Cancer is diagnosed in >12,000 children and adolescents in the United States each year.\(^1\) Progress in cancer therapeutics over the past 40 years has remarkably improved survival rates for most childhood malignancies. For all pediatric cancers, 5-year survival increased from 58% for children diagnosed between 1975 and 1977 to 82% for those diagnosed between 1999 and 2006.\(^2\) In the United States, this success translates into >325,000 survivors of childhood cancer, of whom 24% are now >30 years from diagnosis.\(^3\) During this same period, the incidence of many histological subtypes of childhood cancer has increased, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia, non-Hodgkin lymphoma, neuroblastoma, and soft-tissue and germ-cell tumors.\(^3\) Consequently, the number of childhood cancer survivors is expected to increase as a result of the rising pediatric cancer incidence and improved long-term survival rates.\(^3\)

The increasing number of survivors soon revealed acute and delayed modality-specific toxicities and their impact on quality of life and early mortality. In their seminal 1974 publication, Meadows and D’Angio\(^4\) described the wide array of potential late effects of successful therapy for childhood cancer. In the past 2 decades, the Childhood Cancer Survivor Study has also improved our understanding of the long-term mortality and morbidity in this high-risk population. Among young adult survivors of childhood cancer diagnosed between 1970 and 1986, at least 1 of 6 domains of health status (general health,
mental health, functional status, activity limitations, cancer-related pain, and cancer-related anxiety) declined moderately to severely in 44%.

The cumulative incidence of a chronic health condition 30 years after cancer diagnosis is now 73%, with a cumulative incidence of 42% for severe, disabling, or life-threatening conditions or death attributable to a chronic condition. Also by 30 years after cancer diagnosis, the cumulative mortality rate from causes other than recurrence (eg, second malignancies, cardiac and pulmonary disease) exceeded that from recurrence or progression of the original cancer, and these other causes did not plateau with time. These findings have been confirmed in other large cohort studies and among survivors treated with more current therapy.

Early in the study of late effects after cancer therapy, the developing cardiovascular system of children and adolescents was recognized as being particularly vulnerable. In the proceedings of the first National Cancer Institute's Conference on the Delayed Consequences of Cancer Therapy in 1975, Gilladoga et al reported that 9 of 110 children receiving a cumulative dose of either doxorubicin or daunorubicin >500 mg/m² experienced severe cardiomyopathy with congestive heart failure (CHF) while undergoing therapy or soon thereafter. Not long afterward, Brosius et al described the necropsy findings of 16 cancer survivors diagnosed in childhood or young adulthood who had received >35 Gy of cardiac radiation. All had evidence of radiation-induced cardiac damage, and 6 had at least 1 coronary artery with severe stenosis. Since these early studies, the incidence and risk factors of cardiovascular disease (CVD) have been studied intensely, as described in the present article. Indeed, cardiac-specific disease is the most common noncancer cause of death among long-term childhood cancer survivors.

These investigations, which linked specific treatment and host factors to adverse outcomes, have guided pediatric cancer treatments and health monitoring during and after therapy. For example, in the aforementioned 1975 proceedings, Gilladoga and colleagues recommended maximum cumulative anthracycline doses of 500 and 600 mg/m² in children treated with or without cardiac radiation, respectively. Subsequently, newer protocols have sought to balance the benefits of treatment with the risk of anthracycline-related cardiomyopathy by testing lower cumulative doses and alternative dosing schedules and methods of administration, as well as by adding potentially cardioprotective agents. Similarly, to reduce the risk of cardiac disease and second malignant neoplasms (eg, breast cancer), the use, dose, and volume of radiation to the heart has decreased substantially in frontline trials for children with hematological and low-stage, biologically favorable solid malignancies.

Current therapy for childhood malignancies has evolved into a risk-adapted approach that bases the intensity of therapy on clinical, biological, and genetic factors and on treatment response (Table 1). Most pediatric cancer protocols still rely on cytotoxic chemotherapy and radiation, with few integrating new biological and molecularly targeted agents. Research establishing dose-related toxicity profiles for specific chemotherapeutic agents (eg, anthracyclines; alkylating agents) and radiation has guided their risk-adapted use in current protocols. The universal objective of all pediatric cancer trials is to prescribe treatments at cumulative doses that balance cancer control with preserved health and function of normal tissues.

Although some adverse effects of cytotoxic therapy may be unavoidable, the evolution of pediatric cancer treatments has already changed the prevalence and spectrum of adverse treatment effects. Because threshold doses for vital organ toxicity have been recognized, acute life-threatening treatment effects are relatively uncommon after current therapy, except in survivors who require intensive multimodal therapy for aggressive and refractory or relapsed malignancies. However, life-altering toxicities affecting endocrine, reproductive, musculoskeletal, and neurological function still occur after specific treatments (eg, infertility after high-dose alkylating agent chemotherapy or gonadal radiation). Of increasing concern are the subclinical changes observed after cancer treatment that may contribute to the premature onset of common diseases associated with aging, such as obesity, diabetes mellitus, CVD, hypertension, and cancer.

These data underscore the need for research to evaluate the impact of aging and health behaviors on health outcomes of adults treated for cancer during childhood.

This scientific statement is targeted to pediatric oncologists, general pediatricians, adolescent and young adult specialists and practitioners, as well as the number of other healthcare providers who may care for survivors of childhood cancer.

Pathophysiology of Cardiovascular Toxicity

Pathophysiology of Cardiovascular Toxicity From Chemotherapeutic Agents

Anticancer drugs are designed to interfere with rapidly dividing neoplastic cells; however, these same drugs can also have adverse effects on multiple organs and normal tissues. The most frequently reported toxicities occur in tissues composed of rapidly dividing cells, the capacity of which for recovery tends to minimize long-term consequences. In contrast, the cardiovascular system consists of many cells that have limited regenerative capability, a consequence of which is the potential for increased susceptibility to long-term adverse effects from chemotherapeutic agents. In the cardiovascular system, chemotherapeutic agents may cause adverse effects by directly compromising myocardial function or peripherally by changing vascular hemodynamics. These adverse effects may be predictable or unpredictable, set or cumulative, and potentiated or ameliorated by the use of concomitant antineoplastic agents. However, it is not always possible to predict drug toxicity in children from adult clinical experience.

Anthracyclines, such as doxorubicin, are frequently used to treat the most common form of cancer in children, ALL. Anthracyclines are among the most notorious chemotherapeutic agents that cause cardiotoxicity in both adult-onset and childhood malignancies. Except for anthracyclines, the use of chemotherapeutic agents and reports of associated cardiotoxic events are less extensive in children than in adults. Examples of nonanthracycline agents used in adult and pediatric populations that have been associated with cardiotoxicity include cyclophosphamide, cytarabine, cisplatin, and ifosfamide (Table 2). Other compounds (paclitaxel, 5-fluorouracil [5-FU], and amsacrine), also reported to induce cardiotoxicity in adults, have been used infrequently as first-line agents to
Table 1. Trends in the Use of Cardiotoxic Treatment Modalities for Common Childhood Cancers

<table>
<thead>
<tr>
<th>Histology</th>
<th>Anthracycline Chemotherapy</th>
<th>Cardiac Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>• Increased use of anthracyclines in high-risk patients since 1970s, with cumulative doses ranging from 45 mg/m² (low risk) to 350 mg/m² (high risk)</td>
<td>• Introduction of craniospinal irradiation to treat and prevent CNS leukemia in 1960s–1970s</td>
</tr>
<tr>
<td>Frequency: 18.7%</td>
<td></td>
<td>• Increasing use of cranial irradiation (18–24 Gy) and intrathecal + high-dose chemotherapy for CNS-directed therapy in 1970s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decline in use of craniospinal radiation for CNS-directed therapy since 1970s and now limited to cases of relapse</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>• Introduction of anthracyclines into remission induction regimens in 1970s</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Frequency: 4.5%</td>
<td>• Escalation of anthracycline doses (320–450 mg/m²) in 1990s</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>• Introduction of anthracyclines in ABVD combination in 1970s (6–8 cycles, 300–400 mg/m²)</td>
<td>• Introduction of extended-field high-dose (35–44 Gy) mantle/medialstinal irradiation in 1960s</td>
</tr>
<tr>
<td>Frequency: 8.8%</td>
<td>• Introduction of risk-adapted regimens in 1980s restricting anthracycline dose to ≤200 mg/m² for low-risk and ≤300 mg/m² for high-risk disease presentations</td>
<td>• Introduction of involved-field low-dose (15–25.5 Gy) mantle/medialstinal irradiation in pediatric combined-modality regimens in 1970s</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>• Use of anthracyclines for all histological subtypes since 1960s with dose ranging from 120 to 300 mg/m², based on stage and history</td>
<td>• Selected use of radiation in 2000s for favorable and intermediate- or high-risk patients achieving complete remission to chemotherapy</td>
</tr>
<tr>
<td>Frequency: 6.7%</td>
<td></td>
<td>• Variable use of radiation to involved nodes from 1960s to 1980s</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>• Not applicable</td>
<td>• Use of cranial irradiation for CNS prophylaxis from 1970s to 1990s</td>
</tr>
<tr>
<td>Frequency: 16.7%</td>
<td></td>
<td>• Selected use of involved-field irradiation therapy for cases with relapsed/refractory disease</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>• Use of doxorubicin in combination chemotherapy regimens since 1970s (105–175 mg/m²)</td>
<td>• Use of cranial irradiation for most brain tumors, with only indirect impact on cardiovascular disease risk via neuroendocrine effects</td>
</tr>
<tr>
<td>Frequency: 5.1%</td>
<td>• Escalation of doxorubicin dose (300 mg/m²) in selected trials for high-risk disease</td>
<td></td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>• Introduction of doxorubicin (300 mg/m²) into combination chemotherapy regimens in 1970s</td>
<td></td>
</tr>
<tr>
<td>Frequency: 4.2%</td>
<td>• Use of doxorubicin limited to advanced-stage disease since 1980s and dose reduced to 150 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>• Introduction of doxorubicin into combination chemotherapy regimens in 1970s</td>
<td>• Whole lung radiation (18 Gy) to pulmonary metastatic disease since 1970s and now limited to cases of relapse/refractory disease</td>
</tr>
<tr>
<td>Frequency: 2.9%</td>
<td>• Use of doxorubicin limited to high-risk patients in selected contemporary regimens (375 mg/m²)</td>
<td>• Reduction of whole lung radiation to 14.4 Gy for pulmonary metastatic disease in 1990s</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>• Use of doxorubicin (450 mg/m²) in combination chemotherapy regimens since 1970s</td>
<td>• Standard use of whole lung radiation dose of 15 Gy for pulmonary metastatic disease since 2000s</td>
</tr>
<tr>
<td>Frequency: 3.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>• Use of doxorubicin (375 mg/m²) in combination chemotherapy regimens since 1970s</td>
<td></td>
</tr>
<tr>
<td>Frequency: 1.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frequencies noted represent percent distribution of childhood cancers by ICCC category for age group <20 years, all races, both sexes, SEER, 1975–1995.24

ABVD indicates chemotherapy regimen of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine; CNS, central nervous system; ICCC, International Classification of Childhood Cancer; RT, radiation therapy; and SEER, Surveillance, Epidemiology, and End Results.

treat pediatric tumors.37 Children are also being treated with newer types of antineoplastic compounds (tyrosine kinase inhibitors), some of which have been reported to cause cardiotoxic activity in adult patients.39 In children, cardiac toxicity can be an important complication both during and after cancer treatment. Clinically, cardiac toxicity is an important issue because many children responding to treatment may subsequently experience acute or chronic cardiovascular adverse effects that could impact their quality of life, as well as limit future treatment options.
Table 2. Examples of Pediatric Chemotherapeutic Agents Associated With Cardiotoxicity

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Class/Compound</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Taxanes/paclitaxel</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Arrhythmias/QT prolongation</td>
<td>Amsacrine</td>
<td>Interference with HERG currents</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines (doxorubicin)</td>
<td>Inhibition of cardiac kinases</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>Interference of ion channels</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>Antimetabolites/5-fluourouracil</td>
<td>Coronary vasospasm</td>
</tr>
<tr>
<td>Left ventricular dysfunction/CHF</td>
<td>Anthracyclines (doxorubicin)</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td></td>
<td>Tyrosine kinase inhibitors</td>
<td>Inhibition of Abi kinase</td>
</tr>
<tr>
<td></td>
<td>(imatinib/sunitinib)</td>
<td>mitochondrial dysfunction</td>
</tr>
<tr>
<td></td>
<td>Alkylation agents</td>
<td>Vascular endothelial cell injury</td>
</tr>
<tr>
<td></td>
<td>(cyclophosphamide/isofluramide)</td>
<td>Hypomagnesia, coronary artery fibrosis</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td></td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; and HERG, human ether-a-go-go related.

The types of chemotherapy-induced cardiovascular alterations reported primarily, but not exclusively, in adults include the following: Acute cardiac rhythm abnormalities (arrhythmias including QT prolongation), myocardial ischemia or infarction, hypertension, and significant left ventricular (LV) contractile dysfunction. The pathogenesis of these diverse cardiovascular effects varies and may involve multiple mechanisms.

Cardiovascular Alterations Induced by Chemotherapeutic Agents

Bradycardia

In adults, both paclitaxel and thalidomide cause reversible sinus bradycardia, with an incidence ranging from 0.1% to 31% and from 5% to 55%, respectively. Paclitaxel has been used to treat breast and ovarian cancer in adults and has been suggested for use in children. Paclitaxel may induce bradycardia directly through actions on the Purkinje system or indirectly through its formulation vehicle, Cremophor EL (polyoxyethylated castor oil). When used in combination, paclitaxel appears to enhance doxorubicin cardiotoxicity by altering doxorubicin pharmacokinetics and increasing the myocyte formation of doxorubicinol, the major metabolite of doxorubicin. Although paclitaxel has been found to be ineffective in children, new taxanes such as cabazitaxel require further investigation to determine their effect on children.

Thalidomide is infrequently used in pediatric cancer treatment. The mechanism that reduces heart rate with thalidomide treatment has not been determined. The effect could be the result of central sedative actions or enhanced vasovagal activity. Thalidomide may also cause deep venous thrombosis, edema, and pulmonary hypertension. Further pediatric clinical trials are needed to determine the mechanism and efficacy of thalidomide.

Arrhythmias and QT Interval Prolongation

Amsacrine. Two acute forms of cardiotoxicity have been associated with amsacrine therapy in adults and children. The more common toxicities are arrhythmias (atrial and ventricular tachycardia) and ECG alterations (prolonged QT intervals and nonspecific ST-segment and T-wave changes) that occur within minutes to hours after treatment. It is possible that the cardiotoxic potential of amsacrine may be enhanced by prior exposure to anthracyclines. Amsacrine is not frequently used in children.

Arsenic Trioxide. Prolonged QT intervals (a potential precursor to serious arrhythmias, such as torsade de pointes and ventricular fibrillation) has been reported in adults undergoing therapy with arsenic trioxide, with an incidence ranging from 26% to 93%. The QT interval returned to normal 8 weeks after arsenic trioxide treatment. Arsenic trioxide is highly efficacious in treatment of both newly diagnosed and relapsed acute promyelocytic leukemia; however, a number of studies describe the occurrence of cardiotoxicity when this drug is used in children.

Tyrosine Kinase Inhibitors. Tyrosine kinase inhibitors such as dasatinib, lapatinib, imatinib, and nilotinib have been implicated in prolonging the QT interval in adults, with an incidence of 1% to 10%. These drugs are commonly used for chronic myelogenous leukemia and ALL. Uses of tyrosine kinase inhibitors in pediatric oncology are still limited; however, Dubois et al reported QT-interval prolongation in 2 of 23 children treated with sunitinib in a phase 1 study of refractory solid tumors.

The mechanism and the structural characteristics of drugs most likely to change the duration of the QT interval have not been determined completely. The QT interval is presumed to increase when HERG (human ether-a-go-go) potassium channel activity (delayed rectifier potassium current) is altered. By interfering with these channels, drugs slow potassium ion entry into the myocyte and thereby prolong repolarization. Additional mechanisms may also be involved, because not all drugs that impede HERG potassium channel activity induce QT prolongation. Both adults and children with cancer may be more susceptible to QT prolongation because of comorbid conditions, disease-related electrolyte disturbances, or concomitant treatment with potentially proarrhythmic medications.

Anthracyclines. Anthracyclines, such as doxorubicin, daunorubicin, epirubicin, and idarubicin, have been associated with prolonged corrected QT (QTc) intervals as measured by surface electrocardiography, a finding that indicates a risk of ventricular tachycardia. They have also been directly associated with premature ventricular contractions, sinus node dysfunction, ventricular late potentials, and decreased QRS voltage. The incidence of these findings ranges from 10% to 30%. The mechanism of the electrophysiological cardiotoxicity is unknown, although the efficacy of dextrazoxane in attenuating this injury suggests that the toxicity may be mediated through free radicals. Acute changes that occur during infusion therapy range from fatal ventricular arrhythmias to minor abnormalities. Some patients at higher cumulative doses have permanent damage, whereas most others recover, at least temporarily. Cumulative toxicity is generally a result...
of damage such as cardiomyocyte death and dysfunction caused during therapy but that is not serious enough to cause symptoms immediately.

In most instances, arrhythmias associated with anthracyclines are transient and do not require specific intervention. However, Kilickap et al\(^58\) reported serious consequences in a patient with syncope and complete heart block who required pacemaker implantation during anthracycline therapy at only modest doses (cumulative dose of 120 mg/m\(^2\)). This response has also been described for epirubicin, which is thought to have a more favorable cardiovascular toxicity profile.\(^59\) Pirarubicin, when evaluated in adults with non-Hodgkin lymphoma, was marginally less cardiotoxic than doxorubicin, with the risk of arrhythmia being 9\% versus 14\%, respectively.\(^60\) However, in that same study, both agents were associated with a similar risk of ischemic cardiac injury.

The relationship between myocyte dysfunction and arrhythmogenesis in cancer cardiotoxicity is not completely determined; however, an investigation by Nakamae et al\(^61\) of 72 adults receiving anthracycline therapy suggests a link between these problems. In that study, the QTc interval during anthracycline therapy correlated moderately well with the degree of LV enlargement (r=−0.43) and even more strongly with ejection fraction (r=−0.46), the negative correlation indicating that the reduction in ejection fraction was associated with longer QTc intervals. Interestingly, the QTc interval was not associated with LV diastolic function, which some investigators believe to be the first step in myocardial injury after anthracycline administration. A 1981 case report describes sudden cardiac death in a patient who had received a high cumulative dose of doxorubicin (490 mg/m\(^2\)) =8 months before and who had no evidence of CHF or history of arrhythmia.\(^62\) There was postmortem evidence of cardiac fibrosis and hypertrophy, so perhaps the absence of recognized clinical heart failure did not exclude marked myocardial dysfunction at the time of the (presumed) arrhythmic death.

Other cancer therapies have been associated with a variety of electrophysiological disorders that arise during therapy. Mitoxantrone can cause arrhythmia during infusion (in conjunction with myocarditis), and 5-FU may cause ischemic changes in addition to prolonging the QTc interval.\(^55,56\) Preexisting coronary artery disease (CAD) and chest radiation are risk factors for 5-FU toxicity.\(^36\) Newer agents used mainly in adults are also proving to have marked cardiotoxicity, including arrhythmogenesis. The tyrosine kinase inhibitors (eg, imatinib and sunitinib) prolong the QT interval, as do protein kinase C inhibitors.\(^55,66\) The mechanism is unknown, but the effect is great and is often dose-limiting. Additionally, the cardiotoxicity of trastuzumab, a monoclonal antibody that acts through the HER2 receptor, is potentiated by coadministration of anthracyclines. The cardiotoxicity is typically expressed as reversible myocardial dysfunction but may manifest as conduction block and ischemia, as described in a recent case report.\(^64\)

**Myocardial Ischemia**

The chemotherapeutic drugs noted below can cause ischemia in localized areas of the myocardium or a coronary artery syndrome.

**Antimetabolites (5-FU and Capecitabine).** An ischemic syndrome (symptoms vary from angina pectoris to acute myocardial infarction [MI]) has been reported in up to 68\% of adults after treatment with 5-FU.\(^65\) Signs of ischemia were observed within 2 to 5 days after patients began treatment and persisted for up to 48 hours after treatment.\(^65\) The risk of ischemia appears to be greater in patients with preexisting CAD. The incidence of ischemic events was also increased in patients whose treatment regimens included high doses of 5-FU administered with or without continuous infusion.\(^45\) 5-FU is not commonly used to treat pediatric tumors; however, 2 separate pediatric case reports describe cardiotoxic activity after exposure to 5-FU. In 1 case, the combination of 5-FU with cisplatin and methotrexate caused severe but reversible cardiotoxicity characterized by tachycardia, hypotension, and reduced LV contractility in a 14-year-old boy.\(^66\) The second case was also a 14-year-old patient in whom acute dilated cardiomyopathy developed after 1 cycle of 5-FU and cisplatin therapy. This patient stabilized but died suddenly during the fifth treatment cycle (possibly of arrhythmia).\(^67\)

Capecitabine, a derivative of 5-FU, appears to cause a similar but less frequent incidence of ischemic toxicity in 3\% to 9\% of patients.\(^68\) The mechanisms responsible for 5-FU- and capecitabine-induced myocardial ischemia are not delineated completely. Adverse effects, such as coronary artery spasm, direct myocyte injury, coronary thrombosis resulting from activated coagulation, and autoimmune responses, have all been proposed as possible causative factors.\(^69\) 5-FU has also been reported to affect vascular endothelial function by decreasing nitric oxide synthase activity. This action can facilitate coronary vessel spasm and protein kinase C–mediated vasoconstriction.\(^69\)

**Microtubule-Targeting Agents (Paclitaxel).** In adults, paclitaxel occasionally causes myocardial ischemia and infarction.\(^45\) Coexisting factors, such as concomitant drug treatment and CAD, appear to increase the occurrence of this toxicity.\(^43\) The release of histamine by polyoxyethylated castor oil (the paclitaxel vehicle) may contribute to the onset of ischemia.\(^43\) Paclitaxel can also exert direct toxic effects on cardiac myocytes. A related compound, docetaxel, has also been reported to cause myocardial ischemia.\(^58\)

**Monoclonal Antibody-Based Tyrosine Kinase Inhibitors (Bevacizumab).** Vascular endothelial growth factor (VEGF) is highly expressed in solid tumors and is critical in modulating important cellular and vascular processes. Bevacizumab binds to and inhibits VEGF activity. This drug can promote arterial thrombotic activity, and in a few patients (3.8\% in 1 study), it induces MI, angina, heart failure, stroke, and transient ischemic attacks (TIAs).\(^28\) These adverse effects were not dose related and occurred any time during treatment (median time, 3 months).\(^70\)

The increased risk of arterial thrombotic events is thought to be caused by disturbances in endothelial regeneration.\(^71\) The pathogenesis of bevacizumab-induced heart failure is probably multifactorial and likely involves hypertension, reduced capillary density, the presence of cardiac fibrosis, an overall decline in contractile function, or some combination of these factors.\(^72\) Further research is required to determine the mechanism and efficacy of bevacizumab in children.
Small-Molecule Tyrosine Kinase Inhibitors (Sorafenib and Erlotinib). Sorafenib caused myocardial ischemia in 3% of patients in 1 study. This multitarget inhibitor targets VEGF receptors and other important kinase pathways. Sorafenib-induced ischemic cardiotoxic activity could result from VEGF receptor inhibition or decreased Raf kinase activity. Cardiac ischemia has also been noted after exposure to erlotinib. The incidence of myocardial ischemia or infarction was slightly higher when patients were treated with a combination of erlotinib and gemcitabine than with erlotinib alone (2.3% and 1.3%, respectively). Hypertension

Increases in systemic arterial pressure have been observed in patients treated with anticancer drugs that target the VEGF receptor. The incidence of elevated systemic arterial blood pressure varies according to the drug used, the type of tumor, and the patient’s age and cardiovascular status. Increases in blood pressure often occur in patients treated with bevacizumab (the reported incidence ranges from 7% to 36%). Likewise, hypertension is a marked toxic effect in patients treated with VEGF receptor tyrosine kinase inhibitors, such as sorafenib (where the prevalence ranges between 17% and 43%) and sunitinib (between 5% and 24%). Increases of 20 to 30 mm Hg in systolic arterial pressure and 9 to 17 mm Hg in diastolic pressure have been reported in patients treated with chemotherapeutic regimens containing sorafenib or sunitinib. Systemic arterial pressure increases within hours of drug administration and is quickly reversed when treatment is stopped.

The pathogenic mechanism responsible for increasing systemic arterial blood pressure is not entirely defined, but it is likely related to the consequences of VEGF receptor inhibition. VEGF inhibition reduces the formation of the intrinsically vasodilator nitric oxide in the walls of resistance vessels (arterioles). Reducing the concentrations of nitric oxide favors vasoconstriction, increased peripheral resistance, and ultimately, elevations in systemic arterial blood pressure. Hypertension can further enhance ongoing myocardial alterations induced by other means. LV Dysfunction

Damage or loss of myocardial cells resulting from chemotherapeutic drugs can lead to substantial deterioration of LV function, the development of heart failure, or both. The spectrum and magnitude of toxic effects that can initiate cardiac dysfunction depend on the particular drug, as well as on various drug-related factors (the cumulative dose, the timing of treatment, and the use of drug combinations). An innate functional reserve allows the heart to endure a certain degree of myocyte loss. Cardiac dysfunction occurs when the capacity for reserve compensatory activity is exceeded. Diminished myocardial contractility is a clinical challenge to continued effective cancer therapy.

Anthracycline Antibiotics (Doxorubicin). Anthracyclines are the best-known class of chemotherapeutic drugs associated with cardiotoxicity. These agents (especially doxorubicin) have long been an important component of therapy for hematological and solid tumors in children and adults. Anthracycline cardiomyopathy is characterized by changes in myocyte morphology that indicate nons ischemic cellular degeneration. Electron micrographs of myocardial biopsy specimens from anthracycline-treated patients show alterations in the sarcoplasmic reticulum (vacuolization), myofilaments (distorted shape and depletion), and myocytes (cell death). Light microscopic evaluation of heart tissue from chronic experimental studies in rats and dogs treated with doxorubicin has also detected alterations in the sarcoplasmic reticulum (vacuolization), mitochondria (edema), and myofilaments (loss and disorganization). A continuing loss of functioning myocytes, induced by anthracyclines, is responsible for the initial onset of diastolic dysfunction and a later onset of systolic dysfunction and heart failure.

Anthracycline antitumor activity is thought to depend on several interconnected mechanisms: Intercalation into nuclear DNA, inhibition of topoisomerase II, generation of reactive oxygen species (ROS), and disruption of cell membranes and mitochondria. It appears that these mechanisms are separate from those that cause cardiac toxicity. However, despite several investigations, the exact mechanism of anthracycline-induced myocardial toxicity is not completely understood. Many studies have identified oxidative stress as a major contributor to myocardial injury. Highly reactive oxygen species are toxic to the myocyte. Increases in myocyte ROS (hydrogen peroxide, hydroxyl radical) occur through the formation of anthracycline-iron complexes or the redox cycling of the quinone and semiquinone moieties of doxorubicin. These ROS readily interact with various cellular components, causing lipid peroxidation and membrane damage. Myocytes have limited intrinsic antioxidant defenses against ROS (low concentrations of the antioxidant enzyme catalase). Anthracyclines further increase myocyte susceptibility to ROS by suppressing the activity of another potentially protective antioxidant enzyme (myocardial glutathione oxidase). Increases in oxidant stress activate the kinase pathways (MAPK [mitogen-activated protein kinase] and SAPK [stress-activated protein kinase]) that modulate myocyte apoptosis.

Anthracyclines also initiate cardiotoxic actions through changes in mitochondrial structure and function. Anthracycline-induced changes in mitochondrial membrane permeability (through ROS) can alter the intracellular afflux of calcium ions and ultimately affect contractility. Doxorubicin has several mitochondria-related actions, including suppressing respiratory chain activity by binding to cardiolipin (a phospholipid essential for maintenance of respiratory chain function), interacting with mitochondrial DNA, and facilitating the formation of ROS. Doxorubicin decreases concentrations of mitochondrial respiratory chain subunits in both humans and rats. Abnormal respiratory chain function may enhance the formation of ROS and thereby further injure the respiratory chain or mitochondrial DNA and its encoded respiratory chain subunits. The sum of these actions is to alter mitochondrial function and ultimately cause myocyte death. Doxorubicin can also damage the mitochondria genome by interfering with topoisomerase II-β activity. This ATP-dependent nuclear enzyme is important in regulating the breakage-and-reunion process that occurs during normal replication of DNA. Doxorubicin stabilizes the topoisomerase II–DNA.
complexes and thereby prevents reassembly of the breaks in DNA strands. This action can ultimately restrict the synthesis of mitochondrial DNA-encoded respiratory chain units. Once initiated, altered mitochondrial energetics appear to persist or accumulate over time, even in the absence of doxorubicin. Reduced myocardial high-energy phosphate metabolism has been detected in children treated with anthracyclines years after the end of treatment. In some instances, high-energy phosphate metabolism was impaired without evidence of cardiac dysfunction.

Several other actions ascribed to doxorubicin could contribute to myocyte dysfunction, including transcriptional changes in intracellular ATP, downregulation of sarcoplasmic reticulum calcium-ATP messenger RNA expression, suppression of transcription factors that regulate cell survival and synthesis of sarcomeric proteins, and disruption of the sarcomeric protein, titin.

Recent studies have identified endogenous cells in the myocardium (progenitor cells) that can differentiate into cardiac myocytes. These cells are thought to participate in myocardial growth during adolescence and to provide a means for replacing injured cells in the adult heart. Doxorubicin decreases the number of these progenitor cells, which could further predispose the heart to contractile dysfunction.

