

## Review Article

# Review of Cardiotoxicity in Pediatric Cancer Patients: During and after Therapy

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With the improvement in survival from childhood cancer, late effects of therapy are becoming more apparent. Cardiac disease, one of these late effects, has a significant impact on the life of survivors of childhood cancers. Most survivors are followed by primary care doctors and adult subspecialists after they have graduated from pediatric centers. Since much of the cardiac toxicity of therapy occurs years off of therapy, it is important for these physicians to be aware of how to monitor survivors for the development of cardiac toxicities. In this paper we will discuss the incidence of cardiac disease during treatment and in survivors, what treatment modalities contribute to its development and modalities utilized to screen for cardiac disease. Recommendations for posttherapy monitoring will be emphasized.

## 1. Introduction

Treatment for pediatric malignancies has greatly improved survival since the 1970s. According to SEER data, the mortality rate declined by almost 40 percent between 1975 and 1995 [1]. This decrease in mortality has been accompanied by an increase in the recognition of long-term side effects from the treatment of childhood cancers. The Childhood Cancer Survivor Study (CCSS) was established to monitor these side effects. The study has been following a cohort of patients, who were treated from 1970–1986 and had survived at least 5 years at enrollment in the study [2]. This cohort of survivors was found to have increased relative risk of a chronic health condition compared to their siblings of 3.3 (95% CI, 3.0–3.5) [3]. Chronic healthcare conditions attributed to cancer treatment include, but are not limited to, respiratory dysfunction, infertility, cognitive delays, cardiovascular disease, and renal failure [2, 3]. In a subanalysis of the CCSS population, 14,358 patients returned a survey regarding cardiovascular health [4]. Congestive heart failure had a prevalence of 1.7% versus 0.2% in siblings, valvular abnormalities of 1.6% in survivors versus 0.5% in siblings, and pericardial disease of 1.3% in survivors versus 0.3% among siblings. This increase risk highlights the need for survivors of childhood cancers to

be monitored for the development of cardiovascular disease long term after treatment.

Please note that this is not a systematic review, but an attempt to educate caregivers whose focus does not lie primarily in the fields of hematology-oncology regarding the pediatric cancer treatments which may place survivors at risk for developing cardiac dysfunction. It also includes recommendations for monitoring for the development of cardiac dysfunction. This paper is comprised of published data written in English which was compiled through Medline, with a focus on studies that included patients that were under the age of 18 at time of their cancer treatment. Due to the inclusion criteria, the reader should be aware of a potential bias regarding negative study results which are less likely to be published.

## 2. Risk Factors

The treatment of children with cancer includes chemotherapy, radiation, and surgery. Both chemotherapy and radiation therapy can contribute to the increased risk for cardiovascular disease that survivors of childhood cancer experience (see Table 1).

TABLE 1: Cancer therapies utilized in pediatric population associated with cardiotoxicity.

Type of therapy	Dose that places at highest risk	Time of usual presentation	Cardiac manifestations
Radiation therapy [65]	>30 gray to heart	Up to decades after treatment has ended	Pericarditis, coronary artery disease, valvular disease, arrhythmias
Anthracyclines [5, 7]	>300 mg/m <sup>2</sup> doxorubicin isotoxic cumulative dose	Acute: during therapy Chronic: months to years posttherapy (longer follow higher the incidence)	Acute-arrhythmias, hypotension Chronic-CHF
Cyclophosphamide [33, 34]	>150 mg/kg or >1.55 g/m <sup>2</sup> given as one dose or per one course	ECG changes: 1–3 days after therapy CHF: up to 2 weeks after therapy	CHF, Myocarditis
Cytarabine [33, 34]	High doses	3–28 days after initiation of therapy	Pericarditis, ventricular, and atrial arrhythmias
Cisplatin [33, 34]	Usually when receiving with other chemotherapy	Arrhythmias/hypotension: acute within hours Vascular toxicities: usually days after infusion but reports 4 and 18 mths post therapy	Arrhythmias Vascular toxicities (CVA, AMI)
Ifosfamide [34, 41]	Higher doses	6–23 days after first dose	CHF, arrhythmias

CHF: Congestive Heart Failure, ECG: Electrocardiogram.

