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MODERN APPROACHES TO DETECTING EARLY SUBCLINICAL CARDIOTOXICITY INDUCED BY CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER

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SUMMERY

In recent decades, developed countries of the world have made progress in the treatment of breast cancer, both because of the early detection of cancer and the use of modern methods of treatment (target therapy and chemotherapy, radiation therapy and surgical treatment). Due to this, the time of disease-free course of cancer and the duration of life of patients have increased. However, a number of antitumor drugs have cardiotoxicity [1]. It is shown that cardiovascular diseases are the second leading cause of death among women who have undergone breast cancer [27]. Reduction of systolic function of the heart is the most common manifestation of cardiotoxicity of antitumor therapy [7]. Other manifestations of cardiotoxicity include arterial hypertension (AH), acute coronary syndrome, arrhythmias and thromboses. In recent years, methods such as electrocardiography (ECG); echocardiography (EchoCG) with the classical definition of the left ventricular ejection fraction (LVEF) by the method of Simpson's biplane and the global longitudinal strain of the left ventricular (GLS) using data from the 2D Speckle Tracking Imaging; determination of the level of biomarkers of myocardial damage and magnetic resonance imaging (MRI) of the heart have been used to detect the cardiotoxicity of antitumor therapy.

Thus, the early diagnosis and timely detection of cardiotoxic effects of antitumor drugs are among the tasks of cardiooncology – an area in medicine formed in recent years [1].

Key words: *cardiooncology, arterial hypertension, cardiotoxicity, technology speckle tracking, chemotherapy, breast cancer.*

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RELEVANCE

In the structure of malignant tumors, breast cancer is the most common cancer in women all over the world [22]. Early diagnosis of cancer and the progress of modern therapy led to a longer remission of the disease and prolongation of life of breast cancer patients. However, some antitumor drugs have cardiotoxicity. Risk factors for cardiotoxicity include [5,7]:

- cumulative dose of chemotherapy;
- the age of the patient (> 65 years and <18 years);
- female;
- cardiovascular diseases;
- type of chemotherapy;
- total dose, regimen and route of chemotherapy administration;
- simultaneous introduction of other cardiotoxic drugs;
- combination of chemotherapy with radiotherapy;
- exposure of the mediastinum in the anamnesis.

Arterial hypertension (AH) being one of the most common cardiovascular disease often accompanies the oncological disease. In the Russian Federation, according to the epidemiological study of ECDR (Epidemiology of Cardiovascular Disease in Regions), AH was detected in 45.4% of men and 41.6% of women [21]. According to the hospital register of malignant oncological diseases, in which 17712 patients were included, AH was the most frequent concomitant disease (38%) in cancer patients [20]. Common risk factors for AH and malignant neoplasms are defined, among them are a sedentary lifestyle, obesity, smoking, alcohol abuse, etc. [20]. The increase in the life duration of people reaching the senile age promotes the growth of cardiovascular and oncological diseases.

In addition to toxic effects on the myocardium, chemotherapy can affect the vascular wall of the arteries. According to Paaladinesh Thavendiranathan, increasing arterial stiffness is one of the earliest manifestations of the vasotoxic effect of chemotherapy, which is the cause of the progression of AH or its development against the background of treatment [19].

In a meta-analysis conducted by Ranpura et al., involving 12656 patients with oncological diseases of various locations treated with bevacizumab, the incidence of induced AH was 23.6%, of which 7.9% corresponded to grade 2 or 3 hypertension [23]. Thus, AH is one of the complications of chemotherapy. At the same time, the presence of initial AH or its development during chemotherapy is one of the risk factors for the development of cardiotoxicity.

The mechanisms of cardiotoxicity, induced by chemotherapy:

- direct toxic effect on cardiomyocytes;
- impact on the coagulation system;
- Arrhythmogenic effect (more often by prolonging the QT interval);
- hypertensive action;
- nonspecific inflammation of the myocardium and / or pericardium [6].

