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Modern Instrumental Methods of Diagnostics and Risk Assessment of Developing Antitumor Therapy Cardiovasculotoxicity

The most important component of cardio-oncology is the assessment of the risk of development and diagnosis of cardiovascular toxicity of the antitumor therapy, the detection of which is largely based on visualization of the cardiovascular system. The article addresses up-to-date methods of non-invasive visualization of the heart and blood vessels, according to the 2022 European Society of Cardiology Clinical Guidelines on cardio-oncology. Also, the article discusses promising cardiovascular imaging techniques that are not yet included in the guidelines: assessment of coronary calcium using multislice computed tomography and positron emission computed tomography with 18F-labeled 2-deoxy-2-fluoro-d-glucose.

Keywords Cardio-oncology; visualization of cardiovascular system; cardiovascular toxicity; echocardiography; magnetic resonance therapy; positron emission tomography/computed tomography

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Introduction

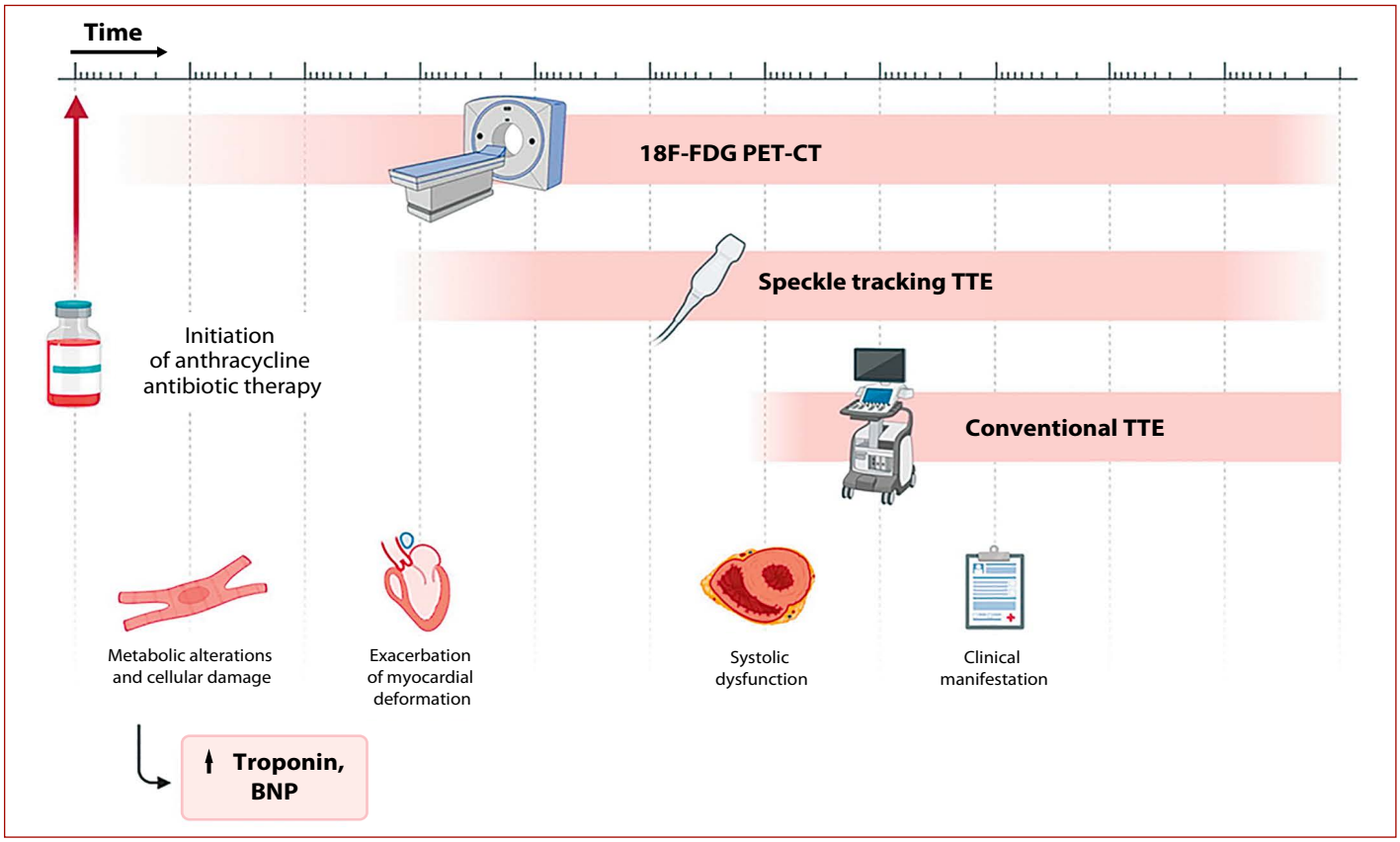
The history of cardio-oncology (CO) as an independent scientific and practical direction is relatively short, having only been established eight years ago, despite the existence of numerous earlier fundamental and clinical studies. The starting point was the release of a position paper «The Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC),» in the European Heart Journal in 2016. Substantial scientific data and practical experience has been accumulated, and in 2022 the ESC, in collaboration with the European Association of Hematologists, the European Society of Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society, published first Clinical Guidelines on Cardio-Oncology [1]. In accordance with these guidelines, the primary concept underlying CO is the integration of clinical disciplines. It is imperative that physicians engaged in the provision of care to cardio-oncological patients possess a comprehensive knowledge base encompassing the disciplines of cardiology, oncology, and hematology [2]. The presented clinical guidelines on CO facilitate the determination of the optimal treatment regimes for cancer patients, based on the most tolerable strategies from a cardiovascular disease (CVD) perspective and the most effective strategies from an oncologic perspective. A further important aspect of cardio-oncology is the early identification and prediction of cardiovascular complications throughout the course of antitumor therapy (ATT) and in the long-term period following its conclusion [3, 4].

