulate the risk of cardiovascular toxicity after cancer treatment. In

an unselected group of cancer patients, even before chemotherapy, the presences of N-terminal pro-brain natriuretic peptide, mid-regional pro-atrial natriuretic peptide, mid-regional pro-adrenomedullin, high-sensitivity troponin T, and copeptin were associated with all-cause mortality.<sup>50</sup> Therapy-related risk factors include use of combination cancer therapy, particularly if administered simultaneously, or as bolus, addition of mediastinal irradiation, and higher doses. Certain agents, such as anthracycline, trastuzumab, and cyclophosphamide, carry higher risk while others, such as bevacizumab, etoposide, and lapatinib, carry lower risk.<sup>51</sup> Prior treatment with anthracyclines increases the risk if a patient presents with recurrent disease or a new malignancy requiring further anthracycline therapy.<sup>52</sup>

### Risk Prediction

Several risk scores have been published, although there is no consensus model. Herrmann et al<sup>53</sup> proposed a risk model including both cancer therapy and patient factors. Romond et al<sup>54</sup> used a model including age and baseline LVEF to estimate HF risk, also reporting LVEF recovery. Dranitsaris et al<sup>55</sup> developed and tested a cycle-based risk-prediction tool in metastatic breast cancer patients receiving doxorubicin or its pegylated liposomal form. This score included age, weight, anthracycline exposure, and performance status, adding points for each additional chemotherapy cycle. Ezaz et al<sup>56</sup> developed a 7-point risk score for 3-year HF risk after trastuzumab therapy in older females. Risk factors such as coronary disease, atrial fibrillation, hypertension, diabetes mellitus, and renal failure all portended higher risk. HF incidence was higher than previously reported, with the oldest patients approaching 45% incidence (Table 1).

### Biomarkers

A biomarker approach for early identification, risk stratification, and monitoring of chemotherapy-related cardiotoxicity holds promise, although challenges exist with respect to timing of measurement, optimal assays, and whether this strategy is best used alone or in conjunction with imaging.

### Biomarker of Injury (Eg, Troponin)

Troponin levels can be monitored before and after each therapy cycle and serve as a predictor of future cardiac dysfunction. A

**Table 1. Overview of Validated Risk-Prediction Models**

Reference	Population	Risk Factors	n	Definition of Cardiotoxicity	Discrimination	Calibration	Validation
Ezaz et al <sup>56</sup>	Women with early-stage breast cancer who underwent surgery and adjuvant trastuzumab therapy	Adjuvant therapy type, Age, CAD, AF, DM, HTN, renal failure	1664	ICD-9CM code for HF or CM that seems in at least 1 inpatient claim or 2 outpatient claims at least 30 d apart	NR	NR	NR
Romond et al <sup>54</sup>	Women with HER2+ breast cancer	Age, baseline LVEF	1830	LVEF drop >10% from baseline to <55% or drop >5% to level below lower limit of normal	0.72 (0.70 after bootstrapping)	NR	Bootstrapping
Dranitsaris et al <sup>55</sup>	Women with metastatic breast cancer receiving anthracycline-based chemotherapy	Age, weight, baseline anthracycline exposure, performance status, no. of cycles	509	(1) LVEF drop 20% but still normal range, (2) LVEF drop 10% if abnormal, (3) signs/symptoms HF	0.84	NR	Bootstrapping

AF indicates atrial fibrillation; CAD, coronary artery disease; CM, cardiomyopathy; DM, diabetes mellitus, HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction NR, not reported.

high negative predictive value with absence of troponin elevation has been reported in patients receiving high-dose anthracyclines.<sup>57</sup> Early increase in troponin I after anthracycline use predicted diastolic dysfunction in 34% of patients.<sup>58</sup> Increased troponin I in patients receiving trastuzumab had a decreased likelihood of LVEF recovery and a higher incidence of cardiac events.<sup>15</sup> Troponin I levels at completion of anthracycline treatment were predictive of subsequent reduction in LVEF and cardiac events.<sup>59</sup> Smaller studies have looked at troponin use for identification of at-risk patients with newer agents, such as anti-VEGF monoclonal antibodies, anti-VEGFR tyrosine kinase inhibitors, and a kinesin inhibitor.<sup>60</sup>

### **Biomarker of Load (Eg, Natriuretic Peptide)**

Natriuretic peptides have been studied in chemotherapy-treated patients with variable results. In one study, brain natriuretic peptide was predictive of LVD at 3-, 6-, and 12-month follow-up.<sup>61</sup> In patients undergoing doxorubicin therapy, an increase in natriuretic peptides during the first 90 days was predictive of LVD at 4 years.<sup>62</sup> Several studies, however, have failed to show an association between these biomarkers and cardiac dysfunction,<sup>59,63</sup> and they may be more useful for their negative predictive value as part of a surveillance strategy. Further studies are needed to understand the role of natriuretic peptide use in this population and to understand the differences in the various types of natriuretic peptides.

