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Cardio-oncology: a new and developing sector of research and therapy in the field of cardiology

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Abstract

Cardio-oncology is a new field of interest in cardiology that focuses on the detection, monitoring, and treatment of cardiovascular disease occurring as a side effect of chemotherapy and radiotherapy. Both cancer treatment modalities can cause cardiac dysfunction, a major cause of morbidity and mortality in the oncologic population. It is necessary to periodically monitor cancer patients under treatment, especially those receiving anthracyclines and trastuzumab (monoclonal antibody), using mainly 3D echocardiography to calculate left ventricular ejection fraction and to estimate myocardial deformation. Additionally, measuring various biomarkers, such as natriuretic peptides, could facilitate early identification and appropriate response to potential cardiotoxicity. In this regard, cardiological assessment before starting cancer treatment is essential and should be continued throughout, since cardiac dysfunction can occur at any time, even several years after therapy onset. High-risk individuals, in particular, should receive a detailed management plan designed in collaboration between an oncology and a cardiology specialist. If heart failure develops, even in the absence of overt clinical symptoms, standard heart treatment is to be followed and causal agent discontinued if possible. One important question is whether and when to stop cardiac medication in case of heart dysfunction reversal, after completion of cancer treatment. Further cardio-oncology evolution can lead to a deeper understanding of the adverse mechanisms and effects causing heart failure, as well as the development of personalized treatment regimens in order to limit cardiotoxicity.

Keywords Cardiotoxicity · Cancer · Heart failure · Echocardiography · Strain

Abbreviations

ACE	Angiotensin-converting enzyme
GLS	Global longitudinal strain
HF	Heart failure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
VEGF	Vascular endothelial growth factors

Introduction

Cardiac dysfunction that develops during or after treatment of a malignant neoplastic disease has become a subject of growing scientific interest. Cardio-oncology is a novel cardiology subspecialty focusing on detection, monitoring, and treatment of cardiovascular disease occurring in the context of cancer treatment.

Recent advances in chemotherapy and radiotherapy have improved treatment of both solid tumors and blood cancers, giving patients hope for a better quality of life and in certain cases complete healing [1]. However, both treatment modalities are causally associated with cardiac dysfunction, which has emerged as a leading cause of morbidity and mortality among cancer patients. Cardiotoxicity may be a direct result of cancer treatment on the structure and/or function of the heart muscle or could be caused by the development of cardiovascular disease progressively, particularly in the presence of traditional risk factors [2]. Damage to the heart may manifest either during cancer treatment or after; it can lead to heart failure (HF), coronary heart disease, arrhythmias, pericarditis, valvular disease, and scarring of the pericardium or/and myocardium [3].

While the necessity for specialized cardio-oncology facilities is well recognized in the USA, in most European countries, this is a relatively new era. However, the clinical need for

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the integrated treatment of patients with malignant neoplasms, as well as the understanding of cardiac adverse effects, has led several hospitals in Europe to develop specialized cardio-oncology departments. Furthermore, the European Society of Cardiology published appropriate position paper for the management of cardiotoxicity that develops during cancer treatment in 2016 [4], while similar guidelines were published by the newly formed American Society of Cardio-oncology a year later [5].

Patients receiving cancer treatment may experience a multitude of cardiovascular complications, directly or not related to their therapeutic regimen. Optimal personalized care requires close collaboration between both cardiology and oncology specialists.

Cardiotoxicity

Conduction disorders

Arrhythmias are often associated with cancer treatment [6], with atrial fibrillation being the most common [7, 8]. However, supraventricular tachycardias as well as repolarization disorders, in particular prolongation of the QT interval and Torsade de Pointes, may also occur. Many studies have found a significant correlation between atrial fibrillation, malignancy, and chemotherapy [7], highlighting a variety of cause and effect mechanisms [9]. On the other hand, medical treatment of atrial fibrillation in patients with cancer is a challenge as various antiarrhythmic agents interact adversely with chemotherapeutic agents. Moreover, although cancer patients exhibit an increased trend for cerebrovascular episodes, anticoagulation presents a significant problem since anemia and low platelet count are characteristic of this population. Atrial fibrillation ablation could offer a solution for these patients, but in this particular area, as well as the cardio-oncology field in general, there is a lack of data with significant quality (class 1 level A) [4].

