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Beyond left ventricular ejection fraction. Speckle tracking imaging echocardiography within oncology services

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ABSTRACT

Cardiac oncology is a dynamically changing field in clinical medicine. Oncological therapies are known to cause cardiovascular side effects. Most importantly, it increases the risk of developing heart failure, even years after treatment. The aim of this study was to present novel (last years) data on cardiac imaging methods that are able to show very early cardiac changes due to the toxicity of some chemotherapy drugs.

Rapid developments in the treatment of oncological diseases have led to a constant need for new data. On one hand, new treatment options that affect the heart and vessels are yet to be determined, and more sophisticated treatment planning and modified schemes that make previously used medications or radiotherapeutic options safer for patients are needed. This allows them to be used in patient groups that were previously disqualified because of their burden and risk–benefit ratio. A multidisciplinary team approach, including oncologists and cardiologists with experience in the field, is necessary to manage this complex patient group. Cardiac imaging plays an essential role in the process of risk assessment, diagnosis, and monitoring of cardiac function and morphology during cancer treatment. Echocardiography plays an important role because of its availability and repeatability. Strain imaging is increasingly used in this field. However, multimodal imaging, including magnetic resonance imaging and computed tomography, can provide crucial information to treating specialists. Another topic was the use of implantable cardiac devices in this patient group. Individual decision-making is crucial, as end-of-life care must be taken into clinical consideration. In this paper, we would like to summarise the current state of the art and discuss some novel findings in the field of cardiac oncology which may change the current guidelines

INTRODUCTION

More than 14 million new patients are diagnosed with cancer annually (Parkin, 2005). Due to more effective treatment options the number of surviving patients is steadily increasing. Oncologic therapies are known to cause a variety of cardiovascular side effects, increasing the risk of developing heart failure even years after treatment. In this group of patients, the mortality rate was up to 60% by 2 years (Felker, 2000; Thavendirathan, 2014). Rapid developments in the treatment of oncological diseases have led to a constant need for new data. Cardiac oncology is a dynamically changing field in clinical medicine. On one hand There are new treatment options whose effects on the heart and vessels are yet to be determined; however, more sophisticated treatment planning and modified schemes that make previously used medications or radiotherapeutic options safer for patients are needed. This allows them to be used in patient groups that were previously disqualified because of their burden and risk–benefit ratio. Boer et al. proposed a classification of cardio-oncology syndromes (COS), which is summarized in Table 1 (Boer, 2021). Here, we focused on Type II. A multidisciplinary team approach, including oncologists and cardiologists with experience in the field, is necessary to manage this complex patient group. Cardiac imaging plays an essential role in the process of risk assessment, diagnosis, and monitoring of cardiac function and morphology during cancer treatment. Echocardiography plays an important role because of its availability and repeatability. Strain imaging is increasingly used in this field. However, multimodal imaging, including magnetic resonance imaging and computed tomography, can provide crucial information to treating specialists. Another topic was the use of implantable cardiac devices in this patient group. Individual decision-making is crucial, as end-of-life care must be taken into clinical consideration. In this paper, we would like to summarise the current state of the art and discuss some novel findings in the field of cardiac oncology which may change the current guidelines.

Table 1. The cardio-oncology syndrome (COS) types described by Boer et al.

I	Direct	Progressive development of cancer leads to CV disease
II	Indirect	Cancer associated treatments causing CV disease
III	Direct	Progressive scarring and remodelling of heart and kidney causing a pro-oncogenic environment

IV	Indirect	CV disease associated treatment and diagnostics causing a pro-oncogenic environment
V	Secondary	Systemic and genetic conditions causing both cancer and CV disease

SEARCH STRATEGY AND SELECTION CRITERIA

The literature was reviewed using the PubMed database. Particular attention has been paid to English language articles in recent years. This allowed the gathering of a large number of papers concerning the cardiotoxicity of cancer treatment (including chemotherapy and radiotherapy), as well as monitoring using both biomarkers and imaging studies. The search keywords were cardio-oncology, chemotherapy, radio-therapy, speckle tracking echocardiography, cardiotoxicity, and troponin.

REVIEW

CARDIOTOXIC ONCOLOGICAL THERAPIES

The development of different therapeutic methods and agents in oncology has similarly raised the quality and quantity of the side effects of these methods. Here, we present cardiotoxic media used in chemotherapy and radiotherapy.

