Review article

Imaging techniques used to detect oncological treatment complications

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ABSTRACT

Oncological drugs are toxic for the cardiovascular system, directly affecting cardiac function and anatomy. Oncological treatment complications may thus take the form of asymptomatic myocardial dysfunction, overt heart failure, exacerbation of the symptoms of ischaemic heart disease, thromboembolic complications, arterial and pulmonary hypertension, pericardial complications, valvular disease and arrhythmia. Presently, we have a number of diagnostic tools at our disposal to detect cardiotoxicity, and the choice of one imaging technique over the others depends on the availability of that particular diagnostic method, and on its ability to provide optimum visualization. The basic method for cardiac assessment in oncological patients is transthoracic echocardiography (TTE). It is a widely available method which enables assessment of cardiac structures and haemodynamics without exposing the patient to an additional dose of ionizing radiation. In the case of poor TTE visualization, a recommended method for the assessment of cardiac function and structures is magnetic resonance. Chest, heart and coronary artery CT is also very useful in the diagnostics of oncological treatment complications. Moreover, cardiotoxicity diagnostics also involves nuclear medicine imaging techniques, including gated radionuclide ventriculography, whose advantage is high repeatability, with the disadvantage being the patient's exposure to ionizing radiation and limited information on the structure and function of the myocardium. Both ECG-gated single photon emission computed tomography (SPECT) and positron emission tomography (PET) deliver information on the global and regional function of the left ventricle, presence of intraventricular synchrony, and myocardial perfusion. Early detection of subclinical dysfunction of the left ventricular myocardium in patients treated with potentially cardiotoxic drugs is well-grounded and aimed at the prevention of cardiovascular mortality by means of a primary prevention strategy.

Key words: cardiotoxicity, cardiac imaging techniques, echocardiography

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Received:
6.03.2017.
Accepted:
30.05.2017.

DOI: 10.24292/01.OR.300617.1

INTRODUCTION

The progress that has been made in oncology over the past 20 years resulted in longer survival of cancer patients. However, anti-cancer treatment involves a significant cardiovascular toxicity, with cardiac diseases potentially leading to premature deaths of oncological patients. It is both the treatment-related cardiotoxicity that is to blame as well as the accelerated development of cardiovascular diseases (especially in the presence of classic risk factors).

Cardiotoxic events may result from the interactions between different therapeutic methods. Such complications may be revealed in the form of a number of cardiovascular dysfunctions, including asymptomatic myocardial dysfunction, overt heart failure, ischaemic heart disease, thromboembolic conditions, pulmonary hypertension, pericardial complications, valvular defects, arrhythmia, e.g. one caused by the QT-prolonging medications, arterial hypertension, peripheral vascular diseases and stroke (tab. 1).

TABLE 1.
Cardiovascular complications associated with anti-cancer treatment.

1. Myocardial dysfunction and heart failure.
2. Ischaemic heart disease, including coronary artery disease.
3. Valvular defects.
4. Arrhythmia, in particular one caused by the QT-prolonging medications.
5. Arterial hypertension.
6. Thromboembolic diseases.
7. Peripheral vascular disease and stroke.
8. Pulmonary hypertension.
9. Pericardial complications.

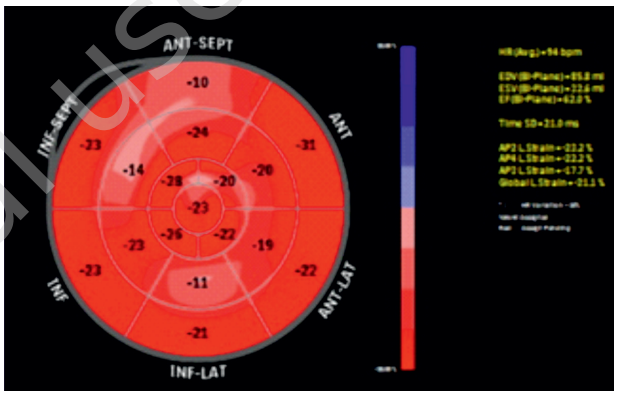
Presently, we have a number of diagnostic tools at our disposal to detect cardiotoxicity, and the choice of one imaging technique over the others depends on the availability of that particular diagnostic method, and on its ability to provide optimum visualization [1].

