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Cardio-oncology today: digest of the first European clinical guidelines (2022)

Over the past few decades, due to the extensive implementation of cancer screening programs, up-to-date early diagnostic methods, and effective combinations of antitumor therapy, it has become possible to significantly improve survival of cancer patients. At the same time, despite the effective treatment of malignancies, most patient face adverse and often life-threatening effects of specific treatment on the heart and blood vessels. All this resulted in active development of a new field in cardiology, cardio-oncology. In recent years, based on the experience of leading experts, data from large studies, and meta-analyses, both international and Russian Consensuses, conciliation documents, have been formed and published. These documents regulate principal methodological approaches to management and control of the cardiovascular conditions in cancer patients. Finally, 2022 was marked by issuing the first official European Guidelines on Cardio-Oncology in the history of medicine. This article highlights the most relevant, in our opinion, positions of these guidelines as well as controversial and unresolved issues.

Keywords Cardio-oncology; cardiotoxicity; vasculotoxicity; guidelines; cancer; chemotherapy; prophylaxis; diagnostics; treatment; monitoring

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1. Development of Cardio-Oncology

Cancer has consistently been one of the leading causes of morbidity and mortality in economically developed countries throughout the past few decades [1]. Sustained remission is achieved owing to population-wide preventive screening programs, early diagnosis, modern chemo- and radiotherapy options, and advanced surgical treatment [2]. However, despite the effective cancer treatment, the severity of the cancer patient's condition is often determined by the development and progression of cardiovascular diseases (CVDs) being either an independent underlying process or related to the cardiovascular toxicity effects of specific treatment [3]. Adverse cardiovascular events are the main cause of death in 30% of patients with complete response to cancer treatment in the following 10 years [4]. Thus, if a patient has both cancer and CVD, it can be clinically reasonable to interrupt/modify cancer treatment. Cancer and cardiovascular comorbidity significantly aggravate the severity of the patient's condition, reduce long-term survival, and increase the likelihood of death due to cardiac complications.

The term «cardiotoxicity» appeared in the 1970s. The adverse effects on the structure and function of the heart and blood vessels were noted with the beginning of the widespread use of anthracycline antibiotics (AAs) for the treatment of various cancers [3]. Many papers on epidemiology, pathogenetic bases, prevention, and treatment of the toxic effects of CT have been published since then in Russia and worldwide. Statistics show that the incidence of different cardiovascular events varies much and is well-proven to depend on the anticancer agent used, its dose, and the combination of drugs. Thus, the development of systolic dysfunction of the heart is associated with the used of AAs in up to 50% of patients, trastuzumab in up to 20%, and tyrosine kinase inhibitors (TKI) in 1% to 10% of patients [3]. As for the pathogenesis of cardiotoxic action, AAs are the most well-studied class. Their mechanism of adverse effects is to inhibit the DNA repair enzyme topoisomerase IIβ in cardiomyocytes and increase activity of oxidative stress, levels of reactive oxygen species, and lipid peroxidation, which also influence on endothelial cells [5]. The use of radiation therapy (RT) to treat malignant tumors was first described in the early 20th century. However, the significance for the progress of cardiac pathology became clear only a century later when the long-term adverse consequences of such treatment began to be verified [3, 4]. That is why an interdisciplinary field of medicine (cardio-oncology) has been actively developing in this decade, which is aimed at assessing the initial cardiac risk, timely detection, monitoring, and treatment of adverse cardiovascular events associated with cancer therapy The term «cardio-oncology» was first officially introduced in 2016 following the publication of the ESC Position paper on cancer treatments and cardiovascular toxicity [3].

Over the years, the ESC published several more major papers on the recommended cardiotoxicity biomarkers, cardiovascular imaging of cardiotoxic effects, and Baseline cardiovascular risk assessment [6–8]. Based on the above document and the experience of Russian scientists, the Russian Society of Cardiology (RSC) issued the Consensus Opinion on Cardiovascular Toxicity of CT in 2021, which was the first Russian regulatory document in this field [9]. Finally, the first official ESC clinical guidelines on cardio-oncology, which contain 272 new recommendations, was issued in August 2022 [10]. This document was the result of scrupulous, evidence-based joint work of leading international cardiologists/cardio-oncologists, hematologists, radiologists, and oncologists. Since 2016, cardio-oncology has become increasingly scientifically and clinically: significant: all guidelines in other fields were updated since to contain sections devoted to cancer patients.

There have been autonomous, highly specialized cardio-oncology clinics in other countries for years, which are usually a part of large multidisciplinary hospitals. However, cardio-oncology is a section of cardiology rather than an independent specialty in the Russian Federation, which requires significant work to be done in this direction to form a regulatory, administrative, and financial base for the activities of such specialized departments.

This paper highlights the most relevant, in our opinion, aspects of the first in the modern guidelines on cardio-oncology and controversial and outstanding issues.

2. Key Aspects of Clinical Guidelines. Definition

Initially, the term «cardiotoxicity» meant only a violation of left ventricular (LV) systolic function manifested by an asymptomatic decrease in the left ventricular ejection fraction (LVEF) or clinically significant heart failure (HF). However, the adverse cardiovascular events of cancer therapy cover a wide range of pathological manifestations, not limited to abnormal heart pumping: rhythm/conduction disorders, myocarditis/pericarditis, arterial hypertension, accelerated atherosclerosis and plaque instability, ischemic phenomena, microcirculatory damage, valvular heart disease (VHD), thrombosis and thromboembolic events etc.