The main side effects of cardiotoxic drugs on the circulatory system are as follows:

CHEMOTHERAPY

The list of cardiotoxic side effects of each group of chemotherapeutic agents is long; therefore, we present only a few examples. More detailed information can be found in the guidelines of various cardiac and oncological societies (Zamorano, 2016).

Antimetabolites: Fluoropirimidynes

These agents are known to cause vasospasm and angina symptoms with an incidence of 0,1 to 19% (Iliescu, 2016). The effect is dose dependent. High-dose therapy in the form of intravenous infusion causes vasospasm-related cardiac events in 5,4% of cases (de Forni, 1992; Campia, 2019).

Antimicrotubule agents: Alkaloids

The use of this treatment may lead to chest pain, hypertension, myocardial ischemia, and thromboembolic events (Campia, 2019).

Alkyl like agents: Platinum

The cardiotoxic effects were similar to those of the alkaloids. The use of platinum agents may lead to myocardial infarction (Campia, 2019). Treatment with cisplatin can lead to myocardial ischemia in 0,2-12% of cases (Iliescu, 2016). To avoid platin-related toxicity high volumes are administered. This may lead to volume overload in patients with preexisting cardiac dysfunction (Zamorano, 2016).

Alkylating agents: Cyclophosphamide

Cyclophosphamide rarely causes cardiotoxicity. Described cases are concerning high doses (> 140 mg/kg) before bone marrow transplantation (Braverman, 1991; Zamorano, 2016). They may cause untreatable pulmonary hypertension due to veno-occlusive disease (Ranchoux, 2015; Kim, 2018).

Antitumor antibiotics:

Anthracycline

The most widely described and studied chemotherapeutic agents are known to cause cardiotoxicity. The risk of developing congestive heart failure after doxorubicin administration was 5% at a cumulative dose of 400 mg/m^2 and increased up to 48% when a dose of 700 mg/m^2 was administered (Swain, 2003; Zamorano, 2016). The cardiotoxic effects can be acute, early or late. Acute symptoms develop in < 1% of patients, immediately after drug infusion. Side effects include supraventricular arrhythmia, transient LV dysfunction, and ECG changes, which are usually reversible. Early effects occurred within the first year of treatment and late after several years (Zamorano, 2016).

Bleomycin

Pulmonary hypertension, myocardial ischemia, and even infarction are the most prominent cardiotoxic effects of this drug (Campia, 2019). Moreover, heart failure with elevated NTpro BNP, reduced ejection fraction (EF) and pulmonary oedema are observed.

Antibody related targeted therapy

Trastuzumab induces reduction of LV; therefore, HF is usually reversible with interruption of treatment or administration of HF therapy (Suter, 2007; Zamorano, 2016). Petricciuolo et al. suggest that a level of 14 ng/l of high-sensitivity TnT (hs-TnT) was the best cut off value to predict negative CV outcomes at 3 months in people treated with anti-PD-1/PD-L1 (Petricciuolo, 2020; Delombaerde, 2021).

Tyrosine kinase-related primarily VEGF-R directed

The risk of arterial thromboembolic events increases 3-folds (Scappaticci, 2007; Lenneman, 2016). These agents are also known for causing arterial hypertension (Campia 2019, Saunderson 2021). QT prolongation is a major problem in patients with cancer. Among these agents Vandetanib's average QT prolongation is the longest at 36 ms. QTc intervals of >500 ms occur in 4,3-8% of patients. The US Food and Drug Administration and European Medicines Agency recommend a temporary interruption of treatment when QTc > 500 ms (or the QTc prolongation is > 60 ms above baseline) (Zamorano, 2016).

Tyrosine kinase-related primarily ABL directed

In patients treated with these drugs, the risk of cerebrovascular events, myocardial ischemia, and venous thromboembolic disease increases. Patients may develop precapillary pulmonary hypertension, especially when treated with dasatinib. This side effect occurs in up to 12% of cases (Guignabert, 2016, Montani, 2012, Kim, 2018) Another drug, ponatinib, is associated with systemic hypertension (Campia, 2019).

Proteasome inhibitors

Drugs such as bortezomib and carfilzomib have been reported to cause similar cardiovascular side effects (Campia, 2019).