On the damaging effect on the myocardium chemotherapy drugs are divided into two types [4]:

Type I includes drugs with direct toxic effects on the heart, which leads to apoptosis of cardiomyocytes and, as a consequence, to irreversible left ventricular (LV) myocardial dysfunction. This type is characteristic for anthracyclines, in the treatment of which the risk of developing cardiotoxicity depends on the cumulative dose.

Type II include drugs that, when treated, develop cardiotoxicity, which is reversible. For drugs of the type II, unlike the type I, the dependence on the cumulative dose is not characteristic, trastuzumab is one of such chemotherapeutic drugs.

The most cytotoxic effect is possessed by anthracyclines, monoclonal antibodies, tyrosine kinase inhibitors, alkylating drugs and interferon alpha [2-4].

Due to the high effectiveness in the treatment of malignant tumors of different locations, anthracyclines are included in many cancer treatment regimens. With an increase in the dose of anthracyclines, the risk of developing LV dysfunction increases, which determines an unfavorable prognosis for the patient who has had cancer, in terms of the development of symptoms of heart failure (CH). In a number of studies, it was demonstrated that a 5% incidence of HF was associated with a cumulative dose of doxorubicin of 400 mg/m^2, a CH risk increased to 48% with a cumulative doxorubicin dose of 700 mg/m^2. There was significant variability in response to treatment with anthracyclines in cancer patients [7].

Timing-wise LV myocardial dysfunction in the treatment of anthracycline-containing antitumor drugs in patients with breast cancer is distinguished between acute and chronic myocardial damage [6,11]. Acute cardiotoxicity usually manifests itself in the form of various supraventricular cardiac arrhythmias, nonspecific changes in the ECG (prolongation of the QT interval and QT corrected) and transient asymptomatic LV dysfunction (reduction of the LV ejection fraction (LVEF)) [6]. It is shown that acute cardiotoxicity develops in less than 1% of cases after the infusion of chemotherapy and is usually reversible. Chronic cardiotoxicity may occur within the first year after the end of antitumor treatment (early cardiotoxicity) or later (late cardiotoxicity) [7].

Period before the development of chronic heart failure during chemotherapy with cardiotoxic drugs may be the one of subclinical lesion of the myocardium of the LV that does not show symptoms of heart failure and is not detected by traditional definition of the LVEF fraction by the method of Simpson's biplane.

Thus, cardiotoxicity in breast cancer patients can vary from subclinical LV myocardial dysfunction to irreversible heart failure with fatal outcome [6]. In connection with this, during chemotherapy, the monitoring of the LV structural and functional status and the level of blood pressure in cancer patients for the detection of subclinical LV myocardium dysfunction and the development of cardioprotection measures is topical.

METHODS FOR DETECTING CARDIOTOXICITY

According to European and Russian recommendations [7,25] (here and after referred to as recommendations), the main methods for diagnosing cardiotoxicity are: electrocardiography (ECG), echocardiography (EchoCG), detection of biomarkers of myocardium damage and magnetic resonance imaging (MRI) of the heart.

Electrocardiography. All patients with oncological diseases are recommended to carry out the ECG before and after treatment with antitumor drugs. Cardiotoxicity of chemotherapy can manifest itself in the form of tachycardia, changes in the ST-T segment, rhythm and conduction disorders, and prolongation of the QT interval [7]. It was shown that of all chemopreparations, prolongation of the QT interval is often observed in the treatment with arsenic trioxide, which is used to treat certain leukemias and myelomas [8]. The prolongation of the QT interval may be caused not only by antitumor drugs, but also by electrolyte disorders, the intake of anti-emetic drugs, antibiotics, etc. [9]