**2.1. Anthracycline Therapy.** Anthracyclines are the class of chemotherapeutic agents that are most frequently linked to cardiac dysfunction in children. The traditionally used anthracyclines, doxorubicin, and daunorubicin were developed in the 1960s from the bacterial strain *Streptomyces peucetius* [5]. After or during administration of an anthracycline, patients can experience acute cardiac toxicity which manifests as acute hypotension or transient rhythm disturbances. This is usually transient and resolves without intervention [6]. Early chronic and late onset chronic cardiotoxicity manifests as a decrease in cardiac function which can lead to congestive heart failure (CHF). This is thought to be due to a decrease in left ventricular wall thickness, indicating a decrease in cardiac tissue [7–10].

The incidence of cardiac dysfunction postanthracycline therapy varies depending upon how cardiac dysfunction is defined and the length of time between the end of therapy and evaluation [11, 12]. In a retrospective cohort study of 6,493 patients who had received therapy on pediatric oncology trials with an anthracycline, Krischer et al. confirmed early cardiotoxicity (defined as congestive heart failure, abnormal measurements of cardiac function that prompted therapy to be disrupted, or sudden death from a presumed cardiac event) in 106 (1.6%) of the patients [13]. Van Dalen et al. followed a cohort of 830 patients for a mean of 8.5 years after anthracycline therapy and found that the risk of clinical heart failure was 2.5% [14]. Some studies evaluate patients for subclinical cardiac disease, patients that are not symptomatic from their cardiac dysfunction. In a systematic review including 25 different studies which each included >50 pediatric patients treated with an anthracycline, the reported frequency of subclinical cardiotoxicity varied from 0% to 57%. Recently De Caro et al. published a cross-sectional study evaluating the presence of subclinical cardiotoxicity in pediatric patients treated with anthracyclines. Seventeen of the 55 patients (30%) were identified as having

subclinical heart disease, but this did not correlate with alterations in the response of the cardiovascular system to dynamic exercise evaluated by cardiopulmonary exercise testing [15].

It has been well established that the development of congestive heart failure can occur at any anthracycline dose, but the risk for development increases with increased cumulative dose of anthracycline, especially doses  $\geq 300$  mg/m<sup>2</sup> [8, 13, 16–28]. It has also been noted that the longer it has been since a patient has received anthracycline treatment the higher their risk is for developing changes in cardiac function [10, 28, 29].

Earlier age at diagnosis and start of treatment with anthracycline-based therapy has correlated with an increase risk of cardiac disease in many studies that evaluated cardiac function after completion of therapy [8, 19, 25, 29, 30]. However, not every study demonstrates this correlation as noted in the systematic review by Kremer et al. [11] and other studies [24, 29, 31]. These studies involve small number of patients from 80–265. A larger study that evaluated 6,493 patients during therapy found that age at time of diagnosis was not a statistically significant predictor of cardiotoxicity, though children less than 9 had an increase risk of sudden death or CHF [13]. In general expert panels have recommend that patients who receive anthracycline therapy at an earlier age are monitored more closely for development of cardiac disease.

Female gender has also been associated with increased risk for cardiac disease in several studies [9, 13, 16, 32]. The reason female gender has been correlated with this increased risk is unknown. Lipshultz et al. hypothesized that it may be due to “differences in oxidative stress, differential expression of the multidrug-resistance gene, and body composition” [9]. As with age, there are some studies that do not echo this correlation [19, 29, 31]. The largest study that found

female sex as predictive factor for CHF was the study by Kirscher et al. As stated above this study evaluated the occurrence of cardiotoxicity during therapy. 585 out of the 6,493 patients received radiation to the heart which may have influenced some of their results [13]. Green et al. also found the correlation between female sex and development of cardiotoxicity in their case control study of 2,710 treated for Wilms tumor. In this study “the risk for girls was estimated to be approximately four times that for boys with the same level of cumulative doxorubicin exposure and radiation to the lung and the left abdomen ( $P, .005$ )” [16]. This leaves the question of whether radiation may be contributing to the increase rate of cardiotoxicity in females in these studies.

