Multimodality Imaging for Cardiac Surveillance of Cancer Treatment in Children: Recommendations From the American Society of Echocardiography

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PREAMBLE

Guidelines for using noninvasive imaging techniques to monitor cardiac function in adults undergoing cancer treatment are available.[1,2] Children with cancer, however, require a different imaging approach. Screening and detection strategies in younger children have largely relied on longitudinal monitoring of echocardiographic measures of left ventricle (LV) systolic function, mainly fractional shortening (FS) and ejection fraction (EF). Despite the important role of echocardiography in the follow-up of this patient group, a recent multicenter study indicated that the overall quality of routine pediatric echocardiograms for childhood cancer survivors was not sufficient to reliably assess LV function.[3] This finding highlights the need to develop recommendations for the standardization of echocardiographic functional assessment as applied to pediatric oncology patients. Additionally, the role of newer echocardiographic techniques such as myocardial

Abbreviations

2D = Two-dimensional

3D = Three-dimensional

ASE = American Society of Echocardiography

CAC = Coronary artery calcium

CCT = Cardiovascular computed tomography

CMR = Cardiac magnetic resonance imaging

CT = Computed tomography

EF = Ejection fraction

FAC = Fractional area change

FS = Fractional shortening

GCS = Global circumferential strain

GLS = Global longitudinal strain

GRS = Global radial strain

HF = Heart failure

LA = Left atrium, atrial

LGE = Late gadolinium enhancement

LV = Left ventricle, ventricular

LVEF = Left ventricular ejection fraction

MRI = Magnetic resonance imaging

RA = Right atrium

RT = Radiotherapy

RV = Right ventricle, ventricular

STE = Speckle-tracking echocardiography

TAPSE = Tricuspid annular plane systolic excursion

deformation imaging and other noninvasive imaging modalities, including cardiac magnetic resonance imaging (CMR) and computed tomography (CT), has not been well defined for this indication.

The aim of this document is to provide guidance on the application of multimodality imaging in children undergoing cancer treatment. The Writing Committee focused on indications for and performance and interpretation of current clinically used imaging techniques. This document is not intended to make recommendations regarding the impact of cardiac imaging results on cancer treatment, as this is highly controversial and should be the topic of separate practice guidelines.

Most of the published literature used for writing the current recommendations studied the cardiac effects of anthracyclines and radiotherapy in children. We acknowledge that over recent years novel treatments have been introduced with potential cardiovascular effects, such as immunotherapies, tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, stem cell transplant treatments, and CAR T-cell therapy. It can be expected that as these therapies are increasingly used in children, novel information on their cardiovascular impacts will become available. We also acknowledge that both the older as well as the newer treatments can have cardiovascular effects beyond changes detectable by cardiac imaging, including vascular and electrophysiologic effects. Thus, monitoring the cardiovascular impact of cancer treatment should go beyond cardiac imaging alone, and treatment-specific monitoring protocols need to be developed. The field of pediatric cardio-oncology is evolving quickly, thus underscoring the importance of involving multidisciplinary teams, including cardiologists, oncologists, pharmacologists, nurses, and geneticists as well as patients and their families. This document is an expert consensus document. During the process of evaluating the evidence currently available, it became obvious that there are important gaps in knowledge that need to be addressed. It is hoped that the availability of a standardized approach to noninvasive cardiac imaging in childhood cancer patients is a first step to optimize cardiovascular care for pediatric cancer patients.

INTRODUCTION

During the past 5 decades, remarkable progress has been made in treating childhood cancer. More than 80% of children diagnosed with cancer today can expect to survive well into adulthood.[4] At the same time, increased survival has exposed the high burden of morbidity of cancer therapy delivered at an early age.[4] Of the 500,000 long-term childhood cancer survivors in the United States, nearly one-third are estimated to experience a severe or life-threatening chronic health condition, such as cancer recurrence, a subsequent malignant neoplasm different from the original cancer, and cardiopulmonary disease within 20 years after primary cancer treatment.[4-6] In these survivors, cardiovascular disease is the third leading cause of premature mortality after cancer recurrence and a subsequent malignant neoplasm, with a 7-fold increased risk of cardiovascular mortality compared to that of the general population.[4-7]

Cardiovascular complications after cancer treatment include left ventricular (LV) dysfunction, cardiomyopathy, heart failure (HF), coronary artery disease, stroke, pericardial disease, arrhythmia, and valvular and vascular dysfunction.[8,9] Different chemotherapeutic agents have different cardiovascular effects (Figure 1), with anthracyclines being the main contributors to the development of cardiac dysfunction with early and late development of HF. Cardiovascular risk is further increased by exposure to chest radiation as this can cause additional myocardial, valvular, and coronary artery damage.[10]

Current cancer treatments are administered with an attempt to minimize the long-term cardiovascular effects.[11] These include lower cumulative doses of anthracyclines and use of cardioprotective agents including dexrazoxane in protocols that include high cumulative anthracycline doses.[12] The preventative use of cardiovascular medications such as neurohormonal inhibitors, angiotensin-converting enzyme inhibitors, beta-blockers, and statins has been studied mainly in adult patients.[5,11,13] Increased precision in chest radiation techniques has resulted in reducing cardiac exposure. These practice changes have reduced the incidence of HF, pericardial disease, and valvular disease in this population.[5,11] Despite these improvements, cardiovascular complications developing during and after cancer treatment remain a significant challenge and continue to compromise the long-term health of this growing patient cohort.[8,14]

Current Practice Guidelines on Monitoring for Cardiac Disease During and After Pediatric Cancer Treatment

The primary goal of cardiac monitoring is to identify early signs of potentially reversible heart disease and to minimize the risk of progression from asymptomatic to clinically overt heart disease.[8,9] A patient who receives cardiotoxic cancer therapy is considered to be at stage A of HF according to the American College of Cardiology/American Heart Association staging system.[15] Cardiac surveillance and monitoring in such patients should seek to prevent progression from stage A (patients at high risk for HF) to stage B (patients with structural abnormalities, including evidence of LV remodeling without symptoms of HF), as well as to stage C (symptomatic HF; Figure 2).

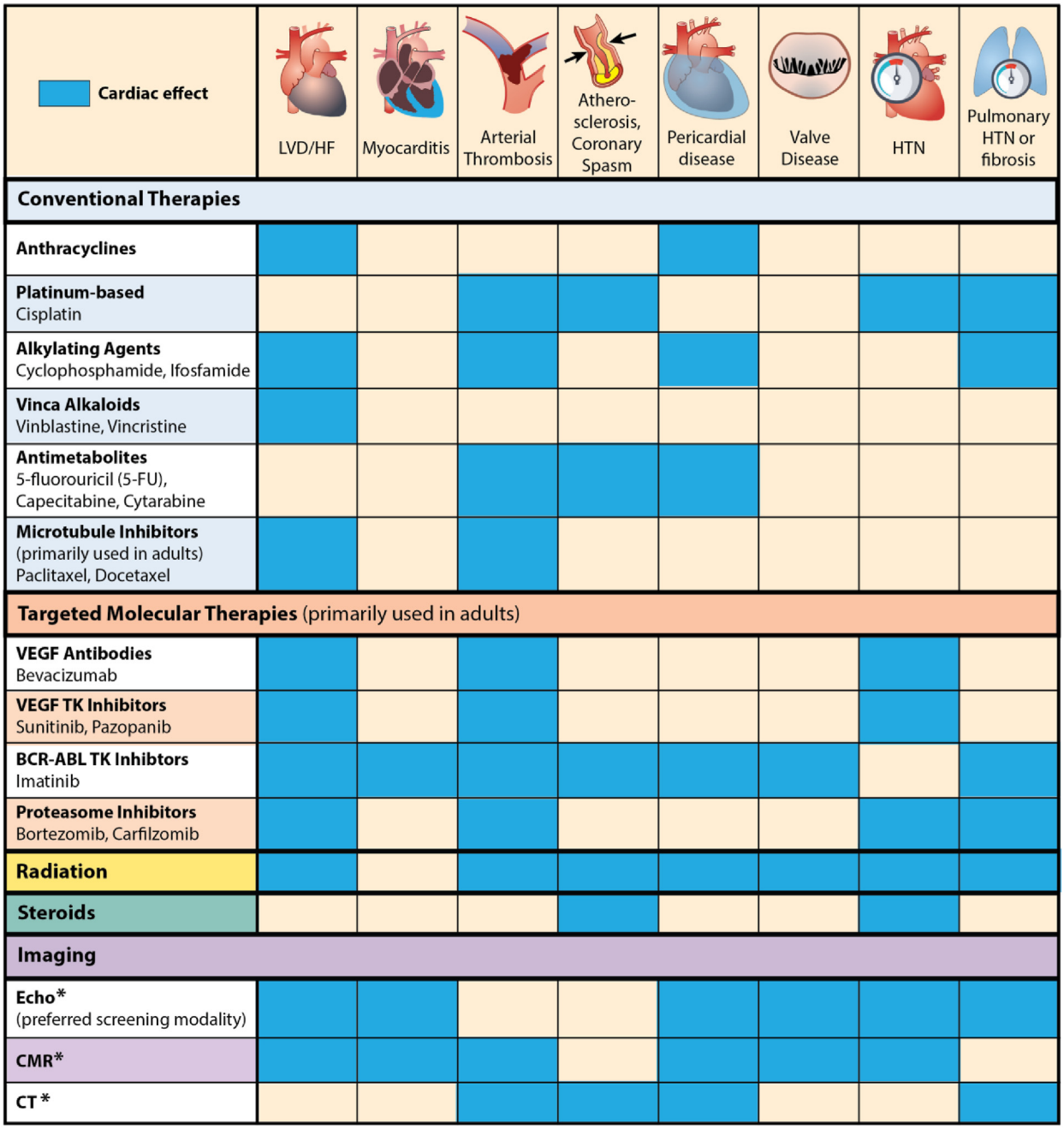


Figure 1 Overview of the cardiovascular effects of cancer treatments and use of imaging modalities. *HTN*, Hypertension; *LVD*, LV dysfunction; *TK*, tyrosine kinase.

Prior to starting cardiotoxic treatment, a full baseline structural and functional echocardiogram should be performed. Most of the current cardiotoxicity surveillance practices are based on consensus-based expert opinion guidelines. Steinherz *et al.*[16] recommended surveillance echocardiograms at baseline, before every other anthracycline cycle until a cumulative anthracycline threshold of 300 mg/m^2 was met. After crossing this threshold, an echocardiogram was recommended before each anthracycline dose and at 12 months of therapy. The guideline recommended discontinuing anthracyclines in the event of marked deterioration of cardiac function, defined as an absolute decline in EF by 10% (e.g., decline from 60% to 50%), an FS less than 29% as measured by echocardiography, or an EF less than 55% as measured by radionuclide angiocardiography on 2 sequential studies. Anthracyclines were to be restarted only with evidence of normal LV function on 2 sequential studies 1 month apart. These guidelines were not informed by prospective studies and are poorly supported by evidence. The Children's Oncology Group clinical trials conducted over the past 2 decades have generally recommended echocardiographic monitoring at least as frequently as that proposed in the Steinherz *et al.* guidelines. Children's Oncology Group protocols typically apply thresholds for withholding anthracyclines for FS between 27% and 29% or EF between 50% and 55%. However,

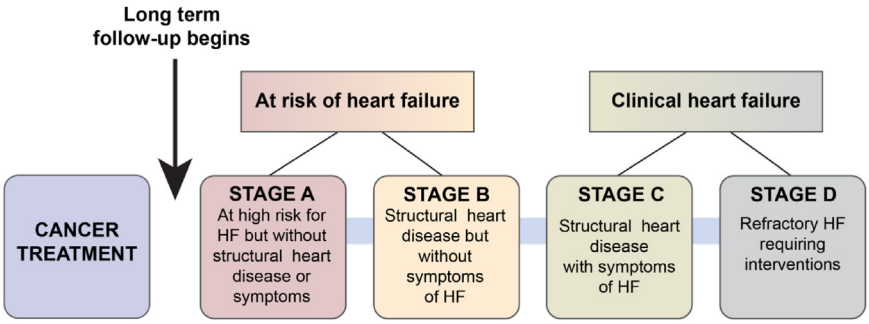


Figure 2 American College of Cardiology/American Heart Association staging system for HF.

these thresholds for anthracycline dose modifications are similarly lacking in evidence-based data to inform the predictive value of acute declines in these functional parameters on early or late adverse cardiac outcomes.

The decision to withhold or modify cancer treatment is not without risk. Among 1,022 children with acute myeloid leukemia treated in the phase 3 Children's Oncology Group study AAML0531,[14] 12% experienced grade 2+ LV systolic dysfunction, defined as an EF <50% or an FS <24%, primarily occurring during cancer treatment, thus potentially leading to early discontinuation of anthracyclines. The occurrence of LV systolic dysfunction was associated with a more than 15% decrement in 5-year event-free and overall survival compared to those without. The inferior cancer survival observed in the setting of anthracycline limiting cardiac dysfunction emphasizes that anthracycline dose modifications should be used cautiously, tailored to each individual child, and informed by a multidisciplinary cardio-oncology team. Current practice guidelines recommend consideration of oncologic regimen changes based on FS or EF calculations and use very strict cutoff values for detecting dysfunction. These recommendations do not take into consideration the technique used or the variability in the measurements.

The International Late Effects of Childhood Cancer Guideline Harmonization Group developed evidence-based guidelines for cardiomyopathy risk stratification and screening for childhood cancer survivors.[17] Based on moderate-to-high-quality evidence, survivors are classified as having low, moderate, or high cardiomyopathy risk based on cumulative anthracycline dose and exposure to chest radiotherapy. Survivors who have received 1 to 99 mg/m^2 of anthracyclines, less than 15 Gy of radiotherapy, or both are considered low risk. Those who have received between 100 and 249 mg/m^2 of anthracyclines or 15 and 30 Gy of chest radiation are at moderate risk, while those who have received ≥250 mg/m^2 of anthracyclines, ≥30 Gy of chest radiation, or the combination of ≥100 mg/m^2 of anthracycline and ≥15 Gy of chest radiation are considered at high risk for cardiomyopathy. In high-risk survivors, screening is recommended starting 2 years after treatment and repeated every 2 years thereafter. In long-term survivors with moderate risk, an every 5-year screening interval is considered reasonable. For low-risk survivors, who constitute approximately 40% of those for whom screening is currently recommended, screening was not demonstrated to be cost-effective, even at 10-year intervals. Based on these findings, the authors suggested against screening the lowest-risk patients.[18] It should be emphasized that this risk stratification is based on historical data. Recent modifications in cancer therapies, including the introduction of cardioprotective agents such as dexrazoxane and novel cancer therapeutic agents, may have modified the cardiovascular risks. Additionally, recent genomic data suggested that individual risk may be further modified by genetic variations, such as in genes involved in drug metabolism or in biological cardioprotective pathways. Thus, future research on individualizing cardiovascular risk will need to consider both the genomic background and environmental factors, such as type of treatment.