Tyrosine Kinase Inhibitors. Tyrosine kinase enzymes modulate a variety of signaling pathways that control important cellular functions. Tyrosine kinase inhibitors are a relatively new category of small-molecule drugs that act at the intracellular concentration to interfere with specific targeted pathways in neoplastic tissue, pathways that are influenced by upregulated kinase enzymes. These drugs also inhibit off-target kinases in tissues such as the heart. Clinically, LV dysfunction has been detected in adults treated with imatinib. Electron micrographs of cardiac biopsy samples from affected imatinib-treated patients show myocyte membrane whorls, pleomorphic mitochondria with effaced cristae, scattered cytoplasmic lipid droplets, and vacuoles and glycogen accumulation. Similar functional and morphological alterations have been found in the hearts of mice treated with imatinib. In mice, imatinib decreased the mitochondrial membrane potential, which can predispose to changes in mitochondrial structure (cytosolic vacuolization) and ultimately to cell death. These new agents are only beginning to be included in pediatric chemotherapy regimens. A small retrospective study that focused on pediatric leukemia found no cardiac toxicity in 34 of 36 patients treated chronically with imatinib; cardiomyopathy developed in 2 patients treated for 68 to 79 days with imatinib who had also received anthracyclines, cyclophosphamide, or radiation.

The pathogenesis of imatinib-induced myocardial toxicity is thought to result in part from inhibition of the bcr-abl signal pathway and a corresponding induction of the endoplasmic reticulum stress response. An analogous pathogenic mechanism would also appear likely for other tyrosine kinase inhibitors, such as dasatinib and nilotinib, which have a similar spectrum of cardiotoxic activity. Several other newer tyrosine kinase inhibitors have also been associated with cardiotoxic actions.

Sunitinib is a multikinase inhibitor that suppresses tyrosine kinase-mediated tumor cell proliferation and angiogenesis activity. This drug inhibits a variety of growth factor and cytokine receptors whose targets include VEGF receptors, platelet-derived growth factor receptors, and stem cell factor receptor. Sunitinib has been administered to adults with a variety of neoplasms, including gastrointestinal stromal tumor and renal cell carcinoma. At present, sunitinib as used in these neoplastic diseases has been associated with CHF, LV dysfunction, and hypertension.

Electron micrographs of endomyocardial biopsy samples obtained from patients with cardiovascular symptoms showed cardiomyocyte hypertrophy, swollen mitochondria with effaced cristae, and membrane whorls. Myocardial tissue from mice treated with sunitinib showed similar changes in myocardial morphology (myocyte hypertrophy and mitochondria that were distended and atypically shaped). The pathogenesis of sunitinib-induced cardiotoxicity appears to be complex. Sunitinib suppresses AMP-activated protein kinase signaling, an action that affects mitochondrial activity. Sunitinib inhibits the platelet-derived growth factor receptor, which reduces myocardial protection against stress-related injury. In addition, the inhibitory effects of sunitinib on VEGF may result in vasoconstriction and microvascular rarefaction. Sunitinib also influences ribosomal S6 kinase activity, which activates the proapoptotic factor BCL2, an effect that facilitates the release of cytochrome C and increases myocyte apoptosis.

In preclinical studies, sunitinib inhibited the growth of certain solid tumors (neuroblastoma and sarcoma) in pediatric cancer models. Subsequently, a pediatric clinical evaluation of sunitinib was conducted in 11 children with gastrointestinal stromal tumor. The toxicity exerted by sunitinib in this small number of children was similar to that observed in adults. More recently, in a phase 1 study of 23 children with refractory or recurrent solid tumors, ejection fraction was markedly decreased in 2. The onset of these cardiac alterations occurred during the first treatment cycle and appeared to subside after sunitinib was discontinued. Adults also develop cardiac toxicity early in sunitinib treatment regimes, and the toxicity may not always be reversible. Given the ventricular dysfunction reported in the above-mentioned study by Dubois et al, the protocol was amended to exclude children previously treated with anthracyclines or exposed to cardiac radiation. It is surmised that future clinical evaluations of sunitinib will likely be restricted to specific populations of children who have not been exposed to anthracyclines (eg, children with primary central nervous system tumors).

Sorafenib is a tyrosine kinase inhibitor with a molecular target profile analogous to sunitinib. This drug exerts a similar spectrum of cardiotoxic activity. At present, there are no reports of children being treated with sorafenib.

Monoclonal Antibodies. Trastuzumab is a humanized monoclonal antibody that interferes with the HER2 (human epidermal growth factor receptor 2) tyrosine kinase receptor and is mainly used to treat breast cancer in adults. Cardiotoxicity was noted in early clinical trials. The primary mechanism for trastuzumab-induced cardiac toxicity appears to be inhibition of the cardiomyocyte HER2, an important protective, growth-promoting, antiapoptotic pathway in the myocyte.
Myocardial alterations in adult patients treated with trastuzumab include LV dysfunction, which if sufficiently severe can progress to CHF. Cardiac dysfunction tends to occur mainly during treatment. The 7% incidence of adverse cardiac effects reported in patients treated with trastuzumab only increases sharply when the drug is combined with anthracyclines. In 1 study in children with metastatic osteosarcoma, patients with HER2 overexpression received trastuzumab concurrently with intensive chemotherapy, which included doxorubicin. All patients were given dexrazoxane with doxorubicin to minimize the risk of cardiotoxicity. Hence, there was no clinically significant short-term cardiotoxicity noted in patients receiving trastuzumab and doxorubicin.

The characteristics of trastuzumab cardiotoxicity appear to differ from those associated with the anthracyclines. Cardiac dysfunction induced by trastuzumab appears to be reversible after treatment is stopped, and as a result, these patients have a good cardiovascular prognosis. Importantly, there are no lingering morphological changes in trastuzumab-treated cardiomyocytes. In contrast, anthracyclines cause persistent cardiomyocyte vacuolization, as well as loss of cardiomyocytes. The occurrence of preexisting myocyte toxicity is important because, as indicated above, patients treated with anthracyclines are more susceptible to trastuzumab and other types of chemotherapy-induced cardiotoxicity.

Lapatinib, reported to have a lower cardiotoxic potential, has emerged as an alternative to trastuzumab. This drug interferes with both HER2 and epidermal growth factor receptor signaling. The difference in cardiotoxic potential between lapatinib and trastuzumab may be the result of divergent actions on myocyte bioenergetics: Lapatinib upregulates the activity of AMP kinase and thereby increases cellular concentrations of ATP. Increased concentrations of ATP protect myocytes against apoptosis from tumor necrosis factor-α and other cytokines. Upregulation of activated protein kinase by lapatinib does not inhibit HER 2 signaling. In contrast, trastuzumab reduces AMP kinase activity and decreases the amounts of ATP available to the myocyte. This disparity in ATP concentrations may account for the apparent difference in cardiovascular risk between the 2 drugs.

**Alkylating Drugs.** Acute adverse cardiac effects have been linked to alkylating drugs, such as cyclophosphamide, ifosfamide, cisplatin, and mitomycin. Clinical symptoms in adults range from asymptomatic pericardial effusions to cardiac failure and myopericarditis. The risk of cardiac toxicity appears to be related more to the amount of a single total administered dose than to the total cumulative dose. Symptoms usually appear within 1 to 2 weeks after the initial dose of cyclophosphamide. The cardiac effects may persist for several days, and in some patients, they resolve without problems.

The pathogenic mechanism(s) may involve direct injury to vascular endothelial cells, followed by leakage of toxic metabolites, interstitial hemorrhage, and edema. Cyclophosphamide can also induce the formation of intracapillary microemboli, an action capable of initiating ischemic myocyte damage. The estimated incidence of cyclophosphamide-myocarditis (doses >150 mg/kg) is 5% in children. The overall incidence of myocardial alterations is lower in children than in adults as a result of age-related differences in cardiotoxic sensitivity or the use of lower treatment doses in children. Ifosfamide is an alkylating drug that can also induce acute dose-related cardiac complications, such as arrhythmias and heart failure. Because ifosfamide and cyclophosphamide have similar structures, cardiotoxicity may occur by analogous mechanisms. Except for the apparent lack of hemorrhagic myocarditis in ifosfamide-treated patients, the morphological alterations induced by the 2 compounds appear to be similar. Ifosfamide also alters renal function, which may indirectly contribute to adverse cardiac activity by delaying the elimination of toxic metabolites and by disturbing fluid, acid-base, and electrolyte homeostasis.

Cisplatin has induced acute myocardial ischemia and diastolic heart failure in adults. Episodes of myocardial ischemia and infarction have been reported in young boys treated with a cisplatin-based regimen for germ-cell tumors of the testis. This toxicity occurred during the infusion of cisplatin or several months after therapy. Cisplatin-induced electrolyte disturbances (particularly hypomagnesemia) associated with renal tubular damage may trigger coronary vasospasm and thereby contribute to cardiac dysfunction. Cisplatin-induced cardiotoxic activity can also be accented by disturbances in platelet aggregation or vascular endothelial damage.

Mitomycin C can induce dose-dependent myocardial failure when given to adults. This agent has also been associated with a cardiomyopathy, especially if given in combination with anthracyclines. Mitomycin C–induced myocyte damage is thought to be mediated through the formation of ROS.

**Pathophysiology of Cardiovascular Toxicity From Radiotherapy**

All structural and functional components of the heart, including the pericardium, myocardium, valves, conduction system, and coronary arteries, are susceptible to radiation damage, although the thresholds for injury differ slightly. The pathophysiology of radiation-induced damage has been studied extensively. Myocardial injury is marked by nonspecific, diffuse interstitial fibrosis. Lesion diameter can measure from a few millimeters to several centimeters, but the entire myocardium is rarely involved. The severity of fibrosis between regions can differ markedly. Microscopically, not only does the total amount of collagen increase, but the proportion of type I collagen increases more in proportion to type III. This increase is thought to alter the compliance of the myocardium and thus contribute to diastolic dysfunction in patients treated with radiation. Cells of the myocardium involved with conduction also appear to be sensitive to radiation-induced fibrosis, as indicated in several reports of arrhythmias occurring after chest radiotherapy, as well as by correlations between pathological and electrophysiological changes. A common pathophysiological pathway of cardiac damage appears to be microcirculatory damage. Experiments on irradiated white rabbits by Stewart et al revealed that the myocardium is damaged in 3 phases. In the first phase, small and medium arteries are the first to show acute inflammation ~6 hours after exposure, and a neutrophilic infiltrate develops that involves all layers of the heart. The
second (latent) phase begins ≥2 days after exposure and has a remarkably healthy pericardium and myocardium, which show only slight, progressive fibrosis. However, electron micrographs of the myocardial capillary endothelial cells reveal progressive damage leading to obstruction of the lumen with thrombi of fibrin and platelets. Although the remaining healthy endothelial cells respond by replicating, the rate is inadequate to provide enough unobstructed capillaries. The reduction in patent capillaries causes ischemia and eventually leads to myocardial cell death and fibrosis.

In the third (late) phase, ≈70 days after irradiation, the animals begin to die. The hallmark of this late stage is extensive fibrosis. Although radiation given to these rabbits was not always fractionated, as it is in humans undergoing radiotherapy, myocardial alterations visible in white rabbits under gross and microscopic examination during the latent and late stages are identical to those in humans, although the timing is different, which suggests that pathogenesis is similar in humans. It remains unclear whether free radicals produced by radiation directly damage the myocardium.126

Inflammatory pathways have increasingly been recognized as pathophysiologically important for causing atherosclerotic disease, including ischemic stroke and MI in the general population.127 As discussed above, fibrotic changes to the heart muscle can also result from chronic inflammation. Radiation activates inflammatory pathways.128 Cells respond to radiation by increasing ROS production, which creates an environment in which other types of injury can be exacerbated by causing oxidative damage to proteins and lipids.129 This exacerbation is thought to occur through activation of mitochondria-dependent and -independent metabolic enzymes, including nitric oxide synthases and oxidoreductase enzymes. This pathway may be particularly relevant for cells exposed to radiation, because it can lead to chronic inflammation, thereby heightening the risk of clinically important atherosclerotic plaque development and rupture.130

Studies of atomic bomb survivors exposed to whole-body irradiation at doses lower than those used to prepare patients for bone marrow transplantation (ie, total body irradiation) suggest a dose-dependent association between radiation exposure and chronic inflammation.116 A recent study had similar findings with very low-level radiation, in which exposure in younger children significantly increased radiation-related cardiovascular morbidity and mortality.131 This association is reflected by elevated concentrations in a variety of markers, including C-reactive protein, even after adjustment for age, sex, and body mass.132,133 Even more dramatic results from a longitudinal cohort study by Lipshultz et al134 suggest that children ≥3 years after cancer therapy are at risk for increased chronic inflammation as measured by C-reactive protein. Chronic inflammation was observed whether or not they received cardiotoxic therapy, defined as treatment with anthracyclines, with or without chest radiation that included the heart in the treatment field.

Pericardium

Extensive fibrous thickening of the pericardium occurred with older radiotherapy techniques, although with the doses and radiotherapy techniques used in children for the past 25 years, this adverse effect is now rare.17 This damage included pericardial adhesions and excessive pericardial fluid. Parietal surfaces were more severely and more frequently affected than the epicardium. As determined microscopically, dense collagen and fibrin replaced normal pericardial adipose tissue. Fibrosis occurred in the stroma and on the mesothelial surfaces. As in the myocardium, when pericarditis occurred, small blood vessels proliferated throughout the irradiated pericardium; however, these vessels were usually damaged, with increased permeability. This vascular damage caused ischemia and eventual fibrosis. Fibrosis of the venous and lymphatic channels of the heart and mediastinum decreases the ability to drain extracellular fluid. Together, these mechanisms lead to the accumulation of a protein-rich effusion.135 Fibrin accumulation may also be expedited by disrupted fibrinolysis.135

Valves

Irradiated valves may become fibrotic, with or without calcification.17,136 The pathophysiology of these valvular changes is not well understood, but it cannot be explained by microvascular damage, because heart valves are avascular. However, this fibrosis may be the consequence of late injury to the surrounding myocardial endothelium.136 The fact that changes to valves on the left side of the heart are more common and severe than changes to those on the right side, regardless of dose distribution, suggests that the higher pressures of the systemic circulation are important in pathogenesis.136,137 Valvular stenosis in the entire pulmonary outflow tract has been reported in at least 5 patients after chest radiotherapy, but only at doses ≥40 Gy.138

Coronary Arteries

The pathology and pathophysiology of CAD after radiotherapy appear to be similar to that in the general population. This similarity is apparent in the location and morphology of lesions. As in more typical CAD, the left anterior descending and the right coronary arteries are most often affected after radiotherapy.139-141 However, disease of the left main coronary artery occurs more often in patients exposed to chest radiotherapy than in patients with typical CAD. It is not clear whether this propensity is a result of the outdated technique of anterior-weighted irradiation.138,141a

Within the diseased vessel, narrowing generally occurs proximally and often involves the coronary ostia.17,136,139,140 Autopsies of 16 patients with radiation-associated heart disease and 10 control subjects found that smooth muscle in the media tended to be much thinner in those treated with radiotherapy but not in the 10 control subjects with typical CAD.17 The media and adventitia were also more densely thickened with fibrous tissue than they were in generic coronary lesions.17 Several investigators have found that intimal plaques are largely composed of fibrous tissues, with little lipid present;17,141; however, this finding remains controversial, because other investigators have found them to be quite lipid-laden, as well as fibrotic.136 Therefore, although certain features, such as plaque location and replacement of smooth muscle with extensive fibrosis, suggest disease caused by radiation, a definitive histological discrimination of a radiation-induced lesion from typical atherosclerosis may be difficult in any one particular case.

Similarly, it is unclear to what degree the pathophysiology of radiation-induced CAD differs from that of typical CAD. After irradiation, coronary artery endothelial cells...
are probably damaged through a mechanism similar to that described above for the microvasculature of the myocardium.145 This damage causes fibrointimal hyperplasia, which leads to thrombus formation and potentially to lipid deposition, a process similar to the typical mechanism of CAD. However, results from animal studies conflict as to whether radiation-associated coronary disease can occur without lipid deposition.144 In studies of rabbits,144,145 a high-fat diet was necessary for lesions to occur after radiation, whereas in studies of dogs,146 plaques developed even with a normal diet. Nevertheless, all these and other studies on animals147,148 show that radiation plus a high-fat diet accelerates atherosclerosis.143 One final mechanism that may be important in some cases of sudden cardiac death is coronary artery spasm143,149, however, this final mechanism was suggested in a single case report published >30 years ago.149

Cerebrovascular Disease

The pathophysiological effects of radiation on the human cerebrovasculature are extrapolated from in vitro or nonprimate models that used nonfractionated, supratherapeutic radiation.150,151 With these data, histological and cellular responses of the human cerebrovasculature to radiotherapy can be characterized according to vessel diameter and time from treatment (Table 3).

Table 3. Vascular Response to Radiation

<table>
<thead>
<tr>
<th>Time Phase</th>
<th>Small Arteries/Arterioles (&lt;1000 µm)</th>
<th>Medium Arteries (100–500µm)</th>
<th>Large Arteries (&gt;500µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute/early delayed</td>
<td>Detachment of endothelium from basement membrane; increased BBB permeability through loss of tight junction or increased vesicular activity; cell pyknosis; cytoplasmic vacuolation; nuclear swelling; perivascular edema; acute oxidative stress response</td>
<td>Intimal fibrosis; myointimal formation; subintimal foam cell plaque formation; thrombosis</td>
<td>Intimal fibrosis; myointimal formation; subintimal foam cell plaque formation; thrombosis</td>
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<tr>
<td>(&gt;6 mo)</td>
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<tr>
<td>Late delayed</td>
<td>Progressive loss/abnormal proliferation of endothelia; fibrinoid necrosis; adventitial fibrosis; media hyalinization; intimal thickening; chronic oxidative stress response; thrombus formation</td>
<td></td>
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<tr>
<td>(&gt;6 mo)</td>
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<tr>
<td>Clinical sequelae</td>
<td>Mineralizing microangiopathy; impaired vasa vasorum; possible brain necrosis</td>
<td>Stenosis; aneurysm; vascular malformation</td>
<td>Stenosis; aneurysm; vascular malformation</td>
</tr>
</tbody>
</table>

BBB indicates blood-brain barrier.

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Radation therapy to the circle of Willis increases the risk for cerebrovascular abnormalities. Moyamoya syndrome, or the complete occlusion of ≥1 of the 3 major cerebral vessels with the development of small, immature collateral vessels, may occur, which reflects an attempt to revascularize the brain. Such patients are at increased risk for cerebrovascular events.150

Carotid Artery Disease

Neck irradiation increases the thickness of the carotid wall in the first year after radiation.151 This increase in the thickness of the intima and media of the carotid artery is associated with an increased risk of stroke.152 Preeexisting atherosclerosis at time of treatment may be an exacerbating factor.153,154 Consequently, risk factors include hypertension, obesity, smoking, diabetes mellitus, and other known associations with both cardiac and cerebrovascular disease in the general population.

Course of Cardiotoxicity

The Epidemiology of Cardiotoxicity in Childhood Cancer Survivors

Overview

Cardiopulmonary diseases are the third-leading cause of death in survivors of childhood cancer, after only the recurrence of primary cancer and the development of second cancers.164,165 Death rates attributable to cardiac causes are 8 to 10 times as high among childhood cancer survivors as they are in age-matched control subjects.14,164 Certain chemotherapeutic and biological agents, as well as radiation therapy (RT), independently and in combination, are well-known causes of cardiotoxicity. Additionally, as discussed in “Pathophysiology of Cardiovascular Cardiotoxicity from Radiotherapy,” increasing evidence indicates that other, previously unsuspected aspects of childhood cancer therapy may increase the cardiac burden in survivors.134

Anthracyclines are among the most effective antineoplastic drugs and are still used in nearly 60% of childhood cancer patients; however, the use of radiotherapy has decreased.166 Since the 1990s, if not before, more than half of childhood cancer patients have been treated at least with anthracyclines, which were first introduced in the 1970s. The use of
cardiotoxic therapy for childhood cancer since the 1960s is described in more detail by diagnosis in Table 1.

At least 2 groups have reported that more than half of survivors treated with anthracyclines have echocardiographic evidence of abnormal cardiac structure and function within 10 years after treatment, although most have no clinically relevant symptoms.\textsuperscript{167,168} More recently, van der Pal and colleagues\textsuperscript{169} evaluated subclinical cardiac function in 514 Dutch childhood cancer survivors treated between 1966 and 1997 with potentially cardiotoxic therapy, defined as treatment with anthracyclines, radiation that included the heart in the treatment field, high-dose cyclophosphamide, ifosfamide, or some combination of these treatments. All survivors were at least 5 years out from diagnosis. Median LV fractional shortening was 33\% (range, 13\%–56\%). Subclinical cardiac dysfunction (LV fractional shortening <30\%) was identified in 27\% of survivors. In a multivariate linear regression model, reduced LV fractional shortening was associated with younger age at diagnosis, higher cumulative anthracycline dose, and radiation to the thorax. Thus, between one fourth and one half of all childhood cancer survivors may have signs of cardiotoxicity within 20 years after therapy and yet be generally asymptomatic.

Although not often documented in a single cohort, the concern is that these subclinical findings will worsen with time and eventually cause clinically important symptoms and even death.\textsuperscript{169a} Vague and nonspecific symptoms, such as fatigue and an inability to keep up physically with peers, can develop gradually but may not be recognized as being caused by cardiovascular problems. Although not yet proven, early detection of cardiac dysfunction and treatment will hopefully prevent or slow deterioration. The biggest concern is that chest radiation and anthracycline therapy at doses >250 to 360 mg/m\textsuperscript{2} are independently associated with an increased risk for premature CVD and death.\textsuperscript{14,170} The increased risk of death attributable to cardiovascular causes appears to become important between 5 and 10 years after diagnosis and does not appear to plateau, even after 30 years of follow-up.\textsuperscript{14}

The Childhood Cancer Survivor Study determined that the prevalence of 4 self-reported cardiac conditions in survivors treated in the United States and Canada between 1970 and 1986 was higher than that of their siblings.\textsuperscript{170} In this study of individuals treated for leukemia, brain cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, or bone cancer, the prevalence of self-reported CHF, MI, pericarditis, and valvular disorders was significantly higher than that in their siblings. Prevalence in survivors was highest for CHF (1.7\% versus 0.2\% among siblings), followed by valvular abnormalities (1.6\% versus 0.5\%) and pericardial disease (1.3\% versus 0.3\%). In survivors, mean (95\% confidence interval [CI]) age-adjusted rates per 10,000 person-years were 9.7 (9.4–10.1) for CHF, 2.8 (2.4–3.3) for MI, 5.8 (5.4–6.4) for pericardial disease, and 6.4 (5.9–7.1) for valvular abnormalities among survivors. However, the number of events was so few in the siblings that stable prevalence rates could not be computed for any of these events.\textsuperscript{170}

Findings from the British Childhood Cancer Survivor Study reinforced the importance of late cardiovascular mortality, which accounted for 26\% of excess mortality after 45 years.\textsuperscript{11} In these studies, cardiovascular mortality was attributed mainly to cardiomyopathy, heart failure, ischemia, and other unspecified cardiovascular causes. For example, the study’s 2001 report listed 83 cardiovascular deaths: 20 of ischemia, 46 of cardiomyopathy or heart failure, and 17 of “other causes.”

Aside from cardiac irradiation and anthracycline chemotherapy, other cancer treatments also increase the risk of CVD. Cranial or cranial-spinal radiotherapy for brain tumors and leukemia can damage the hypothalamic-pituitary axis and thyroid gland, especially at doses >20 Gy.\textsuperscript{171–174} This damage, in turn, may affect metabolism and satiety hormones, thereby affecting CVD risk factors such as obesity, lipid concentrations, insulin resistance, and diabetes mellitus, discussed further under the sections below entitled “Treatment of Radiation-Associated CVD Risk Factors” and “Cardiometabolic Risk Factors for Premature Atherosclerosis.”\textsuperscript{175} Radiation to the neck can damage the carotid arteries, increasing the risk of stroke, even without hormonal changes, as discussed further under the sections below entitled “Treatment of Radiation-Associated CVD Risk Factors” and “Cardiometabolic Risk Factors for Premature Atherosclerosis.”\textsuperscript{179,176,177} In addition, spinal radiation used to treat brain malignancies may include the heart in the treatment field. Jakacki et al\textsuperscript{178} reported in 1993 that subclinical cardiac dysfunction and conduction abnormalities were greater in survivors who received such therapy than in those who received flank radiation, in which the heart was not in the treatment field. Evidence is also emerging that vincristine, a drug commonly used to treat several malignancies, may be associated with a slight but statistically significant increased risk of fatal CVD, possibly caused by autonomic nervous system dysfunction.\textsuperscript{15}

Anthracyclines

Anthracycline-induced cardiotoxicity can manifest as either asymptomatic cardiac dysfunction or clinical heart failure.\textsuperscript{174a} Asymptomatic cardiac dysfunction is characterized by subclinical cardiac abnormalities that can be detected with various diagnostic methods, such as ECG or multigated acquisition scanning. Cardiac pathology in individuals treated with anthracyclines was first described in the 1970s.\textsuperscript{179,180} Through the 1980s and 1990s, the number of case reports and case series describing clinically evident heart failure increased.\textsuperscript{181–184} Overlapping with these reports were larger studies documenting a high frequency of echocardiographically defined systolic dysfunction in long-term survivors of childhood cancer treated with anthracyclines, particularly for ALL and Wilms tumor.\textsuperscript{168,185–188} These studies clearly documented that the risk of dysfunction was associated with the cumulative dose of anthracycline, younger age at diagnosis (particularly age <5 years), and time since diagnosis\textsuperscript{164,167,186} and that no dose was without risk.\textsuperscript{189} Studies since 1997, which we discuss in more detail below, are summarized in Table 4.

Symptomatic Heart Failure

Symptomatic heart failure is one of the cardiac events that occurs after childhood cancer treatment. Other events, such as valvular diseases and MI, are more common in children and survivors treated with radiation that includes the heart in the treatment field. A 2002 systematic review reported a frequency of clinical heart failure of between 0\% and 16\%.\textsuperscript{200} The frequency of such events varies between studies because they differ in several ways, especially in the number of patients, the type of malignancy, and the time since treatment. Since 2002,
### Table 4. Evidence of Anthracycline-Associated Cardiac Damage

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Study Design</th>
<th>Anthracyclines or Radiation</th>
<th>Patients, n</th>
<th>Study Objectives</th>
<th>Study Findings (Anthracycline Exposures)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Childhood cancer survivors in general: mortality</strong></td>
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<tr>
<td>Tukenova et al, 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Both</td>
<td>4112</td>
<td>To study 4112 5-year survivors of childhood cancer diagnosed before 1986 in France and the UK</td>
<td>• CVD mortality 5 times higher among childhood cancer survivors than age-matched population</td>
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<td>• CVD SMR is significantly elevated in all anthracycline dose increments</td>
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<td>— 0, SMR=3.9 (95% CI, 2.6–5.9)</td>
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<td>— &gt;0 to &lt;239, SMR=8.3 (95% CI, 2.1–33.3)</td>
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<td>— 240–259, SMR=12.2 (95% CI, 3.0–48.6)</td>
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<td>— &gt;259, SMR=21.6 (95% CI, 9.0–51.9)</td>
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<td>○ After adjustment for other treatment, compared with survivors not treated with anthracyclines, RR of cardiac death was significantly elevated only with doses &gt;360 mg/m² (RR=4.4; 95% CI, 1.3–15.3)</td>
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<td>• Vascular disease SMR not significantly elevated at 95% CI</td>
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<td>Mertens et al&lt;sup&gt;164&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Mixed</td>
<td>20227</td>
<td>To assess overall and cause-specific mortality in 20227 5-year cancer survivors, diagnosed before age 21 y; measured against age- and sex-matched US population mortality data</td>
<td>• All-cause SMR=10.8 (95% CI, 10.3–11.3)</td>
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<td>• Cardiac SMR=8.2 (95% CI, 6.4–10.4)</td>
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<td>• Anthracycline dose categories not associated with cardiac death after controlling for sex, age at diagnosis, and years since diagnosis, but no test of trend given, and RR estimate went up by dose category</td>
</tr>
<tr>
<td>Green et al&lt;sup&gt;165&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Mixed</td>
<td>474 Survivors</td>
<td>Evaluate overall and cardiac mortality in 15-year cancer survivors diagnosed during childhood or adolescence compared with general population</td>
<td>• No cardiac deaths in female survivors</td>
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<td>• 42 Males received doxorubicin: SMR cardiac=66.1 (95% CI, 8.01–238)</td>
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<td>• 223 Males did not receive doxorubicin: SMR cardiac=4.99 (95% CI, 1.03–14.57)</td>
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<td>• Doxorubicin use was borderline significant after multivariate adjustment for overall survival</td>
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<td><strong>Childhood cancer survivors in general: incidence of symptomatic events</strong></td>
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<tr>
<td>Mulrooney et al&lt;sup&gt;170&lt;/sup&gt;</td>
<td>Cohort</td>
<td>Mixed</td>
<td>14358</td>
<td>To assess incidence and risk of CHF, MI, pericardial disease, and valvular abnormalities of adult survivors of adolescent cancers. Twenty-six institution study of leukemia, HL, NHL, kidney cancer, neuroblastoma, soft tissue sarcoma, and bone cancer survivors diagnosed between 1970 and 1986; 3899 sibling controls used as reference.</td>
<td>• Hazard ratio for CHF, MI, pericardial disease, and valvular abnormalities for anthracycline dose &lt;250 mg/m² (results for lesser doses not significant)</td>
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<td>— &lt;250 mg/m² (results for lesser doses not significant)</td>
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<td>— 2.4 (95% CI, 1.5–3.9), P&lt;0.001</td>
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<td>— 1.3 (95% CI, 0.6–2.8), P=0.50</td>
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<td>— 1.6 (95% CI, 0.9–2.9), P=0.13</td>
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<td>— 1.4 (95% CI, 0.8–2.3), P&lt;0.25</td>
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<td>• Hazard ratio for CHF, MI, pericardial disease, and valvular abnormalities anthracycline dose ≥250 mg/m²</td>
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<td>— 5.2 (95% CI, 3.6–7.4)</td>
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<td>— 1.1 (95% CI, 0.5–2.1), P&lt;0.87</td>
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<td>— 1.8 (95% CI, 1.1–3.0), P&lt;0.02</td>
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<td>— 2.3 (95% CI, 1.6–3.3), P&lt;0.001</td>
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Table 4. (Continued)

