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RESEARCH ARTICLE

Heart failure with preserved ejection fraction in cancer patients and survivors. A scientific statement of the Heart Failure Association of the ESC and the ESC Council of Cardio-Oncology

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Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized in cancer patients and survivors, yet it remains underdiagnosed and its epidemiology largely unknown. This statement underscores the imperative need to include HFpEF in the cardiotoxicities identified during or after anticancer treatments. It also highlights the prognostic value of pre-existing HFpEF for periprocedural and cardiotoxicity risk and it discusses the challenges in the diagnosis and treatment of HFpEF in cancer patients. It also explores the aetiologic role of anticancer therapies (chemotherapy, targeted and hormonal therapies and radiotherapy) in the pathogenesis of HFpEF. Special emphasis is given on the

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importance of considering HFpEF from cancer diagnosis throughout treatment and survivorship and provides useful insights for cardiologists and oncologists in the monitoring and management of these patients. Finally, it highlights the key gaps in current knowledge that require further investigation through well-designed research trials to enhance our understanding and improve clinical outcomes.

Keywords Heart failure with preserved ejection fraction • Cancer • Cardiotoxicity • Chemotherapy • Radiotherapy

Epidemiology of heart failure with preserved ejection fraction in cancer patients and survivors

Cancer and heart failure (HF) with preserved ejection fraction (HFpEF) share common risk factors and are associated with significant morbidity and mortality.[1,2] However, HFpEF has not been consistently evaluated as an outcome in oncology clinical trials, registries, or observational studies.[3] As a result, the epidemiology of HFpEF in cancer survivors, as well as across different types of cancer and anticancer therapies, remains largely unknown. From the limited available observational data, the incidence of HFpEF may range from 6.7% to 14.6% in cancer patients and survivors, with a potential 12.6-fold increased risk of cardiovascular (CV) mortality compared to patients without HF.[4,5] The relative proportion of HFpEF compared to HF with reduced ejection fraction (HFrEF) is also unclear, but HFpEF appears to be more prevalent in certain settings, such as in breast cancer patients treated with radiotherapy (RT) (up to 64%) or during proteasome inhibitor therapy with carfilzomib.[6,7]

The exact incidence of HFpEF in cancer patients during or after treatment remains difficult to determine due to inconsistencies in diagnostic criteria[8] and the reliance on left ventricular ejection fraction (LVEF) as the primary CV metric in oncology trials. In the CARDIOTOX registry, HFpEF prevalence was reported at 1.2% during active cancer therapy,[9] but incidence is higher in other series including patients with ischaemic heart disease or inadequately controlled CV risk factors. These include preexisting or treatment-induced hypertension, central obesity, sedentary life, and smoking, which further amplify HFpEF risk.[5]

Retrospective registries suggest a higher prevalence of HFpEF compared to HFrEF among cancer survivors, particularly following chemotherapy and RT for breast and haematologic malignancies.[10] Survivors of oesophageal, lung, kidney, and ovarian cancers are also at elevated risk of developing HFpEF.[11] Among breast cancer survivors, HFpEF incidence exceeds that of HFrEF, at 6.68% versus 3.96% over a median of 7.2 years. Key risk factors include prior myocardial infarction (hazard ratio [HR] 2.83), greater waist circumference (HR 1.99), and smoking (HR 1.65), highlighting the need for targeted CV risk factors management.[5] Childhood cancer survivors treated with anthracyclines and RT also show a high prevalence of subclinical diastolic dysfunction, although specific HFpEF data in this population are lacking. Up to 30% of childhood cancer survivors with preserved LVEF display abnormalities in myocardial strain. These correlate with reduced exercise tolerance and early-onset CV risk factors.[12,13] Advanced age is a risk factor for both HFpEF and various malignancies.[14,15] Because of this epidemiological interplay in older patients, the two conditions frequently co-exist.[16]

Pre-existing heart failure with preserved ejection fraction in patients diagnosed with cancer

The diagnosis of cancer in patients with HF is not uncommon. In a retrospective population-based cohort, the relative risk of incident cancer in patients with HF, compared to individuals without HF, was higher in patients with HFpEF than HFrEF (adjusted HR 1.69, 95% confidence interval [CI] 1.57–1.81 for HFpEF and 1.32 [95% CI 1.20–1.46] for prevalent HFrEF).[17] Registry data further indicate that the age-adjusted prevalence of cancer is higher in patients with HFpEF than HFrEF (15.6% vs. 12.4%, age-adjusted $p = 0.0042$).[18] Furthermore, cancer is the most common cause of non-CV death in clinical trials of HFpEF, accounting roughly for 35–40% of non-CV deaths.[19] The presence of HF at the time of cancer diagnosis is a major risk factor for the development of cancer therapy-related cardiac dysfunction (CTRCD).[20] Patients with cancer and HF regardless of LVEF require referral for cardiology and if available, cardio-oncology consultation as well as close monitoring during and after anticancer therapy.[21]

