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Cardiovascular toxicity associated with radiotherapy in breast cancer patients

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ABSTRACT

The progress in breast cancer treatment strategies contributes to the extension of life expectancy and an increase in the number of patients after cancer therapy. Risk factors for cardiac diseases largely influence the risk of left ventricular systolic dysfunction, the most common form of manifestation of toxicity in the cardiovascular system associated with oncological treatment. Diagnosis of cancer does not facilitate the modification of factors that the patient can potentially influence. Virtually all structures of the heart may get damaged during radiotherapy.

The diagnostic methods used to assess cardiovascular toxicity include transthoracic echocardiography, magnetic resonance imaging, computed tomography, single-photon emission tomography, and positron emission tomography.

Detection of early changes, often without symptoms, is crucial as it allows the selection of patients with an increased risk of cardiac events in the future.

Cardiac complications related to radiotherapy may be underestimated due to the delay in symptom manifestation and their overlap with cardiac events caused by the "standard" risk factors.

Keywords: breast cancer, radiotherapy, cardiotoxicity

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INTRODUCTION

Radiotherapy as a well-established role in the treatment of breast cancer of all stages [1]. At the same time, advances in treatment strategies in radiotherapy, surgery, and systemic treatment contribute to the extension of life expectancy and an increase in the number of patients after cancer therapy [2, 3].

LITERATURE REVIEW

The problem of cardiotoxicity

For many years, the problem of cardiotoxicity has been largely overlooked. The heart was considered a radioresistant organ, unaffected by doses below 30 Gy (Gray). It was only in the 1990s that randomized trials of breast cancer patients were published, which showed that a significant part of the gain in overall survival obtained after combined treatment for breast cancer may be offset by heart damage associated with oncological treatment [4-6].

The concept of cardiotoxicity has been defined as the appearance of new changes in the cardiovascular system resulting from oncological treatment during or after its completion [7-9].

There are many terms in the literature characterizing damage to the cardiovascular system in patients undergoing radiotherapy, such as Radiation-Induced Heart Disease (RIHD), Radiation-Induced Coronary Artery Disease (RICAD), Radiation-Induced Cardiovascular Toxicity (RICT), or Radiation-Induced Associated Valvular Disease (RAVD) [10-13]. Recently published international guidelines for cardio-oncology present the definition of the entire spectrum of cardiovascular toxicity associated with cancer treatment as "Cancer Therapy-Related Cardiovascular Toxicity" (CTR-CVT) [14].

Risk factors for the development of cardiovascular toxicity associated with radiotherapy

A patient starting oncological treatment often presents with comorbidities, and their lifestyle additionally affects the risk of developing cardiac diseases. The assessment of this risk should include the cancer itself, which may directly or indirectly damage the cardiovascular system, the cardiotoxic effect of oncological treatment, as well as the "standard" risk factors for the development of cardiovascular disease [15]. These factors include age, gender, nicotine addiction, hypertension, diabetes, hypercholesterolemia, and obesity. Many of them are also a risk

factor for cancer. It should be noted that the diagnosis of cancer does not facilitate the modification of factors that the patient can potentially influence. Quitting smoking becomes more difficult, the patient usually limits physical activity, which contributes to weight gain, and sometimes depression occurs. [3, 16, 17].

The above-mentioned risk factors largely influence the risk of left ventricular systolic dysfunction, which is the most common form of manifestation of toxicity in the cardiovascular system associated with oncological treatment [17].

Radiotherapy can affect the heart to varying extent. Risk factors for cardiotoxicity associated with ionizing radiation treatment include age at the time of radiotherapy (younger patients have a higher risk of RIHD), location of the tumor requiring radiotherapy in the anterior or left half of the chest, distance of the irradiated area from the heart, the volume of the heart subjected to radiotherapy, doses deposited within the heart and Left Anterior Descending artery (LAD), fractional dose, and cardiac volume receiving a specific dose, for example 25 Gy [18, 19].

Damaged heart structures

Virtually all heart structures may be damaged in the course of radiotherapy [2, 3, 12, 20, 21].

Pericardium:

Within this structure, early radiation changes most often occur, with clinical manifestation in the form of acute pericarditis. Already a few weeks after treatment, fever, tachycardia, chest pain, and pericardial effusion appear. Characteristic changes in the ECG include elevation of the ST segment, flattening or inversion of the T wave, decreased QRS amplitude, and enlargement of heart dimensions on chest X-ray [3, 20, 22]. Back in the 1970s, acute pericarditis was a common side effect of radiotherapy. Patients presenting symptoms of acute pericarditis received a dose of not less than 40 Gy administered over 4 weeks to more than half of the heart volume.