Echocardiography. In the detection of subclinical cardiotoxicity, echocardiography (EchoCG) is the most important. In cancer patients during preparation for chemotherapy, during and after cancer therapy, EchoCG is recommended as one of the most informative methods for diagnosing the structural and functional

state of the heart [9, 10]. In clinical practice for the detection of cardiotoxicity are used, first of all, generally accepted indicators, in particular, LVEF by the method of Simpson's biplane. Various studies have used different threshold values to determine clinically significant reductions in LVEF. Thus, according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the reduction of LVEF more than 10% of baseline and below 53% is a sign of the development of cardiotoxicity with chemotherapy [11]. According to the guidelines adopted by the European Society of Cardiology [7], a decrease in the LVEF of more than 10% of the baseline and below 50% is a criterion for cardiotoxicity. Some authors defined the cardiotoxicity of antitumor therapy as a reduction of LVEF of >5% of the baseline in patients with symptoms of heart failure and LVEF ≥10% in patients with no symptoms of heart failure and LVEF <55% [26]. Minimization of errors in the definition of LVEF, which can take place in the practice of a doctor, is leveled by the expert class of the ultrasound apparatus, the qualification of a specialist, the conduct of research by the same doctor [7].

It is shown that LVEF is not sensitive enough to detect early subclinical changes in the contractile function of the myocardium [13]. In connection with this, a lot of attention has recently been paid to new echocardiographic technologies – 2D and 3D SpeckleTracking Imaging [7, 18, 25]. Preliminary data have shown that these methods will allow to identify early changes preceding the reduction of LVEF and the development of symptoms of heart failure [18].

2D SpeckleTracking Imaging is used to evaluate LV deformation parameters. The method is based on the analysis of the movement of black or white speckle on a standard echocardiographic image in a two-dimensional mode (B-mode) during the cardiac cycle with the help of special software. The position of each speckle is determined and traced on consecutive frames. The quality of visualization is provided by a high frame rate (50-100 fps). By frame tracking, the distance to which the speckle moves from frame to frame is determined and, the speed of the speckle movement is determined by the given frame rate. Segments with poor image quality are excluded from analysis by the software. The software provides the construction of strain curves for each segment of the myocardium. Thus, according to the movement of spotted structures, data on the deformation of all parts of the myocardium are obtained, longitudinal, radial and circular deformations of the myocardium are evaluated [12].

The limitation of the method is the impossibility of carrying it out in patients with arrhythmias [12]. It is important to note that for a correct and optimal definition of the borders of the endocardium, good visualization and high quality of two-dimensional images are necessary.

To date, of all LV deformities, the most studied one is the longitudinal global strain (GLS), which is estimated from the three top positions and represents the topography of the 17 segments of the left ventricle as the so-called "bull's eye." Until now, there are no generally accepted standards for this indicator, which depends on the age, sex of patients, the echocardiographic device used [11]. At the same time, a number of researchers in the course of the work performed in healthy individuals defined the average values for the GLS , which are >-20.0% [11]. According to the guidelines, a diagnostic criterion for the development of subclinical cardiotoxicity is the decrease in GLS from the baseline level of more than 15% [7]. A number of authors believe that the GLS score before chemotherapy and after treatment with antitumor drugs will allow to identify early cardiotoxicity to a marked decrease in LVEF and the development of symptoms of heart failure [7,10]. In a study by Stoodley et al. a comparative evaluation of LVEF and a parameter of global longitudinal deformation of LV in women with breast cancer before chemotherapy and a week after its completion was made. Statically significant reduction in GLS was shown, while LVEF did not change significantly [14]. Similar results were obtained in a study by A. Boyd et al., which also showed a statistically significant decrease in GLS in chemotherapy, while LVEF decreased, but remained within the normal range [15].

However, a limited number of studies and the lack of convincing evidence of the significance of a decrease in GLS in chemotherapy in cancer patients do not yet provide a basis for interrupting treatment or reducing the dose of a chemotherapy, based only on a decrease in GLS [7].

3D SpeckleTracking Imaging allows simultaneous evaluation of all LV deformation parameters (global longitudinal, circular and radial), which greatly simplifies the procedure for detecting deformation. This technology also defines a new parameter of deformation – Global Area Strain (GAS). It is assumed that the 3D SpeckleTracking Imaging will allow a more complete analysis of the LV function in patients with breast cancer during chemotherapy [18]. In the literature, there are single data on the use of the technology of 3D SpeckleTracking Imaging in patients with breast cancer. In a study by Ciro Santoro et al. the deformation properties of LV myocardium were studied according to the data of 2 D and 3D SpeckleTracking Imaging in 100 women with breast cancer receiving anthracycline containing chemotherapy. The authors noted a reduction in all strain parameters from 2D and 3D SpeckleTracking Imaging, but the most significant decrease was in the GLS and GAS values from the 3D SpeckleTracking Imaging. Thus, the advantage of the technology of the SpeckleTracking Imaging in revealing subclinical cardiotoxicity in comparison with the 2D SpeckleTracking Imaging was shown [18].