Recommendations and Key Points

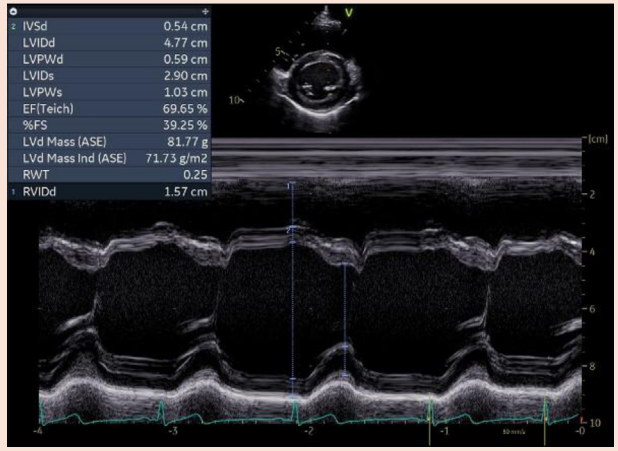
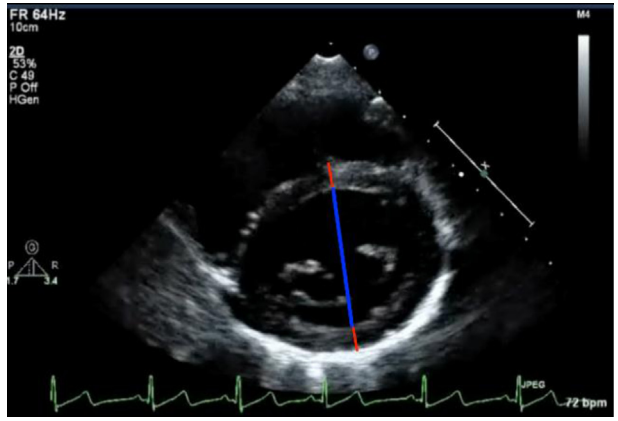
- During cancer treatment inclusive of cardiotoxic medications, echocardiographic screening for early detection of subclinical cardiac dysfunction is recommended. The frequency of screening will depend on doses used and other coexisting risk factors.
- Current criteria for defining early cardiac dysfunction are based on decreased FS or EF that have been poorly validated in prospective studies. Withholding cancer treatment requires multidisciplinary decision-making and must be made cautiously.
- After completion of treatment, cardiac surveillance is recommended at least every 2 years for high-risk and every 5 years for moderate-risk patients. The cost-benefit for low-risk patients is questionable, and evidence-based recommendations for cardiac surveillance after novel treatments have not been established.

PART 1. ECHOCARDIOGRAPHIC EVALUATION OF CHILDREN WITH CANCER

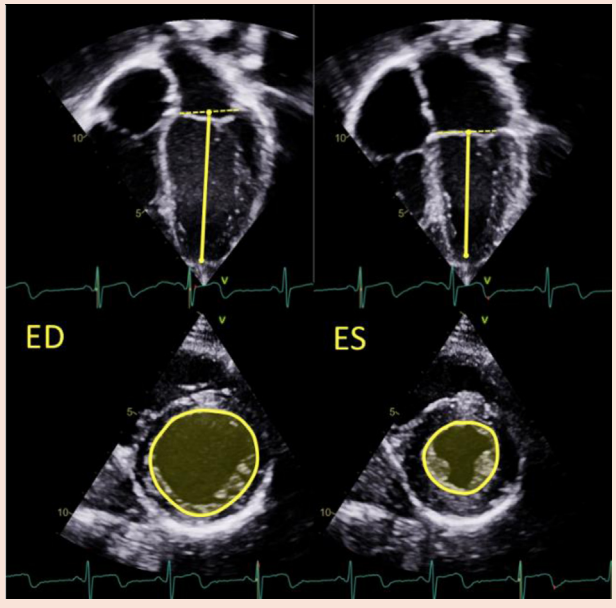
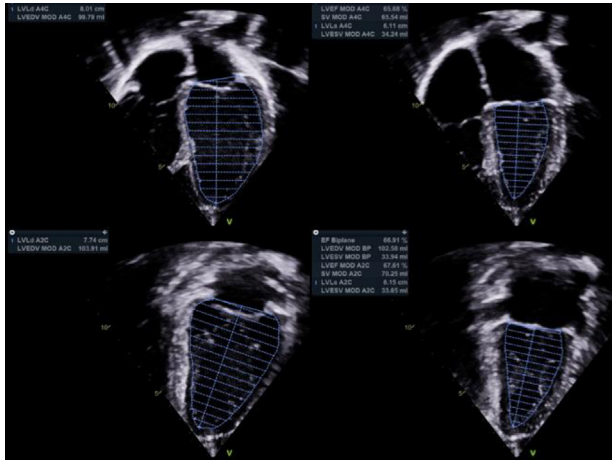
Echocardiography is the primary cardiac imaging technique for children before, during, and after cancer therapy. The first echocardiographic evaluation should include a complete structural and functional examination. Follow-up studies should focus on assessment of LV and right ventricle (RV) function, valve function, and the pericardium. A standardized protocol for measuring functional parameters must be developed, as consistency in echocardiographic methods is crucial for interpreting serial changes in cardiac function that may occur during and after treatment. Measurement variability should be minimized as this is essential for detecting subtle changes in cardiac function.[19,20] Combining and utilizing different measures of LV function for serial assessment, such as EF based on two-dimensional (2D) and three-dimensional (3D) imaging combined with myocardial deformation imaging, may allow more reliable detection of subtle changes in cardiac function.[21] In Table 1 we summarize how to perform the different measurements.

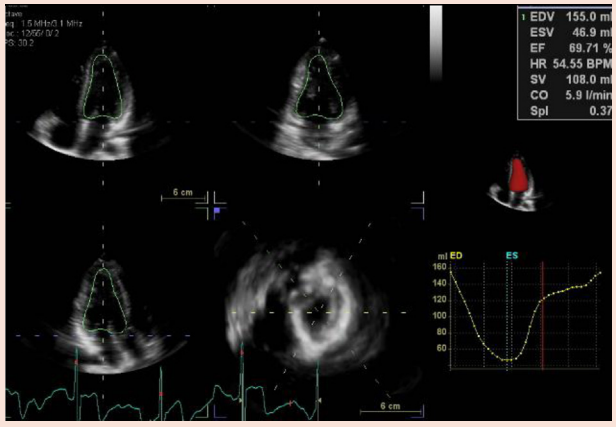
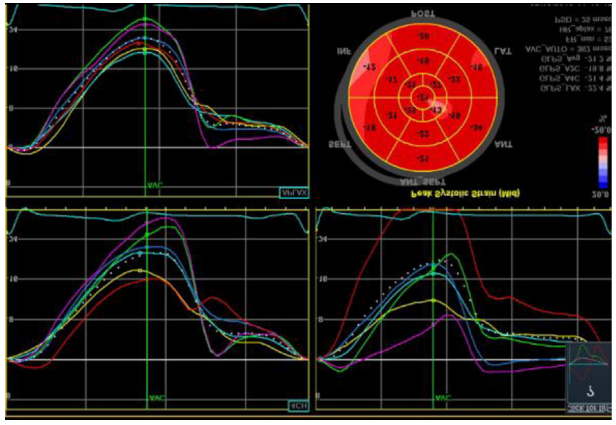
The pathophysiology of cardiac dysfunction in both children and adults undergoing cancer treatment is not fully understood and is beyond the scope of this document.[22-24] Some changes are important to understand when assessing cardiac structure and

Table 1 Echocardiographic measurements in childhood cancer patients

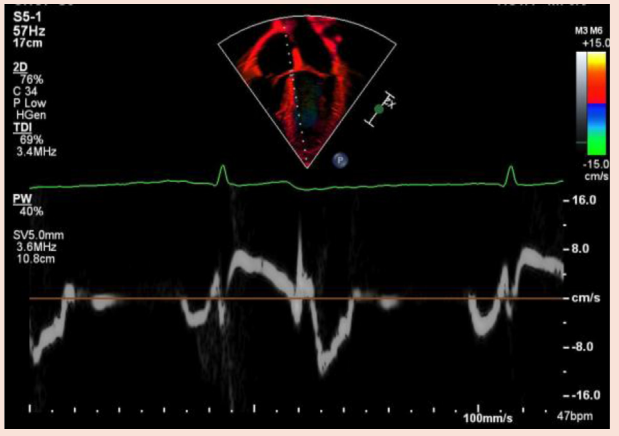
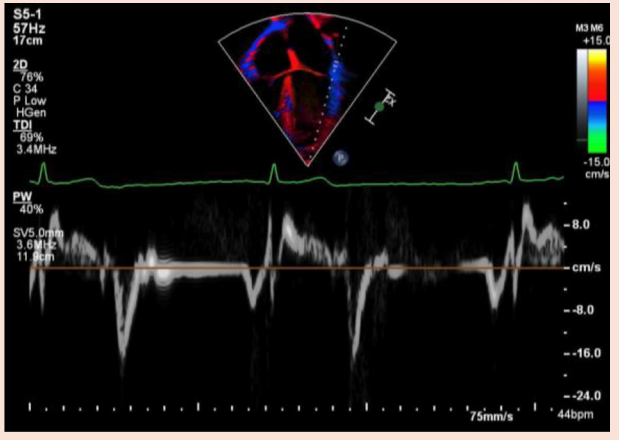
Parameter(s)	Recommended view(s) and modality	Method	Echo images with measurements	Advantages	Pitfalls
LV dimensions	M mode Parasternal short- or long-axis views	• Image optimized to enhance blood-endocardium interface. • Cursor placement perpendicular to IVS, LV, and LV posterior wall at the level of the papillary muscles or tip of mitral valve leaflets in younger patients. • Measurements in ED, defined as the first frame after mitral valve closure or the frame in the cardiac cycle in which the LV dimension measurement is the largest.		• High temporal and spatial resolution. • Reproducible. • Normative pediatric *Z* scores available.	• Assumes normal LV shape. • Depends on good blood endocardial border definition. • **We do not recommend using FS as a measure of LV function.**
LV dimensions	2D Parasternal short or long axis	• Measurements made at the level of the papillary muscles or tip of mitral valve leaflets in younger patients.		• Reproducible. • Normative pediatric *Z* scores available.	• Lower temporal resolution compared to M mode. • **We do not recommend calculating shortening fraction as measure of LV function.**

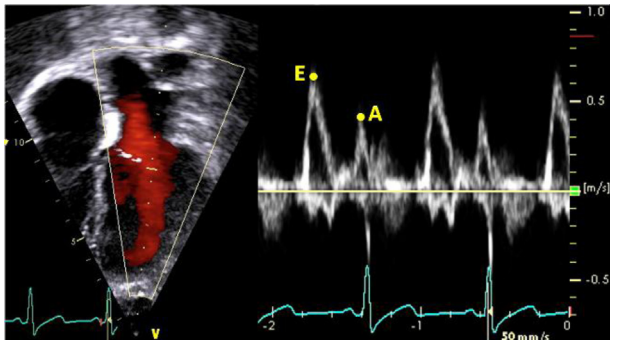
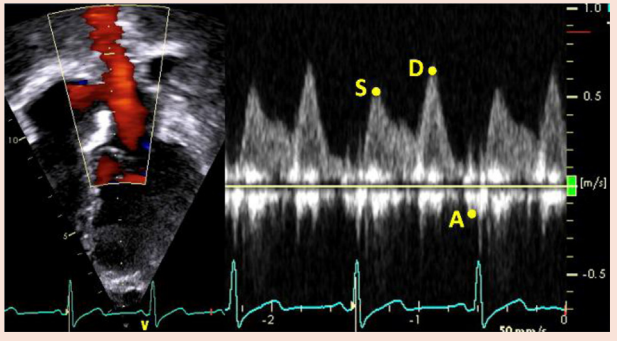
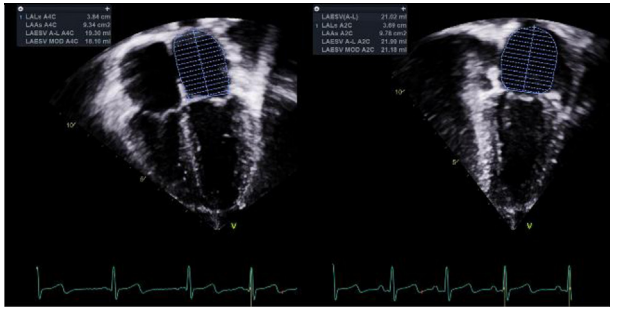
(*Continued*)

LVEF Area-length	2D Apical 4 chamber Parasternal/ subcostal short axis	• Length measured from basal border to apical endocardium in ED and ES, which is defined as the frame after aortic valve closure or the frame in which the LV dimension is smallest. • Manual tracing of the endocardium in ED and ES for CSA. • Papillary muscles included in the area trace. • LV volume = 5/6 × CSA × length		• Calculation influenced by LV shape. • Preferred method in younger children when apical 2-chamber view is difficult to obtain.	• LV apex can be foreshortened. • Manual tracing is user dependent.
LVEF Biplane method of disks	2D Apical 4 chamber Apical 2 chamber	• Image optimized to view the entire LV, taking care to not foreshorten the LV. • ROI tracing from mitral valve hinge points along the LV endocardial contour in both end-diastolic and end-systolic frames. • ED is defined as the first frame after mitral valve closure or the frame in the cardiac cycle in which the LV volume measurement is the largest. ES is best defined as the frame after aortic valve closure or the frame in which the cardiac volume is smallest. • Papillary muscles included in the volume trace.		• Less geometric shape assumptions. • Preferred method when both apical 2- and 4-chamber views can be obtained. • Automated and semiautomated methods have become available.	• Underestimates LV size in smaller patients as 2-chamber view often is foreshortened • Manual tracing results in variability.

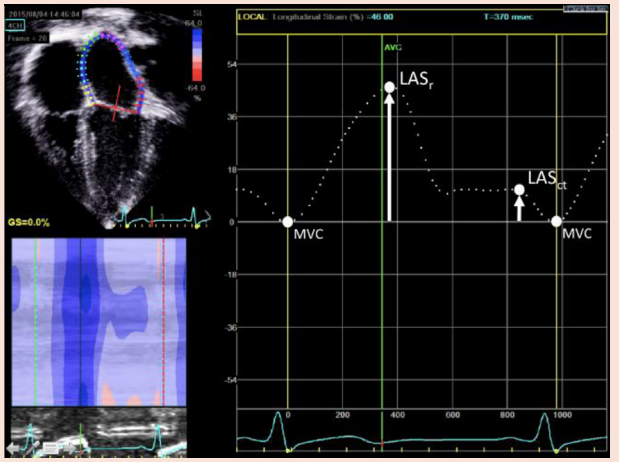
LVEF 3D echo	Apical 4 chamber 3D volume	• 3D volume should include entire LV avoid foreshortening or stitch artifacts. • Temporal resolution of >20-25 volumes per second. • Fully automated border detection available.		• No geometrical assumptions. • Automated analysis available. • Reproducible. • Normative pediatric data available.	• Image quality-dependent. • Lower temporal resolution. • Requires cooperation. • Specific transducers and software analysis package needed.
LV GLS	STE Apical 4 chamber, Apical 2 chamber, Apical 3 chamber	• Image optimized for myocardial definition; avoid foreshortening or dropout. • 3 views selected should have similar heart and frame rates with clear electrocardiogram tracing • Visual inspection to ensure accurate tracking of LV walls; analysis excluded if more than 2 segments per view show poor tracking.		• Highly reproducible. • Automated analysis.	• Image quality dependent • Heart and frame rates need to be comparable in all 3 views. • Specific software analysis package needed. • Vendor dependent.