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<tr>
<th>Author and Year</th>
<th>Study Design</th>
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<th>Study Findings (Anthracycline Exposures)</th>
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</thead>
<tbody>
<tr>
<td>Creutzig et al193</td>
<td>Cohort</td>
<td>Anthracycline + CNS RT</td>
<td>1010</td>
<td>Evaluate the incidence of early and late anthracycline-associated clinical and subclinical cardiotoxicity in survivors of pediatric AML</td>
<td>• Early cumulative incidence of cardiomyopathy was 4.3% - 1.6% Exhibited clinical cardiomyopathy - 2.7% Exhibited subclinical cardiomyopathy (LVFS &lt;30%)</td>
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<tr>
<td>van Dalen et al191</td>
<td>Cohort</td>
<td>Anthracycline ± RT</td>
<td>830, All treated with anthracyclines</td>
<td>Evaluate incidence of and risk factors for clinical heart failure in a cohort of children treated with anthracyclines; long-term follow-up study</td>
<td>• Late cumulative incidence of cardiomyopathy was 5%±1% at a median 5.3 y of follow-up - 1.6% Exhibited clinical cardiomyopathy - 1.3% Exhibited subclinical cardiomyopathy (LVFS &lt;30%) - Risk factor for anthracycline cardiac toxicity: prior history of cancer</td>
</tr>
<tr>
<td>Paulides et al134</td>
<td>Cohort</td>
<td>Anthracycline ± RT</td>
<td>265, All treated with anthracyclines; 18 received 47±10 Gy of thoracic RT</td>
<td>Evaluate incidence of doxorubicin-induced cardiomyopathy in pediatric sarcoma patients in Germany, Austria, and Switzerland</td>
<td>• Total cumulative incidence of cardiomyopathy was 7.5% - 1.5% Exhibited clinical cardiomyopathy - 6% Exhibited subclinical cardiomyopathy - Of those who developed cardiomyopathy, mean cumulative doxorubicin dose was 300±103 mg/m² - No risk factors discovered in univariate or multivariate analysis, but little variability in treatment and short follow-up time compared with other studies</td>
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<tr>
<td>Pein et al135</td>
<td>Cohort</td>
<td>Anthracycline ± RT</td>
<td>229: 24 With CHF, 205 no CHF</td>
<td>Evaluate cardiac clinical status and function in a cohort of survivors of childhood solid tumor all treated with anthracycline</td>
<td>• Median follow-up 15 y (0.3–24 y) - Cumulative incidence CHF=16.4% - Among 205 others studied - 6% had fractional shortening &lt;25% - Only cumulative anthracycline dose and average radiation dose to heart were independent risk factors for CHF (age at treatment was borderline) - Anthracycline dose, average radiation dose to heart, age &lt;8 y, and female sex were risk factors for any cardiac abnormality - In those exposed to anthracycline ≥250 mg/m² and average heart dose ≥5 Gy, incidence of any cardiac abnormality=71%</td>
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Childhood cancer survivors in general: incidence cardiac dysfunction = symptomatic events

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<tr>
<td>Lipshultz et al194</td>
<td>Cohort</td>
<td>Mixed</td>
<td>201 Survivors; 76 siblings</td>
<td>Assessment of echocardiographic characteristics and atherosclerotic disease risk factors in long-term childhood cancer survivors of various diagnosis</td>
<td>• Risk is higher in both exposed and unexposed survivors, which suggests other aspects also drive risk - Unexposed survivors also have cardiovascular abnormalities, systemic inflammation, and increased atherosclerotic disease risk; Framingham risk 2.16, 2.12, and 1.70 for exposed, unexposed, and control subjects, respectively (P&lt;0.01) - 156 Exposed had below-normal LV mass, wall thickness, contractility, and fractional短ening, and above-normal LV afterload.</td>
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<td>45 Unexposed had below-normal LV mass, and females had below-normal LV wall thickness</td>
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<td>Exposed/unexposed/sibling N-terminal probrain natriuretic peptide: 81.7/69.0/39.4 pg/mL, P&lt;0.001</td>
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<td>Exposed/unexposed/sibling fasting serum non-HDL cholesterol: 126.5/121.1/109.8 mg/dL, P&lt;0.001</td>
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<td>Exposed/unexposed/sibling high-sensitivity C-reactive protein: 2.7/3.1/0.9 mg/L, P&lt;0.001</td>
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</table>
| Van der Pal et al<sup>169</sup> | Cohort | Anthracycline and/or cardiac RT | 514 Survivors | Assessment of LVFS in 514 childhood cancer survivors visiting a late-effect outpatient clinic and having received anthracyclines, cardiac irradiation, high-dose cyclophosphamide, or high-dose ifosfamide | • Median follow-up since diagnosis=15.4 y  
• All ORs adjusted for cumulative dose of anthracyclines, age at diagnosis, time since diagnosis, sex, BMI at examination, total RT dose to each of the 4 fields involving the heart  
- Anthracycline dose (LVFS <30%)  
  • 1–150 mg/m<sup>2</sup>, reference group  
  • 151–300 mg/m<sup>2</sup>, OR=7.0 (95% CI, 1.5–10.0)  
  • 301–450 mg/m<sup>2</sup>, OR=7.8 (95% CI, 2.8–21.3)  
  • >450 mg/m<sup>2</sup>, OR=10.6 (95% CI, 3.3–33.4) |
| Aggarwal et al<sup>194</sup> | Cohort | Anthracycline (RT exposure not discussed) | 63 | Evaluate plasma B-type natriuretic peptide as a screening test for detection of late cardiac dysfunction in anthracycline-treated survivors and determine the prevalence of late cardiac dysfunction | • Cardiac dysfunction found in 41% of patients with a median cumulative dose of 165 mg/m<sup>2</sup>  
• No significant difference in median age at diagnosis, at cardiac screening, or follow-up interval between those with normal and abnormal cardiac function  
• ESWS was the most common abnormality  
• Natriuretic peptide concentrations found to be significantly higher in patients with abnormal cardiac function (23.4±25.3 vs 14.2±8.9, P=0.02)  
• Particularly true for differentiation of survivors with normal/abnormal LVFS (32.4±34.9 [n =9] vs 15.6±12.4 [n =54], P<0.008) |
| De Souza et al<sup>195</sup> | Case series | Anthracycline: No cardiac radiation | 47 Survivors, 12 controls | Evaluate LV function and hemodynamics during progressive exercise in anthracycline-treated survivors of childhood cancer | • Anthracycline-treated patients had reduced exercise tolerance compared with controls (P<0.04)  
• Resting LV dimensions of anthracycline-treated patients was lower in high-dose group than in controls (P<0.005)  
• Shortening fraction change from rest to peak exercise was lower in anthracycline-treated patients (both groups; P<0.001)  
• Mean VCFc at rest and peak exercise lower than in controls (P<0.01)  
• Mean stress at peak systole at rest and peak exercise higher than in controls (P<0.001)  
• Peak aortic velocity from rest to peak exercise was significantly different between the 2 groups (P<0.005)  
• Anthracycline-treated patients had minimal stroke volume and cardiac output increase as a result of exercise, both of which were reduced compared with normal (P<0.001 and P<0.01, respectively)  
• There was an inverse relationship between cumulative anthracycline dose and shortening fraction (P<0.001)  
• The most important predictor of worsening cardiac performance (LVFS and LV ESWS) was total anthracyline dose |
| Sorensen et al<sup>168</sup> | Cohort | Anthracycline (RT exposure not discussed) | 184 Survivors, 100 healthy “controls” | Evaluate serial echocardiogram findings in 184 childhood cancer survivors to determine the risk factors for progression in severity of anthracycline-induced subclinical cardiac dysfunction | • Anthracycline-treated patients had reduced exercise tolerance compared with controls (P<0.04)  
• Resting LV dimensions of anthracycline-treated patients was lower in high-dose group than in controls (P<0.005)  
• Shortening fraction change from rest to peak exercise was lower in anthracycline-treated patients (both groups; P<0.001)  
• Mean VCFc at rest and peak exercise lower than in controls (P<0.01)  
• Mean stress at peak systole at rest and peak exercise higher than in controls (P<0.001)  
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<tbody>
<tr>
<td><strong>Green et al</strong></td>
<td>Cohort</td>
<td>Anthracycline ± RT (Wilms tumor only) 2710 Survivors</td>
<td>To determine frequency of and risk factors for CHF after treatment for Wilms tumor that included doxorubicin for original or relapse therapy</td>
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<tr>
<td><strong>Krischer et al</strong></td>
<td>Cohort</td>
<td>Anthracycline ± RT 6493 Survivors</td>
<td>To determine the incidence of clinical cardiotoxicity from anthracycline chemotherapy in children with cancer and to identify associated risk factors treated on Pediatric Oncology Group protocols from 1974–1990</td>
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</table>

**Single Cancer Studies**

<table>
<thead>
<tr>
<th>Gurney et al</th>
<th>Cohort</th>
<th>Mixed</th>
<th>1607 BT survivors 3418 sibs</th>
<th>Evaluate CVD incidence in childhood BT survivors</th>
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<tbody>
<tr>
<td>Rathe et al</td>
<td>Cohort</td>
<td>Anthracycline (no cardiac radiation) 63</td>
<td>Evaluate long-term survivors of childhood ALL with M-mode and Doppler echocardiography treated with cumulative anthracycline doses &lt;300 mg/m²</td>
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**Author and Year**

- **Green et al**: Cohort Anthracycline ± RT 2710 Survivors (Wilms tumor only)  To determine frequency of and risk factors for CHF after treatment for Wilms tumor that included doxorubicin for original or relapse therapy
- **Krischer et al**: Cohort Anthracycline ± RT 6493 Survivors  To determine the incidence of clinical cardiotoxicity from anthracycline chemotherapy in children with cancer and to identify associated risk factors treated on Pediatric Oncology Group protocols from 1974–1990
- **Gurney et al**: Cohort Mixed 1607 BT survivors 3418 sibs  Evaluate CVD incidence in childhood BT survivors
- **Rathe et al**: Cohort Anthracycline (no cardiac radiation) 63  Evaluate long-term survivors of childhood ALL with M-mode and Doppler echocardiography treated with cumulative anthracycline doses <300 mg/m²

**Study Findings (Anthracycline Exposures)**

- **Green et al**: Cumulative frequency of CHF found to be 4.4% 20 y after Dx for patients initially treated with doxorubicin
- **Krischer et al**: In a multivariate analysis, risk factors found to be:
  - Cumulative anthracycline dose >or=550 mg/m² of body-surface area (RR=5.2),
  - Maximal single dose ≥50 mg/m² (RR=2.8)
  - Female sex (RR=1.9)
  - Black race (RR=1.7)
  - Trisomy 21 (RR=3.4)
  - Exposure to amsacrine (RR=2.6)
- **Gurney et al**: One or more cardiovascular conditions were reported by 18% of childhood BT survivors, with an elevated late-onset risk for:
  - Stroke: RR=42.8 (95% CI, 16.7–109.8)
  - Blood clots: RR= 5.7 (95% CI, 3.2–10.0)
  - Angina-like symptoms: RR=2.0 (95% CI, 1.5–2.7)
- **Rathe et al**: Patients had thinner interventricular septum (P<0.0005)
  - Patients had more dilated LV in diastole (P<0.0005)
  - LV mass smaller in females (P<0.0005)
  - 9 Patients (14%) had an EF <60%, and 7 of these patients had cumulative doses >200 mg/m²

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Table 4. (Continued)

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<tbody>
<tr>
<td>Jarfelt et al.198</td>
<td>Cohort (RT exposure not discussed)</td>
<td>Anthracycline</td>
<td>23 Survivors, 12 controls</td>
<td>Evaluate cardiac function using exercise echocardiography in asymptomatic adult survivors of childhood ALL</td>
<td>LV posterior wall was thinner and the LV in diastole was more dilated in patients diagnosed at &lt;5 y of age (P&lt;0.05)</td>
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<td>No patients had cardiac symptoms when studied</td>
<td>67% of patients studied (n=15) had abnormal Doppler velocities indicative of diastolic dysfunction</td>
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<td>• Range of doxorubicin dose=180–400 mg/m²</td>
<td>EF with stress was significantly lower in survivor group: 59.5% (32.6%–81.1%) vs 77.3% (66.2%–85.3%), P&lt;0.0001</td>
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<td>• Age at screening=27.0 (20.0–31.0) y</td>
<td>– Change in EF much lower: 2.2% (−12.1% to 16.0%) vs 12.7% (8.6%–26.4%), P&lt;0.0001</td>
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<td>• Follow-up time=21.0 (17.0–29.0) y</td>
<td>– 43% of survivors vs 0% of healthy controls had decrease in EF with stress</td>
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<tr>
<td>Lipshultz et al.187</td>
<td>Longitudinal case series</td>
<td>Anthracycline ± RT (RT exposure not discussed)</td>
<td>Evaluate course of potential cardiac damage in 115 doxorubicin-treated survivors of childhood ALL from review of 499 echocardiograms</td>
<td>LVFS was reduced on average, and decrease was correlated with cumulative dose of doxorubicin</td>
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<td>• Median age at Dx=4.8 y</td>
<td>Most survivors had transient improvement in LVFS with eventual decrease</td>
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<td>• Median follow-up after completion of doxorubicin=11.8 y</td>
<td>Mean LVFS and LV contractility were significantly decreased in patients receiving &gt;300 mg/m² at 11.8 y or more out</td>
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<td>• Median individual doxorubicin dose=30 mg/m²</td>
<td>Even patients receiving lower cumulative doxorubicin doses experienced reduced mass and dimension</td>
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<td>• Median cumulative dose=352 mg/m²</td>
<td>LVFS and LV dimension at end of therapy predicted these parameters 11.8 y later</td>
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<tr>
<td>Nysom et al.198</td>
<td>Cohort (RT exposure not discussed)</td>
<td>Anthracycline</td>
<td>189 189 childhood ALL survivors at 2 different centers (Copenhagen and Boston), each with a low cumulative dose (0–23 and 45 mg/m²) and high-dose group (73–301 and 244–550 mg/m²) of doxorubicin</td>
<td>Mean LV EDD was significantly increased in highest-dose group (Boston) compared with expected and compared with the other 3 groups</td>
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<td>n=32, 17, 53, and 87, respectively</td>
<td>Mean LVFS was significantly decreased in highest-dose group (Boston) compared with expected (29.0% vs 33.8%) and compared with 3 other groups</td>
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<td>• Median age at Dx=3.8, 3.6, 4.0, and 4.8 y, respectively</td>
<td>Doxorubicin dose &gt;280 mg/m² associated with decreased LVFS</td>
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<td>• Median time since completion of treatment 14.6, 4.6, 6.2, and 8.1 y, respectively</td>
<td>Cumulative dose still significant risk factor for LVFS after adjustment for age at diagnosis, sex, time since completion of therapy, and city of treatment</td>
</tr>
<tr>
<td>Sorensen et al.187</td>
<td>Cohort (RT exposure not discussed)</td>
<td>Anthracycline</td>
<td>120 ALL, 50 controls</td>
<td>Compare cardiac function and survival in 120 ALL survivors treated with 3 different cumulative doses of doxorubicin (90, 180, 270 mg/m²; n=40 in each group) and healthy controls</td>
<td>ALL survivors had reduced LVFS compared with normal (32.3%±4.4% vs 35.9%±4.2%, P&lt;0.005)</td>
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<td>• LV contractility independent of loading conditions was normal for the group as a whole</td>
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<td>• Of 27 patients (23%) with cardiac abnormalities, 25 (21%) had increased end-systolic stress, whereas only 2 (2%) had reduced contractility</td>
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<td>• The proportion with cardiac abnormality was similar in the 3 dose groups (but with 40 patients in each group, there was little power to detect a difference)</td>
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<td>• Reduced incidence and severity of cardiac abnormalities was much less than in other studies of survivors receiving 300 to 550 mg/m² of anthracycline</td>
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ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BMI, body mass index; BT, brain tumor; CCSS, Childhood Cancer Survivor Study; CHF, congestive heart failure; CI, confidence interval; CNS, central nervous system; CVD, cardiovascular disease; Dx, diagnosis; EDD, diameter at end diastole; EF, ejection fraction; ESWS, end-systolic wall stress; HDL, high-density lipoprotein; HL, Hodgkin lymphoma; LV, left ventricular; LVFS, left ventricular fractional shortening; MI, myocardial infarction; NHL, non-Hodgkin lymphoma; OR, odds ratio; RR, relative risk; RT, mediastinal radiotherapy; SMR, standard mortality rate; UK, United Kingdom; and VCFc, corrected velocity of circumferential fiber shortening.
several new studies have focused on this subject. Multivariate analyses of possible risk factors for symptomatic clinical heart failure in these studies indicate that a higher cumulative dose of anthracyclines and concomitant cardiac radiation are risk factors.\textsuperscript{175,191,200–210} Some studies also suggest the risk of symptomatic heart failure is higher in girls and in all children treated at a younger age.\textsuperscript{70,185,186,196}

The maximum safe dose of anthracyclines or cardiac radiation is difficult to determine. Studies have estimated the risk of symptomatic heart failure using different cutoff values, for example, anthracycline doses of 200, 250, or 300 mg/m\textsuperscript{2} or 5, 15, 20, or 35 Gy of cardiac radiation. A recent study showed an exponential relationship between cumulative anthracycline dose, cardiac radiation dose, and risk of a symptomatic cardiac event.\textsuperscript{202}

The prognosis of survivors with symptomatic heart failure is of great concern, especially because these survivors are young when heart failure occurs and because they have a long life expectancy.

**Asymptomatic Cardiac Dysfunction**

Because of the relative rareness of childhood cancer and the difficulty in clinically assessing long-term survivors, most studies in childhood cancer survivors have focused on asymptomatic cardiac disease. Asymptomatic cardiac dysfunction includes various cardiac abnormalities diagnosed with several methods in asymptomatic patients.\textsuperscript{203–205} Another 2002 systematic review showed that the frequency of asymptomatic cardiac dysfunction varies widely.\textsuperscript{200}

Several risk factors for decreased cardiac dysfunction have been identified. Studies that adjusted for important risk factors with multivariate analysis have shown that childhood cancer survivors treated with a higher anthracycline doses and RT that exposes the heart to ionizing radiation are at higher risk.\textsuperscript{168,169,189,200} Longer follow-up has shown that cardiac performance as assessed by echocardiography improved in patients who received <240 mg/m\textsuperscript{2} and deteriorated in those who received higher doses.\textsuperscript{168} Compared with survivors who received 1 to 150 mg/m\textsuperscript{2} of anthracyclines, those who received 151 to 300, 301 to 450, and >450 mg/m\textsuperscript{2} had mean relative risks (95% CI) of decreased systolic function (LV fractional shortening <30\%) of 7.0 (1.5–10.0), 7.8 (2.8–21.3), and 10.6 (3.3–33.4), respectively.\textsuperscript{169} Other suggested risk factors for anthracycline-induced asymptomatic disease are younger age at diagnosis and female sex.\textsuperscript{186,200} The impact of other potentially cardiotoxic drugs, such as (high-dose) cyclophosphamide, (high-dose) ifosfamide, cisplatin, and vincristine, has not been examined in large studies.\textsuperscript{38,206} Proposed risk factors for cyclophosphamide-induced cardiotoxicity include higher dosage, age, and use of the drug in combination with other agents (cisplatin or anthracyclines).\textsuperscript{207}

Furthermore, some recent studies suggest a possible association between genetic factors and anthracycline-induced cardiac dysfunction.\textsuperscript{208–209a} In survivors of high-risk childhood ALL, risk of doxorubicin-associated myocardial injury was elevated in survivors with a C282Y mutation, which is associated with hereditary hemochromatosis.\textsuperscript{209b} Finally, the risk of cardiac dysfunction during or shortly after excess cardiac stress associated with pregnancy and delivery or other sources of cardiovascular stress, such as extreme sports or surgery, is not well known.\textsuperscript{210,211}

Most studies in childhood cancer survivors are cross-sectional. The few longitudinal follow-up studies suggest that cardiac function deteriorates over time (Figure 1).\textsuperscript{167,168}

Recent Doppler echocardiography studies found a high prevalence of diastolic dysfunction, as measured by different indices, even in asymptomatic survivors. Alehan et al\textsuperscript{211} screened survivors of childhood Hodgkin lymphoma with Doppler echocardiography and confirmed that diastolic dysfunction is common after anthracycline therapy, even without thoracic radiotherapy. These findings are even more remarkable when one considers that the median dose of doxorubicin was only 150 mg/m\textsuperscript{2} and that 69% of patients received <300 mg/m\textsuperscript{2}, a cutoff used to designate those at highest risk for systolic dysfunction.\textsuperscript{212} A review of 25 studies of anthracycline therapy found that the proportion of survivors with anthracycline-related subclinical cardiotoxicity ranged from 0% to 57% over anthracycline doses ranging from 45 to 1275 mg/m\textsuperscript{2}. Cumulative dose appeared to be the treatment factor that most correlated with the frequency of subclinical cardiac dysfunction.\textsuperscript{200,212}

**Mortality**

A study of 4122 5-year survivors of childhood cancer, excluding leukemia, diagnosed before 1986 in France and the United Kingdom indicates an independent association between anthracycline dose and death of CVD in survivors of a variety of childhood cancers.\textsuperscript{14} After 86453 person-years of follow-up (average follow-up, 27 years), 32 patients had died of CVDs, 5 times (95% CI, 3.3–6.7) more than expected. The risk of dying of cardiac diseases (n=21) was significantly higher in

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**Figure 1.** z Scores of cardiac measurements from 115 long-term survivors of acute lymphoblastic leukemia treated with doxorubicin, by time since diagnosis (years). The solid line is the overall group mean in this model. The dashed lines are the upper and lower 95% confidence intervals from the predicted mean and are 2 standard errors of the mean. DCM indicates dilated cardiomyopathy; Dox, doxorubicin; LV, left ventricular; RCM, restrictive cardiomyopathy; SD, standard deviation. Reproduced from Lipshultz et al\textsuperscript{167} with permission from the American Society of Clinical Oncology. Copyright ©2005, American Society of Clinical Oncology.
individuals who had received a cumulative dose of anthracyclines >360 mg/m² (relative risk, 4.4; 95% CI, 1.3–15.3) after adjustment for other treatment factors, including radiation dose to the heart. The relative risk in those who received 240 to 369 mg/m² was 1.3 (95% CI, 0.3–6.3). There were an additional 11 vascular deaths during the 86,453 person-years of follow-up, but these were not associated with anthracycline treatment.

Incidence

The incidence of subclinical dysfunction has been directly associated with anthracycline dose in multiple studies. A study of 201 consecutive survivors of a variety of pediatric malignancies reported subclinical dysfunction in 11%, 23%, 47%, and 100% of patients treated with cumulative anthracycline doses of <400, 400 to 599, 600 to 799, and ≥800 mg/m², respectively, at a median of 7 years after completion of therapy (range, 4–20 years). Lipshultz et al reported a progressive increase in LV end-systolic wall stress (an index of afterload) or depression of LV contractility in 75% of childhood ALL survivors who had received a median doxorubicin dose of 334 mg/m². Cumulative incidences up to 57% have been reported, depending on the study population, attained age, duration and completeness of follow-up, how outcomes were defined, and the diagnostic methods used. In a study of 120 survivors of ALL treated with doses of anthracyclines between 90 and 270 mg/m², 23% had subclinical cardiac dysfunction.

The incidence of clinically evident CHF in a broad range of childhood cancer survivors treated with anthracyclines has been studied by 2 groups. In another Dutch study, this time by van Dalen et al, 830 childhood cancer survivors, all treated with anthracyclines at cumulative doses ranging from 15 to 900 mg/m² (mean, 288 mg/m²; median, 280 mg/m²), had a cumulative incidence of physician-diagnosed anthracycline-induced heart failure of 2.5% at a median follow-up of 7.1 years after the start of therapy (range, 4 days to 28.4 years). Of the 21 cases of heart failure, only 6 were diagnosed during therapy. In the 15 cases diagnosed after therapy, all had received a cumulative anthracycline dose of ≥300 mg/m², and this was the only independent risk factor for heart failure (relative risk=8). In this cohort, the estimated incidence of CHF had increased to 5.5% 20 years after the start of anthracycline therapy and was 9.8% among those treated with a cumulative dose of ≥300 mg/m².

In a cohort of 229 French childhood cancer survivors treated between 1968 and 1985 with anthracycline chemotherapy for solid tumors (with or without thoracic radiotherapy) and followed up for ≥15 years, 10% were diagnosed with CHF. Total anthracyline dose was higher in those diagnosed with heart failure than in those without (412 versus 333 mg/m²), and age at first anthracyline dose was also lower (4.8 versus 5.7 years).

The cardiac outcomes study for the Childhood Cancer Survivor Study cohort found that the 30-year cumulative incidence of CHF in the entire cohort was 4.1% (95% CI, 3.2–5.0) and confirmed that cumulative dose is an independent risk factor for the incidence of clinically evident congestive heart disease. Compared with survivors who did not receive anthracyclines, survivors who received <250 mg/m² or ≥250 mg/m² were 2.4 (95% CI, 1.5–3.9) and 5.2 (95% CI, 3.6–7.4) times as likely to experience CHF, respectively, after adjustment for other treatment factors. The cumulative incidence of CHF after 30 years was ≈8% in those receiving a cumulative anthracycline dose of ≥250 mg/m², an incidence similar to the estimated cumulative incidence in the study by van Dalen et al, an important finding given that follow-up in the Childhood Cancer Survivor Study relied on self-report, whereas the Dutch study did not.

The incidence of other clinically important cardiac events associated with anthracyclines is less well studied. The Childhood Cancer Survivor Study found that the cumulative incidence of pericardial disease at 30 years was ≥2.5% in patients either not treated with anthracyclines or receiving <250 mg/m² but 7.5% for those receiving ≥250 mg/m². The difference in incidence from those not treated with anthracyclines was attributable at least in part to the treatment itself, as evidenced by the multivariate hazard ratios (95% CI) of 1.6 (0.9–2.9) and 1.8 (1.1–3.0), respectively, for the 2 nonzero dose groups over 30 years. The cumulative incidence of valvular disease clustered just below 5%, regardless of total anthracycline dose; however, treatment with ≥250 mg/m² was independently associated with a higher incidence of valvular problems (hazard ratio, 2.3; 95% CI, 1.6–3.3), after multivariate adjustment.

Data were not provided on the cumulative incidence of MI by dose category, but anthracycline dose, analyzed in the above 3 categories, was not independently associated with increased risk after multivariate adjustment. The lack of association between MI and anthracycline dose in this US study contrasts with the statistically and clinically significant association between cardiac mortality and anthracycline dose described above. This finding also contrasts with the findings of a British study of Hodgkin lymphoma survivors treated at all ages between 1970 and 1999. In that cohort, even among those treated at <35 years of age without chest radiotherapy, the incidence of fatal MI was significantly higher in survivors treated with anthracyclines than in the general public (Table 5).

This contrast between the mortality and incidence data in anthracycline exposure is likely explained by a combination of factors. Although anthracyclines may not increase the risk of having an MI, they may increase the risk of death if one occurs. Also, different studies used different methods of data collection, and there were differences in statistical power for the subgroup analyses, as well as differences in the characteristics of the populations studied. Nevertheless, the overall message from these studies is the same: Screening childhood cancer survivors treated with anthracyclines for cardiac function and CHD risk factors has the potential to decrease morbidity and mortality in this population.

