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EDITORIAL COMMENT

# Childhood Cancer Survivors

## Screening Little Hearts for Big Problems*

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The American Cancer Society predicts that more than 11,000 children will be diagnosed with cancer during 2020; fortunately, childhood cancer survival has improved significantly in the past few decades, with 84% surviving to 5 years (1). However, with better survival comes an increased burden of short- and long-term complications in these childhood cancer survivors. Cardiovascular complications leading to heart failure are well-known in long-term survivors, particularly in those who received chest radiation or anthracycline chemotherapy (2–4), which have been the mainstay of anticancer therapy for children. However, there are significant challenges in assessing the noninvasive imaging predictors of these complications in children, because there are simply fewer childhood cancer survivors than adult cancer survivors. Single-center studies, which form the bulk of the pediatric cardio-oncology published data, can be limited by the small number of childhood cancer survivors. Consequently, there is an enduring difficulty in timely identification of those children who are at greatest risk for developing cardiac complications and in pinpointing the optimal time for cardiac intervention. In this issue of *JACC: CardioOncology*, Border et al. (5) highlight an innovative, collaborative, multicenter study approach with the use of longitudinal echocardiographic data in children to examine this problem and help mold a model for future studies in this growing field of pediatric cardio-oncology.

In the past several years, there has been a rapid expansion in the field of adult cardio-oncology and standardization of noninvasive imaging for surveillance (6–9). The adult survivorship field has defined specific recommendations for indices of cardiac function in noninvasive imaging of survivors of adult cancers, including novel indices, such as global longitudinal strain for subclinical left ventricular (LV) dysfunction (6). Pediatric cardio-oncology is now similarly focusing on further defining surveillance by noninvasive imaging and correlation with cardiotoxicity (10,11). Echocardiography is usually preferred over other modalities in children because of its noninvasive nature—requiring no needle sticks for children or radiation exposure to developing tissues—and its ready availability. Cardiac magnetic resonance has greater reproducibility in LV volume and ejection measurements, but is more costly, usually requires anesthesia in children, and is less accessible, and therefore is reserved for those with inadequate echocardiographic images. Radionuclide imaging also allows quantification of left ventricular ejection fraction (LVEF) but requires radiation exposure and is not portable. 2-dimensional echocardiographic assessment of fractional shortening (FS) and LVEF have been the traditional indices used in children, but as in adults, are subject to significant variability. The wider clinical use of 3-dimensional echocardiography in childhood cancer survivors promises potentially greater accuracy and reproducibility of echocardiographic indices (9).

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One of the most significant obstacles to studying the importance of surveillance and cardiac effects of cancer treatment in pediatric cancer survivors is the long lag time from treatment exposure to the development of overt cardiac dysfunction. Because cardiac

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events and cardiomyopathy typically develop months or even years after curative cancer therapy, an individual center will often not have a sufficiently large sample to evaluate the relationship between echocardiographic indices and cardiac outcomes. The resulting lag time may contribute to the perception by clinicians that few children develop cardiomyopathy after cancer treatment; childhood cancer survivors may develop cardiomyopathy and heart failure in adulthood, after they are no longer followed by their pediatric providers, thereby reducing the likelihood that the causal relationships will be recognized. This transition also exacerbates the loss of patients to follow-up and, therefore, the loss of opportunity to initiate early therapy for cardiotoxicity. Few clinical centers have integrated programs of pediatric and adult cardiac care or research for childhood cancer survivors.

The small number of patients and the multisystem nature of potential toxicities also make it difficult to carry out longitudinal screening for adverse outcomes in this population outside of a research setting. As a result, most published clinical studies of cardiac outcomes in children, even large ones, rely on cross-sectional imaging data (4,12). However, longitudinal studies provide critical insight into functional changes in the heart over time and the optimal timepoint at which a preventative intervention should be employed, issues that are seldom addressable using cross-sectional data (3). Thus, multicenter, collaborative, longitudinal studies ultimately may be necessary for the optimal study of childhood cancer survivors, and be necessary to obtain the desired number of patients to correlate cardiac imaging indices with long-term cardiac effects. Recently, a Canadian study on cardiac assessment of pediatric cancer survivors utilized this multicenter approach to recruit a sample of over 500 patients (13). In addition, the National Cancer Institute is funding a collaborative, multicenter national study with a central echo core laboratory to prospectively assess childhood cancer survivors previously treated with high-dose anthracycline, who are randomized to receive either placebo or cardioprotective therapy with carvedilol (14). This issue of *JACC: CardioOncology* presents a pioneering multicenter longitudinal study in children using data pooled by 5 participating centers, which further supports this model for future collaborations and efforts (5).

