# Editorial

# Chemotherapy-Induced Cardiotoxicity in the Pediatric Population: What Are the Unique Aspects of Cardiovascular Imaging Follow-Up?

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Cancer remains among the leading public health challenges in Brazil and worldwide. For the three-year period from 2026 to 2028, the Brazilian National Cancer Institute (INCA) estimates that there will be approximately 781,000 new cancer cases per year in Brazil. In the child and adolescent group, an estimated 7,560 new cases are expected annually.[1]

Advances in the treatment of pediatric cancer have significantly increased survival rates in recent decades, exceeding 80% at 5 years, provided that it is diagnosed early and treated in referral centers. In this scenario, cardiovascular disease has become the leading non-oncological cause of morbidity and mortality among childhood and adolescent cancer survivors, with an estimated risk 5 to 6 times higher than what is observed in the general population.[2]

Cardiotoxicity associated with antineoplastic therapy is defined as cardiovascular changes identified through clinical manifestations, biomarkers, or imaging methods, during or after treatment (months or decades), provided that other etiologies are excluded. The clinical spectrum is broad and ranges from subclinical changes to heart failure, arrhythmias, systemic and pulmonary hypertension, pericarditis, valvular heart disease, thromboembolic events, and myocardial ischemia.[3-5]

The risk of cardiotoxicity is associated with isolated or combined exposure to chemotherapeutic agents (anthracyclines, alkylating agents, antimetabolites, tyrosine kinase inhibitors, among others); mediastinal, cervical, and neuraxial radiotherapy; immunotherapies; CAR T-cell therapy; and hematopoietic stem cell transplantation.[3-5] Regardless of the cumulative doses of chemotherapeutic agents, genetic polymorphisms can influence drug metabolism and, consequently, individual vulnerability.[3,5]

In the pediatric population, the impact is potentially more significant due to myocardial immaturity, interference with cardiac growth during physical development, and the increased risk of progressive myocardial remodeling, especially given the comorbidities inherent to aging.[3,5]

Pediatric cardio-oncology is not merely an adaptation of established recommendations for adults, but rather a field with unique biological, epidemiological, and diagnostic features that directly impact screening and cardiovascular follow-up of these patients.

Surveillance strategies must be more sensitive, individualized, and longitudinally structured. Accordingly, multimodal cardiovascular imaging plays a central role in early detection of cardiotoxicity and patient follow-up, allowing timely cardioprotective and/or therapeutic interventions.[6,7]

In this context, international consensus recommends echocardiography as the primary essential technique for cardiological assessment before, during, and after cancer treatment. The two-dimensional method has been validated, although the three-dimensional method is considered the most sensitive for evaluating ventricular systolic function, compared with magnetic resonance imaging, which is the gold standard in myocardial functional assessment.[6,7]

Systolic dysfunction, especially asymptomatic (subclinical), is the most frequent complication in the follow-up of patients with cancer. In addition, early recognition of diastolic dysfunction may be predictive of contractile changes, restrictive changes, and loss of ventricular mass.[6,7]

Cardiotoxicity is defined on echocardiography during treatment when there is a 10 percentage point drop in left ventricular ejection fraction (LVEF) and/or a ≥ 15% relative drop in left ventricular global longitudinal strain (LVGLS) compared to baseline, or values below the normal cutoff points.[6,7] Several studies have shown the sensitivity of left ventricular myocardial strain analysis using speckle tracking in the early detection of dysfunction, where the percentage drop precedes the decrease in LVEF. After treatment, values below the cutoff points for LVEF and/or LVGLS should be used as reference for the diagnosis of ventricular systolic dysfunction.