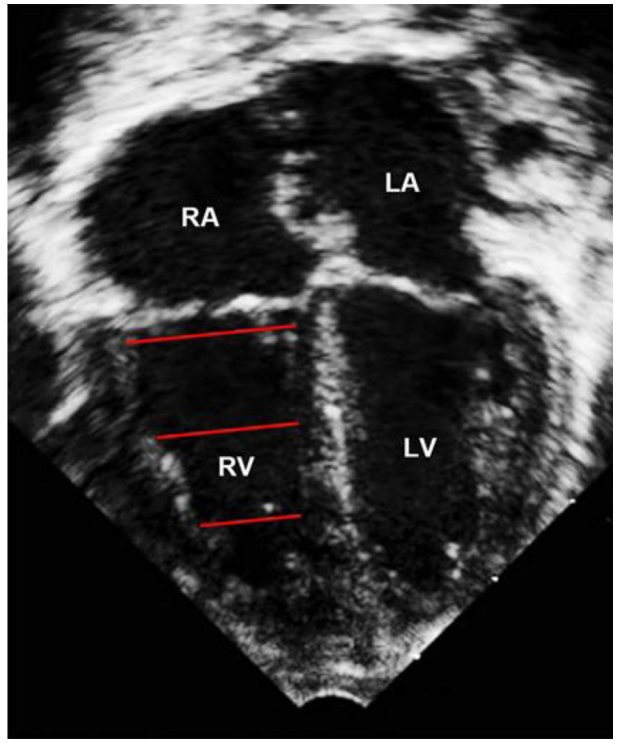
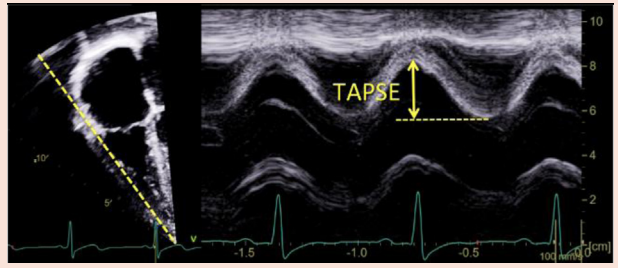
(*Continued*)

Tissue Doppler	TDI Apical 4 chamber	• Image optimized for parallel alignment of ventricular septum and LV free wall. • Sample volume (5 mm) placed at the basal regions of the lateral LV wall and IVS. • Measure systolic peak velocity (s'), early diastolic filling velocity (e') and atrial contraction velocity (a').	 	• Easy to measure. • Reproducible.	• Angle dependent. • Limited as regional assessment (longitudinal motion only). • Not extensively validated for systolic function in pediatric population, limitations in interpretation.

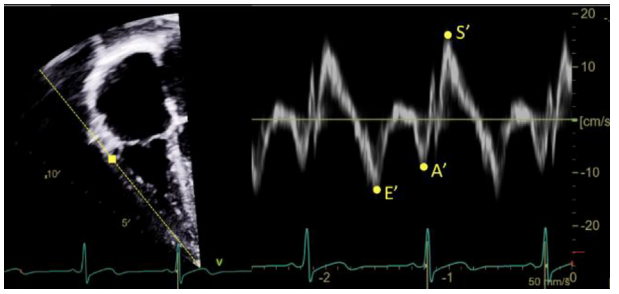
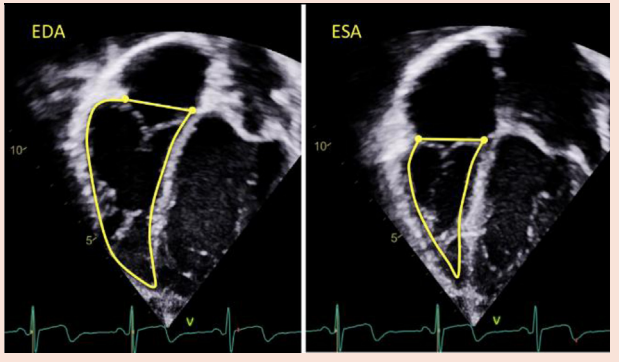
Mitral inflow	PW Doppler Apical 4 chamber	• Color Doppler imaging used for optimal alignment of cursor with mitral inflow • Cursor placed across the mitral valve with sample volume just inside the LV at the tips of the mitral valve leaflets. • Measure early diastolic filling (E) and atrial contraction (A).		• Easy to measure. • Reliable and reproducible. • Normative pediatric data available.	• Increased HR can lead to E- and A-wave fusion. • Influenced by age and loading conditions. • Alignment dependent.
Pulmonary venous velocities	PW Doppler Apical 4 chamber	• Color Doppler imaging used for optimal alignment of cursor with pulmonary venous flow. • Sample volume placed into the right or left upper pulmonary vein, as distally into vein as possible. • Measure systolic (S), diastolic (D) and a-wave reversal (A) velocities.		• Reliable and reproducible. • Normative pediatric data available.	• Alignment dependent. • Data become difficult to interpret if atrial shunt is present.
LA volume	2D Apical 4 chamber, Apical 2 chamber	• Image optimized for clear delineation of LA borders with no foreshortening of the LA. • Measurements obtained at ES. • LA length is the shortest of the 2 long axes measured in the apical 2- and 4-chamber views. • ROI tracings must exclude the LA appendage and pulmonary veins.		• Biplane volume measurement is superior to linear LA dimension for assessment of LA size.	• Can be difficult to exclude pulmonary vein(s) and LA appendage.

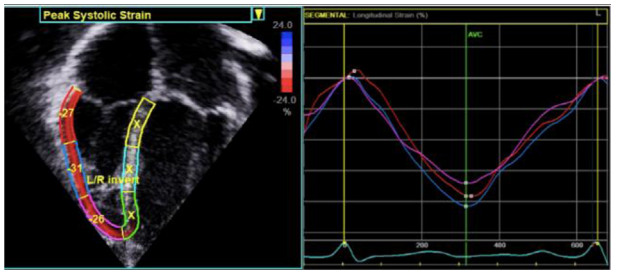
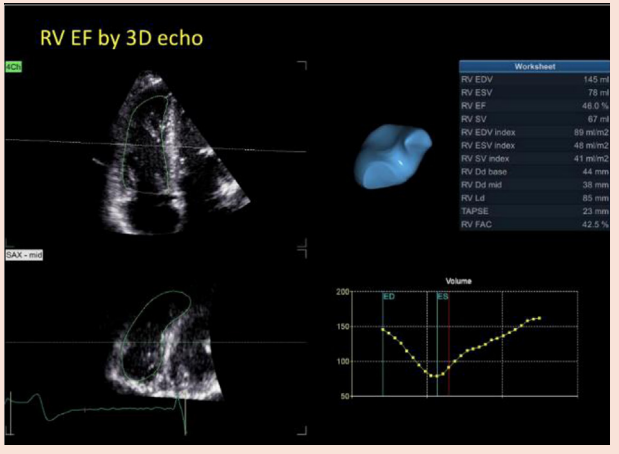
(*Continued*)

LA strain	STE Apical 4 chamber	• Image optimized to view the entire LA with no foreshortening of the LA • ROI tracing from mitral annular hinge point, along the LA contour to the opposite annular hinge point. • ROI extends across orifices of pulmonary veins and LA appendage and ROI thickness should cover only LA endocardial to epicardial border. • Adjust zero strain reference markers to mitral valve closure. • Measure peak strain and peak atrial contraction strain		• Adds LA function quantification to LV diastolic assessment.	• Image quality dependent. • Lack of pediatric data.

RV size	2D RV-centric Apical 4 chamber	• Image optimized for endocardial border definition of the RV throughout cardiac cycle; avoid foreshortening or dropout. • Basal, midcavity, and apical diameters measured at ED.		• Easy to measure basal diameter. • Normal pediatric data available for basal and midcavity diameters. • Apical diameter reflects remodeling in pulmonary hypertension.	• Dependent on good endocardial border definition and adequate visualization of RV lateral wall. • Limited pediatric normal data available for apical diameters. • Weak correlation with MRI volumes.
TAPSE	M mode RV-centric Apical 4 chamber	• Image optimized for alignment of cursor with RV free wall. • Activate M mode with the cursor across the lateral tricuspid annulus. • Measure annular motion from ED to peak systole.		• Easy and fast to perform. • Normal pediatric data available.	• Angle dependent. • Age and cardiac size dependent. • Limited as regional assessment.

(*Continued*)

Tissue Doppler RV free wall	TDI RV-centric Apical 4 chamber	• Image optimized for alignment of cursor with RV free wall. • Sample volume (5 mm) placed in the basal region of free wall. • Measure systolic peak velocity (s'), early diastolic filling (e') and atrial contraction (a').		• Easy to measure. • Reliable and reproducible. • Normal data available.	• Angle dependent. • Limited as regional assessment.
FAC, %	2D RV-centric Apical 4 chamber	• Image optimized for endocardial border definition of the RV throughout cardiac cycle; avoid foreshortening or dropout. • Trace end-diastolic area and end-systolic area along endocardial borders from tricuspid annular hinge point, down to RV apex and back up to opposite hinge point. Close the area with a straight line connecting the 2 hinge points. • Cavity area should include moderator band, tricuspid valve and trabeculations.		• Reflects longitudinal and radial contraction. • Reproducible if well standardized. • Modestly correlates to MRI EF.	• Image quality dependent: RV walls can be difficult to visualize. • Trabeculations can make defining the endocardial border difficult and introduce variability. • Foreshortening • Dilated RV apex may not fit within the sector near field. • Does not include RV outflow segment to estimate RV function.

RV strain, %	STE RV-centric Apical 4 chamber	• Image optimized for myocardial definition, avoid foreshortening or dropout. • ROI covers the RV free wall from base to apex, endocardium to epicardium, taking care to exclude trabeculations. • Visual inspection to ensure accurate tracking of RV free wall; exclude analysis if more than 1 segment shows poor tracking. • RV GLS (%) = average peak systolic strain of 3 RV free-wall segments.		• Easy measurement with good reproducibility.	• Image quality dependent. • Vendor dependent.
RV EF (%)	3D RV-centric Apical 4 chamber 3D full volume	• Image optimized for endocardial border definition; avoid foreshortening or stitch artifacts. • 3D volume should include entire RV with temporal resolution of >20-25 volumes per second. • Labeled calipers placed on the apical 4-chamber and short-axis cuts of the volume. • Visual inspection to ensure accurate endocardial surface detection and include trabeculations and moderator band in the cavity.		• Includes all regions of the RV with no geometric assumptions. • Correlates to RV EF by MRI. • Automated tracking ensures better reproducibility.	• Image quality dependent: poor visualization of anterior wall and outflow. • Requires regular rhythm, patient cooperation and 3D equipment along with user training. • May be time consuming. • Dilated RV apex may not fit within the sector near field.

CSA, Cross-sectional area; *ED*, end diastole; *ES*, end systole; *IVS*, interventricular septum; *PW*, pulsed-wave; *ROI*, region of interest; *TDI*, tissue Doppler imaging.

function by imaging techniques as they explain some of the observed pathological findings. When the myocardium is exposed to cardiotoxic agents such as anthracyclines, this can result in myocyte apoptosis and cell death. In the remaining cells, the contractile apparatus is depleted and mitochondrial function is altered. Loss of cells can result in wall thinning, which increases local wall stress and may cause further maladaptive remodeling. Replacement fibrosis increases myocardial stiffness, which contributes to diastolic dysfunction. In the acute phase of cardiac toxicity following anthracycline administration, an inflammatory response with myocarditis-like presentation can occur. This immune-mediated response can be reversed between treatment cycles.

After therapy, LV wall thickness, mass, and relative wall thickness may be reduced.[25-27] Loss of cells in a younger heart with increased stiffness can affect growth potential and myocardial adaptation to body growth, which puts younger children at higher risk for late effects. In several clinical trials in pediatric cardio-oncology, relative wall thickness was the primary outcome variable, including the 2 largest completed trials of dexrazoxane as a cardioprotective agent and an ongoing trial testing the use of carvedilol as primary prevention.[25,28] Adverse remodeling may occur in the absence of overt cardiac dysfunction, and in longitudinal studies, it has preceded dysfunction.[29] Although a reduction in relative wall thickness is potentially concerning, what constitutes a clinically meaningful reduction is unknown. In addition, there are no evidence-based recommendations for managing specific changes in abnormal remodeling. The potential utility of cardioprotective therapy to mitigate or reverse the adverse remodeling process is an area of investigation.

1.1. Assessing LV Size and Function

1.1.1. Assessing LV Dimensions, Volumes, and Mass. Different echocardiographic methods can be used to measure LV dimensions, mass, and volumes. For longitudinal follow-up, consistency in the methodology used in the echocardiographic laboratory is essential for interpretation of the data. Measurements of cardiac dimensions in children should be corrected for somatic growth. We recommend using the Pediatric Heart Network normative *Z* scores, but echocardiography laboratories may use other normative data as long as there is consistency in reporting.[30]

Most frequently reported are linear dimensions of the LV diastolic cavity, interventricular septum, and posterior wall that can be derived from M mode or 2D echocardiography.[31] Measurements are obtained from the parasternal short-axis or long-axis views, just below the mitral valve leaflets. M mode has higher temporal resolution, which may be an advantage for younger children with higher heart rates. Wall thickness measurements tend to be more variable than those for cavity dimensions, especially in newborns.[32] The thinner the wall, the more important accuracy becomes because a 1-mm error in a 5 mm thick wall is more important than a 1-mm error in a 10 mm thick wall. Averaging multiple measurements can increase accuracy, at the expense of prolonging scan and analysis times. Linear dimensions of LV wall thickness and size must be included in every study.

