

Heart Failure with Preserved Ejection Fraction and Cancer

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality. After hospitalization for heart failure, the 5-year survival of HFpEF is 35%, which is worse than many forms of cancer. HFpEF and cancer share common risk factors. The use of chemotherapy medications such as anthracyclines is associated with increased aortic stiffness and diastolic dysfunction, suggesting that anthracycline therapy may increase the risk of HFpEF, given that worsening of diastolic function, which can be associated with the occurrence of HFpEF, is an early sign of cardiotoxicity. Radiotherapy, widely used in the treatment of breast cancer, leads to an increased risk of developing heart disease since radiation induces coronary microvascular endothelial damage and inflammation, leading to microvascular rarefaction, myocardial inflammation, oxidative stress, and fibrosis, which favor the development of HFpEF. Early diagnosis of cardiotoxicity is an important issue in the care of patients with cancer, and biomarkers have been extensively studied in predicting systolic dysfunction and heart failure with reduced ejection fraction, as well as in the development of HFpEF. HFpEF and cancer have an elevated prevalence, and they share age group, risk factors, and the pathophysiological phenomenon, in which inflammation plays a preponderant role. Biomarkers, especially natriuretic peptides, and ultrasound imaging are fundamental tools in the diagnostic detection and follow-up of these patients.

Introduction

Most elderly patients who develop heart failure (HF) have heart failure with preserved left ventricular ejection fraction (HFpEF). Patients with HFpEF have severe symptoms of exercise intolerance, poor quality of life, frequent hospitalizations, and increased mortality.¹ HFpEF is associated with high morbidity and mortality. After hospitalization for HF, the 5-year survival of HFpEF is 35%, which is worse than many forms of cancer.²

Keywords

Heart Failure with Preserved Ejection Fraction; Cancer; Cardiotoxicity; Chemotherapy; Radiotherapy

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Cancer became the second leading cause of death in Brazil in 2006, and it is expected to surpass cardiovascular diseases (CVD) in 2025.³ The progressive increase in the incidence of cancer in developed countries has been attributed to population growth and aging, sedentary lifestyle, and dietary pattern. HFpEF and cancer share common risk factors (Figure 1),⁴ such as obesity, sedentary lifestyle, hypertension, smoking, diabetes mellitus, older age group, and dietary pattern. Cancer treatment with chemotherapy has increased survival, but it has also increased the risk of cardiotoxicity, the incidence of ventricular systolic dysfunction, and even irreversible cardiomyopathy, which can range from 3% to 26%.⁵

In cardio-oncology, research and clinical monitoring of cardiotoxicity have mainly focused on asymptomatic reductions in left ventricular ejection fraction (LVEF), which we call cancer therapy-related cardiac dysfunction, or heart failure with reduced ejection fraction (HFrEF). However, it is increasingly recognized that different cancer therapies can have adverse cardiovascular (myocardial, vascular, and metabolic) effects that predispose patients to develop HFpEF. Moreover, many patients with cancer may be at a risk of HFpEF due to the presence of different cardiovascular risk factors related to the presence of comorbidities or cancer-related cardiometabolic effects. HFpEF has not been among frequently collected data in clinical trials involving patients with cancer; therefore, the exact incidence and relative risk compared to controls of patients without cancer, as well as between different cancer treatments, remain unknown. Although future research is needed to understand the incidence of HFpEF in cancer survivors, healthcare professionals should now be aware that many cancer therapies can increase the risk of both HFrEF and HFpEF.⁶

Classification

De Boer et al.⁷ proposed a 5-tier classification system to better characterize the intersection between cardiology and oncology (Figure 2). Types I and II of the classification system address how cancer and cancer therapies affect the cardiovascular system, while types III and IV address how CVD, monitoring strategies, and therapies can contribute to unmasking cancer or promote a favorable environment for tumor development. Type V addresses systemic and genetic conditions that can lead to both CVD and cancer.

Cardio-oncology syndrome type I – Effect of the presence of cancer on the cardiovascular system

Patients with cancer are at greater risk of developing venous and arterial thromboembolic events, and the risk of arterial thromboembolism varies according to the type of cancer.⁸ Particularly lung, gastric, and pancreatic cancer have been shown to have higher risks.⁷