Radiation

The effects of thoracic radiation are difficult to separate from those of anthracyclines, because few children undergo thoracic radiation without also receiving anthracyclines. Nevertheless, children treated with RT that includes the heart in the treatment field clearly have an increased risk of death of CVD and an increased incidence of clinically evident CVD, as well as asymptomatic dysfunction. Symptomatic CAD occurs in up to 10% of survivors after mediastinal radiation, and the highest relative risk for fatal myocardial infarction is that for children treated for cancer. Subclinical and
### Table 5. Evidence of Radiation-Associated Cardiac Damage

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<td><strong>Childhood cancer survivors in general—mortality</strong></td>
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<tr>
<td>Tukenova et al14</td>
<td>Cohort</td>
<td>Mixed</td>
<td>4112 Survivors</td>
<td>Evaluate CVD mortality in 4112 5-year survivors of childhood cancer diagnosed before 1986 in France and the United Kingdom</td>
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</table>
• CVD  
  – No: SMR=1.2 (95% CI, 0.3–4.8)  
  – Yes: SMR=6.2 (95% CI, 4.3–8.8), RR=5.0 (95% CI, 1.2–21.4)*  
• Cardiac disease  
  – 0 Gy: SMR=1.1 (95% CI, 0.1–7.4)  
  – 0.1 Gy: SMR=2.8 (95% CI, 1.1–7.6)  
  – 1–4.9 Gy: SMR=2.4 (95% CI, 0.3–17.5)  
  – 5–14.9 Gy: SMR=13.7 (95% CI, 5.1–36.4), RR=12.5 (95% CI, 1.4–116.1)*  
  – ≥15 Gy: SMR=33.3 (95% CI, 18.4–60.1), (RR=25.1 (95% CI, 3.0–209.5)*  
• Vascular disease  
  – No: SMR=1.4 (95% CI, 0.2–10.0)  
  – Yes: SMR=4.7 (95% CI, 2.5–8.8) |
• All-cause SMR=10.8 (95% CI, 10.3–11.3)  
• Cardiac SMR=8.2 (95% CI, 6.4–10.4)  
• Cardiac death with radiation RR=2.2 (95% CI, 1.2–4.4; RR adjusted for sex, age at diagnosis, and years since diagnosis) |
| Green et al165  | Cohort        | Mixed                      | 474 Survivors | Evaluate overall and cardiac mortality in 15-year cancer survivors diagnosed during childhood or adolescence compared with general population  
• 474 15-year survivors among 1441 consecutively treated patients at a single institution from 1960–1990  
  – 265 Males  
  – 209 Females |  
• HR for CHF, MI, pericardial disease, and valvular abnormalities compared with siblings†  
  – 5.9 (95% CI, 3.4–9.6)  
  – 5.0 (95% CI, 2.3–10.4)  
  – 6.3 (95% CI, 3.3–11.0)  
  – 4.8 (95% CI, 3.0–7.6)  
• HR for CHF, MI, pericardial disease, and valvular abnormalities for cardiac radiation 1500–3500 cGy (results for lesser doses not significant‡)  
  – 2.2 (95% CI, 1.4–3.5)  
  – 2.4 (95% CI, 1.2–4.9)  
  – 2.2 (95% CI, 1.3–3.9)  
  – 3.3 (95% CI, 2.1–5.1)  
• HR for CHF, MI, pericardial disease, and valvular abnormalities for cardiac radiation >3500 cGy‡  
  – 4.5 (95% CI, 2.8–7.2)  
  – 3.6 (95% CI, 1.9–6.9)  
  – 4.8 (95% CI, 2.8–8.3)  
  – 5.5 (95% CI, 3.5–8.6)  
• HR for CHF, MI, pericardial disease, and valvular abnormalities for cardiac radiation 1500–3500 cGy (results for lesser doses not significant‡)  
  – 2.2 (95% CI, 1.4–3.5)  
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  – 2.2 (95% CI, 1.3–3.9)  
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• HR for CHF, MI, pericardial disease, and valvular abnormalities for cardiac radiation 1500–3500 cGy (results for lesser doses not significant‡)  
  – 2.2 (95% CI, 1.4–3.5)  
  – 2.4 (95% CI, 1.2–4.9)  
  – 2.2 (95% CI, 1.3–3.9)  
• No cardiac deaths among female survivors |
| Mulrooney et al170 | Cohort        | Mixed                      | 14,358 Survivors, 3899 siblings | To assess incidence and risk of self-reported cardiac events in adult survivors of childhood and adolescent cancers diagnosed between 1970 and 1986  
• Childhood Cancer Survivor Study |  
• Cumulative Incidence of clinical heart failure was 2.5% at median 7.1 y of follow-up (0.01–28.4 y)  
• Only 22% of survivors received RT; study not powered to examine anthracyclines and RT in same model |
| van Dalen et al191 | Cohort        | Anthracycline ± RT          | 830, All treated with anthracyclines | Evaluate incidence of and risk factors for clinical heart failure in a cohort of children treated with anthracyclines; long-term follow-up study |  
• Cumulative Incidence of clinical heart failure was 2.5% at median 7.1 y of follow-up (0.01–28.4 y)  
• Only 22% of survivors received RT; study not powered to examine anthracyclines and RT in same model |

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<th>Study Findings (Mediastinal Radiation Exposures)</th>
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</table>
| Pein et al\(^{133}\) | Cohort       | Anthracycline ± RT        | 229, 24 With CHF, 205 Without CHF | Evaluate cardiac clinical status and function in a cohort of childhood solid tumor survivors all treated with anthracycline | • Median follow-up 15 y (0.3–24 y)  
• Cumulative incidence of CHF=10.4%  
• Among 205 others studied:  
  − 6% had fractional shortening <25%—Only cumulative anthracycline dose and average radiation dose to heart were independent risk factors for CHF (age at treatment was borderline)  
  − Anthracycline dose, average radiation dose to heart, age <8 y, and female sex were risk factors for any cardiac abnormality  
  − In those exposed to anthracycline ≥ 250 mg/m\(^2\) and average heart dose ≥ 5 Gy, incidence of any cardiac abnormality was 71% |
| Lipshultz et al\(^{134}\) | Cohort       | Mixed                     | 201 Survivors, 76 siblings | Assessment of echocardiographic characteristics and atherosclerotic disease risk factors in long-term survivors of childhood cancer of various diagnoses  
• 201 Survivors (median 11 y after diagnosis)  
  − 156 Total cardiotoxic treatment exposed  
  − 97 Anthracycline only  
  − 22 Cardiac radiation only  
  − 37 Both  
  − 45 Neither anthracycline or cardiac RT  
• 76 Sibling controls | • Risk is higher in both exposed and unexposed survivors, which suggests other aspects also drive risk  
• Unexposed survivors also have cardiovascular abnormalities, systemic inflammation, and increased atherosclerotic disease risk; Framingham Risk 2.16, 2.12, and 1.70 for exposed, unexposed, and controls, respectively; P<0.01  
• 156 Exposed had below-normal LV mass, wall thickness, contractility, and fractional shortening and above-normal LV afterload  
• 45 Unexposed had below-normal LV mass and females had below-normal LV wall thickness  
• Exposed/unexposed/sibling N-terminal probrain natriuretic peptide: 81.7/69.0/39.4 pg/mL, P<0.001  
• Exposed/unexposed/sibling fasting serum non-HDL cholesterol: 126.5/121.1/109.8 mg/dL, P<0.001  
• Exposed/unexposed/sibling high-sensitivity C-reactive protein: 2.7/3.1/0.9 mg/L, P<0.001 |
| Van der Pal et al\(^{169}\) | Cohort       | Anthracycline and/ or cardiac RT | 514 Survivors | Assessment of LVFS in 514 childhood cancer survivors visiting a late-effect outpatient clinic and having received anthracyclines, cardiac irradiation, high-dose cyclophosphamide, or high-dose ifosfamide  
• Median follow-up since diagnosis=15.4 y  
• All ORs adjusted for cumulative dose of anthracyclines, age at diagnosis, time since diagnosis, sex, BMI at examination, total RT dose to each of the 4 fields involving the heart | • Thorax OR (LVFS <30%)=3.49 (95% CI, 1.60–7.61)  
• Abdomen OR=2.66 (95% CI, 1.00–7.05)  
• Spine OR=0.64 (95% CI, 0.23–1.74)  
• Total body irradiation OR=0.53 (95% CI, 0.10–2.87) |
| Hudson et al\(^{189}\) | Case-control | Both (few with RT only) | 278 | Assess late anthracycline toxicity by physical examination, laboratory evaluation, echocardiogram, and ECG of 278 childhood cancer survivors (mean age 18.1 y, median 16.8 y):  
• 157 Received anthracycline  
• 60 Anthracycline and cardiac radiation  
• 6 RT only  
• 55 Received neither treatment | • No significant findings with respect to radiation exposure could be determined  
• Study underpowered to evaluate effects of cardiac irradiation |
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<tr>
<td>Green et al(^1)</td>
<td>Cohort</td>
<td>Anthracycline ± RT</td>
<td>2710 Survivors (Wilms tumor only)</td>
<td>To determine frequency of and risk factors for CHF after treatment for Wilms tumor that included doxorubicin for original or relapse treatment</td>
<td>• Cumulative frequency of CHF found to be 4.4% 20 y after Dx for patients initially treated with doxorubicin&lt;br&gt;• Cumulative frequency of CHF found to be 17.4% 20 y after Dx for patients treated with doxorubicin for relapsed Wilms tumor&lt;br&gt;• RR of CHF increased:&lt;br&gt;  – Females (RR=4.5, (P=0.004))&lt;br&gt;  – Cumulative doxorubicin dose (RR=3.3/100 mg/m², (P&lt;0.001))&lt;br&gt;  – Lung irradiation (RR=1.6 per 10 Gy, (P=0.037))&lt;br&gt;  – Left abdominal irradiation (RR=1.8 per 10 Gy, (P=0.013))</td>
</tr>
<tr>
<td>Krischer et al(^3)</td>
<td>Cohort</td>
<td>Anthracycline ± RT</td>
<td>6493 Survivors</td>
<td>To determine the incidence of clinical cardiotoxicity from anthracycline chemotherapy in children with cancer and to identify associated risk factors treated on Pediatric Oncology Group protocols from 1974–1990&lt;br&gt;• 106 Patients (1.6%) had confirmed events:&lt;br&gt;  – 58 Had CHF&lt;br&gt;  – 43 Changes in measures of cardiac function that prompted discontinuation of therapy&lt;br&gt;  – 5 Died suddenly of presumed cardiac causes&lt;br&gt;• 89.5% Events within first year of completing therapy</td>
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<tr>
<td>Swerdlow et al(^2)</td>
<td>Cohort</td>
<td>Mixed</td>
<td>7033 People – 78 382 Person-years – Diagnosed from 1967–2000</td>
<td>Evaluate MI mortality after treatment for Hodgkin lymphoma at any age in a collaborative British cohort study</td>
<td>• MI SMR=2.5 (95% CI, 2.1–2.9)&lt;br&gt;• Absolute excess risk of 125.8 per 100,000 person-years&lt;br&gt;• Age at treatment was a very important risk factor, with those treated at &lt;35 y at highest risk: MI SMR=6.7 at attained age 45–54 y&lt;br&gt;• Risks were increased significantly and independently for patients treated with:&lt;br&gt;  – Supradiaphragmatic radiotherapy&lt;br&gt;  – Anthracyclines&lt;br&gt;  – Vincristine&lt;br&gt;  – Those treated with the first 2 at &lt;35 y had the highest MI SMR: 23.7 (95% CI, 6.5–60.7)</td>
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<tr>
<td>Aleman et al(^5)</td>
<td>Cohort</td>
<td>Mixed</td>
<td>1474 Survivors (28,669 person-years); 1240 mRT</td>
<td>Evaluate CVD incidence in a cohort of HL survivors diagnosed before age 41 y&lt;br&gt;Median follow-up 18.7 y&lt;br&gt;Diagnosed from 1965–1995</td>
<td>• Standard incidence rate&lt;br&gt;  – MI=3.6 (95% CI, 2.9–4.4)&lt;br&gt;  – CHF=4.9 (95% CI, 3.6–6.4)&lt;br&gt;• Absolute excess risk&lt;br&gt;  – MI=35.7 per 100,000 person-years&lt;br&gt;  – CHF=25.6 per 100,000 person-years&lt;br&gt;• mRT independent risk factor after adjustment for recent smoking, age at Dx, and presence of other CVD risk factors&lt;br&gt;  – MI HR=2.42 (95% CI, 1.12–5.24)&lt;br&gt;  – CHF HR=7.37 (95% CI, 1.81–30.0)&lt;br&gt;  – Valvular disorders HR=7.01 (95% CI, 2.59–18.9)&lt;br&gt;• Anthracycline independent risk factor for CHD and valvular disorders only after adjustment for same factors&lt;br&gt;  – CHF HR=2.44 (95% CI, 1.37–4.33)&lt;br&gt;  – Valvular disorders HR=2.24 (95% CI, 1.40–3.59)</td>
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<th>Study Findings</th>
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</table>
| Aleman et al216 | Cohort       | Mixed                      | 1261        | Evaluate mortality in HL patients diagnosed before age 41 y | • CVD was third-leading cause of death (9.4% of all deaths)  
• MI caused 3.0% of all deaths  
• CVD RR=6.3  
• CVD absolute excess deaths=17.8 per 10K person-years  
For those <21 y at Dx, CVD RR=13.6  
Although RR decreased with attained age, absolute excess deaths of CVD and MI specifically increased  
Men had twice the rate of CVD death (likely because of background difference in sexes)  
Even 30 y after therapy, HL survivors had increased incidence of CVD |
| Schellong et al217 | Cohort | Anthracycline ± mRT | 1312 | Incidence of late valvular and other cardiac diseases after treatment of HL in children and adolescents | • Sibling stroke incidence 8 per 100,000 person-years (95% CI, 3.8–14.8)  
• HD survivor stroke incidence 83.6 per 100,000 person-years (95% CI, 54–122)  
• RR stroke=4.32 (95% CI, 2.01–9.29)  
• All HD survivor stroke victims (n=24) had received mantle radiation treatment (median dose=40 Gy)  
Incidence of stroke among HD survivors treated with mantle radiation 109.8 per 100,000 person-years (95% CI, 70–161) with RR=5.62 (95% CI, 2.59–12.25)  
• Differences between survivors and siblings in standard and Doppler echocardiography indices suggest systolic and diastolic dysfunction in survivors  
• Effects of RT and anthracycline not addressed |
| Bowers et al29 | Cohort | Both | 1926 HL survivors, 3846 sibling controls | To compare tissue Doppler echocardiographic evaluation of systolic and diastolic cardiac functions in long-term survivors of childhood HL compared with siblings | • Multiple finding suggestive of association between mRT and restrictive cardiomyopathy  
Mean LV mass, end-diastolic wall stress and dimensions  
Prolonged E/A ratio in 54%  
42.6% Had significant valvular defects  
Mitral and aortic regurgitation was significantly higher than would be expected in a normal older population  
42.6% Had significant valvular defects |
| Alehan et al201 | Case-control | Anthracycline ± mRT | 72 | To compare tissue Doppler echocardiographic evaluation of systolic and diastolic cardiac functions in long-term survivors of childhood HL compared with siblings | • Sibling stroke incidence 8 per 100,000 person-years (95% CI, 3.8–14.8)  
• HD survivor stroke incidence 83.6 per 100,000 person-years (95% CI, 54–122)  
• RR stroke=4.32 (95% CI, 2.01–9.29)  
• All HD survivor stroke victims (n=24) had received mantle radiation treatment (median dose=40 Gy)  
Incidence of stroke among HD survivors treated with mantle radiation 109.8 per 100,000 person-years (95% CI, 70–161) with RR=5.62 (95% CI, 2.59–12.25) |
| Adams et al218 | RT ± anthracycline | 48 HL survivors | To compare tissue Doppler echocardiographic evaluation of systolic and diastolic cardiac functions in long-term survivors of childhood HL compared with siblings | • Multiple finding suggestive of association between mRT and restrictive cardiomyopathy  
Mean LV mass, end-diastolic wall stress and dimensions  
Prolonged E/A ratio in 54%  
42.6% Had significant valvular defects  
Mitral and aortic regurgitation was significantly higher than would be expected in a normal older population  
42.6% Had significant valvular defects | (Continued)
clinical valvular diseases develop in up to 29% of children who receive radiotherapy for cancer, and these children have substantially more aortic regurgitation, tricuspid regurgitation, and aortic stenosis than those who received radiation >20 years before evaluation.220 Radiation alone may cause myocardial fibrosis, leading to restrictive cardiomyopathy, with up to 37% of patients having abnormal LV mass, end-diastolic dimension, or both a decade and a half after radiation treatment with an average dose of 40 Gy.218,218a Chronic constrictive pericarditis may also develop several years after completion of radiotherapy.218b,218c Total dose reduction, subcarinal blocking, and decreasing daily fraction size have substantially decreased the incidence of pericarditis.

Although current treatments strive to eliminate the use of radiation or to reduce the dose and volume, radiation remains a critical component of therapy for some cancers, such as Hodgkin lymphoma. Despite efforts to shield cardiac tissues in children with mediastinal Hodgkin lymphoma, the proximal coronary arteries and some valves continue to be exposed. Other patients in whom cardiac tissues are irradiated include those with brain tumors who require cranial-spinal irradiation, children with Wilms tumors or sarcomas who require pulmonary or abdominal irradiation, and patients receiving total body irradiation for stem cell transplantation.221

Mortality
The seriousness of cardiovascular effects is underscored by the fact that CVD is the third-leading cause of death in survivors of Hodgkin lymphoma, ranking below only disease recurrence and secondary cancers.216,222,223 In 3 reports, representing a total of 4553 survivors treated at all ages between the 1960s and 1990 with mediastinal radiotherapy, CVD accounted for 9.4% to 16% of all deaths.216,222,223 Absolute excess mortality from CVD ranged from 11.9 to 48.9 per 10000 patient-years. Historically, in radiotherapy for Wilms tumor, portions of the heart were exposed to substantial doses of radiation, with marked adverse cardiac effects.188

The above-mentioned French-United Kingdom study of 4122 5-year survivors of various childhood cancers diagnosed before 1986 found evidence for an independent association between radiation dose to the heart and risk of CVD.14 After 86453 person-years of follow-up (average case follow-up, 27 years), the mean standardized mortality ratio from CVD for those who received radiotherapy that exposed the heart was 6.2 (95% CI, 4.3–8.8), whereas the mean for survivors who did not receive chest radiotherapy was nonsignificantly elevated at 1.2 (95% CI, 0.3–4.8). After adjustment for other treatment factors, including anthracycline dose categories, the relative risk of CVD mortality in those who received radiotherapy that exposed the heart was 5.0 (95% CI, 1.2–21.4) compared with survivors who did not receive chest radiation. The association between radiation dose and increased cardiovascular mortality was restricted to an increased risk of cardiac deaths (n=21) as opposed to vascular deaths (n=11). After adjustment for other treatment factors, the relative risk of cardiac death from thoracic radiation doses >5 Gy was greatly elevated (relative risk, 12.5 [95% CI, 1.4–116.1]) for treatment with 5–14.9 Gy and relative risk, 25.1 [95% CI, 3.0–209.5] for treatment with >15 Gy to the heart compared with survivors in the study who received no heart irradiation). The average dose of radiation to the heart was linearly associated with the risk of cardiac mortality, with the incidence increasing by 60% for every 1-Gy increase in mediastinal radiation dose.

Incidence
The recent evaluation of cardiovascular outcomes in the Childhood Cancer Survivor Study revealed that the cumulative incidence of clinically important cardiac events, as well as mortality as described above, is associated with radiation dose (Figure 2).170 After adjustment for sex, age at diagnosis, treatment era (1970–1974, 1975–1979, 1980–1986), and anthracycline dose (0, <250, ≥250 mg/m²), the hazard ratios for those receiving 15 to 35 Gy and ≥35 Gy of cardiac irradiation were significantly elevated for each of the 4 outcomes evaluated (CHF, MI, pericarditis, and valvular problems) compared with those receiving no

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<tr>
<td>Lipshultz et al</td>
<td>CV Toxicity in Young People Who Receive Cancer Therapy 1949</td>
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BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; Dx, diagnosis; HD, Hodgkin disease; HDL, high-density lipoprotein; HL, Hodgkin lymphoma; HR, hazard ratio; LV, left ventricular; LVFS, left ventricular fractional shortening; MI, myocardial infarction; mRT, mediastinal radiotherapy; OR, odds ratio; QOL, quality of life; RR, relative risk; RT, mediastinal radiotherapy; and SMR, standard mortality rate.

- 62% Had monotonous heart rate or persistent tachycardia (24-h heart rate >90 bpm)
- Average maximal oxygen consumption low, with 30% <20 mL·kg⁻¹·min⁻², which is a criterion for listing patient for heart transplantation
- Mean physical component score of QOL on the SF-36 was significantly lower in this sample than the national sample of people the same age
- Multiple abnormalities on screening correlated with poorer physical component score of QOL on the SF-36
cardiac irradiation. However, hazard ratios for those who received 0 to 5 Gy and 5 to 15 Gy were generally not elevated for any of the outcomes, but CIs were quite wide, which suggests a lack of power to evaluate the independent effect of cardiac irradiation on each of these outcomes separately in these dose ranges.

In a German cohort of 1132 survivors of Hodgkin lymphoma who received treatment before 18 years of age in consecutive trials between 1978 and 1995, 50 had been diagnosed with CVD by a median of 19.5 years after diagnosis (range, 3.0–28.2 years). The cumulative incidence of CVD in those who received 36 Gy was 21%, which decreased to 10%, 6%, 5%, and 3%, respectively, in the 30-, 25-, 20-, and 0-Gy dose groups.

Presentation and Progression of Cardiovascular Toxicity
Anthracycline cardiotoxicity has 3 distinct types (acute, early-onset, and late-onset chronic progressive), characterized by the time of onset of signs or symptoms in relationship to treatment, the speed of their development, and the speed of the worsening of heart failure symptoms (Table 6). Acute changes occur within a week of infusion; early-onset chronic progressive cardiotoxicity appears after 1 week and within 1 year after completion of therapy. Late-onset chronic progressive cardiotoxicity occurs after the first year.

In each category, LV dysfunction, decreased exercise capacity, and clinical CHF may develop. Acute changes during infusion therapy range from minor abnormalities to fatal ventricular arrhythmias. Echocardiography can reveal LV systolic dysfunction, which is usually transient, but the rare patient may experience acute and potentially fatal CHF while undergoing therapy. Although most patients recover, at least temporarily, some have permanent damage, especially at higher cumulative doses of anthracyclines. Although electrophysiological changes may occur, they are rarely accompanied by signs or symptoms and manifest late in the disease process. The risk for chronic cardiac dysfunction may be greatest for those diagnosed with abnormal cardiac function during or immediately after completing therapy. Total cumulative dose is the most important risk factor for either type of chronic cardiac dysfunction (Table 7).

Many more survivors experience cardiac dysfunction over the long term than within 1 year of completing therapy. Late-onset anthracycline-related cardiac deterioration has occurred as long as 2 decades after therapy has been completed, but it is unclear whether there is any time limit. Late-onset dysfunction is a result of damage caused during therapy but that is not serious enough to cause symptoms immediately. Myocyte loss and damage, which occur during cancer therapy, lead to progressive LV dilation, LV wall thinning, and decreased contractility. As contractility diminishes over time, the LV dilates further to maintain cardiac output. These changes eventually increase LV wall stress, promoting further LV compromise. A heart with LV dilatation is unable to compensate further when metabolic demands increase. Although the evidence is somewhat anecdotal in nature, the risk of acute deterioration appears to increase in childhood cancer survivors who were treated with anthracyclines when additional stress is placed on the anthracyline-exposed heart by acute viral infection, growth hormone (GH)–induced growth spurts, pregnancy-induced hypervolemic weight gain, vaginal delivery, and weight lifting.
Radiation cardiotoxicity tends to have a gradual onset and usually manifests after a decade or more with the doses used in the past 25 years. Historically, acute pericarditis was rare and only occurred with high radiation doses (>40 Gy) to large cardiac volumes, particularly in the presence of a juxtapercardiac tumor. However, radiation-associated pericarditis is now exceedingly rare. Since the 1980s and 1990s, the greatest risks of mediastinal radiotherapy at doses used to treat childhood Hodgkin lymphoma include MI, occurring well below typical ages for such an event, and restrictive cardiomyopathy. Unfortunately, the clinical harbingers of MI can be subtle or nonexistent.

With regard to myocardial function, the most important sequela of cardiac irradiation is diastolic dysfunction. Often, survivors have no symptoms or only vague reports of fatigue, although in the advanced stages, they report typical heart failure symptoms, and there is no evidence of systolic dysfunction on imaging. Therefore, the evidence for diastolic dysfunction after thoracic irradiation largely derives from studies that screened Hodgkin lymphoma survivors with imperfect echocardiographic measures of cardiac relaxation. Adams et al comprehensively evaluated the cardiac status of 48 long-term survivors of Hodgkin lymphoma diagnosed during childhood or young adolescence and treated with mantle irradiation (range, 27.0–51.7 Gy; median, 40 Gy), only 4 of whom had received an anthracycline. At a median of 14.3 years after diagnosis, 5 survivors (10%) had an abnormal measure of systolic function, but 3 of these 5 had received an anthracycline as well. However, 18 (37%) had an abnormal measure of LV mass or end-diastolic dimension, findings that suggest diastolic dysfunction. Additionally, the E/A ratio (a measure of diastolic dysfunction indicating the ratio of peak early filling to peak late filling of the LV) was measured in 37 survivors. Of these, 12 (32%) had probable abnormal E/A ratios between 1.5 and 2.0, and 8 (22%) had definitively abnormal ratios of ≥2.0.

A substantial percentage of patients with diastolic dysfunction will have ischemia with exercise. Survivors with diastolic dysfunction have substantially worse cardiac event–free survival and worse quality of life than those without it. The prevalence also depends on the screening method, discussed below in “Assessment of Cardiovascular Toxicity.”

The other frequent problem associated with thoracic irradiation that includes the heart in the treatment field is valvular dysfunction. This appears to be progressive, because in the studies that have evaluated valvular problems, the frequency of abnormalities increases with time after diagnosis. In the same study by Adams et al, 20 survivors (42%) had at least 1 valve abnormality that would be unexpected in a healthy population. These findings were consistent with other echocardiographic studies of valvular defects in Hodgkin lymphoma survivors who received similar doses of radiotherapy.

Radiation-associated valvular disease may also be progressive and can lead to CHF. In fact, a study by Hull et al indicates that the frequency of valve repair surgeries in Hodgkin lymphoma survivors (both child onset and young adult onset) is 8 times as high as that in the general population. Valvular disease appears to be the most common clinically evident CVD within the first 20 years after mediastinal radiotherapy for Hodgkin lymphoma, followed by CAD, cardiomyopathy, conduction disorders, and, least commonly, pericardial disease.

### Table 6. Characteristics of Different Types of Anthracycline Cardiotoxicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Cardiotoxicity</th>
<th>Early-Onset Progressive Cardiotoxicity</th>
<th>Late-Onset Progressive Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Within the first week of anthracycline treatment</td>
<td>&lt;1 y after completion of anthracycline treatment</td>
<td>≥1 y after completion of anthracycline treatment</td>
</tr>
<tr>
<td>Risk factor dependence</td>
<td>Unknown</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Clinical features in adults</td>
<td>Transient depression of myocardial contractility</td>
<td>Dilated cardiomyopathy</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Clinical features in children</td>
<td>Transient depression of myocardial contractility</td>
<td>Restrictive cardiomyopathy and/or dilated cardiomyopathy</td>
<td>Restrictive cardiomyopathy and/or dilated cardiomyopathy</td>
</tr>
<tr>
<td>Course</td>
<td>Usually reversible on discontinuation of anthracyline</td>
<td>Can be progressive</td>
<td>Can be progressive</td>
</tr>
</tbody>
</table>


### Table 7. Risk Factors for Anthracycline-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cumulative dose</td>
<td>Most significant predictor of abnormal cardiac function</td>
<td>1, 3, 4, 9, 11, 61</td>
</tr>
<tr>
<td>Age</td>
<td>For comparable cumulative doses, younger age predisposes to greater cardiotoxicity (especially &lt;5 y of age)</td>
<td>4, 11, 13, 62–65</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>Longer follow-up results in higher prevalence of myocardial impairment</td>
<td>4, 11, 13, 66, 67</td>
</tr>
<tr>
<td>Sex</td>
<td>Females more vulnerable than males for comparable doses</td>
<td>1, 3, 13, 14</td>
</tr>
<tr>
<td>Concomitant mantle irradiation</td>
<td>Evidence of enhanced cardiotoxicity; not clear whether additive or synergistic</td>
<td>66</td>
</tr>
<tr>
<td>Others</td>
<td>Concomitant exposure to cyclophosphamide, bleomycin, vincristine, amrascine, or mitoxantrone may predispose to cardiotoxicity; trisomy 21 and black race have been associated with a higher risk of early clinical cardiotoxicity</td>
<td>66</td>
</tr>
<tr>
<td>Rate of anthracycline</td>
<td>Higher rate was thought to predispose to greater toxicity, but current trials do not support this</td>
<td>68, 69</td>
</tr>
</tbody>
</table>

Assessment of Cardiovascular Toxicity

On the basis of evidence from the extant literature supporting an increased prevalence of cardiomyopathy and other cardiovascular complications in survivors treated with anthracyclines and chest radiation for childhood cancer, surveillance of cardiovascular function has been recommended by several pediatric cooperative groups for at-risk survivors. Most advise assessment of LV systolic function and heart valve function by echocardiography, QTc and rhythm abnormalities by ECG, and comorbid conditions influencing cardiovascular health (eg, dyslipidemia). The frequency of screening is informed by findings from history and physical examination, age at treatment, time from treatment, and specific exposures and their cumulative doses.

Monitoring Cardiac Structure and Function During Therapy

There are no evidenced-based guidelines for cardiovascular monitoring during therapy. The only established, if empirically based, guidelines for cardiovascular monitoring in children during treatment were published in 1992, by Steinherz et al. Increasing knowledge about cardiovascular toxicity in long-term survivors, increasing options for cardioprotection, and expanding tools for monitoring all indicate the need to reassess monitoring strategies, to develop evidenced-based monitoring guidelines, and to assess the long-term impact of monitoring during treatment. 233

The primary goal of monitoring is to identify early signs of potentially reversible disease; however, decreasing the risks of cardiovascular toxicity must be balanced by maintaining the efficacy of cancer treatment. 27,234,235 A second reason for monitoring during therapy is to obtain baseline data for long-term follow-up studies. Current digital storage modalities will likely allow follow-up studies to be compared with all previous studies so that subtle changes in cardiac performance can be tracked from year to year over several decades.

The 1992 guidelines by Steinherz et al rely primarily on echocardiographic monitoring of LV shortening and ejection fraction measurements, but they also include ECG, radionuclide angiography, and endomyocardial biopsy. A clinically important deterioration in function is defined as (1) a 10% absolute decrease in LV fractional shortening, (2) an LV fractional shortening with an absolute value <29% as measured by echocardiography, (3) a 10% decrease in LV ejection fraction, or (4) a LV ejection fraction with an absolute value <55%. The guidelines recommend discontinuing anthracycline therapy if deterioration is found on 2 successive tests (preferably by both echocardiography and radionuclide angiography on each occasion) and obtaining a myocardial biopsy, if possible.

Several articles 234,236 have raised concerns about the 1992 guideline recommendations for monitoring during therapy. Lipshultz et al 234 concluded that none of the studies cited in the guidelines prospectively evaluated the effects on morbidity and mortality of cardiac monitoring and the adjustment of anthracycline dose, compared with control subjects who were not monitored. In addition, Lipshultz et al 234 questioned whether the monitoring recommendations and subsequent dose adjustments might do more harm than good. The guidelines provide no evidence that screening for anthracycline cardiotoxicity predicted either early or late adverse cardiac outcomes. The lack of an individualized approach was also criticized; the risk versus benefit of altering therapy varies markedly among patients. Thus, Lipshultz et al 234 called for prospective controlled studies to determine the effects of dose adjustments based on cardiac monitoring results.

The guidelines by Steinherz et al, 233 with modifications, are still used in many practices throughout the world. In an exhaustive literature search, the only guidelines van Dalen et al 236 found for monitoring during therapy were those of Steinherz et al. van Dalen et al 236 also found 12 pediatric cancer protocols: Eleven used only echocardiography; 1 used echocardiography or radionuclide angiography; 3 protocols included baseline ECG; 6 used LV shortening fraction as the primary functional measurement; 4 used a combination of shortening and ejection fractions; and 1 included an assessment of endsystolic wall stress. Definitions of cardiotoxicity were similar to the 1992 guidelines in most of the protocols for shortening fraction; the lower limit for ejection fraction was lower than the 1992 guidelines in several protocols. Frequency of monitoring varied among the 12 protocols; 4 monitored at the frequency recommended in the Steinherz et al guidelines, and 5 monitored less frequently. Responses to altered cardiac function varied widely. Some followed the guidelines for stopping anthracycline treatment, and others modified the dosage.

The validity and practicality of monitoring tools also need to be reassessed. These tools include ECG, echocardiography (including measures other than LV shortening and ejection fraction), radionuclide angiography, cardiac magnetic resonance imaging (MRI), and biomarkers. 236a Although ECGs are universally available and inexpensive, their value is limited because they provide no information about cardiac function, and interrater reliability is not optimal. 237 False-positive results could unnecessarily delay therapy or lead to additional unnecessary testing. In addition to creating excessive costs, this delay could potentially cause morbidity and mortality if treatment is delayed or unneeded invasive procedures are performed. Nevertheless, assessment of the QT interval may help identify patients at higher risk for cardiotoxicity. 61

Echocardiography is likely to continue to be the mainstay of monitoring, given that it is portable, is widely available, causes minimal pain, can usually be performed without sedation, and provides real-time data. The utility of echocardiography currently extends beyond the traditional measures of LV shortening and ejection fractions. These preload- and afterload-dependent measures of systolic function are based on geometric assumptions and may not detect early cardiac dysfunction. 238 Marked changes in a patient from study to study may not reflect changes in contractility and could result in inappropriate adjustment of cancer treatment.

