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Asymptomatic Cardiac Toxicity in Long-Term Cancer Survivors: Defining the Population and Recommendations for Surveillance

Joseph R. Carver[a,b], **Dava Szalda**[c], and **Bonnie Ky**[a]

[a]Cardio-oncology in the Division of Cardiology, University of Pennsylvania, Philadelphia, PA.

[b]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA.

[c]Children's Hospital of Philadelphia, Philadelphia, PA.

Abstract

Advances in the treatment of pediatric and adult cancer have reduced the mortality rates from these disorders and have led to an ever-increasing population of long-term survivors. Chemotherapy and radiotherapy may cause premature cardiac disease that may be asymptomatic or symptomatic. All patients exposed to chemotherapy with cardiotoxic potential or chest radiotherapy have stage A heart failure and the goal of surveillance and treatment is to prevent progression to stages B-D. Screening strategies, including the use of biomarkers, echocardiography, and expert opinion surveillance and treatment recommendations, are presented.

Advances in the diagnosis and treatment of pediatric and adult cancers have dramatically reduced the mortality rates from these diseases. In 2008, there were an estimated 328,000 adult survivors of pediatric cancer[1] and 11.9 million survivors of adult cancer, representing 4% of the US population. Approximately 66%, 37%, and 15% of these survivors are expected to live at least 5, 10, and 20 or more years, respectively, after diagnosis.[2,3] They are particularly vulnerable to a variety of chronic health conditions resulting primarily from the effects of their treatment.[4–8]

Chemotherapy and chest radiotherapy may cause premature cardiac disease that is often initially asymptomatic[9–12] and potentially can affect all structures of the heart, with a disease-free latency period that may last decades before the emergence of overt disease and an incidence that increases with cumulative dosing. The clinical presentations and their prevalence are extensively reviewed in the accompanying articles in this issue of *Seminars in Oncology* and have been extensively reviewed in the past.[13–20] Asymptomatic disease manifested by echo-cardiographic abnormalities is more common than symptomatic disease and, depending on the definitions applied, can be found in ~50% of all survivors of anthracycline- or radiation-based therapy. Although there is acceptance of the potential risks and need for surveillance, there is currently a lack of agreement about the details of follow-

Address correspondence to Joseph R. Carver, MD, 1600 Penn Tower, 3400 Spruce Street, Philadelphia, PA 19104. jrc@mail.med.upenn.edu.

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up testing.[21] As such, a critical need exists to develop a robust clinical approach that is sensitive, specific, cost-effective, and easily adaptable to the care of these patients. The goal of this summary statement was to define the population at risk and present a paradigm for the screening of cardiovascular complications of chemotherapy among the growing survivor population.

THE POPULATION

Although several chemotherapeutic drugs may cause cardiac toxicity during treatment, this discussion is limited to asymptomatic late-adolescents and adults who have survived at least 2 years after treatment with anthracyclines, platinum-based chemotherapy, and/or radiotherapy. To date, exposure to trastuzumab, monoclonal antibodies, tyrosine kinase inhibitors, or 5-fluorouracil/capecitabine have not resulted in the new onset of late cardiac toxicity.

THE LANDSCAPE

Cardiac toxicity from chemotherapy in adult survivors of adult cancer is manifested mainly by dilated cardiomyopathy and characterized by a reduction in systolic function (a decreased left ventricular ejection fraction [LVEF] or fractional shortening [FS]) that may be preceded by isolated diastolic dysfunction. Cardiac toxicity from chemotherapy in survivors of pediatric cancer develops as a restrictive cardiomyopathy with diastolic dysfunction and early preservation of systolic function.

Cardiac toxicity from radiation includes restrictive cardiomyopathy, valvular disease, conduction disease, pericardial disease, coronary artery disease (CAD), and carotid/subclavian disease. Survivors of platinum-based chemotherapy have a higher prevalence of hypertension and obesity, diastolic dysfunction, and cardiac events compared with a matched untreated population.[22,23] Survivors are at increased risk of obesity and metabolic syndrome.[23,24]

Chemotherapy and radiotherapy damage the heart through many potential mechanisms, including oxidative stress, mitochondrial dysfunction, myofilament degradation, endothelial cell dysfunction, and progenitor cell depletion/dysfunction. Because of an innate cardiac functional “reserve,” damage can occur without overt symptoms. After treatment completion, there is a variable period of asymptomatic risk (latency period) that may persist for decades. This duration of asymptomatic latency and progression of disease is likely related to genetic factors and the hemodynamic burden of subsequent cardiac stress resulting from co-morbid conditions and environmental factors.