MYOCARDIAL DYSFUNCTION

Transthoracic echocardiography

The basic method for cardiac assessment in oncological patients is transthoracic echocardiography (TTE). It is recommended to use 3D echocardiographic assessment of left ventricular ejection fraction (LVEF), and if it not available, to apply the Simpson's biplane method. If the echocardiography system includes the necessary software, it is also recommended to determine the global longitudinal strain (GLS) of the left ventricular myocardium. GLS is a parameter which provides information on the quantitative changes in LV myocardial strain. The strain and strain rate may additionally be measured for each of 17 left ventricular segments. GLS values > -16% is considered normal. The cut-off value indicates that left ventricular segments are 16% shorter during systole as compared to their length during diastole (fig. 1) [2].

FIGURE 1.
Echocardiogram of a patient with normal left ventricular function (LVEF 62%). Global longitudinal strain assessment presented in the form of a bull's eye plot – GLS within normal range (GLS -21.1%).



Negative sign of GLS may lead to confusion when comparing serial values, because deterioration in LV function results in a counterintuitive increase in the arithmetic value of myocardial strain. There is recommendation that one should implicitly consider the absolute value of the strain number, so that increases in GLS mean that the number is becoming more negative, and decreases are observed when LV function deteriorates and GLS becomes less negative [3].

Currently, a diagnostic criterion of cardiotoxicity is LVEF drop of more than 10% to a value below the lower limit of the normal range [1]. As regards GLS, on the other hand, cardiotoxicity is suggested by a relative decrease in the parameter of more than 15% with respect to the baseline value (fig. 2). The usefulness and predictive value of GLS has been confirmed in many studies [4–7].

Apart from the LVEF and GLS measurements, echocardiography is used to assess cardiac valves, pericardium and pathological cardiac masses (fig. 3).

Transthoracic echocardiography is a widely available method which enables assessment of cardiac structures and haemodynamics without exposing the patient to an additional dose of ionizing radiation. Its limitations include the imaging quality,

FIGURE 2.
Echocardiogram of a breast cancer patient treated with trastuzumab: A. Before treatment – normal LVEF (57.1%) and GLS (-19.6%) values. B. 3 months into the treatment – normal LVEF value (52.4%), with abnormal GLS (-14.2%). A 28% drop in GLS as compared to the baseline value is a clinically significant finding (difference > 15%).

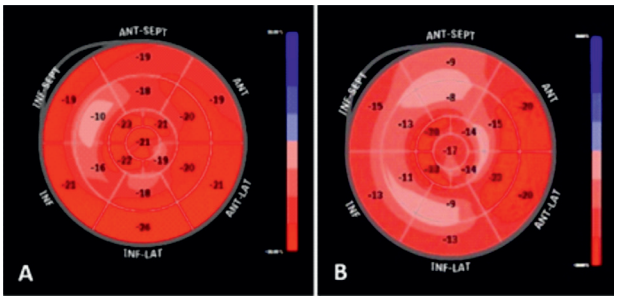
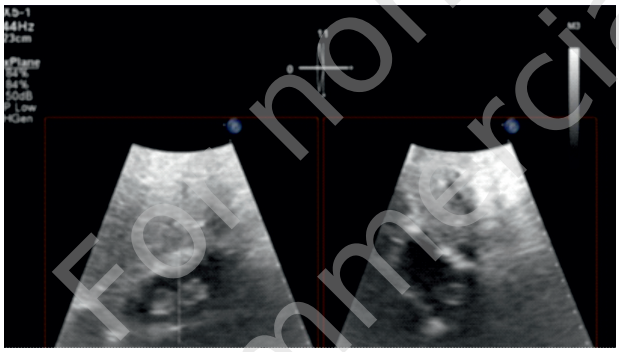


FIGURE 3.
Transthoracic echocardiogram, substernal view – renal cell carcinoma metastases in the right atrium.



dependent on the type of echocardiography device, its software, and on the patient's anatomy (emphysema, chronic lung diseases, obesity, status post thoracotomy), as well as the intraobserver variability in the assessment.

