Curr. Treat. Options in Oncol. (2019) 20: 56
DOI 10.1007/s11864-019-0658-x

Cardio-oncology (MG Fradley, Section Editor)

Pediatric Cardio-Oncology: Development of Cancer Treatment-Related Cardiotoxicity and the Therapeutic Approach to Affected Patients

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Published online: 25 May 2019

This article is part of the Topical Collection on *Cardio-oncology*

Keywords Anthracycline · Cardiomyopathy · Cardio-oncology · Cardiotoxicity · Chemotherapy · Heart failure · Onco-cardiology · Pediatric cardiology

Opinion statement

The past 5 decades have seen significant improvements in outcomes for pediatric patients with cancer. Unfortunately, children and adolescents who have been treated for cancer are five to six times more likely to develop cardiovascular disease as a result of their therapies. Cardiovascular disease may manifest in a plethora of ways, from asymptomatic ventricular dysfunction to end-stage heart failure, hypertension, arrhythmia, valvular disease, early coronary artery disease, or peripheral vascular disease. A number of treatment modalities are implicated in pediatric and adult populations, including anthracyclines, radiation therapy, alkylating agents, targeted cancer therapies (small molecules and antibody therapies), antimetabolites, antimicrotubule agents, immunotherapy, interleukins, and chimeric antigen receptor T cells. For some therapies, such as anthracyclines, the mechanism of injury is elucidated, but for many others it is not. While a few protective strategies exist, in many cases, observation and close monitoring is the only defense against developing end-stage cardiovascular disease. Because of the variety of potential

outcomes after cancer therapy, a one-size-fits-all approach is not appropriate. Rather, a good working relationship between oncology and cardiology to assess the risks and benefits of various therapies and planning for appropriate surveillance is the best model. When disease is identified, any of a number of therapies may be appropriate; however, in the pediatric and adolescent population supportive data are limited.

Introduction

There are more than 1.7 million new diagnoses of cancer each year in the USA, and in pediatrics (≤19-years-old), cancer is diagnosed in 15,700 new patients each year (Table 1) [3]. Recent advances in cancer therapy have led there to be 15.5 million survivors of cancer in the USA [4], and the 5-year survival for all pediatric cancer types is greater than 80% yielding ~ 450,000 total survivors of pediatric cancer [1]. Mixed with this success in treatment is the unintended consequence of cancer treatment-related cardiotoxicity (CTRC) [5, 6]. Indeed, cardiovascular disease has emerged as a leading cause of both morbidity and mortality for survivors of pediatric cancers [7]. Based on data from the Childhood Cancer Survivor Study (CCSS) and other studies, patient- and treatment-related risk factors for developing CTRC have been identified including younger patient age, female gender, African-American race, underlying heart disease, total anthracycline dose, concomitant radiation exposure, pre-modern therapies, and time since therapy. Patients who have been treated for cancer are five to six times more likely to develop cardiovascular disease of various etiologies, including symptomatic heart failure, asymptomatic ventricular dysfunction, valvular disease, coronary disease, arrhythmias, autonomic dysfunction, vascular disease, and pericardial disease [8, 9].

Development of cancer treatment-related cardiotoxicity in pediatric patients

Initial reports of CTRC followed soon after the introduction of anthracyclines as chemotherapy in the 1960s and 1970s [10, 11]. Since then, therapies reported to cause CTRC have included anthracyclines, antimetabolites (e.g., 5-fluorouracil, methotrexate), anti-microtubule agents (e.g., paclitaxel), alkylating agents (e.g., cyclophosphamide, busulfan), small molecule tyrosine kinase inhibitors (e.g., sorafenib), monoclonal antibodies (e.g., trastuzamab, rituximab), interleukins, chimeric antigen receptor T cells (CAR-T), immune checkpoint inhibitors, radiation therapy, and other agents used less frequently [12]. Specific therapy regimen choices are determined by the patient's specific pathologic and molecular diagnosis, clinical features, and site and extent of disease.