Heart failure with preserved ejection fraction and periprocedural risk in cancer patients

Heart failure with preserved ejection fraction is associated with increased perioperative risks in cardiac[22,23] and non-cardiac surgeries[24] compared to patients without HF. Despite that, HFpEF is not included specifically in either the American Society of Anesthesiologists risk score nor in the relevant guidelines by the European Society of Cardiology (ESC) endorsed by the European Society of Anaesthesiology and Intensive Care, that generally mention HF as a risk factor.[25,26] On the other hand, there are conflicting data concerning the comparison of periprocedural risk between patients with HFpEF and HFrEF. Xu-Cai *et al.*[27] did not find differences between the two groups, while other studies disagree with greater risks attributable to HFrEF.[23,28,29]

There is a paucity of data about periprocedural risk in cancer patients with HFpEF but these patients should be considered high risk for complications after surgery, not limited to the cardiopulmonary system.[30] Decreasing periprocedural risk in cancer patients with HFpEF is challenging as there is no strong evidence and thereby, no specific guidelines on how to manage them during the perioperative period. The ESC guidelines suggest similar management for patients with pre-existing HFrEF or HFpEF.[26] The perioperative care of cancer patients with HFpEF is further complicated by the heterogeneous aetiologies, varying clinical presentations, diverse therapy responses, and clinical outcomes, corresponding to different clinical phenotypes of HFpEF.[31] Preoperatively, cardiology, and if available, cardio-oncology assessment is crucial with optimization of comorbidities control and assessment of functional capacity, that can provide important information to cardio-oncologists and anaesthesiologists.[32] Factors that should be managed meticulously during and after surgery in patients with cancer and HFpEF include fluid balance, blood pressure and heart rate, as well as arrhythmias and conduction abnormalities, anaemia, electrolyte abnormalities, pain and infection.[33] Vigilance is also essential for potential development of euglycaemic diabetic ketoacidosis, in patients with diabetes on sodium–glucose co-transporter 2 (SGLT2) inhibitors facing volume depletion, nutritional deficiencies, and significant physiological stress which lead to lipolysis and ketogenesis.[34]

Heart failure with preserved ejection fraction as a result of anticancer treatments

Left ventricular dysfunction caused by cancer treatment is referred to as CTRCD and further classified in asymptomatic or symptomatic (i.e. HF).[21,35] No distinction is made between HFrEF and HFpEF. Completing this framework, a new definition of asymptomatic and symptomatic cancer therapy-related right ventricular (RV) dysfunction has been recently proposed by the Heart Failure Association (HFA) and the ESC Council of Cardio-Oncology.[35]

Heart failure with preserved ejection fraction in cancer patients and survivors is overlooked, as monitoring in patients receiving oncological treatments has traditionally been guided by changes in LVEF. However, due to the risk of developing HFpEF in those receiving antineoplastic therapies or RT and to the increasing prevalence of HFpEF in cancer survivors, it is crucial to raise awareness of the need to avoid relying solely on LVEF as a modifying factor for treatments or overlooking the associated risks. Precise and detailed definition of CV toxicities and events, including HFpEF, is crucial not only for cancer therapy trials but also for reliable records of safety data of anticancer treatments.[36]

Heart failure with preserved ejection fraction can be induced directly or as a consequence of other toxicities such as hypertension, which is associated with a growing number of anticancer therapies. Additionally, the presence of CV risk factors such as diabetes, atrial fibrillation (AF), obesity or sedentary behaviour further increases the risk of HFpEF. AF specifically is a risk factor for and a common comorbidity associated with HFpEF[37] and it has been suggested that symptomatic patients with AF and preserved ejection fraction warrant consideration for HFpEF.[27] The presence of AF in cancer patients and survivors, may be due to several factors related to cancer and anticancer therapies,[38,39] and should therefore be treated as a red flag for the potential co-existence of HFpEF or as a risk factor for subsequent development of HFpEF.