THE CONSTRUCT

All patients exposed to cardiotoxins have stage A heart failure. The American College of Cardiology (ACC)/American Heart Association (AHA) developed guidelines for the treatment of heart failure in the general population[25] delineating four stages that describe the natural progression of patients at risk for heart failure from asymptomatic (stages A/B) (Table 1) to symptomatic (stages C/D) disease. Asymptomatic disease progresses as part of its natural history.[26] Evidence-based treatment recommendations suggest that intervention and treatment at stages A/B can prevent progression.[27] This classification also has been incorporated into the management of pediatric heart failure.[28]

We propose the following construct when approaching screening in the survivor population: From a population standpoint, there is a direct relationship between cumulative dose exposure and risk; for the individual survivor, there is wide variation in risk, ie, toxicity may

occur at low doses (therefore, there is no "safe" dose[29–31]) or may not occur at high doses. The risk of symptomatic heart failure is ~1%–2% at 10 years and 10%–15% at 25 years and beyond.

It is generally accepted that the approximate risk of radiation-induced toxicity is 1% at 5 years and doubles every 5 years. Clinically significant radiation changes more commonly occur 10 or more years post-treatment completion and are unusual before that time.[16] At 20 years post-treatment completion, the risk for clinically significant cardiomyopathy, CAD, valvular disease, pericardial disease, and carotid artery stenosis is 8%, 10%, 7%, 1%–3%, and 6%, respectively.

Chest (mediastinal, mantle, left side for breast cancer), cransiospinal, or total body radiation should be considered as an additional risk factor for atherosclerosis and be added to accepted risk factors, eg, diabetes, cigarette smoking, and hypertension, to guide the goal of treatment targets for those risk factors that can be modified.

A normal LVEF or FS does not exclude cardiac dysfunction. There is a critical need to develop more robust and sensitive measures of LV dysfunction to improve our current methods of monitoring patients. Waiting for the LVEF to decline before therapeutic intervention is no longer an acceptable strategy.

Each adult survivor of pediatric or adult cancer who was treated with at-risk therapy, eg, anthracyclines or chest radiation, has stage A heart failure and, as such, has defined goals of therapy that target modifiable cardiovascular risk factors. The goal of screening is to recognize and then prevent progression to the more advanced stages B, C, and D. Within this population, a high- and low-risk group can be identified to help guide frequency of assessment and surveillance.

Screening Strategies

Current strategies exist, although additional research is critical. Effective screening strategies require a significant burden of disease, the availability of an accurate screening test for detection of asymptomatic patients, and evidence that early detection reduces morbidity and mortality.[21] For cancer survivors, the burden of disease is well recognized, and for patients with cardiovascular disease, early detection improves overall prognosis. However, there is a lack of agreement about the optimal screening test and the frequency of testing.

Screening guideline development has been slowed by the focus on a single test and the assumption that cardiotoxicity risk is binary. A combination of tests rather than a single test may be the most effective population-based strategy that achieves an appropriate balance between lack of screening and over-screening. In the continuum of cardiotoxicity, every long-term survivor is at risk for the future development of cardiac disease. The main goals of screening are thus to identify the presence of structural heart disease and the patient's place in the continuum to intervene to prevent progression and to identify the presence of asymptomatic cardiovascular disease before it results in cardiovascular morbidity.