Several studies have evaluated echocardiographic measures that may be more sensitive to early impairments in cardiac performance in children with cancer. 200,239-241 These measures include load-independent measures of systolic function (end-systolic wall stress and velocity of circumferential fiber shortening), diastolic function, tissue Doppler imaging, global function (myocardial performance index), and measures of cardiac mechanics (2-dimensional strain and strain rate).

The use of newer echocardiographic measures in children during therapy is not well studied, but some studies have
assessed children after therapy. A systematic approach to long-term monitoring that includes these measures has implications for monitoring protocols during treatment. Iarussi et al. showed that increased end-systolic wall stress was associated with the effects of diastolic dysfunction in children after anthracycline treatment. Yildirim et al. reported that tissue Doppler imaging at rest and dobutamine stress echocardiography had a higher sensitivity than traditional measures of LV function for early anthracycline toxicity in children after treatment. Park et al. found abnormalities of regional wall motion using 2-dimensional strain (velocity vector imaging, which is angle-independent) in children 3 to 15 years after low-dose anthracycline therapy who had preserved global function.

Studies of more advanced echocardiographic measures in adults and in animals during therapy can guide the design of studies in children. A decrease in longitudinal strain and an increase in high-sensitivity cardiac troponin I detected 3 months into therapy were independent predictors for reduction of LV ejection fraction of at least 5% to <55% with symptoms of heart failure or an asymptomatic reduction of LV ejection fraction of at least 10% to <55% at 6 months into therapy in an adult woman with breast cancer. LV ejection fraction, measures of diastolic function, and N-terminal pro-B-type natriuretic peptide did not predict cardiotoxicity. Hare et al. showed that myocardial deformation as identified by tissue Doppler and 2-dimensional strain imaging detected myocardial dysfunction in women with normal ejection fraction during treatment with trastuzumab for breast cancer. Stoodley et al. reported that measures of global and regional longitudinal and radial LV 2-dimensional systolic strain were significantly reduced 1 week after chemotherapy in women with breast cancer in whom ejection fraction remained unchanged. Sawaya et al. found that systolic longitudinal myocardial strain <19% and ultrasensitive troponin I measured during therapy in breast cancer patients treated with anthracyclines, taxanes, and trastuzumab predicted subsequent cardiotoxicity over 15 months. Although adult studies have found positive predictive value for strain and cardiac biomarkers, these findings do not validate these screening methodologies. Positive predictive value gives the probability that a positive screening test will correctly identify an outcome of interest and is partially dependent on the prevalence of the condition of interest. Further study is required to determine the validity of these measures, particularly with regard to their ability to improve patient outcomes and their cost-effectiveness. Doppler tissue imaging abnormalities preceded a decrease in ejection fraction and predicted early mortality in mice receiving doxorubicin plus trastuzumab. Cardiac MRI offers great potential and several advantages over echocardiography and radionuclide angiography. Measures of function and ventricular mass are highly reproducible and are not subject to variable image quality or assumptions of cardiac geometry. The ability to assess perfusion abnormalities and subendocardial damage by delayed enhancement provides information not available by echocardiography. Unlike radionuclide angiography, cardiac MRI does not use ionizing radiation. The major limitations of MRI are that it is time-consuming, is costly, may not be universally available, and often requires sedation in children. Several small studies have evaluated the use of cardiac MRI in monitoring for early and late cardiotoxicity in children and adults. In 28 children during and immediately after chemotherapy, Oberholzer et al. using cardiac MRI, found that end-systolic volume increased and that left and right ventricular ejection fraction decreased.

The main advantage of radionuclide angiography is that it has been the reference standard for measuring LV ejection fraction; however, cardiac MRI is probably as reliable and has the other advantages noted above. Most children have reasonable echocardiographic windows, which makes radionuclide angiography less necessary in pediatric cancer protocols. Additionally, radionuclide angiography ejection fraction is subject to the same load dependency that affects echocardiographic shortening and ejection fractions, and radionuclide angiography provides no information about diastolic function.

Monitoring Cardiac Structure and Function After Therapy
Cardiotoxicity may manifest as cardiomyopathy, pericarditis, CHF, valvular heart disease, or premature coronary artery disease. Long-term cardiovascular monitoring of cancer survivors diagnosed in childhood, adolescence, and young adulthood should be aimed at early, preclinical detection, when interventions can be expected to have the greatest benefit; however, evidence-based, comprehensive screening recommendations to standardize and direct follow-up care for cancer survivors have not fully evolved. The discussion below regarding the screening of cardiac structure and function after exposure to cardiotoxic chemotherapeutic agents and radiotherapy is based on the efficacy of methods for detecting CVD related to childhood cancer therapy and on newer but not yet fully established modalities for assessing subclinical CVD.

Anthracycline-Induced Cardiomyopathy
Assessment modalities and measures for determining abnormality vary by center and by study. The most commonly used characteristics of LV systolic function with M-mode and 2-dimensional echocardiography—LV fractional shortening and LV ejection fraction—are load dependent, have variable results, and do not evaluate regional myocardial function and therefore may not detect early stages (stage B by American College of Cardiology/American Heart Association (AHA) classification of heart failure) of LV dysfunction, which is one reason reports of anthracycline-related subclinical cardiotoxicity range from 0% to 57%. Because asymptomatic LV systolic dysfunction in adults is associated with increased cardiovascular and all-cause mortality, and because the late consequences of subclinical cardiac dysfunction in childhood survivors are not known, long-term serial cardiac monitoring should be considered. However, an evidence-based regimen for such monitoring needs to be established.

Assessment of Cardiac Function
Echocardiography is the modality of choice for monitoring cardiac structure and function after exposure to cardiotoxic chemotherapeutic agents and RT. LV systolic function can be assessed with M-mode and 2-dimensional echocardiography-based measurements of fractional shortening and ejection
fraction, respectively. The load dependency of these measures can be overcome by using the M-mode–based stress-velocity relationship calculated from the velocity of fiber shortening and corrected for heart rate and estimated LV end-systolic wall stress.218 However, estimation of the stress-velocity relationship is time and skill intensive and may not be practical for use in the routine echocardiographic assessment of patients after anthracycline treatment.

New echocardiographic techniques for evaluating ventricular function have been introduced during the past decade. Myocardial velocity and deformation, namely, strain and strain rate, have potential value for measuring global and regional systolic and diastolic myocardial function.241 Myocardial velocity reflects displacement per unit of time and is measured by tracking tissue motion with Doppler tissue imaging. Reference age- and sex-specific normal myocardial velocities have been established for children.203,240,262,263 The maximal systolic myocardial velocity (S'), the early and late diastolic myocardial velocities (E' and A'), the time between the closing and opening of the mitral valve (a'), and the systolic time (b') can be used to calculate the myocardial performance index: (a'−b')/b'. Both prolonged isovolumic relaxation time and an increased myocardial performance index late after treatment reportedly can indicate anthracycline-induced cardiotoxicity in the presence of normal LV ejection fraction.203,240,262,263

Myocardial strain is a dimensionless measure of regional and global ventricular deformation. Myocardial strain rate, a time derivative of strain, correlates with LV peak elastance, which is a load-independent global measure of ventricular systolic function.203,264 Strain and SR are currently measured by speckle-tracking echocardiography, a relatively new, largely angle-independent technique, which has been validated both in adults266 and children.267 Asymptomatic patients with a normal ejection fraction long after chemotherapy have reduced LV annular motion and systolic and diastolic longitudinal and radial peak systolic strain rate and strain.241,244,268

Regional longitudinal dysfunction can be detected earlier than global dysfunction. The speckle-tracking echocardiography–estimated strain and strain rate can detect early cardiac dysfunction, both systolic and diastolic, in asymptomatic patients with normal conventional measures of cardiac function.241 Thus, estimation of myocardial deformation with speckle-tracking echocardiography shows great promise, but the values currently vary greatly, depending mostly on the imaging system and image quality.269

Assessment of Ventricular Structures (Myocardium, Valvular Structures, and Coronary Arteries)

Assessment of the acoustic properties of the myocardium could detect myocardial damage sooner after anthracycline chemotherapy. Ultrasonic tissue characterization by integrated backscatter is a noninvasive means of determining the physiological and pathological changes in myocardium. Normal myocardium shows cardiac cycle–dependent integrated backscatter variations. Its magnitude decreases in both ischemic and nonischemic myocardial diseases, so it is disease sensitive but not disease specific.270−272 The value of cycle–dependent integrated backscatter variations of the LV septal and posterior walls decreases in patients after chemotherapy with 5-FU in the absence of clinical symptoms and before the manifestation of systolic dysfunction.273 However, backscatter values depend on the angle between the myocardial fibers and the ultrasound beam and can be affected by this anisotropy and by the translational and rotational motion of the heart. The importance of the findings of cycle–dependent integrated backscatter varia-
tions over the long-term still needs to be determined.

As alluded to in “Monitoring Cardiac Structure and Function During Therapy,” cardiac MRI is a versatile imaging modality that provides high spatial resolution and limitless windows without ionizing radiation or dependence on contrast material. In 36 20-year survivors of Hodgkin disease, cardiac MRI detected 25 cases of radiation-induced heart disease, including 6 with reduced function, 11 with hemodynamically relevant valvular dysfunction, 7 with late myocardial enhancement suggestive of myocardial fibrosis or scarring, and 17 with a perfusion deficit, many of whom were asymptomatic.251

Timing and Frequency of Monitoring

Evidence-based guidelines for timing and frequency of monitoring for cardiovascular toxicity in cancer survivors have not evolved for implementation in clinical practice. Few studies can be used to guide recommendations for the timing and frequency of cardiac monitoring, and fewer studies have investigated the importance of screening asymptomatic survivors for CVD. Several studies describe childhood blood cancer and lymphomas treated with strategies that are mostly no longer used, which makes it difficult to design monitoring programs for current patients. Early detection of CVD in cancer survivors will require the application of newer and sensitive modalities to develop a strategy for early intervention. This may require an epidemiological study to develop such screening tools with high sensitivity, negative predictive value, and cost-effectiveness. In the meantime, long-term follow-up screening guidelines recommended by the Children’s Oncology Group can be applied to the cardiovascular screening of childhood cancer survivors.274 European studies275 have recommended that patients treated with combined therapy and radiation for lymphomas be screened by coronary artery calcium score measurements or computed tomography (CT) angiography; they recommended that such monitoring should begin 10 years after radiotherapy. An ECG is recommended at each cardiovascular screening visit to detect arrhythmias or conduction abnormalities. These screening tests can be repeated every 5 years or at the onset of cardiovascular signs or symptoms.

Monitoring Cardiac Structure and Function After Radiation Treatment

Survivors of childhood cancers exposed to cardiac radiation intentionally or incidentally as a component of chest radiotherapy are at increased risk for ischemic CVDs, such as MI, as well as for other forms of cardiac dysfunction, including valvular disease, conduction abnormalities, pericarditis, and a restrictive-like cardiomyopathy, all of which can result in heart failure or death.14,118,170,218,219 Additionally, cardiac radiation can exacerbate anthracycline-related cardiac damage, and recent evidence indicates that other radiation exposures to organs such as the brain and kidney can also have indirect cardiac effects.185,276,277 Given the heterogeneity of the cardiac
complications associated with RT, regular screening with several modalities must be considered to assess myocardial structure and function, the development of CAD, and the presence of conduction abnormalities. In all survivors exposed to cardiac radiation, the possibility of cardiac impairment should be considered during the annual follow-up visits.

Survivors have substantially higher risks of premature CAD, with a risk of fatal MI that is 2 to 8 times as great as the risk in the general population. Many are also often asymptomatic, even when they have severe CAD. As a result, noninvasive screening with stress echocardiography, ECG, and scintigraphy to detect stress-induced ischemia has been investigated; however, the test characteristics of noninvasive screenings, compared with those of coronary angiography, are disappointing, and the predictive value of such noninvasive screening modalities for actual clinical events has not been studied in this population. New diagnostic tools, such as CT angiography, magnetic resonance angiography, and coronary artery calcium scores, have been investigated. The sensitivity for marked (>50%) angiographic stenosis varies between 81% and 97% in men and between 76% and 98% in women, but the specificity has been >77% in predicting marked stenosis in survivors.

Echocardiography is noninvasive and provides information on LV structure and function, the pericardium, and the cardiac valves. LV structure can be assessed from measurements of LV wall thickness and dimension, as well as by calculating the ratio of the two. As stated in previous sections, LV systolic function can be assessed from measurements of LV wall stress, fractional shortening, and the stress-velocity index. LV diastolic function can be assessed from the ratio of peak early filling to peak late filling during diastole (the E/A index). LV diastolic function and the LV thickness-to-dimension ratio may be particularly valuable in patients at risk for a restrictive-like cardiomyopathy in which LV systolic dysfunction and dilation may not occur until later in the disease process. When the quality of echocardiographic measurements is limited, nuclear cardiac scans (single-photon emission CT or positron emission tomography) may be used to acquire similar measurements, albeit without diastolic function information, which may be the most important in this population. Such monitoring is consistent with the recommendations of the Children’s Oncology Group. The optimal frequency for assessment of LV structure and function in survivors exposed to cardiac irradiation has not been established, although assessment once every 1 to 5 years may help identify abnormalities early, depending on the patient’s age at exposure, anthracycline dose, time since treatment, and the presence of other risk factors.

The development of CAD in survivors exposed to cardiac radiation should be assessed regularly after cancer treatment. This assessment should include traditional CVD risk factors, such as dyslipidemia and hypertension, and cardiac stress testing with exercise ECG, which can identify cardiac ischemia in asymptomatic patients. However, the results of the test should be interpreted with caution, because exercise electrocardiography may have false-positive and false-negative findings. For patients with evidence of conduction abnormalities, including complete left bundle-branch block, preexcitation syndrome or another similar abnormality, or >1 mm of ST-segment depression at rest, stress echocardiography or myocardial perfusion imaging is preferred. For patients unable to stress the heart through exercise, pharmacological stress induction should be considered. Because coronary events are rare in younger patients, even those at increased risk, stress testing may be best used as survivors reach adulthood. These recommendations are also consistent with those of the Children’s Oncology Group, although again, the optimal frequency of cardiac stress testing and the age at which screening should be conducted have not been established.

Exercise stress testing may be helpful in monitoring not only CAD risk but also cardiac function if the stress testing also measures maximum oxygen consumption ($V_{O_{2max}}$), a predictor of mortality in heart failure. Adams et al found that maximum oxygen consumption was severely depressed ($<20 \text{mL.kg}^{-1}\text{min}^{-1}$) in 30% of the Hodgkin lymphoma survivors screened. In addition, $V_{O_{2max}}$ was correlated with quality of life, specifically the physical component score on the SF-36 and potentially explained 25% of the variability in this score. Furthermore, in a follow-up study of half of these patients, $V_{O_{2max}}$ continued to explain 25% of the physical aspects of quality of life an average of 2 years later. Given that echocardiography has limited ability to evaluate diastolic function and such indices have not been demonstrated to be prognostic, the monitoring of $V_{O_{2max}}$ may be particularly important in survivors treated with chest radiotherapy; however, more research is needed to determine its value.

Conduction abnormalities in patients exposed to cardiac radiation should be assessed at the end of cancer treatment and regularly thereafter if there is evidence of other forms of cardiotoxicity. A baseline ECG may help identify conduction blocks and arrhythmias after treatment. The value of repeat testing in survivors without other evidence of cardiotoxicity may be limited, because conduction abnormalities usually develop late in the course of cardiotoxicity, likely as a result of remodeling in response to cardiac damage. In patients with evidence of cardiotoxicity, a 24-hour ECG may provide additional information. This recommendation is also consistent with those of the Children’s Oncology Group.

Screening for cardiac abnormalities in survivors exposed to brain and kidney radiation may also be warranted. These exposures are associated with endocrine abnormalities and renal disease, which may lead to cardiac dysfunction through GH deficiency and hypertension, as discussed more thoroughly below. Although these pathways are still being investigated, they can be considered in patients with other exposures known to cause cardiotoxicity, such as anthracyclines and cardiac radiation.

**Cardiometabolic Risk Factors for Premature Atherosclerosis**

**Obesity in Survivors of Childhood Cancer**

Obesity is strongly associated with premature CVD. Several large epidemiological studies have documented an increased incidence of early cardiovascular events and death in both men and women with increasing weight. Currently, nearly 30% of all children and adolescents in the United States are overweight. Childhood obesity has been associated with...
elevated blood pressure, elevated triglyceride concentrations, low high-density lipoprotein (HDL) cholesterol concentrations, abnormal glucose metabolism, insulin resistance, inflammation, and abnormal vascular function. Obesity tracks from childhood to adulthood, and childhood adiposity is a strong predictor of obesity, insulin resistance and abnormal lipid concentrations in adulthood.

Cancer survivors are not immune to the obesity epidemic and, in fact, have a higher than expected frequency of obesity. Large retrospective cohort studies, such as the Childhood Cancer Survivors Study, report a higher prevalence of obesity and a greater rate of increase in body mass index (BMI) in adult survivors of childhood ALL than in healthy control subjects, especially in women treated with cranial radiation as girls.

The increased prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus and their long-term effects on the development of premature CVD has made measurement of body fatness increasingly relevant and has intensified the need to establish simple and reliable clinical methods for its assessment.

BMI, based on height and weight measurements, is routinely used to assess adiposity and weight in adults and children. It requires minimal training to perform, and in adults, repeated values can be obtained with good agreement. Waist circumference is considered an adequate marker of abdominal obesity in adults, but in children, the measurement is highly operator dependent. An expert committee of the American Medical Association and the Centers for Disease Control and Prevention Task Force on Assessment, Prevention, and Treatment of Childhood Obesity was unable to recommend the use of waist circumference for routine clinical use in children because of “incomplete information and lack of specific guidance for clinical application.”

Several other, more elaborate measures of body composition used primarily in research include underwater weighing, dual-energy x-ray absorptiometry (DEXA), estimates of total body water, total body electrical conductivity, total body potassium, MRI, and CT. Among these, DEXA is the most widely used in research, because of its accuracy and ease of acquisition for both the patient and the technician. Considered by many to be the “reference standard” for estimating body fatness, DEXA has been limited to research studies because of its complexity and cost.

The methods used to assess adiposity may affect the prevalence of obesity. In a report of risk factors in adult survivors of pediatric cancers, obesity, as defined by BMI, was not more common in cancer survivors than it was in healthy siblings; however, other measures of central adiposity, such as waist circumference and visceral fat content, increase in some cancer survivors. In a recent prospective study of childhood cancer survivors evaluated while still children, BMI and waist circumference were calculated from simple anthropometrics, and body composition (fat body mass, lean body mass) was measured with DEXA. In this young cohort, although BMI did not differ between groups, waist circumference and fat mass were significantly greater and lean body mass was significantly lower in cancer survivors than in healthy control subjects, independent of exposure to cranial radiation. These findings suggest that in populations of young cancer survivors, BMI may less accurately measure adiposity than waist circumference or body composition measures obtained from DEXA.

Pathophysiology of Obesity in Childhood Cancer Survivors
In adult survivors of childhood ALL, various factors, including female sex, genetic predisposition, exposure to steroids, and cranial radiation, have been implicated in the development of excess body fat independently of other more common factors.

Leptin, an adipocytokine produced by adipocytes, controls energy metabolism at the level of the hypothalamus by suppressing appetite and stimulating energy expenditure. Leptin concentrations are elevated in otherwise healthy obese adults and children, which indicates resistance to the effects of leptin in these individuals. Elevated leptin concentrations and leptin receptor abnormalities have been reported in childhood cancer survivors.

Radiation exposure to the hypothalamic-pituitary axis in childhood can result in late-onset deficiency of GH secretion and subsequent development of obesity in adulthood. GH helps determine fat cell size, fat cell differentiation, and concentrations of resistin, all of which are important determinants of insulin sensitivity. Impaired GH concentrations in survivors potentially affect the development of obesity, insulin resistance, and type 2 diabetes mellitus. In a study of young adult ALL survivors, cranial radiation was a risk factor for elevated total, abdominal, and visceral adiposity; reduced lean body mass; a higher risk of metabolic syndrome; and altered insulin-like growth factor-1 and leptin concentrations. Cachexia acutely affects 50% of cancer patients and is characterized by weakness, fatigue, loss of lean body mass, and abnormal metabolism. It may be associated with an increased risk of CVD in childhood cancer survivors in a manner similar to that of fetal malnutrition in healthy populations.

The induction and intensification stages of therapy include prolonged continuous administration of high-dose steroids, which induce hunger and decrease lean body mass. The combination of initial malnutrition and muscle wasting from cancer followed by treatment-induced increases in appetite underlies the propensity to develop obesity later in life.

The Children’s Oncology Group recommends annual height, weight, and BMI evaluation for survivors and healthy lifestyle (physical activity and nutrition) counseling as needed. In the general population, assessment of adiposity by BMI offers the advantage of low cost, low technical error, and high reproducibility; however, its utility is low in assessing changes in adiposity from one visit to the next. Given the evidence presented in this document, BMI as a sole screening tool may not be sufficient for assessing excessive adiposity and unfavorable body composition in young cancer survivors.

Atherosclerosis in Childhood Cancer Survivors
Epidemiological and pathobiological studies have shown that atherosclerosis begins in childhood if children and adolescents have an earlier onset of the “classic” risk factors: dyslipidemia, hypertension, obesity, insulin resistance, and cigarette smoking. The prevalence of these cardiovascular risk factors in cancer survivors increases from childhood to late adolescence and adulthood. The prevalence of dyslipidemia
has increased in both child and adult survivors.\textsuperscript{71} In the Childhood Cancer Survivor Study, long-term survivors with a mean age of 32 years were twice as likely to be hypertensive as were their siblings.\textsuperscript{31} Aggregate cardiovascular disease risk factor scores are increased in childhood cancer survivors.\textsuperscript{352a}

Among young adult ALL survivors treated with cranial radiation during childhood, increased adiposity with a reduced fat-free mass, often in the presence of borderline hypertension, accompanied higher BMI measurements.\textsuperscript{338} Having 3 of 5 of interrelated metabolic cardiovascular risk factors (obesity, dyslipidemia from low HDL or elevated triglyceride concentration, hypertension, and impaired glucose tolerance) has been termed metabolic syndrome. The major underlying link to the risk factors in the general population is thought to be insulin resistance.\textsuperscript{333–336} Indeed, cancer survivors are more insulin resistant and more likely to have adverse concentrations of cardiovascular risk factors than their healthy siblings.\textsuperscript{317,346} In particular, when compared with older women in the control cohort, women treated with cranial radiation as children were more likely to be insulin resistant.\textsuperscript{13}

In obese people with higher percentages of visceral adipose tissue, increasing plasma free-fatty acid concentrations also induces oxidative stress, inflammation, and subnormal vascular reactivity, in addition to causing insulin resistance.\textsuperscript{357} Obesity in survivors itself may be an inflammatory state, because C-reactive protein concentrations are increased in survivors.\textsuperscript{31} Adipose tissue expresses most of these proinflammatory mediators.\textsuperscript{358} Leptin, which is secreted by visceral adipose tissues, favors inflammation and platelet aggregation. Leptin concentrations are elevated in obese people and in survivors and may contribute to atherosclerosis in the long term.\textsuperscript{338,359}

Radiation therapy may also induce and contribute to the development of atherosclerotic CVD with lesions morphologically similar to those in spontaneous atherosclerosis.\textsuperscript{124,360} The dose of mediastinal radiation and treatment techniques that increase the cardiotoxic dose are significantly associated with coronary artery abnormalities.\textsuperscript{319,328,361} The incidence of CAD in patients receiving cumulative mediastinal radiation doses \(>20\) Gy is 6 to 7 times as high as that in patients who received \(<20\) Gy.\textsuperscript{362} Radiation may initiate or promote atherosclerosis; however, classic cardiovascular risk factors confer a greater risk of clinically important heart disease among survivors who received mediastinal radiotherapy than among the general population.\textsuperscript{363} It is therefore likely that survivors are at increased risk of premature atherosclerotic CVD that can manifest as CAD or peripheral vascular disease.

In a study of survivors of Hodgkin lymphoma with a median age at diagnosis of 25 years (range, 4–75 years) who had chemotherapy and radiotherapy with radiation fields that included the heart or carotid or subclavian arteries, the incidence of CAD was 3% at 5 years, 6% at 10 years, and 10% at 20 years. The mid-mediastinal radiation dose was similar in patients in whom CAD subsequently developed (median dose, 35 Gy; range, 25–42 Gy) to that of patients in whom CAD did not develop (median dose, 33 Gy; range, 10–47 Gy). All traditional cardiac risk factors tested (male sex, hypertension, hypercholesterolemia, and age) were significantly associated with the development of CAD.\textsuperscript{219}

Atherosclerotic changes with areas of stenosis and calcification in the proximal segments of all branches of coronary arteries have been reported.\textsuperscript{364} Many adult survivors with these lesions are often asymptomatic, even in the presence of severe CAD.\textsuperscript{372} Coronary CT angiography and calcium scoring in patients receiving mediastinal radiotherapy for childhood Hodgkin lymphoma indicate that the risk of a coronary artery abnormality is 7 times as high as in patients who did not receive mediastinal radiotherapy. The incidence in this and other survivor groups is 10% to 16% at a mean remission of \(\approx 10\) years.\textsuperscript{362,364,365}

**Noncoronary Atherosclerotic Vascular Disease**

High-dose radiotherapy to the neck has been associated with increased incidence of premature atherosclerosis and stroke in survivors treated for head and neck cancer.\textsuperscript{366} In a study of long-term survivors of Hodgkin lymphoma, the risk of stroke in survivors was 5 times as high as that in sibling control subjects.\textsuperscript{29} A significantly higher risk of stroke has also been reported among survivors of childhood leukemia and brain tumors, particularly in those who received a cranial radiation dose \(>30\) Gy.\textsuperscript{38}

**Lipid Abnormalities**

As anticipated, obese childhood cancer survivors have the typical lipid pattern associated with obesity: elevated triglycerides and reduced HDL cholesterol.\textsuperscript{319} The lipid abnormalities associated with the metabolic syndrome, namely, elevated triglycerides and low HDL cholesterol, have been widely reported in adult survivors of childhood cancer in both the presence and the absence of obesity.\textsuperscript{171,174,367} Recent reports have described similar dyslipidemia profiles in childhood cancer survivors while still children.\textsuperscript{317,351}

Elevated total cholesterol and low-density lipoprotein (LDL) cholesterol, the classic “atherogenic lipid profile,” is less common in cancer survivors; however, this profile has been reported in a small group of childhood cancer survivors with suprasellar tumors, especially in patients with high BMI.\textsuperscript{368} Recently, a study of children who survived cancer showed that total cholesterol, non-HDL cholesterol, LDL cholesterol, triglyceride concentrations, and the triglyceride-to-HDL cholesterol ratio were significantly higher in survivors of leukemia and central nervous system tumors than in healthy control subjects.\textsuperscript{317} Although guidelines for the cardiovascular health of children and adolescents have been published recently by the National Heart, Lung, and Blood Institute,\textsuperscript{169} these recommendations have initiated a discussion as to the validity of the screening guidelines. Further long-term clinical trials are needed to assess the benefits, risks, limitations, and cost-effectiveness of universal and comprehensive childhood cholesterol screening.\textsuperscript{370}

Among different treatment modalities for childhood cancers (Table 1), radiation exposure in the presence or absence of GH deficiency\textsuperscript{276,364} and treatment with corticosteroids\textsuperscript{371,372} have been proposed as possible mechanisms leading to the abnormal lipid profile in cancer survivors. A number of chemotherapeutic agents have also been implicated in dyslipidemia. Cyclophosphamide administration in animal models results in hypertriglyceridemia and impairment of vascular lipoprotein lipase.\textsuperscript{373,374} Asparaginase, a drug effective in treating...
Hypertension

Hypertension is an important and common risk factor for ischemic CAD378,379 and heart failure380 and is 1 of the 5 defining criteria of metabolic syndrome.381,382 Indeed, among adults with their first MI, hypertension is the most common risk factor (52.3%) among the traditional cardiovascular risk factors.383

In the Childhood Cancer Survivor Study, Meacham et al31 reported that 8.8% of long-term survivors, with a mean age of 32 years, reported taking a medication for hypertension, and they were twice as likely to be hypertensive as their siblings. As in the general population, the likelihood of hypertension increased with age and was more common among black survivors.

Hypertension is relatively uncommon before a childhood cancer is diagnosed, although this trend may change with the increasing prevalence of childhood obesity.384 During cancer therapy, some patients may have transiently elevated blood pressures and hypertension. For example, among 183 patients undergoing corticosteroid therapy for ALL, Esbenshade et al385 reported that median systolic and diastolic blood pressure z scores were elevated through the induction and maintenance phases of therapy, and 16% of the cohort required antihypertensive therapy. However, by the end of maintenance therapy, blood pressure had returned to normal in almost all patients, with only 1% taking antihypertensive medications during this time.

Chow et al386 noted a similar trend in systolic and diastolic pressures during induction. At the end of therapy, the average systolic and diastolic z scores were still elevated; 5 years from diagnosis, diastolic z scores were normal, whereas systolic pressures remained modestly elevated. Mean systolic or diastolic pressures did not differ between young adult women who were survivors of childhood ALL (mean age, 23 years) and a population-based cohort living in the same geographic region. Notably, mean systolic and diastolic blood pressures were significantly lower in male ALL survivors than in the population-based cohort. In a cohort of somewhat older ALL survivors (mean age, 30 years), the proportion of men with hypertension was modestly higher than expected from population-based norms (30% versus 24%), but the proportion of women with hypertension was not. Given that obesity and insulin resistance promote development of the metabolic syndrome,381,386 and that the risk for both of these conditions in long-term survivors of childhood ALL is high,25,33,317 the incidence and prevalence of hypertension will likely increase sharply as these survivors enter their fourth and fifth decades of life.