Heart failure with preserved ejection fraction as a result of chemotherapy

Heart failure with preserved ejection fraction is an increasingly recognized but underdiagnosed condition in cancer patients, particularly among those exposed to chemotherapy, targeted therapies, and RT[5] (*Figure 1*). Apart from them, treatments such as intravenous (IV) fluids, blood product transfusions, steroids and IV antibiotics (volume/salt load) administered with a variety of anticancer therapies can precipitate HF exacerbation in patients with pre-existing HFpEF or even lead to incident HFpEF in patients with underlying appropriate CV substrate. Anticancer treatments often lead directly or indirectly to structural and functional cardiac alterations, including fibrosis, microvascular dysfunction, diastolic dysfunction, and increased arterial stiffness, which may precede overt HF.[40] Cytotoxic anthracycline chemotherapy and trastuzumab may impair diastolic function, contributing to HFpEF.[20] Furthermore, the use of alkylating agents (e.g. platinum-based drugs), antimetabolites (e.g. fluoropyrimidines), and mitotic inhibitors (e.g. taxanes) significantly increases vascular risk, particularly in patients with uncontrolled hypertension or pre-existing cardiac conditions, predisposing to HFpEF.[21,41] Platinum-based chemotherapies also increase the risk of endothelial dysfunction and renal toxicity, adding complexity to CV management in this population.[42,43] Endothelial dysfunction which has a significant pathophysiological implication in the pathogenesis of HFpEF,[44] has been shown to be prevalent in oncological patients even without overt cardiotoxicity.[45]

Anticancer treatments can also induce RV dysfunction, directly because of negative effects on the RV myocardium or via pulmonary hypertension (PH). Specifically, a sustained increase in afterload in the context of PH can result in RV dilatation and impaired contractility. Irrespective of the pathophysiology, RV dysfunction and right HF can in turn complicate concomitant HFpEF. Several studies have shown that RV dysfunction is prevalent in HFpEF patients and is associated with worse clinical outcomes.[46–48] Cancer treatment-induced PH can be classified as group 1 or pulmonary arterial hypertension (PAH), as group 2 when associated with left heart disease, or group 3 related to restrictive lung disease induced by antineoplastic treatments.[49,50] Group 1 PH (PAH) is most notably associated with tyrosine kinase inhibitors (TKIs)—especially dasatinib, which has a well-established causal link through off-target inhibition of c-src kinases, leading to pulmonary vasoconstriction, endothelial apoptosis, and smooth muscle proliferation.[51] Other TKIs such as bosutinib, ponatinib, and lapatinib have also been implicated, though with weaker evidence.[50] Other drug classes that have been associated with