Screening for Structural Heart Disease

The Role of Biomarkers—Natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide are secreted from the myocardium in response to increased hemodynamic stress and have been widely used in the management of heart failure.[32,33] Elevated levels have been found in asymptomatic patients treated with anthracyclines preceding the development of overt heart failure.[34,35] However, natriuretic peptides have not been consistently effective for population-based screening, with little

incremental value over standard clinical variables. Their major strength, however, may be in their negative predictive value, as it is atypical to have clinically significant structural heart disease with LV dysfunction and a normal BNP level.[36,37]

The Role of Echocardiography—The single most useful diagnostic test in the evaluation of cardiac function before, during, and after cancer treatment is the two-dimensional echocardiogram coupled with Doppler flow studies to quantitate systolic and diastolic function, cardiac chamber dimensions, wall thickness/mass, valvular disease, and the pericardium. In addition to systolic function, the echocardio-gram provides a comprehensive assessment of diastolic function that also is critical, as early abnormalities that precede decreases in systolic function have long-term consequences in the anthracycline-treated population.[38,39] Furthermore, echocardiograms provide insight into the degree of cardiac remodeling from hypertension; wall motion abnormalities from CAD; and valvular/pericardial disease that may result from radiation exposure.

Measurements of LVEF and FS are load dependent and limited by multiple technical considerations. As a measure of global LV function, they are unable to detect subtle, early changes in regional myocardial wall motion. Newer methods to assess cardiac function are also under investigation and include the measurement of regional myocardial strain.[40,41] Strain imaging in the adult cancer survivor population demonstrates abnormalities that occur and persist in survivors despite preserved LVEF.[42,43] A three-dimensional echocardio-gram may also provide incremental value in assessing LV function.

Screening for CAD

Tests available to screen for CAD include the electrocardiogram (ECG), exercise treadmill test, exercise myocardial perfusion imaging, exercise (stress) echo-cardiography, electron-beam computed tomography (CT) scanning for coronary calcium, coronary CT angiography, cardiac magnetic resonance imaging, and carotid intima-media thickness measurement. The sensitivity, specificity, and predictive accuracy of these tests for the non-cancer population have been recently reviewed in detail.[44]

The US Preventive Services Task Force guidelines for CAD detection in asymptomatic patients in the non-cancer population do not recommend routine ECG, exercise treadmill test, exercise myocardial perfusion imaging, exercise (stress) echocardiography, and other nontraditional testing (scanning for coronary calcium, coronary CT angiography, magnetic resonance imaging, measurement of carotid intima-media thickness) for either the presence of severe coronary artery stenosis or the prediction of coronary heart disease (CHD) events in adults at low risk for CHD events.[45] For higher-risk patients, they found inadequate evidence that testing (beyond that obtained by assessment of conventional CHD risk factors) would result in interventions that lead to improved CHD-related health outcomes.[46]

These recommendations do not specifically address the survivor population at risk for radiation-induced premature CAD,[13,20,47] which differs from atherosclerotic CAD in onset (beginning at 10 years' post-treatment completion), lesion location (ostial or proximal left main, left anterior descending, or right coronary artery), and possibly presentation (both forms may present with sudden death as the initial manifestation, and it is not clear what the actual prevalence of this is in either population). Therefore, the efficacy of screening tests in the survivor population may not be generalizable from the US Preventive Services Task Force recommendations but may be used to help in decision making and should guide the needed future research in this area.

DEFINING A HIGH-RISK POPULATION

It should be assumed that every survivor exposed to anthracyclines and/or chest radiation is at stage A and "at risk." Subsequent sub-characterization as low- or high-risk should be matched and drive the frequency and intensity of screening. Patient and treatment high-risk variables are listed in Table 2. The presence of any one variable defines a high-risk patient among all who should be considered at stage A.

Guidelines/Recommendations: The Landscape

The recognition that there are long-term health concerns after chemotherapy prompted the Institute of Medicine to publish two reports providing general recommendations for ongoing care and research for survivors of childhood and adult cancers.[48,49] Specific recommendations about the nature and frequency of cardiac testing are not addressed.