The multicenter, retrospective study by Border et al. (5) published in this issue demonstrates the utility of serial echocardiograms, analyzed in a core laboratory, to retrospectively detect cardiomyopathy-related changes in children who are cancer survivors, often several years before the onset of clinically apparent disease. They compared longitudinal changes in echocardiographic parameters that were present in 50 children who eventually developed cardiomyopathy, with a matched cohort of 50 childhood cancer survivors who did not develop cardiomyopathy, after anthracycline and radiation exposure. These cohorts were matched for cumulative anthracycline and chest radiation dose, duration of follow-up, and age at cancer diagnosis. All echocardiograms were retrospectively analyzed by a single core laboratory. The authors concluded that there were significant differences in several traditional systolic and some diastolic parameters, including FS, LVEF, LV end-diastolic dimension, mitral E/A, and LV myocardial performance index, between the 2 groups. Intriguingly, the authors found all of these echo indices, except myocardial performance index, remained significant between the 2 groups, as far back as 2 years prior to the recognition of cardiomyopathy. Given the era of the echocardiograms available, retrospective analysis of global longitudinal strain analysis for these patients was not possible, and only traditional systolic and diastolic indices could be analyzed. Also, with the overlapping range of the measurements between the 2 groups, it was not possible to prospectively identify individual patients as at-risk from echocardiographic indices alone. Importantly, this study underscores the importance of examining longitudinal trends of systolic and diastolic echocardiographic indices on serial studies, instead of focusing just on the binary categorization of indices (e.g., LVEF, FS, LV end-diastolic dimension) as normal or abnormal.

Measurements by a single observer in an echocardiographic core laboratory reduce interobserver error of any measurement and, therefore, increase the power to detect changes between groups. Unfortunately, because of the large range of LVEF between cardiomyopathies and control subjects in the study, a clinician, unlike a core laboratory, may not find that FS or LVEF alone helps identify an individual patient at risk for ensuing cardiomyopathy. Both LVEF and FS are indices that have traditionally been used, but they are very sensitive to afterload and preload changes as can be seen during cancer treatment (3). Therefore, the ability of the physician to clinically alter therapy based on a single LVEF or FS value would be limited. However, analyzing and plotting trends over time in an individual patient, even those with a "normal LVEF," might be potentially useful, but even this approach warrants prospectively evaluation of its efficacy.

The ability to identify the patients at risk at the time of their echocardiographic screening would be

important because it represents the opportunity for early introduction of cardioprotective agents such as beta-blockers or ACEI while the patient continues anticancer therapy. However, because we know that even a single dose of anthracycline is cardiotoxic (3), consideration of cardioprotection for all patients at the time of anticancer therapy may be studied in a prospective manner.

## FUTURE DIRECTIONS

High-quality right and left heart functional imaging, which is easily accessible, is critical to the management of pediatric cancer survivors. Therefore, routine measurement of LV volumes from 3-dimensional echocardiography and the integration of novel indices, such as global longitudinal strain assessment, may be useful and need further investigation. Furthermore, in older children who are near adult size, the acquisition of biplane Simpson's LVEF, in addition to the traditional 5/6 area-length method, also may improve correlation of assessments from pediatric and adult centers. As a child grows to adult size, the configuration of the heart in the chest typically changes and the LV apex moves both more laterally and toward the feet. Therefore, further standardization of functional assessment in pediatric oncology patients will increase the reproducibility and sensitivity of echocardiographic measures, and the incorporation of newer echocardiographic indices into routine practice will potentially allow for earlier detection for cardiac dysfunction in children.

In the future, more prospective, multicenter cardio-oncology studies in children will be needed to assess—and ultimately, predict—cardiovascular events. Prediction models that include patient- and treatment-specific variables, noninvasive imaging indices, and biomarkers will continue to be refined (10,15), and help inform future recommendations for cardiac surveillance. In addition, greater integration of cardiac care for childhood cancer survivors will be crucial as these patients reach adulthood (16). In short, the paper by Border et al. (5) underscores the importance of examining trends in echocardiographic indices over time in pediatric cardiology, and exciting opportunities for multicenter collaboration and early detection of cardiotoxicity await.

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