It is therefore imperative that proper and timely detection of cardiovascular toxicity (CVT) should be an integral component of cancer patients' management. In accordance with the 2022 ESC Guidelines on Cardio-Oncology, the following clinical manifestations of CVT have been identified [1]:

1. CVT-related cardiac dysfunction:
   - Symptomatic heart failure (HF): very severe, severe, moderate, mild;
   - Asymptomatic systolic dysfunction: severe, moderate, mild.
2. Myocarditis associated with immune checkpoint inhibitors.
3. Vasculotoxicity:
   - Symptomatic: acute coronary syndrome/chronic coronary syndrome, transient ischemic attack/cerebrovascular incident, Raynaud's syndrome, thrombosis;
   - Asymptomatic: multifocal atherosclerosis, abnormal vasoreactivity.
4. Arterial hypertension.
5. Arrhythmias: QTc prolongation, bradycardia, supraventricular tachycardia/ventricular tachycardia, atrial fibrillation/atrial flutter.

In accordance with the 2022 ESC Guidelines on Cardio-Oncology, the management protocol of a cancer patient from the perspective of CVT development risk stratification, as well as the identification and monitoring of CVT, should commence with a comprehensive clinical examination and standard 12-lead electrocardiography (ECG) (Class 1C)

Central illustration. Modern Instrumental Methods of Diagnostics and Risk Assessment of Developing Antitumor Therapy Cardiovasculotoxicity



Adapted from Becker M.M.C. et al. Cardio-Oncology 2023;9(1):17 doi.org/10.1186/s40959-023-00161-6.

[1]. It is important to acknowledge that ECG abnormalities indicative of dilated or overloaded heart chambers, conduction irregularities, arrhythmias, ischemia or transient myocardial infarction, low voltages, and QT interval prolongation must be interpreted in conjunction with the clinical manifestations and results of laboratory tests and clinical investigations. These abnormalities cannot be used as a primary method for detecting CVT [2]. Nevertheless, as evidenced by a recent study conducted by S. Luna-Alkala et al. (2024) [5], alterations in heart rate variability in patients with breast cancer (BC) enabled the reliable prediction of early cardiotoxicity during therapy with anthracycline antibiotics (AAs).

Ultrasound imaging techniques

Cardiac imaging is a valuable tool in the identification of cardio-oncology patients exhibiting subclinical signs of myocardial damage, particularly prior to the selection of an ATT regimes. Furthermore, it serves as a reliable method for the detection of early signs of CVT during ongoing therapy and long-term patient monitoring [6–8]. Transthoracic echocardiography (TTE) is the most prevalent imaging modality for baseline risk stratification. It enables a quantitative evaluation of a number of cardiac parameters, including left ventricular (LV) and right ventricular (RV) function, cardiac chamber dilatation, hypertrophy, and regional wall motion abnormalities, diastolic function, signs of pulmonary hypertension, and pericardial lesions that may influence therapeutic decision-making (Class 1C) [1, 8, 9]. The recommendations for implementation of baseline echocardiogram are summarized in Figure 1 (adapted from [1]). In accordance with the 2022 ESC Guidelines for Cardio-oncology, the presence of subclinical cardiac dysfunction during ATT, assessed by conventional TTE, is detected by a decrease in left ventricular ejection fraction (LVEF) to less than 50% (mild), a decrease in LVEF by 10% or more from baseline to 40–49% (moderate), or a de novo decrease to less than 40% (severe) [1].

In a recent study conducted by S.A. Kardanova et al. (2022), a comparative analysis of intracardiac hemodynamic parameters in patients with oncohematologic disease (the study group) and those with CVDs (the comparison group) presented the following findings (Table 1). According to the TTE findings, only 2 (8%) patients in the study group had a lower-than-normal LVEF before starting ATT. These patients had a worsened cardiac history (ischemic heart disease, arterial hypertension, atrial fibrillation). The remaining group presented normal global LV wall motion. Therefore, despite the presence of a symptomatic oncohematologic disease, the cardiac pumping function, as determined