The published papers of various scientific medical communities on cardio-oncology cited various terms for the description and diagnosis of CT-associated cardiotoxicity events, which, in turn, gave rise to different approaches to their verification and treatment. The first attempt to generalize and give unified definitions of different variants of cardiovascular toxicity was made in the 2022 by International Society of Cardio-Oncology (IC-OS) consensus document [11]. The working group identified 5 main cardiovascular complications of CT most described in the literature:

- Systolic dysfunction/heart failure;
- Myocarditis;
- Vasculotoxicity;
- Arterial hypertension;
- Arrhythmia/QTc prolongation.

Thus, this paper was one of the key prerequisites for the development and release of the first guidelines on cardio-oncology in the history of medicine.

One of the main tasks for the authors was to develop a universal definition of cardiovascular toxicity of CT. It should be emphasized that this paper provided precise definitions for cardiotoxicity and approaches to laboratory tests and clinical investigations used verify the condition. Given the wide range of manifestations, neither the definition nor the diagnostic approaches have been clarified for the concept of vasculotoxicity, which entails the need for further research.

The guidelines included other important new aspects:

a) Personalized approaches to the management, prevention, and monitoring of cancer patients depending on their baseline CV toxicity risk and the chosen anti-cancer regimen;
b) Precise protocols for the management and treatment of adverse cardiovascular events during cancer therapy;
c) A new recommendation on the management of patients with breast cancer receiving trastuzumab who developed asymptomatic moderate cardiac dysfunction (LVEF 40–49%);
d) A clearly structured algorithm for prescribing anticoagulant therapy for new-onset paroxysmal atrial fibrillation (AF) or an episode of venous thromboembolism (VTE) during cancer treatment;
e) The high significance of Long-term follow-up of the cardiovascular system (CVS) was first emphasized for patients with the history of cancer: close dynamic monitoring within the first year after the end of cancer treatment and lifelong follow-up is fundamental;
f) Special attention is paid to patients with the history of cancer in childhood/adolescence.

It should be noted that the authors repeatedly point out throughout the guidelines that decisions

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on the discontinuation/continuation of therapy with potential cardiovascular toxicity must be made only by the multidisciplinary team (MDT) and only after assessing the risk/benefit ratio between the efficacy of cancer treatment and the severity and type of cardiovascular toxicity.

Definition

1. The authors suggest using a few fundamental terms for a variety of CT-associated adverse cardiovascular events, including:
2. More broad «cancer therapy-related cardiovascular toxicity (CTR-CVT)», including cardiomyopathy and HF, myocarditis, vascular complications, arterial hypertension, arrhythmias, QT prolongation, diseases of the pericardium, and heart valve disease. It is recommended to use the term «cancer therapy-related cardiac dysfunction (CTRCD)» for signs of heart damage, cardiomyopathy, and heart failure, since it covers a wide range of possible manifestations and indicates an etiological relationship with cancer treatment, including CT, targeted and immune therapy, RT (Table 1).

3. Baseline cardiovascular toxicity risk assessment

It is recommended to stratify cardiovascular risk (Class IC) and determine the baseline CV toxicity risk (Class IIaC) for each cancer patient before starting CT with potential cardiovascular toxicity using special scales to predict the likelihood of adverse cardiovascular events more accurately. The authors of the guidelines

Table 1. Cancer therapy-related cardiovascular toxicity definitions, adapted from [10]

Cancer therapy-related cardiac dysfunction			
Symptomatic cardiac dysfunction (HF)[a, b]			
Very severe	**Severe**	**Moderate**	**Mild**
HF requiring inotropic support, mechanical circulatory support, or considering heart transplantation	Hospitalization for HF	Outpatient enhancement of HF drug therapy (including diuretic) is required	Minimal symptoms of HF that do not require treatment enhancement
Asymptomatic cardiac dysfunction			
Severe	**Moderate**	**Mild**	
De novo LVEF reduction < 40 %	De novo LVEF reduction by ≥ 10 % to LVEF 40–49% OR De novo LVEF reduction by < 10% to LVEF of 40–49 % or De novo relative decrease in GLS by > 15 % from baseline, or De novo elevation of biomarker levels	LVEF ≥ 50 % AND De novo relative decrease in GLS by > 15 % from baseline AND/OR de novo elevation of biomarker levels[c]	
Myocarditis associated with immune checkpoint inhibitors			
Histological diagnosis (EMB)			
Multifocal inflammatory cell infiltrates with obvious loss of cardiomyocytes in light microscopy			
Clinical diagnosis[d]			
Elevated cTn (de novo or significantly different from baseline)[e] + 1 major or 2 minor criteria after exclusion of ACS and acute infectious myocarditis based on clinical data[f]			
Major criterion	**Minor criteria**		
MRI diagnosis of acute myocarditis (modified Lake Louise criteria)[g]	• Clinical syndrome (including any of the following: fatigue, myalgia, chest pain, diplopia, ptosis, dyspnea, orthopnea, leg swelling, palpitations, near syncope/dizziness, fainting, muscle weakness, cardiogenic shock) • Ventricular arrhythmia (including cardiac arrest) and/or new-onset cardiac conduction disorder • Decreased LV systolic function with or without regional wall movement disorders in patients without CMP/Takotsubo CMP • Other immune-mediated adverse effects including myositis, myopathy, myasthenia • Controversial cardiac MRI findings		
Severity of myocarditis			

• Fulminant myocarditis: hemodynamic instability; HF requiring non-invasive or invasive circulatory support; complete or high degree heart block and/or life-threatening ventricular arrhythmias
• Nonfulminant myocarditis: symptomatic but hemodynamically and electrophysiologically stable patients; and cases identified concurrently with other immune-mediated adverse events. Patients may have reduced LVEF but no signs of decompensation
• Steroid-resistant myocarditis: unresolved or progressive myocarditis (clinical worsening or persistent increase in troponin levels after ruling out other causes) despite high-dose methylprednisolone