Immune checkpoint inhibitors

This group of agents may cause myocarditis (Valabhaneni, 2021), which is associated with poor outcomes, as the reported fatality rate ranges from 30 to 50% (Varricchi, 2017, Salem, 2018; Ederhy, 2021). Studies using magnetic resonance found LGE (late gadolinium enhancement – pathological fibrosis and elevated T2-weighted STIR signal with a lymphocytic infiltration) localised in the anteroseptal, inferoseptal, inferior and inferolateral segments of the myocardium (Zhang, 2020, Ederhy, 2021).

RADIOTHERAPY

Approximately 50% of patients with cancer receive radiotherapy during treatment (Baskar, 2012). Modern radiotherapeutic approaches cause less cardiovascular side effects and cardiac damage than before due to more sophisticated radiation schemes, which allow treatment using less radiation on a more focused area – sparing the heart and great vessels. The manifestations of radiation-induced cardiac damage include vasculopathies, pericardial and conduction system, and myocardial and valvular diseases (Desai, 2019).

Research has shown a 34-fold increase in the risk of valvular disease in patients receiving radiotherapy (Heidenreich, 2003; Rosmini, 2021). Anthracycline exposure has been shown to increase the risk of heart failure and valvular disorders from mediastinal radiotherapy, which suggests an additive cardiotoxic effect (Aleman, 2007; Lenneman, 2016).

The incidence of major coronary events increases by 7,4% per mean Gray dose directed to the heart. The characteristic of radiation-induced cardiac damage is that the likelihood of CVD stays increased up to three decades after the initial treatment (Darby, 2013; Bloom, 2016), and in experimental models, cholesterol plaques and thrombosis formed within days after exposure (Stewart 2006; Iliescu 2016). The risk of acute coronary syndrome increases by 16% per Gray in breast cancer patients treated with this method (van den Bogaard, 2017; Rosmini, 2021).

DEFINITIONS OF CARDIOTOXICITY

Cardiotoxicity from cancer therapy includes acute and chronic coronary syndromes, arrhythmias, conduction disturbances, and cancer-therapy-related cardiomyopathy. The latter is based on the left ventricular ejection fraction, which is key information from echocardiography to continue or cease therapy.

Table 2. Different definitions of cardiotoxicity

Source	Definition of cardiotoxicity
FDA (for anthracyclines)	>20% decrease if EF remained normal, or >10% decrease if EF is less than normal
British Society of Echocardiography	LVEF decline by > 10 percentage points to a value of < 50%
Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials	'(1) decrease in cardiac LV ejection fraction (LVEF) that was either global or more severe in the septum; (2) symptoms of congestive heart failure (CHF); (3) associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms [Curigliano 2012]

CARDIAC MONITORING OF ONCOLOGIC PATIENTS

Clinical strategies for oncological patients should be based on safety and should lead to therapy completion. Therefore, some monitoring methods have been implemented to detect the early side effects of oncotherapy and promptly initiate secondary pharmacological cardioprotection. For those reasons biomarkers and imaging modalities are used. Detailed diagnostic and follow up schemes for different types of chemotherapeutic agents are summarized in the 2022 European Society of Cardiology guidelines on cardio-oncology (Lyon, 2022).

A. Biomarkers.

1. Troponin

The release of cardiac troponins into the bloodstream may damage the cardiac tissue. They are widely available and have comparatively low costs. Testing of this biomarker is not only crucial in monitoring patients during their cancer treatments (Auner 2003), but also allows stratification of the risk, as research shows that elevated baseline levels of troponins are a risk factor for chemotherapy-related complications (Dobson, 2021). In this group of patients closer monitoring of cardiac function may be of benefit (Alvarez-Cardona, 2020). However, the impact on long-term clinical outcomes of routine assessment remains unknown (Yu, 2016; Narayan, 2020).

2. NT-pro BNP

In contrast to troponin, this biomarker is characteristic of cardiac volume overload. It is most widely associated with heart failure. The guidelines of the American Society of Clinical Oncology recommend the use of biomarkers to detect HF only in patients with clinical signs (Armenian, 2017). However the negative predictive value of this test seems to be more useful in clinical practice (Bloom, 2016), and NT-proBNP may also serve as a predictor of clinical outcome and risk of cardiovascular damage during oncologic treatment. Lower baseline levels of it are a predictor of LVEF recovery (Hamo, 2016). It is worth mentioning that certain types of cancer may produce this marker in their vascular endothelium (Narayan, 2020), which may mislead clinicians.