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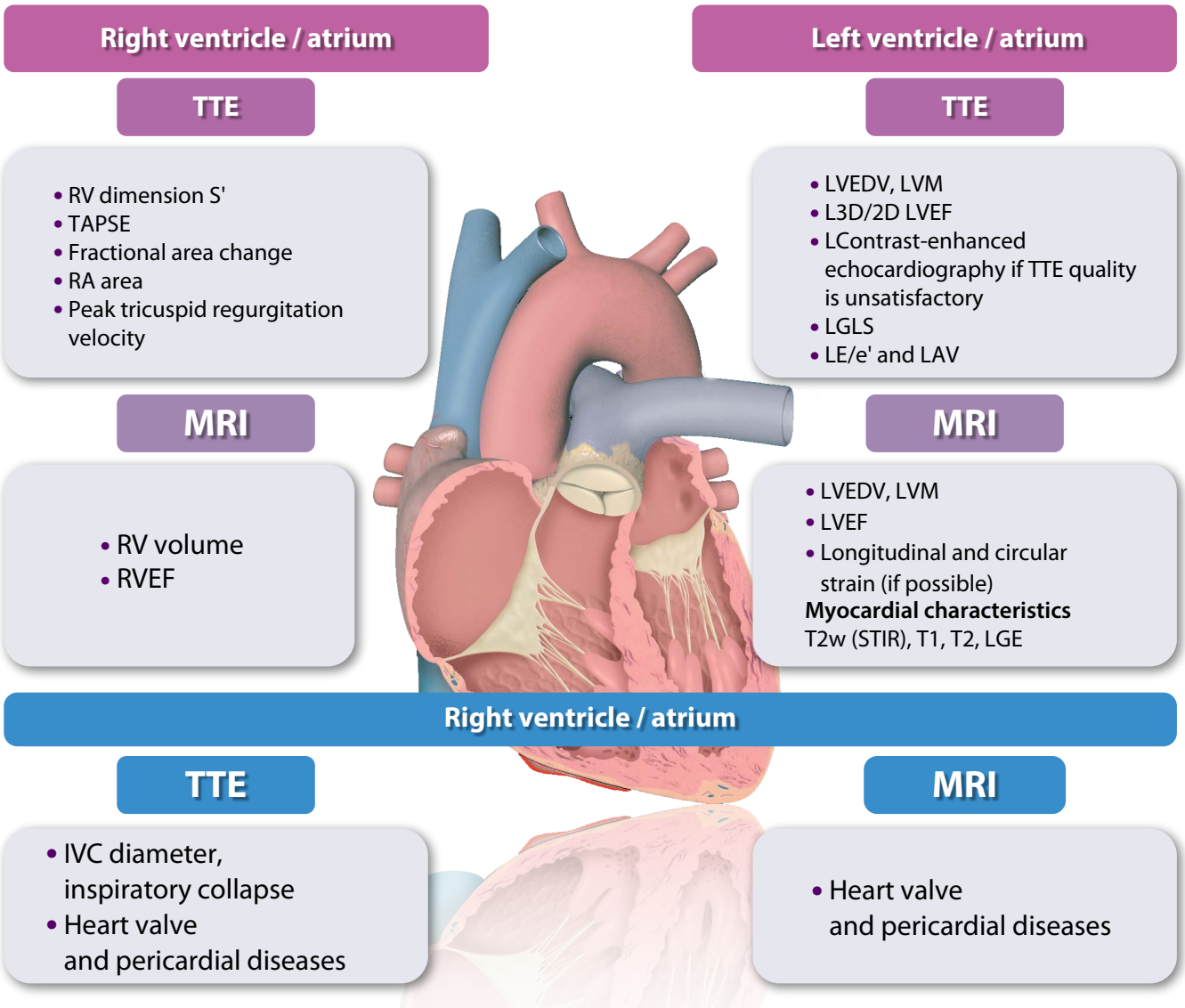
by conventional TTE, was not reduced. This method is therefore applicable only in cases of diagnosis of moderate and severe CVT.

In the group of patients with CVDs, LVEF was decreased in 5 (20%) patients, and signs of diastolic dysfunction (E/A < 1.0) were observed in 11 (44%) patients. It is noteworthy that, in the absence of myocardial thickening and in the context of normal LV relaxation, patients with oncohematologic diseases presented higher left atrial (LA) volume than the comparison group and lower left ventricular end-diastolic volume (LVEDV). This may be indicative of increased myocardial stiffness. Modifications in the dimensions of cardiac chambers are well documented in conditions that are directly associated with chronic systemic inflammation. TTE frequently reveals augmented LA dimensions and fibrosis in such patients, which are not correlated with impaired intracardiac hemodynamics. This can be attributed to a thicker layer of epicardial adipose tissue, which also produces pro-inflammatory mediators that affect the adjacent LA when released [11, 12]

As previously stated, a normal LVEF during chemotherapy, as determined by standard TTE, does not exclude early-stage myocardial damage. In this case, the 2022 ESC Guidelines for Cardio-oncology additionally recommend

Figure 1. Figure 1. Recommended parameters for transthoracic echocardiography and cardiac magnetic resonance imaging in patients with cancer



2D, two-dimensional imaging; 3D, three-dimensional imaging; MRI, magnetic resonance imaging; E, early diastolic mitral annular velocity derived from pulse wave; e′, early diastolic mitral velocity derived from tissue Doppler imaging; TTE, transthoracic echocardiography; FAC, fractional area change; FWLS, free wall longitudinal strain; GLS, global longitudinal strain; IVC, inferior vena cava; LAV, left atrial volume; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; LVV, left ventricular volume; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction; RVV, right ventricular volume.