The association of other chemotherapeutic agents and hypertension has been less well studied. Acute ifosfamide-induced nephrotoxicity may result in progressive renal dysfunction and hypertension.387,388 Similarly, methotrexate therapy has been associated with long-term renal impairment.389,390 Although an association between cisplatin and hypertension has been reported among adult testicular cancer survivors,378,391–393 a similar association has not been reported in childhood cancer survivors.31,394 In a small, nested case-control study (44 case subjects, 123 control subjects), Cardous-Ubbink et al395 found a modest but nonsignificant association between hypertension and cisplatin therapy; however, the lack of an association may be the result of the relatively small sample of survivors treated with cisplatin studied to date. In the Childhood Cancer Survivor Study,31 the adjusted risk of hypertension was 1.5 times as high in survivors treated with anthracycline chemotherapy at a cumulative dose of ≥100 mg/m² as in survivors who were not treated with an anthracycline. However, no other studies have reported an association between anthracycline chemotherapy and a subsequent risk of hypertension; thus, the findings of this single study should be interpreted with caution.

Perhaps the most widely recognized cancer therapy associated with hypertension is abdominal radiotherapy, which is used primarily in treating Wilms tumor and neuroblastoma.33,396,397 The resultant hypertensive may be secondary to radiation-induced renal artery stenosis, radiation nephropathy, or a radiation-chemotherapy interaction.387,397

In survivors of childhood cancer treated with hematopoietic cell transplantation, several factors increase the prevalence of hypertension. Intensive chemotherapy and acute or chronic graft-versus-host disease often result in permanent glomerular injury, chronic kidney disease, and related hypertension.399 Total body radiation may also cause a radiation-induced nephropathy, as noted with abdominal radiotherapy above, and it commonly causes insulin resistance and metabolic syndrome, and consequently, hypertension.400–402

Given these multiple pathways to elevated blood pressure, it is not surprising to find that 70% of 180 allogeneic hematopoietic cell transplant recipients became hypertensive within 2 years after transplantation.400 Although the hypertension resolved for many of these survivors (at least over a short follow-up period), 2 years after transplantation, 34% of children had persistent hypertension. In a large cohort of long-term survivors treated with hematopoietic stem cell transplantation, the 30-year cumulative incidence of hypertension was 36%.403

Many pediatric cancer survivors will become hypertensive as they age for reasons unrelated to their cancer therapy (eg, genetic predisposition; lifestyle behaviors and practices). The influence of comorbid hypertension on the risk of CAD after mediastinal radiotherapy or heart failure after anthracycline chemotherapy has been understudied. Although hypercholesterolemia and smoking independently increase the risk of MI in Hodgkin lymphoma survivors treated as children or adults with mediastinal radiotherapy, Aleman and colleagues415 reported that hypertension did not appear to modify this risk. Similarly, they reported that hypertension was
not independently associated with heart failure in survivors treated with mediastinal radiotherapy or anthracycline chemotherapy.\textsuperscript{215} In contrast, comorbid hypertension increased the risk of MI and heart failure in survivors of adult non-Hodgkin lymphoma.\textsuperscript{404} Otherwise, few studies have investigated the interaction between hypertension and other traditional cardiovascular risk factors with cardiotoxic cancer therapies.

In summary, hypertension is a common outcome among survivors of childhood cancer and may develop years later for reasons unrelated to cancer therapy. Regardless, because hypertension increases the risk of CVD, blood pressure should be monitored regularly. The Children’s Oncology Group recommends annual measurements of blood pressure for survivors treated with ifosfamide, cisplatin/carboplatin, methotrexate, total body irradiation, cranial radiotherapy, chest radiotherapy (eg, mantle, mediastinal), or nephrectomy.\textsuperscript{345} Also, survivors with 1 of the criteria for metabolic syndrome, such as hypertriglyceridemia, hyperglycemia, decreased concentrations of HDL cholesterol, increased waist circumference, or elevated blood pressure, should be evaluated and monitored periodically for the other clinical manifestations of metabolic syndrome.

**Risky Health Behaviors**

When one assesses modifiable risk factors for CVD among survivors treated with cardiotoxic therapy, it is important to evaluate lifestyle behaviors, including smoking, physical inactivity, excessive alcohol consumption, and illicit drug use. Smoking\textsuperscript{378,405–407} and physical inactivity\textsuperscript{408–412} are well-known risk factors for ischemic CAD, other forms of CVD, and cardiac-specific mortality. Large cohort studies suggest that smoking among survivors is lower in women than in men, particularly among women in ethnic minorities.\textsuperscript{416} Also, survivors with 1 of the criteria for metabolic syndrome, such as hypertriglyceridemia, hyperglycemia, decreased concentrations of HDL cholesterol, increased waist circumference, or elevated blood pressure, should be evaluated and monitored periodically for the other clinical manifestations of metabolic syndrome.

Excessive alcohol consumption is also common among adult survivors of childhood cancer than it is in young adults in the general US population. More than a quarter of survivors in the Childhood Cancer Survivor Study had smoked ≥100 cigarettes in their lifetime, and 17% were current smokers.\textsuperscript{416} Similarly, in Britain, 48% of long-term survivors were ex-smokers, and 20% were current smokers.\textsuperscript{417} Importantly, cigarette use does not differ substantially among survivors treated with or without cardiotoxic therapy.\textsuperscript{416,418} As in the general population, smoking rates among survivors are higher among those of lower socioeconomic status and those with lower levels of education.\textsuperscript{416–418} In the United States, the prevalence of smoking among survivors is lower in women than in men, particularly among women in ethnic minorities.\textsuperscript{416}

Excessive alcohol consumption is also common among survivors, but it is modestly lower than that in the general population.\textsuperscript{419–422} Among 10,398 young adult survivors in the Childhood Cancer Survivor Study, 16% reported risky drinking behaviors (defined as >3 drinks per day or 7 drinks per week for women, and >4 drinks per day or 14 drinks per week for men), and 8% reported heavy drinking (≥5 drinks per day for women and ≥6 drinks per day for men at least once a month in the past year).\textsuperscript{419} Risk factors for risky and heavy drinking were similar and included being young or male, having less than a high school education, and beginning to drink at a young age.\textsuperscript{419} Black and Hispanic survivors drank significantly less heavily than did their non-Hispanic white counterparts.

Illicit drug use among survivors has not been studied as extensively as smoking and alcohol consumption. Schultz et al\textsuperscript{423} reported that among 117 young adult survivors of childhood acute myeloid leukemia, <10% reported cocaine, heroin, or methamphetamine use. As with smoking and alcohol rates, men were more likely to report this behavior. The prevalence of using cannabis or other illicit drugs was lower among adolescent survivors than it was among their healthy peers.\textsuperscript{421}

In general, survivors are less physically active than the general population. Among 9301 adult survivors, survivors were less likely than their siblings to meet physical activity requirements (46% versus 52%) and were more likely than their siblings to report a sedentary lifestyle (23% versus 14%).\textsuperscript{424} Survivors treated with cranial radiation, amputees, and particularly women are more likely to have sedentary lifestyles.\textsuperscript{418,424–427}

Not surprisingly, survivors who engage in 1 unhealthy risk behavior are more likely to engage in other risky behaviors. In 796 survivors enrolled in a smoking cessation trial, 8.1% also had risky drinking habits.\textsuperscript{428} Among 541 current smokers, 29% spent <150 minutes per week in moderate-intensity physical activity.\textsuperscript{428} Those who were not physically active also reported feeling less confident in their ability to refrain from smoking in challenging situations.

**Endocrine Dysfunction**

In addition to direct cardiac damage caused by radiation and chemotherapeutic agents, such as anthracyclines, survivors are also at risk of cardiovascular consequences from several forms of endocrine dysfunction. Survivors exposed to cranial radiation or certain surgical procedures, such as transphenoidal surgery, are at increased risk of various forms of hypopituitarism, most commonly isolated GH deficiency.\textsuperscript{429–431} Survivors are also at increased risk of insulin resistance and diabetes mellitus, which are associated with radiation exposure and may also be related to lifestyle.\textsuperscript{27,33,316,317}

GH deficiency is the first and most common endocrine complication to appear in survivors exposed to cranial radiation. It can occur after even relatively limited exposures and degrades cardiac health, both through an increase in traditional CVD risk factors, such as obesity and dyslipidemia, and through altered cardiac structure.\textsuperscript{174,175,276,352,422,423} The assessment of survivors for GH deficiency in childhood and adolescence is especially relevant given that replacement therapies may reduce CVD risks and improve quality of life.\textsuperscript{434,435} GH deficiency should be considered as a possibility, even in survivors with normal growth for some period after treatment, because it can first present many years after treatment.

Guidelines exist for the evaluation and diagnosis of GH deficiency in adults, but its assessment in children requires further investigation.\textsuperscript{436–439} GH deficiency in children is often investigated after a finding of short stature or decreased height velocity. Childhood cancer survivors, especially those who...
exposed to cranial radiation or brain surgery, should be monitored closely for these findings. The Children’s Oncology Group’s guidelines for follow-up of survivors recommend assessing nutritional status every 6 months for those treated with cranial radiation.\textsuperscript{345}

In the general population, the risk of CVD associated with diabetes mellitus is considered to be equivalent to that of a previous MI.\textsuperscript{176} In 45-to-64-year-olds, diabetes mellitus triples CVD risk.\textsuperscript{460} Compared with sibling control subjects, survivors are nearly twice as likely to report having diabetes mellitus, which is associated with total body, abdominal, and cranial radiation exposure, even after adjustment for BMI and level of physical activity.\textsuperscript{27} Another follow-up study of >200 long-term survivors, all of whom were <40 years old when they were tested, found that not only did 4% have diabetes mellitus, but another 7% had impaired glucose tolerance, and another 4% had hyperinsulinemia in that group.\textsuperscript{316}

Screening for alterations in glucose metabolism, such as those consistent with diabetes mellitus and insulin resistance, should include regular assessment of fasting glucose in all survivors.\textsuperscript{441} Results of hemoglobin A\textsubscript{1c} and 2-hour oral glucose challenge tests may provide additional information.\textsuperscript{442,443} In the general population, screening for alterations in glucose metabolism is recommended to begin at 45 years of age in patients without additional risk factors, such as a family history of diabetes mellitus or being overweight.\textsuperscript{443} For patients with these additional risk factors, screening is recommended regardless of age. Survivors are at increased risk of CVD and diabetes mellitus, and therefore, screening for altered glucose metabolism should begin as part of survivorship care and be repeated every 3 years; this advice is consistent with other recommendations.\textsuperscript{345,441}

**Cerebrovascular Screening for Stroke Prevention**

In a report from the Children’s Cancer Survivor Study, the relative risk for cerebrovascular accidents (CVAs) among survivors was almost 10 times as high as that of the sibling control group.\textsuperscript{6} Risks were highest among the adult survivors of childhood ALL, brain tumors, and Hodgkin lymphoma.\textsuperscript{28,29} Leukemia survivors were 6 times as likely to experience a CVA as their siblings, whereas brain tumor survivors were 29 times as likely to experience a CVA. Of 1411 patients with brain tumors treated with RT, 69 (4.9%) reported a CVA, with a cumulative incidence of 6.9% (95% CI, 4.47–9.33) at 25 years. Survivors exposed to >30 Gy of cranial RT had an increased risk for CVA, with the highest risk among those who received >50 Gy.\textsuperscript{28} Treatment with an alkylating agent significantly modified the risk of stroke in brain tumor survivors who had undergone treatment with cranial RT. Compared with siblings, the relative risk of late-occurring stroke in brain tumor survivors treated with cranial RT plus an alkylating agent was 78.3. Long-term cerebrovascular mortality in 4227 5-year childhood cancer survivors, at a median follow-up of 29 years after radiation to the brain, was reported by French investigators. Survivors who received >50 Gy to the preportal cistern had a hazard ratio of 17.8 (95% CI, 4.4–73) for death of cerebrovascular disease compared with those who had not received radiotherapy or who had received <0.1 Gy to this region.\textsuperscript{176}

Adult survivors of childhood Hodgkin lymphoma treated with thoracic RT, including to the mediastinum and neck, had a 5.6-fold higher risk for CVA than their siblings (median dose, 40 Gy).\textsuperscript{29} In a study from the Netherlands of 2201 5-year survivors of Hodgkin lymphoma, 547 of whom were <21 years old, and with median follow-up of 17.5 years, 96 patients developed cerebrovascular disease (55 CVAs, 31 TIAs, and 10 both CVA and TIA), with a median age at diagnosis of 52 years.\textsuperscript{444} Most ischemic events were from large-artery atherosclerosis (36%) or cardioembolism (24%). The standardized incidence ratio was 2.2 for CVA and 3.1 for TIA. The cumulative incidence of ischemic CVA or TIA 30 years after Hodgkin lymphoma treatment was 7%. For patients <21 years of age, the standardized incidence ratio was 3.8 for CVA and 7.6 for TIA. Radiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (hazard ratio, 2.5; 95% CI, 1.1–5.6) compared with no RT. Treatment with chemotherapy was not associated with increased risk. Hypertension, diabetes mellitus, and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease, whereas smoking and overweight were not.\textsuperscript{444}

Evidence supporting any routine surveillance strategies for carotid artery or cerebrovascular disease is currently lacking, although consideration can be given to the performance of carotid artery ultrasound in high-risk populations (eg, patients with hypertension, obesity, or diabetes mellitus who were treated with >40 Gy to the neck). However, definitions and implications of abnormal tests are not clear.\textsuperscript{445} In the general population, the association between carotid intima-media thickness progression assessed from ultrasound scans and cardiovascular risk remains unproven. Thus, no conclusion can be derived from the use of this screening tool as a prevention strategy.\textsuperscript{446} Routine surveillance for cerebral vascular disease is also unsupported by evidence. Dedicated vascular imaging such as magnetic resonance angiography can be performed to evaluate patients considered at high risk or who are symptomatic, but a specific screening recommendation cannot be identified.

**Screening for Arrhythmias and Conduction Defects**

Arrhythmias have been reported during chemotherapy, including supraventricular and ventricular premature beats or tachycardias.\textsuperscript{210,447–449} Interaction with cardiac ion channels has been considered to be important in the genesis of these arrhythmias, as well as in changes detected by ECG, such as QT-interval prolongation and nonspecific T-wave changes.\textsuperscript{449–451} Prolongation of the QT interval is dose dependent, and high plasma concentrations may cause marked QT prolongation and increase the risk of torsade de pointes.\textsuperscript{55,452,453} These changes have been found primarily in adults, with only a 2% incidence of supraventricular tachycardias reported in children during treatment with anthracyclines.\textsuperscript{454}

Only scattered reports address the issue of arrhythmias late after chemotherapy. A study of 11 children reported that anthracycline treatment may be a risk factor for torsade de pointes weeks or years after therapy for leukemia, and such cases are generally related to QT-prolonging agents or to hypokalemia.\textsuperscript{453} A few studies have considered the incidence and importance of cardiac arrhythmias long after chemotherapy.
during childhood. Although some have reported occasional instances of sudden death that may be related to repolarization abnormalities (QT prolongation and abnormal QT dispersion) in association with ventricular dysfunction, others have described only infrequent and clinically unimportant arrhythmias. Other studies of pediatric cancer survivors have described ventricular arrhythmias in association with late ventricular dysfunction, but in general, these studies have been small and were not systematic evaluations of the population at risk. There are no data about whether the risk of arrhythmia exceeds that found in other causes of ventricular dysfunction.

Without data about the risk factors for cardiac arrhythmias long after chemotherapy for childhood cancer, and, in particular, with the absence of data indicating that this risk is different from that associated with other forms of cardiomyopathy, the general recommendations included in the American College of Cardiology/AHA heart failure guidelines are endorsed. Holter monitoring might be considered in patients presenting with heart failure who have a history of MI and are being considered for electrophysiological study to document ventricular tachycardia inducibility (Class III; Level of Evidence C). The routine use of signal-averaged electrocardiography is not recommended for the evaluation of patients presenting with heart failure (Class III; Level of Evidence C).

Prevention of Cardiovascular Toxicity

Strategies to Reduce the Cardiotoxic Effects of Chemotherapy

As summarized above, the cardiotoxicity of cancer therapy is potentially great and can cause early mortality and significant morbidity. Although clinically significant events may be delayed, the frequency of subclinical damage can be quite high, and it is likely this damage can deteriorate over time to cause clinical events. Thus, it is important to minimize or eliminate this initial subclinical damage if possible.

Anthracycline Dose

Treatment protocols have tested several methods to reduce the cardiac complications associated with anthracyclines. In the 1970s, before the association between cumulative dose and cardiotoxicity was recognized, children with ALL in clinical trials would receive cumulative doxorubicin doses ≥400 mg/m². These survivors eventually experienced clinically important adverse LV effects that continued to progress and persist even decades after treatment. In response, cumulative doxorubicin doses in this population were reduced to between 45 and 60 mg/m² for standard-risk children and between 345 and 360 mg/m² for high-risk children, doses associated with a much lower risk of delayed cardiotoxicity.

Despite having a lower frequency of overt CHF, high-risk children are still at risk for delayed long-term LV abnormalities. Furthermore, in the 1990s, an analysis of 189 survivors of ALL showed that the risk of LV abnormalities was lower in those who received ≤300 mg/m² of doxorubicin than in those who received >300 mg/m² after a median follow-up of 8 years. In turn, later protocols in childhood ALL lowered the cumulative doxorubicin dose even further for high-risk ALL patients, to 300 mg/m². Lowering cumulative anthracycline doses may be cardioprotective but may also reduce treatment efficacy. In addition, even the smallest doses of anthracyclines may still cause cardiac complications in this vulnerable group of children; there is no safe dose of anthracyclines.

Liposomal Anthracyclines

Another cardioprotective strategy is to modify the structure of the anthracycline compound. Encapsulation of the anthracycline in a liposome enables it to escape the capillary system of tumors more easily than the tight junctions of the heart’s capillary system. This ability causes more of the anthracycline to accumulate in the target area of the tumor and to reduce the serum plasma concentrations of free doxorubicin. Reducing plasma concentrations of free doxorubicin is also believed to reduce cardiotoxicity.

Currently, the only liposomal doxorubicin approved by the US Food and Drug Administration is Doxil, a pegylated liposomal doxorubicin. Pegylated liposomal doxorubicin reduces the overall risk of cardiotoxicity compared with conventional doxorubicin. Although further research is required to fully understand the effect of liposomal-encapsulated anthracyclines in children, biopsy samples have shown that this structural modification lowers the chance of early cardiotoxicity without compromising the antineoplastic activity of conventional anthracycline.

Anthracycline Analogs

Various anthracycline analogs have been developed to reduce cardiotoxicity. Epirubicin was added to protocols in the 1970s as an epimer of doxorubicin. In one randomized study, epirubicin was evaluated in 125 children who received either a 450-mg/m² cumulative dose of epirubicin or a 240-mg/m² cumulative dose of doxorubicin. After 1 year, echocardiography showed that the incidence of both clinical and subclinical cardiomyopathy was low in both treatment groups (0% in patients treated with epirubicin and 0.9% in patients not treated with epirubicin). Epirubicin was less toxic to cardiomyocytes than was doxorubicin at equimolar doses, but it increased cardiotoxicity slightly when administered at equally myelotoxic doses.

Idarubicin is a structural analog of daunorubicin, another common anthracycline. Its C-methoxyl group in the D ring is replaced with a hydrogen moiety that is less cardioxic than daunorubicin. A phase 3 study of 218 patients aged ≥14 years with acute myoblastic leukemia treated with either idarubicin or daunorubicin found that the incidence of CHF did not differ between groups.

The cardiotoxicity of mitoxantrone combined with cytarabine has been evaluated in several trials of children. In a review of mitoxantrone for treating acute myoblastic leukemia, the 4 trials that compared mitoxantrone with daunorubicin in previously untreated adults found no difference in cardiotoxicity. However, a systematic review of 16 studies on the cardiotoxic effects of mitoxantrone on patients <18 years old found the incidence rates of various anthracycline-induced cardiotoxicities difficult to compare, given methodological differences between studies. Therefore, further randomized studies are required to determine whether mitoxantrone or other anthracycline structural analogs can prevent cardiac damage during therapy.
Continuous Anthracycline Infusion

Lowering peak serum concentrations of an anthracycline through continuous infusion, as opposed to bolus administration, might reduce its cardiotoxic effect.20 The risk of acute cardiotoxicity was reduced in adults who underwent continuous infusion,460 but evidence for a long-term effect on cardiotoxicity in children is insufficient to reach the same conclusion. Despite this lack of evidence, continuous infusion has been incorporated into pediatric protocols on the basis of the findings in adults.19,487 A randomized controlled trial of 121 children with high-risk ALL found that a 48-hour continuous infusion of doxorubicin was not more cardioprotective than bolus infusion after a median of 1.5 years after diagnosis.19 After a median follow-up of 8 years in this same cohort, both groups had similarly persistent long-term echocardiographic abnormalities.487 Retrospective reviews of the echocardiographic results from patients 5 to 7 years after they completed treatment also found no remarkable differences between children who received continuous infusion and those who received bolus infusion.20,488

Dexrazoxane

Iron-chelating agents, such as dexrazoxane, help prevent ROS-related cardiotoxicity.21,22,88,489,490 Dexrazoxane interferes with the formation of anthracycline-iron complexes that produce the highly charged ROS. Other methods that are independent of oxidative stress, such as DNA mutation mitigation, may mediate the cardiac protection involved with iron chelation.474,491 These discoveries have led to a great deal of interest in the cardioprotective effects of dexrazoxane490,492; however, concern has arisen over whether dexrazoxane might increase the risk of second malignancies by reducing the antineoplastic effect of doxorubicin. Several studies have not found an association (Figure 3),22,493,494 but one did,495 although its findings have been questioned.496,497

In a randomized trial of children with high-risk ALL who received either dexrazoxane plus doxorubicin or doxorubicin alone, children who received doxorubicin alone had marked LV abnormalities 5 years after completing therapy.22 An additional study of this cohort showed that at the end of therapy, cardiac troponin T and N-terminal probrain natriuretic peptide (bio-markers for cardiac injury and cardiomyopathy, respectively) were elevated in more children who received doxorubicin alone than in those who also received dexrazoxane (Figures 4A and 4B).23 Furthermore, the 8-year event-free survival rate was 77% for the doxorubicin alone group and 76% for the dexrazoxane plus doxorubicin group,22 which indicates that dexrazoxane can protect cardiomyocytes from the long-term effects of doxorubicin without reducing its efficacy (Figure 3).

Recent animal studies have indicated that the protective effect of dexrazoxane may be related to the sex of the

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Figure 3. Event-free survival. All patients randomly assigned to treatment (n=205) were eligible for assessment of event-free survival, but by convention, events of induction failure and induction death have been recorded at 0 years. Reproduced from Lipshultz et al22 with permission from Elsevier Ltd. Copyright ©2010, Elsevier Ltd.

Figure 4. A, Model-based estimated probability of having an increased cardiac troponin T (cTnT) concentration at each depicted time point in patients treated with doxorubicin with or without dexrazoxane. The doxorubicin-dexrazoxane group is indicated by the blue line, the doxorubicin group by the gold line. Vertical bars show 95% confidence intervals. Increased cTnT is defined as a value >0.01 ng/mL. *P vs dexrazoxane group ≤0.05; †P vs dexrazoxane group ≤0.001. An overall test for dexrazoxane effect during treatment was significant (P<0.001). B, Model-based estimated probability of having an increased N-terminal probrain natriuretic peptide (NT-proBNP) concentration at each depicted time point in patients treated with doxorubicin with or without dexrazoxane. The doxorubicin-dexrazoxane group is indicated by the blue line, the doxorubicin group by the gold line. Vertical bars show 95% confidence intervals. Increased NT-proBNP is defined as a value ≥150 pg/mL for children <1 year old and ≥100 pg/mL for children aged ≥1 year. *P vs dexrazoxane group ≤0.05; †P vs dexrazoxane group ≤0.001. An overall test for dexrazoxane effect during treatment was significant (P<0.001) and after treatment was not significant (P=0.24). Reproduced from Lipshultz et al22 with permission from American Society of Clinical Oncology. Copyright © 2012, American Society of Clinical Oncology.
recipient. Similarly, in children with high-risk ALL, dexrazoxane was significantly cardioprotective in girls but not in boys 5 years after completion of doxorubicin therapy.22 Although sex-related differences in the transport and clearance of doxorubicin have been reported, the mechanism responsible for these differences is still largely unidentified.22,498–501

Dexrazoxane protects against anthracycline-induced cardiotoxicity in childhood leukemia and other cancers.460–490 Nevertheless, further research is required to establish its long-term safety and efficacy in these children and to identify additional cardioprotective strategies without reducing the antineoplastic efficacy of cancer treatments.502

**Amifostine**

Amifostine is another cardioprotectant that selectively protects normal tissue from the toxicity of chemotherapy drugs.460 The acidic pH of tumor tissue does not favor the conversion of amifostine to the active metabolite, whereas the neutral pH of normal tissue does.503 Several preclinical and clinical studies have suggested that amifostine protects normal tissue against chemotherapy-associated toxicities without decreasing antineoplastic effects.504,505 Animal studies suggest that amifostine scavenges hydroxyl radicals and thus markedly improves cardiac function when added to doxorubicin treatment506–508; however, amifostine is less cardioprotective than dexrazoxane,509 perhaps because dexrazoxane prevents the formation of radicals, whereas amifostine scavenges them.

**Nutritional Supplements**

Cardiotoxic agents generated by anthracycline treatment, such as free radicals, may be neutralized by introducing antioxidants, both endogenously and exogenously, through nutritional supplements.460 Dietary antioxidants, such as vitamins, coenzyme Q, and carnitine, may prevent the cardiotoxic effects of anthracyclines without reducing their antineoplastic activity.460 Vitamin A is a well-known dietary antioxidant that has been given during or after anthracycline treatment510,511.

Retinoids, one of the most active forms of vitamin A, have antioxidant effects through radical scavenging without impacting the antitumor activity of anthracyclines502,512,513; however, high storage concentrations of vitamin A can be toxic to the liver and can reduce bone mineral density.514 Therefore, storage concentrations of vitamin A can be monitored.

Vitamin C is a water-soluble dietary antioxidant that protects against oxidative damage by scavenging aqueous radicals and oxidants.515 Some animal studies have also found that vitamin C prevents doxorubicin-induced cardiac toxicity without reducing its antineoplastic effects; however, the protective qualities of vitamin C are lost at doses >500 μg/mL.516 Different effects of vitamin C in various studies are attributed to different concentrations and oxygen pressures within cells.516

Vitamin E is a lipid-soluble antioxidant that scavenges free radicals and prevents their propagation in biological membranes.518 In animal studies, α-tocopherol, the most active form of vitamin E, reduced the cardiotoxic effects of high doses of doxorubicin.519,520 Other animal studies have found that α-tocopherol does not protect against cardiotoxicity when doxorubicin is administered long-term.521 Vitamin E added to anthracycline therapy as a cardioprotectant has not been tested in randomized trials.522 Nonrandomized clinical trials have found that vitamin E does not protect against anthracycline-induced cardiotoxicity.523

Selenium is a trace element bound to selenoprotein enzymes involved in antioxidant protection. Metabolites of selenium are anticarcinogenic.524 Cancer patients have lower concentrations of selenium than do healthy control subjects.525 Although several animal studies have found that selenium deficiency increases toxicity from doxorubicin treatment,526,527 the evidence on whether selenium supplementation protects the heart from doxorubicin-induced damage is conflicting.528,529 Selenium intake can be closely monitored to avoid selenosis, which can cause gastrointestinal upset, fatigue, irritability, and nerve damage.530

Coenzyme Q10, also known as ubiquinone, is another lipid-soluble antioxidant found in membranes that is essential for the proper functioning of the mitochondrial respiratory chain.531,532 Doxorubicin inhibits coenzyme Q enzymes in the mitochondria.533 Coenzyme Q supplementation can prevent doxorubicin from inhibiting these enzymes534,535; although some studies have found that treatment with coenzyme Q and doxorubicin prevents cardiac toxicity,536,537 others have not.538 Further investigation is required to determine whether coenzyme Q supplementation prevents cardiac dysfunction.

**Angiotensin-Converting Enzyme Inhibitors and β-Blockers**

Children treated with doxorubicin commonly experience reduced LV wall thickness and elevated LV afterload. Many of these children are given angiotensin-converting enzyme inhibitors.526,538a In clinical trials of adults, these drugs reduced afterload and improved cardiac function.539,540 Afterload reduction therapy with these drugs in long-term survivors of childhood cancer improved LV dimension, afterload, mass, and fractional shortening; however, these improvements were lost after 6 to 10 years. Patients with heart failure who had started treatment had either died or undergone cardiac transplantation after 6 years. Thus, treatment with angiotensin-converting enzyme inhibitors improves structure and function in the short term but does not prevent LV wall thinning and exacerbates the long-term consequences of cardiac hypertrophy.460

β-Blockers improve hemodynamic symptoms, decreasing morbidity and mortality of adults with heart failure from a variety of causes.541,542 Although the mechanism of β-blockade is not fully understood, it is thought to prevent the reversal of adrenergically mediated intrinsic myocardial dysfunction and remodeling.543 One study found that children with heart failure treated with β-blockers increased fractional shortening by 23% and ejection fraction by 41%.544 Another study found short-term improvement in 31 of the 46 children; however, 15 patients experienced adverse effects.545 Further investigation is required to determine whether β-blocker therapy is beneficial to children with heart failure.

**Strategies to Reduce the Cardiotoxic Effects of RT**

During the years in which childhood cancer therapies were developing, the radiation doses and techniques used were standard for adults; however, as the adverse consequences of such treatment became apparent and other therapies (ie, chemotherapy) evolved, so did RT dose and delivery. As
discussed in other sections of this report, therapeutic chest radiation has created a large population of patients at risk for long-term cardiac consequences. Determination of the risk for these consequences is confounded by several variables, including the technique used, the dosage, the patient’s age, the time since irradiation, other cancer therapies received, and other traditional CVD risk factors. Moreover, the spectrum of radiation-induced cardiac injury is broad and includes direct and indirect cardiovascular effects.