Additionally, LV volumes and mass can be calculated from M-mode/2D measurements using the Teichholz (LV volume) and Devereux (LV mass) formulas, respectively.[31,33] The Teichholz formula is based on linear dimensional measurements at the base of the LV and assumes a regular geometric LV shape when calculating volumes. The M-mode/2D echocardiography-based mass calculation formula combines different linear measurements, including thickness measurements of both the septum and posterior walls. While this is associated with measurement variability, it has been reported to correlate well with CMR mass calculations. Mass calculations require different corrections for body size in children, especially for obese children. Adjustments for height or lean body mass can improve the accuracy of detecting abnormal cardiac mass and have been proposed for monitoring patients with LV hypertrophy.[30,34-36]

Mass and volume can be derived from the area-length method.[31] As generally the endocardial and epicardial borders are well defined on short-axis imaging, this reduces the potential for measurement errors. The calculation for mass and volume in this method relies, however, on geometric assumptions, which can introduce potential errors. Volume can also be determined using the biplane method of disks. This method has the advantage of requiring fewer geometric assumptions than the area-length method does, but in younger children the 2-chamber view can be more difficult to obtain for reasons related to limitations in rib spacing. It is our recommendation that the biplane method should be the preferred method, with the possibility of using area-length in case of limited apical imaging windows and with the option of allowing individual laboratories to define their preferred technique, as long as they are consistent in their approach. Three-dimensional echocardiography can also be used to determine both mass and volume. The lack of geometric assumptions and (semi)-automated analysis are attractive features of 3D echocardiography-derived volume measurements. A meta-analysis comparing measurements taken with 3D echocardiography to those taken with magnetic resonance imaging (MRI), as the reference standard, concluded that 3D echocardiography may underestimate LV volume,[37] whereas data suggest that 3D echocardiography can reliably measure LV mass.[38] Temporal resolution can be problematic when acquiring 3D echocardiographic images, especially in younger children with higher heart rates.

Recommendations and Key Points

- Serial assessment of LV chamber size and wall thickness must be included when evaluating children with cancer before, during, and after treatment.
- Linear dimensions of the LV cavity, interventricular septum, and posterior wall can be measured either by M-mode echocardiography or by 2D echocardiography. Consistency in the method used for measuring linear dimensions is crucial for interpreting serial changes. The measurements should be corrected for body size, and *Z* scores should be included in the reports.
- Left ventricle volume and mass measured by 2D echocardiography using the method of disks or the area-length method can provide additional and more detailed information on LV size.
- Three-dimensional echocardiography is an emerging technique in pediatrics for assessing LV volume and mass without geometric assumptions.

1.1.2. Assessing LV Systolic Function.

1.1.2.1. Left Ventricular FS. Historically, LV FS has been used as a surrogate measure of EF, particularly in children with cancer. Fractional shortening is calculated from 2D echocardiographic or M-mode measurements of LV cavity dimensions in end diastole and end systole from parasternal short- or long-axis views. The reliability of FS based on M-mode calculations in children has been challenged because of high variability in measurements.[39] More recently, the reproducibility and accuracy of the FS calculation based on 2D echocardiographic measurements was questioned.[40] Fractional shortening should be considered a regional functional parameter that it is based on the motion of the basal segments of the interventricular

septum and the posterior wall and that only assesses radial thickening. In case of regional wall motion abnormalities, it cannot be used as a measure of global LV function. Given these limitations, adult guidelines recommend calculating EF in cancer patients rather than using FS. Given its high variability, FS should not be used in the follow-up of pediatric cancer patients.

1.1.2.2. Assessing LVEF. Ejection fraction is the most widely used echocardiographic measure for monitoring global LV function. As the same limitations apply to EF calculated by M mode (Teicholz method) as to FS, it should be avoided in the follow-up of pediatric cancer patients. Common 2D echocardiographic algorithms to measure EF include the biplane method of disks and the 5/6 area-length (bullet) method. The method of disks is recommended in adult guidelines because it is less dependent on geometric assumptions.[41] It requires acquiring 2 imaging planes from apical views. In younger children, obtaining the apical 2-chamber view can be challenging because of the large probe imprint relative to rib spacing. This can result in foreshortening of the 2-chamber view, affecting volumetric calculations. The area-length method can be easier as it can also use subcostal short-axis views in case of poor parasternal windows. Both methods require high-quality images for defining the endocardial borders using either manual or automated tracing. We recommend using the biplane or 3D echocardiographic methods for calculating EF. In cases where the apical images are suboptimal, the area-length method can be a good alternative. The use of the method of disks is consistent with the adult guidelines and allows EF measurements to be used for serial follow-up. Most importantly, each laboratory should consistently follow a single method for surveillance and serial measurements for assessing EF. Fully automated tracking and analysis methods using machine learning–based software have become available and can rapidly compute EF with high accuracy (98%), low inter- or intrareader variability, and good agreement with EF measurements derived from manual tracking.[42] However, these algorithms have not been widely tested in children and specific applications need to be developed for pediatric use.

In adults, EF calculated by 3D echocardiography has been recommended for following oncology patients with the method of disks as the alternative if 3D echocardiography is not available. However, using 3D echocardiography has unique challenges in children, including the need for patient cooperation to acquire high-quality data with good spatial and temporal resolution. Moreover, at higher heart rates, the relatively low volume rates can affect the accuracy of identifying the end-systolic and end-diastolic frames needed to calculate EF. The feasibility of 3D volumetric LV functional assessment in children ranges between 70% and 91%, with lower values for younger children.[43-45] The accuracy of 3D echocardiography for measuring LV volumes and function is indicated by its excellent agreement with CMR-based LV volumes and EF calculations in both children and adults.[46,47] The clinical utility of 3D-based volumetric acquisitions is facilitated by increasing automation, often using artificial intelligence–based technology. It can be assumed that 3D EF calculations will become the gold standard in the future. While we recommend using it in adolescents and young adults, 2D-based volumetric calculations remain the most commonly used methods in pediatric echocardiography.

1.1.2.3. Detecting Meaningful Change in LV Systolic Function. Given the measurement variability, different guidelines have attempted to describe a clinically significant change in LV functional echocardiographic parameters in children, although the changes have not been evaluated in prospective studies. Early consensus-based guidelines have defined a significant decrease in LV function as (1) an absolute 10% decrease in FS (e.g., FS from 39% to 29%), (2) an absolute value of FS <29%, (3) a 10% decrease in EF (e.g., from 65% to 55%), or (4) an EF <55%.[16] The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group 2012 guidelines defined LV function as borderline abnormal when FS was between 25% and 29% or EF was between 45% and 49%. Abnormal function was defined as an FS <25% or an EF <45%.[48] Because of higher reproducibility, our group recommends using EF measurements rather than FS. Changes within the normal range are challenging to interpret, given that EF may be influenced by multiple variables, such as anemia or hyperdynamic loading conditions at cancer diagnosis/baseline assessment. Additionally, the clinical predictive value of a 10% decrease in EF has not been demonstrated. Therefore, it is more clinically useful to identify when EF is abnormal, as this may require consultation with a cardio-oncology team. For this purpose, an EF ≥55% is considered normal, between 50% and 54% as borderline normal, and below 50% as abnormal. When EF is borderline or abnormal, an earlier echocardiographic reassessment, typically within 1 to 2 weeks, is recommended, or EF could be assessed using another imaging modality such as cardiac MRI before therapeutic changes are considered. Especially during treatment, early reassessment overcomes some of the measurement variability and allows for additional recovery time from the last chemotherapy dose. When EF is <50%, this is considered abnormal, and earlier reassessment within 1 to 2 weeks or confirmation with a different imaging modality such as cardiac MRI may be considered. When EF is abnormal, a cardiology consultation is recommended.

Recommendations and Key Points

- We recommend the use of EF and not FS for monitoring LV function in children with cancer.
- For measuring EF by 2D echocardiography, we recommend using the biplane method of disks for serial follow-up. If apical 2-chamber views are limited, the area-length method is a reasonable alternative, especially in young children. When available, 3D echocardiography-based EF calculations are preferable in adolescents and young adults.
- Each laboratory should consistently utilize a single method for serial assessment of LV function. The method used should be identified in the report.
- Normal EF is ≥55%. An EF value between 50% and 54% is borderline function and should be confirmed by a second echocardiogram acquired within 1 to 2 weeks (during treatment) or within 6 months (after treatment). In case of borderline LV function, assessment of LV function by other imaging modalities, such as cardiac MRI, can be considered. When EF is <50% a cardio-oncology consultation is recommended (Figures 3 and 4).

1.1.3. Use of Tissue Doppler and Myocardial Deformation Imaging.

1.1.3.1. Tissue Doppler Velocities. Myocardial function can be measured directly from myocardial velocities and myocardial deformation with tissue Doppler imaging and speckle-tracking echocardiography (STE).[49] Tissue Doppler imaging measures myocardial velocities and thus assesses myocardial motion. Typically, these images are obtained at or just inferior to the mitral annulus from the apical 4-chamber view to measure longitudinal annular motion as a characteristic of LV longitudinal function. For assessing systolic function, peak systolic velocity is typically measured. Although some data suggest tissue Doppler velocities are reduced in children exposed

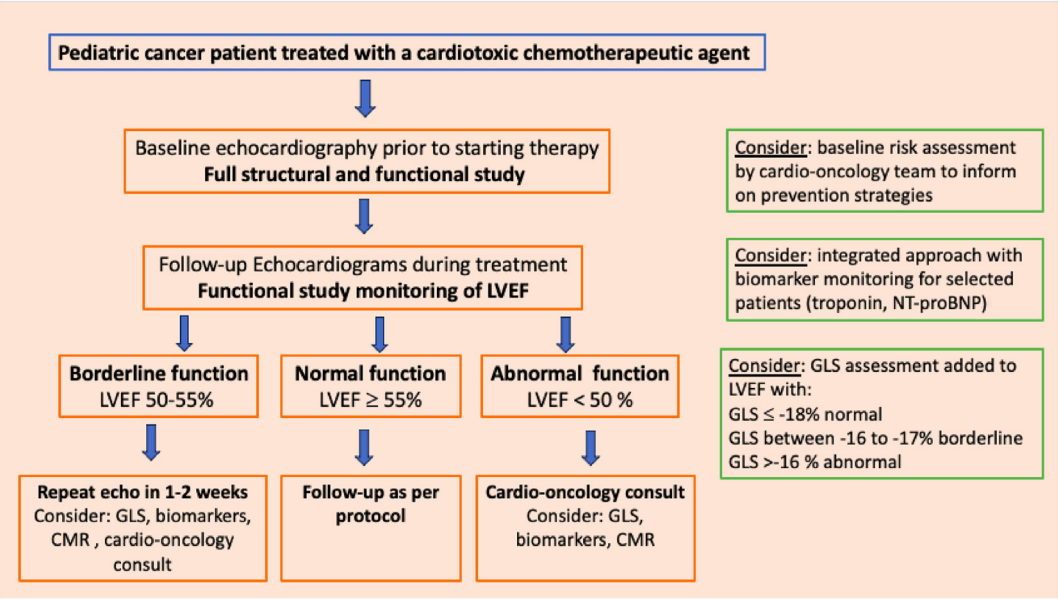


Figure 3 Monitoring of cardiac function in children with cancer during treatment with cardiotoxic agents.

to anthracyclines, the reductions were mainly in diastolic velocities rather than in systolic velocities.[50] Clinical utility of tissue Doppler velocities in children is limited as they are influenced by age, heart size, heart rate, cardiac translation, and intersegmental tethering. Myocardial deformation imaging by STE has largely replaced tissue Doppler imaging for assessing systolic function.

1.1.3.2. Myocardial Deformation Imaging by STE. Speckle-tracking echocardiography is a grayscale imaging technique based on identifying echocardiographic reflectors in the myocardium (speckles), whose motion can be tracked throughout the cardiac cycle in 2 or 3 dimensions.[51] The most commonly used method is 2D STE. Strain reflects how much a myocardial segment shortens or thickens, whereas strain rate reflects the rate of deformation. Left ventricle myocardial deformation is described in a Cartesian system with myocardial fiber shortening or lengthening in the longitudinal and circumferential directions and myocardial thickening or thinning in the radial direction. By convention, myocardial strain is defined as the percentage change in myocardial segment length from its original length, with systolic myocardial segmental shortening or thinning denoted by a negative value (–%) and lengthening or thickening by a positive value (+%). Longitudinal myocardial strain can be assessed from the LV apical views, whereas circumferential and radial strains are measured in LV short-axis views. The conventional 17- or 18-segment models of the LV are typically used. Strain measurements in the different LV segments are averaged to calculate global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS). The most frequently used parameter is GLS, which is a global index of LV longitudinal function that has been studied in various diseases in both children and adults. Global circumferential strain and GRS are less reproducible, and their clinical value in addition to GLS is uncertain. Global longitudinal strain is measured from the apical 2-, 3-, and 4-chamber views. Importantly, the effect of foreshortening on strain measurements can be considerable in adults.[52] The impact of foreshortening in children has not been well studied but could be important for retest variability. In the absence of 2- or 3-chamber views, average 4-chamber strain can be reported. Processing is largely automated and can be performed on the ultrasound machine or using dedicated software. In children, the higher heart rates can be a limitation as frame rates have to be at least 2/3 of the heart rate, which can be difficult to achieve. Strain measurements are influenced by heart rate and loading conditions, and changes in strain measurements must be interpreted cautiously.

The advantage of using GLS is that it is highly reproducible, with a variability ranging between 5% and 10%, which is much lower than the variability of a 2D EF calculation that ranges between 15% and 20%.[53,54] Adult cardio-oncology guidelines have recommended that GLS be included in the baseline assessment and follow-up of patients treated with cardiotoxic drugs.[1,2,55] In these guidelines, a reduction in absolute strain by greater than 15% of its baseline value (for instance from −20% to −17%) is considered to be clinically important on serial evaluations. An absolute GLS value more negative than −18% is considered normal, a value between −16% and −18% is considered borderline, and a value less negative than −16% is considered to indicate LV dysfunction. Several studies in adults found that a reduction in GLS preceded a reduction in EF when used for surveillance during treatment,[56,57] with some data suggesting that GLS may also be useful in cardiotoxicity monitoring during pediatric cancer treatment.[58]

Introducing STE to a clinical echocardiography laboratory can be technically challenging, mainly because strain measurements can vary slightly by vendor and among software packages.[53] Intervendor variability has also been reported in pediatric applications.[59-63] Accordingly, using STE for clinical follow-up requires either using the same ultrasound equipment or using vendor-neutral software to analyze the strain data obtained on ultrasound machines from different vendors. The second approach requires exporting data into a specific analysis program, which adds complexity to the workflow. Other obstacles to introducing STE in pediatric echocardiography laboratories have been identified, which all have possible solutions.[64] Some software packages can calculate layer-specific strain values including endocardial or midlayer strain, but

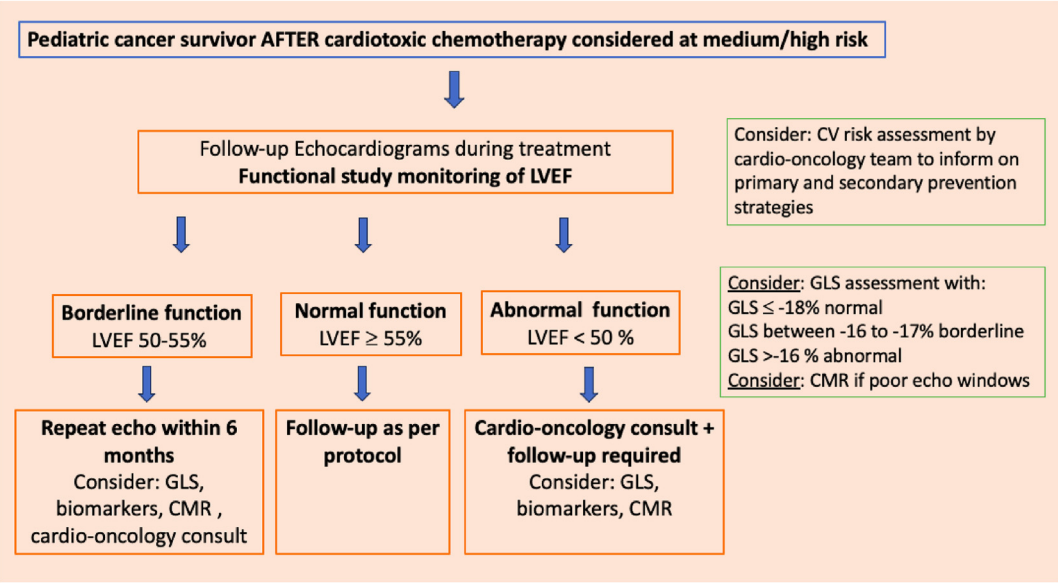


Figure 4 Monitoring of cardiac function in children with cancer after treatment with cardiotoxic agents. *CV*, Cardiovascular.

these values may also vary by vendor.[62] Both endocardial and mid-myocardial strain values can be used for follow-up, as long as there is consistency in the method used as the values slightly differ between both methods. Every laboratory should develop a workflow and standard method for assessing GLS in pediatric cancer patients.