B. Cardiac multimodality imaging strategies

1. 2D echocardiography

Echocardiography with evaluation of the left ventricular ejection fraction (LVEF) remains the paramount image modality in monitoring cancer patients for cardiac damage as the change of this parameter is part of most definitions of cardiotoxicity. According to Dobson et al. most of the echocardiograms in cardio-oncology are performed to monitor treatments using anthracyclines and/or trastuzumab. Lenarczyk et al. showed that echocardiography is the most common method of screening used in 93% of centres implanting

cardiac implantable electronic devices (CIEDs) (Lenarczyk, 2017). The low cost and high availability makes it a good choice for routine repeated control testing. Monitoring of LVEF for 12 months after anthracycline treatment led to early detection of 98% of cardiotoxicity cases (Cardinale, 2016). In the absence of global longitudinal strain (GLS, more information below) quantification of LV longitudinal function using mitral annular excursion (MAPSE) by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave TDI (tissue Doppler imaging) is recommended (Plana, 2014). These are widely used methods of ultrasound imaging, available in almost every modern ultrasound machine, normally used in daily clinics.

Besides the assessment of the left ventricle it is also crucial to check the systolic function of the right ventricle, as in many cases cancer therapy may impair it function (Plana, 2014). The new British Society of Echocardiography guidelines suggest using all the routinely used parameters including tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC) and peak systolic velocity (S') of the free wall of the right ventricle to assess the systolic function of the right ventricle (Dobson, 2021). Repeated assessments of all the above mentioned parameters are necessary to notice any relevant changes during oncologic treatment and the observation afterwards.

Full echocardiographic studies of the heart are recommended as they allow diagnosing a variety of cardiotoxic effects besides LVEF reduction and heart failure. Wall motion abnormalities for instance may be a sign of acute coronary syndrome in combination with other findings. As mentioned before the risk of it rises especially during chemotherapy using fluoropyrymidines (Zamorano, 2016, Saunderson, 2021).

Pericardial effusion has also to be evaluated. Screening for signs of tamponade is crucial as it is a life threatening condition.

Chemotherapy may lead to pancytopenia and as a result to sepsis. Echocardiographic studies of cardio-oncologic patients should take endocarditis into clinical consideration and check for vegetations on valves (Plana, 2014). It is important to remember the limitation of transthoracic echocardiography and that transesophageal echocardiography will be often necessary to rule out endocarditis.

All the mentioned above diseases should be diagnosed and treated according to their specific guidelines.

The echocardiographic assessment of an oncologic patient may be challenging and should be performed by an experienced echocardiographer. The cancer treatment itself may alter the image. For example for patients after mastectomies or with breast implants the American Society of Echocardiography suggests using contrast agents for better visualisation of the endocardial border (Mulvagh, 2008; Bloom, 2016).

2. Speckle tracking echocardiography

Speckle tracking echocardiography (STE) is a novel echocardiographic technique, which allows a more precise assessment of systolic function of the left ventricle. Each region of the myocardium has a specific speckle pattern, which allows it to track its movement during the cardiac cycle. Strain defined as the percentage change is then measured in one of the three main dimensions: longitudinal, circumferential, and radial. All of the currently available societies guidelines concerning the echocardiographic evaluation of oncologic patients suggest the use of strain analysis as it provides important information when it comes to treatment outcome (Dobson, 2021, Kim, 2018, Plana, 2014, Virani, 2016). The most studied and used is the longitudinal strain measurement. Global longitudinal strain (GLS) is defined normal

Moreover research suggests that impairment in global longitudinal strain (GLS) may precede LVEF reduction in patients treated using thymidine kinase (TKis) and therefore allow the clinician team to act sooner and prevent negative cardiovascular outcomes (Biersmith, 2022). The new 2022 european guidelines on cardio-oncology are the first to incorporate GLS measurements as a clinical tool (Lyon, 2022). A change of the global longitudinal strain (GLS) > 15% compared to baseline seems to be abnormal and suggests cardiotoxicity (Plana, 2014, Thavendirathan 2014). The Strain Surveillance of Chemotherapy for improving Cardiovascular Outcomes (SUCCOUR) trial has validated the use of GLS in monitoring cardio-oncologic patients undergoing treatment using anthracyclines. Patients monitored using GLS had less meaningful falls of LVEF to the abnormal range compared with the second group monitored using only LVEF (Saunderson, 2021, Thavendiranathan, 2021). Research showed that using myocardial deformation analysis, early epirubicin cardiotoxicity can be detected at a dose of only 200 mg/m^2, which is considered to be low and therefore safe according to current guidelines (Mele, 2015). The British Society of Echocardio-

graphy suggests an echocardiographic classification during surveillance of patients undergoing anthracycline and trastuzumab treatment. Based on LVEF and GLS measurements their change can be defined as: cardiotoxicity, probable subclinical cardiotoxicity and possible subclinical cardiotoxicity. GLS serves here as an indicator of subclinical cardioxic side effects. The definitions are summed up in table 3 (Dobson, 2021).