### **Other Biomarkers**

High-sensitivity C-reactive protein predicts cardiotoxicity in patients treated with trastuzumab.<sup>64</sup> Other studies of patients receiving anthracycline-containing regimen followed by taxanes and trastuzumab showed no association between C-reactive protein, galectin-3, ST-2 or growth differentiation factor 15, and cardiotoxicity but 1 study reported that changes in myeloperoxidase levels were associated with cardiotoxicity.<sup>59,65</sup> In a recent study of multiple biomarkers, myeloperoxidase levels rose early, persisted throughout the course of therapy, and were associated with cardiotoxicity<sup>66</sup> (Table 2).

## **Imaging**

### **Echocardiography**

#### ***Two-Dimensional Echocardiography***

Because of its widespread availability and safety, 2-dimensional echocardiography (2DE) is increasingly used in monitoring patients with cancer; 2DE allows for characterization of systolic and diastolic function, pulmonary pressures, valvular function, right ventricular (RV) function, and the pericardium. Assessment of LVEF is based on assumptions of cardiac geometry, depends on image quality, cannot detect small regional alterations in myocardial function, and may vary based on loading conditions.<sup>74</sup> The American Society of Echocardiography suggests the addition of contrast to 2DE for better definition of endocardial borders in patients with breast implants or mastectomy.<sup>75</sup> One of the drawbacks of 2DE is in its inability to detect small (<10%) changes in LVEF, a limitation in patients with cancer in whom subtle differences in cardiac function may have important implications on treatment dose adjustment or cessation.<sup>13,76</sup>

#### ***Three-Dimensional Echocardiography***

Three-dimensional echocardiography increases the accuracy of detecting more subtle changes in LVEF, with a higher reproducibility.<sup>77</sup> Thavendiranathan et al<sup>78</sup> demonstrated that non-contrast three-dimensional echocardiography had the highest inter- and intraobserver reproducibility for LVEF and LV volume detection in sequential 1 year follow-up of patients receiving cancer therapy. Unlike with 2DE, the study of use of contrast in three-dimensional echocardiography has not been firmly established.<sup>78,79</sup>

#### ***Diastolic Function***

Diastolic dysfunction often precedes systolic dysfunction in patients receiving chemotherapy.<sup>80</sup> Although findings have been inconsistent, changes in diastolic parameters, such as isovolumetric relaxation and deceleration time, have been shown in patients as early as 3 months following doxorubicin and were predictive of systolic dysfunction at 6 months, with a sensitivity similar to strain imaging.<sup>81</sup> Early reductions in early diastolic mitral inflow velocity and early diastolic mitral inflow velocity/late diastolic mitral inflow velocity ratio, or increase in early diastolic mitral inflow velocity/early diastolic mitral annular velocity, predict future decrement in systolic function years after chemotherapy.<sup>82</sup> Still, the use of diastolic parameters to predict subsequent cancer-related cardiotoxicity remains unclear, given the variability based on loading conditions in patients with cancer.<sup>79</sup>

#### ***Strain and Speckle Tracking***

More recent techniques, including strain and speckle tracking may allow for earlier detection of more subtle changes in myocardial function. Strain imaging assesses myocardial function based on measurements of myocardial velocities in adjacent areas as they relate to distance between those areas during the cardiac cycle. Speckle tracking has largely replaced tissue Doppler imaging for analysis of myocardial deformation and holds promise in early prediction of chemotherapy cardiotoxicity. Global longitudinal strain reduction precedes LVD in patients who later develop HF.<sup>59</sup> Strain abnormalities can be seen early despite preserved LVEF. Persistent abnormalities were found in patients receiving high-dose anthracyclines.<sup>83</sup> In patients receiving trastuzumab alone or with anthracyclines, a change in global longitudinal strain of >11% was the strongest predictor of cardiotoxicity.<sup>84</sup> This technique is limited by availability, image quality, variability of quantification between vendors, and lack of universal definitions. In addition to measuring linear deformation, speckle tracking can assess torsion, a newer parameter requiring further study in patients receiving anthracyclines.<sup>85</sup>

#### ***Right Ventricular Function***

Subclinical changes in RV systolic and diastolic parameters have been described early after anthracycline therapy and correlated with elevations in N-terminal pro-brain natriuretic peptide levels.<sup>86</sup> RV involvement after chemotherapy has been noted in earlier studies involving RV myocardial biopsies, but frequency is not known.<sup>87</sup> In patients receiving isolated left ventricular mechanical support in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), markers of RV dysfunction were more common and more

