Cardiovascular Disease: Cause of Morbidity and Mortality in Adult Survivors of Childhood Cancers

Thomas Force, Guest Editor

Cardiovascular Disease

Cause of Morbidity and Mortality in Adult Survivors of Childhood Cancers

Ming Hui Chen, Steven D. Colan, Lisa Diller

Abstract: Although important advances have been made in curing childhood cancer in the last several decades, long-term survivors face considerable morbidity and mortality because of late effects from their initial anticancer therapy. By 30 years after treatment, the cumulative mortality from treatment-related medical illness actually exceeds that of mortality from cancer recurrence. Cardiovascular disease, in particular, is a leading threat to the well-being of adult survivors of childhood cancers. Unfortunately, the mechanisms of these late cardiac effects are understudied and poorly understood. This article reviews cardiotoxicity associated with 2 major anticancer regimens used in treating childhood cancer patients: anthracycline treatment and radiation therapy. The known pathophysiology and clinical cardiac risk factors that further predispose these patients to late-onset cardiac events are discussed. Basic and translational research is urgently needed to clarify pathophysiologic mechanisms of late cardiac effects and to develop therapies to improve both long-term survival and quality of life of adults cured of pediatric cancers. (Circ Res. 2011;108:619-628.)

Key Words: anthracycline  radiation  cardiotoxicity  cancer survivor  childhood

The great majority of children who develop childhood cancer today are cured. In the last 40 years, the 5-year survival for childhood cancers has increased from 30% to 80%.1 Currently, there are an estimated 328 000 childhood cancer survivors in the United States,2 and it is estimated that 1 in 640 young adults between the ages of 20 and 39 is a survivor of childhood cancer.1,3 This ever-increasing population of young adult cancer survivors is a testament to the enormous progress made by modern anticancer therapeutics and medical care.

Despite a high cure rate, childhood cancer survivors exhibit a long-term survival rate that significantly lags behind age- and gender-matched population controls (Figure 1A). These patients face considerable mortality during adulthood; excess risks in patients may shorten the lifespan of a survivor by an average of 10 years, as compared with the general population of the United States.4 Surprisingly, it is not recurrence of the original cancer that is the cause; instead, the intensity of anticancer therapy to achieve cure increases the risk of treatment-related medical illnesses, organ dysfunction, and
secondary cancers. These “late effects,” defined as medical complications occurring greater than 5 years after cancer treatment, significantly reduce the long-term health of childhood cancer survivors. The risk of late effects progressively increases with time following completion of anticancer therapy so that, at 30 years after cancer therapy, the cumulative mortality of childhood cancer survivors from treatment-related medical illnesses exceeds that of mortality from cancer recurrence (Figure 1B). As survival from childhood cancer increasingly becomes an expectation, we are now grappling with how to balance cancer cure with a long and healthy postcancer life.

Of all etiologies of noncancer mortality, cardiovascular disease remains one of the most important for patients who have survived childhood cancers, especially patients with a history of leukemia, lymphoma, rhabdomyosarcoma, brain tumors, and bone marrow transplantation. Overall cardiovascular mortality of childhood cancer survivors is 7-fold higher (standard mortality ratio of 7) than expected from an age-matched population. Late cardiac effects may be diverse, range in severity, and are related to the type of anticancer treatment received. In a large retrospective analysis of more than 14,000 participants, adult survivors of childhood cancers were significantly more likely than their siblings to report heart failure, myocardial infarction, pericardial disease, or valvular abnormalities. For patients treated with anthracycline, dilated cardiomyopathy or systolic heart failure (HF) are common findings at the time of clinical presentation. The initial clinical presentation for patients who have received radiation therapy (RT) may include restrictive cardiomyopathy, diastolic HF, valvular heart disease, conduction system abnormalities, angina, and/or premature myocardial infarction/sudden cardiac death.