A study by Negishi et al., suggests that GLS may be used to assess a cardioprotective response after administering beta blockers (Negishi, 2014, Male 2015). The higher sensitivity of GLS compared to LVEF and resulting from it better clinical decision making makes it an essential tool for monitoring cardio-oncologic patients.

Radial strain has not been yet widely studied, however research suggests that it may change earlier and to a greater extent compared to GLS (Jurcut, 2008; Wildiers, 2008, Male, 2015).

Using layer-specific strain analysis showed a change in rotational parameters across different layers of the myocardium (Thavendirathan, 2014).

Speckle tracking analysis of the right ventricle and left atrium can be also performed, however these are less studied techniques. One of the major problems using this technique is inter-vendor variability so results should be compared only between vendors from the same producer. Moreover speckle tracking analysis requires specialistic software, which may not be available. As mentioned before this echocardiographic technique may be challenging and should be performed by a trained echocardiographer. In figure 1 we present a short guide to perform GLS measurements.

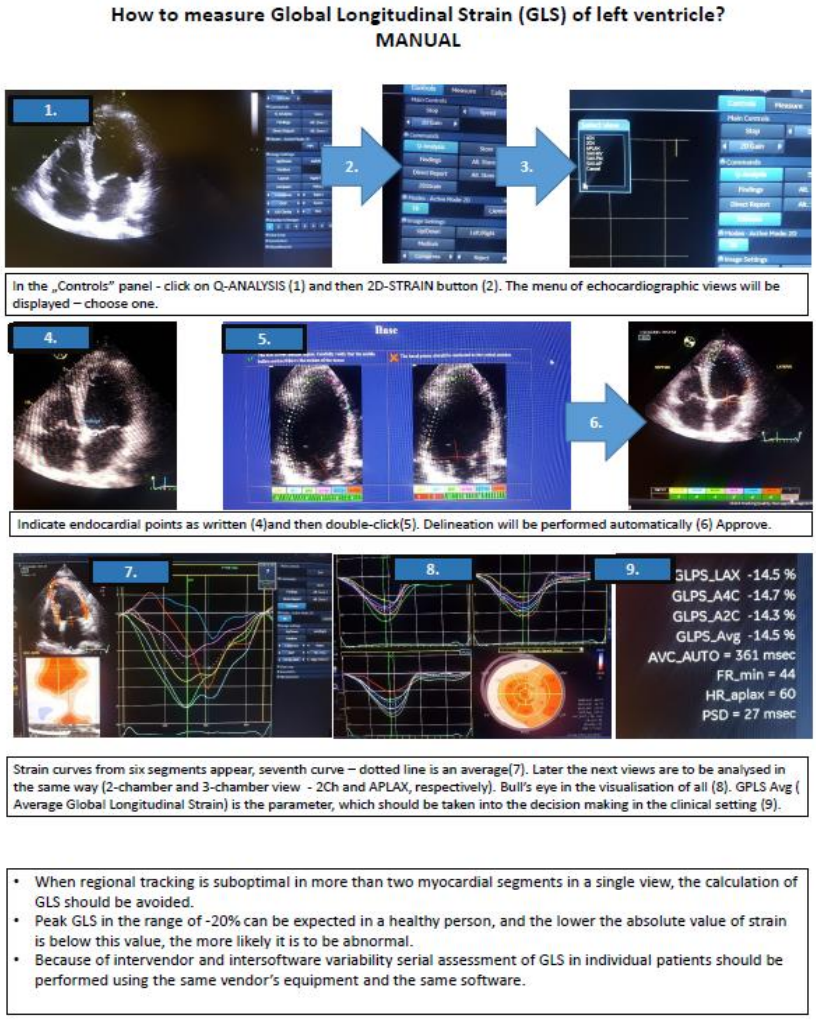

Figure 1. How to measure Global Longitudinal Strain of left ventricle – manual

Table 3. Surveillance criteria proposed by the British Society of Echocardiography (Dobson, 2021)