**Table 2. Role of Cardiac Biomarkers in Chemotherapy-Induced Cardiotoxicity**

Reference	Patient Population	N	Chemotherapy	Biomarker	Value Cutoff	Timing of Measurement	Results
Ky et al <sup>65</sup>	HER2+ breast cancer	78	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab	Tnl, CRP NT-proBNP GDF-15, MPO PIGF, sFit-1 gal-3		Biomarkers measured at baseline, 3, and 6 mo LVEF measured at baseline, 3, 6, 9, 12, and 15 mo	Tnl and MPO rise at 3 mo was associated with subsequent cardiotoxicity
Skovgaard et al <sup>67</sup>	Breast cancer, hematologic malignancies, uterine/ovarian cancer	333	Anthracycline	BNP	100 pg/mL	No standard interval of measurements	BNP and LVEF independently predicted CHF Only BNP was associated with overall mortality
Sawaya et al <sup>69</sup>	HER2+ breast cancer	81	Anthracycline, paclitaxel, trastuzumab	Troponin NT-proBNP ST-2	≥30 pg/mL >125 pg/mL >35 pg/mL	Baseline, 3,6,9,12, and 15 mo	Elevated Tnl at 3 mo was predictive of subsequent cardiotoxicity No change in NT-proBNP and ST-2
Lipshultz et al <sup>62</sup>	Children with high-risk ALL	156	Doxorubicin	TnT NT-proBNP hs-CRP	Any detectable amount ≥150 pm/mL, age<1; ≥100 pm/mL, age>1 ≥1.9 mg/L	Biomarkers measured at baseline, days 1–7 of doxorubicin induction, 7 days after a doxorubicin dose, and at end of doxorubicin therapy LVEF measured at baseline, after therapy, and every 2 y thereafter	Increase in TnT and NT-proBNP during first 90 days predicted cardiac dysfunction at 4 y
Onitilo et al <sup>63</sup>	HER2+ breast cancer	54	Trastuzumab adjuvant	BNP hs-CRP Tnl	≥200 pg/mL ≥3 mg/L ≥0.01 ng/mL	Biomarkers measured at baseline, every 3 wk up to 1 y LVEF measured every 3–4 mo	Only hs-CRP was associated with increased risk for clinically significant decline in LVEF
Morris et al <sup>68</sup>	HER2+ breast cancer	95	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, lapatinib	Tnl CRP	>0.04 n g/mL (DF/HCC); >0.06 ng/mL (MSKCC) ≥0.8 mg/dL (MSKCC) ≥0.3 mg/dL (DF/HCC)	Biomarker measured every 2 wk during chemo, 6, 9, and 18 mo LVEF measured at months 0,6,9, and 18	Tnl rise (peaking at ≈14 wk) preceded maximal decline in LVEF but no relation to max LVEF decline CRP did not correlate with LVEF decline
Romano et al <sup>61</sup>	Breast cancer	92	Anthracycline, taxane, 5-fluorouracil, cyclophosphamide	NT-proBNP Tnl	>153 pg/mL, age ≤50; 222 pg/mL, age >50 5 ng/mL, age ≤50; 0.08 ng/mL, age >50	Biomarkers measured at baseline, before, and 24 h after each drug administration LVEF measured at baseline, every 2 cycles, end of chemo, 3, 6, and 12 mo follow-up	NT-proBNP was predictive of LV impairment at 3,6, and 12 mo follow-up
Cardinale et al <sup>15</sup>	Breast cancer	251	Trastuzumab, anthracycline, cyclophosphamide, paclitaxel	Tnl	>0.08 ng/mL	Biomarker measured before and after each cycle LVEF measured at baseline, every 3 mo during therapy and every 6 mo after	Tnl was an independent predictor of cardiotoxicity and LVEF recovery
Mavinkurve-Groothuis et al <sup>69</sup>	Various pediatric cancers	122	Anthracycline-containing regimen	NT-proBNP TnT	>10 pmol/L, male; >18 pmol/L, female >0.01 ng/mL	Measured once	Elevated NT-proBNP was associated with cumulative anthracycline dose
Dodos et al <sup>70</sup>	Solid or hematological malignancy	100	Anthracycline-containing regimen	TnT NT-proBNP	>0.010 ng/mL <153 pg/mL, female, age < 50; <334 pg/mL, female, age, 50–70; <88 pg/mL, male, age < 50; <227 pg/mL, male, age, 50–70	Measured 24–72 h, 1, 6, and 12 mo after last course of chemo	TnT and proBNP did not predict cardiac dysfunction
Jingu et al <sup>71</sup>	Esophageal cancer	197	Radiotherapy	BNP		Measured before, <1 mo, 1–2, 3–8, 9–24, >24 h after radiotherapy	BNP higher in patients who had high FDG accumulation
Sandri et al <sup>72</sup>	Various	179	Various regimens including epirubicin, cyclophosphamide, taxotere, carboplatin	Tnl	>0.08 ng/mL	Biomarkers measured at baseline, at end of infusion, 12, 24, 36, 72 h after each cycle LVEF measured at baseline, 1, 2, 3, 4, 7, and 12 mo after end of treatment	Increase in Tnl as early as first cycle predicted subsequent LVEF decline
Cardinale et al <sup>73</sup>	Breast cancer, ovarian cancer, small-cell lung cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma	204	Various regimens including epirubicin, cyclophosphamide, taxotere, carboplatin, etoposide	Tnl CK CK-MB	>0.5 ng/mL >190 U/L >5 ng/mL	Before, immediately after, and then 12, 24, 36, and 72 h after every cycle of chemo	Tnl elevation predicted future LVEF decline