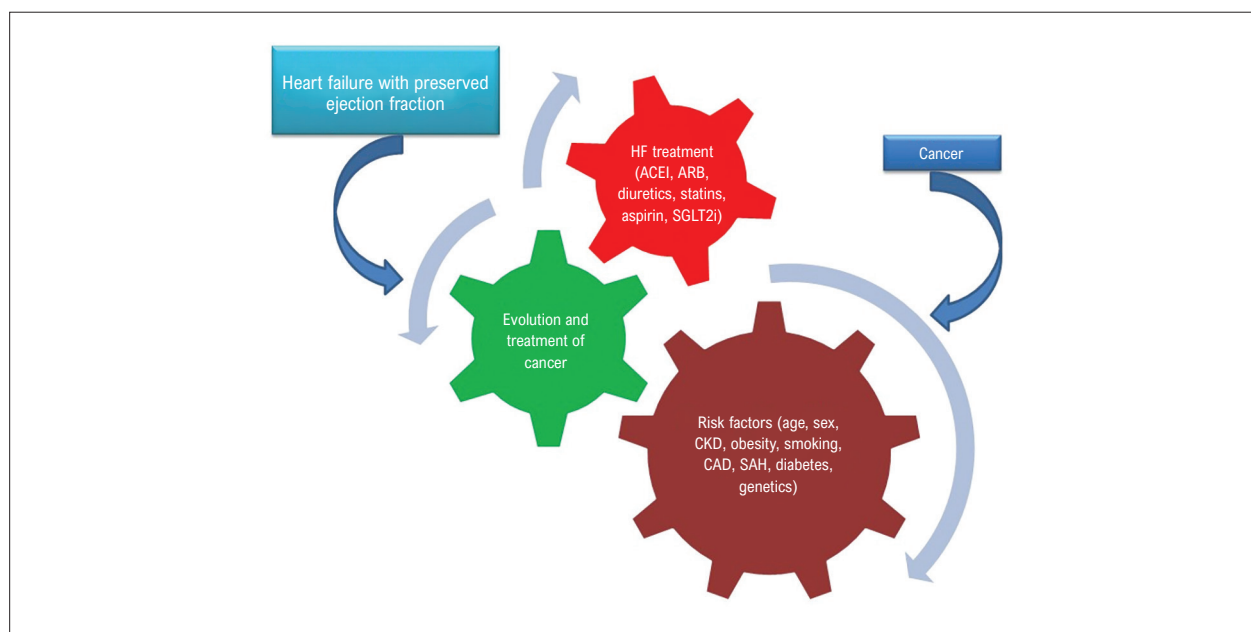


Figure 1 – Interaction between heart failure and cancer involving risk factors, heart failure treatment, and cancer treatment. Adapted from Wouter C. Meijers and Rudolf A. de Boer, reference 4. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease; CKD: chronic kidney disease; HF: heart failure; SAH: systemic arterial hypertension; SGLT2i: sodium-glucose cotransporter-2 inhibitor.

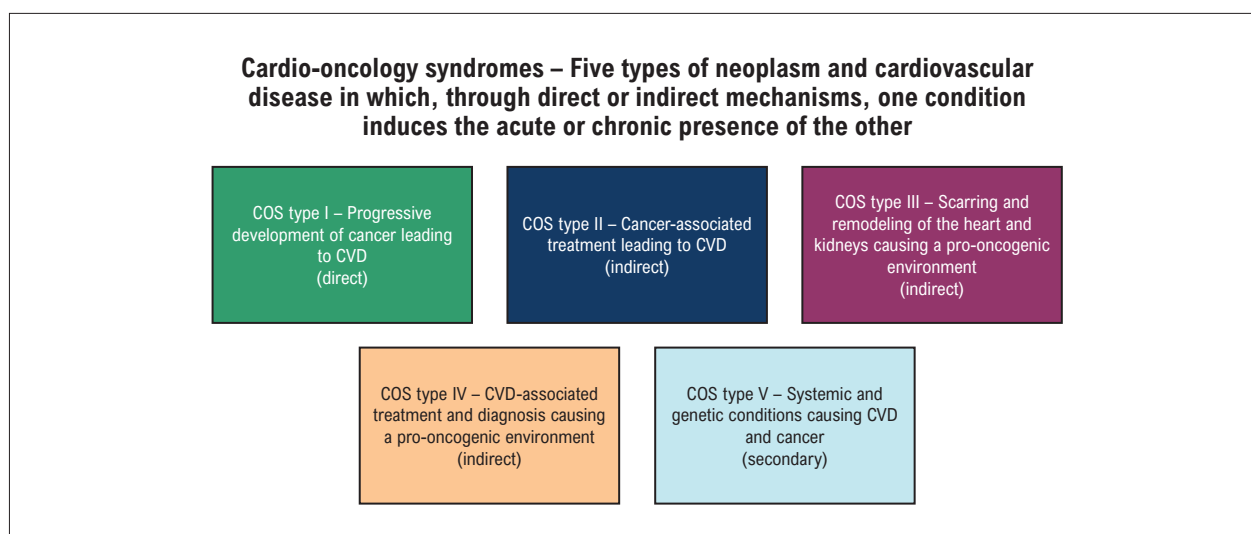


Figure 2 – Cardio-oncological syndromes: The five types of cardio-oncological syndromes are classified as direct, indirect, or secondary. Adapted from de Boer RA reference 7. CVD: cardiovascular disease; COS: cardio-oncological syndrome.

Cachexia is a state of involuntary weight loss. It is commonly seen in patients with cancer, and it has an impact on the heart. Cancer-associated cachexia is characterized by the secretion of inflammatory mediators and hormonal factors from tumors and their microenvironment. Eating disorders have multiple consequences, such as potentially fatal cardiovascular complications characterized by hemodynamic and structural changes, cardiomyopathy, and premature death.⁹

Cardio-oncology syndrome type II – Cancer treatments cause acute or chronic cardiovascular disease

Modern cancer therapies can lead to structural and functional cardiovascular dysfunction, and cardiotoxicity is one of the most worrying side effects of chemotherapy.¹⁰

Myocardial dysfunction and HF are important consequences of several classes of commonly used chemotherapy agents, most notably anthracyclines and human epidermal growth

factor receptor 2 antagonists.¹¹ Although both agents can cause reversible myocardial dysfunction, irreversible myocyte damage is classically reported with anthracyclines and can lead to HF years after drug administration.⁷

Radiotherapy can cause damage to the epicardial arteries and microcirculation both in the short and long term, which can cause regurgitation related to valve retraction and stenosis and induce fibrotic changes in the parietal pericardium.¹¹