	Definition
Cardiotoxicity	LVEF decline by > 10 percentage points to a value of < 50%
Probable subclinical cardiotoxicity	LVEF decline by > 10 percentage points to a value of ≥ 50% with an accompanying fall in GLS > 15%
Possible subclinical cardiotoxicity	LVEF decline by < 10 percentage points to a value of < 50% OR GLS relative percentage reduction by > 15% from baseline

3. Cardiac Magnetic Resonance

Magnetic resonance of the heart remains the gold standard to evaluate left and right ventricular systolic function. Typically it is used when echocardiographic assessment is not possible (Zamorano, 2016). The previously mentioned study by Lenarczyk et al. showed that cardiac MRI was used in only 13% of centres implanting cardiac implantable electronic devices (CIED's) for cardio-oncologic screening (Lenarczyk, 2017). The lower availability of this imaging study makes it less useful in everyday clinical practice, however when used it provides very precise information thanks to tissue characterization, which may be crucial for example in detecting myocarditis. The change of cardiomyocyte size which can be assessed using MR as the basis of reduction of LV mass is studied (Saunderson, 2021). Cardiac MR may also be used to evaluate the valves, but echocardiography is more accessible, which allows repeatability.

4. Cardiac computed tomography

Thanks to modern advances in imaging technology the radiation used for computed tomography is lowered – this is important especially in the setting of oncologic patients, which are already exposed to high doses of it during their treatment. The average cardiac CT delivers a lower effective radiation dose of 2–5 vs. 6–21 mSv for single-photon emission CT and 2–20 mSv for invasive angiography (Rosmini, 2021). This allows the use of cardiac computed tomography in the evaluation and diagnosis of cardio-oncologic patients. The main use of cardiac computed tomography in patients undergoing oncologic treatment is screening for coronary artery disease (CAD), by determining the coronary artery calcium score, especially in patients with a higher bleeding risk due to their disease, where traditional coronary angiography would be contraindicated (Biersmith, 2022). A score of 400 agatston units and higher is associated with a higher risk of acute coronary events. Negative values suggest a very low risk of such events (Hecht, 2015, Rosmini, 2021). Current guidelines recommend screening for CAD 5-10 years after radiotherapy (Lancellotti, 2013, Rosmini 2021). It is important to remember that this group of patients may be asymptomatic in terms of angina symptoms due to nervous damage caused by chest irradiation, so special precaution is needed (van Leuwen, 2011; Rosmini, 2021).

Another important application of this technique in this clinical setting is the evaluation of pericardial disease, which, as mentioned before, may be caused by radiotherapy but also certain chemotherapeutic agents.

The role of valvular diagnostics using CCT is limited, as echocardiography will be the method of choice in most cases.

With the rapid development in this field of radiology (for example quantification of epicardial and pericoronary fat) there may be more indications for CCT in cardio-oncology the nearest future (Rosmini 2021).

Table 4. Comparison of the available imaging modalities

	Function assessment	**Tissue characte-rization**	**Availability**	**Cost**	**Myocarditis**	**Pericardial disease**	**Valve disease**	**Coronary disease**
Echocardiography	++	+	+++	+++	+	+	+++	+

Cardiac computed tomography	+	+	++	++	-	++	+	+++
Cardiac magnetic resonance	+++	+++	+	+	+++	+++	++	++

ONCOLOGIC PATIENTS WITH CARDIAC IMPLANTABLE DEVICES

An European Heart Rhythm Association (EHRA) survey from 2017 showed that 89% of centres implanting cardiac implantable electronic devices (CIED's) are managing patients treated for oncologic diseases (Lenarczyk, 2017). According to a Danish survey the annual rate of radiotherapy in patients with CIED was 4,33 therapies per 100 000 persons (Zaremba, 2015; Stuhlinger, 2022). CIED's are almost never a contra-indication for radiotherapy, as it is mostly possible to perform it while keeping the generator outside the beam range. Negative effects described in literature are limited to single case reports. The group at highest risk are patients with pacemaker dependency or ICD's, so these cases require special consideration. If the cumulative dose is more than 5 Gy or the radiation beam energy greater than 10 MV supervision by a trained cardiologist is recommended (Tajstra 2019). A recent European Heart Rhythm Association (EHRA) consensus document provides more detailed information about this topic (Stuhlinger, 2022).