Studies ordered by date with sample size >50 patients. ALL indicates acute lymphoblastic leukemia; CHF, congestive heart failure; CK, creatinine kinase; CK-MB, creatinine kinase, MB fraction; CRP, C-reactive protein; DF/HCC, Dana Farber/Harvard Cancer Center; FDG, fludeoxyglucose; gal-3, galactin 3; GDF-15, growth differentiation factor 15; HER2+, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; MSKCC, Memorial Sloan-Kettering Cancer Center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIGF, placental growth factor; sFit-1, soluble fms-like tyrosine kinase receptor 1; ST-2, interleukin family member; Tnl, troponin I.

severe in chemotherapy-induced cardiotoxicity compared with ischemic or nonischemic cardiomyopathy. These included higher levels of transaminases, lower systolic pulmonary pressures, moderate tricuspid regurgitation, and higher ratios of central venous to pulmonary capillary wedge pressures. Echocardiographic assessment of the RV should involve careful attention to chamber size, tricuspid annular plane systolic excursion, estimation of pulmonary artery systolic pressure, and RV diastolic parameters.<sup>88</sup> Areas of future interest include usage of speckle tracking for more in depth understanding of chemotherapy-related RV involvement.

### Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is the gold standard for detection of ventricular volumes and function. CMR has a greater intra- and interobserver reproducibility than echocardiography and may identify a higher prevalence of cardiomyopathy compared with echocardiography in patients with cancer.<sup>89</sup> CMR affords the opportunity for noninvasive tissue characterization including myocardial edema, inflammation, and fibrosis, thus, playing an important role in identification of early and late cardiotoxicity in patients with cancer.<sup>90</sup> Early increases in pre- and postcontrast signal intensity may predict reductions in LVEF at 28 days and 6 months. Subepicardial delayed enhancement with gadolinium has been noted in the lateral wall of trastuzumab-treated patients who developed cardiomyopathy<sup>91</sup>; however, studies on delayed enhancement have demonstrated mixed results.<sup>90</sup> CMR may also have prognostic value in detection of late cardiotoxicity. LV mass index has been shown to be an independent predictor of major adverse cardiac events in cancer patients with cardiomyopathy following treatment with anthracyclines.<sup>92</sup> Larger patient cohorts require study to further define the role of CMR in the prediction of cardiotoxicity. As with use of CMR in the general cardiac population, higher cost, lack of universal availability, and patient-related factors, such as pacemakers and claustrophobia, limit its widespread use, though it plays an important role particularly in patients with technical limitations to echocardiography.

### Radionuclide Imaging

Multiple-gated acquisition used to be the mainstay for cardiac functional assessment in patients with cancer because of high reproducibility and availability<sup>93</sup>; however, these advantages are now limited because of changes in equipment and technique.<sup>79</sup> Other limitations include the inability to obtain other structural and functional information, which can be obtained by echocardiogram. Multiple-gated acquisition relies on ejection fraction being the most appropriate parameter to measure, at a higher cost compared with echocardiography. The largest disadvantage of multiple-gated acquisition is radiation exposure, which must be weighed against necessity on an individual basis when other options are available.

### Positron Emission Tomography/Magnetic Resonance

Positron emission tomography/magnetic resonance is an emerging modality, though currently largely limited to research algorithms. In the assessment of cardiomyopathy,

positron emission tomography allows for the determination of myocardial perfusion and glucose metabolism. Furthermore, positron emission tomography allows for the evaluation of myocardial viability.<sup>94,95</sup> The combined use of positron emission tomography /magnetic resonance allows not only for the acquisition of complimentary data on cardiac structure and function<sup>96</sup> but also limits exposure to radiation.<sup>97</sup> This is an important advantage when imaging patients with cancer, who may have already been exposed to large amounts of radiation.

### Conclusion

Cancer therapy–related cardiotoxicity has become a topic of growing concern. Early toxicity can limit a patient’s ability to complete effective cancer therapy. Late-onset toxicity impacts cardiac mortality among cancer survivors. This complex population of patients presents unique challenges to clinical care. Overlaps in clinical symptomatology can make the delineation between symptoms of cardiac dysfunction and expected side effects of chemotherapy difficult. Additional barriers include a lack of a universal definition of cardiotoxicity as well as the absence of established guidelines for monitoring and surveillance. Certain biomarkers and novel imaging techniques have been investigated, but further study is necessary to clarify and optimize their role in routine clinical practice. Enhanced recognition and awareness of this unique patient population, and more universally accepted definitions of cancer-related cardiac toxicities, will allow advancement in the field of cardio-oncology.

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### References

1. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, Hagerty KL, Somerfield MR, Vaughn DJ; ASCO Cancer Survivorship Expert Panel. 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. doi: 10.1200/JCO.2007.10.9777.
2. Silber JH, Cnaan A, Clark BJ, Paridon SM, Chin AJ, Rychik J, Hogarty AN, Cohen MI, Barber G, Rutkowski M, Kimball TR, Delaat C, Steinherz LJ, Zhao H. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol*. 2004;22:820–828. doi: 10.1200/JCO.2004.06.022.
3. Patnaik JL, Byers T, DiGiuseppi 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. doi: 10.1186/bcr2901.