**2.2. Other Chemotherapeutic Agents.** Other chemotherapy agents that have cardiotoxic side effects include cyclophosphamide, ifosfamide, cytarabine, and cisplatin. Paclitaxel, fluorouracil, and amsacrine also have cardiotoxic side effects, but are rarely used in the first-line treatment of pediatric tumors [33, 34]. Newer agents, such as tyrosine kinase inhibitors, have also been found to be cardiotoxic [35–37]. For extensive review of cardiotoxic chemotherapeutic agents please refer to the review by Pai and Nahata [34].

Cyclophosphamide, an alkylating agent, can produce CHF or myocarditis. These symptoms are usually present by 14 days after therapy [34]. Cyclophosphamide is rarely cardiotoxic at low/standard doses but can cause severe cardiotoxicity when administered at high doses, such as when used for myeloablation in stem cell transplant [38, 39]. When Goldberg et al. recalculated the normal dose in mg/kg that is given during transplant as dose per  $m^2$ , patients with higher dose per  $m^2$  have an increased risk for cardiotoxicity. It was also noted that patients less than age 12 had far less cardiotoxicity compared to older patients, though younger patients tended to receive a lower dose/ $m^2$  than older patients [38]. The advantage to Goldberg study, though it had a small sample size of 84, is that the patients had not received other cardiotoxic therapy such as anthracycline therapy or radiation. The incidence of CHF in Golderbergs study was 0/32 in patients receiving  $\leq 1.55 g/m^2$  and 6/52 in patients receiving  $>1.55 g/m^2$ . Van der Pal et al. evaluated a cohort of 601 patients of which 514 had evaluable echocardiograms. 164 of these patients received  $<10 g/m^2$  of cyclophosphamide and 60 received  $>10 g/m^2$ . Their analysis did not find a correlation between high doses of cyclophosphamide and decrease in left ventricular shortening fraction, but this could be due to the fact that all but 10 of the patients also received other cardiotoxic therapy.

Ifosfamide, also an alkylating agent, can illicit congestive heart failure or arrhythmias [34, 40–42]. CHF usually occurs within 6–23 days after initiation of ifosfamide and the risk of CHF is generally thought to increase with higher dose delivery of the medication [41, 42], though, as with cyclophosphamide, study by van der Pal et al. did not support this correlation.

After administration of cytarabine, an antimetabolite, patients are also at risk for cardiac complications. Review of the literature also reveals case reports of pericarditis

associated with the administration of cytarabine [43–45]. It is also associated with atrial and ventricular arrhythmias along with CHF [33, 46–48]. These complications are rare and associated with administration of high doses.

Cisplatin has been reported to be associated with arrhythmias in several case reports [49–52]. Most of these reports were in patients receiving cisplatin in combination with other chemotherapeutic drugs. Cisplatin decreases levels of calcium and magnesium, both of which can increase the risk for arrhythmias if not corrected [33]. There have been case reports of vascular toxicity and acute myocardial infarctions/cerebral vascular accidents with the administration of cisplatin, specifically as part of the treatment of germ cell tumors [53–57]. The rare occurrence of vascular accidents should not deter clinicians from using this efficacious drug, but even in young patients one needs to consider vascular toxicities in a differential diagnosis of a patient presenting with consistent symptoms following cisplatin therapy [54].

Tyrosine kinase inhibitors include drugs such as imatinib and sunitinib. Imatinib (Gleevec) is the most well-known tyrosine kinase inhibitor and is used mainly for the treatment of chronic myelogenous leukemia, but more recently has also been used in phase I and II studies treating relapsed solid tumors [58–61]. Tyrosine kinase inhibitors as a drug class have been linked with development of left ventricular dysfunction, heart failure, and arrhythmias [35, 37, 62]. These events have been rarely reported with imatinib [63, 64], but the incidence of symptomatic events in patients treated with sunitinib or sorafenib was 18% in an observational study of 74 patients [62]. This emphasizes the importance of closely monitoring patients for the development of cardiotoxicity when treating them with a tyrosine kinase inhibitor, especially if they have previous cardiac disease, risk factors for the development of cardiac dysfunction, or if one is employing a newer, less studied tyrosine kinase inhibitor.