Normal values for LV strain data in healthy children are available across vendors. A meta-analysis of data from 2,300 healthy children found that mean LV GLS is −20.2% (95% CI, −19.5% to −20.8%), mean GCS is −22.3 (95% CI, −19.9% to −24.6%), and mean GRS is 45.2% (95% CI, 38.3% to 51.7%).[65] Different reference ranges vary, but the above analysis is independent of differences in demographics, age, and vendor. The wide normal ranges for GCS and GRS make them less useful for serial monitoring in cancer patients. A meta-regression analysis suggested that LV end-diastolic dimension helps explain variation in measurements of GLS. A study in healthy children of the effect of body size and age on GLS measurements, converted to *Z* scores, found a statistically significant but weak nonlinear correlation between GLS and body surface area.[66] However, the influence of body surface area is small and can be clinically ignored. As normal ranges for children are very similar to adult values, we propose using the values suggested for defining normal ranges in adults. When GLS becomes borderline or abnormal, with preserved EF, more frequent follow-up may be indicated, but the data supporting this are still missing.

1.1.3.3. Speckle-Tracking Echocardiography for Monitoring Acute Cardiotoxicity. The potential utility of STE during cancer treatment in children to detect acute cardiotoxicity has been explored in different studies, all including a relatively small number of patients. The acute effect of anthracycline infusions on myocardial function resulted in increased myocardial wall thickness and decreased radial and longitudinal strain values.[67] Several studies have investigated strain indices before and during the first year of cancer therapy in children showing a decrease in GLS when serially followed over time, although with most values remaining within the normal range.[67-69] The predictive value of an early decrease in GLS, in the presence of preserved EF during treatment and in long-term survivors, is uncertain and is in need of prospective longitudinal studies. The concomitant monitoring of GLS and EF as parameters for global LV function, however, allows detection of early changes in LV function. When GLS becomes abnormal in the presence of preserved EF, more frequent surveillance may be recommended. Due to the lack of evidence of the prognostic significance, EF remains the clinical reference parameter for the diagnosis of abnormal LV function in pediatric cancer patients. More data are needed before declines in strain can be used in therapeutic decisions during cancer treatment in children.

1.1.3.4. Speckle-Tracking Echocardiography for Monitoring Late Cardiotoxicity in Children. Most studies utilizing end-of-treatment myocardial deformation imaging in childhood cancer survivors are cross-sectional and have limited outcome data. Myocardial strain was assessed with a variety of techniques, including tissue Doppler-derived strain calculations as well as 2D and 3D STE measurements. Most studies found statistically significantly lower longitudinal strain in childhood cancer survivors compared to healthy controls. However, the differences were small and often within the normal range.[70] The prognostic value of these relatively lower values is still unknown. The St. Jude Lifetime Cohort Study includes adult survivors of childhood cancer.[71] This study also suggested that measuring GLS can help to identify patients with subclinical cardiac dysfunction, but its prognostic value also remains uncertain in adult survivors of childhood cancer. We recommend adding GLS as an additional measurement to follow children after cancer treatment. If GLS becomes abnormal in the presence of preserved EF, an earlier follow-up within 6 months may be indicated, but the utility requires further validation in prospective studies.

Recommendations and Key Points

- Measurement of GLS by STE is a reproducible measurement of LV function that should be included in the assessment of LV function.
- Given intervendor variability, the use of either a single-vendor or a vendor-neutral strain analysis software is recommended for serial follow-up.
- Values of GLS equal to or more negative than −18% are considered normal, of −16% to −17% are considered borderline normal, and less negative than −16% are considered abnormal. The predictive value of an early decrease in GLS during treatment and in long-term survivors is uncertain in the presence of preserved EF.
- If LVEF is >55% but GLS is > –18%, more frequent follow-up could be considered.

1.1.4. Assessing LV Diastolic Function. In adults, echocardiographic measurements of diastolic function are essential in assessing LV function.[72] Diastolic dysfunction is highly prevalent in women being treated for breast cancer, and it precedes the development of systolic dysfunction.[73] Also, in children, changes in diastolic function after anthracycline treatment can be present, although isolated diastolic failure with preserved EF is extremely rare.

Diastolic function is assessed based on a combination of variables, including mitral inflow flow patterns, mitral annular tissue Doppler velocities, left atrial (LA) volume, and peak tricuspid regurgitation velocity.[72] Additional techniques include pulmonary venous flow patterns and, more recently, LA strain measurements.[74]

Adult guidelines on assessing diastolic function distinguish between an algorithm for patients with preserved EF to determine whether diastolic function is normal or abnormal and an algorithm for patients with decreased EF to assess LV filling pressures.[72] In children after chemotherapy with preserved systolic function, detecting diastolic abnormalities is important because they are possibly the first sign of cardiac dysfunction, enabling identification of isolated diastolic dysfunction with preserved EF. For children with reduced EF, estimating filling pressures may be useful for clinical management and outcomes.

Unfortunately, the echocardiographic assessment of diastolic function has been shown to be unreliable in children with cardiomyopathies.[75] Different factors contribute to this problem. Mitral inflow and tissue Doppler velocities are influenced by age, body size, and heart rate.[76,77] Pulsed-wave Doppler inflow velocities are especially sensitive to loading conditions and heart rate. Tachycardia is common during cancer therapy and can confound interpretation of Doppler measures of diastolic function, especially when it results in fusion of mitral E and A waves. The E/A ratio is influenced by heart rate, as with increasing heart rate the velocity of the A wave increases relative to the E wave, resulting in a decreased E/A ratio.[78,79] Adult guidelines should be applied to children with caution as the myocardial substrate in adults exposed to chemotherapy differs from that in children, as age-related diastolic abnormalities (e.g., early relaxation abnormalities) and associated diseases (e.g., ischemic heart disease, hypertension, diabetes, obesity) are more prevalent in adults. Finally, the typical progression from normal to delayed early relaxation to restrictive physiology has not been well documented in children.[80]

The above factors explain why data on diastolic dysfunction in children exposed to anthracyclines are contradictory, with some studies reporting overall preserved diastolic function and others reporting changes in diastolic parameters in childhood cancer survivors. The St. Jude Lifetime Cohort Study identified diastolic dysfunction in 8.7% of adult childhood cancer survivors who had received anthracyclines.[71] In children, diastolic dysfunction is not well defined and this makes it difficult to provide data on how frequently diastolic dysfunction occurs during or after cancer treatment. In children followed after treatment, it was observed that the mitral E/A ratio was significantly lower in patients who developed cardiomyopathy compared to matched controls who did not develop cardiomyopathy.[81] In a long-term follow-up of survivors of childhood cancer treated with anthracyclines, some developed a restrictive-type cardiomyopathy characterized by a normal-to-small LV chamber with wall thinning and decreased systolic function.[29] These data suggest that serial assessment of some diastolic parameters could have predictive value, but larger prospective studies are needed to identify which parameters are the most clinically relevant.

Given the variability of Doppler measurements in children, LA volume assumes greater importance in the assessment of LV diastolic function in children treated with anthracyclines. In contrast to other diastolic measurements, LA volume remains relatively stable during growth when corrected for body surface area.[82] When assessed by the biplane method, a normal LA volume is < 34 mL/m^2.[83] Especially in younger children, there may be technical limitations such as foreshortening, particularly in the 2-chamber view, which can result in underestimation of LA volume. Three-dimensional echocardiography can potentially overcome this limitation, and normal pediatric LA volumes and Z scores have been published.[84] An increase in LA volume index may reflect a chronic increase in LV filling pressures and can reflect underlying LV diastolic dysfunction.

Left atrial function can be assessed using STE to describe LA deformation through the different phases of LA filling and emptying. Left atrial strain assessment is an emerging technique that is used to identify changes in LV diastolic function.[74] A European Association of Cardiovascular Imaging/American Society of Echocardiography (ASE)/Industry Task Force recommended a standardized nomenclature for describing the 4 atrial phases during the cardiac cycle.[85] Phase 1 begins with LV end diastole, where the atrium is at a minimum volume (LAVmin). Phase 2 starts when the mitral valve is closed and the left atrium (LA) fills through the pulmonary veins to reach a maximum volume at end systole. This is measured as LA reservoir strain and is a positive number. In phase 3, as the mitral valve opens, the atrium functions as a conduit during early ventricular filling, as the strain curve declines and flattens into diastasis. The conduit strain ends with the onset of the P wave. Phase 4 is associated with atrial contraction and is called LA contractile strain, which is a negative value. Normal values from cross-sectional studies that describe maturational changes in these measures have been published.[84,86] Normal reference values for 3D echocardiographic LA volumes and LA strain have also been published.[84]

This ability to discriminate among the phases of LA function raises the prospect of evaluating children with cardiomyopathy with strain measures of LA function. In an STE analysis of LA strain in 136 children with a variety of cardiomyopathies, peak LA reservoir strain was lower than in healthy controls.[87] Left ventricular end-diastolic pressure measured through a catheter was significantly and inversely correlated with LA peak systolic strain in a cross-sectional study of 45 children treated with anthracyclines 1 year after chemotherapy.[88] In these survivors, the conventional measurements of diastolic function and LV GLS did not differ significantly from healthy controls.

Recommendations and Key Points

- Despite their limitations, assessment of LV diastolic parameters should be considered an essential part of LV functional assessment.
- We recommend serial assessment of mitral inflow velocities, tissue Doppler velocities at the septal and lateral mitral annulus, LA volume by the biplane method, and peak tricuspid regurgitation velocity.
- Serial assessment of these parameters can help to identify development of diastolic abnormalities. Diastolic dysfunction remains poorly defined in children, as no specific guidelines have been developed.
- Left atrial volume assessment is a more stable parameter of LV diastolic function in children. Progressive LA dilatation without obvious explanation could indicate increased LV stiffness and LV filling pressures.
- Left atrial strain is a promising measure of LA function that requires further validation in children exposed to cancer treatment.

1.2. Assessing RV Function

The effects of cancer therapy on the RV are less well studied than those on the LV. Several factors could affect RV function, including treatment-related pulmonary hypertension and direct cardiotoxic effects of chemotherapy on the RV. Assessment of RV pressure is an essential part of every echocardiographic study to assess the presence of pulmonary arterial hypertension. This is based on tricuspid regurgitation jet, pulmonary insufficiency jet, and assessment of septal flattening in systole. In adults treated for cancer, several studies have found changes in RV functional parameters, sometimes in the absence of LV dysfunction.[89-91] Data about RV function in children early after cancer therapy are limited, with some studies demonstrating statistically significant differences between patients and healthy controls.[92,93] Right ventricular (RV) enlargement and reduced RV systolic function have also been detected by CMR in childhood cancer survivors.[94] Overall, data on the effects of anthracycline therapy on the RV are scant and the clinical importance of RV dysfunction still remains unclear. The increasing literature on the impact of anthracycline treatment on RV function indicates the need for including RV functional assessment in a comprehensive functional follow-up protocol. In case RV dysfunction is suspected, a CMR could be performed to better characterize RV size and function.

Guidelines for evaluating adult cancer patients recommend qualitative and quantitative assessments of RV chamber size (at least RV basal diameter) and right atrium (RA) area, as well as measures of RV longitudinal function, such as tricuspid annular plane systolic excursion (TAPSE), tricuspid annular s′ velocity, and fractional area change (FAC).[1] For RV size assessment, we recommend at least a qualitative assessment and an RV size measurement, such as RV basal diameter. For functional assessment, at least RV systolic function should be qualitatively assessed. If RV function quantification is performed, RV FAC is useful in children. Given the age and heart rate dependency of tissue Doppler velocities, they have a more limited clinical utility. Tricuspid annular plane systolic excursion can be used, but normal values are also age and body size dependent. Recent studies have included 2D or 3D echocardiographic STE measurements of RV free-wall longitudinal strain, but this needs further validation.[95]

Recommendations and Key Points

- Comprehensive echocardiographic surveillance of pediatric cancer patients should include serial assessment of RV size, RV function, and RV systolic pressure.
- Assessment of RV size should include qualitative assessment of RV size and at least 1 measurement such as RV basal diameter.
- Quantification of RV function in children includes FAC and TAPSE.
- Right ventricular free-wall strain and 3D echocardiographic measurements of RV EF are emerging techniques for evaluating RV systolic function, but their utility in monitoring cardiac effects of cancer treatment requires further validation.

1.3. Role of Stress Echocardiography

Stress echocardiography allows assessment of contractile reserve in nonischemic cardiomyopathy, with an abnormally low reserve helping to identify subclinical systolic dysfunction. In adults, both exercise and dobutamine stress echocardiography have been used extensively to measure contractile reserve.[96,97] Echocardiographic imaging of LV systolic function during cardiac stress allows both qualitative and quantitative assessment of LV contractile reserve. In asymptomatic patients with normal LVEF, it could theoretically identify reduced systolic reserve, which is a marker of early dysfunction. Pediatric stress echocardiography is evolving.[98-102] Most of these studies used exercise stress echocardiography to ease performance and improve tolerability for the child. Only a few studies used dobutamine echocardiography because, unlike adults, younger children typically require sedation or general anesthesia. The most common echocardiographic findings at rest were that EF, FS, and percentage of LV posterior wall thickening were lower and LV wall stress was higher in survivors compared to healthy controls. At peak stress, FS, EF, percentage of LV, and posterior wall thickening were lower in survivors than in healthy controls. While the observed peak values are different between patients and controls, cutoff values for identifying an abnormal response have not been published. It was also observed that myocardial functional response did not differ between survivors and healthy controls when correcting for heart rate during exercise.[98] There is also no evidence that stress echocardiography predicts systolic dysfunction.[103] Based on these data, there is no proven additional utility of stress echocardiography for monitoring anthracycline cardiotoxicity within 10 to 20 years after the end of therapy.