4. Rowinsky EK MW, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. *J Clin Oncol*. 1991;9:1704–1712.
5. Sorrentino MF KJ, Eoderaro AE, Truesdell AG. 5-Fluorouracil induced cardiotoxicity: review of the literature. *Cardiol J*. 2012;19:453–458.
6. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077–1084. doi: 10.1056/NEJM200004133421502.
7. NCI Dictionary of Cancer Terms. Definition of cardiotoxicity. <http://www.cancer.gov/dictionary?CdID=44004%3E. Accessed October 31, 2015.
8. NCI. Common Terminology Criteria for Adverse Events (CTCAE); 2009.
9. FDA Drug Label for DOXIL-doxorubicin hydrochloride injection, suspension, liposomal. Available at: <http://dailymed.nlm.nih.gov.ezproxy.hsclib.sunysb.edu/dailymed/drugInfo.cfm?setid=21d9c619-7e94-49e2-ac41-31e9ea96554a%3E>. Accessed October 31, 2015.
10. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, Murphy M, Stewart SJ, Keefe D. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215–1221.
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Gatrex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–1672. doi: 10.1056/NEJMoa052306.
12. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buysse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283. doi: 10.1056/NEJMoa0910383.
13. Plana JC GM, Barac A, Ewer M, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. 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;27:911–939.
14. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23:2900–2902. doi: 10.1200/JCO.2005.05.827.
15. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, Lamantia G, Colombo N, Cortinovis S, Dessanai MA, Nolè F, Veglia F, Cipolla CM. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol*. 2010;28:3910–3916. doi: 10.1200/JCO.2009.27.3615.
16. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131:1981–1988. doi: 10.1161/CIRCULATIONAHA.114.013777.
17. Blum RH, Carter SK. Adriamycin. A new anticancer drug with significant clinical activity. *Ann Intern Med*. 1974;80:249–259.
18. Tewey KM, Rowe TC, Yang L, Halligan BD, Liu LF. Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. *Science*. 1984;226:466–468.
19. Vejpongsa P, Yeh ET. Topoisomerase 2β: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clin Pharmacol Ther*. 2014;95:45–52. doi: 10.1038/clpt.2013.201.
20. Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, Liu LF. Topoisomerase IIβ mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res*. 2007;67:8839–8846. doi: 10.1158/0008-5472.CAN-07-1649.
21. Monsuez JJ, Charniot JC, Vignat N, Artigou JY. Cardiac side-effects of cancer chemotherapy. *Int J Cardiol*. 2010;144:3–15. doi: 10.1016/j.ijcard.2010.03.003.
22. Pein F, Sakiroglu O, Dahan M, Lebidois J, Merlet P, Shamsaldin A, Villain E, de Vathaire F, Sidi D, Hartmann O. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. *Br J Cancer*. 2004;91:37–44. doi: 10.1038/sj.bjc.6601904.
23. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev*. 2011;7:214–20.
24. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozenzweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;91:710–717.
25. Gershwin ME, Goetzl EJ, Steinberg AD. Cyclophosphamide: use in practice. *Ann Intern Med*. 1974;80:531–540.
26. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol*. 1991;9:1215–1223.
27. Quezado ZM, Wilson WH, Cunnion RE, Parker MM, Reda D, Bryant G, Ognibene FP. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med*. 1993;118:31–36.
28. Field JJ, Kanakkanthara A, Miller JH. Microtubule-targeting agents are clinically successful due to both mitotic and interphase impairment of microtubule function. *Bioorg Med Chem*. 2014;22:5050–5059. doi: 10.1016/j.bmc.2014.02.035.
29. Giordano SH, Booser DJ, Murray JL, Ibrahim NK, Rahman ZU, Valero V, Theriault RL, Rosales MF, Rivera E, Frye D, Ewer M, Ordonez NG, Buzdar AU, Hortobagyi GN. A detailed evaluation of cardiac toxicity: a phase II study of doxorubicin and one- or three-hour-infusion paclitaxel in patients with metastatic breast cancer. *Clin Cancer Res*. 2002;8:3360–3368.
30. Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, Zambetti M, Sabadell D, Raab G, Llombart Cussac A, Bozhok A, Martinez-Agullo A, Greco M, Byakhov M, Lopez Lopez JJ, Mansutti M, Valagussa P and Bonadonna G. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. *Clin Cancer Res*. 2005;11:8715–21.
31. Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med*. 2006;354:2103–2111. doi: 10.1056/NEJMoa054504.
32. Goldenberg MM. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, a novel agent for the treatment of metastatic breast cancer. *Clin Ther*. 1999;21:309–318. doi: 10.1016/S0149-2918(00)88288-0.
33. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Gatrex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659–1672. doi: 10.1056/NEJMoa052306.
34. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst*. 2012;104:1293–1305. doi: 10.1093/jnci/djs317.
35. Network NCC. *Breast Cancer Version 3.2015*; 2015.
36. Valachis A, Nearchou A, Lind P, Mauri D. Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence. *Breast Cancer Res Treat*. 2012;135:655–662. doi: 10.1007/s10549-012-2189-z.
37. Krop IE, Suter TM, Dang CT, Dirix L, Romieu G, Zamagni C, Citron ML, Campone M, Xu N, Smitt M, Gianni L. Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo) adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. *J Clin Oncol*. 2015;33:1136–1142. doi: 10.1200/JCO.2014.58.7782.
38. Ferrara N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. *Am J Physiol Cell Physiol*. 2001;280:C1358–C1366.
39. Yang B, Papoian T. Tyrosine kinase inhibitor (TKI)-induced cardiotoxicity: approaches to narrow the gaps between preclinical safety evaluation and clinical outcome. *J Appl Toxicol*. 2012;32:945–951. doi: 10.1002/jat.2813.
40. Groarke JD, Choueiri TK, Slosky D, Cheng S, Moslehi J. Recognizing and managing left ventricular dysfunction associated with therapeutic inhibition of the vascular endothelial growth factor signaling pathway. *Curr Treat Options Cardiovasc Med*. 2014;16:335. doi: 10.1007/s11936-014-0335-0.



41. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115–124. doi: 10.1056/NEJMoa065044.
42. Richards CJ, Je Y, Schutz FA, Heng DY, Dallabrida SM, Moslehi JJ, Choueiri TK. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. *J Clin Oncol*. 2011;29:3450–3456. doi: 10.1200/JCO.2010.34.4309.
43. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. *JACC Heart Fail*. 2013;1:72–78. doi: 10.1016/j.jchf.2012.09.001.
44. Choueiri TK, Mayer EL, Je Y, Rosenberg JE, Nguyen PL, Azzi GR, Bellmunt J, Burstein HJ, Schutz FA. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. *J Clin Oncol*. 2011;29:632–638. doi: 10.1200/JCO.2010.31.9129.
45. Filopei J, Frishman W. Radiation-induced heart disease. *Cardiol Rev*. 2012;20:184–188. doi: 10.1097/CRD.0b013e3182431c23.
46. van Nimwegen FA, Schaapveld M, Janus CP, Krol AD, Petersen EJ, Raemaekers JM, Kok WE, Aleman BM, van Leeuwen FE. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med*. 2015;175:1007–1017. doi: 10.1001/jamainternmed.2015.1180.
47. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998. doi: 10.1056/NEJMoa1209825.
48. 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. doi: 10.1093/jnci/djp440.
49. Blanco JG, Sun CL, Landier W, Chen L, Esparza-Duran D, Leisenring W, Mays A, Friedman DL, Ginsberg JP, Hudson MM, Neglia JP, Oeffinger KC, Ritchey AK, Villaluna D, Relling MV, Bhatia S. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children’s Oncology Group. *J Clin Oncol*. 2012;30:1415–1421. doi: 10.1200/JCO.2011.34.8987.
50. Pavo N, Raderer M, Hülsman M, Neuhold S, Adlbrecht C, Strunk G, Goliasch G, Gisslinger H, Steger GG, Hejna M, Köstler W, Zöchbauer-Müller S, Marosi C, Kornek G, Auerbach L, Schneider S, Parschalk B, Scheithauer W, Pirker R, Drach J, Zielinski C, Pacher R. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. *Heart*. 2015;101:1874–1880. doi: 10.1136/heartjnl-2015-307848.
51. Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A. Cardiac toxicity from systemic cancer therapy: a comprehensive review. *Prog Cardiovasc Dis*. 2010;53:94–104. doi: 10.1016/j.pcad.2010.05.006.
52. Valachis A, Nilsson C. Cardiac risk in the treatment of breast cancer: assessment and management. *Breast Cancer (Dove Med Press)*. 2015;7:21–35. doi: 10.2147/BCTT.S47227.
53. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc*. 2014;89:1287–1306. doi: 10.1016/j.mayocp.2014.05.013.
54. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673–1684. doi: 10.1056/NEJMoa052122.
55. Dranitsaris G, Rayson D, Vincent M, Chang J, Gelmon K, Sandor D, Reardon G. The development of a predictive model to estimate cardiotoxic risk for patients with metastatic breast cancer receiving anthracyclines. *Breast Cancer Res Treat*. 2008;107:443–450. doi: 10.1007/s10549-007-9803-5.
56. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc*. 2014;3:e000472. doi: 10.1161/JAHA.113.000472.
57. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, Civelli M, Peccatori F, Martinelli G, Fiorentini C, Cipolla CM. Prognostic value of troponin I in cardiac stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109:2749–2754. doi: 10.1161/01.CIR.0000130926.51766.CC.
58. Cardinale D, Bacchiani G, Beggiano M, Colombo A, Cipolla CM. Strategies to prevent and treat cardiovascular risk in cancer patients. *Semin Oncol*. 2013;40:186–198. doi: 10.1053/j.seminoncol.2013.01.008.
59. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, Cohen V, Banchs J, Carver JR, Wieggers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. 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. doi: 10.1161/CIRCIMAGING.112.973321.
60. Ederhy S, Massard C, Dufaitre G, Balheda R, Meuleman C, Rocca CG, Izzedine H, Cohen A, Soria JC. Frequency and management of troponin I elevation in patients treated with molecular targeted therapies in phase I trials. *Invest New Drugs*. 2012;30:611–615. doi: 10.1007/s10637-010-9546-8.
61. Romano S, Fratini S, Ricevuto E, Procaccini V, Stifano G, Mancini M, Di Mauro M, Ficorella C, Penco M. Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients. *Br J Cancer*. 2011;105:1663–1668. doi: 10.1038/bjc.2011.439.
62. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, Colan SD, Neuberg DS, Dahlberg SE, Henkel JM, Asselin BL, Athale UH, Clavell LA, Laverdière C, Michon B, Schorin MA, Sallan SE. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. *J Clin Oncol*. 2012;30:1042–1049. doi: 10.1200/JCO.2010.30.3404.
63. Onitilo AA, Engel JM, Stankowski RV, Liang H, Berg RL, Doi SA. High-sensitivity C-reactive protein (hs-CRP) as a biomarker for trastuzumab-induced cardiotoxicity in HER2-positive early-stage breast cancer: a pilot study. *Breast Cancer Res Treat*. 2012;134:291–298. doi: 10.1007/s10549-012-2039-z.
64. Onitilo AA, Engel JM, Stankowski RV, Liang H, Berg RL, Doi SA. High-sensitivity C-reactive protein (hs-CRP) as a biomarker for trastuzumab-induced cardiotoxicity in HER2-positive early-stage breast cancer: a pilot study. *Breast Cancer Res Treat*. 2012;134:291–298. doi: 10.1007/s10549-012-2039-z.
65. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr, Sebag IA, Plana JC, Cohen V, Banchs J, Carver JR, Wieggers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol*. 2014;63:809–816. doi: 10.1016/j.jacc.2013.10.061.
66. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, Picard MH, Carver JR, Halpern EF, Kuter I, Passeri J, Cohen V, Banchs J, Martin RP, Gerszten RE, Scherrer-Crosbie M, Ky B. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. *Clin Chem*. 2015;61:1164–1172. doi: 10.1373/clinchem.2015.241232.
67. Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography. *PLoS One*. 2014;9:e96736. doi: 10.1371/journal.pone.0096736.
68. Morris PG, Chen C, Steingart R, Fleisher M, Lin N, Moy B, Come S, Sugarman S, Abbruzzi A, Lehman R, Patil S, Dickler M, McArthur HL, Winer E, Norton L, Hudis CA, Dang CT. Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. *Clin Cancer Res*. 2011;17:3490–3499. doi: 10.1158/1078-0432.CCR-10-1359.
69. Mavinkurve-Groothuis AM, Groot-Loonen J, Bellersen L, Pourier MS, Feuth T, Bökkerink JP, Hoogerbrugge PM, Kapusta L. Abnormal NT-pro-BNP levels in asymptomatic long-term survivors of childhood cancer treated with anthracyclines. *Pediatr Blood Cancer*. 2009;52:631–636. doi: 10.1002/pbc.21913.
70. Dodos G, Halbsguth T, Erdmann E, Hoppe UC. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. *Clin Res Cardiol*. 2008;97:318–326. doi: 10.1007/s00392-007-0633-6.
71. Jingu K, Nemoto K, Kaneta T, Oikawa M, Ogawa Y, Ariga H, Takeda K, Sakayauchi T, Fujimoto K, Narazaki K, Takai Y, Nakata E, Fukuda H, Takahashi S, Yamada S. Temporal change in brain natriuretic peptide after radiotherapy for thoracic esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2007;69:1417–1423. doi: 10.1016/j.ijrobp.2007.05.054.
72. Sandri MT, Cardinale D, Zorzino L, Passerini R, Lentati P, Martinoni A, Martinelli G, Cipolla CM. Minor increases in plasma troponin I predict