Reduction or elimination of the risk of radiation-induced cardiotoxicity relies primarily on minimizing both the radiation dose and the exposed cardiac volume while maintaining therapeutic effectiveness. As a general principle, radiation fields must be meticulously designed to obtain this goal. Field definition for any malignancy depends on the anatomy of the region, including lymph node distribution and patterns of disease extension. Similarly, a succession of clinical trials in children has determined the lowest radiation doses that balanced effectiveness with long-term safety. A prime example of this reduction in radiation dose is that of pediatric Hodgkin lymphoma, for which radiation doses have been reduced from between 35 to 45 Gy to between 15 to 25 Gy in most clinical trials. Simultaneously, radiation volumes have been reduced from regional RT (ie, mantle radiation), to involved-field RT, to involved-node RT. The importance of this reduction is illustrated by data from patients treated for Hodgkin lymphoma, in whom cardiac (subcarinal) blocking reduced the relative risk of death of cardiac causes (other than MI) from 5.3 to 1.4. The incidence of pericarditis decreased when the LV and subcardiac regions were shielded. In a study comparing the doses to normal tissue, the mean heart dose from involved-node RT was an average of 50% lower than that from involved-field RT. Similar reductions in the predicted risk of cardiovascular events were recently reported by another group.

CT-based planning and anterior-posterior opposed parallel pair beam radiation remain common in the treatment of childhood malignancies; however 3-dimensional conformal RT using nonopposed beams, intensity-modulated RT (IMRT), or proton therapy can reduce the dose to cardiac structures adjacent (in any direction) to the target tumor volume. Although the efficacy of IMRT and the decrease in the median dose to normal surrounding tissues are still being studied, the potential for increased late effects from IMRT is uncertain, particularly for secondary malignancies or long-delayed cardiac effects (including cardiomyopathy and CAD, as discussed elsewhere), because IMRT provides a lower dose to a larger volume than conventional techniques.

Proton therapy may further decrease the mean dose to normal adjacent or surrounding normal tissues below that of IMRT or 3-dimensional conformal RT without increasing the volume of normal tissue that receives a lower dose of radiation. Although the efficacy of these more conformal techniques has been reported for sites other than the heart, the benefits of a lower dose to critical organs are unlikely to be fully appreciated for decades. Finally, precisely targeted radiation fields are appropriate in some situations, such as in the treatment of pulmonary metastases adjacent to cardiac structures. In this situation, stereotactic RT can target the involved tumor while largely eliminating potentially harmful radiation exposure to adjacent tissues. With stereotactic RT, high doses of radiation are administered in a small number of fractions. Some of the possible approaches for administering stereotactic RT are described below.

Three-Dimensional Conformal Radiotherapy
Three-dimensional conformal radiotherapy uses CT imaging radiation treatment planning. The CT scan provides not only 3-dimensional images of the target and surrounding normal tissues but also information about tissue density and tissue depth, from the skin to the target. This information is critical in calculating dose distribution. In addition to CT, supplemental imaging modalities, such as MRI or positron emission tomography, can improve target delineation.

With 3-dimensional conformal RT, conformal beams shape the dose delivered to the target, and wedges or compensators can optimize the dose distribution. Conformal beams are shaped either with a high-density material (ie, Wood’s metal) that allows beam contouring or with multileaf collimators, which consist of an array of high-density leaves (most often made of tungsten) in the head of a linear accelerator, the position of which is controlled by independent step motors for beam shaping. Wedges are high-density, wedge-shaped devices on the head of the linear accelerator that act either as a tissue compensator or beam modifier. The effect of a wedge can also be created by a moving jaw at the head of the accelerator. With 3-dimensional conformal RT, variable-field weighting and different energies (with higher energies being more penetrating) are additional tools for optimizing dose distribution.

Intensity-Modulated RT
IMRT is a 3-dimensional conformal RT radiation planning and delivery tool for shaping the radiation dose distribution and thereby minimizing the dose to normal tissues. The unifying principle of all IMRT planning and delivery methods is the use of inverse algorithms, in which the radiation treatment characteristics are chosen to maximize the dose to the target and to minimize the dose to normal tissues. The planning algorithm maximizes these characteristics by modifying the beam spatially, temporally, or both. Spatial and temporal beams are often modified by dynamically moving multileaf collimators, as mentioned in the section “Three-Dimensional Conformal Radiotherapy” above. Radiation can also be modified with custom-made beam compensators derived from inverse planning algorithm or by tomotherapy, a new technique in which a bank of collimated leaves shutter open and closed while spiraling around the patient.

Stereotactic Radiotherapy
Stereotactic is derived from the Greek stereos, meaning solid (as in 3-dimensional) and taxis, meaning arrangement, order, or orientation. Stereotactic radiotherapy refers to technologies that improve targeting accuracy and that allow for hypofractionated radiation delivery. Generally, a 3-dimensional coordinate system is used to more accurately localize the target(s). Whereas stereotactic techniques can be used with conventional fractionation (1.8–2 Gy per day), improved targeting accuracy allows stereotactic RT to deliver hypofractionated radiotherapy with larger doses per fraction, a fewer number of fractions, and shorter treatment courses.
Proton and Charged-Particle Therapy
Charged particles (such as protons and carbon) can be used to deliver therapeutic radiation. “Standard radiation” is delivered with photon therapy (akin to high-energy light) generated by a linear accelerator, whereas protons and other charged particles are generated from a cyclotron. The difference between charged-particle and photon radiation is that charged particles stop abruptly in the tissue (the Bragg peak), which reduces the exit dose through normal tissue. A disadvantage of charged-particle therapy is neutron exposure that does not occur with photons; however, the amount of neutron exposure is much less with newer proton-delivery systems. Despite this, the benefit of protons in reducing radiation-associated malignancies is both unknown and debated. Proton therapy can deliver IMRT, stereotactic radiosurgery, or stereotactic body radiation therapy.

Management and Treatment
Heart Failure Therapies in Survivors of Childhood Cancer
Heart failure encompasses a variety of clinical, neurohormonal, and structural abnormalities.549 The incidence of CHF accelerates with time, which highlights the ongoing risk of cardiovascular events these patients face as they grow older (Figure 5). The American College of Cardiology/AHA “Guidelines for the Diagnosis and Management of Heart Failure in Adults” use a classification system that divides the spectrum of heart failure into 4 stages, which range from patients at risk for developing ventricular dysfunction (stage A) to patients with intractable heart failure not responsive to medical therapy (stage D).380 This classification system serves as a framework for developing recommendations for medical and surgical therapies to reverse remodeling, relieve symptoms, improve cardiac output, and replace the diseased heart with mechanical circulatory support or transplantation. The classification has also been applied to heart failure in children550 and is well suited to survivors of childhood cancer. Cardiotoxic chemotherapy agents place survivors “at risk” for heart failure (stage A), and as subsequent manifestations of heart failure appear, survivors progress to stage D. Unlike children with idiopathic cardiomyopathy, who often present in stages C and D, the asymptomatic survivor of childhood cancer in whom regular cardiac follow-up detects stage B disease may be treated before symptoms appear.

The approach to managing heart failure in children with heart disease caused by chemotherapy or radiation does not differ substantially from managing children with heart failure caused by idiopathic, genetic, or other acquired causes of cardiomyopathies.530 Data from observational and randomized clinical trials are sparse, so specific therapies are directed empirically or by extrapolating treatment data from adults. However, extrapolation of data to children has substantial limitations, particularly because the cause and pathophysiology of heart failure in adults differ widely from those in children. Heart failure in adults is most commonly caused by ischemic heart disease or idiopathic cardiomyopathy, whereas the causes in children are multifactorial. In particular, the mechanisms of cardiac injury after chemotherapy or radiation differ greatly from those involved in ischemic or genetic cardiomyopathies. The lack of a mechanistic approach may lead to treatment that lacks the intended benefit and that carries higher risks than estimated.461 The therapeutic approaches to treatments for pediatric heart failure can be classified into 3 categories: (1) Pharmacological interventions directed to reversal of remodeling, (2) pharmacological therapies directed to relief of symptoms, and (3) surgical interventions, such as mechanical assist device support, cardiac replacement, or regeneration.

Heart Failure Stage A: Patients at High Risk for Heart Failure
The same behavior changes for adults at risk for heart failure are recommended for children: smoking cessation, limiting or stopping alcohol or illicit drug use, treating hypertension, and controlling metabolic syndrome. No studies have tested medical therapies to prevent heart failure in survivors of childhood cancer.

Heart Failure Stage B: Patients With Evidence of Ventricular Dysfunction Without Signs or Symptoms of Heart Failure
Angiotensin-converting enzyme inhibitors and β-blockers can improve ejection fraction and decrease ventricular dilation in adults with LV dysfunction. These agents have been recommended for treatment of survivors at risk for ventricular dysfunction.380 However, a single 2004 multicenter, randomized, placebo-controlled trial of asymptomatic children with LV dysfunction after anthracycline therapy531 found that enalapril did not affect the clinical status of survivors and had no long-lasting effect on ventricular remodeling. Thus, no data support the use of enalapril to prevent progression of LV dysfunction in asymptomatic patients. β-Blockade has not been studied in asymptomatic survivors with ventricular dysfunction.

Heart Failure Stage C: Patients With Ventricular Dysfunction and Prior or Current Symptoms of Heart Failure
The most common manifestations of heart failure in children include gastrointestinal symptoms and dyspnea. Diuretic therapy is indicated to relieve the symptoms of venous congestion or pulmonary edema. Evidence that angiotensin-converting enzyme inhibitors are effective in treating symptomatic patients with LV dysfunction is lacking; however, expert consensus,

Figure 5. Cumulative incidence and 95% confidence interval of congestive heart failure among childhood cancer survivors. Reproduced from Mulrooney et al170 with permission from BMJ Publishing Group Ltd. Copyright © 2009, BMJ Publishing Group Ltd.
based on trial results in adults, is that angiotensin-converting enzyme inhibitors are indicated in symptomatic patients.\(^{380,550}\) In a retrospective study of 18 survivors treated with enalapril, Lipshultz et al.\(^{462}\) found that all 6 children in heart failure and 3 of 12 children who were asymptomatic at the start of the study had undergone cardiac transplantation or died within 6 years. Thus, the onset of symptoms in survivors with ventricular dysfunction may indicate a rapid decline in functional status.

In 2007, Shaddy et al.\(^{552}\) reported the results of a multicenter, placebo-controlled, randomized trial of carvedilol in pediatric patients with ventricular dysfunction. This study failed to demonstrate a benefit of \(\beta\)-blockers in the study population of moderately symptomatic children; however, the study has some important weaknesses that affect the generalizability of its results. The sample included children with cardiomyopathy and others with congenital heart disease, and the global improvement score was better than expected in both the placebo and treatment groups. In addition, there was some evidence for reverse remodeling in the children with cardiomyopathy who received carvedilol, but the study was underpowered for this subgroup analysis. Because of these limitations, clinicians continue to use \(\beta\)-blockers in children with acquired or idiopathic cardiomyopathy, despite the lack of evidence for efficacy in the study.

**Heart Failure Stage D: Patients in Heart Failure Refractory to Medical Management**

Childhood cancer survivors in clinical heart failure can rapidly progress to marked functional impairment that is refractory to medical therapy. In this situation, there is no specific contraindication for extracorporeal membrane oxygenation or implantable pulsatile or continuous-flow ventricular assist devices to provide short- and mid-term cardiac support. These devices have been used to rescue cancer survivors from acute decompensated heart failure or as a bridge to transplantation in patients with end-stage heart failure.\(^{553-555}\) The best time to implant a mechanical assist device has not yet been defined in children in heart failure or specifically in survivors of childhood cancer. The risk of adverse events with mechanical assist devices, including infection, thrombosis, bleeding, and neurological impairment, can be as high as 40%.\(^{556}\) Thus, the potential benefit of mechanical assistance in children must be tempered by the high risk of serious device-related morbidity and mortality.

Heart transplantation therapy is highly effective in treating children with cardiomyopathy.\(^{557}\) One-year survival after transplantation for intractable heart failure in children with dilated cardiomyopathy is \(\approx92\%\).\(^{558}\) Heart transplantation has been performed in patients with doxorubicin-induced cardiomyopathy since the earliest days of transplantation.\(^{559-561}\) Survival of children with doxorubicin-induced cardiomyopathy appears to be similar to that of children with cardiomyopathy from other causes.\(^{558,562}\)

Malignancy occurs more often than normal in immunosuppressed patients with transplanted hearts. Evaluation of an immunosuppressed cancer survivor for heart transplantation must include an assessment of the risk for recurrence of the primary malignancy or for secondary malignancies. The risk for posttransplantation malignancy should be determined by a multidisciplinary team of cardiologists, oncologists, and infectious disease specialists. Excellent cancer-free survival has been reported after heart transplantation in pediatric cancer survivors.\(^{563}\)

**Treatment of Radiation-Associated CVD Risk Factors**

As discussed in the “Cardiometabolic Risk Factors for Premature Atherosclerosis” section, childhood cancer survivors, especially those treated with certain types of radiotherapy, are at increased risk of obesity, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, and GH deficiency. Survivors treated with abdominal radiotherapy or total body irradiation appear to be at increased risk of the first 4 conditions, whereas survivors treated with \(>18\) Gy of cranial irradiation are clearly at risk for all 5 conditions as a result of GH deficiency.\(^*\) Survivors who received cranial irradiation also experience a decrease in LV mass and dimension.\(^{564}\) Survivors treated with total body irradiation appear to be at increased risk for GH deficiency or GH resistance, because their clinical picture falls somewhere between those treated with abdominal irradiation and cranial irradiation in terms of metabolic disorders and growth problems. Finally, as discussed in the section “Pathophysiology of Cardiovascular Toxicity from Radiotherapy,” childhood cancer survivors treated with radiotherapy that included the heart in the treatment field are at increased risk of restrictive cardiomyopathy and valvular disorders. Here, we consider the management of insulin resistance and diabetes mellitus in childhood cancer survivors; the evidence for managing GH deficiency, particularly in adult survivors of childhood cancer; and the treatment of restrictive cardiomyopathy.

**Diabetes Mellitus and Metabolic Syndrome**

Treatment of dyslipidemia is discussed elsewhere in this article, so we focus here on treatment of the glucose abnormalities in type 2 diabetes mellitus. In considering which survivors are most likely to experience diabetes mellitus or metabolic syndrome, risk factors in the general population and those specific to childhood cancer survivors should be considered. Examples of the latter include the types of radiotherapy discussed above, female sex, and increasing time since treatment.

Many treatment risk factors act not only through increasing overall BMI but also by decreasing lean body mass. Indeed, many survivors with metabolic syndrome are not overweight as defined by BMI and may in fact be underweight if treated with total body irradiation.\(^{565}\) This paradox is supported by a recent case-control study of 319 childhood cancer survivors and sibling control subjects. At a mean of 14.5 years after diagnosis, survivors had higher abdominal adiposity, lower lean body mass, and higher insulin resistance than age-matched control subjects, but both groups had similar mean BMI measurements.\(^{317}\)

Unfortunately, there are no studies of treatment of diabetes mellitus or metabolic syndrome in childhood cancer survivors in the absence of GH deficiency. However, the scientific statement from the AHA and other groups on reducing cardiovascular risk in high-risk children indicates that

\(^*\)References 27, 33, 174, 317, 351, 352, 433, 564–567.
treatment of diabetes mellitus or insulin resistance is likely to be as effective in childhood cancer survivors as in the general population, unless there are underlying causes for glucose metabolism dysfunction, such as hypothalamus-pituitary axis abnormalities.441

As in the general population, lifestyle and behavior change are as important to therapy as medications. Furthermore, considering that many of the medications used to treat diabetes mellitus and metabolic syndrome are not as well studied in children as in adults, that they have unknown or harmful effects on the unborn child, and that increasing physical activity and a healthy diet improve health in many domains with little risk, lifestyle changes should probably be the mainstay of treatment for most survivors while they are children, along with hormone replacement when necessary.

The 2006 and 2010 AHA scientific statements describe the most effective strategies for improving physical activity among people of all ages.569,570 An intriguing strategy that could help not only survivors during childhood but their siblings and parents as well is to engage the parents as “agents of change” to improve the lifestyle habits of the entire family. Unfortunately, a recent AHA review of randomized controlled clinical trials studies using this approach to treat childhood obesity in the general population did not conclusively demonstrate that greater parental involvement was necessarily associated with better outcomes in children, although some studies showed better outcomes 2 to 5 years after an intervention that included parents.571

**GH Deficiency**

Concerns about the association between GH concentrations or its activity and cardiovascular risk factors predate the 1980s, but treatment in adults was not possible until recombinant human GH was introduced in the late 1980s.572 Dyslipidemia and metabolic syndrome are more likely to occur in individuals with GH deficiency, but individuals with chronic heart failure are also generally resistant to GH. Although there is no evidence that GH deficiency itself causes substantial clinical cardiac dysfunction in childhood cancer survivors specifically, numerous studies of adults with chronic heart failure have shown that the GH–insulin-like growth factor-1 axis activity in this condition is reduced.573 In a case-control study of 34 anthracycline-treated childhood cancer survivors evaluated by serial echocardiography while undergoing GH replacement therapy, Lipshultz et al82 found that before, during, and after therapy, LV contractility was lower than that of 86 similarly treated survivors who were not GH deficient. The GH-treated children also had thinner LV walls before GH replacement, which improved after 3 years of therapy; however the effect on wall thickness was lost once GH therapy ended.226

The use of GH in childhood cancer survivors has raised concern, however. First, GH replacement might increase the risk of recurrence or second cancers. These concerns stem from the biological mechanisms of GH (specifically, that it has mitogenic and proliferating properties) and from some early case reports of cancer in patients receiving GH,574,575 including one of a second cancer in a childhood cancer survivor receiving GH.576 A 1993 retrospective review of the prevalence of leukemia and lymphoma among 6284 pituitary-derived GH recipients treated between 1963 and 1985 also increased concern about higher cancer risk.577 The relative risk of leukemia in pituitary GH recipients for the entire follow-up was 2.6 (90% CI, 1.2–5.2), but 5 of the 6 subjects with leukemia were treated for brain tumors before receiving GH therapy. Thus, the increased risk of leukemia was the sole result of its occurrence in cancer survivors in whom it could have resulted from the toxic effects of therapy and not GH replacement. The comparison group was the general US population, so adjustment for cancer therapies that increase the risk of second cancers, and of leukemia in particular, was not possible.

Two large studies of childhood cancer survivors suggest that GH therapy does not increase the recurrence of primary cancers and that the increased risk of subsequent leukemia is likely the result of confounding. However, these studies cannot eliminate the possibility that GH replacement increases the risk of second cancers in these survivors.

A multicenter retrospective study of British children who survived brain cancer treated with cranial radiation between 1965 and 1996 revealed that cancer recurred in 35 of the 180 children who received GH-replacement therapy (for a crude prevalence rate of 19%) and in 434 of the 891 children who did not receive this therapy (for a crude prevalence rate of 49%).578

Another analysis in this cohort of the incidence of second cancers found that the crude risks for colon and bone cancers were higher than those of the general population. This risk was greatly attenuated when patients at high risk for a second cancer (defined as survivors treated with cranial irradiation, with chromosome abnormality or instability, or a glycogen storage disease) were removed from the analysis. In this same adjusted analysis, only the incidence of colon cancer remained higher than that in the general population. Unfortunately, there was no adjustment for other known risk factors for second cancer.578

Sklar et al579 compared the risk of disease recurrence and second neoplasms in the 361 GH-treated survivors in the Childhood Cancer Survivors Study to that of the nearly 13,000 survivors in the study who did not receive GH. The relative risk of disease recurrence ≥5 years after diagnosis was 0.83 (95% CI, 0.37–1.86) for GH-treated survivors overall and was not increased for any of the major cancer diagnoses. After adjustment for age at diagnosis, sex, radiation, and treatment with an alkylating agent, the overall adjusted hazard ratio was 3.21 (95% CI, 1.88–5.46), a result caused mainly by the small excess number of second cancers observed in GH-treated survivors of acute leukemia. In a reevaluation of this cohort with an average of 32 months more of follow-up, 5 additional survivors (4 of brain cancers and 1 of neuroblastoma) developed second cancers (4 brain cancers and 1 thyroid cancer). The overall multivariable adjusted hazard ratio in GH-treated survivors for second cancers was 2.15 (95% CI, 1.3–3.47). Most concerning was the fact that after stratification by original diagnosis and adjustment for the same treatment factors as in the original analysis, this reanalysis found that the relative risk for second cancers was 2.3 (95% CI, 0.9–5.8) in GH-treated ALL survivors and 1.4 (95% CI, 0.67–3.02) in GH-treated survivors of central nervous system cancer.580 Overall, these 2 studies suggest that GH replacement does not increase the risk of recurrence, the risk of a second cancer, or the risk of...
mortality in survivors of most types of childhood cancer; however, in survivors of childhood brain cancers and of ALL, these studies cannot eliminate the possibility that GH replacement increases the incidence of second tumors. Thus, these risks need to be considered in the decision to start GH therapy in these survivors. These results also highlight the need for studies on survivors of these 2 diagnoses, especially because cranial irradiation is now used much less frequently in survivors of ALL compared with the ALL survivors in these 2 studies, who were diagnosed no later than 1986.

A third major concern is that GH therapy may exacerbate insulin resistance, especially in survivors who received large doses of cranial irradiation and are therefore already at risk for insulin resistance and diabetes mellitus. These results did not include cancer survivors per se, a retrospective cohort study of GH-insufficient adults suggested that GH replacement reduced overall mortality and in particular decreased CVD morbidity without increasing mortality from cancer. Members of a population-based registry of 1411 Swedish adults with hypopituitarism not treated with GH had significantly higher overall and cancer-specific mortality and higher rates of MI, cerebrovascular events, and malignancies than the general population. Among the 289 adults in the registry treated with GH, rates of malignancies, MIs, cerebrovascular events, and overall death were similar to those in the general population, with most point estimates of the risk ratios <1. These results suggest that any perturbation in glucose control caused by GH replacement is not clinically important enough to increase the risk of coronary heart disease, which is the leading cause of death in those with diabetes mellitus, and that GH replacement improves survival among adults with GH deficiency.

Only 1 clinical trial has evaluated the use of GH replacement in adult survivors of childhood cancer. This open-label, nonrandomized trial of ALL survivors compared 16 GH-deficient survivors after 5 years of GH replacement with 13 untreated GH-deficient survivors. All participants had been treated for childhood ALL, with therapy that included 18 to 24 Gy of cranial irradiation, and were between 19 and 32 years old at the end of the study. The survivors who received GH replacement had significantly better plasma glucose control (change of −0.5 versus 0.6 mmol/L), apolipoprotein B/A1 ratios (change of 0.1 versus 0.0), and HDL cholesterol concentrations (0.20 versus −0.01 mmol/L) and a significantly lower prevalence of metabolic syndrome than untreated survivors. LV systolic function and quality of life did not differ between treatment groups, but the sample size may have limited the power to detect smaller but still clinically important changes in these outcomes.

Studies of adults in the general population with chronic CHF have shown that GH replacement improves quality of life, exercise endurance, peak oxygen consumption, and LV ejection fraction. Thus, in childhood cancer survivors with GH deficiency, GH replacement may improve cardiac function in ways not measured by echocardiographic indices of systolic function. Alternatively, GH replacement may need to be given in a certain window to improve systolic cardiac function, or whatever benefit GH replacement has, it cannot overcome the effects of other cardiotoxic treatments, particularly anthracyclines and cardiac irradiation.

In summary, evidence mostly from the general population with some from childhood cancer survivors indicates that GH replacement has many positive effects on metabolism and CVD risk factors and so has the potential to increase both quantity and quality of life in GH-deficient survivors. Previous concerns about GH replacement increasing the risk of diabetes mellitus and metabolic syndrome based on shorter-term studies have mostly been laid to rest, because longer studies have found the opposite results, at least in the general population.

The one remaining concern is that in childhood cancer survivors, GH replacement may increase the risk of second cancers, but this possibility is not clear, and even if true, the risk is minimal and does not appear to affect overall mortality. This concern should not preclude treatment, but it should be considered and suggests the need for further research, particularly in survivors of childhood ALL and childhood brain tumors treated since 1986 who received only recombinant human GH.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy, which may develop as a consequence of radiation-induced cardiac injury, is treated the same way as idiopathic restrictive cardiomyopathy; however, treatment options must be considered in the context of the patient’s overall health and comorbidities. Treatment of restrictive cardiomyopathy consists of appropriate fluid management to minimize cardiovascular symptoms and includes limiting dietary sodium and fluid intake, combined with the use of diuretics. The goal of treatment is to reduce intravascular filling pressures, which are the source of early symptoms of heart failure. This treatment does not alter the progression of the underlying myopathic process.

As restrictive cardiomyopathy progresses, diuretics need to be increased but eventually will not maintain normal intravascular pressure. The only option at this point is cardiac transplantation. Cardiac transplantation is constrained by donor availability, and the applicability of transplantation must be carefully evaluated in terms of the underlying prognosis and the relevant comorbidities using the principles established in all heart transplantation evaluations. Of particular concern are the recurrence rates of the primary cancer, the occurrence rates of new malignancies, and the health of the kidneys. In addition, the optimal timing of transplantation in patients with restrictive cardiomyopathy is controversial, with some groups advocating for transplantation at the time of diagnosis and others advocating a less aggressive approach.

The natural history of restrictive cardiomyopathy is described only in several small series, so this issue cannot be definitively addressed and remains an area of individual decision making. Notwithstanding these difficulties, heart transplantation can be lifesaving in carefully selected candidates with restrictive cardiomyopathy.

Cardiometabolic Syndrome: Secondary Prevention and Management

Atherosclerosis

The risk of cardiovascular dysfunction in survivors of childhood cancers persists throughout life and increases with time, which makes frequent long-term follow-up a priority if dysfunction is to be detected early.
As discussed previously, BMI may not be an adequate measurement of adiposity. Furthermore, clinical evaluations may be misleading, because many patients are asymptomatic, despite evidence from cardiac MRI studies of late myocardial enhancement that suggests that ≥30% of survivors have myocardial fibrosis or scarring and that ≥70% have perfusion deficits. The diagnostic performance characteristics of noninvasive screening modalities, including stress echocardiography, ECG, and scintigraphy, to detect stress-induced ischemia are not as good as those of coronary angiography. The sensitivity of new diagnostic tools, such as computed CT, magnetic resonance angiography, and coronary artery calcium scores, for detecting clinically important (>50%) stenosis as measured by angiography varies from 81% to 97% for men and from 76% to 98% for women, with specificity >77%. The effectiveness of these modalities in screening for cardiovascular dysfunction has not been evaluated prospectively in large studies of survivors.

The mainstays for preventing cardiometabolic disease in most populations are a sound diet, regular physical activity, and healthy lifestyle choices (eg, not smoking, not drinking to excess). Medications are used to treat advanced conditions or when lifestyle changes are not successful. Survivors of pediatric cancers are at risk for atherosclerotic heart disease because of the aforementioned factors, and their need to adhere to good preventive nutrition and physical activity practices may be even greater than that in the general population. Despite this need, rates of unhealthy eating and sedentary behavioral patterns in both adult and child survivors are similar to those of the general population.

Nutrition

Diet rich in fats, sugars, and total calories and low in fiber are associated with obesity and increased atherosclerotic risk. A few studies have evaluated the diets of survivors. In general, >50% do not follow dietary recommendations, and higher fat intake was positively associated with greater body weight. Another survey of 209 survivors showed that 79% did not meet the requirements for fruit and vegetable consumption, 68% did not meet the recommendation for calcium intake, and 84% consumed >30% of calories from fat. One small study showed parents of survivors restricted their child’s choice of foods, which may eventually contribute to overweight and poor dietary quality.

The nutritional approach to decreasing atherosclerotic cardiovascular risk in survivors parallels recommendations for children and adolescents in general; these recommendations have been detailed by the American Cancer Society, the AHA, and the National Heart, Lung, and Blood Institute. In principle, the focus is on optimizing weight and consuming a healthy diet that emphasizes plant sources, little salt, and consumption of nutrients through foods rather than supplements. Although the effects of diet on cancer recurrence are well studied, the effects of a healthy diet and weight maintenance on preventing or reducing long-term cardiovascular problems in survivors are equally important.

Exercise Capacity and Physical Activity Interventions

Exercise capacity is below age and sex norms in as many as 31% of long-term pediatric cancer survivors. Abnormal exercise responses, including lack of endurance, cardiac rhythm disturbances, and ischemic changes have been reported in 43% of survivors receiving anthracyclines before 1991. Single-site studies and meta-analyses show that survivors of childhood leukemia have an aerobic capacity 13% lower than that of age- and sex-matched control subjects. However, other studies have found fewer differences in exercise outcomes between survivors >13 years of age exposed to anthracyclines or chest radiation and healthy control subjects. Recommendations for sports participation and physical activity for children with cardiovascular abnormalities have been published by expert task force groups. Exercise capacity is a topic of active discussion among pediatricians.

Cardiac dysfunction in long-term survivors exposed to anthracyclines is associated with abnormal cardiac structure and function that can cause restrictive cardiomyopathy (Figure 1) and that may be one factor that decreases exercise capacity. However, exercise capacity is sometimes poorly correlated with cardiac function, because several other late factors can influence exercise capacity. These factors include overall deconditioning as a result of a sedentary lifestyle, psychosocial problems, depression, increased body fat, mitochondrial dysfunction, chronic fatigue, other late endocrine effects, peripheral neuropathies, abnormal pulmonary function, scoliosis, and autonomic dysfunction. One recent study showed that despite subclinical cardiac dysfunction, children treated with anthracyclines (median dose, 240 mg/m²) had normal physiological responses to exercise.

Studies on the effects of cancer and cancer treatment on daily physical activity have had inconsistent results. Some report normal activities, and others report decreased physical activity after cancer diagnosis that persists for years and that children who were generally inactive before cancer treatment tend to remain so after treatment. Physical activity for survivors has not been promoted historically because of the concern that cardiac dysfunction induced by chemotherapy or RT could be worsened with exercise. However, limited but emerging data show that physical activity and training programs can improve exercise capacity, weight control, mental status, and cardiometabolic risk with little compromise of cardiac function. Supervised exercise programs appear to be more effective than those undertaken at home.

Smoking Prevention and Cessation

Smoking is one of the most important modifiers of risk for CVD and second cancers among childhood cancer survivors. Although smoking rates are lower in survivors than in the general population, as described above, services to promote tobacco avoidance and smoking cessation are an essential component of care. However, only a few childhood cancer centers provide such services. In a survey of institutions affiliated with the Children’s Oncology Group, only 39% of sites provided smoking prevention services. Furthermore, only 25% offered smoking cessation services on site, and only 58% had at least 1 mechanism to refer survivors for smoking cessation services.