Anthracyclines

The overwhelming majority of data pertaining to the mechanism of CTRC are related to anthracyclines. A number of pathways are involved, including mitochondrial DNA damage, apoptosis from generation of reactive oxygen species, and damage to nuclear DNA through direct interaction of anthracyclines on topoisomerase 2ß (Fig. 1) [9, 13]. The presumed safe range for doses of chemotherapy (i.e., unlikely associated with CTRC) has decreased steadily over time, with a number of studies showing effects on echocardiographic

Table 1. ***Distribution of cases of childhood and adolescent cancers in the U.S. with common, potentially cardiotoxic treatment exposures*****. Treatment is highly variable based on diagnosis, patient age, disease stage, site of disease, and several other factors. Represented in this table are general trends only. Modified from Figure 1 in [1] and [2]**

	Proportion of cancers, children (0–14 year)	Proportion of cancers, adolescents (15–19 year)	Cumulative anthracycline dose^	Potential thoracic radiation exposure scenarios
Leukemia				
Acute lymphocytic leukemia	26%	8%	Low†	Craniospinal photon radiation
Acute myeloid leukemia	5%	4%	High	–
Lymphoma				
Hodgkin lymphoma	4%	15%	Low or high†	Site dependent
Non-Hodgkin lymphoma	6%	8%	Low or high†	Site dependent
Central nervous system*	21%	10%	–	Craniospinal photon radiation
Neuroblastoma	7%	–	Low†	Site dependent
Retinoblastoma	3%	–	–	–
Wilms tumor	5%	–	Low†	Select metastatic patients or abdominal radiation
Bone tumors**	4%	7%	High	Select metastatic patients
Soft tissue sarcoma	7%	7%	High‡	Select metastatic patients
Germ cell tumors	3%	12%	–	–
Carcinoma and melanoma	4%	20%	–	Site dependent

*Includes ependymoma, astrocytoma, and medulloblastoma
**Includes osteosarcoma and Ewing sarcoma
^High (cumulative > 250 mg/m^2) and low dose (< 250 mg/m^2) applies to doxorubicin or doxorubicin equivalent of other anthracyclines
†Anthracyclines included only in select high and intermediate risk regimens, not all treatment protocols
‡Anthracycline inclusion dependent on the specific tumor type and therapy treatment selected included only in select high-risk regimens, not all treatment protocols
Table taken from Anderson's Pediatric Cardiology, 4th Edition (Elsevier)

parameters after just a single dose administration (doxorubicin equivalent 60 mg/m^2) [14, 15]. The current generally accepted definition of low- vs. high-dose anthracycline exposure is 250 mg/m^2 doxorubicin equivalent.

Radiation

Radiation therapy also increases the risk for development of CTRC, accounting for much of the reported injury to the pericardium, coronaries, conduction pathways, and myocardium [9]. Again, there is a dose dependence of injury; however, it has not been established whether there is a limit below which injury does not occur, rather the dose may affect timing of manifestation [16]. Mechanisms of injury include induction of proinflammatory cascades, endothelial injury, generation of fibrosis, and initiation of oxidative stress [9, 16]. Alternate therapeutic approaches, such as proton therapy, may spare the heart from