Drugs used in the treatment of cancer can cause prolongation of the QT interval either directly, through electrophysiological mechanisms, or indirectly by causing heart ischemia or failure. At the same time, a number of concomitant factors, such as dehydration, electrolyte disturbances, renal and hepatic dysfunction, can affect QT interval and even cause Torsade de Pointes. Chemotherapeutic agents most commonly implicated are cyclophosphamide, taxanes, thalidomide, and tyrosine kinase inhibitors. Other medicines used as second-line treatment, such as antiemetics, antidepressants, antipsychotics, antihistamines, and antifungals [10], are also implicated. On the other hand, proper estimation of QT interval may prove elusive as 75% of cardiologists and 38% of electrophysiologists are not able to calculate it correctly, as pointed out by Viskin et al. [11]. While Bazett's formula—$QTc = QT/\sqrt{RR}$, where RR is the RR interval in seconds—is widely used in clinical practice, Fridericia's formula—$QTc = QT/3\sqrt{RR}$—seems to be more appropriate for cardio-oncology patients in particular, since it allows more accurate calculations in cases of low heart rate [12]. An additional problem in the oncologic population is that a properly calculated and prolonged QT interval does not necessarily correspond to a pathological condition as it is a frequent not statistically significant finding [13].

In addition, as life expectancy increases, technologic breakthroughs lead to a high number of oncologic patients who bear implantable cardiac devices, such as pacemakers, cardiac defibrillators (ICDs), and cardiac resynchronization (CRT) devices [14]. This subgroup faces a set of special problems when receiving treatment, particularly regarding chest irradiation, that could require careful device reprogramming [15], or in some cases complete device removal before starting therapy [16].

Hypertension

There is a high coprevalence of hypertension and cancer, since both diseases share the same risk factors, such as sedentary lifestyle, obesity, smoking, unhealthy diet, and alcohol abuse. The use of chemotherapy, especially vascular endothelial growth factors (VEGF) inhibitors [17] and adjuvant drugs, such as erythropoietin [18], effective in the treatment of cancer have increased the survival rate of these patients but, consequently, have also increased the incidence of hypertension. The aim of angiogenesis inhibitor therapy is to target molecules with increased expression in patients with cancer. However, such molecules are also present in non-tumoral cells and have a physiological role in several systems, including the cardiovascular system [19]. Therefore, when acting in the tumor by inhibiting VEGF, angiogenesis inhibitors also cause hypertension. This generates a paradox, since the presence of hypertension is simultaneously an adverse cardiovascular effect and a sign of favorable oncological therapeutic response [19]. The main angiogenesis inhibitors associated with the development of hypertension are bevacizumab, sorafenib, and sunitinib [20]. Treatment with angiotensin-converting enzyme (ACE) inhibitors and dihydropyridine calcium channel blockers may help protect from the vascular effects promoted by these agents.

Furthermore, studies in humans have shown that radiotherapy can provoke bilateral or unilateral carotid baroreceptor denervation leading to blood pressure lability, unsustained hypertension, orthostatic intolerance, and tachycardia [21]. Another mechanism of baroreflex dysfunction due to late effects of radiation is considered to be an acceleration of the process of atherosclerosis and chronic hypertension [22].

Coronary artery disease

Myocardial infarction with angiographically normal coronary arteries can occur due to several factors such as hypercoagulable state, coronary spasm, embolism, arteritis, congenital condition, and drugs including chemotherapeutic agents because of both acute and/or delayed cardiotoxicity [23]. Most chemotherapeutic agents are associated with coronary artery disease [24]. Emerging studies have shown that they can induce a spectrum of adverse cardiac effects including chest pain, dyspnea, and hypotension [25–27]. Other clinical presentations include arrhythmias, heart failure, myocardial infarction, cardiogenic shock, and sudden death [28, 29]. In this case, it seems that cardiotoxicity is mediated through a direct action on myocytes or due to production of reactive oxygen species (ROS) which induce oxidative stress and are pro-thrombotic. Cardiotoxicity has been explained by the result of oxidative stress on the cardiac cells with ensuing lipid peroxidation which causes physical injury and functional damage, the mechanism accounting for elevation of the leaked cardiac enzymes and markers, i.e., troponin I [30]. Possible risk factors are duration of treatment, capecitabine-based chemotherapy, pre-existing cardiac diseases, and hypertension.