Although smoking cessation has been the focus of adult interventions, smoking prevention has been emphasized in adolescent oncology. Educational and behavioral
risk-counseling interventions can reduce smoking risk among adolescents with a history of cancer for up to a year after the intervention. A comparison of preadolescents undergoing cancer therapy to a similarly aged population without cancer found that the cancer patients were more likely to recall messages about the negative health effects of smoking and to have smoking bans in place at home. In contrast, preadolescents with cancer were less likely to report receiving messages from their physicians about not smoking, a missed opportunity to improve care.

Klosky et al recently published an excellent review of smoking cessation interventions and the use of pharmacotherapy for smoking cessation among survivors of cancer diagnosed in adolescence and young adulthood. Collaborating with the Childhood Cancer Survivor Study, Emmons and colleagues, in a randomized trial among adult survivors of childhood cancer, reported that survivors receiving peer counseling by telephone had a significantly higher rate of smoking cessation at 12 months than those attending a self-help group (15% versus 9%, respectively). These differences were sustained over the long term. Tobacco control among childhood cancer survivors remains a critical issue warranting further study.

Hyperlipidemia

No single large study offers guidelines for the pharmacological treatment of hyperlipidemia in survivors of childhood cancer; however, guidelines for pharmacological treatment for children in general have been published by the National Institute of Health’s Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. These guidelines suggest treating hyperlipidemia in children ≥10 years of age and in boys who were at least Tanner stage II or girls ≥18 g/d can reduce LDL cholesterol concentrations by 17% to 19%, however, adherence is poor because of the unpleasant taste, particulate consistency, and gastrointestinal discomfort.

Fibrates

Fibrates are used primarily to treat hypertriglyceridemia and are less effective than statins in reducing LDL cholesterol concentrations. They have a poorer record in preventing CVD and have been associated with a higher risk of myopathy and other adverse effects.

Ezetimibe

Ezetimibe is a cholesterol-absorption blocker that acts at the brush border of the small intestine. It selectively inhibits the intestinal absorption of dietary and biliary cholesterol and phytosterols. Ezetimibe as monotherapy lowers total serum cholesterol concentrations by 10% to 13%, LDL cholesterol concentrations by 15%, and triglyceride concentrations by 5% to 8%, although it has little effect on HDL cholesterol concentrations. These effects are amplified when ezetimibe is taken with statins.

Hypertension

Although established guidelines address the management of hypertension in adults and children in the general population, their application to cancer survivors should be informed by both the heterogeneous origin of hypertension and the potential of elevated baseline risk of CVD from various treatments, such as cardiac irradiation. These important issues may alter decisions about the appropriateness of specific treatments and the point in patient care at which they are initiated. The treatment history of survivors with elevated blood pressure should be reviewed to identify possible secondary causes, such as those identified in as those identified in the section “Cardiometabolic Risk Factors for Premature Atherosclerosis.”

Current recommendations for managing primary hypertension in the general population include both healthy lifestyle promotion and medications. All patients, regardless of blood pressure status, should be encouraged to lead a healthy lifestyle, including maintaining normal body weight, eating a healthy diet, restricting sodium intake, engaging in regular physical activity, eliminating tobacco use, and consuming alcohol in moderation, if at all. With the exception of survivors who are unable to be physically active, promotion of a healthy lifestyle should be considered an important part of blood pressure control for survivors, although little evidence is available to indicate whether healthy lifestyle habits have the same effect in cancer survivors as in the general population. This recommendation is consistent with those of the Children’s Oncology Group.

For patients with elevated blood pressure, medications are indicated when a healthy lifestyle does not return blood pressure to normal. The recommended aggressiveness of prescribing in the general population is based on the severity of blood pressure elevation. Adults are classified according to systolic...
and diastolic blood pressures as having prehypertension (a systolic pressure of 120–139 mm Hg or a diastolic pressure of 80–89 mm Hg), stage 1 hypertension (a systolic pressure of 140–159 mm Hg or a diastolic pressure of 90–99 mm Hg), or stage 2 hypertension (a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg). Children are classified according to systolic and diastolic blood pressure as having either prehypertension (systolic or diastolic pressures between the 90th and 95th percentile of age- and sex-adjusted norms) or hypertension (systolic or diastolic pressures above the 95th percentile of these norms).

Medications are recommended for adults and children with hypertension, as well as for adults with prehypertension and a compelling indication, either chronic kidney disease or diabetes mellitus. As in adults, children with prehypertension resistant to healthy lifestyle changes should be treated with medications, depending on the clinical situation. Given the increased baseline risk of CVD of many survivors treated with cardiac irradiation or possibly other exposures, a history of childhood cancer may be a compelling indication for treatment of adults with prehypertension. However, few data exist to indicate whether survivors will benefit as much from antihypertensive medications as the general population.

Cerebrovascular Event Prevention

As discussed in “Treatment of Radiation-Associated CVD Risk Factors,” which addressed the mitigation of radiation-associated cardiovascular complications, preventing cerebrovascular toxicities will include a constellation of approaches that include the following: (1) Changes in treatment strategies to avoid the use of RT that includes the carotid arteries or cerebrovascular surgery; (2) refinement of radiation approaches such that smaller volumes of normal tissues are treated; (3) reduction of the dose of RT used in situations in which it remains important and includes the carotid arteries or cerebrovascular surgery; and (4) addressing the various other risk factors that increase the risk of cerebrovascular events, such as obesity, smoking, hypertension, and diabetes mellitus.

Arrhythmias and Conduction Defects

Some acute electrophysiological changes, such as premature atrial or ventricular contractions, are self-limited and benign in the majority of cases, whereas ischemic changes or conduction block may occasionally require cardiology consultation and intervention. Prolonged QT intervals are a risk factor for ventricular tachycardia. The severity of this problem is classified by the National Cancer Institute as follows:

- **Grade I:** QTc between 450 and 470 ms
- **Grade II:** QTc between 470 and 500 ms or 60 ms above baseline
- **Grade III:** QTc >500 ms and the presence of torsade de pointes or signs or symptoms of life-threatening conditions
- **Grade IV:** Death

Appropriate responses to QT prolongation may include protocol modifications to reduce exposure to the causative agent(s), more intense observation and intervention in the event of ventricular tachycardia, and avoidance of other agents that may further prolong cardiac repolarization. There are many such agents, including ondansetron, erythromycin, and sertraline (see the Sudden Arrhythmia Death Syndromes Web site at http://www.sads.org). Because some of these agents may be therapeutic, their oncological benefit must be balanced against their cardiovascular risk, which may require consultation between a cardiologist and oncologist.

Cause of death in registry studies is determined from medical records, family interviews, and death certificates; however, even with considerable effort, these studies cannot discern the contribution of arrhythmia to overall cardiovascular mortality. For this information, smaller studies need to be examined. The Dutch Childhood Leukemia Group evaluated cardiac function in 90 survivors of childhood ALL =15 years after therapy containing low-dose anthracyclines (a cumulative dose of 100 mg/m²). In these survivors, myocardial function was normal, and arrhythmias were limited to premature atrial contractions (6%) and premature ventricular contractions (2%). There were no instances of sustained tachycardia.

In contrast, one of the earlier descriptions of late cardiotoxicity by Lipshultz and colleagues is of 4 patients with ventricular tachycardia (detected by Holter surveillance from a cohort of 89 children, an incidence of 4.4%). Of these 4 patients, 3 were symptomatic with either syncope or palpitations, and all 4 episodes of ventricular tachycardia occurred in patients with severe LV dysfunction, each of whom had heart failure within 1 year. Similarly, a 1991 report by Steinherz et al described 2 patients with late cardiovascular events consisting of deteriorating ventricular function accompanied by ventricular enlargement, prolonged PR and QRS intervals, and ventricular ectopy; all culminated in arrhythmic death. Additionally, 1 patient with chronic heart failure experienced sudden cardiac death with no prior arrhythmia. More recently, Gupta et al described the clinical course of 64 long-term cancer survivors treated with high doses of anthracyclines. All 10 patients who died had diminished cardiac function and at least a 1-year history of prolonged QTc dispersion before sudden death. Survivors had higher shortening fractions than those who died.

The 3 series reported by Lipshultz et al, Steinherz et al, and Gupta et al described above affirm a strong link between cardiac dysfunction and clinically relevant arrhythmias. This link is the basis for the 2008 recommendation by the Children’s Oncology Group that patients with prolonged QTc intervals and LV dysfunction should be considered for evaluation by a cardiologist. In this regard, the delayed arrhythmic disease seen long after cancer therapy parallels that of acute arrhythmic disease. In both cases, clinically important arrhythmias occur in patients with compromised ventricular function, and it is this group of patients in whom treatment decisions are most critical.

Although there is little specific guidance for treating oncological cardiomyopathies, the general principles for managing arrhythmias in the context of reduced systolic function are well established in cardiology and include optimization of myocardial function with appropriate heart failure medications and the judicious use of implantable cardioverter defibrillators (ICD) in selected patients. However, specific indications for treating cancer survivors with ICDs have not been established.
In general, mortality rates from arrhythmias in children with cardiomyopathy are much lower than in adults.\textsuperscript{641} For example, in 443 children with ICDs described by Berul and colleagues,\textsuperscript{644} mortality was 4\% over 7.5 years. Mortality attributable to sudden cardiac death was even lower, at 1\%.\textsuperscript{644} In contrast, in a randomized trial by Bardy et al\textsuperscript{645} comparing medical therapy with ICD therapy in adult patients with dilated cardiomyopathy, 5-year mortality was 36\% in the placebo (ie, medical) group and 29\% in the group receiving ICDs. The ICD discharge rate was nearly 8\% per year in that study. Whether arrhythmias in adult survivors of childhood cancer more closely resemble those in the children with ICDs studied by Berul et al\textsuperscript{644} or those in the adults studied by Bardy et al\textsuperscript{645} remains to be determined. In the meantime, the use of ICDs in cancer survivors must remain individualized.

### Overall Impact of CVD in Survivors of Childhood Cancer

Childhood cancer survivors face a lifetime of serious health risks.\textsuperscript{645a–645g} By 30 years after cancer diagnosis, almost 75\% of survivors will have at least 1 chronic health condition, and >40\% will have a serious or life-threatening condition.\textsuperscript{6.9} This burden of morbidity contributes to the excess risk of mortality from CVD and second cancers.\textsuperscript{7,11,14} Thus, the development of CVD, regardless of stage or severity, is important to the life and physical and emotional well-being of a childhood cancer survivor.\textsuperscript{x} Furthermore, there are substantial economic implications of screening for and managing CVD in this population that warrant sophisticated, careful cost-effectiveness studies.

Although asymptomatic heart failure obviously is associated with reduced activity in survivors, even asymptomatic heart failure may affect exercise capacity and insidiously lead to a sedentary lifestyle. Reduced physical activity and cardiorespiratory fitness, regardless of cause, are associated with worsening metabolic derangements and obesity so common among childhood cancer survivors.\textsuperscript{27,31,33,38,564} Furthermore, more than ample evidence indicates that a reduction in fitness is associated with the eventual development of future cancers, as well as all-cause and cardiovascular-specific mortality.\textsuperscript{408,410,411}

Most childhood cancer survivors treated with anthracyclines or chest radiotherapy show only modest changes in LV function by their early adult years; however, there remains much concern about the impact of this marginal loss of ventricular reserve on the overall health of survivors as they experience the cascade of cardiovascular risk factors and comorbidities so common with aging. What may appear to be an inconsequential ejection fraction of 50\% with some mild global hypokinesis may progress more rapidly in the face of long-standing hypertension or diabetes mellitus. Moreover, heart disease is the leading cause of death among all men and women in the United States and other industrialized societies.\textsuperscript{646} In a cancer survivor with marginal LV function, even a modest MI may result in progressive end-stage heart failure, given the lack of reserve. The same paradigm exists for CAD or cerebrovascular disease. Modest changes to the atherosclerotic process early in life may accelerate disease when compounded by the ever-present comorbidities associated with aging.

Not surprisingly, long-term survivors of childhood cancer often live with a daily sense of uncertainty, wondering when the next major adverse event will occur. This threat is underscored by the need for cardiac and other survivor-focused monitoring, an ever-present reminder of their vulnerability.\textsuperscript{647–651} Anecdotally, survivors often say they are more emotionally equipped to deal with another cancer than a cardiac event, because they have a sense of the pathway of cancer therapy. Although these fears and concerns add to the psychosocial morbidity observed in this population, adult survivors of childhood cancer remain amazingly resilient, even those with multiple serious health problems.

The economic costs of cardiac monitoring and management of cardiac disease in this population remain woefully understudied. Individual costs associated with regular and lifetime monitoring with echocardiography or other advanced modes of cardiac imaging are substantial, both in the direct costs of testing and in the indirect costs of time away from work and other responsibilities; however, the cost of potentially preventable cardiac events, including MI, end-stage heart failure, and valve replacement, must be balanced with the cost of screening. After a sophisticated analysis, Wong and colleagues\textsuperscript{652} presented very provocative data suggesting that annual echocardiography may be more cost-effective than other strategies for screening long-term survivors of childhood cancer treated with anthracycline chemotherapy, with or without chest radiotherapy. However, more studies in this area are critical, not only in the United States but also in other countries and other healthcare systems. Integral to such discussions are potential noneconomic harms associated with screening, such as overtreatment of patients with false-positive testing, uncertainty about the course and outcome of an abnormality, potential impediments in purchasing insurance, and side-effects of the potential treatment. The survivor and healthcare professional should discuss all possibilities and together decide on the optimal follow-up of the survivor.

In summary, it is time we move beyond our current focus on the young adult years to address the entire life span of patients who survive a childhood cancer.\textsuperscript{653} The pediatric oncological community, in the development of new protocols, operates under the mantra, “maximize the cure, minimize the cost.”\textsuperscript{654} As investigators focused on the long-term outcomes of cancer survivors, an equally important mantra for us is to “maintain the cure and maintain the quality of the cure.” Recognizing that cardiac outcomes affect both longevity and quality of life, it is imperative that we better understand how we can prevent or slow the progression of CVD while managing the assortment of other health risks and comorbidities in this population.

### Future Directions

Explaining the long latency between the cardiotoxic exposures from cancer therapies and the development of cardiovascular events is one of the greatest challenges in cancer research. Although cardiovascular events occasionally occur during adolescence or young adulthood, most occur ≥2 decades after the original exposure. This long latency is often best addressed epidemiologically, with prospective cohort studies. Both the Bogalusa and Framingham studies have demonstrated the feasibility of this approach, but both relied on a relatively small, if representative, population in a defined geographic area.

A study of cardiovascular risk among survivors of pediatric cancers would require follow-up of a very large sample for many decades. In an era of limited research funds, investigators...
need to be innovative in undertaking such research. One promising approach is to use new surrogate end points for cardiovascular events. Genomic, proteomic, and transcriptomic studies performed early in life may identify valuable surrogate markers for cardiovascular events that develop decades later. Recent studies have shown that traditional serum biomarkers of ventricular structure and function, such as N-terminal pro-B-type natriuretic peptide and cardiac troponin T, can reliably detect preclinical cardiotoxic injuries. As newer generations of potential cardiac biomarkers are discovered, their sensitivity, specificity, and utility in predicting cardiac events should be tested. Moreover, less cardiotoxic cancer therapies and better cardioprotective chemoprevention agents can be developed. Lastly, research on how to prevent and control diabetes mellitus, obesity, hypertension, and tobacco use could reduce the cardiovascular risks of these patients. These research strategies should not only improve the long-term cardiovascular health of survivors but also potentially maximize third-party coverage of new therapies and monitoring plans.

Radiation Dose and Volume Practices That Impact Subclinical Cardiovascular Dysfunction
RT is evolving from traditional anterior-posterior approaches to 3-dimensional conformal and intensity-modulated approaches that reduce exposure to cardiac tissues. Predicting toxicity from RT requires data based on 3-dimensional radiation and intensity-modulated dosimetry. The few existing parameters that are evidence-based radiation dose-volume predictors of cardiac morbidity need to be confirmed or modified by retrospective analysis of larger data sets of patients treated with various doses to various cardiac volumes that are correlated with cardiac end points (eg, events or laboratory or imaging measures of cardiac function). Improved toxicity predictions will require careful data collection and analysis from prospective clinical trials. Several issues must be considered:

- Determining whether modern radiation approaches in fact reduce cardiotoxicity.
- Determining whether reducing radiation to exposed cardiac tissues reduces the potential for toxicity or simply delays its onset.
- Determining associations between radiation doses and specific subvolumes (anatomic regions) of the heart and clinical cardiac events.
- Using modern imaging techniques to better define and measure radiation exposure to specific cardiac structures.
- Identifying any potential interactions between traditional baseline cardiovascular risk factors and radiation.
- Defining the impact of noncardiac radiation exposures, such as that to the hypothalamic-pituitary axis, on increasing the risk of cardiovascular toxicity.
- Characterizing the interactions between radiation-induced pulmonary injury and cardiac performance and their impact on subclinical cardiac dysfunction.

Interactions Between Cardiotoxic Systemic Therapy (Chemotherapy and Biologics) and RT
All of the challenges in defining the specific characteristics of chemotherapy, biological therapy, and RT that influence cardiac function and the risk for adverse cardiac events are complicated by the interactions between these therapies. Although such interactions may augment the risk for cardiac dysfunction, it is not clear whether any augmentation might be additive or synergistic, because the mechanisms of injury differ. For example, anthracyclines primarily damage myocytes, whereas radiation damage is mediated primarily through vascular effects. However, both treatments have inflammatory effects, which further complicates the potential for injury. In addition, combined chemotherapy and RT could conceivably increase the risk for injury beyond that associated with either therapy alone; however, when both therapies are used, the doses of each are often decreased. Thus, precise data collection and analysis are necessary to define the risk of cardiotoxicity and to improve predictions of clinical events.

Long-term Impact of Subclinical Cardiovascular Dysfunction
Dilated cardiomyopathy is observed immediately after anthracycline exposure, but many long-term survivors will eventually experience a restrictive cardiomyopathy characterized by LV diastolic dysfunction, which places these patients at risk for heart failure. Although anthracycline cardiotoxicity is progressive in cancer survivors in general, this progression varies greatly among individuals (Table 6). Angiotensin-converting enzyme inhibitors are effective in treating adults with heart failure. However, the After Anthracycline trial found that enalapril did not prevent the decline in ventricular function in survivors with anthracycline-related cardiotoxicity; similar findings were reported by Lipshultz et al from an observational study. In another study of enalapril in a similar population, some initial improvements in ventricular function and structure were lost after 6 to 10 years of therapy, and LV wall thickness and contractility decreased over the entire course of treatment.

The long-term effects of enalapril are also a concern, including chronic neurohormonal suppression, a possible risk for gastrointestinal cancers, and other unknown effects. Finally, subclinical LV dysfunction in the presence of other treatment-related toxicities, such as valvular disease, CAD, and conduction abnormalities, will markedly increase the risk for a variety of cardiac events, including MI, sudden death, heart failure, and stroke. Clearly, long-term prospective studies using either cardiac events or surrogate end points are needed to better understand the molecular, genetic, and epigenetic factors that increase the risk of cardiac events in an individual with subclinical ventricular dysfunction. Such an understanding is necessary to develop better prevention and treatment strategies.

Monitoring Guidelines for Detection of Early Signs of Cardiovascular Damage
The substantial proportion of pediatric cancer survivors treated with potentially cardiotoxic modalities and the increasing prevalence of preclinical disease and cardiovascular events reported in aging survivors underscore the need to prevent and detect CVD as early as possible. Despite an abundance of research documenting the excess risk of cardiovascular morbidity and mortality among survivors treated with anthracyclines and radiation, basic questions remain...
regarding who is at highest risk; how aging, familial-genetic, and lifestyle factors modify risk; when risk becomes clinically relevant and screening becomes cost-effective; what screening modality is most sensitive, specific, and cost-effective, given the latency of preclinical and symptomatic disease; what interventions remediate or preserve cardiovascular health; and, most importantly, whether prevention and screening or surveillance measures improve survival and quality of life.

The research needed to address these questions requires the tracking of health outcomes that may occur many decades after cancer treatment, as well as the recruitment and tracking of representative survivors who eventually move from pediatric oncology clinics to community primary care providers as they age. These initiatives need to consider the diversity in models of survivorship care, which may range from comprehensive, risk-based long-term follow-up in an academic cancer center by knowledgeable providers to follow-up by community providers who are generally unfamiliar with cancer-related health issues. In addition, collaboration among oncologists, primary care providers, and cardiologists in these initiatives will be important to ensure the use of appropriately defined outcomes and emerging technologies.

Given the small numbers of pediatric cancer survivors relative to adults and the long time to presentation of many treatment-related cardiovascular events, randomized studies of asymptomatic survivors to determine whether screening reduces mortality are likely not feasible. However, research is feasible in the first 5 years after diagnosis, when follow-up at a pediatric cancer center is most consistent. These studies are needed to more accurately characterize survivors at high risk for early cardiovascular morbidity; define the optimal modality, frequency, and cost-effectiveness of screening; and implement interventions to preserve cardiovascular health.

Standardization of follow-up care can enhance opportunities to preserve cardiovascular health and facilitate late-effects research. Several pediatric cooperative groups have developed evidence-based clinical practice recommendations for long-term survivors based on the magnitude of cardiovascular risk and the frequency and intensity of screening programs. These recommendations are geared toward oncology and primary care providers and focus largely on cardiomyopathy screening with echocardiography, assessment of comorbid conditions that may affect the risk of cardiovascular disease (e.g., overweight, hypertension, diabetes mellitus, and dyslipidemia), and heart-healthy lifestyle counseling. Study of the utility of incorporating newer modalities of echocardiography-based screening, including strain imaging, will provide insight into earlier identification of patients who may benefit from treatment. Ongoing evaluations of the yield from risk-based screening based on survivor and treatment characteristics and screening modality and frequency will no doubt refine these recommendations. Partnerships with cardiology providers are critical for evaluation of the use of serum biomarkers in characterizing cardiovascular risk, the utility of new cardiovascular imaging modalities in defining cardiovascular health status, and the effectiveness of drugs in preserving cardiovascular health.

Dietary and Exercise Recommendations for Cancer Survivors

Structured nutritional and physical exercise interventions can maintain and improve cardiovascular health in several chronic diseases of childhood.660 Several guidelines for diet and exercise are available for survivors and their physicians. The guidelines from the Children's Oncology Group are representative and provide general guidance on dietary content and portion size that is consistent with recommendations from the US Department of Agriculture; however, the guidelines do not address the specific issues of people with cancer-related cardiovascular damage or disease. The physical activity recommendations have historically been conservative, but the benefits of physical activity throughout survivorship are increasingly recognized.

Desirable dietary behaviors, body composition, physical activity, and the prevalence of obesity and diabetes mellitus among pediatric cancer survivors have been determined by several investigators. More definitive dietary and exercise intervention studies are needed to identify whether and how much they reduce cardiovascular risk and what subpopulations may benefit the most or the least. Other unanswered questions include the utility of body composition measurements (beyond BMI), nutritional and exercise needs during pregnancy, and who should or should not participate in athletic programs. Americans spend tens of billions of dollars annually on some type of complementary and alternative medicine. Cancer survivors use complementary and alternative medicine at a similar rate. Further research is needed to determine the effectiveness of these therapies in decreasing global cardiovascular risk compared with standard therapies.

Challenges of Targeted Cardiovascular Medication Regimens

The development of effective, targeted treatments for both cardiotoxic and cardioprotective regimens requires a detailed understanding of their mechanisms at the molecular and genetic levels. Studies of anthracycline-related cardiotoxicity have identified several mechanisms of cardiac injury, including the generation of ROS and lipid peroxidation of the cardiac myocyte membrane, direct damage to mitochondria, and decreased ATP production. However, how these various mechanisms interrelate in individual patients is not known. The results of genetic and epigenetic studies into the susceptibility to anthracycline-related cardiotoxicity in animals are only beginning to be translated into studies in humans. The increasing use of cardiotoxic tyrosine kinase inhibitors in pediatric cancer protocols underscores the importance of research into their cardiotoxicity in the developing heart, as well as their importance in the risk of future cardiovascular events in survivors.

In addition to our limited understanding of the cardiotoxicity associated with cancer therapy, the development of targeted therapies to decrease lifelong cardiovascular risk in survivors will be challenging. These challenges include overcoming the reluctance of pharmaceutical companies to make large investments in drug development for small populations, litigation concerns, and difficulties in designing and conducting randomized clinical trials. There are also a number of ethical implications a pediatrician must consider when treating children with cardiomyopathy.664 We cannot confidently apply
the results of studies on adults to these survivors, especially because the restrictive cardiomyopathy in those exposed to cardiotoxic therapies in childhood differs from the dilated cardiomyopathy seen in children and adults from causes other than cancer therapy. There are also regulatory challenges, as exemplified by the 2011 decision by the European Medicines Agency that the cardioprotectant dexrazoxane is contraindi-
cated in children and adolescents with cancer. All of these challenges need to be addressed if new, evidence-based pediatric cancer regimens are to be developed that will reduce lifetime cardiovascular risk.

**Scientific Statement, Systematic Reviews, and Evidence-Based Guidelines**

**Scientific Statement**
The present scientific statement summarizes a large amount of evidence in the field of cardiotoxicity after treatment of cancer in children, adolescents, and young adults. The methods used to identify the existing evidence are based on literature searches along with the knowledge and experience of the experts. The authors avoided formulating specific recommendations. This statement will help inform professionals and patients to make the best clinical decisions based on the provided scientific evidence. A wide range of topics have been covered in detail, and pathophysiological aspects or future challenges have been highlighted within a fixed time frame. As a result, this statement is not meant to be a complete systematic review of the existing knowledge or an evidence-based guideline.

**Systematic Review**
A systematic review is the most intensive strategy of summarizing evidence and serves as one of the cornerstones of evidence-based medicine. In a systematic review, the first steps of evidence-based medicine are as follows: Formulate a clinically relevant question, perform an extensive search for literature and assess the methodological quality of the selected studies, and perform a meta-analysis when possible. A systematic review aims to minimize the occurrence of bias via the process of searching and summarizing the evidence. However, a disadvantage of systematic reviews is that it can take months to answer 1 question. The Cochrane Collaboration is the largest single provider of systematic reviews for health care, with ≈6000 systematic reviews included in the Cochrane Library. The Cochrane Childhood Cancer Group has been registered within the Cochrane Collaboration since 2006 (http://www.ccg.cochrane.org).

**Evidence-Based Guidelines**
Another important product of evidence-based medicine is an evidence-based guideline. The US Institute of Medicine of the National Academies defined clinical guidelines as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” A clinical guideline includes every step of evidence-based medicine. A systematic search for literature relevant to the intended key clinical questions and summaries of the selected evidence according to a set of validity criteria are included in clinical guidelines. The evidence is summarized in evidence tables for each separate clinical question, and conclusions are based on grading of evidence. Finally, recommendations are based on consensus of the evidence along with other considerations such as patient values, ethical issues, clinical experience, and costs. The arguments to recommend a clinical decision and the link between evidence and practice should be described transparently in an evidence-based guideline. It is important to realize that the term evidence-based refers to the entire process of evidence-based guideline development and does not apply solely to recommendations supported strongly with evidence. Because of lack of time and money, each guideline group decides how much time should be allotted to identify all relevant evidence. As a result, guidelines can have pitfalls. For example, suboptimal evidence summaries could make it difficult to keep knowledge on the subject up-to-date. Physicians could and should describe why they choose alternate options when they do not follow the recommendations formulated in the guideline.

The present scientific statement is not meant to be an evidence-based guideline. Specific recommendations for care have not been provided, and other initiatives are currently focused on guideline development for survivors of childhood, adolescent, and young adult cancer.

Within the worldwide community of research and care for survivors of childhood and adolescent cancer, initiative has been taken to develop worldwide guidelines based on discordance in existing guidelines for surveillance of late effects. Important questions, evidence tables, conclusion of evidence, and recommendations will be formulated. The link between evidence and recommendations has been described transparently in the observations of Kremer et al and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The surveillance of breast cancer after treatment for childhood and adolescent cancer has been completed by the International Late Effects of Childhood Cancer Guideline Harmonization Group. Other topics will be covered in the future, and collaboration will be sought with new groups that focus on developing guidelines for surveillance of late effects for survivors of cancer.

**Conclusions**
Although definitive data on which to base evidence-based guidelines for cardiovascular monitoring during cancer therapy are lacking, the developing field of cardio-oncology is beginning to provide clinicians with a better model to identify adverse cardiac effects of antineoplastic therapy. It is crucial that an optimal monitoring regimen is developed based on clinically based evidence. As clinicians continue to learn about the cardiovascular effects of cancer treatment, the importance of primary prevention becomes abundantly clear. The objective of effective monitoring is to identify signs of cardiac disease early enough to potentially prevent, reverse, or slow the deterioration of the structure and function of the heart. We must tailor therapies to decrease the risk of cardiotoxicity while balancing the beneficial effects of the cancer therapy. Further long-term prospective studies are needed to better understand the risks of cardiac events in this population and develop strategies to better treat the patient.
### Disclosures

#### Writing Group Disclosures

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†Modest.
*Significant.

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Key Words: AHA Scientific Statements ■ adolescent ■ antineoplastic agents ■ cancer ■ children ■ prevention and control ■ toxicity
Long-term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions: A Scientific Statement From the American Heart Association

Steven E. Lipshultz, M. Jacob Adams, Steven D. Colan, Louis S. Constine, Eugene H. Herman, Daphne T. Hsu, Melissa M. Hudson, Leontien C. Kremer, David C. Landy, Tracie L. Miller, Kevin C. Oeffinger, David N. Rosenthal, Craig A. Sable, Stephen E. Sallan, Gautam K. Singh, Julia Steinberger, Thomas R. Cochran and James D. Wilkinson

on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Basic Cardiovascular Sciences, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity and Metabolism

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In the article by Lipshultz et al, “Long-term Cardiovascular Toxicity in Children, Adolescents, and Young Adults Who Receive Cancer Therapy: Pathophysiology, Course, Monitoring, Management, Prevention, and Research Directions: A Scientific Statement From the American Heart Association,” which published ahead of print on September 30, 2013, and appeared in the October 22, 2013, issue of the journal (Circulation. 2013;128:1927–1995), a correction was needed:

On page 1927, an endorsement line was added, “Endorsed by the American Academy of Pediatrics.”

This correction has been made to the print version and to the current online version of the article, which is available at http://circ.ahajournals.org/content/128/17/1927.