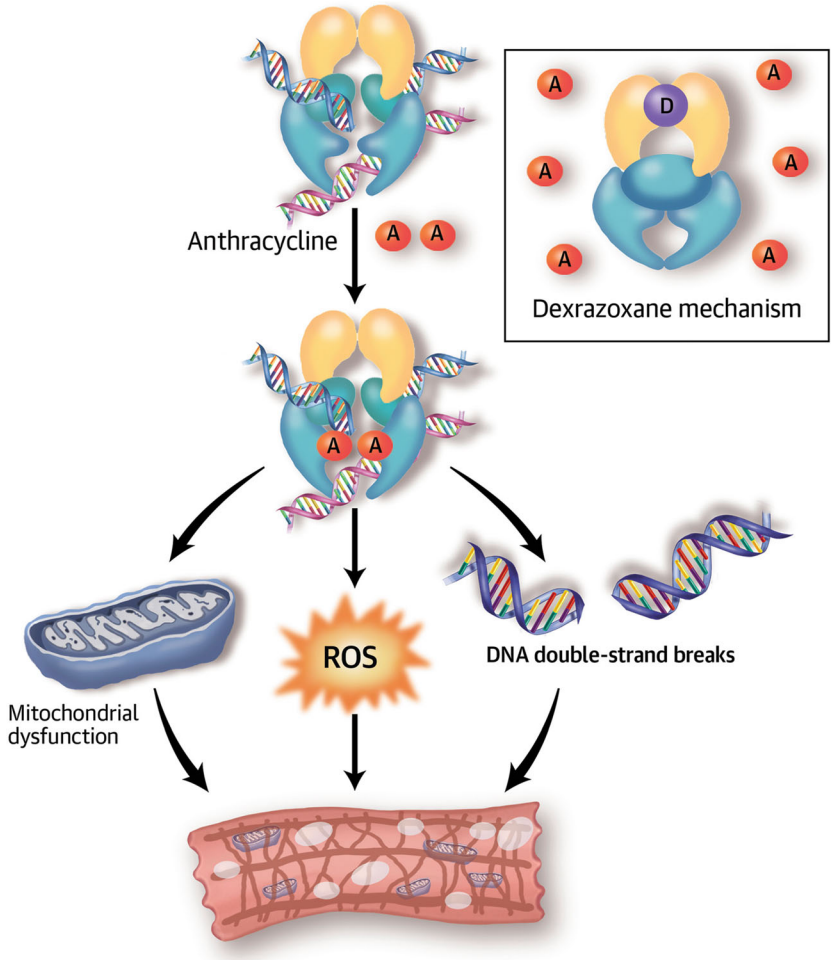

Fig. 1. *Mechanism of anthracycline-induced cardiotoxicity*. Anthracyclines (A) interact directly with topoisomerase 2ß, disrupting its normal function and inducing breaks in DNA. This leads to defects in mitochondria and increase in production of reactive oxygen species (ROS). The inset shows dexrazoxane (D) exerting a protective effect by blocking the binding of anthracycline to topoisomerase 2 ß. Reprinted from the Central Illustration in [13], with permission from Elsevier and the American College of Cardiology.

radiation exposure and thus reduce cardiotoxicity although this is not yet definitively proven [17].

New cancer therapies

Several emerging cancer therapies also exhibit potential effects on the cardiovascular system. These novel therapies, including targeted cancer therapies, cancer immunotherapy, and chimeric antigen receptor T cells (CAR-T), have revolutionized cancer therapy in the era of precision medicine. However, with these advances has come the recognition of potential adverse effects, including the potential for CTRC.

Targeted cancer therapies

Our improved understanding of some of the driving forces of cancer and molecular pathways has led to the development of directed therapies [18••].

These mechanisms include the development of cancer-directed antibodies and small molecules to inhibit the various molecular pathways (e.g., kinase inhibition—PDGFR, VEGF, HER2). This is exemplified by the successful introduction of imatinib to treat chronic myeloid leukemia, which was FDA approved in 2001, and specifically for pediatric patients in 2003 [19–23]. Inhibition of kinases became an attractive therapeutic strategy given their function as regulators of cellular proliferation, differentiation, and survival as well as evidence of tyrosine kinase dysregulation in the setting of malignancy [19]. Presently, over 20 small molecule tyrosine kinase inhibitors are available for clinical use [24]. Notably, off-target binding with disruption of cellular signaling has been implicated in the adverse cardiac effects associated with tyrosine kinase inhibitors, which vary considerably across therapeutic agents [25]. Kinase inhibitors have been associated with hypertension, thromboembolism, pulmonary hypertension, and ventricular dysfunction [26–30]. It is unclear if the risk profile of these agents will differ between adults and children.