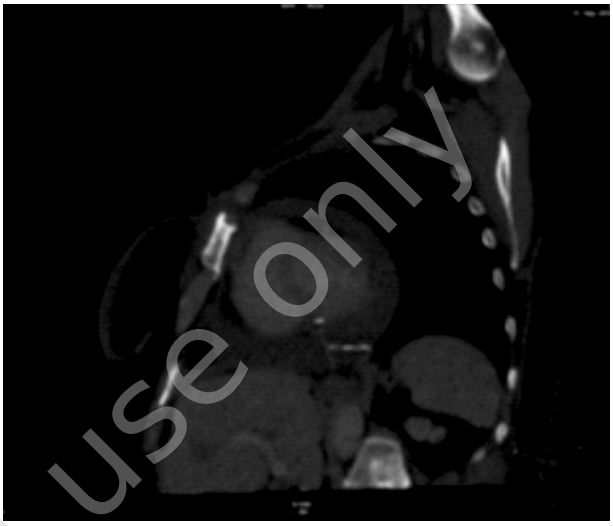
Computed tomography

Another imaging method used to detect oncological treatment complications is chest, cardiac and coronary artery computed tomography (CT). Commonly available and inexpensive, it is a static method serving to assess the anatomy and structure of the chest organs and tissues, enabling the visualization of pericardial fluid and other abnormalities (fig. 4).

ISCHAEMIC HEART DISEASE, INCLUDING CORONARY ARTERY DISEASE

Coronary artery disease diagnostics in cancer patients is based on the assessment of CAD risk as determined on the basis of the patient's history, age, gender and the anti-cancer treatment involved (chemotherapy, radiotherapy). In order to determine the degree of myocardial ischaemia, the same diagnostic methods

FIGURE 4.
Chest CT – pericardial fluid in a patient with lung cancer



are used as in the case of patients without the diagnosis of cancer, including:

- dobutamine stress echocardiography
- coronary CT angiography with calcium score assessment (fig. 5)
- myocardial perfusion scintigraphy
- positron emission tomography.

Coronary computed tomography angiography (CCTA) remains the only examination that enables reliable and non-invasive visualization of coronary arteries, making it possible to identify patients at risk of rupture of the ulcerated atherosclerotic plaque, and development of an acute coronary syndrome. This is especially significant for those undergoing radiotherapy and chemotherapy as part of their anti-cancer treatment [8]. Cancer patients require long-term coronary disease monitoring due to their increased risk associated with oncological treatment.

If echocardiographic visualization is poor, magnetic resonance imaging (MRI) is recommended for the assessment of cardiac structures and function (fig. 6). The method is highly accurate and repeatable. In cancer patients, it makes it possible to detect myocardial fibrosis, with the use of T1 and T2 mapping, and to assess the extracellular volume fraction (fig. 7). MRI enables accurate assessment of cardiac tumours, including the differential diagnostics of their character (thrombus, metastasis, primary tumour, myxoma), and visualization of myocardial infiltration by neoplastic masses (fig. 8). Unfortunately, MRI use is limited due to the small number of centres that have the method on offer, and an insufficient number of specialists who are capable of interpreting MRI results. Other limitations include the

FIGURE 5.
Coronary computed tomography angiography – numerous atherosclerotic lesions in the left anterior descending artery (LAD) of a gastric cancer patient.