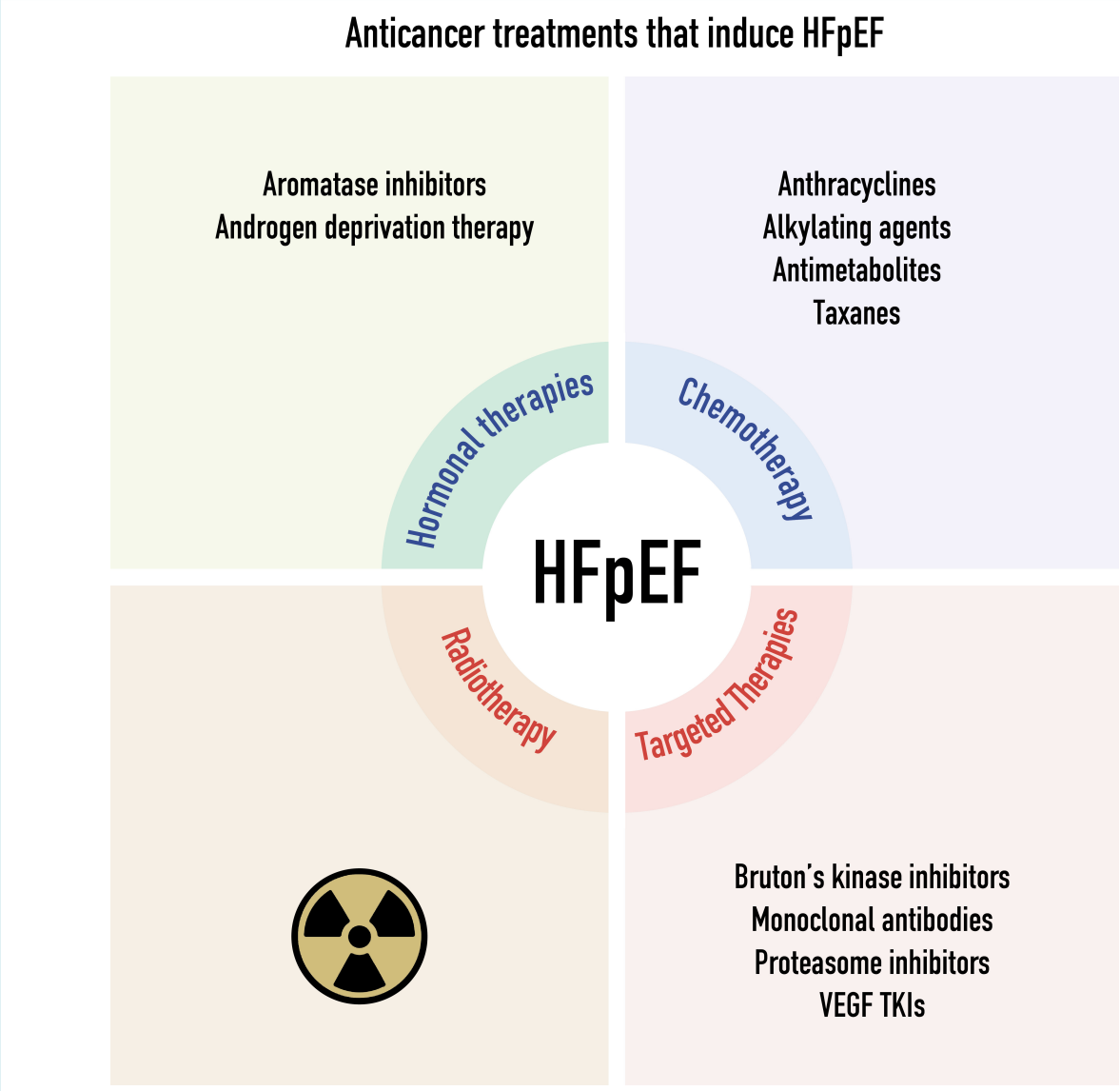

Figure 1 Anticancer treatments that induce heart failure with preserved ejection fraction (HFpEF). TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

PAH are proteasome inhibitors (e.g. carfilzomib), immune checkpoint inhibitors (ICIs) (e.g. nivolumab), and interferons (e.g. interferon-α).[49,50] Additionally, alkylating agents like cyclophosphamide and mitomycin-C may induce pulmonary veno-occlusive disease, a severe subset of group 1 PH, characterized by venous remodelling and obliteration.[52] Group 2 PH often arises from CTRCD, most commonly due to anthracyclines (e.g. doxorubicin) and HER2-targeted therapies such as trastuzumab, which impair myocardial function and elevate left-sided filling pressures. Group 3 PH involves parenchymal lung damage and hypoxia, and is frequently linked to bleomycin, busulfan, and thoracic radiation therapy.[53,54] These agents can cause interstitial lung disease and pulmonary fibrosis, ultimately leading to increased pulmonary vascular resistance and PH.

Heart failure with preserved ejection fraction as a result of targeted therapies

Targeted therapies heralded the era of precision medicine in oncology. They usually consist of small molecule drugs or antibodies for the treatment of cancer and target specific molecules that cancer cells need to grow or survive.[55] Since the introduction of tamoxifen and subsequently anti-HER2 therapy (trastuzumab) for patients with breast cancer, targeted therapies have grown exponentially.[56–58] However, based on their mechanism of action, some of therapies may also target molecules or receptors in normal, non-cancer tissues including the CV system and lead to adverse CV effects. As noted previously, the focus on left ventricular systolic dysfunction and HFrEF in CTRCD evaluation prevents true estimation of HFpEF related to these agents. The