Recommendations and Key Points

- The clinical utility of stress echocardiography for monitoring childhood cancer survivors has not been defined. Currently there is no clinical indication to monitor function in pediatric cancer patients based on stress echocardiography.

1.4. Quality Assessment and Quality Improvement

Better reproducibility of echocardiographic measurements through quality improvement processes should be an integral part of pediatric echocardiography laboratory operations. Every laboratory should a have a quality improvement plan to improve consistency in acquiring and interpreting oncology-specific echocardiograms and measurements in children. Every laboratory should also have a process for evaluating and addressing variability among its operators. This process should include cross-modality comparisons when available and blinded interpretations by a second echocardiographer to assess reproducibility.[104] The availability of a specific cardio-oncology imaging protocol can improve the quality and completeness of image acquisition and analysis.[105] Given that measurements by 2D and M-mode echocardiography and the various volumetric algorithms are not interchangeable, measurements should be standardized across operators and reporting staff.[19] The report should indicate the method used to compute EF. Similarities and disparities in image acquisition and interpretation should be discussed in quality improvement laboratory staff meetings. Formalized teaching sessions can reduce interobserver variability.[106] These educational sessions can include reviewing guidelines, demonstrating preferred measurement techniques and visual prompts and providing continued feedback.[107] Cycles of testing, training, and retesting can reduce variability. Every pediatric laboratory should consider the Intersocietal Accreditation Commission standards and obtain accreditation through the Intersocietal Accreditation Commission or a body with a similar formal quality improvement program.

PART 2. USE OF CMR IN EVALUATING CHILDREN WITH CANCER

The current role of CMR in the assessment of children with cancer is not well defined. Cardiac magnetic resonance imaging offers some advantages to echocardiography as it allows for measurement of

ventricular volumes and global and regional function with low variability and generally high interstudy reproducibility.[1,108] Additionally, tissue characterization by T1- and T2-weighted imaging and late gadolinium enhancement (LGE) can identify myocardial fibrosis, edema, and inflammation. The limitations for its use in children include that CMR is not always readily available, requires general anesthesia or sedation in younger children, and is more resource intensive, which limits its utility in routine follow-up. For serial follow-up, echocardiography remains the primary imaging modality. Currently no data would support the routine or serial use of CMR in the follow-up of childhood cancer patients.

Cardiac magnetic resonance imaging techniques to evaluate the cardiac effects of cancer treatment are largely based on studies of adult cancer patients.[109] Currently, only limited data on the use of CMR in childhood cancer patients are available.

Nevertheless, there are indications for when performing a CMR in pediatric cancer patients may be considered. These include (1) when echocardiographic imaging windows are limited and do not allow reliable functional assessment; (2) when borderline or abnormal cardiac dysfunction is detected by echocardiography, defined as EF between 50% and 55% or below 50% as an alternative method to confirm the echocardiographic finding; (3) when myocarditis is suspected and tissue characterization could help with identifying myocardial edema; (4) when constrictive pericarditis is suspected; or (5) when the cancer is involving the heart. Specific CMR protocols based on Society of Cardiac Magnetic Resonance Imaging guidelines should be utilized for these indications with quality assurance and standardization of acquisitions and measurements as part of the CMR protocol development.

2.1. Assessment of Ventricular Mass, Volumes, and Global Systolic Function

Every CMR protocol should include assessment of LV and RV volumes, LVEF and RV EF, and LV mass. Measurement of LV and RV size and function will often be the primary indication for performing a CMR study in children. Similar to echocardiographic findings, CMR studies in adults cancer patients have demonstrated that early cardiac injury is characterized by a progressive decline in global and regional myocardial function with a gradual increase in LV end-systolic volume during the first year after chemotherapy.[110-112] Furthermore, an early decrease in LV mass after anthracycline exposure is associated with HF symptoms, independent of the decline in EF.[113] Late cardiac injury results in increased LV and RV end-systolic and end-diastolic volumes, decreased EF, and reduced ventricular mass. In adults with reduced EF, the relationship between anthracycline dose and LV mass index as measured by CMR is inverse, and a reduced LV mass <57 g/m^2 is strongly associated with adverse cardiovascular events.[114]

Data on using CMR for measuring RV function in childhood cancer survivors are sparse; one study describes 17 (27%) of 62 such patients exposed to anthracyclines as having abnormal RV function, with an EF $< 45\%$.[92] However, outcome data for patients with decreased RV function are not available, and much of the functional CMR data are only in adults and should not be directly extrapolated to children without further evidence. Furthermore, general anesthesia, which is rarely used in adults, can have a deleterious effect on EF measurements. While CMR is more accurate and reproducible than echocardiography for biventricular volumes, EF, and LV mass, the aforementioned limitations preclude routine use for serial measurements; however, if CMR is being used for a select population, it is recommended to measure biventricular size, biventricular function, and LV mass as all of these measurements can be derived from the same acquisition and have shown value in the limited literature to date.

2.2. Measuring Global and Regional Myocardial Function With CMR-Based Myocardial Deformation Imaging

Cardiac magnetic resonance imaging can also be used for measuring myocardial segmental strain similar to echocardiographic strain measurements. Different CMR techniques have been used to measure myocardial deformation and include techniques that require specific predefined sequence acquisitions or can be based on routinely acquired cine images. Myocardial tagging is the most validated technique for assessing myocardial deformation.[115] It involves the planned acquisition of magnetically labeled (tagged) cine sequences with subsequent postprocessing to measure deformation of the tagged lines. Strain-encoded MRI can measure regional deformation and has been found to be useful in the assessment of subclinical myocardial dysfunction in adult cancer patients.[116,117] Strain-encoded MRI utilizes images from the 2-, 3- and 4-chamber views to calculate circumferential strain and 3 short-axis slices (basal, mid-ventricular, and apical) to measure longitudinal strain.[118] Feature tracking uses readily available standard steady-state free precession cine images. The principle of feature tracking is based on optical flow technology and the ability to identify and track features at the blood-myocardium interface through a sequence of images.[119] Longitudinal strain is calculated from long-axis images, and circumferential and radial strain from short-axis images.

Studies have found that measurements of GLS obtained by CMR-based feature-tracking techniques correlate well with STE-based measurements and EF.[120,121] Glocal circumferential strain measured by CMR has better reproducibility than that measured by STE.[120,121] Similar to STE, global peak longitudinal and circumferential strain magnitude, as measured by CMR-tagged imaging, decrease early, before changes in EF. A decrease in GLS and GCS has been described in childhood cancer survivors early and late after cancer therapy.[110,111,122-125] The lack of uniformity in measuring CMR-based myocardial deformation, the absence of larger studies comparing the different techniques, and the lack of standard values among vendors have limited its wide use in cardio-oncology. Speckle-tracking echocardiography has been better validated for serial follow-up of cancer patients when compared to CMR-based myocardial deformation imaging. The main utility of CMR-based strain at this time is in patients with limited echocardiographic windows.

2.3. Left Ventricular Diastolic Function

The clinical use of CMR for assessing LV diastolic function is limited compared to that of echocardiography. Some of the same indices typically obtained by echocardiography can also be measured with CMR, but similar to the echocardiographic-based diastolic parameters, their interpretation in children is problematic. Phase-contrast CMR provides analogs of spectral Doppler measures, including mitral valve and pulmonary vein inflow tracings, typically averaged over many cardiac cycles. Phase-contrast CMR can also provide an analog of tissue Doppler imaging using a technique called tissue-phase mapping to measure regional myocardial velocity.[126] Cine steady-state free precession can measure LA size by geometric methods or by obtaining images of the entire LA and using a summation-of-disks method.[127] The high reproducibility of LA and RA volume measurements can be considered a potential advantage of CMR. A few studies have reported using CMR for assessing LV diastolic function in survivors of childhood cancers or in children undergoing chemotherapy. One study found

that an increase in LA volume correlated with total anthracycline dose in children with a mixed group of solid tumors, leukemia, and lymphoma; another found that the E/e′ ratio in young adult survivors of childhood cancer receiving stem cell transplants was higher than that of healthy controls without providing outcome data.[124,128]

2.4. Cardiac Magnetic Resonance Imaging–Based Tissue Characterization

Tissue characterization based on T1 and T2 mapping could be used for detection of diffuse myocardial fibrosis, which is associated with the pathological remodeling of anthracycline cardiotoxicity.[129] Both early and late diffuse myocardial fibrosis, as detected by T1 mapping based on increased extracellular volume, have been reported after exposure to high doses of anthracyclines.[125,130-132] Extracellular volume (ECV) has been reported in children to be inversely correlated with exercise capacity and also correlated with anthracycline dose.[133] These data suggest that ECV may be potentially clinically relevant but require further validation in larger studies. T2 mapping sequences allow for assessing the presence of myocardial edema caused by inflammation, ischemia, and other pathological conditions affecting myocardial water content.[134] Studies show that myocardial edema peaks subacutely early after anthracycline infusion but does not persist in long-term survivors.[135,136] Cardiac magnetic resonance imaging provides strong evidence for acute myocardial inflammation if a T1- (LGE or ECV) or T2-based sequence is abnormal. Although having both a positive T1- and T2-based marker increases specificity, clinically suspected myocarditis can be diagnosed if only 1 marker is positive.[137] Tissue T2 relaxation (T2*) can detect iron deposition in the liver and myocardium, which can be present after multiple blood transfusions and can cause myocardial dysfunction.[138] Measurements of cardiac T2* may identify this further insult to myocardial function in children who received multiple blood transfusions.[139] Longitudinal studies are needed to investigate the prognostic utility of T1, T2, and T2* mapping techniques and ECV in survivors of childhood cancer.

Gadolinium-based contrast agents shorten T1, thereby increasing the signal in the blood pool and tissues that absorb gadolinium. Delayed washout of the contrast medium from diseased myocardium can be assessed by LGE and T1 mapping. Late gadolinium enhancement is, however, an infrequent finding in patients after anthracycline treatment both acutely as well as late after treatment, even in patients with cardiomyopathy.[94,125,140] After anthracycline and trastuzumab adjuvant chemotherapy, LGE has been reported in some patients with acute LV systolic dysfunction at 6 months follow-up, with the subepicardial linear LGE pattern in these patients being characteristic of myocarditis. The use of contrast agents has raised some concerns and resulted in contrast being used only when thought necessary. Acute adverse events after these agents are administered are rare (0.07%), with most events characterized as mild. Hypersensitivity reactions occur in 4/100,000 patients.[141] Nephrogenic systemic fibrosis has been almost completely eliminated after gadolinium-based contrast agent dose reductions and routine screening of patients to identify renal disease.[142,143] Gadolinium retention in tissue, including bone and brain, is often asymptomatic.[144] However, some patients manifest symptoms secondary to possible immunologic reaction, which is categorized as "gadolinium deposition disease."[145] Our recommendation is to only use contrast agents when indicated and, if they are used, use the lowest possible dose in patients without evidence of impaired kidney function.

2.5. Assessment of Pericardium and Valve Function

Pericardial disease may be a long-term consequence of mediastinal radiation, although chronic constrictive pericarditis in children is now rare, given the lower radiation doses and improved radiotherapy techniques.[9] Cardiac magnetic resonance imaging can be used for detecting pericardial thickness when constrictive pericarditis is suspected. Radiation may also cause valve damage and valve dysfunction. The left-sided heart valves are disproportionately affected as a consequence of mediastinal radiation therapy, suggesting that the higher pressure in the systemic circulation is important in pathogenesis.[146,147] While echocardiography remains the primary technique for diagnosing valvular regurgitation and stenosis, CMR can quantify valvular regurgitation and can be useful for assessing the impact of valve dysfunction on chamber sizes and function.

Recommendations and Key Points

- Cardiac magnetic resonance imaging is considered a valuable adjunct to echocardiography (1) when echocardiographic imaging windows are limited and do not allow reliable functional assessment; (2) when borderline cardiac dysfunction is detected by echocardiography, defined as EF between 50% and 55%; (3) when myocarditis is suspected and tissue characterization could help with identifying myocardial edema; (4) when constrictive pericarditis is suspected; or (5) when tumor is involving the heart.
- Every CMR assessment in a pediatric cancer patients must include assessment of LV and RV volumes and EF as well as LV mass. Left atrial and RA volumes can be included in the assessment.
- If CMR is performed on children with cancer during early or late follow-up to assess LV volumes and function, it is reasonable to include myocardial deformation imaging and tissue characterization (T1 and T2 mapping) to assess diffuse myocardial fibrosis, edema, and iron load (when indicated). Our recommendation is to only use contrast agents when indicated and, if they are used, at the lowest possible dose in patients without evidence of impaired kidney function.
- Cardiac magnetic resonance imaging can provide additional information about valve function and pericardial disease, including pericardial effusion, and thickening and inflammation of the pericardium if echocardiography is not diagnostic.[148]
- Quality assurance and development of dedicated imaging protocols is recommended to standardize image acquisition and analysis.

PART 3. USE OF CARDIAC CT IN EVALUATING CHILDREN WITH CANCER

Cardiovascular CT (CCT) is not a first-line technique for cardiovascular imaging in children with cancer, given concerns about radiation exposure. It can be used as a possible alternative modality for obtaining ventricular volumetric and functional information should echocardiography and CMR not be suitable. Cardiovascular CT can provide accurate and reproducible volume and EF measurements; it is a third-line imaging modality for this indication.[149-151] Cardiovascular CT can be considered for noninvasive evaluation of coronary anatomy in case of symptoms of ischemia and is an alternative imaging technique to assess for cardiac tumors, mediastinal tumors contiguous to the heart, and pericardial thickness assessment in case MRI is contraindicated or not feasible.

For adult survivors of childhood cancers with a history of radiotherapy (RT) where the heart is in the treatment field, CCT may be useful. Surveillance for atherosclerotic disease in this population is important, and lipid monitoring and ischemia evaluation with stress tests may be insufficient to identify early asymptomatic atherosclerosis

related to RT.[152] The coronary artery calcium (CAC) score is a robust imaging biomarker that can predict the 10-year risk of cardiovascular events in patients without cancer.[153] Gated, noncontrast CT with a small field of view focused on the heart can measure CAC deposition.[154] While coronary CT is used to identify coronary artery obstructions, it has higher radiation doses than a CAC scan and requires iodine-based contrast agent administration.[155] In patients who received high-risk RT above 18 years of life, surveillance CAC scans could be considered every 5 to 10 years, while coronary CT scans should be reserved for the same patient group with abnormal CAC or when they develop cardiac symptoms.[156] This strategy could identify atherosclerotic disease earlier than other noninvasive techniques.