This article reviews anthracycline-associated and radiation-associated cardiovascular disease (CVD) in adult survivors of childhood cancers, the known pathophysiology, clinical cardiac risk factors, and cardiac stressors that predispose to increased late cardiac effects. Cardiotoxicity associated with newer anticancer therapeutics and monoclonal antibodies has been reviewed by accompanying articles in this series and other recent publications; therefore, those agents will be mentioned only as they relate to anthracyclines and radiation. Cardiotoxicity in adult survivors is difficult to diagnose and is underrecognized, partly because the interval between cancer therapy and onset of late cardiac effects can be decades long. Moreover, treatment histories of prior cancer therapies are not routinely obtained in adult patients presenting with cardiac symptoms, potentially leading to misattribution of etiology. Even when such histories are obtained, the appreciation of risks for developing cancer-related cardiac problems remains underestimated. With the increasing success of traditional and novel anticancer therapeutics in achieving cancer remission, the clinical issues of adult survivors of pediatric cancer represent a growing and important area for translational research.

### Anthracycline Cardiotoxicity

For the common malignancies of childhood, treatment with anthracycline agents, including doxorubicin, epirubicin, and daunorubicin, has produced superior disease-free survival compared with other agents. As a result, more than 50% of all childhood cancer survivors have been treated with anthracy-

---

**Non-standard Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>RT</td>
<td>radiation therapy</td>
</tr>
</tbody>
</table>

---

**Figure 1. All-cause mortality and cumulative cause-specific mortality of childhood cancer survivors.**

**A.** Mortality from all causes for childhood cancer survivors compared with age-matched US population. Childhood cancer survivors have much greater mortality 30 years after diagnosis. **B.** Cumulative cause-specific mortality for childhood cancer survivors. Late effects from the initial cancer treatment (nonrecurrence, nonexternal causes) exceed recurrence of original cancer as the leading cause of late mortality. **A** and **B** are based on data from the Childhood Cancer Survivor Study and adapted from Armstrong et al. Reprinted with permission © 2008 American Society of Clinical Oncology.
However, the clinical cardiovascular side effects of these agents are well recognized and can be severe. Cancer survivors treated with these regimens develop primarily a dilated cardiomyopathy, with systolic dysfunction that can lead to HF. Of note, in children, a restrictive cardiomyopathy can also develop.\(^{14}\)

The severity and prevalence of anthracycline cardiomyopathy is directly related to cumulative dose. HF occurs in 3% to 5% of patients exposed to 400 mg/m\(^2\), with the percentage increasing to 7% to 26% at 550 mg/m\(^2\). Therefore, the maximum lifetime cumulative dose of doxorubicin for an individual has been set to 400 to 550 mg/m\(^2\), with most patients receiving far less (\(<240\) mg/m\(^2\)).\(^{7,15–17}\) Importantly, there is no dose of anthracycline that is deemed completely safe.\(^{11}\) Therefore, all patients treated with anthracyclines are at risk for cardiac dysfunction.\(^{7,18–23}\)

Endomyocardial biopsies from anthracycline-treated patients may demonstrate vacuolar degeneration, cell loss, compensatory hypertrophy, and interstitial fibrosis with even a low dose of anthracyclines, suggesting that all doses of anthracycline cause cardiac damage on a cellular level.\(^{24}\) On electron microscopy, loss of myofibrils, mitochondrial swelling, disordered nuclear chromatin, increased lysosomal number, and distention of the sarcoplasmic reticulum are findings in patients treated with anthracyclines.\(^{25–27}\)

Anthracycline-associated cardiomyopathy is progressive and irreversible. Therefore, increased time following anthracycline exposure increases both the risk for significant cardiomyopathy and the severity of disease. In other words, anthracycline therapy may initiate a process of injury that can be clinically silent, followed by a period of years, or decades, of compensatory response to injury, where patients have no clinical symptoms, and eventually followed by overt symptomatic HF, when contractility and adequate cardiac hemodynamics can no longer be maintained.\(^{28}\) Therefore, the traditional segregation of anthracycline cardiotoxicity into acute, early-onset, and late-onset categories, according to time of occurrence of cardiac problems, may be more artificial in terms of underlying pathophysiological processes.\(^{22,28,29}\)