Left ventricular dysfunction-heart failure

While novel therapies have dramatically reduced the mortality of cancer patients, new chemotherapeutic agents appear to cause significant cardiotoxicity [31]. Anthracyclines (doxorubicin, daunorubicin, epirubicin), alkylating agents (cyclophosphamide), monoclonal antibodies (trastuzumab), and tyrosine kinase inhibitors have been shown to cause left ventricular (LV) dysfunction. High cumulative doses of anthracyclines are associated with a higher risk of developing HF [32]. It appears that cardiotoxicity caused by anthracyclines is permanent, as it is due to extensive destruction of myocytes in the presence of a limited regenerative capacity [33], and it is characterized as type I cardiotoxicity. On the other hand, cardiotoxicity occurring after treatment with trastuzumab (Herceptin) is usually reversible because as it is due to impaired myocyte contractile function [34] and is characterized as type II cardiotoxicity [35]. Furthermore, anthracycline cardiotoxicity is dose-dependent while trastuzumab has no cumulative-related effect noted. However, it seems that several, still, unknown factors play a role in the mechanism and extent of cardiotoxicity caused by various chemotherapeutic regimens [36]. Cytotoxic myocardial dysfunction after the onset of chemotherapy or radiotherapy may occur suddenly, early in the first year, or later [37].

The presence of risk factors such as diabetes mellitus or coronary artery disease may increase the incidence of HF in the specific population [38]. The combined administration of anthracyclines with trastuzumab doubles the risk of developing HF compared to the administration of anthracyclines alone (5.2 versus 2.5% over 5 years), but if the interval between the administration of the two drugs is greater than 3 months, it does not increase the cardiotoxicity [39]. There are studies that examined the contribution of some biomarkers and imaging methods to the early diagnosis of heart damage, but also the role of different drugs in treating cardiotoxicity caused in the context of the treatment of cancer [40]. ACE inhibitors, beta-blockers, statins, and dexrazoxane appear to play an important protective role.

In addition, radiotherapy in patients with tumors can cause a wide range of cardiac damage, including HF [41, 42]. With the older methods of irradiation, induced cardiac injury was more frequent and more extensive; in recent years, however, the localized and carefully planned irradiation of an area by specialist radiotherapists has significantly reduced the impact of the destruction of myocardial cells [43]. In any case, when the patient's cardiological history is examined, previous irradiation should always be taken under consideration since it is an important risk factor for HF that may often be missed. With age, macro/microvascular damage may lead to progressive atherosclerosis, myocardial infarction or local fibrosis, and a relative decrease in systolic and/or diastolic function. In addition, radiation therapy can cause pericardial inflammation and restrictive cardiomyopathy [44], as well as significant endothelial damage to the valves of the heart, leading to valvular insufficiency and/or stenosis and ultimately HF [45].

Basic cardiological assessment of the oncology patient

It is thus clear how important is the cardiological assessment of the patient before the start of chemotherapy or radiotherapy. For individuals at high risk, a detailed and appropriately adapted management plan should be designed for both during and after treatment. The first step is to identify high-risk individuals, such as people with bad lifestyle habits (smoking, obesity, lack of physical exercise) or significant comorbidities (arterial hypertension, diabetes mellitus, angina, HF) [46, 47], patients with a previous history of coronary artery disease, or cerebrovascular or thromboembolic episodes, as well as individuals who have undergone chemo/radiotherapy and are more likely to exhibit cardiotoxicity [48] (Table 1). Hematological testing should be performed in conjunction with blood pressure measurement and electrocardiographic and echocardiographic examinations. This assessment of the patient's cardiological profile should be taken seriously into account by the oncologist, in conjunction with the cardiologist, in order to select the appropriate treatment.

Table 1 Patients who will undergo treatment for cancer and have an increased risk of developing cardiac dysfunction

(A) *Treatment involving any of the following:*

- High doses of anthracycline, such as a cumulative dose of ≥ 250 mg/m^2 doxorubicin.
- High doses of radiation, ≥ 30 Gy, when the heart is included in the irradiation field.
- Lower anthracycline dose combined with lower dose of radiation when the heart is included in the irradiation field.