Another example is trastuzumab, a humanized monoclonal antibody, which has been shown to be a significant step forward in the treatment of human epidermal growth factor 2 positive (HER2+) breast cancers. While it is currently the standard of care in this patient population, the most frequent adverse outcome with the use of trastuzumab is CTRC [31]. In pediatric patients, other antibody therapies have demonstrated effectiveness in various pediatric cancers [32–35]. Similar to the cardiotoxic effects seen in small molecule inhibitors of kinases, monoclonal antibodies with a similar mechanism of action can also cause CTRC [36]. Completed clinical trials have shown the ability to offer protection against CTRC with these agents [37], and other trials are underway to better understand this process [38].

Cancer immunotherapy

Cancer immunotherapy represents an important breakthrough in the approach to cancer treatment, with the ability to target the host immune response itself [39]. There are now multiple FDA-approved immune checkpoint inhibitors with applications in metastatic melanoma, lung cancer, and renal cancer [40]. These monoclonal antibodies block inhibitory signaling downstream from either cytotoxic T lymphocyte-associated antigen 4 or programmed cell death protein-1 and thereby prevent tumor evasion of the immune response through T cell downregulation [41]. While generally well tolerated, these medications can disrupt the balance between self-tolerance and autoimmunity. Cardiac toxicity is rare, occurring in < 0.1% of patients receiving these medications [39, 42]. However, severe and potentially fatal myocarditis as well as arrhythmias have been reported with their use and represent important considerations as these therapies expand into the pediatric population [42–47]. Recent clinical guidelines have been published with recommendations for management of adverse events related to use of immune checkpoint inhibitors [48••].

Chimeric antigen receptor T cells

Despite significant advances, patients with relapsed or refractory disease after anthracycline therapy demonstrate poor survival [49••]. CAR-T cell therapy, designed to specifically target cancer cells, has achieved a nearly 90% overall

remission rate in children with refractory or relapsed acute lymphocytic leukemia [49•, 50, 51]. Unfortunately, cytokine release syndrome can occur and may result in vasoplegic shock and/or ventricular dysfunction. While tocilizumab has been shown to be beneficial in treating these side effects, hypotension necessitating the use of inotropic support is common, and ventricular dysfunction can persist [52, 53].

Treatment strategies in pediatric cancer treatment-related cardiotoxicity

Primary prevention of CTRC development is the ultimate goal in patient management for cardio-oncology. Short of that, developing surveillance tools that allow early intervention for secondary treatment once CTRC is present becomes the best approach. Continuation of cancer therapy in the face of CTRC then becomes an assessment of risk vs. benefit between the oncologist, cardiologist, and patient.

Cardioprotection and prevention

Strategies for the primary prevention of CTRC range from modified dosing strategies to alternative anthracycline formulations to use of medications thought to prevent myocardial damage.

Alternate dosing schedules and anthracycline derivatives

The effect of dosing schedule and various anthracycline derivatives on development of CTRC have been summarized in a systematic review by van Dalen et al. [54••]. Anthracycline infusion duration of 6 h or longer reduced the risk of developing subclinical cardiac injury or heart failure, and liposomal-encapsulated doxorubicin had a favorable profile regarding CTRC when compared to standard doxorubicin. There was no protective benefit with lower peak doses of anthracycline [55–58].

Preventing cardiotoxicity with pharmacologic intervention

Dexrazoxane (Zinecard), a derivative of EDTA that acts as a chelator of iron, was first approved by the Food and Drug Administration (U.S.) for prevention of cardiomyopathy associated with doxorubicin in breast cancer patients in 1991, and in 2014, it was designated an orphan drug for prevention of cardiomyopathy in pediatric and adolescent patients treated with anthracyclines. The primary protective mechanism against anthracycline CTRC is currently thought to be due to a decrease in the formation of superoxide free radicals, and prevention of the action of anthracyclines on topoisomerase 2ß (Fig. 1). The use of dexrazoxane to prevent CTRC in children with leukemia has been reported as far back as two decades, and evidence of cardioprotection is manifested by blunted elevations in troponins and natriuretic peptides and prevention of ventricular remodeling without negatively impacting long-term survival [59–62]. More recent data have supported its use in patients with sarcoma undergoing anthracycline therapy [63–65]. Despite the evidence for cardioprotection, dexrazoxane is not used in a

standardized fashion across all diagnoses [66]. Concerns over impact on the treatment effect of anthracyclines and risk of secondary malignancies may limit its use, although registry studies have argued against these claims in patients with a variety of childhood cancers [67••, 68••, 69].