Acute toxicity is defined as occurring during anthracycline administration and occurs in \(<1\)% of patients. It is usually characterized by a transient decrease in left ventricular systolic function, often with cardiac arrhythmias, that rapidly resolves.\(^{28}\) Early-onset cardiotoxicity occurs within the first year after therapy in up to 2.1% of patients and can be progressive.\(^{11}\) The third, and the most common and most troublesome, type of cardiac effect is late-onset, progressive cardiotoxicity that has been reported in 5% to 50% of patients depending on the dose.\(^{14}\) However, the exact incidence of the late cardiotoxicity, especially in adults, has been difficult to ascertain, given its insidious onset, the dearth of systematic long-term follow-up, and the lack of standardized detection and reporting of cardiovascular events that are distantly removed from initial therapy.\(^{27}\)

**Pathophysiology**

The effects of anthracycline on cardiomyocytes have been previously well described\(^{26–28}\); however, recent data have demonstrated that this agent also affects noncardiomyocyte cells including the vascular endothelial cells, fibroblasts, and also cardiac stem cells. These effects on different cardiac tissues are described in detail by recent publications and reviews\(^{30–31}\); we present a synthesis of this information in Figure 2.

Despite a remarkably extensive literature on many aspects of anthracycline cardiotoxicity, a single unifying model for its effects has not yet emerged. Anthracycline-associated myocardial damage has been long regarded as occurring primarily through the generation of reactive oxygen species (ROS), or free radicals, especially in the setting of increased cellular iron.\(^{41}\) The “ROS and iron” theory is supported by the formation of ROS in response to anthracycline treatment\(^{34,35}\) and the cardioprotective effects associated with iron chelators.
such as dextrazoxane (ICRF-187). The mechanism of action of the latter is attributed, at least in part, to its hydrolytic transformation into the iron-chelating metabolite ADR-925 that displaces iron from anthracycline–iron complexes or chelates free or loosely bound cellular iron, thereby preventing site-specific iron-catalyzed ROS damage.

However, recent evidence has suggested that the ROS theory is inadequate to account for all features of anthracycline toxicity. Studies with a variety of antioxidants have not demonstrated cardioprotection from anthracycline-induced toxicity. Although the exact molecular and cellular mechanisms of anthracycline cardiotoxicity are not completely understood, there is broad agreement that anthracycline-associated cardiotoxicity stems from cardiomyocyte apoptosis or necrosis and disruption of normal sarcomere structure and function. One of the critical proteins of the sarcomere is titin, a very large myofilament protein that is central to normal regulation of sarcomere turnover and function. Degradation of titin by anthracycline in turn accelerates cardiac myofilament degradation. Furthermore, titin also regulates diastolic function in the heart by aiding the return of the sarcomere to resting state during diastole, as well as initiating contraction during systole. Therefore, proteolysis and degradation of titin could lead to diastolic and systolic dysfunction, as seen in anthracycline-treated patients. Dystrophin, another large structural protein of the sarcomere and a common target of other etiologies of dilated cardiomyopathy, has also been identified as a potential target of anthracycline toxicity. Mice with dystrophin mutations are more susceptible to anthracycline-induced cardiomyopathy compared with controls. Perhaps several large cardiac structural contractile proteins are damaged by anthracyclines, leading to the observed greater susceptibility to dilated cardiomyopathy.

Several other effects of anthracyclines on cardiac muscle may also be relevant to their toxic effects. For instance, anthracyclines may irreversibly alter the energetics of the cardiomyocyte and its ability to generate adequate contraction. Anthracycline can change intracellular ATP production in cardiomyocytes, downregulate messenger RNA expression for SR calcium-ATPase, depress cardiac glutathione peroxidase activity, and cause respiratory defects associated with mitochondrial deoxyribonucleic acid damage.

Recent insights into the effects of anthracyclines on the heart may come from the observation of synergistic cardio-
toxic effects of anthracyclines with trastuzumab, a monoclonal antibody to the ErbB2 (HER-2) growth factor receptor. Trastuzumab (Herceptin, Genetech) causes cardiac dysfunction by disrupting ErbB2 signaling both in tumors, as well as in the heart. ErbB2 and ErbB4 are thought to be essential for cardiomyocyte survival, and to potentially regulate sarcomere structure. When activated by the binding of its ligand neuregulin-1, ErbB2 dimerizes with ErbB4 to activate downstream tyrosine kinase signaling pathways that promote cardiomyocyte survival. The combination of anthracyclines inducing cardiomyocyte apoptosis and necrosis, combined with inhibition of cardiomyocyte prosurvival pathways by trastuzumab, is postulated to have led to HF observed in adult patients treated for breast cancer.