(B) *Treatment with lower doses of individual anthracycline or trastuzumab and the presence of any of the following:*

- Multiple (≥ 2) cardiovascular risk factors, such as smoking, hypertension, diabetes mellitus, dyslipidemia, and obesity, during treatment or after its completion.
- Age ≥ 60 years.
- Impaired heart function, as in the case of a left ventricular ejection fraction ≤ 55%, history of myocardial infarction, ≥ moderate valvular disease, at any time before or during treatment.

(C) *Treatment with lower anthracycline dose followed by trastuzumab administration.*

Cardiovascular monitoring during cancer treatment

Left ventricular ejection fraction

A reduction in left ventricular ejection fraction (LVEF) is mainly used as an index of cardiotoxicity. In many clinical studies, as well as in the guidelines ("position paper") of the European Society of Cardiology, cardiotoxicity is defined as a > 10% reduction of LVEF from the original value and an absolute value < 50% [4, 49, 50]. LVEF is the most important parameter for the patient's prognosis, as patients with a reduced LVEF have a worse prognosis [51].

Echocardiography, nuclear imaging, and magnetic resonance imaging (MRI) have been used to assess LVEF. Of these methods, two-dimensional echocardiography is the most widely used method for evaluating LVEF during and after chemo/radiotherapy. It is a widely available, non-invasive technique that is easy to follow up for patients and has a low cost, while providing a safe and accurate assessment of cardiac function. Of course, the technical and observational ability of each cardiologist-sonographer are limitations of the method [52]. Here, however, three-dimensional echocardiography [53] [Fig. 1] offers significant help, reducing the subjectivity of the operator and yielding results comparable with those of MRI; it is thus recommended as the method of choice for calculating LVEF [53]. Nuclear imaging also reduces observer subjectivity in the evaluation of LVEF, but has the disadvantage of exposing the patient to radiation while providing limited information about the cardiac structure [54]; consequently, it is better to be avoided. On the other hand, cardiac MRI can contribute significantly to the non-invasive estimation of LV volumes and LVEF in the cancer patient, as well as to the diagnosis of edema, fibrosis, and cardiac reperfusion [46]. However, because of its high cost and low availability, it cannot be used routinely.

Myocardial deformation of the heart ("strain")

Although LVEF remains the most commonly used parameter for assessing left ventricular systolic function, it has shown poor sensitivity and predictive value in the diagnosis of underlying cardiac damage [51]. In particular, when a cancer patient exhibits a decrease in LVEF, that patient will already have irreversible myocardial damage [55]. Therefore, other markers have been sought for the diagnosis of subclinical cardiotoxicity. The echocardiographic evaluation of myocardial deformation ("strain") using speckle tracking is a promising method for the early detection of cardiotoxicity [56] [Fig. 2]. A decrease in global longitudinal strain (GLS) of > 15% from the baseline value during cancer is considered as a significant parameter in the early diagnosis of cardiotoxicity according to European Society of Cardiology position paper [4]. To this direction, a large systematic review of 1504 patients demonstrated that a 10 to 15% early reduction in GLS by speckle tracking echocardiography during cancer chemotherapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or HF [56]. However, there are still important limitations on the use of the method, as calculations are heavily dependent on the imaging quality—which is affected by both the particular anatomy of some patients and the skills and training of the echocardiographer—the technology of the device, and the software it uses, thereby reducing the comparability of results when patients are followed up using different devices [57].

Biomarkers

In the diagnosis of acute cardiotoxicity, the calculation of plasma troponin I and T concentrations, which are markers of myocardial cell damage, plays an important role [58]. B type natriuretic peptides, which are cardiac neurohormones secreted specifically by the ventricles in response to increased wall stress, can also be used as indicators of cardiotoxicity. However, there is still insufficient evidence to demonstrate the diagnostic or prognostic role of these markers for the occurrence of cardiomyopathy after chemotherapy [51].