Cardio-oncology syndrome type III – Cardiovascular disease promotes a pro-oncogenic environment

Epidemiological data suggest an increased risk of cancer in patients with prevalent CVD compared to individuals without CVD. In a Danish study, all age groups demonstrated higher rates of cancer incidence 1 year after the diagnosis of myocardial infarction.¹² The association of CVD with an increased risk of cancer is further supported by a long-term prospective study that evaluated the clinical characteristics and the prevalence of malignancy in patients with acute coronary syndrome during a 17-year follow-up. The incidence rate was 17.8 cases per 1000 person-years in patients with acute coronary syndrome, 3 times higher than that observed in the general population. Patients who developed cancer after the diagnosis of acute coronary syndrome showed worse prognosis.¹³

Atrial fibrillation may also be associated with cancer. The RE-LY Study revealed that malignant tumors were the main cause of non-cardiovascular death in patients with atrial fibrillation.^{14,15} Furthermore, the Women's Health Study (WHS) showed that 10% of patients who had new-onset atrial fibrillation developed subsequent cancer.¹⁵ However, most evidence derives from retrospective analyses with primarily non-causal relationships. Furthermore, available data tend to show positive associations, due to publication bias.⁷

Cardio-oncology syndrome type IV – Association between CVD treatments and diagnostic methods and cancer

Studies have suggested the possibility of an association of cumulative radiation for cardiovascular diagnosis with subsequent cancer.^{16,17} The prevalence of cancer attributed to radiation exposure due to cardiovascular diagnosis has been extensively investigated, and existing data suggest that children and adolescents are more likely to develop radiation-associated malignancies than older individuals.^{16,17} Consequently, there has been a discussion about the ideal type of imaging modalities that should be used for specific indications in younger patients with a focus on reducing imaging with exposure to radiation.⁷

Cardio-oncology syndrome type V – Systemic and genetic conditions

Research over the decades has established risk factors, such as smoking, alcoholism, diabetes, obesity, and sedentary lifestyle, associated with the development of cancer and CVD. These factors were previously interpreted as separate entities associated with cancer or CVD. More recently, however, the overlapping model has surfaced in relation to risk factors common to both CVD and cancer.^{7,18,19}

While the mechanisms involved in the development of CVD in patients with cancer have largely been elucidated, the pathways that lead to the increased prevalence of malignancies in patients with CVD have not yet been fully explored.²⁰ There are common molecular pathways central to CVD and cancer, such as inflammation, genetic predisposition, clonal hematopoiesis, that is, inflammation and clonal hematopoiesis of undetermined potential.⁷

Chemotherapy and the risk of HFpEF

The use of anthracyclines can cause left ventricular systolic dysfunction (stage B HF) that can progress to HFrEF. Anthracyclines are associated with increased aortic stiffness²¹ and diastolic dysfunction,²² suggesting that anthracycline therapy may increase the risk of HFpEF, given that the worsening of diastolic function, which can be associated with the occurrence of HFpEF, is an early sign of cardiotoxicity.^{23,24}

In several cohort studies, significant changes in echocardiographic measurements of diastolic function have been observed with modern breast cancer therapy, particularly in patients treated with anthracycline therapy.^{25,26} Nearly half of patients treated with anthracyclines develop HF. Although the anthracyclines epirubicin and doxorubicin are effective antineoplastic drugs used in the treatment of numerous malignancies, their use is restricted due to serious side effects, the main one being chronic cardiotoxicity followed by HF.²⁷ The risk of cardiotoxicity is dose-related, and it is promoted by several risk factors.²⁸ The pathophysiology is complex, but a central mechanism is oxidative stress.²⁹ Cardiotoxic damage appears in cell membranes, mitochondria, and DNA, affecting both energy metabolism and ion handling.^{30,31}

One study showed that the development of diastolic dysfunction was observed in more than 50% of patients treated with anthracycline chemotherapy in the first year of treatment.²⁵ Using data from SEER-Medicare, breast cancer survivors aged 66 years and older had increased risk of HF compared to controls without cancer.³² Although the study provided results, use of a statement-based dataset is not able to distinguish between HFpEF and HFrEF, and older women are at a greater risk for both. Further studies are needed to better understand the clinical impact of these changes in vascular and diastolic function; however, we should be aware that cardiotoxicity following anthracycline therapy may present as HFpEF.⁶

Radiotherapy and the risk of HFpEF

Breast-conserving surgery combined with radiotherapy has emerged as the standard approach for treating localized breast cancer, and, in more advanced disease, radiotherapy improves local control and survival.^{33,34} The high doses of chest radiation used in treatment of thoracic tumors and older radiotherapy techniques for breast cancer lead to an increased risk of developing heart disease.^{35,36} With the advance in radiotherapy planning, including the use of radiotherapy planning assisted by computed tomography, we can achieve a substantial reduction in cardiac radiation exposure during contemporary breast cancer radiotherapy. Nevertheless, even low levels of

cardiac radiation during breast cancer radiotherapy increase the risk of coronary events.³⁷ Cardiomyocytes are largely resistant to radiation. However, radiation induces coronary microvascular endothelial damage and inflammation leading to microvascular rarefaction, myocardial inflammation, oxidative stress, and fibrosis, which favor the development of HFpEF.^{38,39}