The synergy between trastuzumab and anthracyclines suggests the potential importance of crosstalk between important cardiomyocyte survival pathways and the sarcomere pathways previously implicated in anthracycline-induced toxicity. Furthermore, the findings above support the hypothesis that when anthracycline cardiomyocyte damage is combined with inhibition of normal cardiac survival pathways from other cardiac stressors, HF or clinical cardiotoxicity is more likely to result (Figure 2).

**Clinical Risk Factors**

The risk and severity of anthracycline-induced cardiomyopathy depend on both treatment-related and patient-related risk factors (Table 1). Anthracycline cardiotoxicity may be exacerbated by other anticancer agents including new targeted therapies. For pediatric cancer survivors, sunitinib (Sutent, Pfizer), a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor, platelet-derived growth factor receptor, and Flt3, is now being used to treat children with sarcomas. The agent has been associated in some adult patients with HF and accelerated hypertension. Given what is known about tyrosine kinase inhibitors, children, especially those who have received anthracycline, may be at greater risk for cardiotoxicity. However, direct data on children are not yet available.

Patient-related risk factors for anthracycline toxicity include female gender, African American descent, prior history of cardiac disease, and hypertension. Of the subset of pediatric cancer survivors treated before age 18 years, individuals treated before age 4 years are at the highest risk for cardiomyopathy. There are recent data to suggest that the

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Anthracycline-Induced Cardiomyopathy and Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-Related Factors at Time of Treatment</strong></td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>African American ancestry</td>
</tr>
<tr>
<td>Age &lt;4 years at time of cancer treatment</td>
</tr>
<tr>
<td>Genetic polymorphisms (see Appendix)</td>
</tr>
</tbody>
</table>

H/o indicates history of.
heart actually has regenerative capacities. However, Huang recently demonstrated that anthracycline causes depletion of the cardiac stem cells in mice exposed to anthracycline as "juveniles." This destruction of cardiomyocyte progenitors in the young heart may lead to inadequate myocardial mass as the child grows. Low myocardial mass results in a pathological increase in afterload, even in normotensive patients. Other important cardiac stressors may include pregnancy for women, surgery, myocarditis, or ischemia.

The range in severity of anthracycline cardiotoxicity suggests the possibility of genetic predispositions. Polymorphisms that alter anthracycline pharmacodynamics may correlate with suggestive differences in rates of cardiotoxicity. Interindividual differences and interethnic variability in processing and detoxifying anthracycline may lead to differing severity of cardiotoxicity. A detailed discussion of these differences are beyond the scope of this review; for additional information, see the review by Lal et al and references therein.

It has been hypothesized that cardiotoxicity of anthracyclines is more severe in the setting of increased ROS. Genes that regulate the NADPH oxidase complex, which is involved with ROS generation, may potentially have an effect on cardiotoxicity. Other exploratory studies suggest genes regulating anthracycline transport, such as the efflux drug pumps MPR1 and MPR2, may also modify anthracycline cardiotoxicity; however, the statistical associations of these genes, and hence their clinical significance, are still preliminary. Systematic population studies will be required to assess potential genetic susceptibility to anthracycline toxicity on a genome-wide level, which could be of significant importance for stratifying patients to doses that might be best tolerated. Finally, the cumulative burden of other cardiac stressors, including cardiac risk factors and exposure to other anticancer therapeutic agents, also strongly influences severity and clinical symptoms of anthracycline-induced cardiotoxicity.