Table 1 (continuation). Cancer therapy-related cardiovascular toxicity definitions, adapted from [10]

Recovery from myocarditis
• Complete recovery: complete disappearance of acute symptoms, normalization of biomarker levels, and recovery of LVEF after discontinuation of immunosuppressive therapy. MRI may still detect late accumulation of gadolinium or enhanced T1 signal due to fibrosis but there should be no data supporting acute edema • Recovery: continuing improvement of clinical symptoms, signs, biomarker levels, and imaging parameters but only partial disappearance as doses of immunosuppressants are decreased gradually
Vasculotoxicity

Asymptomatic	Symptomatic
CAD, peripheral atherosclerosis, carotid artery atherosclerosis, venous and arterial thrombosis, pathological vasoreactivity (peripheral, coronary, microvascular)	Stroke, TIA, myocardial infarction, ACS, chronic coronary syndrome, peripheral arterial disease, vasospastic angina, microvascular angina, Raynaud's syndrome

Arterial hypertension
Threshold for the initiation of antihypertensive therapy before, during, and after CT
Patients at high cardiovascular risk: systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mm Hg Other patients: systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mm Hg
Threshold for discontinuing CT
Systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg
Hypertensive emergency
(Severe increase in blood pressure associated with acute damage to target organs (heart, retina, brain, kidneys, and large arteries) requiring an emergency decrease in BP to limit further damage
Cardiac arrhythmias
QTc prolongation – QTc (F) > 500 ms[j]
Bradycardia
Supraventricular tachycardia
Ventricular arrhythmia
Atrial fibrillation

[a] Based on LVEF and diagnostic biomarkers (2021 ESC Guidelines on the diagnosis and treatment of acute and chronic HF) [12].
[b] Symptomatic cardiac dysfunction associated with cancer therapy reflects HF, a clinical syndrome consisting of symptoms (dyspnea, leg swelling, astenia), which may be accompanied by signs (for example, increased jugular venous pressure, pulmonary rales, and peripheral edema), and is traditionally divided into individual types based on LVEF: HFrEF – ≤40 %; HFmrEF – 41–49 %; HFpEF – ≥50 %.
[c] *c*TnI/*c*TnT >99th percentile, BNP ≥35 pg/mL, NT-proBNP ≥125 pg/mL, or a new significant increase compared to baseline.
[d] Clinical diagnosis should be confirmed by MRI of the heart or EMB, if it is possible and does not interfere with treatment. Immunosuppressive therapy should be initiated immediately, while pending results of the confirmation tests in symptomatic patients.
[e] Both troponin I and troponin T may be used, but clinical observations suggest that troponin T may be false elevated in patients with concomitant myositis and without myocarditis.
[f] In accordance with local protocols.
[g] MRI diagnosis: based on modified Lake Louise criteria: T2 mapping + T1 mapping ± additional criteria (T2 mapping: focal or diffuse enhancement of the native T2 signal or enhanced T2 signal; T1 mapping: focal or global enhancement of the native T1 signal, or focal or global increase in extracellular volume, or presence of late gadolinium accumulation; additional criteria: pericarditis and/or focal or global left ventricular systolic dysfunction).
[h] Controversial MRI findings: meet some modified Lake Louise criteria, but not all of them. The presence of T2- or T1-based criteria may confirm the diagnosis of acute myocardial inflammation in the relevant clinical scenario.
[i] SCORE2 (<70 years), SCORE2 OP (≥70 years) or equivalent. Stratification of cardiovascular risk: <50 years: low risk <2.5 %, moderate risk from 2.5 % to <7.5 %, high risk ≥7.5 %; 50-69 years: low risk <5 %; moderate risk 5 % to <10 %; high risk >10 %; ≥70 years: low risk <7.5 %, moderate risk from 7.5 % to <15 %, high risk <15 %.
[j] QTc (F) 480–500 ms: elimination of reversible causes, minimization of other drugs that prolong the QT interval, careful monitoring of QTc (F). Correction is recommended using the Fridericia formula (QTcF = QT/3√RR).

BP, blood pressure; CAD, coronary artery disease; CMP, cardiomyopathy; MRI, magnetic resonance imaging; ACS, acute coronary syndrome; CT, chemotherapy; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; EMB, endomyocardial biopsy; BNP, B-type natriuretic peptide; *c*Tn, cardiac troponin; GLS, global longitudinal strain; NT-proBNP, N-terminal pro-brain natriuretic peptide; QTc (F), corrected QT interval using Fridericia formula.

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believe that the primary risk assessment should be conducted by the attending oncologist / chemotherapist to determine the indications / need for a consultation by the cardio-oncologist. However, the risk is assessed by cardiologists in the Russian Federation since there are no clear documents regulating this process.

The basic risk assessment scales developed by Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) are the most common simple and easy-to-use scores [8]. There are scales for 6 groups of anticancer drugs: anthracyclines, HER2 inhibitors, vascular endothelial growth factor (VEGF) inhibitors, second- and third-generation Abelson's tyrosine kinase inhibitors (BCR-ABL TKI), proteasome inhibitors / immunomodulators, RAF and MEK inhibitors. The following reference information is included in each scales: underlying CVDs (HF, cardiomyopathy, history of documented cardiovascular toxicity, MI, VHD, thrombosis / thromboembolism, arrhythmia), cardiac imaging findings (baseline LVEF), biomarkers (cTnI / T, BNP / NT-proBNP), the presence of major cardiovascular risk factors (age, arterial hypertension, diabetes mellitus, chronic kidney disease (CKD), dyslipidemia, smoking, obesity), and the history of chemoradiation therapy (AAs, RT in the mediastinal area or left chest). Based on the sum of the available factors, the patient is classified to one of the four risk groups for adverse cardiovascular events (low risk, moderate risk, high risk, and very high risk).