TREATMENT AND PREVENTION OPTIONS

The target of all monitoring strategies is to decide on the moment of cardioprotective treatment. However, at first – the main emphasis– like in any other patient – should be on the cardiovascular disease risk assessment and control. Secondly some specific preventive medical treatment should be implemented (eg. c. Angiotensin-converting-enzyme inhibitors) (Zamorano, 2016).

A. The risk assessment and control of cardiovascular risk factors

Patients can be assigned to different risk categories according to their pre-treatment risk factors (Tab. 5) (Čelutkienė, 2020). Preventive measures including smoking cessation and control of blood pressure, blood glucose and cholesterol levels are recommended before starting cancer treatment to lower the risk of cardiotoxicity (Cardinale, 2016).

Table 5. Patient-related risk factors considering cardiotoxicity risk (Čelutkienė, 2020)

Risk category	Patient-related factor
Low	Age > 18 < 50 years
Medium	Age 50 - 64 years 1 -2 CV risk factors (hypertension, dyslipidemia, obesity, insulin resistance, smoking)
High	Age 65 years > 2 CV risk factors Diabetes Underlying CV disease: CAD, PAD, CMP, severe VHD, heart failure, Reduced or low-normal LVEF (50-54%) pre-treatment Prior cancer therapy

CV – cardiovascular, CAD – coronary artery disease, PAD – peripheral artery disease, CMP – cardiomyopathy, VHD – valvular heart disease

B. Dexrazoxane

Dexrazoxane is a protectant which may be used during anthracycline treatment. The mechanism of action is thought to be iron chelating and thereby decreasing the production of free radicals, which would damage the heart (Jones, 2008; Hamo, 2016). The American Society of Clinical Oncology recommends the use of dexrazoxane only in adult patients with metastatic breast cancer and other malignancies who have received >300 mg/m^2 and who may benefit from use of additional anthracyclines (Hensley 2009; Hamo, 2016).

C. Angiotensin-converting-enzyme inhibitors (ACEI)

Enalapril may be started when myocardial injury is detected through elevated troponin levels (Cardinale, 2016). A combination of ACEI and BB is recommended in the treatment of reduced LVEF without symptoms of heart failure (Cardinale, 2016). The results of the OVERCOME trial showed that a combination of carvedilol and enalapril preserved the LVEF of patients undergoing anthracycline treatment (Bosch, 2013; Cardinale, 2016).

D. Beta-blockers

They may be used in primary prevention (Cardinale, 2016). Like previously stated a combination with ACEI should be prescribed once a reduction in LVEF is detected, even without symptoms of heart failure (Cardinale, 2016). Non-selective beta-blockers like propranolol however may be cardiotoxic (Choe, 1978; Cardinale, 2016). The PRADA trial (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy), a randomised, placebo-controlled, double-blind study tested if candesartan or metoprolol can prevent a decline in LVEF due to breast cancer chemotherapy using epirubicin, with or without trastuzumab. It reported that only candesartan showed this effect (Gulati, 2016). The LVEF-change was assessed using cardiac magnetic resonance, which makes this result even more important. These may indicate that not all beta blockers should be used in this indication. Metoprolol seems to be neutral (Cardinale 2016). The previously mentioned OVERCOME study may suggest that carvedilol is effective (Bosch, 2013). The multivariate analysis of the MANTICORE-101 study showed a preservation of LVEF associated with bisoprolol and perindopril (Pituskin 2017). These findings show that beta blockers seem to be more effective in combination with ACEI.

E. Aldosterone antagonists

Akpek et al. found in a study with 83 patients treated because of breast cancer that aldosterone antagonists prevented LVEF reduction (Akpek, 2015). Some studies suggest that this group of drugs can attenuate trastuzumab induced cardiotoxicity through inhibition of the EGFR receptor (Hamo, 2016).

F. Statins

Statins may be beneficial in the clinical setting of cardio-oncology thanks to their pleiotropic effects (Hamo, 2016). In patients without preexisting cardiovascular burden, the use of atorvastatin allowed a higher preservation of LVEF, which was shown in the only, to our knowledge, clinical trial concerning the use of statins for this indication (Acar, 2011; Cardinale, 2016; Hamo, 2016). In animal models pre-treatment using fluvastatin and lovastatin showed positive effects (Riad, 2009; Henninger, 2015; Cardinale, 2016). It should be noted that the use of statins in combination with hepatotoxic chemotherapy or in patients with impaired liver function should be avoided (Iliescu, 2016).