**Diagnosis**

Because anthracyclines are known to cause HF, screening of cardiac function is recommended in patients who have received anthracyclines. Two-dimensional echocardiography, including the use of tissue Doppler imaging, is the most commonly used noninvasive imaging modality to assess systolic and diastolic dysfunction in this population, given the portability and cost-effectiveness of ultrasound. Cardiac MRI provides excellent assessment of left ventricular function, but is less widely available, more costly, and may require sedation in children. Other noninvasive modalities such as radionuclide ventriculography can assess left ventricular ejection fraction (LVEF) but exposes the patient to radiation and does not provide comprehensive assessment of diastolic dysfunction or restrictive cardiomyopathy. Endomyocardial biopsy can be used to diagnose anthracycline cardiotoxicity but is currently not frequently used, given its invasive nature and its lack of correlation with clinical symptoms.

More than half of pediatric survivors show cardiac abnormalities on echocardiography or radionuclide angiography 10 to 20 years after treatment, with the incidence of cardiotoxicity increasing significantly with time. Left ventricular dysfunction is particularly prevalent after treatment, occurring in 5% to 20% of all patients treated with anthracyclines. One study found that 56% (22/39) of pediatric patients who received anthracyclines had an LVEF less than \( -2 \) SD of healthy children. It has also been suggested that diastolic dysfunction in children may be an early sign of anthracycline-induced cardiac dysfunction.

In patients with known anthracycline-associated dilated cardiomyopathy receiving serial monitoring, the onset of HF can be more readily attributed to anthracycline cardiotoxicity. Even so, other precipitants, such as myocarditis and recreational drug use, including steroids, must be excluded.

Recommendations for type and frequency of screening in children treated with anthracyclines are summarized by Shankar et al. More comprehensive recommendations for long-term follow-up of adult survivors of childhood cancer are available at the Children's Oncology Group website (www.survivorshipguidelines.org).

**Prevention and Treatment**

The only compound found to be cardioprotective for long-term cardiac dysfunction is dexrazoxane, although whether its efficacy reflects antioxidant effects or other mechanisms remains under debate. In children treated with high-dose doxorubicin for acute lymphoblastic leukemia, concomitant administration of dexrazoxane resulted in less troponin T elevation during therapy than with standard therapy. After 8 years of follow-up, the dexrazoxane-treated group also had higher LVEFs, as compared with those who received standard therapy. However, the broad use of dexrazoxane has been limited out of concern over its possible interference with the anticancer activity of anthracycline. This ever-present tension between cancer cure and cardioprotection continues to be an area of active investigation and interest.

Pegylated or uncoated liposomal anthracycline formulations also have been shown in some studies to induce less cardiotoxicity than standard anthracycline therapy, but this has not been widely used. Surprisingly, despite the long-standing use of anthracyclines, many prominent areas of research still remain incompletely explored to describe their mechanism of action and of side effects.

Treatment of anthracycline cardiomyopathy has been extremely limited; the most promising potential option to date is angiotensin-converting enzyme inhibitors (ACEIs). A recent study of adults showed that ACEIs, initiated within 6 months of dysfunction, resulted in decreased cardiovascular damage at 2.5 years. However, in a small cohort of children with long-standing anthracycline-induced systolic dysfunction, a trial of enalapril did not change the long-term course of the disease, despite temporarily increasing the LVEF. The reasons for these differing findings are unclear and perhaps reflect differences in pathophysiology or timing of intervention. Further investigation regarding optimal timing of therapy with ACEIs is warranted, and novel strategies are needed.

**Mediastinal Radiation**

Cardiovascular disease is also one of the leading causes of late mortality in pediatric patients treated with mediastinal radiation. Radiation to the chest causes direct damage to
cardiac muscle, valves, and coronary arteries, whereas RT for neuroblastoma and bone marrow transplantation also can increase cardiac risk factors for premature coronary artery disease (CAD).63–65 Hodgkin’s lymphoma (HL) is the paradigm for cardiac irradiation and its subsequent late effects. Much of our understanding about late cardiovascular sequelae is derived from HL survivors, who typically receive high-dose irradiation to a fairly stereotyped mediastinal field that includes the heart.63,66–71 Recent findings also suggest other cancer survivors (eg, bone marrow transplantation recipients), who receive total body radiation in addition to anthracycline-based therapy and methotrexate, an agent known to cause endothelial dysfunction, are also at high risk for cardiovascular complications.72