In a 2020 retrospective study in France, Wolf et al. evaluated 79 pediatric patients treated with anthracyclines for acute leukemia and Hodgkin lymphoma over a 10-year period and observed that 28% presented with abnormal LVGLS, despite preserved LVEF.[8] Another retrospective study conducted in Germany in 2024 by Rique et al. evaluated 38 children with acute leukemia treated with anthracyclines and detected LVGLS alterations in 28.9% of cases.[9] In Brazil, a study in this population evaluated the frequency of cardiotoxicity in 45 children and

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adolescents with cancer (75.5% with hematological neoplasia). Echocardiographic alterations were identified in 42.2% of patients undergoing chemotherapy, with a marked reduction in LVGLS, even in the absence of a decrease in LVEF. These findings reinforce the relevance of more sensitive imaging methods in early detection of myocardial dysfunction.[10]

### Special considerations for the pediatric population[6,7]

- **Baseline echocardiographic examination:** Should be performed before the start of potentially cardiotoxic therapy to assess myocardial anatomy and function, as a comparative baseline for subsequent assessments. If it is not possible to perform the examination at this stage, normal cutoff values should be considered when echocardiographic assessment becomes feasible.
- **Echocardiographic assessment during treatment:** Should be performed during the week preceding the infusion of potentially cardiotoxic chemotherapy, avoiding the subsequent 2 weeks due to the hypermetabolic state. For comparison between examinations, the patient should be hemodynamically similar to the baseline.
- **LVEF:** LVEF varies depending on preload and afterload, may remain normal during treatment, and does not define subclinical injury; therefore, it should not be used in isolation to define cardiotoxicity. The biplanar Simpson method is recommended, and the normal value in the pediatric population is ≥ 55%.
- **LVGLS:** LVGLS is currently the most sensitive marker of subclinical myocardial dysfunction and should be systematically assessed before, during, and after the end of treatment. Serial follow-up should ideally be performed with the same equipment/software and examiner. This technique allows for the early identification of myocardial damage, even in the presence of preserved LVEF. The cutoff point for normality in cardio-oncology is −18.0%. Values between −16% and −17.0% are considered signs of subclinical impairment, supporting the initiation of a cardioprotective medication strategy.
- **Linear and volumetric echocardiographic measurements:** Should be adjusted for body surface area and interpreted using Z-scores.
- **Diastolic function:** Should be part of the routine (E/A, E/e', indexed left atrial volume). Changes in heart rate can precede systolic dysfunction, especially with high cumulative chemotherapy exposure. Consider limitations due to the influence of preload, afterload, and heart rate. Left atrial strain has been gradually incorporated into diastolic functional analysis.
- **Right ventricle:** Systolic function should be assessed using classic parameters (Fractional Area Change [FAC], Tricuspid Annular Plane Systolic Excursion [TAPSE], tricuspid S') and right ventricular free wall strain.
- **Echocardiographic assessment during complications:** Findings should be considered as a snapshot in time. After the situation has been resolved, schedule a new evaluation to document functional status and continue with individualized follow-up.
- **Vascular ultrasound:** Plays a complementary role in evaluating signs of peripheral thrombosis and endothelial injury, especially of the carotid arteries, since signs of early atherosclerosis are part of survivor assessment.
- **Cardiac magnetic resonance imaging**: Recommended when there is diagnostic uncertainty, inadequate echocardiographic window, or suspicion of myocardial fibrosis, as well as for assessment of the pericardium and intracardiac or adjacent masses. In pediatrics, its routine use is limited due to the need for sedation, availability, and cost.

The pediatric perspective in cardio-oncology presents particular challenges, given that cardiotoxicity related to cancer treatment is not limited to an acute event, but represents a dynamic process that can interfere with myocardial growth and maturation over time. The vulnerability of the developing heart, associated with early exposure to potentially cardiotoxic therapies, confers a prolonged risk of progressive myocardial dysfunction. In this context, the use of more sensitive, reproducible, and integrated cardiovascular imaging strategies becomes fundamental. The multimodal approach, with emphasis on echocardiography (and cardiac magnetic resonance imaging in selected situations), increases diagnostic accuracy and contributes to better risk stratification. Additionally, structured longitudinal follow-up, with interpretation based on clinical individualization, is essential for adequate follow-up of these patients.

Finally, the incorporation of genetic, clinical, and therapeutic factors into risk models, coupled with continuous imaging monitoring, represents a promising perspective for precision medicine, with the goal of reducing cardiovascular morbidity and mortality and improving the quality of life of pediatric cancer survivors.

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