Recommendations and Key Points

- When echo and CMR are not adequate or feasible, CCT can be used to assess cardiac volumes and EF.
- Other possible indications include cardiac tumors, mediastinal tumors close to the heart, and pericardial thickness as an alternative modality for CMR.
- In asymptomatic adult survivors who have been exposed to high-risk radiation, surveillance for atherosclerotic coronary artery disease with CAC scans at 5- to 10-year intervals after RT can be considered.
- Coronary CT angiography is appropriate in symptomatic survivors older than 18 years with a history of RT to assess for RT-related atherosclerotic cardiovascular disease.

The multimodality approach has been summarized in Figure 3.

PART 4. KNOWLEDGE GAPS AND OPPORTUNITIES OR FUTURE RESEARCH

Important knowledge gaps were identified when developing the current recommendations.

1. One of the main limitations for the use of imaging markers in decision-making during cancer treatment is the lack of data on their prognostic value. While fluctuations in cardiac function are common in patients undergoing cancer treatments, the current recommendations for what is considered a clinically relevant change in EF and GLS are mainly based on expert consensus without strong data regarding their clinical prognostic value. Even a reduction below normal values during treatment may be temporary. Recommendations for changes in cancer treatment based on imaging findings alone should therefore be made cautiously and require a multidisciplinary approach, carefully weighing risks and benefits. Further longitudinal data are needed to understand how imaging findings should be used to guide cancer treatment decisions. Additionally, there are very few data informing how imaging data could be used for decision-making regarding initiation of cardioprotective drugs and early cardiac treatment.
2. For long-term survivors, echocardiographic values of EF and strain are often reported to be lower than in healthy controls but remain in the normal range for the majority of children. Further longitudinal data, requiring follow-up through adult life, are needed to demonstrate whether these differences have prognostic significance.
3. Current recommendations on the frequency of repeat imaging studies in this population are primarily based on limited prognostic data and expert consensus, mainly taking cancer treatment history into consideration. More research is required on how these follow-up recommendations need to be individualized, taking into consideration overall individual cardiovascular risk profiling. A personalized risk and preventative strategy for individual patients should be developed based on generating more information on the long-term outcomes of these patient cohorts.
4. Individualized risk profiling will require integration of imaging information with clinical information, as well as biochemical and genetic markers. These models are currently being developed, but given the relatively low incidence of clinical events during childhood, long-term follow-up data will be needed to fully inform these models.

Current available data informing cardiotoxicity surveillance in childhood cancer patients and survivors are largely based on anthracycline-treated children. Furthermore, long-term outcome data are currently based on survivors treated under older pediatric oncology treatment protocols and don't account for more recent adaptations to anthracycline and radiotherapy dose limitations or cardioprotective therapies. With the development of novel cancer therapies and modern anthracycline dosing strategies, more recently treated cohorts may demonstrate different long-term cardiovascular prognosis.

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REVIEWERS

This document was reviewed by members of the 2023–2024 ASE Guidelines and Standards Committee, the ASE Board of Directors, the ASE Executive Committee, and designated reviewers. Reviewers included Piers Barker, MD, FASE, Brittany Byrd, RDCS, FASE, David Dudzinski, MD, FASE, Lanqi Hua, ACS, APCA, RDCS, FASE, Noreen Kelly, MD, FASE, Anuj Mediratta, MD, FASE, Matthew Parker, MD, FASE, Alan Pearlman, MD, FASE, Andrew Pellet, PhD, RDCS, FASE, David A. Orsinelli, MD, FASE, Anita Sadeghpour, MD, FASE, Brian Soriano, MD, FASE, Kenan Stern, MD, FASE, Elif Seda Tierney, MD, FASE, and David H. Wiener, MD, FASE.

CONFLICTS OF INTEREST

S.E.L. was a consultant to Clinigen Group. A.P. was Principal Investigator for Philips to test next-generation transducers and ultrasound equipment. K.J.L. received honoraria for participation on the Advisory Board for Jazz Pharmaceuticals and Abbott Laboratories. The remaining authors have nothing to disclose.

REFERENCES

1. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27:911-39.

2. Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the heart failure association (HFA), the European association of cardiovascular imaging (EACVI) and the cardio-oncology Council of the European society of cardiology (ESC). Eur J Heart Fail 2020;22:1504-24.
3. Sachdeva R, Stratton KL, Cox DE, et al. Challenges associated with retrospective analysis of left ventricular function using clinical echocardiograms from a multicenter research study. Echocardiography 2021;38:296-303.
4. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 2014;14:61-70.
5. Gibson TM, Mostoufi-Moab S, Stratton KL, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970-99: a report from the childhood cancer survivor study cohort. Lancet Oncol 2018;19:1590-601.
6. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
7. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the childhood cancer survivor study. J Clin Oncol 2009;27:2328-38.
8. Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. J Clin Oncol 2018;36:2135-44.
9. Lipshultz SE, Adams MJ, Colan SD, 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. Circulation 2013;128:1927-95.
10. Bates JE, Rancati T, Keshavarz H, et al. Cardiac disease in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. Int J Radiat Oncol Biol Phys 2023;14:S0360-3016(23)00285-7.
11. Mulrooney DA, Armstrong GT, Huang S, et al. Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional study. Ann Intern Med 2016;164:93-101.
12. de Baat EC, van Dalen EC, Mulder RL, et al. Primary cardioprotection with dexrazoxane in patients with childhood cancer who are expected to receive anthracyclines: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Child Adolesc Health 2022;6:885-94.
13. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 2016;374:833-42.
14. Getz KD, Sung L, Ky B, et al. Occurrence of treatment-related cardiotoxicity and its impact on outcomes among children treated in the AAML0531 clinical trial: a report from the Children's Oncology Group. J Clin Oncol 2019;37:12-21.
15. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.
16. Steinherz LJ, Graham T, Hurwitz R, et al. Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the cardiology committee of the childrens cancer study group. Pediatrics 1992;89:942-9.
17. Ehrhardt MJ, Leerink JM, Mulder RL, et al. Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2023;24:e108-20.
18. Ehrhardt MJ, Ward ZJ, Liu Q, et al. Cost-effectiveness of the International late effects of childhood cancer guideline Harmonization group screening guidelines to prevent heart failure in survivors of childhood cancer. J Clin Oncol 2020;38:3851-62.
19. Lee CK, Margossian R, Sleeper LA, et al. Variability of M-mode versus two-dimensional echocardiography measurements in children with dilated cardiomyopathy. Pediatr Cardiol 2014;35:658-67.
20. Selamet Tierney ES, Hollenbeck-Pringle D, Lee CK, et al. Reproducibility of left ventricular dimension versus area versus volume measurements in pediatric patients with dilated cardiomyopathy. Circ Cardiovasc Imaging 2017;10:1-8.
21. Mason JW, Bristow MR, Billingham ME, et al. Invasive and noninvasive methods of assessing adriamycin cardiotoxic effects in man: superiority of histopathologic assessment using endomyocardial biopsy. Cancer Treat Rep 1978;62:857-64.
22. Cowgill JA, Francis SA, Sawyer DB. Anthracycline and peripartum cardiomyopathies. Circ Res 2019;124:1633-46.
23. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart 2018;104:971-7.
24. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639-42.
25. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic Non-Hodgkin lymphoma: a report of the Children's Oncology Group randomized trial Pediatric Oncology Group 9404. J Clin Oncol 2016;34:854-62.
26. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995;332:1738-43.
27. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol 2010;11:950-61.
28. Armenian SH, Hudson MM, Chen MH, et al. Rationale and design of the Children's Oncology Group (COG) study ALTE1621: a randomized, placebo-controlled trial to determine if low-dose carvedilol can prevent anthracycline-related left ventricular remodeling in childhood cancer survivors at high risk for developing heart failure. BMC Cardiovasc Disord 2016;16:187.
29. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23:2629-36.
30. Lopez L, Colan S, Stylianou M, et al. Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the Pediatric Heart Network Normal Echocardiogram Database. Circ Cardiovasc Imaging 2017;10:1-7.
31. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the pediatric measurements writing group of the American society of echocardiography pediatric and congenital heart disease Council. J Am Soc Echocardiogr 2010;23:465-95.
32. Sillesen AS, Pihl C, Raja AA, et al. Repeatability and reproducibility of neonatal echocardiography: the Copenhagen Baby heart study. J Am Soc Echocardiogr 2019;32:895-905.e2.
33. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-70.
34. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251-60.
35. Foster BJ, Khoury PR, Kimball TR, et al. New reference centiles for left ventricular mass relative to lean body mass in children. J Am Soc Echocardiogr 2016;29:441-7.e2.
36. Foster BJ, Mackie AS, Mitsnefes M, et al. A novel method of expressing left ventricular mass relative to body size in children. Circulation 2008;117:2769-75.
37. Shimada YJ, Shiota T. A meta-analysis and investigation for the source of bias of left ventricular volumes and function by three-dimensional

echocardiography in comparison with magnetic resonance imaging. Am J Cardiol 2011;107:126-38.
38. Chu BJ, Lee T, Gilbreth JG, et al. Left ventricular mass quantification by two-dimensional echocardiography in a pediatric population: correlation with cardiac magnetic resonance imaging. Pediatr Cardiol 2019;40:412-20.
39. Lipshultz SE, Easley KA, Orav EJ, et al. Reliability of multicenter pediatric echocardiographic measurements of left ventricular structure and function: the prospective P(2)C(2) HIV study. Circulation 2001;104:310-6.
40. Frommelt PC, Minich LL, Trachtenberg FL, et al. Challenges with left ventricular functional parameters: the pediatric heart Network normal echocardiogram Database. J Am Soc Echocardiogr 2019;32:1331-8.e1.
41. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.
42. Knackstedt C, Bekkers SC, Schummers G, et al. Fully automated versus standard tracking of left ventricular ejection fraction and longitudinal strain: the FAST-EFs multicenter study. J Am Coll Cardiol 2015;66:1456-66.
43. Cantinotti M, Scalese M, Giordano R, et al. Three-dimensional echocardiography derived nomograms for left ventricular volumes in healthy caucasian Italian children. J Am Soc Echocardiogr 2019;32:794-7.e1.
44. Krell K, Laser KT, Dalla-Pozza R, et al. Real-time three-dimensional echocardiography of the left ventricle-pediatric percentiles and head-to-head comparison of different contour-finding algorithms: a multicenter study. J Am Soc Echocardiogr 2018;31:702-11.e13.
45. Kuebler JD, Ghelani S, Williams DM, et al. Normal values and growth-related changes of left ventricular volumes, stress, and strain in healthy children measured by 3-dimensional echocardiography. Am J Cardiol 2018;122:331-9.
46. Laser KT, Bunge M, Hauffe P, et al. Left ventricular volumetry in healthy children and adolescents: comparison of two different real-time three-dimensional matrix transducers with cardiovascular magnetic resonance. Eur J Echocardiogr 2010;11:138-48.
47. Ylänen K, Eerola A, Vettenranta K, et al. Three-dimensional echocardiography and cardiac magnetic resonance imaging in the screening of long-term survivors of childhood cancer after cardiotoxic therapy. Am J Cardiol 2014;113:1886-92.
48. Sieswerda E, Postma A, van Dalen EC, et al. The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors. Ann Oncol 2012;23:2191-8.
49. Friedberg MK, Mertens L. Tissue velocities, strain, and strain rate for echocardiographic assessment of ventricular function in congenital heart disease. Eur J Echocardiogr 2009;10:585-93.
50. Kapusta L, Thijssen JM, Groot-Loonen J, et al. Tissue Doppler imaging in detection of myocardial dysfunction in survivors of childhood cancer treated with anthracyclines. Ultrasound Med Biol 2000;26:1099-108.
51. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011;24:277-313.
52. Unlu S, Duchenne J, Mirea O, et al. Impact of apical foreshortening on deformation measurements: a report from the EACVI-ASE Strain Standardization Task Force. Eur Heart J Cardiovasc Imaging 2020;21:337-43.
53. Farsalinos KE, Daraban AM, Unlu S, et al. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: the EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr 2015;28:1171-81.e2.
54. Koopman LP, Slorach C, Hui W, et al. Comparison between different speckle tracking and color tissue Doppler techniques to measure global and regional myocardial deformation in children. J Am Soc Echocardiogr 2010;23:919-28.
55. Dobson R, Ghosh AK, Ky B, et al. BSE and BCOS guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. JACC CardioOncol 2021;3:1-16.
56. Liu JE, Barac A, Thavendiranathan P, et al. Strain imaging in cardio-oncology. JACC CardioOncol 2020;2:677-89.
57. Thavendiranathan P, Poulin F, Lim KD, et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751-68.
58. Poterucha JT, Kutty S, Lindquist RK, et al. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr 2012;25:733-40.
59. Amedro P, Bredy C, Guillaumont S, et al. Speckle tracking echocardiography in healthy children: comparison between the QLAB by Philips and the EchoPAC by General Electric. Int J Cardiovasc Imaging 2019;35:799-809.
60. Anwar S, Negishi K, Borowszki A, et al. Comparison of two-dimensional strain analysis using vendor-independent and vendor-specific software in adult and pediatric patients. JRSM Cardiovasc Dis 2017;6:2048004017712862.
61. Koopman LP, Slorach C, Manlhiot C, et al. Myocardial tissue Doppler velocity imaging in children: comparative study between two ultrasound systems. J Am Soc Echocardiogr 2010;23:929-37.
62. Ramlogan S, Aly D, France R, et al. Reproducibility and intervendor agreement of left ventricular global systolic strain in children using a layer-specific analysis. J Am Soc Echocardiogr 2020;33:110-9.
63. Ferraro AM, Adar A, Ghelani SJ, et al. Speckle tracking echocardiographically-based analysis of ventricular strain in children: an intervendor comparison. Cardiovasc Ultrasound 2020;18:15.
64. Ziebell D, Bettermann E, Lipinski J, et al. Current practice and barriers to implementation of strain imaging in pediatric echocardiography labs: a national survey. J Am Soc Echocardiogr 2021;34:316-8.
65. Levy PT, Machefsky A, Sanchez AA, et al. Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis. J Am Soc Echocardiogr 2016;29:209-25.e6.
66. Dallaire F, Slorach C, Bradley T, et al. Pediatric reference values and Z score equations for left ventricular systolic strain measured by two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr 2016;29:786-93.e8.
67. Ganame J, Claus P, Eyskens B, et al. Acute cardiac functional and morphological changes after anthracycline infusions in children. Am J Cardiol 2007;99:974-7.
68. Mavinkurve-Groothuis AM, Marcus KA, Pourier M, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. Eur Heart J Cardiovasc Imaging 2013;14:562-9.
69. Pignatelli RH, Ghazi P, Reddy SC, et al. Abnormal myocardial strain indices in children receiving anthracycline chemotherapy. Pediatr Cardiol 2015;36:1610-6.
70. Slieker MG, Fackoury C, Slorach C, et al. Echocardiographic assessment of cardiac function in pediatric survivors of anthracycline-treated childhood cancer. Circ Cardiovasc Imaging 2019;12:e008869.
71. Armstrong GT, Joshi VM, Ness KK, et al. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude Lifetime Cohort Study. J Am Coll Cardiol 2015;65:2511-22.
72. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the