Table 1. Echocardiographic parameters in oncohematologic patients before antitumor therapy and in patients with cardiovascular diseases [10]

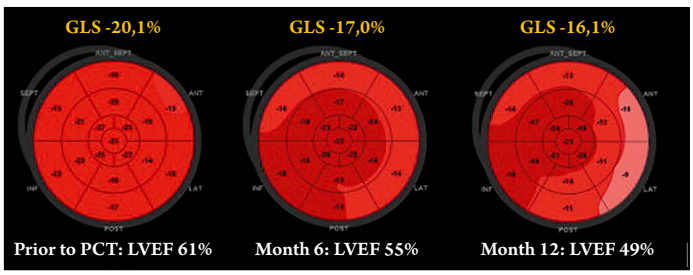
Parameter	Treatment group (n = 25)	Control group (n = 25)	p
LV ejection fraction, % (normal range > 55 %)	60 ± 4.17	58 ± 7.5	0.352
LV posterior wall thickness, cm (normal range < 1.0 cm)	0.95 ± 0.28	1.14 ± 0.13	0.004
Interventricular septal thickness, cm (normal range < 1.0 cm)	1.03 ± 0.2	1.5 ± 0.7	0.521
LV diastolic dysfunction, E/A (normal range 1.0–1.5)	1.1 ± 0.2	0.8 ± 0.2	0.294
Left atrial volume, mL (normal range < 52 mL)	59.2 ± 19.3	55.4 ± 15.1	0.374
Right atrial volume, mL (normal range < 52 mL)	46.6 ± 13.5	47.2 ± 14.8	0.976
LV end-diastolic dimension, cm (normal range <5.2 cm)	4.84 ± 0.5	4.59 ± 0.27	0.662
LV end-diastolic volume, mL (normal range 34–75 mL)	90.8 ± 19.3	99.8 ± 37.6	0.364
LV end-systolic volume, mL (normal range 11–31 mL)	40.2 ± 14.7	43.9 ± 22.9	0.892

the evaluation of the LV global longitudinal strain (GLS) (Class 1C) [1], as this approach may facilitate the detection of early systolic dysfunction with sufficient reliability [12–14]. An analogous diagnostic strategy is illustrated in Figure 2 (adapted from [15]).

LVEF was measured by 2D TTE and LV GLS was determined during ATT. Following a six-month course of treatment, there was a decrease in LVEF, which did not reach the 50% threshold, and a reduction from the baseline value was less than 10%. Thus, in consideration of the relevant criteria, a diagnosis of cardiotoxicity cannot be stated. Concurrently, the decline in LV GLS reached the diagnostic threshold, with disturbances evident in four LV segments on the «bull's-eye» plot. LVEF decreased to the diagnostic level only after 12 months of therapy. At the same time, a determination of GLS in two LV segments suggests the presence of severe, potentially irreversible myocardial alterations [12].

Therefore, it is recommended that GLS, determined by speckle tracking using three apical sections for all patients undergoing ATT as a reliable method of CVT development monitoring (Class 1C) [1, 16–22]. It is recommended that LV GLS values to be obtained via serial measurements for each patient using the same device and software, as these values may be subject to variability [23]. The diagnostic threshold for LV GLS reduction as a criterion for asymptomatic cardiac dysfunction has yet to be definitively established; however, it is currently accepted as a reduction of 15% or more from baseline values [21]. This level enhances the precision of predictive outcomes, establishing a threshold value that facilitates the identification of cardiotoxicity with a sensitivity of 95%.

Figure 2. Left ventricular global longitudinal strain (LV GLS) and left ventricular ejection fraction (LVEF) determined by transthoracic echocardiography in a cancer patient undergoing polychemotherapy



Speckle tracking TTE is a valuable tool that can be employed not only to examine the LV state, but also to study other heart chambers. In recent years, there has been a notable focus on the structural and functional abnormalities of the LA myocardium. In 2016, the European Cardiac Arrhythmia Society (ECAS) published a consensus on LA myopathy, defining this condition as a set of structural and functional LA abnormalities, as well as electrophysiological irregularities that may potentially result in significant clinical manifestations [24].

It is hypothesized that LA myopathy may develop in cancer patients as a consequence of persistent subclinical systemic inflammation influence, as well as toxic effects of ATT [25]. The aforementioned factors may contribute to damage to the thin wall of the LA myocardium, which may subsequently result in remodeling and dysfunction. This, in turn, may lead to the development of arrhythmias [26].

A total of 30 patients with lymphoproliferative disorders (LPDs) who had undergone six courses of polychemotherapy (PCT) were examined [27, 28]: Holter monitoring, two-dimensional speckle tracking TTE to evaluate LV strain parameters, and the assessment of inflammatory markers. A comparison was made with the data from a similar examination of the comparison group including healthy individuals without LPDs and diagnosed CVDs at the time of inclusion.