There are no specific guidelines for monitoring patients treated with chemotherapy drugs besides, anthracyclines, likely due to the relatively low frequency of these events. Providers should be aware that cyclophosphamide, ifosfamide, cytarabine, cisplatin, and tyrosine kinase inhibitors may induce cardiotoxicity so that they can watch for signs and symptoms of these events during and after treatment.

**2.3. Radiation Therapy.** Radiation therapy that is directed at the mediastinum increases the risk for cardiovascular damage and sequela postcancer therapy. Radiation to the mediastinum is most often utilized for the treatment of Hodgkin's lymphoma and breast cancer. Presentations of radiation damage include pericarditis, cardiomyopathy, coronary artery disease (which may lead to acute myocardial infarction), valvular disease, and conduction system arrhythmias [65, 66]. Pericarditis clinically presents either as sudden onset of pleuritic chest pain, dyspnea, fever, and friction rub or can be clinically silent. On ECG (electrocardiogram), ST segment elevation and/or T wave inversion can be seen. Patients exposed to thoracic radiation can develop systolic and/or diastolic dysfunction (with diastolic being more common) and go on to develop dilated, hypertrophic, and restrictive

cardiomyopathies [67]. Radiation primarily affects the mitral and aortic valves [65, 68, 69] and presents with fibrosis with or without calcifications [67]. Conduction system arrhythmias can be early, which are usually transient or late, occurring months to years after treatment. Late conduction abnormalities include atrioventricular nodal bradycardia, intranodal blocks, and all other types of heart block [65, 67].

Incidence of radiation-induced cardiovascular damage varies depending upon several variables including the end point measured, time postcompletion of therapy, radiation techniques, and dosing. Pericarditis prior to newer radiation techniques was seen in up to 40% of the patients, but with new techniques and attempt at lowering doses this incidence has been greatly reduced [65]. In study by Carmel and Kaplan the incidence of pericarditis in patients treated for Hodgkins was reduced from 20% with whole pericardial irradiation to 2.5% when subcarinal blocking was utilized along with thin lung block technique [70]. Adams et al. screened asymptomatic patients who were diagnosed with Hodgkin's disease prior to age 25 that were  $\geq 5$  years out from therapy with ECG, echocardiograms, and exercise stress tests. The majority (41/47) of the patients received 36–44 gray of radiation. 42.6 percent of these patients had a significant valvular defect, 5/43 had findings suggestive of systolic dysfunction, and 16/43 had findings suggestive of diastolic dysfunction. 35/43 had conduction abnormalities including sinus tachycardia and bradycardia [71]. In pediatric studies evaluating patients that had received doses of radiation  $\leq 25$  gray the incidence of cardiac dysfunction seen on echocardiograms or nuclear imaging were much lower ranging from 0–2.5% [22, 72, 73]. In a study evaluating patients for death from cardiac dysfunction in patients who were treated for Hodgkin's disease 4/544 patients treated at age  $< 19$  died from valvular heart disease, CHF, pericarditis or cardiomegaly, 6/544 died from an acute myocardial infarction. All of the patients that died had received a radiation dose of  $> 30$  gray. There were no deaths in the group of patients treated at age  $< 19$  that had received  $< 30$  gray [22, 72–74].

The factors that increase the risk of developing postradiation cardiotoxicity are the volume of the heart exposed to the radiation beam, higher total dose of radiation [66, 74], the length of followup time from radiation (the farther out from therapy the more likely you will develop cardiotoxicity), younger age at exposure and higher fractionated dose [65, 75]. The majority of the trials involving pediatric patients that evaluate for cardiac radiation toxicity focus on Hodgkin's disease survivors, have small sample sizes, recruit patients postcompletion of therapy and include patients treated with chemotherapy. Patient's treated with lung irradiation for solid tumors such as Ewing's sarcoma or Wilm's tumor can experience an increased risk for cardiac disease, though there are limited studies evaluating cardiotoxicity in these subgroups [16, 31].