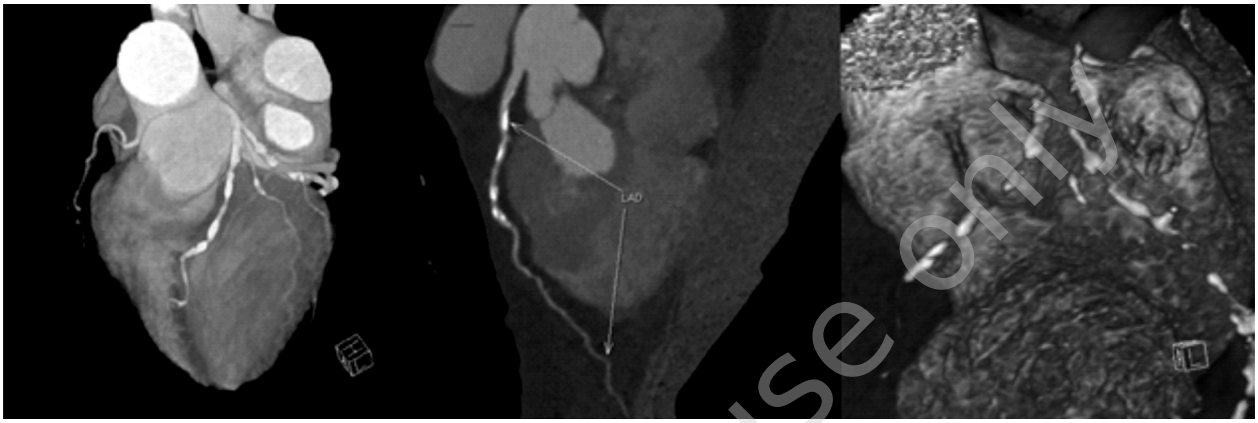


FIGURE 6.
Cardiac MRI. 60-year-old breast cancer patient, following breast conserving surgery, without cardiovascular symptoms (suboptimal acoustic window in echocardiography). After the 6th course of trastuzumab, LVEF dropped to 40%, with visible signs of myocardial non-compaction.

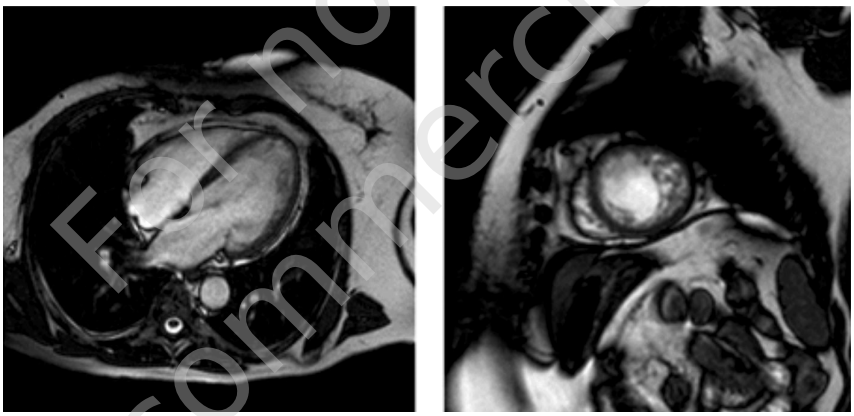


FIGURE 7.
Cardiac MRI. Signs of chemotherapy-induced (idarubicin) myocardial damage in the form of late contrast enhancement areas within the left ventricular, with subepicardial and intramyocardial location in anterolateral and inferolateral basal segments in a patient with acute promyelocytic leukaemia.