The large loss of cardiomyocytes due to myocardial infarction or other factors is the primary etiological insult in HFrEF. On the other hand, the development of microvascular endothelial inflammation due to the presence of comorbidities with similar subsequent myocardial effects may contribute to myocardial dysfunction; it is thus considered a key factor in the pathophysiology of HFpEF.⁴⁰ Exposure to cardiac radiation, which functions as a comorbidity, during radiotherapy for the treatment of breast cancer may increase the risk of HF, in particular HFpEF.^{40,41}

Studies have documented new cardiac perfusion defects (without transient myocardial infarction) after breast cancer radiotherapy consistent with microvascular rarefaction.⁴² Coronary microvascular endothelial inflammation caused by comorbidity is believed to play a key role in the pathophysiology of HFpEF. Microvascular endothelial inflammation leads to microvascular dysfunction and rarefaction with reduced coronary flow reserve and inflammation and to myocardial fibrosis, in addition to oxidative stress, which can impair nitric oxide–cyclic guanosine monophosphate signaling and potentiate cardiomyocyte hypertrophy and diastolic myofibril stiffness.⁴⁰

A study³⁵ has shown that, in elderly women with breast cancer treated with radiotherapy, the chances of HF after radiotherapy increased with a higher mean dose of cardiac radiation. The predominant form of HF was HFpEF or HF with “intermediate” ejection fraction (40% to 49%), and the odds of any HF and HFpEF increased with mean cardiac radiation dose, even after adjustment for other known risk factors and cancer stage. The mean time since the onset of HF after radiotherapy was 5.8 years. A minority of women developed ischemic events between radiotherapy and the diagnosis of HF, suggesting that myocardial infarction due to epicardial coronary disease was not the predominant mediator of incident HF. The effect of mean cardiac radiation dose on the incidence of HF was still apparent in sensitivity analyses addressing the potential for surveillance bias associated with more advanced cancer stage.³⁵

In women over 40 years of age, the lifetime risks of breast cancer (12%) and HF (20%) are significant.⁴³ Adjuvant radiotherapy reduces breast cancer recurrence and mortality in some subgroups of women; however, the excellent survival after treatment for breast cancer requires attention regarding survival issues, including cardiovascular complications of radiotherapy,⁴⁴ and the risk of cardiotoxicity with high-dose thoracic radiotherapy has been well documented.^{38,39}

Therefore, in older women undergoing radiotherapy for breast cancer, the relative risk of HFpEF increases proportionally to radiation, begins a few years after radiotherapy, and is not mediated by coronary events alone. These data suggest that radiation dose and risk factors for

HF should be considered in decisions about breast cancer radiotherapy, and they underscore the importance of techniques to reduce cardiac radiation dose. Furthermore, there is additional support for the importance of coronary microvascular impairment in the pathophysiology of HFpEF.³⁵

The role of inflammation in cancer development in patients with heart failure

Cancer and CVD are currently the main causes of death worldwide, which may suggest that these diseases have pathogenetic mechanisms that are common to both situations. Studies have demonstrated that patients with cancer develop heart disease not only as a consequence of chemotherapy-induced cardiotoxicity, but also because tumor cells release factors that affect various distant organs, including the heart.⁴⁵ Cancer-derived pro-inflammatory molecules cause cardiomyocyte atrophy and tissue remodeling, which can degenerate into cachexia and HF.⁴⁶

The causal relationship between HF and cancer has been an important issue of current research, showing controversial results in epidemiological and clinical studies. An elevated risk of cancer incidence has been shown in some studies,⁴⁷ reinforcing the hypothesis that HF may predispose to cancer and that a low-grade inflammatory mechanism may mediate both conditions.^{46–48}

Extensive evidence has shown that HF is associated with a chronic inflammatory state and activation of the immune response. Inflammation arises locally as a consequence of lesion in HFrEF and systemically as a consequence of various comorbidities in HFpEF.⁴⁶

In HFpEF, inflammation drives the development of HF through a complex sequence of events.⁴⁰ Comorbidities induce a systemic pro-inflammatory state. Myocardial disease then begins with coronary endothelial dysfunction and expression of vascular cell adhesion molecules and selectins, which causes leukocyte infiltration. Endothelial cells begin to produce reactive oxygen species which, in turn, trigger a cascade of events with downregulation of nitric oxide production, decreased levels of nitric oxide-stimulated cyclic guanosine monophosphate, and decreased protein kinase G activity.⁴⁶

This sequence of events culminates in protein kinase G-dependent hypophosphorylation of titin, and titin is responsible for cardiomyocyte stiffness, depending on its state of phosphorylation. Stiff cardiomyocytes, in association with interstitial fibrosis and capillary rarefaction, contribute to the loss of diastolic relaxation that is a characteristic of HFpEF.⁴⁹ Thus, oxidative stress and inflammation can be considered the consequence or the cause of HF, generating a chronic systemic condition with adverse clinical outcomes. This low-grade, chronic systemic inflammation, however, is often clinically silent, and its consequences can also increase the risk of different types of cancer. According to these observations, genetic polymorphisms in genes encoding anti-inflammatory interleukin (IL)-1 β , IL-6, IL-8, and IL-10 have been shown to predispose individuals with HFpEF to cancer.⁵⁰

Several epidemiological and clinical studies have reported that patients with HF are at an increased risk of developing cancer, and chronic low-grade systemic inflammation has been proposed as the main pathophysiological process linking HF and carcinogenesis.⁴⁶ There are still unanswered questions that cardiologists and oncologists need to address by means of cooperative actions. The main one is whether HF variants, including most cases of HFpEF, are prone to developing cancer.