For the other seven groups of cancer therapy (fluoropyrimidine drugs, Bruton tyrosine kinase inhibitors, immune checkpoint inhibitors (ICIs), epidermal growth factor receptor (EGFR) inhibitors, RT, hematopoietic stem cell transplantation, CAR-T therapy, non-validated calculators for cancer patients are indicated to assess the baseline cardiovascular risk, as well as identify traditional cardiovascular risk factors (SMART [Second manifestations of arterial disease], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation], SCORE2 [Systematic Coronary Risk Estimation 2], SCORE2 OP [Systematic Coronary Risk Estimation 2 – Older Persons], ASCVD [AtheroSclerotic Cardiovascular Disease], U-Prevent) [10].

A generalized approach to the stratification of the initial cardio-oncological risk and the management of cancer patients is shown in Figure 1.

Electrocardiograhy

It is recommended to perform baseline ECG in all cancer patients before the start, during, and after the end of cancer therapy (Class IC). More frequent monitoring is indicated during the administration of the drugs that prolong the QTc interval, provoke arrhythmias and conduction disorders (BCR-ABL TKI, MEK and RAF inhibitors, ICIs) [13].

Cardiac serum biomarkers

The significance of the determination of cardiotoxicity biomarkers (cTnI / T, BNP / NT-proBNP) has increased substantially in the current guidelines. In the previous papers, they were optional, only for some patient groups, and now, «the baseline assessment is indicated to all cancer patients, provided that the changes of biomarker levels are monitored during treatment to verify cardiac dysfunction associated with cancer therapy». Elevated levels of biomarkers directly affect the strategy of cardioprotective therapy (the start of drug treatment if cTn and / or BNP / NT-proBNP are increased even in normal LVEF) (Class IIa) [10, 14].

Cardiovascular imaging

Conventional transthoracic echocardiography is a main diagnostic tool for cardiotoxicity events, taking into consideration the standardized definition of CTRCD (Class IC). It should be considered that the sensitivity of conventional echocardiography with a 2D assessment of left ventricular systolic function is low. The gold standard is 3D echocardiography with LVEF assessment (Class IB) as and speckle tracking with LV global longitudinal strain (GLS) estimation (Class IC). If echocardiography is inaccessible and / or uninformative, cardiac MRI should be considered as a diagnostic technique (Class IIaC).

It is strictly indicated in the guidelines that echocardiography is required for all cancer patients at high and very high risk of cardiovascular toxicity before, during, and after cancer treatment.

4. Strategies for Prevention and Monitoring of cardiovascular complications during cancer therapy

It should be noted that CTR-CVT risk is not a constant sum parameter and may vary depending on the type and stage of cancer, the combination of anticancer drugs and their total dose administered, and concomitant diseases. Experts recommend assessing the risk not only at baseline but also repeatedly during treatment, especially if it is planned to modify the anticancer regimen.

Cardiovascular and oncological diseases have similar pathogenesis and common modifiable and non-modifiable risk factors [3, 15]. The strict correction and adequate physical activity (according to the patient's

tolerance) are indicated before, during, and after specific treatment (Class IC). Primary or secondary strategies for the prevention of cardiovascular complications of CT are indicated for all cancer patients (Figure 2). Neurohumoral modulators (ACE inhibitors or ARBs, beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs)) and statins may be recommended as part of primary prevention for patients at high and very high risk, to whom AA and/or HER2 inhibitor (Class IIaB), targeted therapy, and other CT (Class IIaC) are scheduled. The reduction of doses and infusion times, the use of dexrazoxane and liposomal drugs are reasonable to decrease anthracycline-induced cardiotoxicity only in adult patients at high and very high risk. Only liposomal doxorubicin is approved now in the Russian Federation. Management of cancer patients in terms of secondary prevention of CT-associated cardiovascular events is limited to the management of known CVD based on relevant current clinical guidelines for a specific nosology before, during, and after specific treatment (Class IC).

The new guidelines clearly define for the first time what parameters of laboratory tests and clinical investigations should be monitored depending on the baseline cardiovascular toxicity risk assessment and the option/regimen of cancer therapy. The authors suggested appropriate protocols for monitoring cardiovascular state during treatment for the following drug groups: AAs, HER2 inhibitors, fluoropyrimidine drugs, VEGF inhibitors (monoclonal antibodies, tyrosine kinase inhibitors), second- and third-generation BCR-ABL TKIs, Bruton tyrosine kinase inhibitors, proteasome inhibitors (+ other drugs for multiple myeloma, such as alkylating agents, immunomodulators, monoclonal antibodies), RAF and MEK inhibitors, ICIs, androgen-deprivation therapy for prostate cancer, hormone therapy for breast cancer, cyclin-dependent kinase (CDK) 4/6 inhibitors, anaplastic lymphoma kinase inhibitors, EGFR inhibitors, CAR-T therapy, RT, hematopoietic stem cell transplantation, and other anticancer drugs (cyclophosphamide, platinum-based drugs, ifosfamide, taxanes).

For example, ECG + echocardiography + biomarker analysis is initially indicated for all patients receiving anthracycline-containing therapy. During the treatment of patients at low and moderate risk, monitoring of biomarkers should be performed every 2 cycles, echocardiography after 4 cycles and 12 months after the end of treatment; for patients at high and very high risk: biomarkers before each next administration, echocardiography after 2, 4, 6 cycles and 3, 12 months after the end of treatment.