Prevention and treatment of cardiotoxicity

Primary prevention of heart failure

The most important strategy for primary prevention is the complete avoidance or minimal use of chemotherapeutic

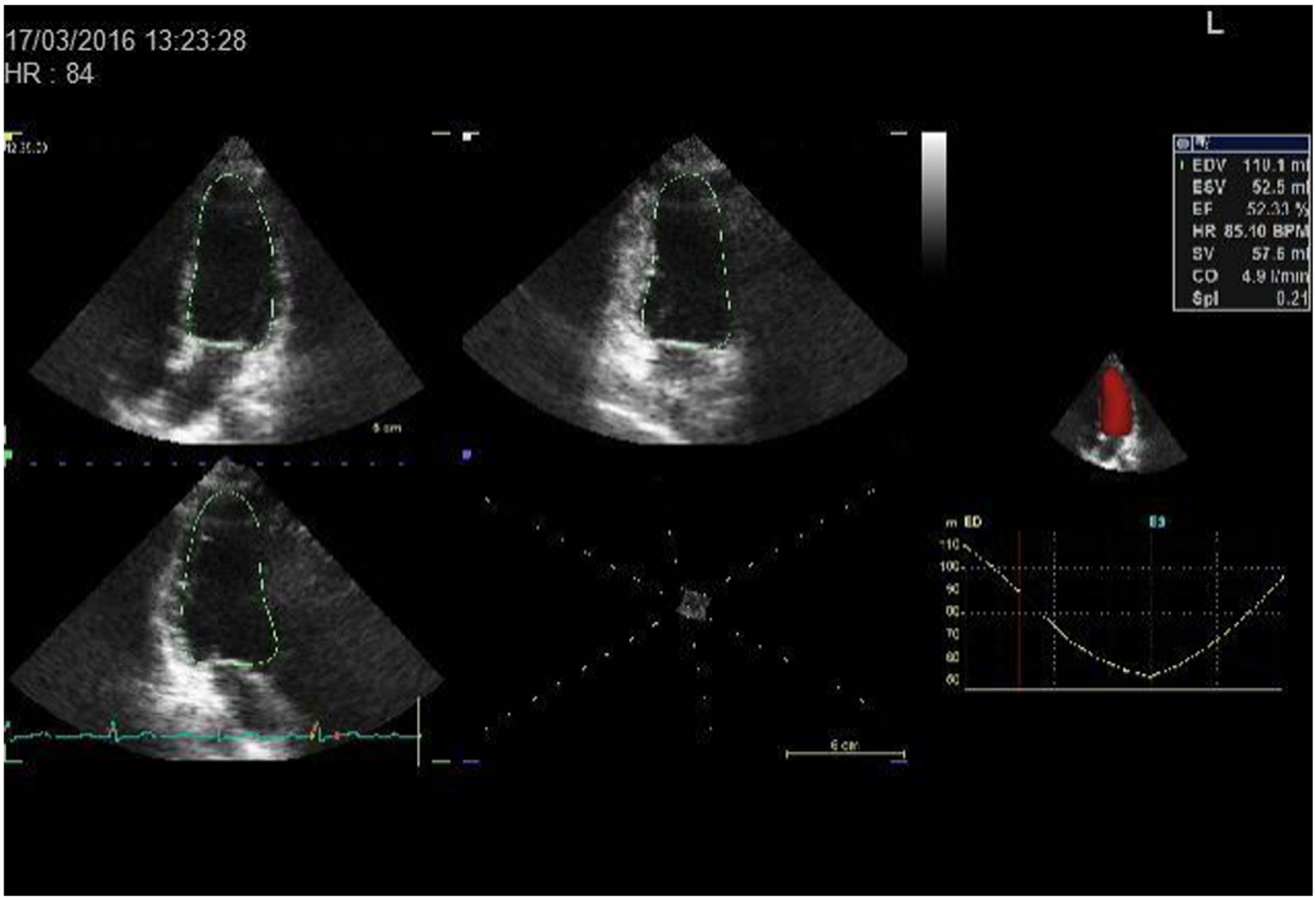

Fig. 1 Calculation of left ventricular ejection fraction (EF) using three-dimensional echocardiography in a patient with breast cancer under treatment with anthracycline and trastuzumab

substances with potentially cardiotoxic action if there is a documented alternative therapy [5]. In patients with an indication for radiotherapy, we try to reduce radiation exposure using modern techniques to determine the region to be irradiated [5]. Decisions are made taking into account both the efficacy of the tumor reduction treatment and the possibility of cardiotoxicity occurring directly or over time. In patients prescribed high doses of anthracyclines, co-administration of cardioprotective dexrazoxane may be one option for reducing heart damage, with very little probability of diminishing treatment effect [5].