Risk factors associated with HFpEF and breast cancer

Advances in cancer treatment have led to increased survival, which is offset by increased risk of long-term comorbidities, including HF.⁵¹ Most studies performed in cardio-oncology have focused predominantly on HFrEF, mainly due to well recognized associations between cancer treatment and reduced LVEF.^{52,53} The development of HFpEF in breast cancer survivors is an understudied topic, even though HFpEF is more common than HFrEF in older women, and breast cancer and HFpEF share multiple risk factors, for example, obesity and hypertension.⁵⁴

It is currently unclear to what extent differences in risk factors for HF subtypes hold true for breast cancer survivors for whom cancer treatment may alter the causal pathways of traditional risk factors.³⁵ For example, elevated body mass index and increased central adiposity are associated with a decline in LVEF in cancer survivors,⁵⁵ even though there is no relationship between obesity and LVEF in the general population.⁵⁶ There are few data on the incidence of HFpEF and the risk factors associated with HFpEF in breast cancer survivors.⁵³

A study⁵³ evaluated the incidence of HFpEF and HFrEF in menopausal breast cancer survivors and associations with risk factors. The results demonstrated a relatively higher rate of hospitalizations for HFpEF compared to HFrEF. The study also demonstrated that anthropometric factors, previous history of cardiometabolic disorders, and smoking were associated with an elevated risk of HFpEF; in general, the same characteristics were suggestive of an elevated risk of HFrEF, indicating that breast cancer survivors are affected by conventional risk factors for HF subtypes.⁵³

In the literature to date, little attention has been paid to HFpEF in breast cancer survivors,⁵⁴ potentially due to the fact that HF diagnosis is largely based on LVEF measurements that can fail to diagnose cases of HFpEF, and associated symptoms of HFpEF, such as lack of air, can be attributed to side effects of chemotherapy/radiotherapy or deconditioning rather than HFpEF. In most clinical trials on breast cancer and cardioprotection, the focus of monitoring during treatment has been based on LVEF, rather than a more holistic view of cardiac function that incorporates diastolic parameters in addition to systolic function.⁵⁷

In the same manner that has been observed in population studies,⁵⁴ the study observed a higher incidence of HFpEF in this elderly population of breast cancer survivors. Despite an increased risk of HFpEF in older women, the HFpEF phenotype remains an understudied component after breast cancer. However, HFpEF contributes to an equal proportion of hospitalizations as HFrEF and an equally increased risk

of long-term mortality after diagnosis.⁵⁸ Risk factors for HF were very similar to that of the general population, with the exception of prior myocardial infarction for HFpEF. Notably, both waist circumference and smoking represent potentially modifiable factors.⁵³

Biomarkers in the prediction and diagnosis of HFpEF in patients with cancer

Therapies used to treat cancer, particularly anthracyclines and trastuzumab, can damage the heart. Most studies have focused on asymptomatic left ventricular dysfunction caused by these agents and HFrEF. However, although little recognized, these treatments can cause cardiac, vascular, and metabolic damage that can evolve with HFpEF. This can occur as an initial manifestation and later evolve to HFrEF or even be the only manifestation, during treatment or months after treatment, in cancer survivors.⁵⁹ Furthermore, due to the presence of comorbidities and the direct effect of the cancer itself, these patients have an increased baseline risk of developing HFpEF (Figure 3).⁵⁹

Biomarkers are substances secreted into the circulation or urine that provide us with early information about diagnosis and prognosis in a given condition. In this section, we will address the main biomarkers involved in the prediction of HFpEF and its prognosis, including the classic cardiac biomarkers troponins and natriuretic peptides, as well as systemic, non-cardiac biomarkers related to both cancer and the cardiovascular system. These biomarkers have been extensively studied in the prediction of systolic dysfunction and HFrEF, but they are also related to the development of HFpEF.

Cardiac biomarkers in cancer

Cardiac biomarkers can be used in different ways in the management of cancer patients: 1) before starting cancer treatment, as predictors of cardiac complications during treatment; 2) in monitoring during cancer treatment to detect early cardiotoxicity; and 3) in cancer survivors to monitor long-term cardiotoxicity.

Cardiac troponins

Cardiac troponins T and I are the gold-standard markers of acute myocardial infarction. However, cardiac troponins, especially high-sensitivity cardiac troponins, may be elevated in situations unrelated to forms of myocardial damage other than ischemia, for example, in myocardial injury. They are the main marker used to detect cardiotoxicity in cardio-oncology.⁵⁹⁻⁶¹ They can detect early subclinical myocardial alterations, which can guide the prevention of irreversible systolic dysfunction.^{60,61} Furthermore, they can predict the risk of cardiotoxicity before beginning cancer treatment. The presence of cardiovascular comorbidities, systemic alterations such as inflammation and oxidative stress, and the effects of cancer itself on the heart can cause elevations in cardiac biomarkers, indicating a greater risk of toxicity.⁶² In a study with 452 patients with breast cancer, naive to treatment, the basal dosage of troponins T and I was a predictor of increased risk of developing myocardial dysfunction with trastuzumab treatment.⁶³ However, there are no specific studies for the prediction of HFpEF.