Late cardiovascular effects after radiation may be extremely diverse, more so than with anthracycline. These effects, occurring more than 5 years after treatment, range from valvular heart disease, premature CAD, carotid disease, cardiomyopathy, and HF to constrictive pericarditis and complete heart block.7 The cumulative incidence of cardiac disease in survivors of HL rises from 2% at 5 years after treatment, to 23.2% at 25 years after treatment.73 The most severe cardiac effects typically involve the cardiovascular structures that fall within the radiation portal. This may lead to unusual, atypical clinical presentations that can usually be related in retrospect to the original radiation portal. The coronary arteries, the carotid arteries, the subclavian arteries, the internal mammary arteries, the mesenteric arteries, and also the peripheral vasculature have all been reported to be involved.

Mediastinal radiation can result in development of premature CAD,7,63,66,67,69,70,74 with cumulative risk for myocardial infarction being 14.2% at 20 to 25 years for young adults treated with RT.70 Other studies have shown that RT increases risks for myocardial infarction and HF 2- to 7-fold at a median follow-up of 18.7 years.74 Furthermore, childhood cancer survivors also have an increased risk for stroke, because the carotid arteries and/or the cerebrovasculature are frequently included in the radiation field.75 It was observed that 50% of all Childhood Cancer Survivor Study patients who had a stroke also have concomitant cardiac issues.76

Patients with a history of mediastinal radiation are also at increased risk for valvular heart disease, with these risks also increasing with time following RT: 60% of HL survivors treated with RT have moderate to severe valvular dysfunction at >20 years after treatment.67,68 Studies of asymptomatic long-term HL survivors have detected substantial subclinical valvular disease.68 Therefore, routine periodic screening for valve disease in patients treated with mediastinal radiation has been recommended.7

Patients who have received RT are at greater risk for developing cardiomyopathy. In contrast to anthracycline toxicity that causes a dilated cardiomyopathy, radiation toxicity is predominantly restrictive in nature. Significant systolic dysfunction is relatively infrequent with RT, without a history of ischemia, with the majority of patients having LVEFs or fractional shortening at the lower limits of normal or mildly reduced (Table 2).68,77–79 Mediastinal radiation has been shown to result in predominantly diastolic dysfunction that is recognized as primarily restrictive changes. Diastolic dysfunction in long-term childhood cancer survivors treated with RT results in decreased exercise tolerance and a reduction of MvO2 of <20 mL/kg per square meters.78

Pathophysiology

Whereas RT is widely thought to cause tumor cell death via DNA damage, the mechanisms for the arterial complications of RT are not entirely certain but are thought to be mediated by endothelial cell dysfunction by several possible mechanisms.82 It has been hypothesized that decreased bioavailability of endothelial-derived nitric oxide may result in increased platelet aggregation and proliferation of vascular smooth muscle cells.82 Abnormal endothelium-dependent vasodilation has also been demonstrated in vitro and in humans after radiation exposure.83–85 Furthermore, RT can cause chronic impairment of endothelium-dependent vasodilation in patients in irradiated axillary arteries of breast cancer patients.82 Irradiation of muscular arteries resulted in endothelial cell death with abnormal luminal surfaces after radiation.86 Less is known about the exact mechanisms of other radiation-associated cardiovascular events such as valvular heart disease. Greater understanding of the etiologies of radiation-induced CVD would allow development of future preventative therapies to ameliorate radiation-associated cardiotoxicity.

### Risk Factors

Several treatment-related risk factors for late cardiovascular complications have been identified (Table 3). Treatment-related factors include the use of older RT protocols, anteriorly weighted radiation fields, lack of subcutaneous shielding, and radiation doses of ≥40 cGy in patients who have not received anthracycline, or doses of ≥30 cGy in those who

<table>
<thead>
<tr>
<th>Patient-Related</th>
<th>Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of treatment</td>
<td>Anteriorly-weighted radiation fields</td>
</tr>
<tr>
<td>Presence of traditional cardiac risk factors</td>
<td>Lack of cardiac shielding</td>
</tr>
<tr>
<td>Years since treatment</td>
<td>Dosage of ≥40 cGy</td>
</tr>
<tr>
<td></td>
<td>Dosage of ≥30 cGy with anthracycline treatment</td>
</tr>
<tr>
<td></td>
<td>Concurrent treatment with other chemotherapy</td>
</tr>
</tbody>
</table>