European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
73. Upshaw JN, Finkelman B, Hubbard RA, et al. Comprehensive assessment of changes in left ventricular diastolic function with contemporary breast cancer therapy. JACC Cardiovasc Imaging 2020;13:198-210.
74. Singh A, Addetia K, Maffessanti F, et al. LA strain for categorization of LV diastolic dysfunction. JACC Cardiovasc Imaging 2017;10:735-43.
75. Dragulescu A, Mertens L, Friedberg MK. Interpretation of left ventricular diastolic dysfunction in children with cardiomyopathy by echocardiography: problems and limitations. Circ Cardiovasc Imaging 2013;6:254-61.
76. Dallaire F, Slorach C, Hui W, et al. Reference values for pulse wave Doppler and tissue Doppler imaging in pediatric echocardiography. Circ Cardiovasc Imaging 2015;8:e002167.
77. Eidem BW, McMahon CJ, Cohen RR, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. J Am Soc Echocardiogr 2004;17:212-21.
78. Harada K, Suzuki T, Shimada K, et al. Role of left ventricular mass/volume ratio on transmitral flow velocity patterns from infancy to childhood. Int J Cardiol 1998;63:9-14.
79. Harrison MR, Clifton GD, Pennell AT, et al. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. Am J Cardiol 1991;67:622-7.
80. Mawad W, Friedberg MK. The continuing challenge of evaluating diastolic function by echocardiography in children: developing concepts and newer modalities. Curr Opin Cardiol 2017;32:93-100.
81. Border WL, Sachdeva R, Stratton KL, et al. Longitudinal changes in echocardiographic parameters of cardiac function in pediatric cancer survivors. JACC CardioOncol 2020;2:26-37.
82. Taggart NW, Cetta F, O'Leary PW, et al. Left atrial volume in children without heart disease and in those with ventricular septal defect or patent ductus arteriosus or hypertrophic cardiomyopathy. Am J Cardiol 2010;106:1500-4.
83. Bhatla P, Nielsen JC, Ko HH, et al. Normal values of left atrial volume in pediatric age group using a validated allometric model. Circ Cardiovasc Imaging 2012;5:791-6.
84. Ghelani SJ, Brown DW, Kuebler JD, et al. Left atrial volumes and strain in healthy children measured by three-dimensional echocardiography: normal values and maturational changes. J Am Soc Echocardiogr 2018;31:187-93.e1.
85. Badano LP, Kolias TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2018;19:591-600.
86. Cantinotti M, Scalese M, Giordano R, et al. Left and right atrial strain in healthy caucasian children by two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr 2019;32:165-8.e3.
87. Sabatino J, Di Salvo G, Prota C, et al. Left atrial strain to identify diastolic dysfunction in children with cardiomyopathies. J Clin Med 2019;8:1243.
88. Loar RW, Colquitt JL, Rainusso NC, et al. Assessing the left atrium of childhood cancer survivors. Int J Cardiovasc Imaging 2021;37:155-62.
89. Barthur A, Brezden-Masley C, Connelly KA, et al. Longitudinal assessment of right ventricular structure and function by cardiovascular magnetic resonance in breast cancer patients treated with trastuzumab: a prospective observational study. J Cardiovasc Magn Reson 2017;19:44.
90. Chhikara S, Hooks M, Athwal PSS, et al. Long-term prognostic value of right ventricular dysfunction on cardiovascular magnetic resonance imaging in anthracycline-treated cancer survivors. Eur Heart J Cardiovasc Imaging 2022;23:1222-30.
91. Zhao R, Shu F, Zhang C, et al. Early detection and prediction of anthracycline-induced right ventricular cardiotoxicity by 3-dimensional echocardiography. JACC CardioOncol 2020;2:13-22.
92. Kocabas A, Kardelen F, Ertug H, et al. Assessment of early-onset chronic progressive anthracycline cardiotoxicity in children: different response patterns of right and left ventricles. Pediatr Cardiol 2014;35:82-8.
93. Christiansen JR, Massey R, Dalen H, et al. Right ventricular function in long-term adult survivors of childhood lymphoma and acute lymphoblastic leukaemia. Eur Heart J Cardiovasc Imaging 2016;17:735-41.
94. Ylänen K, Poutanen T, Savikurki-Heikkilä P, et al. Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyclines among long-term survivors of childhood cancer. J Am Coll Cardiol 2013;61:1539-47.
95. Xu H, Mao L, Liu H, et al. Assessment of subclinical deterioration of right ventricular function by three-dimensional speckle tracking echocardiography in breast cancer patients undergoing anthracycline-based chemotherapy. Int J Gen Med 2021;14:885-93.
96. Lancellotti P, Pellikka PA, Budts W, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:101-38.
97. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:1-41.e8.
98. Cifra B, Chen CK, Fan CS, et al. Dynamic myocardial response to exercise in childhood cancer survivors treated with anthracyclines. J Am Soc Echocardiogr 2018;31:933-42.
99. De Souza AM, Potts JE, Potts MT, et al. A stress echocardiography study of cardiac function during progressive exercise in pediatric oncology patients treated with anthracyclines. Pediatr Blood Cancer 2007;49:56-64.
100. De Wolf D, Suys B, Maurus R, et al. Dobutamine stress echocardiography in the evaluation of late anthracycline cardiotoxicity in childhood cancer survivors. Pediatr Res 1996;39:504-12.
101. Hauser M, Gibson BS, Wilson N. Diagnosis of anthracycline-induced late cardiomyopathy by exercise-spiroergometry and stress-echocardiography. Eur J Pediatr 2001;160:607-10.
102. Ryerson AB, Border WL, Wasilewski-Masker K, et al. Assessing anthracycline-treated childhood cancer survivors with advanced stress echocardiography. Pediatr Blood Cancer 2015;62:502-8.
103. Sieswerda E, Kremer LC, Vidmar S, et al. Exercise echocardiography in asymptomatic survivors of childhood cancer treated with anthracyclines: a prospective follow-up study. Pediatr Blood Cancer 2010;54:579-84.
104. Picard MH, Adams D, Bierig SM, et al. American Society of Echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011;24:1-10.
105. Parthiban A, Levine JC, Nathan M, et al. Implementation of a quality improvement bundle improves echocardiographic imaging after congenital heart surgery in children. J Am Soc Echocardiogr 2016;29:1163-70.e3.
106. Johri AM, Picard MH, Newell J, et al. Can a teaching intervention reduce interobserver variability in LVEF assessment: a quality control exercise in the echocardiography lab. JACC Cardiovasc Imaging 2011;4:821-9.
107. Chaves AH, Sebastian J, Hoopes S, et al. The effect of a quality improvement intervention on variability of measurements of left ventricular dimensions in a pediatric echocardiography laboratory. Congenit Heart Dis 2015;10:340-5.
108. Armstrong GT, Plana JC, Zhang N, et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol 2012;30:2876-84.
109. Thavendiranathan P, Wintersperger BJ, Flamm SD, et al. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. Circ Cardiovasc Imaging 2013;6:1080-91.
110. Drafts BC, Twomley KM, D'Agostino R Jr, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging 2013;6:877-85.
111. Jolly MP, Jordan JH, Meléndez GC, et al. Automated assessments of circumferential strain from cine CMR correlate with LVEF declines in cancer patients early after receipt of cardio-toxic chemotherapy. J Cardiovasc Magn Reson 2017;19:59.

112. Jordan JH, D'Agostino RB Jr., Hamilton CA, et al. Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. Circ Cardiovasc Imaging 2014;7:872-9.
113. Jordan JH, Castellino SM, Melendez GC, et al. Left ventricular mass change after anthracycline chemotherapy. Circ Heart Fail 2018; 11:e004560.
114. Neilan TG, Coelho-Filho OR, Pena-Herrera D, et al. Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines. Am J Cardiol 2012;110:1679-86.
115. Shehata ML, Cheng S, Osman NF, et al. Myocardial tissue tagging with cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2009;11:55.
116. Ibrahim el SH, Stuber M, Fahmy AS, et al. Real-time MR imaging of myocardial regional function using strain-encoding (SENC) with tissue through-plane motion tracking. J Magn Reson Imaging 2007;26: 1461-70.
117. Pan L, Stuber M, Kraitchman DL, et al. Real-time imaging of regional myocardial function using fast-SENC. Magn Reson Med 2006;55: 386-95.
118. Osman NF, Kerwin WS, McVeigh ER, et al. Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. Magn Reson Med 1999;42:1048-60.
119. Pedrizzetti G, Claus P, Kilner PJ, et al. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. J Cardiovasc Magn Reson 2016;18:51.
120. Obokata M, Nagata Y, Wu VC, et al. Direct comparison of cardiac magnetic resonance feature tracking and 2D/3D echocardiography speckle tracking for evaluation of global left ventricular strain. Eur Heart J Cardiovasc Imaging 2016;17:525-32.
121. Onishi T, Saha SK, Delgado-Montero A, et al. Global longitudinal strain and global circumferential strain by speckle-tracking echocardiography and feature-tracking cardiac magnetic resonance imaging: comparison with left ventricular ejection fraction. J Am Soc Echocardiogr 2015;28: 587-96.
122. Gong IY, Ong G, Brezden-Masley C, et al. Early diastolic strain rate measurements by cardiac MRI in breast cancer patients treated with trastuzumab: a longitudinal study. Int J Cardiovasc Imaging 2019;35: 653-62.
123. Haslbauer JD, Lindner S, Valbuena-Lopez S, et al. CMR imaging biosignature of cardiac involvement due to cancer-related treatment by T1 and T2 mapping. Int J Cardiol 2019;275:179-86.
124. Paiman EHM, Louwerens M, Bresters D, et al. Late effects of pediatric hematopoietic stem cell transplantation on left ventricular function, aortic stiffness and myocardial tissue characteristics. J Cardiovasc Magn Reson 2019;21:6.
125. Toro-Salazar OH, Gillan E, O'Loughlin MT, et al. Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. Circ Cardiovasc Imaging 2013;6:873-80.
126. Berhane H, Ruh A, Husain N, et al. Myocardial velocity, intra-, and interventricular dyssynchrony evaluated by tissue phase mapping in pediatric heart transplant recipients. J Magn Reson Imaging 2020;51:1212-22.
127. Maceira AM, Cosín-Sales J, Roughton M, et al. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2010;12:65.
128. de Ville de Goyet M, Brichard B, Robert A, et al. Prospective cardiac MRI for the analysis of biventricular function in children undergoing cancer treatments. Pediatr Blood Cancer 2015;62:867-74.
129. Billingham ME, Mason JW, Bristow MR, et al. Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 1978;62: 865-72.
130. Meléndez GC, Jordan JH, D'Agostino RB Jr, et al. Progressive 3-month increase in LV myocardial ECV after anthracycline-based chemotherapy. JACC Cardiovasc Imaging 2017;10:708-9.
131. Jordan JH, Vasu S, Morgan TM, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. Circ Cardiovasc Imaging 2016;9:e004325.
132. Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol 2013;111:717-22.
133. Tham EB, Haykowsky MJ, Chow K, et al. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. J Cardiovasc Magn Reson 2013;15:48.
134. Thavendiranathan P, Walls M, Giri S, et al. Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using T2 mapping. Circ Cardiovasc Imaging 2012;5:102-10.
135. Grover S, Leong DP, Chakrabarty A, et al. Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: a prospective study using novel cardiac imaging and biochemical markers. Int J Cardiol 2013;168:5465-7.
136. Lustberg MB, Reinbolt R, Addison D, et al. Early detection of anthracycline-induced cardiotoxicity in breast cancer survivors with T2 cardiac magnetic resonance. Circ Cardiovasc Imaging 2019;12:e008777.
137. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158-76.
138. Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009;120:1961-8.
139. Cheung YF, Lam WW, Ip JJ, et al. Myocardial iron load and fibrosis in long term survivors of childhood leukemia. Pediatr Blood Cancer 2015;62: 698-703.
140. Maestrini V, Cheang MH, Kotwinski P, et al. Late anthracycline-related cardiotoxicity in low-risk breast cancer patients. J Am Coll Cardiol 2017;69:2573-5.
141. Holowka S, Shroff M, Chavhan GB. Use and safety of gadolinium based contrast agents in pediatric MR imaging. Indian J Pediatr 2019;86:961-6.
142. Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 2006;21:1104-8.
143. Forghani R. Adverse effects of gadolinium-based contrast agents: changes in practice patterns. Top Magn Reson Imaging 2016;25:163-9.
144. Kanda T, Ishii K, Kawaguchi H, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014;270:834-41.
145. Ramalho J, Ramalho M, Jay M, et al. Gadolinium toxicity and treatment. Magn Reson Imaging 2016;34:1394-8.
146. Carlson RG, Mayfield WR, Normann S, et al. Radiation-associated valvular disease. Chest 1991;99:538-45.
147. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. Hum Pathol 1996;27:766-73.
148. Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, et al. Multi-modality imaging in the assessment of cardiovascular toxicity in the cancer patient. JACC Cardiovasc Imaging 2018;11:1173-86.
149. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of cardiology Foundation appropriate Use criteria task force, the society of cardiovascular computed tomography, the American College of Radiology, the American heart association, the American society of echocardiography, the American society of Nuclear cardiology, the North American society for cardiovascular imaging, the society for cardiovascular angiography and Interventions, and the society for cardiovascular magnetic resonance. J Am Coll Cardiol 2010;56:1864-94.
150. Baldassarre LA, Ganatra S, Lopez-Mattei J, et al. Advances in multimodality imaging in cardio-oncology: JACC state-of-the-art review. J Am Coll Cardiol 2022;80:1560-78.
151. Lopez-Mattei JC, Yang EH, Ferencik M, et al. Cardiac computed tomography in cardio-oncology: JACC: cardiooncology primer. JACC CardioOncol 2021;3:635-49.

152. Bravo-Jaimes K, Marcellon R, Varanitskaya L, et al. Opportunities for improved cardiovascular disease prevention in oncology patients. Curr Opin Cardiol 2020;35:531-7.
153. McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol 2015; 66:1643-53.
154. Hecht HS, Blaha MJ, Kazerooni EA, et al. CAC-DRS: coronary artery calcium data and reporting system. An expert consensus document of the society of cardiovascular computed tomography (SCCT). J Cardiovasc Comput Tomogr 2018;12:185-91.
155. Sims JR, Anavekar NS, Chandrasekaran K, et al. Utility of cardiac computed tomography scanning in the diagnosis and pre-operative evaluation of patients with infective endocarditis. Int J Cardiovasc Imaging 2018;34:1155-63.
156. Lopez-Mattei J, Yang EH, Baldassarre LA, et al. Cardiac computed tomographic imaging in cardio-oncology: an expert consensus document of the society of cardiovascular computed tomography (SCCT). Endorsed by the International cardio-oncology society (ICOS). J Cardiovasc Comput Tomogr 2023;17:66-83.