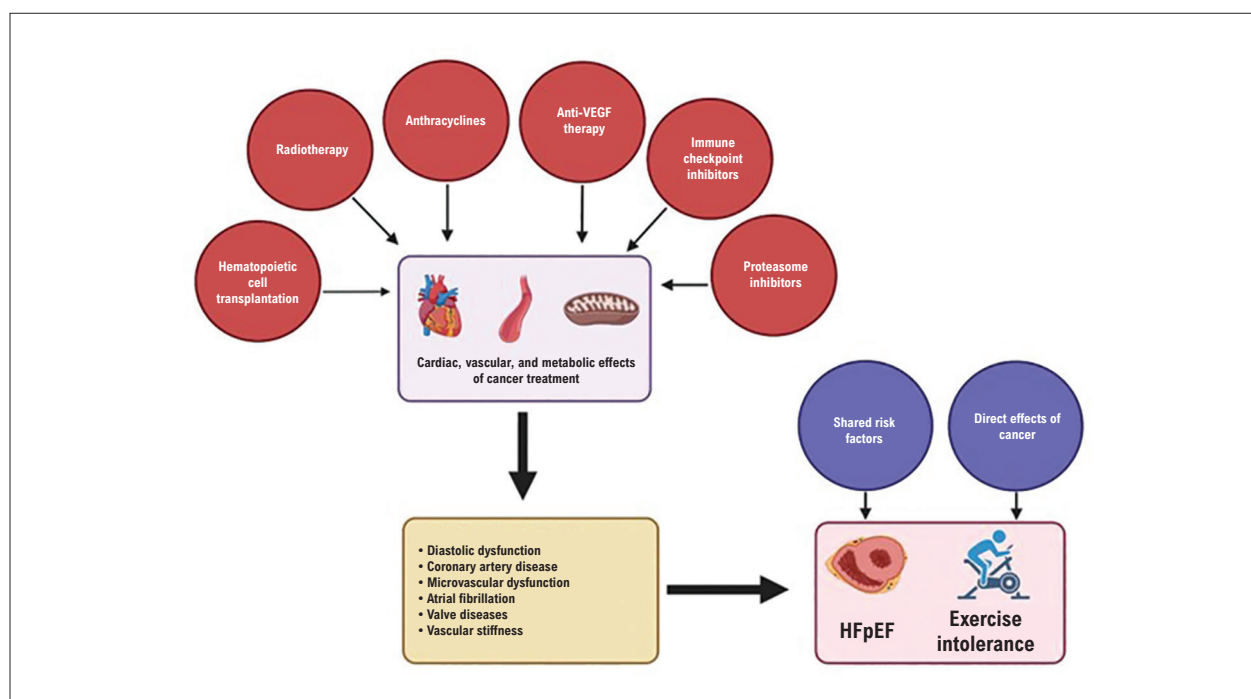


Figure 3 – Mechanisms involved in the development of HFpEF in patients with cancer. HFpEF can be caused by chemotherapy or radiotherapy leading to diastolic changes, which may be associated with coronary artery disease and atrial fibrillation. Additionally, the patient may have HFpEF even before starting treatment, due to comorbidities common to cancer and HFpEF, as well as due to the direct action of the cancer itself on the myocardium. HFpEF: heart failure with preserved ejection fraction; VEGF: vascular endothelial growth factor.

Natriuretic peptides

Natriuretic peptides may be increased in patients with cancer undergoing treatment.^{60,61,64} In a study of 40 women with cancer (37 with breast cancer, 2 with lymphoma and 1 with sarcoma) treated with doxorubicin, BNP was altered early in the patients who developed left ventricular systolic dysfunction, none of whom developed clinical HF.⁶⁴ It is interesting to note that the left ventricular diastolic function parameters on the echocardiogram also changed early, but BNP was the only marker that correlated with the cumulative dose of doxorubicin. Although natriuretic peptide levels may increase with cancer treatment, it has been reported that cancer cells themselves may secrete BNP.⁶⁵ Baseline levels of natriuretic peptides, prior to initiation of cancer treatment, are associated with cancer progression and severity. In a study by Pavo et al., with 555 patients with a primary diagnosis of cancer and without previous treatment, NT-ProBNP and other markers (troponins, C-reactive protein, copeptin, IL-6, among others) were elevated according to tumor staging and were predictors of mortality.⁶⁶

Oncological biomarkers and inflammatory markers

Several biomarkers associated with cancer are used as diagnostic and prognostic markers in this disease. Many of them are associated with cardiovascular severity, for example, the New York Heart Association functional class, and cardiovascular mortality outcomes.⁶⁰ They also correlate with natriuretic peptide levels. Among oncological markers

and inflammatory markers, we can mention CA125, CEA, galectin-3, GDF-15, PIGF, CHIP, IL-1, IL-6, IL-8, C-reactive protein, TNF- α , ST2, and myeloperoxidase.⁶⁰

Figure 4 displays the bidirectional relationship between cancer and the heart, with cardiac biomarkers predicting cardiac complications from cancer, and inflammatory and cancer-related biomarkers predicting cancer itself and cardiac complications.

Perspectives for biomarkers in HFpEF

Most studies to date have evaluated the role of biomarkers in predicting left ventricular systolic dysfunction or mortality outcomes. There are no specific studies on the prediction of HFpEF. However, ongoing studies may eventually identify useful markers in this bidirectional relationship between CVD and cancer, including baseline HFpEF or HFpEF acquired after cancer treatment.