- decreased left ventricular ejection fraction after high-dose chemotherapy. *Clin Chem*. 2003;49:248–252.
73. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinelli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517–522.
  74. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas AS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; American College of Cardiology; American Heart Association; American Society of Echocardiography. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation*. 2003;108:1146–1162. doi: 10.1161/01.CIR.0000073597.57414.A9.
  75. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, Burns PN, Castello R, Coon PD, Hagen ME, Jollis JG, Kimball TR, Kitzman DW, Kronzon I, Labovitz AJ, Lang RM, Mathew J, Moir WS, Nagueh SF, Pearlman AS, Perez JE, Porter TR, Rosenbloom J, Strachan GM, Thanigaraj S, Wei K, Woo A, Yu EH, Zoghbi WA; American Society of Echocardiography. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr*. 2008;21:1179–1201; quiz 1281. doi: 10.1016/j.echo.2008.09.009.
  76. Kongbundansuk S, Hundley WG. Noninvasive imaging of cardiovascular injury related to the treatment of cancer. *JACC Cardiovasc Imaging*. 2014;7:824–838. doi: 10.1016/j.jcmg.2014.06.007.
  77. Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. *Eur Heart J*. 2009;30:98–106. doi: 10.1093/eurheartj/ehn484.
  78. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović 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. doi: 10.1016/j.jacc.2012.09.035.
  79. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhães A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. 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. *Eur Heart J Cardiovasc Imaging*. 2014;15:1063–1093. doi: 10.1093/ehjci/jeu192.
  80. Oretto L, Todaro MC, Umland MM, Kramer C, Qamar R, Carerj S, Khandheria BK, Paterick TE. Use of echocardiography to evaluate the cardiac effects of therapies used in cancer treatment: what do we know? *J Am Soc Echocardiogr*. 2012;25:1141–1152. doi: 10.1016/j.echo.2012.09.001.
  81. 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;20:62–69.
  82. Tassan-Mangina S, Codorean D, Metivier M, Costa B, Himmerlin C, Jouannaud C, Blaise AM, Elaerts J, Nazeyrollas P. 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;7:141–146. doi: 10.1016/j.euje.2005.04.009.
  83. Stoodley PW, Richards DA, Boyd A, Hui R, Harnett PR, Meikle SR, Byth K, Stuart K, Clarke JL, Thomas L. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: a comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. *Eur J Cancer*. 2013;49:3396–3403. doi: 10.1016/j.ejca.2013.06.046.
  84. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr*. 2013;26:493–498. doi: 10.1016/j.echo.2013.02.008.
  85. Motoki H, Koyama J, Nakazawa H, Aizawa K, Kasai H, Izawa A, Tomita T, Miyashita Y, Kumazaki S, Takahashi M, Ikeda U. Torsion analysis in the early detection of anthracycline-mediated cardiomyopathy. *Eur Heart J Cardiovasc Imaging*. 2012;13:95–103. doi: 10.1093/ejehocad/jer172.
  86. Tanindi A, Demirci U, Tacoy G, Buyukberber S, Alsancak Y, Coskun U, Yalcin R, Benekli M. Assessment of right ventricular functions during cancer chemotherapy. *Eur J Echocardiogr*. 2011;12:834–840. doi: 10.1093/ejehocad/jer142.
  87. Mason JW, Bristow MR, Billingham ME, Daniels JR. Invasive and noninvasive methods of assessing adriamycin cardiotoxic effects in man: superiority of histopathologic assessment using endomyocardial biopsy. *Cancer Treat Rep*. 1978;62:857–864.
  88. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhães A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. 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;27:911–939. doi: 10.1016/j.echo.2014.07.012.
  89. Armstrong GT, Plana JC, Zhang N, Srivastava D, Green DM, Ness KK, Daniel Donovan F, Metzger ML, Arevalo A, Durand JB, Joshi V, Hudson MM, Robison LL, Flamm SD. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. *J Clin Oncol*. 2012;30:2876–2884. doi: 10.1200/JCO.2011.40.3584.
  90. Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. *Circ Cardiovasc Imaging*. 2013;6:1080–1091. doi: 10.1161/CIRCIMAGING.113.000899.
  91. 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. doi: 10.1186/1532-429X-10-5.
  92. Neilan TG, Coelho-Filho OR, Pena-Herrera D, Shah RV, Jerosch-Herold M, Francis SA, Moslehi J, Kwong RY. Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines. *Am J Cardiol*. 2012;110:1679–1686. doi: 10.1016/j.amjcard.2012.07.040.
  93. Jiji RS, Kramer CM, Salerno M. Non-invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs. *J Nucl Cardiol*. 2012;19:377–388. doi: 10.1007/s12350-012-9512-2.
  94. Rischpler C, Nekolla SG, Dregely I, Schwaiger M. Hybrid PET/MR imaging of the heart: potential, initial experiences, and future prospects. *J Nucl Med*. 2013;54:402–415. doi: 10.2967/jnumed.112.105353.
  95. Nappi C, El Fakhri G. State of the art in cardiac hybrid technology: PET/MR. *Curr Cardiovasc Imaging Rep*. 2013;6:338–345. doi: 10.1007/s12410-013-9213-5.
  96. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc*. 2014;3:e000665. doi: 10.1161/JAHA.113.000665.
  97. Catana C, Guimaraes AR, Rosen BR. PET and MR imaging: the odd couple or a match made in heaven? *J Nucl Med*. 2013;54:815–824. doi: 10.2967/jnumed.112.112771.

### **Cancer Therapy–Related Cardiac Dysfunction and Heart Failure: Part 1: Definitions, Pathophysiology, Risk Factors, and Imaging**

Michelle W. Bloom, Carine E. Hamo, Daniela Cardinale, Bonnie Ky, Anju Nohria, Lea Baer, Hal Skopicki, Daniel J. Lenihan, Mihai Gheorghiuade, Alexander R. Lyon and Javed Butler

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