A cardiac ultrasound was performed in accordance with the current Russian guidelines and those of the American Society of Echocardiography [29] by a certified specialist who was not privy to the patients' clinical data. A conventional transthoracic echocardiography (TTE) protocol was conducted, with supplementary investigations of LA structure and function.

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Study of the phase structure and function of LA

The reservoir phase (filling phase), which characterizes LA compliance, was determined during LV systole with closed mitral valve leaflets, at the end of the T wave on ECG. In this phase, the maximum LA volume index (LAVImax) was evaluated, and the LA compliance index and total LAEF were calculated:

$$LAEF = (LAV_{max} - LAV_{min}) / LAV_{max},$$

where LAV_{max} is the maximum LA volume and LAV_{min} is the minimum LA volume;

$$LAEF = (LAV_{max} - LAV_{min}) / LAV_{min},$$

where LAV_{max} is the maximum LA volume and LAV_{min} is the minimum LA volume.

The conduit phase was studied in early diastole, during which LAVI (LAVIc) was also determined, along with passive LAEF (LAEFpas):

$$LAEFpas = (LAV_{max} - LAVpre) / LAV_{max},$$

where LAV_{max} is the maximum LA volume and LAVpre is the precontraction LA volume.

The LA active contraction phase, which characterizes the contractility of the LA myocardium, was assessed in late diastole during active contraction of the LA myocardium. This involved the estimation of minimum LAVI ($LAVI_{min}$) and the calculation of active LAEF (LAEFact):

$$LAEFact = (LAVpre - LAV_{min}) / LAVpre,$$

where LAVpre is the precontraction LA volume and LAV_{min} is the minimum LA volume [29].

LA strain echocardiography

The LV strain was determined using 2- or 4-chamber views, with the value calculated as the mean of the six segments of these two views [29]. The reservoir, conduit, and active contraction strain were determined using the obtained monophasic LV strain curve, where the first and second peaks corresponded to the reservoir and active contraction phases, respectively, and the difference between them corresponded to the conduit phase. The following values of LA strain were considered to be within the normal range: >39% for the reservoir phase, >23% for the conduit phase, and >17% for the active contraction phase [29, 30].

A reduction in left atrial deformation is a sensitive marker of myocardial damage and may serve as a predictor of future LV dysfunction. In the study by M. Tadic et al. [25], phase analysis of LA strain was performed in 92 patients with cancer. A decrease in the reservoir and conduit phases was observed, and it was found that the presence of cancer serves as an independent predictor of these changes. In our study, we also observed a decline in LA phase parameters over time, with a notable correlation between their deterioration and the activity of inflammatory process and the onset of supraventricular cardiac arrhythmias.

The following data were obtained: in patients with LPDs, a notable reduction in LA strain was observed during the reservoir and conduit phases, both prior to PCT and throughout six courses of ATT (Table 2). Notwithstanding the observed decline in all functional parameters of the LA throughout the study, statistically significant differences were identified for the LA GLS, which aligns with the criteria for LA myopathy. No statistically significant differences were observed between the LPD patient group and the comparison group with regard to LAVImax, LAVImin, LAVIc, total LAEF, LAEFpas, and LAEFact. No correlation was identified between the structural and functional parameters of the LA and the parameters characterizing LV systolic and diastolic function (E/e'). The E/e' ratio was observed to be statistically significantly elevated in patients with LPDs relative to the comparison group, despite the values of this parameter remaining within the normal range.

Therefore, the study prospectively evaluated the LA functional abnormalities, systemic inflammatory markers (ESR, CRP), and supraventricular arrhythmias before and throughout six courses of PCT in a relatively homogeneous cohort. A close correlation was observed between these parameters, which gives an indication of early LA myopathy manifestation due to the influence of both LPD and ATT cardiotoxicity. There is literature evidence suggesting that the degree of systemic inflammation is associated with increased risk of developing LV dysfunction. Further studies will determine whether LA GLS may be a more sensitive marker of CVT than LV GLS.

Magnetic resonance imaging (MRI)

MRI is the gold standard for assessing LV function [30]. It was first included in the 2022 ESC Guidelines on Cardio-oncology as a potential diagnostic method for ATT cardiotoxicity [1]. MRI enables the precise measurement of cardiac chamber dimensions and myocardial mass, with minimum geometric distortion, thus providing reproducible determination of LV stroke volume and LVEF. Furthermore, supplementary computer processing of the acquired data enables the assessment of GLS, global circular strain, and global radial strain. One of the most significant advantages of MRI is its capacity to detect regional and subclinical myocardial alterations prior to the emergence of global dysfunction. In general, MRI is a valuable method for monitoring the cardiovascular system in patients undergoing and recovering from cancer treatment due to its capacity to characterize tissue, reproduce results with high accuracy, and quantify global and regional cardiac structure and function without ionizing radiation. This allows more precise control, monitoring, and, if necessary, adjustment of the treatment plan [30–33].