A recent study identified the biomarker of collagen type XXVIII that may play a role in the future. Collagen XXVIII was recently described; it is located at the interface between the basement membrane and the interstitial matrix, and it may be involved in tissue repair.⁶⁷ Reese-Petersen et al. developed an ELISA technique that is able to detect the C-terminal fragment of type XXVIII collagen, known as PRO-C28. They observed that this biomarker is elevated in HFpEF and in patients with various types of cancer compared to healthy individuals.⁶⁷ This elevation was more significant in lung cancer, where the area under

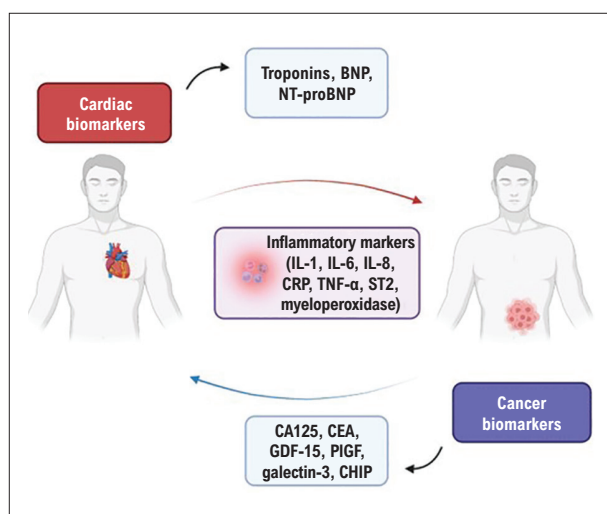


Figure 4 – Bidirectional relationship between the heart and cancer. Cardiac biomarkers assess the impact of cancer and cancer treatments on the heart, and cancer and inflammatory biomarkers are also predictors of cardiovascular severity in cancer. BNP: brain-type natriuretic peptide; CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CHIP: clonal hematopoiesis of undetermined potential; CRP: C-reactive protein; GDF-15: growth differentiation factor-15; IL: interleukin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PIGF: placental growth factor; ST2: suppression of tumorigenicity 2; TNF- α , tumor necrosis factor alpha.

the curve was 98% for differentiating individuals with lung cancer from healthy individuals. Furthermore, PRO-C28 correlated with NT-proBNP levels. Future studies should establish the usefulness of this new marker in predicting HFpEF in patients with cancer, as well as its prognostic role.

Role of biomarkers in the diagnosis of HFpEF in patients with cancer

The diagnosis of HFpEF in patients with cancer is made in the same way as in patients without cancer, although there is no validation in specific studies in this population. In general, HFpEF is characterized in patients with signs and symptoms of HF, cardiac structural alterations in the presence of LVEF $\geq$ 50%, and natriuretic peptide elevation.⁶⁸ Two risk scores can be used in the diagnosis of HFpEF, the H2FPEF score and HFA-PEFF score (of the European Society of Cardiology). The HFA-PEFF score uses natriuretic peptides in its flowchart.⁶⁸ The detailed steps for the diagnosis of HFpEF are beyond the scope of this review, but they can be found in the Brazilian Heart Failure Guideline.⁶⁸

Immune checkpoint inhibitors and HFpEF

Immune checkpoint inhibitors (ICIs) represent an innovative treatment for a large number of cancer types. ICIs have been prescribed for primary tumors and metastases, as well as adjuvant and neoadjuvant therapy. ICIs become toxic because they lead to autoimmune processes that affect all organs. Regarding the heart, it has

been noted that ICIs lead to acute HF with preserved or reduced LVEF and even to death by several mechanisms, such as myocarditis, pericarditis, arrhythmia, and takotsubo cardiomyopathy.⁶⁹

Therefore, there is a need for improved methods for detection and risk stratification of heart diseases associated with the use of ICIs, including myocarditis. The study by Mahmood et al.⁷⁰ in patients using ICIs showed that, among patients who developed myocarditis, ECG was altered in 89%; NT-ProBNP was elevated in 66%, and only 49% of patients had LVEF below 50%.⁷⁰

The study showed that, among patients with myocarditis due to the use of ICIs, global longitudinal strain, which is a sensitive marker of cardiotoxicity among patients receiving standard chemotherapy, was lower among patients with preserved and reduced LVEF. In the follow-up of these patients, decreased global longitudinal strain was strongly associated with major adverse cardiac events in myocarditis due to ICI use and, more importantly, among those with preserved LVEF.⁷⁰ Thus, to identify myocardial involvement and establish the risk of HFpEF, global longitudinal strain is useful in monitoring patients with cancer receiving ICI therapy.

Imaging in HFpEF associated with cancer

The detection of HFpEF associated with cancer is related to cardio-oncological syndromes types I, II and V according to de Boer RA et al.⁷ (Figure 2), as previously mentioned in this article. For imaging diagnosis of this HF phenotype, comprehensive transthoracic echocardiogram is the most widely used tool, providing information on 3 basic phenomena that must be detected:

- 1 – Presence of normal or very slightly reduced global systolic function;
- 2 – Atrioventricular remodeling, including left atrial and right chamber dilation, but not including left ventricular dilation;
- 3 – Diastolic dysfunction causing pulmonary circulation overload.