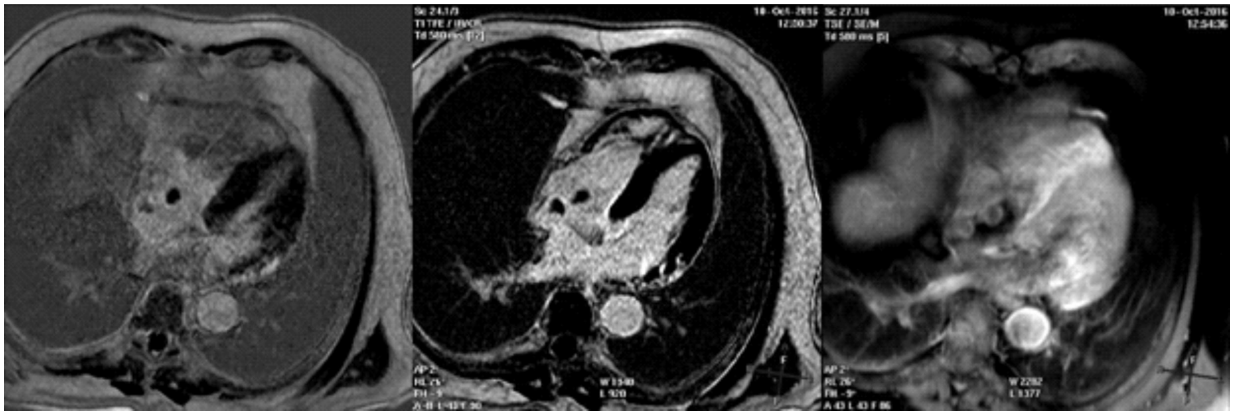
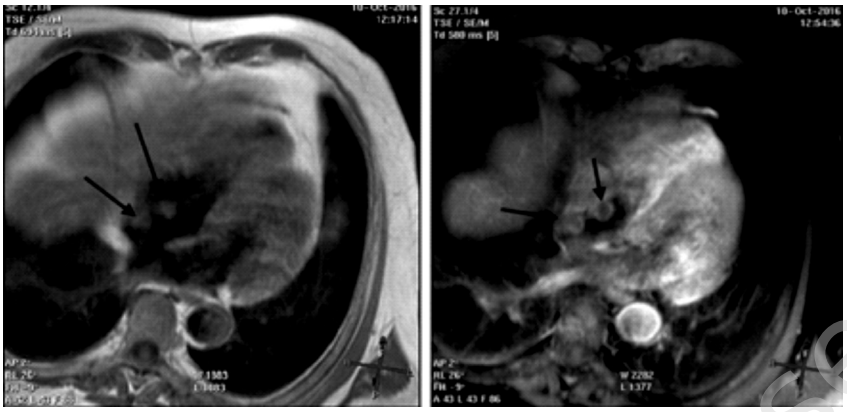


FIGURE 8.
Cardiac MRI. Thrombi in the right atrium of a patient diagnosed with acute promyelocytic leukaemia.



long image acquisition time, and patient-related conditions, including claustrophobia and inability to hold one's breath for a longer while.

MYOCARDIAL DAMAGE

Myocardial imaging in the course of anti-cancer treatment is aimed at the earliest possible detection of myocardial injury. LVEF drop is a late sign of cardiotoxicity. Nuclear medicine methods enable visualization of pathophysiological tissue processes, making it possible to detect myocardial damage at an earlier stage, before the LVEF drop, as a certain critical mass of myocardial cells undergo damage, before a decrease in LVEF is even recorded. Functional imaging of the myocardium is thus rendered possible. In patients who receive cardiotoxic drugs, early diagnostics is aimed at the identification of those at risk. Diagnosing unfavourable processes within the myocardium, resulting from oncological treatment, may help implement cardioprotective strategies, thus contributing to a reduction in cardiovascular mortality. The cellular mechanisms that damage cardiomyocytes involve, inter alia, the release of oxygen-derived free radicals, oxidation of cardiomyocyte membranes, calcium ion overload, inhibition of protein synthesis, increased number of proinflammatory cytokines, accumulation of toxic metabolites, and activation of apoptotic pathways, all leading to cell death.

One of the recognized cardiotoxicity diagnostic methods is multigated radionuclide angiography (MUGA), whose advantage is high repeatability, with the disadvantage being the patient's exposure to ionizing radiation and limited information on the structure and function of the myocardium [9–11]. Based on MUGA, cardiotoxicity is defined as a decrease in LVEF of more than 10 percentage points to a value < 50%.