### 3. Monitoring

Patients receiving therapy that has potential cardiotoxicity require close monitoring during and after therapy. The goal of monitoring during therapy is to identify early signs of cardiotoxicity in order to modify a patient's therapeutic plan so that the risks of further development of cardiac disease are decreased. These modifications of therapy have to be balanced with risk of decreasing antitumor effect of the therapy. Posttherapy patients may require life-long monitoring for late cardiotoxic effects, especially if they have received mediastinal radiation or higher doses of anthracyclines. The following is an analysis of several different modalities available for the monitoring of cardiotoxicity.

**3.1. Echocardiogram.** Echocardiograms are the most frequently used modality in the screening for cardiac disease during or after therapy. Echocardiograms are noninvasive and readily available. They provide means to evaluate the left ventricular ejection fraction (LVEF) along with systolic and diastolic cardiac function. As per Altena et al., "diastolic measurements are probably the most sensitive to early changes in cardiac function [76]." Many studies also use the measurement of fractional shortening (FS). In the only published guidelines for monitoring therapy during anthracycline treatment in pediatric population [77] Steinherz et al. recommended that a drop in FS by an absolute value of  $\geq 10$  percentile units or  $FS \leq 29\%$  be considered a significant deterioration of function [78]. The disadvantage of echocardiograms is that they are preload dependent for several of the parameters and are dependent on the expertise and interpretation of echocardiographer [76]. The question of whether decline in cardiac function during therapy correlates with long-term development of cardiac impairment still remains [79]. In the evaluation of pericarditis echocardiograms provide information regarding long-term sequela of this disorder such as development of a pericardial effusion, but may be normal in the setting of acute pericarditis [80]. Echocardiograms also provide useful information after radiation therapy by evaluating for valvular defects.

**3.2. Radionuclide Angiocardiography (RNA) (Includes MUGA and Radionuclide Ventriculography).** RNA is considered the gold standard for estimating LVEF. Unlike echocardiograms, there is low intraindividual and intraobserver variation when obtaining and analyzing results, but only limited information regarding diastolic function is obtained. RNA's also expose patients to radiation [76]. Another concern with using LVEF as a screening tool lies in its ability to accurately predict which patients will go on to develop cardiac impairment [76, 81]. Steinherz et al. included RNA testing along with an echocardiogram as part of their recommendations for monitoring for deterioration of function during anthracycline therapy [78]. Despite these recommendations, RNAs are not widely utilized in protocols enrolling pediatric cancer patients for monitoring for cardiotoxicity of the therapy [77]. In order to minimize confounding variables, it is recommended that RNAs or echocardiograms are obtained

at least 3 weeks after anthracycline therapy, when patients are normothermic and have a hemoglobin greater than 9 g/dL [77].

**3.3. Electrocardiograms (ECG).** ECGs are a noninvasive, inexpensive tool in the evaluation of conduction abnormalities that may develop after radiation and during the administration of certain chemotherapeutic agents. In addition ECGs can demonstrate signs of cardiomyopathies. They do not provide any information regarding LVEF and interpretation of the study varies between observers [76]. There is some evidence to suggest that prolonged corrected QT intervals may predict cardiac disease [82]. For the above reasons, obtaining an ECG is recommended as part of monitoring for cardiac dysfunction in some protocols and as part of long-term followup.

**3.4. Biomarkers.** Due to the concern regarding the ability of echocardiograms and RNAs to predict which patients will go on to develop cardiac impairment during treatment [76, 79, 81] and lack of sensitivity to detect early stages of cardiomyopathy [83–85], there has been much recent interest in the use of biomarkers. Biomarkers include B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), cardiac troponin T (cTnT), and cardiac troponin I (cTnI). Mavinkurve-Groothuis wrote a review regarding biomarkers in the detection of pediatric anthracycline cardiotoxicity. The review included a total of 14 studies with patient numbers ranging from 15–63 per study and time from last dose of anthracycline until the evaluation point varying from immediately until 17.5 years after therapy. These variations made it difficult for the authors to make recommendations regarding the most sensitive method to use to detect cardiomyopathy, and when the best timing for obtaining echocardiograms and biomarkers is. Ultimately, it was concluded that there was a significant relation between elevated biomarkers and cardiac dysfunction in 6 of the 14 studies [83]. Mavinkurve-Groothuis et al. recently published a study on a cohort of 122 asymptomatic survivors, a large number compared to previous studies of this type. None of the patients had an elevated cTnT and 16 had elevated NT-pro-BNP levels [86]. The elevated NT-pro-BNP levels correlated with increased dose of anthracycline received, but not with changes in ejection fraction.