The National medical research center of cardiology of the Ministry of healthcare of the Russian Federation is conducting a study whose objective is to identify early subclinical cardiotoxicity in breast cancer patients with anthracycline-containing chemotherapy. The deformation properties of the myocardium of the LV are studied by the EchoCG method using the technology 2D and 3D SpeckleTracking Imaging in comparison with the traditional definition of EF LV. Preliminary results in individual breast cancer patients before and after treatment with anthracycline-containing chemotherapy show the advantage of the 3D SpeckleTracking Imaging technique in assessing the deterioration of the deformation of the LV.

Figure 1 shows the clinical case of a patient A., 40 years old, with an established diagnosis of malignant neoplasm of breast tissue, cancer of the right breast. At the initial examination by a cardiologist (before chemotherapy), blood pressure, heart rate, ECG, echocardiogram – within the limits of the normal values.

Treatment of breast cancer was carried out for 2 months by anthracycline-containing chemotherapy drugs, including doxorubicin, as well as cisplatin and paclitaxel. LVEF by the method of Simpson's biplane was initially 68%, after chemotherapy – 62%. In the 2D SpeckleTracking Imaging, GLS was initially within the normal range (-21.5%), after chemotherapy it was -18.8%, thus, its decrease was noted, which did not reach the diagnostic criterion of subclinical cardiotoxicity. The study in the 3D SpeckleTracking Imaging showed a more pronounced decrease in all parameters of deformation on the background of chemotherapy: the GLS index decreased by 60.0%, the GCS index by 41.0%, the GRS index by 50.0% and the GAS by 48.0% . Thus, in this patient,