Commonly used cardiovascular medications have also demonstrated at least partial amelioration of CTRC in adults. Angiotensin converting enzyme (ACE) inhibitors [70••], beta blockers [70••, 71], and HMG-CoA reductase inhibitors (statins) all show benefit [72]. Similar data in pediatric and adolescent patients are limited. In survivors of pediatric cancer placed on an ACE inhibitor, wall stress was reduced without other functional benefits [73], while another study of the same drug reported that echocardiographic indices were initially preserved but the benefit was lost after 6 years on therapy [74]. In a study of patients with acute lymphoblastic leukemia receiving anthracycline chemotherapy, pretreatment with a beta blocker prevented changes in echocardiographic measures and serum cardiac troponin; however, numbers were small [75]. Currently, a study is ongoing to assess the effect of the beta blocker carvedilol in preventing development of left ventricular dysfunction in survivors of childhood cancer [76•]. There are no data available on the cardioprotective effect of statins in children.

Non-pharmacologic interventions

Evidence from animal models suggests that aerobic exercise can mitigate certain aspects of CTRC when employed before, during, or after therapy. Multiple mechanisms for this benefit have been proposed, but the specific pathways remain unlcear [77]. In patients, the benefits of exercise include improvement in cardiovascular function, body composition, immune function, chemotherapy completion rates, muscle strength and flexibility, and mood; and reduction in medication side effects, stress, and anxiety [78••].

Surveillance for development of CTRC

Guidelines are available for monitoring adult patients undergoing cancer therapy, covering assessment of the cardiovascular system from diagnosis through survivorship [78••, 79••, 80]. No such unified guidelines exist in pediatric oncology for cardiovascular assessment during therapy, though treatment protocols do incorporate periodic monitoring in appropriate settings [81]. However, formalized surveillance recommendations for those patients who have completed cancer therapy are produced by the Children's Oncology Group (COG), most recently updated in 2018 (www.survivorshipguidelines.org). These guidelines include recommendation for exam, electrocardiogram (ECG), and echocardiogram; they do not include specific imaging protocols or use of serum biomarkers.

Studies in adult patients have demonstrated that frequent surveillance during and immediately after anthracycline administration can detect subclinical asymptomatic ventricular dysfunction in ~ 10% of patients [82••]. The importance of early identification of CTRC was demonstrated by Cardinale et al., with clinically important response to cardiovascular treatment following early diagnosis and initiation of treatment, and with delay in treatment of just 1–2 months significantly reducing the proportion of patients responsive to therapy which ultimately affected outcomes [82••, 83]. And recent data in children treated for acute myeloid leukemia show that early CTRC (i.e., during on-

protocol therapy) was significantly associated with reductions in event free survival and overall survival over a 5-year follow-up [84•].

Electrocardiography

Most chemotherapy protocols include serial assessment of the ECG, with emphasis on the corrected-QT interval in order to reduce likelihood of the development of *torsades de pointes* [78••]. Monitoring for prolongation of the QT interval and management of electrolytes are important when QT prolonging medications are required for therapy (e.g., arsenic trioxide) and/or the management of therapy- and disease-related side effects (e.g., 5-HT_3 antiemetics, methadone for pain).