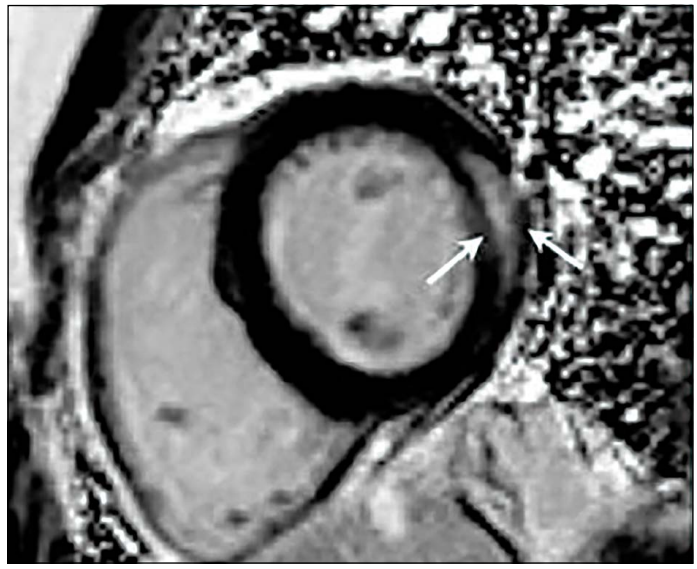
Table 2. Functional parameters of the left atrium in patients with lymphoproliferative disorders after 6 courses of polychemotherapy in comparison with healthy volunteers [27, 28]

Parameter	Control group (n = 30)	Patients with LPDs (n = 30)			p
	(1)	Prior to PCT (2)	3 courses of PCT (3)	6 courses of PCT (4)	
LA, reservoir phase					
LAVImax, mL/m² (normal range 26.8 ± 4.8)	21.6 [18.75; 25.8]	23.7 [19.8; 29.7]	25.5 [20.6; 30.2]	24.5 [20.8; 30.2]	$p_{1-2} = 0.9$; $p_{2-3} = 0.482$; $p_{2-4} = 0.75$
Total LAEF, % (normal range 55 ± 7)	56 [55; 61]	55 [50; 62]	5649; 64]	55 [50; 58]	$p_{1-2} = 0.21$; $p_{2-3} = 0.25$; $p_{2-4} = 0.014$
Strain, reservoir phase, % (normal range ≥ 39)	32.5 [26; 37]	30.5 [25; 41]	26 [18; 31]	28 [20; 31]	$p_{1-2} = 0.375$; $p_{2-3} = 0.001$; $p_{2-4} = 0.015$
LA, conduit phase					
LAVIc, mL/m² (normal range 18.3 ± 5.5)	14.6 [12.5; 18.2]	17.7 [14.6; 21.35]	18.75 [16.3.5; 22.9]	17.2 [13.8; 19.3]	$p_{1-2} = 0.044$; $p_{2-3} = 0.049$; $p_{2-4} = 0.077$
$LAEF_{pas}$, % (normal range 32 ± 6)	31 [22; 39]	26.5 [22; 32.5]	29 [22; 35]	27 [25; 40]	$p_{1-2} = 0.23$; $p_{2-3} = 0.32$; $p_{2-4} = 0.16$
Strain, conduit phase, % (normal range ≥ 23)	19 [12; 24]	17 [13; 24]	18 [15; 23]	19 [16; 23]	$p_{1-2} = 0.3$; $p_{2-3} = 0.8$; $p_{2-4} = 0.9$
LA, active contraction phase					
LAVImin, mL/m² (normal range 12 ± 3.9)	9.4 [8.3; 12.5]	9.9 [8.3; 14.6]	11.5 [7.8; 14.6]	12 [8.3; 14.6]	$p_{1-2} = 0.2$; $p_{2-3} = 0.1$; $p_{2-4} = 0.2$
LAEFact, % (normal range 34 ± 7)	39 [30; 46]	37 [28.5; 42]	38 [32; 45]	37 [20.5; 42]	$p_{1-2} = 0.6$; $p_{2-3} = 0.56$; $p_{2-4} = 0.1$
Strain, active contraction phase, % (normal range ≥ 17)	13.9 [9; 16]	14 [11.7; 16.9]	14.3 [9.8; 16.4]	14.3 [9.8; 16.4]	$p_{1-2} = 0.01$; $p_{2-3} = 0.46$; $p_{2-4} = 0.64$
LA GLS, % (normal range 38 ± 8)	33.6 [25; 41]	30.5 [26.8; 37.8]	29.6 [25; 32]	24.5 [15; 31.5]	$p_{1-2} = 0.89$; $p_{2-3} = 0.017$; $p_{2-4} = 0.001$

LA, left atrium; LAVI, left atrial volume index; LAEF, left atrial ejection fraction; GLS, global longitudinal strain; p_{1-2}, for the LPD group prior to PCT and the comparison group (Mann-Whitney test); p_{2-3}, for the LPD group before treatment and after 3 courses of PCT (Wilcoxon test); p_{2-4}, for the LPD group before treatment and after 6 courses of PCT and the comparison group (Wilcoxon test).