In this context, according to the most recent European Society of Cardiology Guideline on Cardio-oncology,⁷¹ the respective suggested ultrasound indices are as follows:

- 1 – LVEF, estimated by the 3- or 2-dimensional method
- 2 – Dimensions, chamber volumes, and cardiac mass indexed by body surface area;
- 3 – E and A velocities of diastolic inflow in the left ventricle, e' and a' diastolic velocities of the myocardium, the E/e' ratio of estimated diastolic pressure in the left ventricle, the rate of myocardial deformation (global longitudinal strain), and estimated pulmonary pressure, translating the repercussion of left chamber pressures on pulmonary circulation (Figure 5).

Other parameters related to right ventricular function, heart valves, and the pericardium have also been suggested for pre-therapy baseline examination of the specific neoplasm and follow-up.

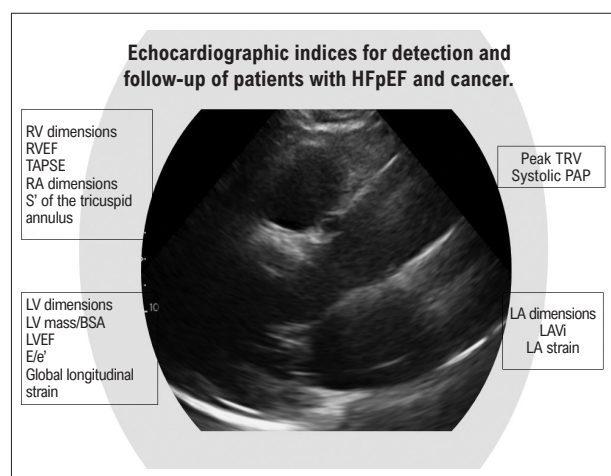


Figure 5 – Echocardiographic indices for detection and follow-up of patients with HFpEF and cancer. BSA: body surface area; E/e': ratio of early diastolic mitral inflow velocity to early diastolic velocity of the mitral annulus; HFpEF: heart failure with preserved ejection fraction; LA: left atrium; LAVi: left atrial volume indexed by body surface area; LV: left ventricle; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure; RA: right atrium; RV: right ventricle; RVEF: right ventricular ejection fraction; S': systolic velocity obtained by Doppler tissue imaging; TAPSE: tricuspid annular plane systolic excursion; TVR: tricuspid regurgitation velocity.

In the pre-cancer therapy evaluation, the indices of LVEF⁷² and global longitudinal strain are used as the main baseline markers, as well as for monitoring cardiotoxicity during chemotherapy. Especially in patients who already present diagnosis of HFpEF, global longitudinal strain is a more sensitive summary marker than ejection fraction. In patients from a case series of 2234 patients in pre-therapy with anthracyclines, global longitudinal strain and left ventricular end-diastolic volume indexed to body surface area volume (LVEDVI) stood out as independent predictors of major cardiac events. When compared, the means for global longitudinal strain of patients who presented the event were lower ($-17.8\% \pm 2.5\%$ versus $-16\% \pm 2.5\%$; $p = 0.0015$), and the means for LVEDVI were higher in patients who developed events ($53 \pm 12 \text{ ml/m}^3$ versus $61 \pm 5 \text{ ml/m}^3$; $p = 0.02$). It is noteworthy that, in this study, LVEF was not statistically significant as a risk predictor in this type of population with preserved systolic function ($54\% \pm 3\%$ versus $53\% \pm 3\%$; $p = 0.27$).⁷³ Therefore, from the point of view of risk prevention, determination of initial global longitudinal strain using the speckle tracking technique is well supported and recommended, especially in patients at moderate or high risk of developing toxicity.⁷⁴

Diastolic dysfunction on pre-cancer treatment examination may be associated with an increased risk of systolic dysfunction. Upshaw et al. detected, in a population of participants undergoing treatment for breast cancer, that diastolic dysfunction was associated with a subsequent decrease in LVEF (2.1%; 95% confidence interval: 3.1 to 1.2; $p < 0.001$) and worsening in longitudinal strain (0.6%; 95% confidence interval: 0.1 to 1.1; $p = 0.013$) over time. Changes in E/e' were not statistically significant.²²

From a contemporary point of view, the most recent consensus on cardio-oncology published this year lists the following as class I recommendations: a) echocardiography as a first-line modality for assessing function in cancer patients; b) 3-dimensional echocardiogram as the preferred echocardiographic modality for measurements; c) global longitudinal strain, if available, in all patients with cancer; d) comprehensive echocardiography in all patients with cancer and high risk or very high risk of cardiovascular toxicity before initiating cancer treatment.

Other imaging tests may also be useful in HFpEF and cancer. Chest computed tomography or cardiac magnetic resonance imaging can elucidate images of patients with difficult acoustic windows and identify subclinical ischemic disease and intracardiac masses. Functional exams that provoke ischemia are also important in patients with HFpEF and elevated pre-test probability of significant atherosclerotic disease, especially in patients in need of treatment with drugs with vascular toxicity, such as fluoropyrimidines, vascular endothelial growth factor inhibitors, tyrosine-kinase inhibitors, among others.⁷⁵

Conclusion

HFpEF and cancer have an elevated prevalence, with a growing trend. They share age group, risk factors, and the pathophysiological phenomenon, in which inflammation plays a preponderant role. Biomarkers, especially natriuretic peptides, and ultrasound imaging are fundamental tools in diagnostic detection and follow-up. It is important to emphasize that we are following a huge evolution in treatments, both for HFpEF and for neoplastic diseases, but, in this review, we have found many gaps in knowledge involving populations where both clinical conditions overlap.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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