Echocardiography

Studies of CTRC in pediatric populations have typically been based on shortening fraction (SF) and less often ejection fraction (EF). Guidelines are available for the multimodality imaging assessment of adult patients throughout cancer therapy and include recommendations for 2D and 3D assessments of function, strain imaging, and measures of right ventricular function [85]. Both 3D EF and parameters of tissue deformation (myocardial strain and tissue Doppler) have demonstrated the ability to detect subclinical dysfunction in adult and pediatric studies [86–88]. Despite this, the majority of current screening efforts in pediatric patients focus on SF and EF and only in long-term survivors [89]. One recent study did detail abnormal myocardial strain in a heterogeneous group of 25 pediatric patients immediately after their final treatment, but did not include time points during treatment [90]. As opposed to studies in adult patients, those in pediatric and adolescent populations have yet not proven the ability of changes in myocardial strain to predict later changes in symptomatic heart failure or even EF [86]. A study enrolling patients to determine the effect of beta blocker in preventing development of CTRC in pediatric cancer survivors includes timepoints throughout treatment and after that may help elucidate the time course of echocardiographic changes following exposure to anthracyclines [76•].

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) has utility in detecting CTRC, particularly in patients with limited imaging windows related to lung shadows, body habitus, or interference from medical equipment, and for assessment of the right ventricle which is incompletely assessed by echocardiogram. One study of adult survivors found nearly 15% had left ventricular EF less than 50% by CMR, with 75% of this group misclassified as left ventricular EF > 50% by 2D echocardiography [87]. In another group of survivors, at least 2 years out, increased extracellular volume, suggesting fibrosis, was demonstrated in the setting of normal left ventricular EF; echocardiogram cannot assess for fibrosis. This increase in extracellular volume correlated with decreased VO_2, suggesting an effect of cancer therapy on cardiac function [91].

Serum biomarkers and other testing modalities

Serum cardiac biomarkers have not yet been incorporated into CTRC surveillance for pediatric and adolescent patients. Troponins, brain natriuretic peptide

(BNP), and n-terminal proBNP (NT-proBNP) are elevated before initiation of therapy, particularly anthracycline therapy, indicating a baseline state of cardiac stress or injury related to cancer, with further increase in these biomarkers throughout the treatment course [59–61, 92]. Patients in long-term follow-up may continue to show elevations in these biomarkers as evidence for ongoing or subclinical cardiotoxicity [93, 94]. There are also gene polymorphisms described that may identify susceptibility to CTRC for individuals with a given genotype [95–98]. Ultimately, a combination of imaging, serum biomarkers, and genetic profile is likely to yield the most sensitive method to predict or detect CTRC.

Additional testing modalities, such as cardiopulmonary exercise testing, multigated radionuclide angiography, and ambulatory rhythm monitoring, are also included as potentially useful in adult-based guidelines; however, their utility is dependent on the clinical scenario [78••].

Medical therapy for established cancer treatment-related cardiotoxicity

Existing adult heart failure guidelines are supplemented by cardio-oncology–specific recommendations that include guidance for therapy in response to changes in imaging and serum biomarkers, and symptomatic heart failure, and directed by specific chemotherapy exposures. While there are a number of studies reviewing treatment strategies for CTRC in adult survivors of pediatric cancers, those for patients still in the pediatric age range are limited [99, 100]. Recent data suggest that angiotensin converting enzyme inhibitors can reproducibly improve markers of subclinical cardiac dysfunction in young patients [101]. It has been suggested that all patients exposed to potentially cardiotoxic cancer therapies should be considered ACC/AHA stage A heart failure (at high risk to develop heart failure), with the goal being to prevent progression to stages B–D [102]. Given lack of data assessing efficacy and potential adverse effects, the use of standard heart failure therapies in pediatric CTRC, however, remains controversial [103, 104].

Other treatment strategies for cancer treatment-related cardiotoxicity

Advanced heart failure therapy

Patients with CTRC may fail maximal oral therapy and progress to the need for continuous inotropic infusion or mechanical circulatory support, or even consideration of heart transplantation. Active neoplasm and ongoing chemotherapy and/or radiotherapy are contraindications to transplantation at most centers, but transplantation can be considered if cancer therapy is completed and there is no evidence of active cancer and recurrence of the tumor is deemed to be low [105]. Reports of heart transplantation in pediatric patients with heart failure related to chemotherapy go back 2 decades [106]. According to recent data, for appropriately selected patients, there is no difference in long-term graft survival when compared to non-chemotherapy dilated cardiomyopathy [107]. For patients unable to wait, or for whom it is not currently appropriate to consider transplantation, mechanical circulatory support may be offered either as a bridge to transplantation, a bridge to decision, or as destination therapy [108].