anti-angiogenic therapies (vascular endothelial growth factor [VEGF] inhibitor antibodies, e.g. bevacizumab, and small molecule VEGF TKIs, for example sunitinib, cabozantinib, axitinib, lenvatinib) are associated with frequent and accelerated hypertension and HFpEF, in addition to left ventricular systolic dysfunction/HFrEF. Studies with VEGF TKIs report acute and chronic effects on the vasculature including increased arterial stiffness leading to significant new or worsening hypertension.[59–61] Overall, VEGF inhibitors increase the odds of hypertension and severe hypertension by 5.3 and 5.6 fold, respectively, with an incidence of severe hypertension of ~7.5%,[61] although the timing and severity of hypertension vary among the different VEGF inhibitors, and is partially or completely reversible when the therapy is stopped. In addition to the rapid and severe increase in blood pressure, VEGF inhibitor-related microvascular disease causing myocardial ischaemia[61] may also contribute to HFpEF. Careful monitoring of blood pressure after initiation of VEGF inhibitors and early aggressive control of hypertension could potentially mitigate HFpEF. Angiotensin-converting enzyme inhibitors and calcium channel blockers have been demonstrated to increase large arterial compliance and can be useful to treat hypertension in such patients, although multiple antihypertensive agents may be required.[62] Other targeted therapies such as Bruton's kinase inhibitors (e.g. ibrutinib, acalabrutinib, zanubritinib, pirtobrutinib) are associated with a risk of hypertension and AF, which may both precipitate HFpEF.[21,63] The potent irreversible proteasome inhibitor, carfilzomib, used in the treatment of myeloma, has also been associated with development of hypertension and HFpEF.[7,64]

Heart failure with preserved ejection fraction as a result of hormonal therapies

Hormonal therapy is a cornerstone of the treatment of hormone receptor-positive breast cancer but presents significant CV challenges. Many women undergoing hormonal therapy have already received other cardiotoxic treatments, such as anthracyclines, HER2-targeted therapies, or thoracic RT, which substantially increase the risk of HFpEF, especially in those with sub-optimally controlled CV risk factors. Oestrogen depletion has been shown to impair microvascular function, coronary vasculature maintenance, and nitric oxide signalling—key mechanisms involved in HFpEF development.[65] Notably, recent studies suggest that aromatase inhibitors, commonly used in postmenopausal women, further heighten CV risks, including hypertension and myocardial infarction, with prolonged therapy over 5–10 years exacerbating these effects.[21] Aromatase inhibitors may double the risk of HF compared with tamoxifen, which modulates oestrogen receptors without reducing oestrogen production; however, these studies did not specifically investigate HFpEF. In premenopausal women, ovarian suppression compounds metabolic risks, including insulin resistance, dyslipidaemia, and visceral adiposity, collectively increasing the likelihood of HFpEF at an earlier age.[66]

Similarly, androgen deprivation therapy, a pivotal treatment for prostate cancer, also poses significant CV risks.[65] By suppressing testosterone, adrogen deprivation therapy exacerbates cardiometabolic derangements, including obesity, dyslipidaemia, and insulin resistance, which contribute to a heightened risk of atherosclerosis and HFpEF. Gonadotropin-releasing hormone (GnRH) agonists have been associated with increased incidence of HF, myocardial infarction, and arrhythmias. However, emerging evidence suggests that GnRH agonists may present a comparatively lower risk of CV events.[21] Additionally, newer androgen receptor antagonists, such as enzalutamide and abiraterone, have demonstrated potential CV toxicities, including hypertension and fluid retention, further compounding risk for and even confounding the diagnosis of HFpEF.

Heart failure with preserved ejection fraction as a result of radiotherapy

Thoracic RT is a treatment modality for childhood cancers, as well as mediastinal lymphoma, breast cancer, non-small-cell lung cancer, and oesophageal cancer in adults.[67] RT techniques have improved significantly over time, substantially reducing the amount of ionizing radiation delivered to the heart due to its proximity to RT targets in the chest.[68] Nonetheless, cardiac damage may still occur after RT, and current cancer survivors may experience long-term side effects of old two-dimensional RT protocols with higher doses and/or larger irradiation volumes to the heart. The risk of HFpEF was found to be higher in women who received RT for breast cancer than in matched controls and proportional to the mean cardiac radiation dose.[6] Data from experimental studies demonstrate that exposure of the heart to radiation results in diastolic dysfunction without reducing LVEF, by inducing endothelial injury in coronary arteries and in capillaries ending up in microvascular rarefaction and impaired myocardial perfusion. Myocardial fibrosis and increased myocardial stiffness, being the sequelae of these alterations induced by RT, contribute to the development of HFpEF.[69]

Restrictive cardiomyopathy many years after RT is one of the potential phenotypes of HFpEF in cancer survivors.[70] Signs of fibrosis have been described in cardiac magnetic resonance (CMR) scans performed after cardiac exposure to RT.[71] Similarly, a stiff left atrium may also contribute to HFpEF after RT.[72] RT may interact with other factors to promote the development of HFpEF, rather than being the sole cause, such as advanced age and concomitant CV disease. The risk of RT-induced cardiotoxicity may also be influenced by genetic predisposition.[73]

Heart failure with preserved ejection fraction and inflammation in cancer patients