It appears that biomarkers for cardiomyopathy may provide some clinical utility, but studies with larger number of patients need to be performed. It will also be necessary to serially follow children with elevated levels long term in order to monitor the future development of cardiomyopathy and to determine best timing of biomarkers.

#### 4. Monitoring during Therapy

The only published guidelines for monitoring for cardiotoxicity during therapy in pediatrics was published by Steinherz et al. in 1992 [78]. These guidelines pertain specifically to monitoring when anthracyclines are being administered or a patient receives mediastinal radiation. Prior to the beginning

of therapy, ECG, echocardiogram, plus/minus RNA should be collected. When the total anthracycline dose given is  $<300 \text{ mg/m}^2$ , an echocardiogram should be obtained before every other course of anthracycline administration. Once a patient has received greater than  $299 \text{ mg/m}^2$ , an echocardiogram should be performed before every cycle of anthracycline administration. The recommendation that is currently not frequently followed [77] is the addition of RNA once anthracycline dose is  $>399 \text{ mg/m}^2$  or  $>299 \text{ mg/m}^2$  and patient has received radiation therapy  $>1000 \text{ cGy}$  to mediastinum.

#### 5. Late Effect Monitoring Recommendations

The Children's Oncology Group (COG) published the most recent recommendations for long-term followup of childhood cancer survivors on line at <http://www.survivorshipguidelines.org/> [87]. These recommendations give detailed guidelines regarding frequency of monitoring based on the age of exposure to anthracycline, total dose of anthracycline received, and administration of potentially cardiotoxic radiation therapy. Page 34 and 35 of the guidelines pertain particularly to the cardiac monitoring after anthracycline dosage. In order to calculate total dose of anthracycline a patient received, one must convert the dose to doxorubicin isotoxic doses. Recommended conversions are doxorubicin multiply the dose by 1; daunorubicin multiply the dose by 0.833; epirubicin multiply the dose by 0.67; idarubicin multiply the dose by 5; mitoxantrone multiply the dose by 4. These dose conversions are per the COG long-term followup guidelines, but there is "a paucity of literature" to support the conversions. They are solely intended to be used to base monitoring on. Pages 91 and 92 pertain specifically to monitoring for cardiotoxicity after radiation therapy. Modalities of monitoring include scheduled echocardiograms's (ECG), detailed history and physical exam. For timing of echocardiograms or MUGA scan, please refer to Table 2. The Scottish Intercollegiate Guidelines Network (SIGN) has also developed long-term followup of survivors of childhood cancer guidelines that were published online in 2004. They recommend that echocardiograms are obtained at regular intervals during treatment with anthracyclines and every three years thereafter in patients who have received a modest dose  $<250 \text{ mg/m}^2$ . A detailed cardiac assessment should be performed for survivors of childhood cancer who are pregnant or planning a pregnancy or who wish to take part in competitive sports. As far as radiation they state that "health-care professionals should be aware that mediastinal irradiation over 30 Gy is a risk factor for cardiac disease later in life and monitoring is necessary." Details of this monitoring are not specifically given [88].

Another key component to long-term followup of patients is to screen for cardiovascular risk factors. This screen includes a fasting lipid profile, smoking history, family history of early coronary artery disease in expanded first degree pedigree (Male  $\leq 55 \text{ y}$ ; Female  $\leq 65 \text{ y}$ ), blood pressure (BP) on 3 separate occasions interpreted for age/sex/height, body mass index (BMI), fasting glucose (FG), and physical

TABLE 2: Timing of echocardiograms or MUGA scan postcancer therapy as per children's oncology group long-term followup guidelines for survivors of childhood, adolescent, and young adult cancers version 3.0 [87].