Figure 1. Generalized approach to the baseline cardiovascular toxicity risk assessment, adapted from [10]

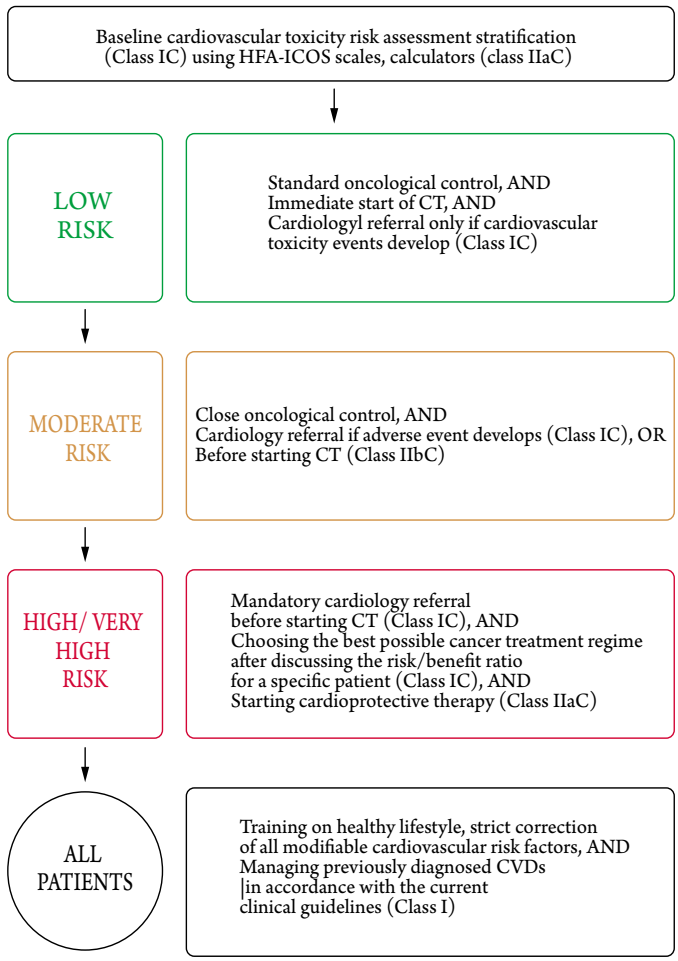
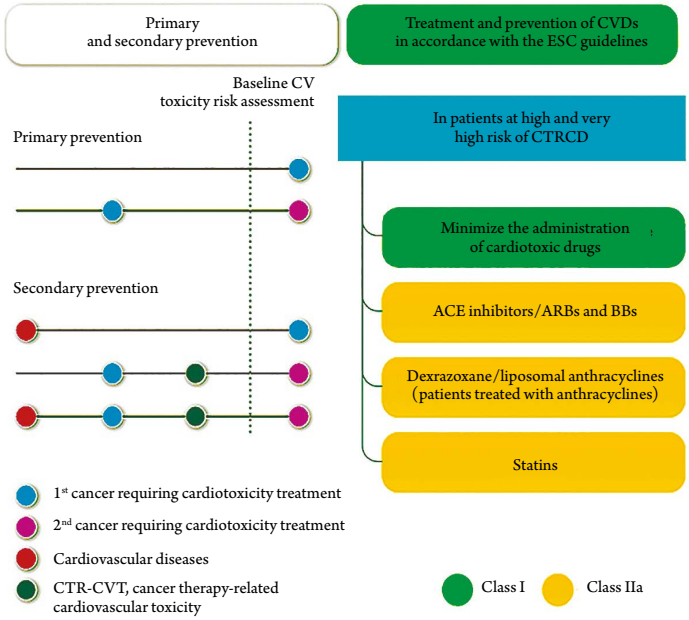


Figure 2. Primary and secondary cancer therapy-related cardiovascular toxicity prevention, adapted from [10]



BB, beta-blocker; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme; ESC, European Society of Cardiology; CVD, cardiovascular disease.

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It is recommended to close monitoring of CVS (ECG, biomarkers, echocardiography) in patients of all risk groups, to whom HER2 therapy is scheduled, at baseline and every 3 months during the 12-month therapy and 12 months after the end of treatment.

Before prescribing fluoropyrimidine drugs (5 fluorouracil, capecitabine) in the groups of patients at high risk and very high risk (based on SCORE2/SCORE2 OP), they should be screened for coronary pathology (stress tests, stress echocardiography, coronary artery CT angiography).

During the administration of VEGF inhibitors therapy, strict constant monitoring of blood pressure and QTc duration is indicated for all patients; biomarker analysis and echocardiography are performed every 4 months of treatment within the first year in the groups of moderate cardio-oncology risk, every 3 months in patients at high/very high risk, and subsequently every 6–12 months in all patients.

Special attention should be paid to patients, to whom RT in the heart region (left breast cancer, lung cancer, Hodgkin and non-Hodgkin lymphomas) are planned. According to the expert opinions and research data, there is no safe dose of radiation for the heart. There are also no specific preventive measures (for example, cardioprotective drugs) to reduce the risk of adverse events. Given the documented effects of traditional cardiovascular risk factors on the incidence of adverse effects of RT, strict correction of all modifiable risk factors is indicated for all patients before and after therapy, as well as lifelong follow-up, given the high incidence of long-term sequelae after many years.

5. Diagnosis and management of acute and subacute cardiovascular toxicity in patients receiving anticancer treatment

If any variant of cardiovascular toxicity of CT develops, the case should be discussed by the MDT to determine further patient management and treatment strategy and assess the possibility of continuing specific cancer treatment.