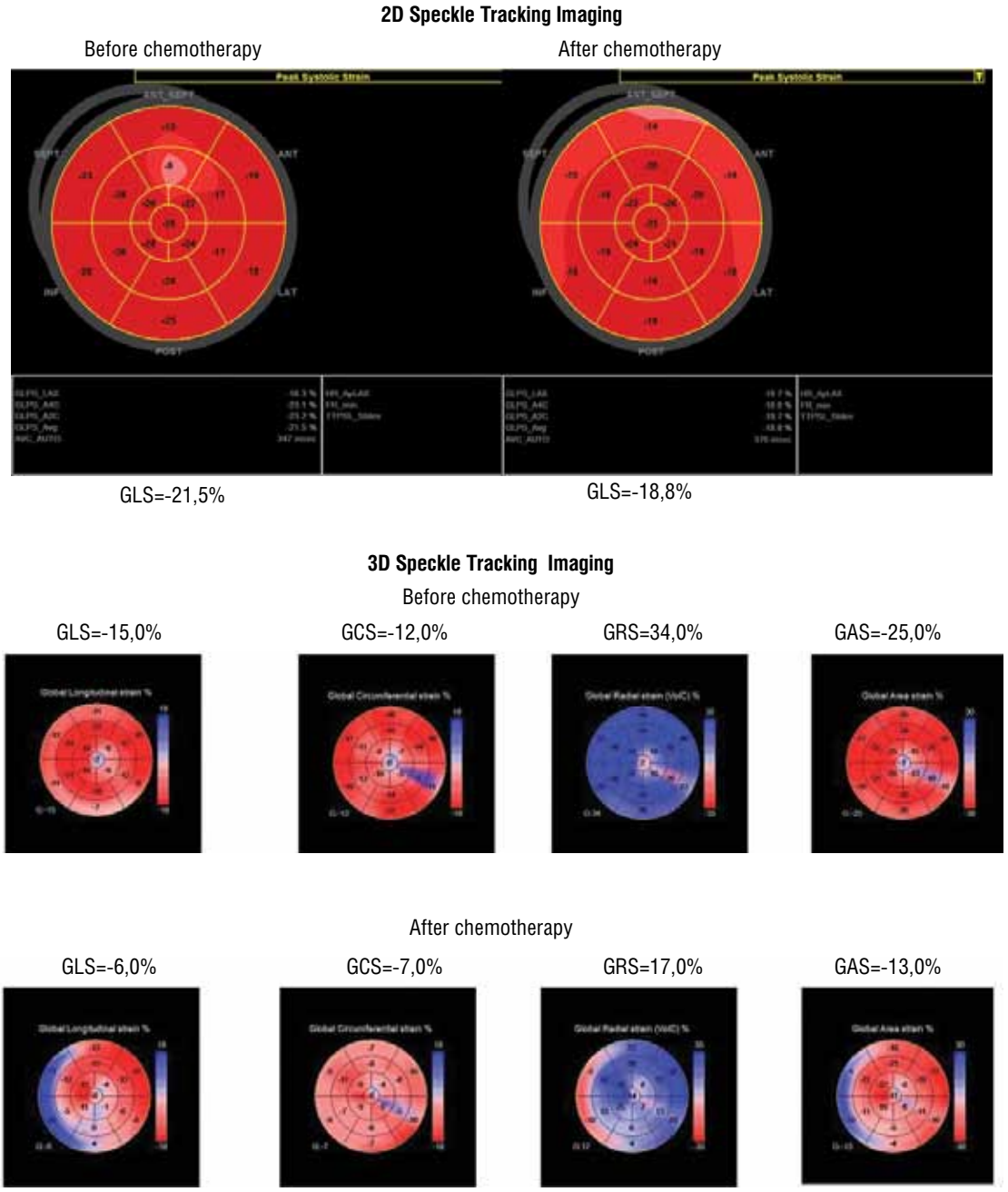

Figure 1. 2D and 3D Speckle Tracking Imaging initially and after 8 courses of chemotherapy

the 3D SpeckleTracking Imaging was more effective in detecting subclinical cardiotoxicity during chemotherapy.

Biomarkers of myocardial damage. In recent years in cardiooncology, cardiac biomarkers (high-sensitivity troponins and natriuretic peptides) have been used to assess the risk of developing cardiotoxicity against the backdrop of antitumor therapy.

In the diagnosis of myocardial infarction, cardiac troponins such as troponin T (TnT) and troponin I (TnI) are widely used as sensitive and specific diagnostic markers. These biomarkers have also been used to detect cardiotoxicity induced by chemotherapy. In the literature, there are data on the sensitivity of troponins depending on the applied dose of the chemotherapeutic agent. It is shown that the increase of troponins in the treatment of malignant neoplasms is associated with the treatment with high doses of anthracyclines [16].

However, in a study by Sawaya and Ky et al. it has been shown that cardiac troponins have predictive value in terms of the risk of developing cardiotoxicity in breast cancer patients receiving moderate doses of anthracyclines in combination with trastuzumab. Elevation of troponins was associated with a delayed development of symptoms of heart failure [17]. To date, the level of diagnostically significant increase in highly sensitive troponins as markers of the risk of cardiotoxicity during and after chemotherapy has not been determined.

In chemotherapy, natriuretic peptides (atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and peptide-prodrug (pro-BNP)) are also used as a marker of cardiotoxicity. Natriuretic peptides are peptide hormones that stimulate natriuresis in response to excessive mechanical stress or overload with a volume of heart cavities [16]. In the study, Feola et al. found an increase in the level of NT-pro BNP for two years after treatment with anthracycline-containing chemotherapy drugs. The increase in natriuretic peptides is attributed to a decrease in LVEF of ≥10% [24].

At the same time, an increase in the concentration of biomarkers indicates an increased risk of cardiotoxicity. At present, there is

no evidence for the interruption or cancellation of chemotherapy, based solely on an increase in the level of cardiac biomarkers during treatment [7].

Patients with asymptomatic reduction of LVEF, corresponding to the definition of cardiotoxicity, especially with the concomitant increase in natriuretic peptides, according to the guidelines (2016), can be considered as patients with structural heart disease with preserved LVEF, that require monitoring of LV structural myocardial function [7].