Age at treatment	Radiation with potential impact to the heart	Anthracycline dose converted to doxorubicin isotoxic dose	Recommended frequency
<1 year old	Yes	Any	Every year
	No	<200 mg/m <sup>2</sup>	Every 2 years
1–4 years old	No	≥200 mg/m <sup>2</sup>	Every year
		Any	Every year
	Yes	<100 mg/m <sup>2</sup>	Every 5 years
		≥100 to <300 mg/m <sup>2</sup>	Every 2 years
≥5 years old	Yes	≥300 mg/m <sup>2</sup>	Every year
		<300 mg/m <sup>2</sup>	Every 2 years
		<200 mg/m <sup>2</sup>	Every 5 years
	No	≥200 mg/m <sup>2</sup> to <300 mg/m <sup>2</sup>	Every 2 years
		≥300 mg/m <sup>2</sup>	Every year
		Any age with decrease in serial function	Every year

activity history [89]. Kavey et al. separates patients into three stratifications high, moderate, and at risk. In general cancer survivors are considered to be at risk for cardiovascular disease, but if they have 2 or more risk factors, as per above, they are considered to be at moderate risk. When a patient is considered to be at moderate risk from at risk the goal for LDL (low density lipoprotein) changes from ≤160 mg/dl to <130 mg/dl, BMI goal from ≤95% to ≤90% and BP goal from ≤95% + 5 mm Hg to just <95%. Goal for FG is <100 mg/L and Hemoglobin A1c < 7% regardless of risk stratification. In general lifestyle modifications are recommended if patients do not meet these goals with close followup and then possible medications in the future to treat hyperlipidemia and hypertension. In the case of FG > 125 an endocrine referral needs to be made to initiate treatment for diabetes mellitus. These recommendations were published by the American Heart Association and endorsed by the American Academy of Pediatrics.

## 6. Conclusion

Currently, there is ongoing research into developing methods to deliver treatment for childhood cancers that reduce the risk of developing long-term sequela from treatment. Different formulations of anthracyclines have been and continue to be developed that are hoped to be less cardiotoxic. There is clinical trial literature to support that liposomal doxorubicin is less cardiotoxic than doxorubicin. Also, pretreatment with dexrazoxane has been found to decrease the risk of anthracycline-induced CHE, but most of these studies have been performed in adults [90, 91]. Pediatric clinical trials continue to be developed to evaluate if we can decrease doses of cardiotoxic chemotherapeutic agents or reduce radiation therapy doses in order to prevent long-term side effects from the therapy without decreasing survival. Hodgkin's lymphoma is a good example of this. Doses of radiation

administered in modern trials have been greatly reduced. The most recently closed COG trial for intermediate risk Hodgkin's lymphoma evaluated whether or not radiation can be eliminated based on response to multiagent chemotherapy.

Until we can eliminate the cardiotoxic side effects of treatment for pediatric cancers it is important that clinicians providing care to survivors are aware of the potentially cardiotoxic treatments their patients have received and to be well versed in the methods used in the detection of cardiotoxic developments. This is to try and initiate early treatment and hopefully reduce worsening of symptoms. Well-designed prospective studies that evaluate monitoring modalities and the frequency at which monitoring should occur have yet to be published. There are online guidelines available that are based on review of the current literature and expert opinion. The COG and SIGN have published guidelines that are accessible to clinicians and families for reference online at <http://www.survivorshipguidelines.org/> and <http://www.sign.ac.uk/guidelines/fulltext/76/index.html> [88]. These are not to take place of clinical judgment, but to serve as a good starting point for designing a monitoring plan [87]. Patients need also to be made aware of their risk so that they can implement lifestyle modifications that will decrease their risk of development of cardiac disease.

## Conflict of Interests

I, Joy M. Fulbright, as the author of the paper, do not have any direct financial relations with any commercial identity mentioned in this paper that might lead to a conflict of interests.

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