The preventive administration of ACE inhibitors, beta-blockers, or angiotensin antagonists to prevent cardiotoxicity is currently the subject of ongoing research. There is a meta-analysis [40] supporting their prophylactic use in cancer patients, but data is limited by the small number of patients and the lack of adequate follow-up. However, it is certainly a treatment option in patients with cancer and high risk of imminent heart failure. Certainly, though, risk factors for cardiovascular disease should always be addressed and modified [59].

Treatment of patients with asymptomatic cardiac dysfunction

In case of asymptomatic patients with significant reduction of LVEF or LVGLS (decreased LVGLS corresponds to subclinical LV dysfunction), treatment should be initiated with ACE inhibitors, beta-blockers, or angiotensin antagonists, as per standard HF therapy [59]. In fact, patients who show cardiotoxicity after treatment with anthracyclines may have better long-term results if they commence treatment with ACE inhibitors and/or beta-blockers immediately cardiac dysfunction is detected [49, 60]. In addition, the combination of the above drugs appears to have better results compared to monotherapy [49, 60]. The time interval between the initiation of HF treatment and the end of chemotherapy is crucial for the reversal of cardiac damage [60]. At this point, it should be noted that there is limited evidence to show a benefit from early treatment initiation with ACE inhibitors [50] or beta-blockers [61] in patients with increased levels of troponin I or pathological LVGLS. However, especially in case of subclinical dysfunction with a > 15% reduction of LVGLS, cardioprotective medications are recommended (ACE inhibitors or beta-blockers) [62].