The Children's Oncology Group also has published guidelines[50] for long-term care for pediatric cancer survivors. The guidelines are expert panel, consensus-derived, based on a recognized risk, with monitoring frequency matched to risk. After baseline screening, specific testing is recommended from yearly to every 5 years based on age at treatment, dose of anthracycline, and associated exposure to radiotherapy. In addition, the panel recognizes that the risk of CAD associated with radiotherapy is manifested between 5 and 10 or more years after treatment completion, and they recommend testing strategies. These guidelines are reproduced in Table 3 as an example of expert opinion–based guidelines that are currently accepted and used in survivors of pediatric cancers. Other groups have developed similar expert opinion guidelines, with minor variations,[51–53] and it is recognized that revisions are necessary for more population-based and cost-effective screening. All are based on expert opinion and are not evidence-based.

For survivors of adult cancer, the landscape is less clear; cardiac monitoring has been included in some post-treatment disease-specific guidelines generated by the National Comprehensive Cancer Network and the American Society of Clinical Oncology.[54,55] Aside from the National Comprehensive Cancer Network Lymphoma Guidelines that recommend a baseline stress test/echocardiogram at 10 years' post-treatment completion,[56] all other published guidelines only recommend monitoring of cardiovascular risk factors and reinforce the value of a healthy lifestyle. Various other independent recommendations also have been published[57–59] that are expert opinion based and not evidence-based.

EXPERT OPINION SURVEILLANCE RECOMMENDATIONS

This section provides a general strategy to approach the screening and care of adult cancer survivors. We assume that follow-up care will be provided by a primary care physician, nurse practitioner, or medical/radiation oncologist.

This information does not represent a standard of care but provides a clinically relevant approach to guide the care of these patients based on existing data defining cardiac risk and the value of therapeutic intervention. These recommendations are not absolute, can be used as a broad roadmap with individual practitioner discretion, and are subject to change as knowledge and technology advances are made. For all patients, the recommendations can be simplified into four questions that guide subsequent testing: (1) What are the details of previous cancer treatment?; (2) What is the patient's cardiovascular risk independent of treatment?; (3) What is the patient's current functional status?; and (4) Is there any clinical evidence of structural heart disease or CAD? This strategy is displayed schematically in Figure 1.

Assess Prior Cancer Therapy

A detailed treatment summary should be obtained that includes the cancer diagnosis, age at diagnosis, dates of all treatments (including doses and fields), previous cardiac testing, and treatment-related cardiac complications. One user-friendly and detailed on-line treatment summary form is offered by Oncolink and is available at http://livestrongcareplan.org/pdf/CancerTherapyTreatmentSummary.pdf.

Assess Risk Status Independent of Treatment

Patients should be specifically asked about traditional cardiac risk factors (which magnify and increase the risk for cardiotoxicity), current medications, and lifestyle/behavior. A thorough family history helps to define the potential for atherosclerotic disease and inherited cardiomyopathy.

Assess Current Functional Status at Initial and Follow-up Examinations

A thorough history should be obtained, with special focus on dyspnea, cough, chest pain, palpitations, edema, orthopnea, orthostatic symptoms, and syncope. Attention should be paid to symptoms and minor, subtle longitudinal changes in exercise status.

For patients who have had radiation, there is an increased risk for transient ischemic attacks and stroke; patients should be specifically asked about transient neurologic symptoms, such as weakness, speech problems, or visual changes.[60]

A complete physical examination should include determination of blood pressure in both arms in the supine, sitting, and standing positions because there is an increase in autonomic dysfunction after chemo-therapy and radiotherapy.[13] Body mass index and waist circumference should be recorded. In addition, the response of systolic blood pressure during phase 2 of the Valsalva maneuver has been recognized as a surrogate of LV end-diastolic pressure.[61] This is a simple bedside maneuver based on the observation that elevated LV end-diastolic pressure prolongs the duration of phase 2. This pressure can be easily measured with a sphygmomanometer. Examination of the jugular pulse provides information about filling pressures, and examination of the ocular fundus provides information about the overall arterial vasculature and the presence of other cardiac risk factors. Any abnormality should result in a referral for cardiology consultation.

Assess Cardiac Structure

We propose that all at-risk survivors should have a baseline ECG, two-dimensional transthoracic echocardio-gram, and BNP level measured at initial examination. The echocardiogram includes a standard assessment of cardiac size and function as well as valvular, pericardial, and diastolic function. Coupled with a resting ECG, screening for the major structural manifestations of cardiotoxicity is accomplished. We propose the use of BNP for its negative predictive value. With no abnormal results on these three tests, the patient is at stage A.