5.1. Cancer therapy-related cardiac dysfunction

5.1.1. Anthracycline-induced cardiac dysfunction

AAs often cause cardiovascular toxicity, in up to 48% of cases [3]. Asymptomatic systolic dysfunction and symptomatic HF are the most common toxicities (Table 1). The diagnosis is made based on complaints, clinical presentation, cardiac imaging findings, and/or elevated biomarkers of cardiotoxicity. AAs should be discontinued if very severe/severe symptomatic HF develops; moderate HF requires temporary discontinuation of the regimen (Class IC). The MDT may decide to continue AA therapy in patients with mild symptoms of HF (Class IC).

Temporary discontinuation of CT regimens is also recommended in moderate to severe asymptomatic dysfunction (Class IC). Patients with mild asymptomatic dysfunction continue chemotherapy with frequent monitoring of the cardiovascular system (biomarkers, GLS) (Class IC).

HF therapy is absolutely indicated to all patients with confirmed symptomatic HF and moderate-to-severe asymptomatic myocardial dysfunction following the 2021 ESC guidelines for heart failure (ACE inhibitors/ARBs, sacubitril/valsartan, BBs, MRAs, SGLT2 inhibitors with dose titration to the maximum tolerated doses (Class IB)) [10, 12, 16].

5.1.2. HER2 induced cardiac dysfunction

Chemotherapy using targeted HER2 inhibitors can also contribute to the development of symptomatic and asymptomatic cardiac dysfunction in 15–20% of patients. CT should be discontinued in patients with moderate-to-very-severe symptomatic and severe symptomatic HF (Class IC). Appropriate HF therapy should be carried in all indicated cases out following the current clinical guidelines (Class IB).

The authors present a new strategy for managing patients with an asymptomatic moderate decrease in LVEF to 40–49%: HER2 inhibitor therapy can be continued with careful cardiac monitoring and maximum cardioprotective therapy (Class IIaB).

5.1.3. Immune checkpoint inhibitor-associated myocarditis and non-inflammatory systolic dysfunction

The most common complications of ICI therapy are myocarditis (odds ratio (OR) 4.42), dyslipidemia (OR 3.68), acute coronary syndrome (ACS), vasculitis, pericarditis/pericardial

effusion, stroke, etc. [17]. ICI-induced myocarditis should be suspected if patients have relevant clinical symptoms, elevated troponin levels, and new changes on the ECG (rhythm and conduction disorders). ICI-induced myocarditis is verified by ruling out other possible causes of the condition/complaints (Table 1).

If myocarditis is confirmed, immunotherapy is discontinued, and the patient is hospitalized (Class IC). Treatment of the adverse event implies early initiation of high doses of intravenous methylprednisolone (500–1000 mg) followed by switching to oral prednisolone during the recovery period (Class IC; IIaC). If the clinical manifestations persist for three days or more,

Table 2. Cancer therapy highly associated with ACS, adapted from [10]

Accelerated atherosclerosis, plaque instability, rupture	Androgen deprivation therapy, ICIs, nilotinib, ponatinib, RT, VEGF inhibitors
Vasospasm	Bleomycin, fluoropyrimidines, taxanes, VEGF inhibitors, vinca alkaloids
Coronary artery thrombosis	Alkylating agents (cysplatin, cyclophosphamide), ICIs, lenalidomide, thalidomide, monoclonal antibodies (VEGF inhibitors, anti-CD20 monoclonal antibodies), nilotinib, platinum-based drugs, protease inhibitors, ponatinib, etc.

VEGF, vascular endothelial growth factor; ICI, immune checkpoint inhibitor.

the condition is regarded as steroid-resistant myocarditis, the second line of immunosuppressive therapy (mycophenolate mofetil, anti-CD3 monoclonal antibodies, immunoglobulins, plasmapheresis, tocilizumab, abatacept, alemtuzumab, and tofacitinib) is indicated.

Prednisolone in combination with colchicine should be administered in immunotherapy-associated pericarditis (Class IC).

5.2. Coronary Artery Disease

5.2.1. Acute coronary syndrome

Cancer patients are at high risk of coronary artery disease (CAD). This is explained by similar risk factors, the proinflammatory and prothrombogenic activity of the underlying disease, and the use of certain drugs (Table 2). Diagnosis of CAD is often complicated in such patients due to atypical or masked clinical symptoms.

If ACS develops, temporarily discontinuation of CT is recommended, individual management of the patient should be considered by the MDT given the oncological status, including abnormalities in peripheral blood (anemia, thrombocytopenia, leukopenia), prognosis, and patient preferences.

Percutaneous coronary intervention (PCI) is a safe intervention for cancer patients [18, 19]. Invasive treatment of ST-segment elevation ACS and non-ST-segment elevation ACS (cardiogenic shock, pulmonary edema, ventricular arrhythmias) is recommended in life expectancy ≥ 6 months (Class IB), third-generation drug-eluting stents should be preferred due to a lower risk of intrastent thrombosis. The preferred antiplatelet strategy after stenting is dual antiplatelet therapy (DAPT) for 1–3 months. At the same time, aspirin is not recommended only when platelet levels drop <10,000, clopidogrel in <30,000, and prasugrel and ticagrelor in < 50,000. Conservative management is preferred for cancer patients with low life expectancy (<6 months) and/or very high risk of bleeding (Class IIaC).

It is recommended after ACS to reconsider the anticancer regimens, cancel any drugs associated with the development of thrombosis and acute myocardial infarction (MI). Cancer therapy not associated with acute MI can be resumed after stabilization of the patient's condition and completion of revascularization, but not earlier than 1 month after the event [10].

5.2.2. Chronic coronary syndromes

Certain groups of anticancer drugs contribute to the accelerated development of atherosclerosis, chronic forms of CAD (for example, stable angina pectoris). They include 5 fluorouracil, capecitabine, platinum-based drugs, VEGF inhibitor monoclonal antibodies and tyrosine kinase inhibitors, nilotinib, ponatinib, immunotherapy. Careful cardiac monitoring, strict modification of cardiovascular risk factors, management following the current clinical guidelines for the diagnosis and treatment of chronic coronary syndromes are recommended for patients with angina pectoris without signs of myocardial damage shown by laboratory tests and clinical investigations [20, 21].