A distinctive attribute of MRI is the evaluation of myocardial status through the analysis of T1 / T2 parameters and late gadolinium enhancement (LGE) signal intensity. This approach enables the identification of pathological conditions such as fibrosis, myocardial edema, and scars (Figure 3, adapted from [34]), which is a valuable tool for the cardio-oncological practice [30, 33]. The LGE parameter facilitates not only the enhancement of MRI quality, but also the detection of local and diffuse myocardial abnormalities. In the field of cardio-oncology, the most pronounced image changes with LGE were observed most frequently at longer follow-up periods exceeding 20 years and in patients who received a higher cardiac radiation dose (22.9 ± 4 Gy or more). At shorter follow-up intervals (3–5 months), increased LGE signal intensity following radiation therapy was observed only in some myocardial segments. A number of studies have demonstrated a linear correlation between elevated levels of LGE and mean radiation dose (25.9 Gy). Similarly, a progressive increase in the LGE signal intensity was observed at a dose exceeding 30 Gy (marginal). The alterations in signal intensity were more pronounced at shorter follow-up intervals (6 months versus 1.5 years). This suggest that the myocardial inflammatory response to radiation therapy may persist for a period of approximately 6 months and subsequently diminish after 1.5 years.

Figure 3. Detection of an area of left ventricular myocardial fibrosis (indicated by arrows) using late gadolinium-enhanced MRI



In patients who have undergone radiotherapy, a segmental analysis of MRI parameters of strain revealed a potential correlation between the reduction of local strain and radiation dose [30]. A noteworthy reduction in strain (independent of dosage) was observed in studies with longer follow-up periods. It is currently unclear whether this

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reduction is due solely to the passage of time, or whether concomitant ATT and/or the presence of CVD risk factors play a significant role. Further research is necessary to investigate the effects of combined cancer treatments over longer and shorter follow-up periods. The available evidence indicates that strain may provide an earlier indication of myocardial abnormalities than, for example, LVEF. The compensatory properties of the heart may serve to preserve LVEF by increasing ventricular wall stress, even in the event of a decrease in circular strain due to myocardial fiber dysfunction. It may therefore be preferable to use strain measurements rather than LVEF alone, if the objective is to assess cardiac function in patients undergoing ATT.

In accordance with the 2022 ESC Guidelines for Cardio-oncology, the established cardiac imaging techniques utilized in the protocol for CVT risk stratification, diagnosis, and monitoring in the follow-up of cancer patients encompass a range of TTE techniques, including a standard examination, with the potential for incorporating 3D-mode and assessment of LV GLS [1, 35]. MRI should be considered in cases of poor quality or uninterpretable TTE images and in cases where complex clinical issues need to be assessed (e.g., presence of a pre-existing congenital cardiac anomaly, cardiomyopathy, etc. in a cancer patient) (class IIaC).

Prospective imaging methods for the diagnosis of cardiovasculotoxicity

In the near future, new methods and diagnostic techniques will be introduced into widespread cardio-oncologic practice. The first of these is the assessment of coronary blood flow and coronary calcium index using multi-slice computed tomography (MSCT) (Figure 4).

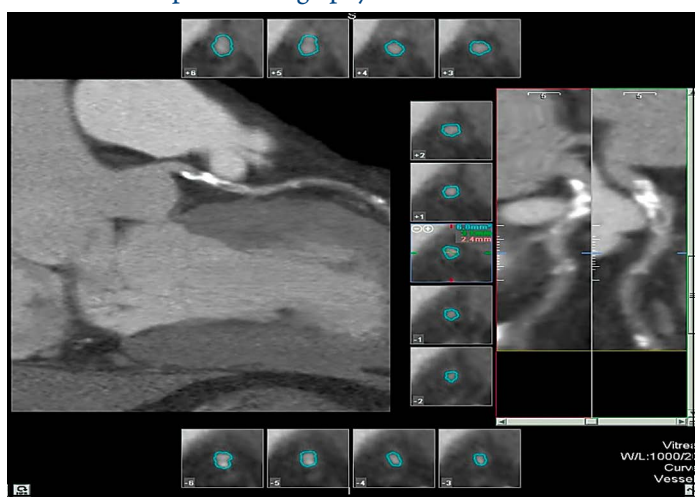
The coronary calcium index (CCI) is one of the most extensively studied, rapid, and widely accessible tests in the field of cardiovascular medicine that does not require contrast enhancement. A substantial body of evidence has been amassed from numerous large, long-term, population-based observational studies conducted in the USA, Germany, and the Netherlands. This evidence demonstrates a robust association between CCI and the emergence of cardiovascular complications, even in patients who are asymptomatic [36]. The current American and European clinical practices recommend CCI as a reliable method for predicting the risk of developing CVDs in patients who are asymptomatic. This enables the selection of the most appropriate subsequent diagnostic and therapeutic strategy [37]. For example, a low level of CCI may reduce the necessity for additional unfeasible examinations and interventions. Conversely, a high level of CCI may indicate an elevated risk of cardiovascular complications and the necessity for more rigorous preventive measures.

Although CCI is a powerful tool for risk stratification in general population, specific recommendations for its use in cancer patients have yet to be developed, despite the recent appearance of several encouraging studies.