Fasting lipid levels should be measured at baseline, given the high incidence of obesity and metabolic syndrome in cancer survivors.[62] Treatment should be targeted to National Cholesterol Education Program/Adult Treatment Panel guidelines.[63] In addition to counseling about healthy lifestyle and risk factor modification, treatment guidelines aligned with stage A should be applied: treatment of diabetes and hypertension, encouraging smoking cessation, encouraging regular exercise, discouraging alcohol intake and recreational drug use, and controlling the metabolic syndrome. Patient education about recognition and requirement for immediate follow-up for any subtle change in performance or new symptom development should be provided.

Each stage A patient can be classified as low or high risk, according to Table 2. For the low-risk stage A patient, in the absence of new symptoms or a change in performance status, re-evaluation can be scheduled approximately every 2 years. At each visit, in addition to a detailed history and thorough physical examination, measurement of a BNP level is recommended as a follow-up screening tool, given its negative predictive value. No regular cardiac imaging is recommended as long as performance status, absence of symptoms, examination findings, and BNP levels remain normal.

For any low-risk stage A survivor who has borderline normal findings on ECG (minor ST-T wave changes, nonspecific intraventricular conduction delay, or arrhythmias) or who has borderline normal echocardiogram findings (LVEF at lower limit of normal for the laboratory or mild diastolic dysfunction), we treat cardiovascular comorbidity, eg, aggressive blood pressure control and weight loss if overweight, and then re-evaluate with a follow-up ECG and echocardiogram at 1 year. If the results are improved (normalized), the patient remains stage A and can be managed according to the aforementioned outline. If these borderline abnormalities persist, the patient has progressed to stage B and is managed accordingly.

High-risk and stage B patients should be observed yearly, and we encourage evaluation by a cardiologist knowledgeable in the late effects of cancer treatment for these patients. At follow-up, any change in performance, symptoms, examination findings, or elevation of the BNP level should result in further evaluation with an echocardiogram. In the absence of any change in status or BNP level, echocardiograms can be repeated at 5-year intervals or at the discretion of the treating practitioner.

The patients who have received chest radiation less than 30 Gy without chemotherapy are managed as low-risk stage A patients with the addition of treating lipids to secondary prevention targets (low-density lipoprotein less than 70 mg/dl, high-density lipoprotein more than 45 mg/dl). These patients can be evaluated every 2 years. Special emphasis regarding symptoms related to CAD and carotid disease, as well as diligence in looking for subtle changes in exercise activity and endurance, should be part of their routine evaluation. Those who received 30 Gy or more of radiotherapy should be considered high-risk stage A and re-evaluated yearly. In the absence of any change in status or evidence of vascular disease on physical examination, there is no current recommendation for stress testing or coronary artery calcium scoring. Any subtle change in overall status or any hint of exertion-related symptoms, regardless of radiation dose, should trigger stress testing.

Because there is a documented increased risk of atherosclerotic risk factors, vascular disease, and arterial events in patients treated with platinum-based chemotherapy,[24] aggressive management of cardiac risk factors is recommended along with regular reinforcement of weight control, smoking cessation, lipid control, and temperance with alcohol.

Special Caveats

With the development of hypertension, preferred treatment should be with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers because of their beneficial effects on cardiac remodeling.[64]

Because cardiac dysfunction may become apparent first during pregnancy,[65] we encourage management input from a cardiologist before, during, and after pregnancy with individualized testing algorithms.

Any low-risk stage A survivor who has a cancer recurrence and/or further malignancy requiring additional chemotherapy or radiotherapy should subsequently be considered and managed as high-risk stage A, with consideration for a cardiology consultation to help guide treatment decisions.

Survivors of autologous stem cell transplantation are at risk for the late development of accelerated atherosclerosis and the metabolic syndrome,[66] and they should be followed up according to the high-risk stage A pathway.