### Table 2. Cardiomyopathy Associated With Anthracycline Toxicity and Radiation Toxicity

<table>
<thead>
<tr>
<th>Anthracyclines</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated</td>
<td>Primarily systolic dysfunction</td>
</tr>
<tr>
<td>Normal to mildly decreased LVEF</td>
<td>Primarily diastolic dysfunction</td>
</tr>
<tr>
<td>Decreased LVEF</td>
<td>Dilated</td>
</tr>
<tr>
<td>Dilation</td>
<td>Systolic</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Diastolic</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction.
have received anthracyclines.28 Because radiation-associated CVD is progressive, longer time since radiation exposure increases the risk of cardiovascular events.7,63,68 Traditional coronary disease risk factors such as hyperlipidemia, hypertension, and smoking, as well as younger age67 at the time of RT (age, <21 years), are also associated with increased radiation-related injury.64,65,74 Moreover, patients diagnosed with cancer frequently have other comorbidities, such as diabetes and hypertension, many of which result in an increased risk of CVD.87 Hull et al found in a younger population of HL survivors that 14.2% (59/415) had hypertension.67 Multiple cardiovascular risk factors were also common in other populations of cancer patients, such as those with testicular88 and lung89 carcinomas.

Radiation therapy has been shown to compound the cardiotoxicity of anthracyclines, and simultaneous use of these treatment techniques increases the risk for developing a cardiac event.7,18,20,22,23,63,74,78,90 Myrehaug et al found increased risk for cardiac morbidity, as measured by 15-year cumulative incidence of cardiac hospitalizations, in patients of all ages who have received both mediastinal radiation and doxorubicin, compared with those receiving either modality alone.91 Patients receiving both RT and anthracyclines have a relative risk of 13.0 (10.4 to 16.3) for developing a grade 3 or 4 (severe or life-threatening) condition23 and a 7.9% cumulative incidence of HF and cardiomyopathy.74 Systolic dysfunction was frequently found in patients with treatment regimens including both RT and anthracyclines.78 Currently, it is unclear whether the effects of RT and anthracyclines represent synergistic effects via a common final pathway or additive effects on cardiac muscle via distinct pathways.

Diagnosis

Echocardiography remains the most widely used screening techniques for detecting cardiac abnormalities following RT and has proven to be especially well suited for assessment of the diverse cardiovascular pathology that may result. Echocardiography is also beneficial in that it permits portable, noninvasive, serial evaluation of disease progression that is necessary in long-term cardiac follow-up of cancer survivors.7,92 Novel, noninvasive techniques such as tissue Doppler imaging, strain and strain rate imaging, and myocardial deformation imaging can be performed during the echocardiographic examination and have been shown to detect subclinical myocardial dysfunction in vivo and in patients.93–96 Development of noninvasive imaging techniques for early detection of cardiac dysfunction associated with cancer therapeutics continues to be an active area of investigation.

Radionuclide ventriculogram is able to evaluate right ventricular function more effectively than echocardiography,57 although echocardiography is far superior to radionuclide ventriculogram in the assessment of diastolic and restrictive abnormalities commonly seen in children who have received chest radiation.79,92,97 Recommendations for type and frequency of screening of adult survivors of childhood cancer are also summarized by Shankar et al,7 as well as the Children’s Oncology Group.55

Prevention and Treatment

Given that cardiovascular risk factors are prevalent in cancer survivors, assessment of a patient’s history of cardiac risk factors is strongly recommended. Because the risk for CAD increases significantly 10 years after RT, screening for CAD should be undertaken in long-term survivors.7,63,74 There is a dearth of data about therapies that might ameliorate other types of radiation-related CVD. Therefore, prevention of long-term CVD in cancer survivors focuses on modification of treatment-related risk factors at the time of administration of chest radiation, such as dose reduction and limitation of the size of radiation portals. All of these approaches must be balanced with the importance of adequately treating the patient’s tumor.