Monitoring of heart failure patients involves both methods assessing myocardial perfusion as well as those examining the function of the autonomic nervous system, including adrenergic imaging in particular. The current guidelines on nuclear medicine imaging do not refer specifically to heart failure patients after anti-cancer treatment, but they may be useful in their assessment [12]. Both ECG-gated myocardial perfusion single photon emission computed tomography (GSPECT) and positron emission tomography (PET) deliver information on the global and regional function of the left ventricle, intraventricular synchrony and myocardial perfusion. Additionally, scintigraphy with the use of ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) is the only method which makes it possible to assess the adrenergic function of the heart. ^{123}I-MIBG is a norepinephrine analogue that is subject to uptake by sympathetic neurons, but is not metabolized. An increase in noradrenergic tone results in faster tracer washout, whereas in the case of anthracycline-induced cardiomyopathy tracer washout is reduced as a result of cardiac sympathetic denervation; reduced tracer washout rate in patients with left ventricular dysfunction is an independent predictor of cardiac death [13, 14]. Radiotherapy-induced cardiac innervation damage involves inappropriate sinus tachycardia, and may lead to silent myocardial ischaemia in cancer patients in whom coronary heart disease is revealed [15].

Due to the addition of the computed tomography method, GSPECT additionally eliminates artefacts, as the superimposition of CT images helps locate the image and eliminate artefacts responsible for false positive results suggestive of myocardial ischaemia. The imaging test involves the use radioactive technetium-labelled methoxyisobutylisonitrile (^{99m}Tc-MIBI, ^{99m}Tc- methoxyisobutylisonitrile), which under normal perfusion is carried freely to myocytes, where it is retained by means of mitochondri-

al electric potential. Ischaemia causes a reduction in mitochondrial cell membrane potential, leading to tracer washout from the cells. Radioisotope tests serve to detect cardiotoxicity before the appearance of the symptoms of irreversible left ventricular damage (LVEF drop). Rest and stress scintigraphy is performed with the use of dipyridamole, adenosine and dobutamine for the assessment of LVEF and myocardial perfusion. SPECT ensures qualitative assessment of regional perfusion, and cardiac ischaemia is determined based on the relative difference between tracer uptakes in different regions of the heart. The test is long due to the time of tracer absorption.

PET scan, on the other hand, makes it possible to differentiate between foci of physiological tracer accumulation and those of pathological accumulation. A commonly used and universal radioisotope is 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG). Routine FDG PET/CT tests may be used to assess not only the patient's response to oncological treatment, but also to monitor the treatment-related cardiotoxicity [16, 17]. PET enables qualitative assessment of myocardial perfusion abnormalities, using a high-energy tracer to guarantee a high spatial resolution. PET has a higher sensitivity and specificity than SPECT, additionally enabling quantitative assessment of myocardial blood flow (MBF) and myocardial flow reserve (MFR). Moreover, PET serves to measure the myocardial flow reserve in a non-invasive manner, while being just as accurate as the invasively measured fractional flow reserve (FFR). Dynamic PET test also helps to determine the difference in resting and stress LVEF, assessing the absolute decrease in the peak exercise EF. Additionally, the test offers a higher resolution, higher spatial distribution, and takes a shorter time than SPECT. PET is performed (on its own or – more frequently – together with cardiac CT) with the use of reagents such as N-13 ammonia or O-15 water [18, 19]. The tests require the presence of a cyclotron on site. The main limitations associated with PET include its low availability, patient's exposure to ionizing radiation and relatively high costs of the procedure.

New tracers are thus sought for in order to reduce the duration of the examination and the dose of radiation. A promising new tracer is regadenoson, a selective A2A adenosine receptor agonist [20]. However, there are presently very few studies on the use of PET with new tracers for the assessment of cancer treatment-related cardiotoxicity, and the few available have been conducted on animal models [21].

CONCLUSION

Despite the availability of many cardiac imaging methods, transthoracic echocardiography remains the method of choice in terms of monitoring the safety of cancer patients. LVEF drop is a relatively late sign of progressive myocardial damage, which is why the new techniques that measure GLS are very promising, as they detect earlier abnormalities, before the emergence of irreversible cardiomyocyte damage, and before the development of overt heart failure. Early detection of subclinical left ventricular dysfunction in patients treated with cardiotoxic medications is well-grounded and aimed at the prevention of cardiovascular mortality by means of a primary prevention strategy.

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Authors' contributions:
Barbara Sosnowska-Pasiarska: 80%; Stanisław Góźdź: 20%.
Conflict of interests:
None.
Financial support:
None.
Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.