5.3. Cardiac arrhythmias

5.3.1. Atrial fibrillation

Malignancy is significantly associated with the risk of AF, the degree of which varies depending on the type, location, and spread of the tumor. On the other hand, most groups of chemotherapy drugs (AAs, antimetabolites, ICIs, tyrosine kinase inhibitors, proteasome inhibitors, etc.) increase the likelihood of AF. Cancer patients are two times more likely to develop AF compared to the general population. Cardiac arrhythmia occurs in 2% to 16% of cases during CT depending on the combination of risk factors [3]. Elevated levels of pro-inflammatory cytokines (interleukins 1, 6, C-reactive protein, tumor necrosis factor α, etc.), vasoactive peptides, and the activation of RAAS and the sympathetic nervous system are considered as the key triggering mechanisms of arrhythmia in cancer patients [22], which may contribute to the development/aggravation of left atrial (LA) myopathy.

De novo AF or higher frequency of paroxysms in cancer patients, including during specific therapy, is associated with the increased risk of VTE, stroke, HF,

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and the increased risk of all-cause death, to a greater extent compared to the general population due to the active prothrombogenic status of cancer. Such patients should be managed under the strict control of MDT following the current clinical guidelines for the diagnosis and treatment of AF [23, 24]. The strategy of rate control with BBs is more preferable in cancer patients than rhythm control (Class IIaC). The decision on prescribing anticoagulants to patients with active cancer should be based on the increased risk of thrombosis and/or bleeding, and other indicators of risk prediction used for the general population of non-cancer patients with AF. The HAS-BLED and CHA2DS2 VASc scales can be used to assess the risk of bleeding and thromboembolism, respectively (Class IIaC). Noteworthy, both scales are not validated for patients with cancer. Long-term anticoagulant therapy is recommended for cancer patients with AF and the CHA2DS2 VASc scores ≥2 (male) and ≥3 (female). Direct oral anticoagulants (DOACs), rather than low molecular weight heparins (LMWH) and vitamin K antagonists, should be used for the prevention of thromboembolism in patients without a high risk of bleeding and severe renal dysfunction (except in patients with mechanical heart valves or moderate-to-severe mitral stenosis) (Class IIaB). Left atria appendage occlusion is indicated if anticoagulants cannot be prescribed and the patient's life expectancy is >12 months (Class IIbC).

It should be taken into account that neither AF nor its risk is a contraindication to the initiation/continuation of cancer therapy.

5.3.2. QTc prolongation and ventricular arrhythmia

QTc prolongation of ≥ 500 ms is associated with a 3 fold risk of torsade de pointes. Such patients should be managed under the strict control of MDT, following the current clinical guidelines for the diagnosis and treatment of ventricular arrhythmias [25, 26]. QTc prolongation to the specified level during cancer therapy is rare, intervals of ≥ 480 ms are more common, which requires closer monitoring of the patient's condition.

Discontinuation of CT is recommended if torsade de pointes, persistent ventricular tachyarrhythmia develops in patients with asymptomatic QTc prolongation ≥500 msec. In QTc of 480–500 ms, it is possible in some cases to continue the previous treatment regimens, but only subject to weekly monitoring of ECG and blood electrolytes. The target values of electrolytes in such patients are the following: potassium >4 mmol/L, magnesium >1.1 mmol/L, normal levels of albumin-corrected calcium. The final decision on the discontinuation/continuation/resumption of cancer therapy associated with QTc prolongation and the choice of an alternative treatment regimen is made by the expert team (Class IC).

5.4. Arterial Hypertension

De novo arterial hypertension (AH) or severe destabilization of existing AH can be caused by several of anticancer drugs, such as VEGF inhibitors, second and third generations BCR-ABL TKIs, brigatinib, ibrutinib, fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide, etc., as well as glucocorticosteroids, nonsteroidal analgesics. The risk of developing AH also increases if the patient has other risk factors, including stress, pain syndrome, excessive alcohol consumption, impaired renal function, sleep apnea, obesity, and reduced physical activity.

Severe hypertension (SBP ≥ 180 mm Hg or DBP ≥110 mm Hg) is the indication for temporary discontinuation of specific cancer therapy. The MDT should then consider and assess the risk-benefit ratio between cancer and cardiovascular pathology, decide whether treatment can be continued, or doses of anticancer drugs should be reduced. Resumption of therapy is possible when controlled AH is achieved (SBP < 160 mm Hg and DBP < 100 mm Hg). Initial combination therapy (ACE inhibitors/ARBs and dihydropyridine calcium channel blockers) is recommended to correct AH (IC class). If the target BP values are not achieved, BBs, spironolactone, nitrates, hydralazine are added. SBP and DBP targets during CT are < 140 mm Hg and <90 mm Hg, respectively, for most individuals (Class IC), 140–160 mm Hg and 90–100 mm Hg, respectively, for some asymptomatic patients with metastatic cancer (Class IIbC). Diltiazem and verapamil are not recommended for in cancer patients due to many adverse drug interactions (Class IIIC) [10].

5.5. Thrombosis and Thromboembolic events

Cancer-associated (associated with malignancy and its treatment) thrombosis include venous and arterial thromboembolism. Cancer patients face a 5 fold risk of developing venous thromboembolism, and cancer-associated thrombosis account for up to 30% of all VTE [27]. They develop mainly due to the prothrombotic status of the cancer, the pronounced prothrombotic effects of some cancer treatments, and known patient-associated risk factors (age, female sex, genetic predisposition, hormone replacement therapy, concomitant diseases). Patients with symptoms or signs

of VTE should be examined urgently using the standard protocol for verification of deep vein thrombosis (DVT) and pulmonary embolism (PE) [28–30].