With the development of radiotherapy techniques that allow limiting the doses deposited in the heart structures, the incidence of acute pericarditis is decreasing significantly. Currently, this is a rare complication [21, 23]. Chronic or constrictive pericarditis appears within 5 years-10 years after treatment, most often in patients who have had acute inflammation. It is manifested by chest pain, increased body temperature, and rapid breathing [11].

Coronary vessels:

The heart muscle is a relatively radioresistant structure due to the low mitotic activity of cells [23]. Following radiotherapy, widespread interstitial fibrosis occurs, which may lead to heart failure [20, 24].

Late radiation reaction involves increased fibrosis, which may result in restrictive cardiomyopathy. Diastolic dysfunction most often occurs as a result of stand-alone radiotherapy. Following combined treatment with anthracyclines, systolic dysfunction predominates [25-30].

Many studies indicate that the heart is an organ that responds early to radiotherapy. Studies assessing myocardial perfusion just a few months after treatment showed perfusion disturbances in 27%-70% of patients irradiated for breast cancer [31-34]. Perfusion disturbances occur through direct radiation exposure, through degenerative changes and fibrosis of muscle cells, and indirectly as a result of damage to vessels to the endothelium and smooth muscle [32].

Heart valves:

The incidence of heart valve diseases increases with time after radiotherapy. The problem may affect as many as 30% of patients undergoing chest radiotherapy. Most often, changes in the valve apparatus concern the aortic and mitral valves. The disease may present as mild, asymptomatic damage to the valve apparatus, or as a disorder causing serious hemodynamic disturbances, requiring surgical intervention. As many as 70% of patients have a clinically silent course of the disease. Carlson et al. showed that it takes at least 5 years for symptoms of valvular heart disease to appear as a result of radiation therapy (Radiation-Associated Valvular Disease-RAVD). In the observed group, patients reported symptoms only after an average interval of 16.5 years after radiotherapy [13].

Conduction system:

Conduction disturbances usually occur after a long time after radiotherapy, after several years or later, although some studies have described ECG changes as early as 6 months after radiotherapy. Another study reported the occurrence of complete heart block in the range from less than one year to 23 years after treatment with ionizing radiation [11].

Prolongation of the QT interval has been observed after high doses administered to the heart, especially in high fractional doses [23]. Other disorders, such as heart blocks of various degrees, sick sinus syndrome, persistent tachycardia, and loss of circadian and respiratory rhythms, have also been described, which may be the result of damage to the autonomic nervous system [20].

The importance of early detection of changes in the heart

For many years, the prevailing belief was that the risk of serious cardiac events, including death due to heart damage, increases only after at least 10 years after treatment with ionizing radiation [22, 28, 35].

Some disorders appear as an acute reaction to radiation, such as acute pericarditis, pericardial effusion, arrhythmias, or conduction disorders, while others, such as coronary heart disease, chronic pericarditis, or valvular system diseases, appear many years after exposure [2]. Detection of early changes, often without symptoms, is crucial as it allows the selection of patients with an increased risk of cardiac events in the future [21]. It should be emphasized that a significant percentage of patients seeking oncological treatment already have atherosclerotic lesions, and radiotherapy in such a situation may accelerate this process [22].

In studies assessing early changes after radiotherapy, a transient decrease in ejection fraction was observed in women with breast cancer immediately after radiotherapy, with normalization of this parameter within 2 months-6 months after treatment [36, 37].

In other studies, perfusion disturbances in the SPECT examination occurred already in the period from 6 months to 2 years after radiation treatment, and then partially disappeared [30, 38].

Diagnostic methods

The most used test in the assessment of cardiotoxicity is

Transthoracic Echocardiography (TTE). This test allows the assessment of the structures of the heart, its dynamics, as well as systolic and diastolic function in real-time. It is a basic tool in the assessment of the myocardium both during oncological treatment and in follow-up after treatment. The definite advantages of this method include its availability, low cost, repeatability, non-invasiveness, safety, and mobility. In clinical practice, the most frequently used parameter for assessing systolic function is Left Ventricular Ejection Fraction (LVEF) [10, 16, 39-41]. The sensitivity of classical echocardiography in the context of detecting early cardiovascular toxicity related to oncological treatment isn't perfect, as LVEF declines only at a later stage after the compensatory mechanisms have been exhausted [39]. Erven et al. assessed early cardiotoxicity by myocardial Strain Rate Imaging (SRI) immediately after radiotherapy, and then 8 and 14 months after treatment. In this study, SRI turned out to be a promising method for detecting early, subclinical changes in cardiac function that were not visualized in classical cardiac echocardiography [42]. Currently, methods of analyzing myocardial deformation are a recognized tool for assessing cardiotoxicity in the early phase, when LVEF has not yet decreased [16, 43].