For example, S. Patel et al. (2024) demonstrated that cancer patients with a moderate (101–400) and high (> 400) CCI was associated with a statistically significantly higher prevalence of coronary artery atherosclerosis compared to that observed in non-cancer patients with similar sex, age, and cardiovascular risk factor profiles. This finding is consistent with the results of previous studies. For example, M. C. Whitlock et al. (2015) [37] demonstrated an association between the presence and treatment of cancer and the development of coronary calcifications. CCI can be regarded as a novel risk stratification instrument for the identification of cancer patients at elevated cardiovascular risk

The underlying pathophysiological mechanisms of the association between cancer and atherosclerosis are primarily attributed to the role of neoplasia in the activation of local and systemic inflammatory cascades. The elevated activity of inflammasomes, interleukins, and proinflammatory cytokines observed in cancer patients is associated with an accelerated process of atherogenesis [38, 39]. In addition to the direct pathophysiological effects of the cancer process itself, the influence of numerous antitumor drugs must be taken into account. The development of CVDs is associated with the use of various agents, including tyrosine kinase inhibitors, platinum drugs, taxanes, 5 fluorouracil, and hormonal therapy. These agents exert their adverse cardiovascular effects by a number of mechanisms, including direct damage to endothelial cells, oxidative stress, vasospastic ischemia, arterial thrombosis, and the development of persistent arterial hypertension [40]. The detection of high CCI in a patient with cancer necessitates a

Figure 4. Determination of coronary calcium and imaging of coronary arteries using multi-slice computed tomography



more comprehensive contrast-enhanced examination of the coronary arteries, employing both MSCT and endovascular methods. This approach allows expeditious correction of treatment strategies for both the oncological process and coronary pathology.

Recent studies have indicated the potential utility of 18F-labeled 2-deoxy-2-fluoro-d-glucose ([18F] FDG) positron emission tomography-computed tomography (PET-CT) in the early detection of ATT-related myocardial damage [41, 42]. If it is assumed that myocardial damage resulting from cancer treatment leads to an increase in glycolytic metabolism, this metabolic alteration can be quantified. Following administration, [18F] FDG gains access to the cell via the glucose transporter protein (GLUT) [43]. In a healthy heart, the GLUT-4 protein is expressed on the membrane of cardiomyocytes, primarily regulating glucose entry under conditions of elevated plasma insulin concentration. The GLUT-1 protein plays a pivotal role in the uptake of [18F] FDG by tumor cells.

Given the considerable diversity of CVT among various antitumor drugs, both in terms of their direct impact on cardiomyocytes and through the induction of systemic or local chronic inflammation, it is reasonable to anticipate alterations in glucose metabolism. Accordingly, [18F] FDG PET-CT may be applied for CVT risk stratification, the detection of CVT, and the subsequent monitoring of the response to ATT in patients with cancer [44]. For example, C. Borde et al. (2012) conducted an analysis of myocardial uptake of [18F] FDG in patients with lymphoma who were undergoing treatment with AAs. A notable elevation in radiopharmaceutical uptake was documented, which was regarded as an early indicator of cardiotoxicity in patients receiving doses exceeding 250 mg/m^2 [42]. In a study by M. Bauckneht et al. (2017) [45] including patients with Hodgkin's lymphoma (n = 69), an increase in myocardial [18F] FDG uptake was observed during the course of treatment, which persisted for a period of six months following the conclusion of treatment. The authors put forth the hypothesis that low myocardial uptake of [18F] FDG prior to AA therapy is a predictor of cardiotoxicity. In another study (Hodgkin's lymphoma, induction course including AAs) [46], it was demonstrated that the standard value of [18F] FDG uptake by LV myocardium presented a gradual increase in comparison to the baseline results. In the subgroup of patients who underwent TTE, no statistically significant differences were observed in the mean values of LVEF and LVEDV before and after ATT. Thus, no evidence of cardiotoxicity was identified by TTE [46].

Conclusion

The introduction of increasingly sophisticated imaging techniques into clinical practice has facilitated earlier detection of cardiovascular toxicity signs (central illustration, adapted from [41]). Only the most recent signs of cardiovascular toxicity may be detected during the assessment of the clinical condition of the patient.

The use of ultrasound modalities, particularly in the assessment of left ventricular global longitudinal strain, significantly accelerates the diagnosis, albeit only at the stage of violation of myocardial mechanical properties related to contraction and relaxation. The potential to study myocardial structure using multi-slice computed tomography and magnetic resonance imaging is rapidly developing, but these techniques are not yet able to detect the onset of early signs of cardiovascular toxicity during the onset of metabolic disturbances. The use of positron emission tomography-computed tomography with 18F-labeled 2-deoxy-2-fluoro-d-glucose appears to be a highly promising avenue in this regard. The initial metabolic alterations and cellular injury can be evidenced by an elevation in the concentration of particular biomarkers, including troponin and brain natriuretic peptide. However, due to their very low specificity, their interpretation should be carried out only in conjunction with the findings of modern imaging techniques.

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