MRI is one of the modern, informative methods for assessing the structural and functional state of the heart. The method allows to estimate the volume of the heart cavities, myocardial contractile function, wall thickness, etc. In connection with this, this method is promising in the evaluation of subclinical cardiotoxicity. There are single studies in the literature showing that chemotherapy in cardiomyocytes develops signs of inflammation, which, as the authors suggest, are subclinical signs of cardiotoxicity [19]. According to the recommendations, the sites of scarring and fibrosis of the myocardium, obtained with the accumulation of gadolinium in the late phase, may also have prognostic value in the development of cardiotoxicity [7].

To date, the role of MRI in the diagnosis of cardiotoxicity of antitumor treatment is poorly understood and requires further research.

CONCLUSION

In the detection of subclinical cardiotoxicity, classical methods for determining the systolic function of the heart are not sensitive enough. To date, new echocardiograms of the technology of the the 2D and 3D Speckle Tracking Imaging with the determination of deformation of the LV; MRI, as well as determining the level of biomarkers of myocardial damage (high-sensitivity troponins and natriuretic peptides) are the promising methods.

Preliminary data have shown that these methods are more sensitive in detecting early subclinical cardiotoxicity, and, consequently, in carrying out measures for timely cardioprotection in order to improve the prognosis and quality of life of breast cancer patients.

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REFERENCES

1. *Yuand Jones. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. Cardio-Oncology. 2016;2:1 DOI 10.1186/s40959-016-0011-5*
2. *Чазова И.Е., Ощепкова Е.В., Канторова А.Ю. – Коморбидность сердечно-сосудистых и онкологических заболеваний: проблемы диагностики кардиотоксических эффектов химио- и лучевой терапии. Терапевтический архив. 2015;87(9): 4-10. doi: 10.17116/terarkh20158794-10 / Chazova I.E., Oshchepkova E.V., Kantorova A.Yu. Comorbidity of cardiovascular diseases and cancers: Problems in the diagnosis of cardiotoxic effects of chemo- and radiation therapy. Terarkh. 2015;87(9): 4-10. doi: 10.17116/terarkh20158794-10 [in Russian]*
3. *А.А. Авалян, М.Ю. Кириллова, В.Н. Шитов, Е.В. Ощепкова, М.А. Саидова, М.Б. Стенина, И.Е. Чазова. Поиск ранних маркеров кардиотоксичности противоопухолевого лечения у больных раком молочной железы в зависимости от уровня артериального давления. Системные гипертензии 2017; 14 (3): 21–27. DOI: 10.26442/2075-082X_14.3.21-27 / Avalyan A.A., Kirillova M.Yu., Shitov V.N., Oshchepkova Ye.V., Saidova M.A., Stenina M.B., Chazova I.Ye. Markers of early cardiotoxicity in patients with breast cancer undergoing chemotherapy depending on blood pressure level. Systemic hypertension 2017; 14 (3): 21–27. DOI: 10.26442/2075-082X_14.3.21-27 [in Russian]*
4. *Fausto Pizzino, Giampiero Vizzari, Charles A. Bomzeretall. Diagnosis of Chemotherapy-Induced Cardiotoxicity. Journal of Patient-Centered Research and Reviews 8-13-2014: 121-127*
5. *D. Bovelli, G. Plataniotis, F. Roila. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. Annals of Oncology. 21 (Supplement 5): 277–282, 2010*
6. *Maria Florescu et all. Chemotherapy-inducedCardiotoxicity. A Journal of Clinical Medicine 2013; 8(1): 59-67*
7. *Jose Luis Zamorano, Patrizio Lancellotti, Daniel Rodriguez Mun˜oz, Victor Aboyans, Riccardo Asteggiano et al. 2016 ESC Position Paper on cancer treatment and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. European Heart Journal. 2016,August 26.*
8. *Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associatedwith tyrosine kinase inhibitors. Oncologist 2013;18:900–908*
9. *Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am CollCardiol. 2009;53:2231–2247*
10. *Daher IN, Kim C, Saleh RR, Plana JC, Yusuf SW, Banchs J. Prevalence of abnormal echocardiographic findings in cancer patients: a retrospectiveevaluation of echocardiography for identifying cardiac abnormalities in cancer patients. Echocardiography. 2011;28:1061-7.*
11. *Juan Carlos Plana 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 SocEchocardiogr. 2014;27:911-39*
12. *Sergio Mondillo, Maurizio Galderisi, Donato Mele, Matteo Cameli, MD et al. Speckle-Tracking Echocardiography: A New Technique for Assessing Myocardial Function. J Ultrasound Med. 2011; 30:71–8*
13. *Cardinale D, Colombo A,Lamantia G. et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am CollCardiol. 2010;55:213–20*
14. *Stoodley PW, Richards DA, Boyd A, et al. Altered left ventricular longitudinal diastolic function correlates with reduced systolic function immediately after anthracycline chemotherapy. Eur Heart J Cardiovasc Imaging. 2013 Mar;14(3): 228-34*
15. *Anita Boyd, Paul Stoodley, David Richards, et al. Anthracyclines induce early changes in left ventricular systolic and diastolic function: A single centre study- PLoS One. 2017 Apr 13;12(4):e0175544; 15.*
16. *Moazeni et al Anthracycline induced cardiotoxicity: biomarkers and "Omics" technology in the era of patient speci c care. Clin Trans Med (2017) 6:17 DOI 10.1186/s40169-017-0148-3*
17. *Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr, Sebag IA et al (2014) Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am CollCardiol 63(8):809–816*
18. *Ciro Santoro1 et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancerpatients: a balance*