Carotid artery stenosis also is a recognized radiation treatment complication with an increased late incidence of transient ischemia and stroke.[67,68] Carotid bruits may be audible on physical examination. A baseline carotid duplex study can be obtained 5 years after treatment completion.

DIRECTIONS FOR FUTURE RESEARCH

With increasing recognition of the complexity of care for long-term cancer survivors, a model of comprehensive, multi-specialty care teams and cardio-oncology has emerged.[69,70] Future research should be focused on defining a care delivery model that is consistent with the projected health care work force and scalable to the rapidly increasing survivor population.

The factors affecting the rate of progression from stage A to symptomatic, structural cardiovascular disease are still incompletely defined.[71] Global risk models specific to community-based populations predicting the risk of heart failure have been validated,[72,73] and additional refinement to develop a comparable screening tool specific to late chemotherapy cardiotoxicity would be useful.

The fact that there is individual variation in the development of late cardiotoxicity suggests a genetic predisposition, but identification of target pathways has been elusive. The establishment of an international group to organize the banking of blood samples coupled with long-term clinical follow-up would help to resolve this issue.

Future screening recommendations require an accurate quantification of the risk of sudden death as the first manifestation of radiation-induced CAD in the survivor population. Existing bias has emerged from small series of patients, generally treated with pre-modern radiotherapy techniques and before the contemporary treatment of coronary risk factors. Understanding the risk also would help to define the role of non-traditional testing in this population.

Finally, the predictive value of biomarkers, such as the monitoring of troponins/BNP during high-dose chemotherapy,[74] and the benefit of early intervention[75] have not been consistent. A large-scale study to define the true benefit of single or multiple biomarkers and early intervention also is needed.

Many of the current knowledge gaps and questions posed could be resolved by adequately addressing both early and late cardiotoxicity routinely in cancer clinical trials.[76] We suggest that clinicians maintain a heightened awareness of the prevalence and need for surveillance and early treatment for all long-term cancer survivors who were exposed to potentially cardiotoxic therapy. We reiterate that no evidence-based guidelines currently exist but recognize that there is a real risk for late cardiotoxicity. We provide these recommendations for long-term follow-up and care until there is ample research and data to create evidence-based guidelines.

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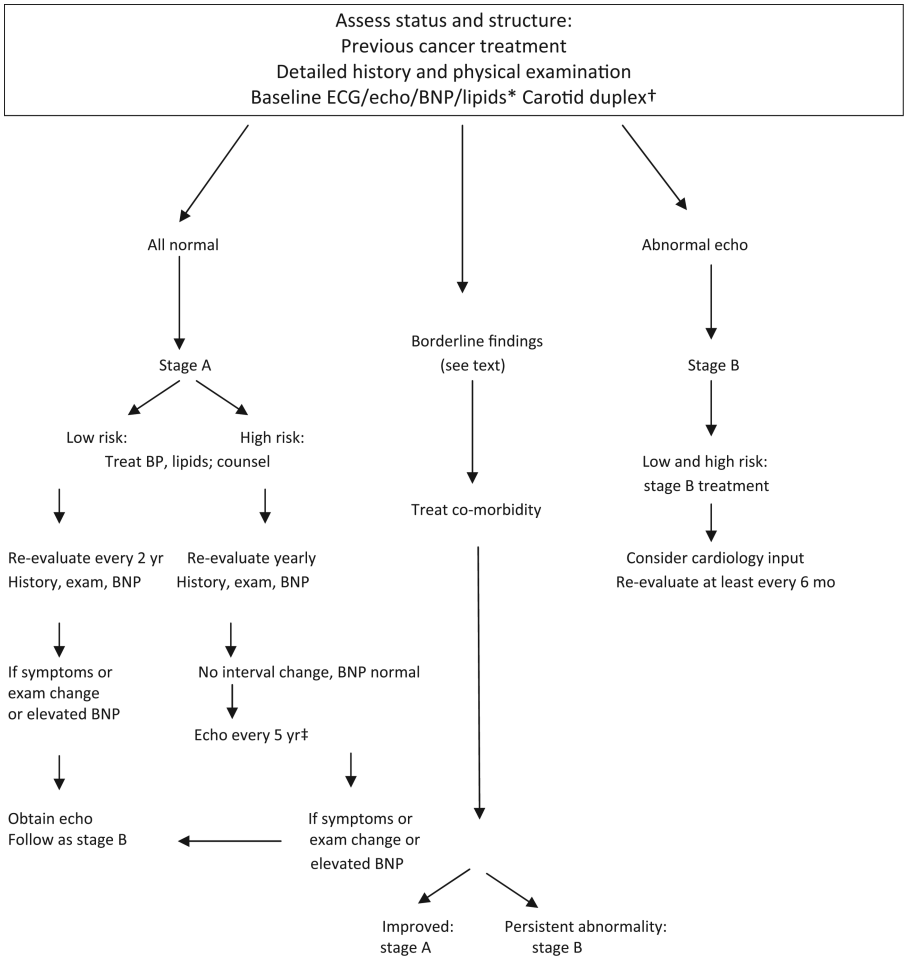