The Khorana scale can be used to predict the risk of VTE in cancer patients. It is reasonable to use this scale in patients with solid tumors and lymphomas before the start of a CT regimen in order to determine the indications for preventive anticoagulant therapy [31]. The TBIP (thromboembolic risk, bleeding risk, drug-drug interactions, patient preferences) scale is a more generalized/expanded score for the assessment of the risks of VTE and bleeding presented in the current guidelines [32].

According to large randomized clinical trials (RCTs) and meta-analyses, LMWH reduces the risk of recurrent cancer-associated VTE by 40% compared to vitamin K antagonists [33, 34]. Other studies showed that DOACs are not inferior to LMWH (dalteparin) in reducing the risk of recurrent VTE in cancer patients [35–37]. Based on their findings, apixaban, edoxaban, and rivaroxaban are recommended for venous thromboembolism (DVT, PE) in cancer patients if there are no contraindications (inoperable gastrointestinal or genitourinary cancers, recent history of bleeding or less than 7 days after major surgery, thrombocytopenia <50,000/μL, CKD grade 5 (creatinine clearance <15 mL/min/1.73 m^2) (Class IA). LMWH is recommended with the same level of evidence for VTE in cancer patients, only if the platelet count is >50,000/μL. Half doses of LMWH may be used in thrombocytopenia 25,000–50,000/μL. The optimal duration of anticoagulant therapy is 6 months, but some patient groups may need longer [10].

In other subsections of the current guidelines, the authors also present a management strategy for patients with other CTR-CVT as severe VHD, bleeding, peripheral arterial diseases/pathological hyperreactivity of blood vessels, pulmonary hypertension, pericardial diseases (pericarditis, pericardial effusion [10].

6. End-of-cancer therapy cardiovascular risk monitoring

Cardiovascular monitoring after the end of CT with potential cardiovascular toxicity and no complications during treatment includes the 12-month follow-up after the last administration of the drug and mandatory patient training [10]. Echocardiographic parameters and biomarkers should be evaluated in 3 and 12 months after the end of treatment in asymptomatic patients at high/very high cardiovascular risk (Class IB) and 12 months in patients at moderate/low risk (Class IIaB, Class IIbC, respectively). Cardiac imaging is recommended to be carried out in 3 years and then every 5 years. Thus, the follow-up should be lifelong in this cohort of patients. Stress echocardiography or ergospirometry is indicated to some patients with low exercise tolerance within 12 months after the end of cancer therapy if there are no abnormalities in ECG and biomarker levels are normal (Class IIbC).

A separate section of the new guidelines is devoted to the aspects of long-term follow-up of adult patients with the history of cancer in childhood and adolescence, and correction of chronic cardiovascular pathology in these individuals. These patients were treated mainly with AAs, mitoxantrone, RT (if the heart was exposed to radiation) and, as a result, face an increased risk of HF, VHD, pericardial complications, CAD, arrhythmias [38, 39].

Annual clinical assessment of cardiovascular status, including ECG, natriuretic peptide levels, cardiovascular risk (SCORE2, SCORE2 OP calculators), modification of risk factors, and correction of CVDs are recommended for all adult patients. Additional methods of examination are indicated to patients with the history of RT. Non-invasive screening for coronary artery pathology (stress echocardiography, CT angiography, cardiac MRI, etc.) should be considered every 5–10 years in asymptomatic patients who were exposed to > 15 Gy starting from the 5th year after the end of treatment. If the head/neck areas were exposed to radiation, ultrasonography of the brachiocephalic arteries should be carried out every 5–10 years starting from the 5th year. A similar approach should be considered for renal arteries involved if RT was performed on the abdomen and pelvis [10].

The guidelines also include the first approved protocols for monitoring the cardiovascular system in pregnant women with the history of cancer, active cancer, and those who undergo treatment during pregnancy.

Conclusion

Cardio-oncology is an actively developing subspecialty of cardiology and clinical medicine in general that attracts the attention of the international scientific community, which is evident in the formation of national and international working groups, communities, associations. Previous years saw a breakthrough in this area. Numerous randomized clinical studies involving large patient samples are carried out, and several framing regulatory documents have been published. All this became an important prerequisite for the world's first official clinical guidelines for cardio-oncology presented by the ESC in the fall of 2022. In 2023, it is planned to publish the adaptation of these

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recommendations for the Russian experts with the support of the Council on Cardio-oncology of the Russian Society of Cardiology. It is obvious today that there is a high need in the Russian Federation not only for clinical guidelines, but also for regulatory documents that would allow:

- Defining cardio-oncology as an independent specialty with appropriate advanced training and accreditation programs;
- Increasing the awareness of oncologists about the possibilities of cardio-oncology through the organization of narrow-focus educational trainings;
- Regulating the work of cardio-oncology services in hospitals based on the interaction of a MDT to improve the provision of medical care to these patients at all stages of cancer therapy;
- Arranging cardio-oncology rooms in outpatient facilities;
- Determining the fundings channels cardio-oncology patients, their routing, and continuity between different medical facilities;
- Increasing public awareness through the creation of patient schools, preventive and monitoring programs;
- Conducting clinical trials, creating epidemiological registers, unified digital databases with access throughout the Russian Federation.

To implement the above tasks and develop cardio-oncology in Russia as an independent clinical specialty, a well-coordinated and long-term interaction of specialized medical communities, state agencies, and governing bodies is required in order to improve quality of life and survival of this polymorbid cohort of patients who often have unfavorable prognosis.

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