Implantable cardiac defibrillators and cardiac resynchronization therapy

Although no specific guidelines exist, the indications for implantable cardiac defibrillators and cardiac resynchronization therapy in adult patients with CTRC are similar to those in other disease processes. Currently, data are lacking on the efficacy of these therapies in CTRC [109]. However, the Multicenter Automatic Defibrillator Implantation Trial - Chemotherapy-Induced Cardiomyopathy (MADIT-CHIC) trial is nearing completion and has as outcome measures change in left ventricular EF, effects on all-cause mortality, and change in New York Heart Association functional class, all in response to cardiac resynchronization therapy (clinicaltrials.gov, Identifier NCT02164721). For pediatric patients, at present, adult guidelines are modified and applied as appropriate.

Activity restrictions and modifiable risk factors

Patients who have undergone therapy for cancer may be at higher risk from modifiable cardiovascular risk factors [110]. Counseling regarding diet and appropriate exercise are recommended by the COG, particularly given that data show patients in the survivorship period (3 and 5 years after therapy) are less likely to meet expectations for exercise and healthy diet [111•]. Indeed, for patients considered to be ACC/AHA stage A for heart failure, the first method of treatment is to address issues like hypertension, hyperlipidemia, and smoking cessation. For patients who wish to engage in competitive sports, standard guidelines for athletic participation should be followed [112]. Aerobic exercise is considered safe in most cases and should be encouraged. Intensive isometric activities should be avoided, while higher-repetition, lighter-weight exercises are considered more likely to be safe.

The field of cardio-oncology has evolved through recognition of the impact that cardiovascular disease has on outcomes in survivors of cancer therapies, aiming to provide cardiovascular care to patients throughout treatment and during long-term follow-up [113]. There are numerous established adult cardio-oncology programs; however, the field of pediatric cardio-oncology remains in its infancy.

There are many potential advantages to the establishment of a cardio-oncology program focused on the care of children with cancer. A formal pediatric cardio-oncology program is likely to improve the consistency of cardiology involvement in the care of this population. It also provides a cardiology resource for the oncology team, helping to improve communication and collaboration. Detection of cardiovascular changes during cancer therapy can impact treatment and prompt discussion of cardioprotective strategies. Additionally, cardiac dysfunction may be subclinical and not easily detectible by practitioners not familiar with the field [113–116]. Early cardiology involvement may improve recognition of abnormalities, leading to earlier intervention, resulting in improved patient outcomes. Families may benefit from cardiology involvement to discuss the spectrum of cardiac disease seen in cancer survivors, learn to recognize the signs and symptoms of cardiac disease, and minimize other potential cardiac risk factors.

The field of pediatric cardio-oncology will continue to expand as pediatric cancer treatments evolve. Although therapies for pediatric cancers are becoming more tailored to the patient, with the ability to avoid or decrease the use of

cardiotoxic therapies, some patients still require aggressive cardiotoxic therapies. Additionally, the impact of novel therapies (targeted therapies, immunotherapy, etc.) on the cardiovascular system has not been fully realized and only through time and careful monitoring will we appreciate the long-term impact in children. When examining large cohort studies, recent data demonstrate that more contemporary therapies in general have had less cardiac-related mortality [117, 118]; however, the incidence of severe heart failure in childhood cancer survivors is increasing [119••]. Therefore, the population of childhood cancer survivors who require cardiology involvement is increasing. As this occurs, it will be important to develop a standardized approach to cardiology involvement in the care of this complex group of patients. A coordinated effort among pediatric cardio-oncology programs will help to facilitate multi-center research efforts to optimize care for childhood cancer survivors and further define the role of the cardiologist in this population.

Compliance with Ethical Standards

Conflict of Interest
Thomas D. Ryan, Rajaram Nagarajan, and Justin Godown declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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