Perhaps surprisingly, use of respiratory maneuvers during RT may have the potential to reduce cardiac irradiation and, thus, long-term risks of cardiovascular effects. Preliminary studies in adults receiving chest radiation, specifically those with breast cancer, may show some relevance for other populations.98 The heart lies in close proximity to the left breast and is frequently irradiated during RT for left-sided breast cancer, whereas the heart is not included in the right breast radiation plane.99 Traditionally, RT is given over approximately 45 seconds with the patient lying supine and breathing quietly. Deep inspiratory breath holding during RT for left-sided breast cancer appears to decrease inclusion of the heart in the RT field, while maintaining radiation dose to the tumor.98–100 The diaphragm is pulled downwards, displacing the heart caudally. Inspiration increases the anterior–posterior diameter of the chest and displaces the left breast away from the heart. These anatomic changes result in decreased cardiac irradiation, with complete displacement of the heart outside the field in 21% of patients.99,100 Respiratory gating for radiotherapy beam delivery is now a widely available technique at most of the major radiotherapy machine vendors.101,102 Although the design of mediastinal fields for some cancers may not allow the use of respiratory maneuvers, it is worth exploring every possible means to decrease cardiac and valvular exposure when designing radiation portals.

Future Directions

Greater understanding of mechanisms of late cardiovascular effects is greatly needed for long-term cancer survivors. Identification of mechanisms of cardiotoxicity is critical for developing preventative strategies or targets to ameliorate cardiovascular late effects of cancer treatment. In vivo models of cardiotoxicity focused beyond the acute complications of therapy, toward studying the chronic effects of anticancer therapy are vitally needed. In vitro models studying not only neonatal but also adult cardiomyocytes may lead to greater understanding of cardiotoxicity in humans.

In the future, greater tailoring of anticancer treatment to minimize therapy to those with excellent prognoses, while maintaining more intensive treatments for those at high risk of cancer recurrence, will decrease the risk of cardiovascular complications. As patients age, they may likely accumulate increasing medical comorbidities and cardiac risk factors that further compound the risk of late-onset cardiotoxicity.
Patient-based cardiac risk assessment, coupled with assessment of likelihood of cancer recurrence, ultimately will allow for intelligent tailoring of modern anticancer therapy to maximize cure while decreasing both short- and long-term late effects of curative therapy.

Acknowledgments

We thank Tammy Chu, Rebecca Randall, Christopher Walsh, Anita Li, and Elizabeth Abernethy for help with the preparation of this manuscript.

Sources of Funding

M.H.C. is supported by the Translational Fund for Cardiology and Oncology and the Department of Cardiology at Children’s Hospital Boston.

Disclosures

None.

References

Cardiovascular Disease: Cause of Morbidity and Mortality in Adult Survivors of Childhood Cancers
Ming Hui Chen, Steven D. Colan and Lisa Diller

Circ Res. 2011;108:619-628
doi: 10.1161/CIRCRESAHA.110.224519

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/108/5/619

An erratum has been published regarding this article. Please see the attached page for:
/content/108/8/e11.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/
Correction

Cardiovascular Disease: Cause of Morbidity and Mortality in Adult Survivors of Childhood Cancers

In the article that appears on page 619 of the March 4, 2011, issue, Figure 2 included a typographical error. The correct figure is as follows:

**Figure 2.** Effects of anthracycline on cardiovascular system that lead to cardiomyopathy and HF. Anthracycline results in direct cardiomyocyte loss, decreased contractility, and compromise of the microvasculature. Furthermore, the effect of anthracycline on cardiac progenitor cells and fibroblasts reduces the ability of the already-compromised heart to recover from additional cardiac stressors or cardiac injuries.

The authors regret this error. This error has been noted and corrected in the online version of the article, which is available at [http://circres.ahajournals.org/cgi/content/full/108/5/619](http://circres.ahajournals.org/cgi/content/full/108/5/619)

**Reference**


DOI: 10.1161/RES.0b013e31821bc2f1

(Circ Res. 2011;108:e11)  
© 2011 American Heart Association, Inc.  
*Circulation Research* is available at [http://circres.ahajournals.org](http://circres.ahajournals.org)