G. Cardiac rehabilitation

Current research indicates that cancer survivors may benefit from exercise in terms of the previously discussed cardiotoxic side effects. In animal models aerobic exercise reduced the cardiotoxic effect of doxorubicin treatment (Cardinale, 2016). However larger studies, including randomised control trials (RCT's) are needed to confirm these findings (Gilchrist, 2019).

Pareek et al suggested a classification of cardiotoxic effects of cancer treatment with appropriate management strategies, in the sense of cancer as well as cardiologic therapy, which we summarised in table 6 (Pareek, 2018).

Table 6. Management strategies for cardiotoxic cancer treatment according to Royal Brompton Hospital myocardial toxicity class

Cardiotoxicity group	Classification	Definition		Management strategies	
		Biomarkers	Echocardiographic findings	Oncology therapy	Cardiology therapy
1	Early biochemical cardiotoxicity	Rise of BNP or troponin I above norm or > 20%	Normal imaging	Continue	Cardiooncology review. Consider closer monitoring or

2	Early functional cardiotoxicity	Normal	New reduction in GLS OR III-IV diastolic dysfunction		start low dose ACEI or BB cardioprotection
3	Early mixed cardiotoxicity	Abnormal	Normal LVEF with GLS or diastolic dysfunction		
4	Symptomatic HFpEF		Symptomatic HFpEF	Interrupt and review risk/benefit	Cardiooncology review. Diuretic for fluid congestion. ACEI or BB cardioprotection if continuing cancer therapy
5	Asymptomatic LVSD		New LVEF reduction to <50% or a reduction of >10% to <55%	Review and balance risk/benefit	Cardiooncology review. Start ACEI and/or BB and up-titrate to 50-100% target dose for HF as tolerated.
6	Symptomatic LVSD		Symptomatic LVEF reduction to <50% or a reduction of >10% to <55%	Interrupt and review risk/benefit	Cardiooncology review. Start ACEI and/or BB and up-titrate to 100% target dose for HF as tolerated.

HFpEF – heart failure with preserved ejection fraction, LVSD – left ventricular systolic dysfunction

DISCUSSION

As mentioned in the introduction the connection between cardiology and oncology is more complex than just treatment side effects. Research suggests that cardiologic conditions may predispose to certain cancer types (Boer, 2021). Heart failure showed prooncogenic effects in animal models (Meijers, 2018). When it comes to cardiotoxic side effects of cancer treatments there are mostly observational retrospective studies. They do not cover every type of agent equally. The prevalence of cancer treatment induced heart failure (HF) is most likely underestimated, as the population of cancer trials are usually younger and healthier than the patients one may encounter in everyday practice (Hamo, 2016).

A multidisciplinary team approach, including oncologists and cardiologists with experience in the field, is necessary to manage this complex patient group. There is no specialty or subspecialty for this medical field for now. Some medical societies are working on determining how training in this field should look like. Leihan et al suggest that centres offering such program should allow the trainee a minimum of 100 patients encounters per year (Lenihan, 2016).

The COVID-19 pandemic had an impact also on the field of cardio-oncology. In a survey by Sadler et al. a decrease in the use of cardiovascular imaging was reported by up to 89% of cardiologists, but only 39% of oncologists. The way in which this particular group of patients, often immunocompromised, is taken care of also changed. More than 85% of the surveyed specialists adopted telemedicine in their everyday clinical practice (Sadler, 2020).

CONCLUSION

Close cooperation, beginning with the diagnostic workup till palliative care decisions, of specialists in the field of oncology as well as cardiology, is essential to ensure optimal patient treatment. Using modern multimodality imaging enables a more detailed and precise diagnostic of cardiotoxicity. Combined with widely used cardiac biomarkers as well as newly studied ones this allows clinical staging and optimal therapy. Pharmaceuticals which were already used in cardiology, show in an increasing number of studies cardioprotective properties in this specific group of patients. This makes it possible to avoid harmful side effects of effective treatment options. Rehabilitation, widely studied in cardiovascular disease management, seems to have positive effects here as well. Cardio-oncology is a novel, but rapidly developing field of medicine. Despite the growing amount of data, there are still knowledge gaps and the lack of randomised

controlled trials and clear guidelines based on their findings make clinical decision making more challenging. A multidisciplinary team approach with experienced physicians specialising in this field of medicine is essential. For now there is no subspecialty or formalised training in cardio-oncology, but experienced centres offer programmes. The first European guidelines in this field were published in 2022 (Lyon, 2022).

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