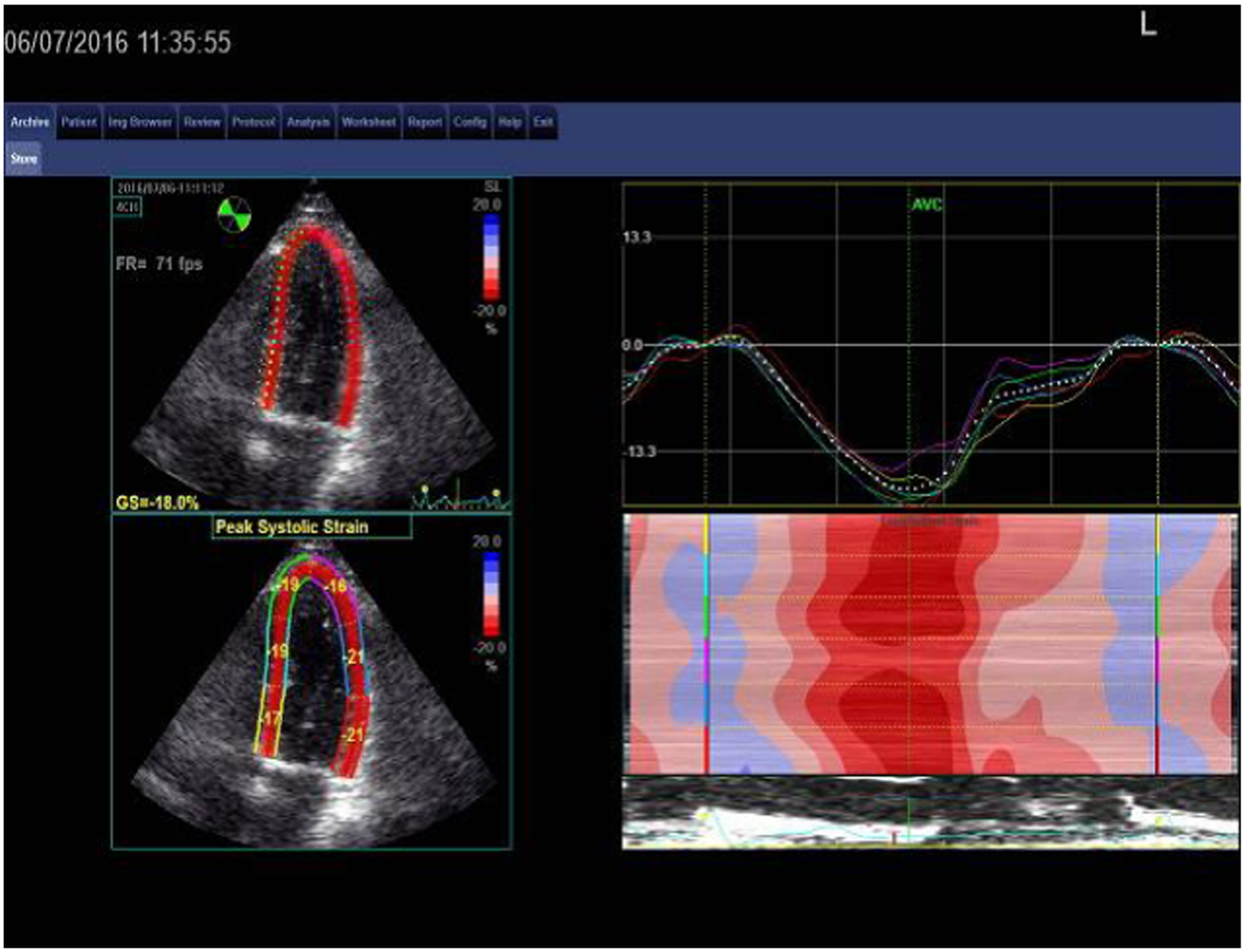

Fig. 2 Calculation of left ventricular myocardial deformation (GS) in a patient with breast cancer after chemotherapy with anthracycline and trastuzumab

Finally, there is insufficient evidence to show whether HF treatment should cease when cardiac function is restored to the normal range or should be continued on a lifelong basis. In this case, there should be discussion among the scientific team with contributions from physicians of different specialties who will jointly design the treatment strategy.

Treatment of patients with symptomatic cardiac dysfunction

Typically, symptomatic HF due to cancer treatment resists traditional HF treatment and is associated with a poor prognosis. Felker et al. [63] found that survival was lower than 45% after 5 years of follow-up in patients with cardiomyopathy due to doxorubicin therapy. Recent data, however, show an improvement in the survival of these HF patients [64], probably because of their more careful and thorough management in accordance with guidelines issued in Europe and in America [4, 5].

If patients exhibit symptomatic HF, they should be treated based on the standard medication: ACE inhibitors or angiotensin blockers, beta-blockers, aldosterone receptor antagonists, diuretics and digoxin, according to the case [59]. Biventricular pacing using a resynchronization device also has a place in these patients and can lead to an improvement in their symptoms [65], especially in those whose cardiotoxicity is due to the use of anthracyclines [66]. If patients develop end-stage HF, it will be necessary to assess their overall condition and life expectancy in order to decide whether a heart transplant or LV assist device could be an option [55, 59].

Long-term follow-up and treatment of patients who have survived cancer treatment

In recent years, the total number of surviving cancer patients has continued to increase and the percentage of those who

exhibit cardiotoxicity has increased accordingly. Indeed, heart disease has been found to be the leading cause of death in patients surviving after treatment of malignant neoplastic disease during childhood [67], such as lung cancer [68] or Hodgkin's lymphoma [69]. In addition, patients who have a history of tumor treatment and have exhibited cardiac dysfunction show a higher incidence of all-cause mortality compared with patients who have survived cancer and have normal cardiac function [70].

It is very important to adopt long-term strategies with a view to improving the cardiovascular health of patients who have undergone cancer treatment at some point in their lives. Special concern must be given to childhood cancer survivors since they are at increased risk of cardiac morbidity and mortality [67, 71]. This is because in most cases, the cardiotoxicity that occurs after anthracycline chemotherapy for example may occur in the first year, but in certain cases appeared quite late, even after 10 years or more [67, 72]. Periodic monitoring of these patients with cardiac ultrasound imaging and the measurement of biomarkers such as natriuretic peptides is essential, especially for those who have experienced reversible heart dysfunction during therapy. Early discontinuation of heart failure treatment in high-risk patients is not recommended.

Conclusion

Cardiac dysfunction that occurs during or after cancer treatment is increasingly the subject of targeted study and interdisciplinary interest. Many questions remain unanswered: how can we predict the development of cardiotoxicity, which is the best precautionary strategy, how should we monitor high-risk patients, what are the best treatment strategies, and how long should HF treatment be continued in patients with asymptomatic myocardial dysfunction? There is a significant need for collaboration between oncologists and cardiologists to address these issues in the future, always aiming at a holistic approach to the patient with cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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