The gold standard in assessing systolic and diastolic function, volume, mass, and viability of the myocardium is Magnetic Resonance Imaging (MRI) [39, 44]. It is an excellent tool in the diagnosis of areas of fibrosis, inflammatory infiltrates, or edema within the myocardium [16].

Unfortunately, due to the cost of the test, availability, limitations related to the presence of a strong magnetic field, and the duration of the test, it is not commonly used. This method requires the patient's cooperation, and a stationary position during the long image acquisition period and is not recommended for patients with claustrophobia [16]. MRI provides greater repeatability of measurements compared to echocardiography [45].

A very important parameter in the assessment of early changes after radiotherapy is the examination of myocardial perfusion. Promising techniques for that purpose are offered by nuclear medicine with tests such as Single-Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET). The risk of heart damage is proportional to the volume of the heart treated with radiotherapy. Cardiac perfusion scintigraphy showed that perfusion disturbances affected more than half of the subjects in the area receiving a high dose. Lind et al. assessed myocardial perfusion disturbances in areas of the heart corresponding to the blood supply ranges of individual branches of coronary arteries. The patients underwent radiotherapy using tangential fields as part of the combined treatment of breast cancer. Perfusion disturbances mainly concerned the extent of blood supply to the LAD and appeared within 6 months, and their severity correlated with the left ventricular volume receiving a dose of >25 Gy. No disorders were observed in the areas supplied by the right coronary artery and circumflex artery [30].

Żyromska et al., in a prospective study on a group of 15 patients, analyzed the Myocardial Blood Flow (MBF) using the 15O-H_2O PET/CT method. The tests were performed before and after 2 months and 8 months after radiotherapy. The study concluded that PET is a valuable and safe test in the assessment of early, subclinical changes in myocardial perfusion in patients undergoing radiotherapy as part of the treatment of breast cancer [46]. A significant limitation in the widespread use of PET examination is its cost, availability, and unsatisfactory spatial resolution. Moreover, unlike an MRI examination, a PET/CT examination exposes the patient to ionizing radiation [47]. The use of fast sequences in MRI significantly improves the resolution of images. This allows precise assessment of the blood supply to individual parts of the heart muscle, and identification of zones of necrosis or scars after a heart attack [48].

A less frequently used diagnostic method for assessing the myocardium is Computed Tomography (CT). This test is most widely used in the assessment of the pericardium and coronary vessels [40]. These vessels have small dimensions, a tortuous course, and are highly mobile, which poses many difficulties in their evaluation by MRI. The advantages of CT include high spatial resolution, short examination time, and high sensitivity of calcification detection. Similarly to MRI, CT can be synchronized with the ECG [10, 49-52].

CONCLUSION

The prolongation of overall survival of breast cancer patients and the growing population of cured patients and those with controlled disease undergoing long-term treatment necessitates greater attention to the risk of side effects of oncological treatment, and in this group of patients, the most serious consequences undoubtedly concern the heart.

It is worth noting that the risk factors for cardiovascular diseases and cancer are mostly the same. This means that eliminating them through a healthy lifestyle, quitting smoking, and effective treatment of, for example, diabetes reduces the risk of developing these diseases.

The effect of radiotherapy on the heart may manifest itself as a disorder of any of the heart structures in the form of arrhythmia, ischemic heart disease, pericarditis, congestive heart disease, or valvular dysfunction.

The pathogenesis of these disorders may be fibrosis or damage to the atrioventricular node or other elements of the cardiac conduction system, inflammation, fibrosis, and intensification of coronary atherosclerosis.

The risk factors with which the patient begins cancer treatment cannot be omitted in the risk assessment. Moreover, during treatment, the treatment of cardiac diseases should be continued and, if necessary, modified.

In addition to the impact of radiotherapy on the heart, the cardiotoxicity of systemic treatment, including chemotherapy and immunotherapy, should also be considered.

Cardiovascular toxicity related to oncological treatment most often concerns left ventricular dysfunction, which may not cause symptoms for a long time. Long before so-called cardiac events occur, certain changes in the heart may occur. It is crucial to find methods that can detect these dysfunctions or anomalies in the heart at an early stage.

Early diagnosis of such dysfunction is extremely important because it enables the implementation of preventive treatment, subjecting the patient to close cardiological observation, and in the oncological aspect, it increases the patient's chances of qualifying

for systemic treatment in the event of relapse.

Furthermore, it should be noted that cardiovascular complications related to radiotherapy may be underestimated due to the delay in symptom manifestation and their overlap with cardiac events caused by the "standard" risk factors.

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