Figure 1.

Follow-up of asymptomatic survivors exposed to anthracycline chemotherapy and/or chest radiation. * If chest radiation: lipids treated to secondary prevention targets. †If chest/head and neck radiation exposure. ‡Or at discretion of treating practitioner. ECG, electrocardiogram; Echo, echocardiogram; BNP, B-type natriuretic peptide; BP, blood pressure; exam, examination.

Table 1

Stages of Asymptomatic Heart Failure*

Stage A		Stage B
At risk for heart failure but without structural heart disease or symptoms of heart failure; eg, patients with hypertension, CAD, diabetes mellitus, previous treatment with anthracyclines or chest radiotherapy	⇒	Structural heart disease but without symptoms of heart failure, eg, patients with previous MI, LV dysfunction, valve disease
Therapy		Therapy
Treatment of hypertension		All measures for stage A plus ACE inhibitors and/or β-blockers in appropriate patients
Encourage smoking cessation		
Treatment of lipids		
Discourage alcohol/recreational drug use		
Use of ACE inhibitors in appropriate patients		

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; LV, left ventricular; ACE, angiotensin-converting enzyme.

*Stages C and D patients have symptoms of heart failure.

Table 2

High-Risk Characteristics*

Patient factors
Age (<15 yr; >65 yr)
Female gender
Any cardiac symptom or physical examination abnormality
Associated pre-existing cardiac risk (hypertension, hyperlipidemia, LV dysfunction, CAD)
Obesity
Treatment factors
Acute cardiotoxicity during treatment, including asymptomatic abnormality on echocardiogram
Cumulative anthracycline dose >350 mg/m^2, doxorubicin or equivalent
Chest radiation ≥30 Gy
Combination chest radiation with any anthracycline
Pre-“modern” (before 1975) radiotherapy (orthovoltage, no subcarinal block)
Length of follow-up 10 years or more post-treatment completion

Abbreviations: LV, left ventricular; CAD, coronary artery disease.

*Any 1 factor implies “high-risk” stage A.

Table 3

An Example of Expert Opinion Guidelines for Survivors of Pediatric Cancer

Age at Treatment*	Chest Radiation	Total Anthracycline Dose†	Recommended Frequency of Echo or MUGA‡
<1 y	Yes	Any	Annually
	No	<200 mg/m^2	Every 2 yr
		200 mg/m^2	Annually
1–4 y	Yes	Any	Annually
	No	<100 mg/m^2	Every 5 yr
		<300 mg^2/m^2	Every 2 yr
		300 mg/m^2	Annually
5y	Yes	<300 mg/m^2	Every 2 yr
		300 mg/m^2	Annually
	No	<200 mg/m^2	Every 5 yr
		200 to <300 mg/m^2	Every 2 yr
		300 mg/m^2	Annually

*Age at first treatment with anthracycline or chest radiation, whichever was given first.

†Based on total doses of doxorubicin/daunorubicin or the equivalent doses of other anthracyclines.

‡Multi-gated acquisition (MUGA) scans may be used for patients who received anthracycline chemotherapy without radiation; echocardiograms (Echo) are the preferred test for those who received radiation involving the heart because the test provides more detailed information regarding structural issues, including valve structures.