with feasibility. European Heart Journal – Cardiovascular Imaging, Volume 18, Issue 8, 2017, Pages 930–936, doi.org/10.1093/ehjci/jex033

19. *Paaladinesh Thavendiranathan et al. Cardiac MRI in the Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy. A Systematic Review. CircCircCardiovasc Imaging. 2013;6:1080-1091, DOI:10.1161/CIRCIMAGING.113.000899*
20. *Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291(20):2441-7.*
21. *Чазова И.Е., Жернакова Ю.В., Ощепкова Е.В. и др. Распространенность факторов риска сердечно-сосудистых заболеваний в российской популяции больных артериальной гипертонией. Кардиология. 2014; 10: 4–12. / Chazova I.Ye., Zhernakova Yu.V., Oshchepkova E.V. The prevalence of risk factors for cardiovascular diseases in the Russian population of patients with arterial hypertension. Cardiology. 2014; 10: 4-12 [in Russian]*
22. *Pedro Veronese, Denise Tessariol Hachul, Mauricio Ibrahim Scanavacca et al. Effects of anthracycline, cyclophosphamide and taxane chemotherapy on QTc measurements in patients with breast cancer. PLOS ONE. 2018; 2-10. doi.org/10.1371/journal.pone.0196763*
23. *Ranpura V, Pulipati B, Chu D, Zhu X, Whu S. Increase risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. Am J Hypertens. 2010;23(5):460-8.*
24. *Feola M, Garrone O, Occelli M et al. Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol. 2011;148(2):194–198. doi: 10.1016/j.ijcard.2009.09.564*
25. *Чазова И.Е., Тюляндин С.А., Виценя М.В. и др. Руководство по диагностике, профилактике и лечению сердечно-сосудистых осложнений противоопухолевой терапии. Часть I. Системные гипертензии. 2017;14(3); 6-20 / Chazova I.Ye. Tyulyandin S.A., Vitsenya M.V. et al. A guide to the diagnosis, prevention and treatment of cardiovascular complications of antitumor therapy. Part I. Systemic hypertension. 2017; 14 (3); 6-20 [in Russian]*
26. *Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby Metal. Cardiac dysfunction in the trastuzumab clinical trials experience. J ClinOncol. 2002 Mar 1;20 (5):1215–21*
27. *M.A. Nicolazzi, A. Carnicelli, M. Fuorlo et al. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. European Review for Medical and Pharmacological Sciences 2018; 22: 2175-2185*

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