Although not definitively proven by the outcome of anti-inflammatory intervention trials, systemic inflammation appears to be a major risk factor for both tumourigenesis and HFpEF. Systemic inflammation predisposes to cancer development and the tumour microenvironment triggers an immune response boosting pre-existing systemic inflammation. Systemic inflammation also plays a role in mediating the deleterious effects of

comorbidities, mainly metabolic comorbidities such as obesity and diabetes, on myocardial function leading to HFpEF through induction of coronary microvascular inflammation, which modifies paracrine signalling from endothelial cells to cardiomyocytes and fibroblasts.[74] Systemic inflammation therefore occupies a central position in a cascade of events ranging from metabolic comorbidities to both tumourigenesis and HFpEF. This central position of inflammation in the pathophysiology of HFpEF in patients with cancer is nicely illustrated by recent findings on (i) clonal hematopoiesis of indeterminate potential (CHIP) and (ii) incident HF in patients receiving immunotherapy for cancer consisting of ICIs, chimeric antigen receptor T (CAR-T) cells, tumour-infiltrating lymphocytes (TILs) or bispecific T-cell engagers (BiTEs).

Over time, mutated stem cells accumulate in the bone marrow and their progeny appears in the peripheral blood. This process has been called CHIP. These mutant clones constitute an important risk for haematological malignancies such as acute myeloid leukaemia.[75] The excess mortality observed in elderly patients with these mutant clones is however also related to CV diseases such as myocardial infarction and stroke.[75] Only four mutated proteins account for most of the CHIP cases, among them mutations in Tet2. Mutations within Tet2 are especially relevant because high glucose and low AMP-activated kinase activity, both of which occur in diabetes mellitus, have been shown to destabilize Tet2 and reduce its tumour suppressive function.[76] Recently HFpEF,[77–79] ventricular arrhythmias[80] and AF[81] were added to the list of CV diseases related with increased CHIP. The association between excess CHIP and increased rates of HFpEF is compatible with the systemic inflammation hypothesis previously proposed for HFpEF[82] because CHIP cases have higher plasma levels of proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and CXC chemokine ligand. Of interest, the incidence of CHIP-induced arrhythmias has been related to myocardial fibrosis on CMR T1 mapping.[80] This finding again corroborates the previously proposed inflammatory hypothesis for HFpEF whereby fibrosis results from preceding inflammation.[74]

Cardiovascular complications of immunotherapy for cancer have recently been summarized.[83] They have been observed following administration of ICIs, CAR-T cell therapy, TILs or BiTEs. Myocardial dysfunction in ICIs has so far been divided into inflammatory (i.e. myocarditis) and non-inflammatory phenotypes. The distinction is mainly based on the presence of myocardial oedema on CMR imaging and uncommonly confirmed by endomyocardial biopsy. When both phenotypes are compared, the inflammatory myocarditis presents with the higher LVEF (60% vs. 49%), consistent with a central role of inflammatory activation.[84] A HF phenotype compatible with HFpEF in the setting of myocarditis has previously been described in parvovirus myocarditis and attributed to preferential involvement of endothelial cells.[85] Experimental evidence suggests the non-inflammatory phenotype to result from metabolic defects induced by ICIs in cardiomyocytes. If these findings are confirmed clinically, the non-inflammatory phenotype would be candidate for treatment with dapagliflozin, which has been shown to improve metabolomics in patients with HFrEF.[86] These latter findings were supported by the recent demonstration in HFrEF of improved exercise haemodynamics during short-term ketone treatment.[87] In HFpEF, however, the metabolomic profile remained unaltered during dapagliflozin treatment[88] despite similar improvement of exercise haemodynamics during short-term ketone treatment.[89]

The cardiotoxic effects of CAR-T cell therapy have recently been reviewed.[90] In a retrospective analysis of 4789 pooled patients, a 19.7% incidence of CV events was reported consisting mainly of arrhythmias (7.7%), HF (5.7%) and reduced LVEF (3.9%). These numbers suggest that one third of HF patients suffered from HF without reduced LVEF, a condition compatible with HFpEF. Interestingly, T cells involvement in HFpEF was also recently demonstrated in a 2-hit cardiometabolic HFpEF animal model.[91] In this model, myocardial and splenic T cells were characterized by impaired activation of proteins involved in the unfolded protein response. Activation could be restored by removal of the metabolic risk and resulted in partial improvement of myocardial dysfunction. The same impaired activation of the unfolded protein response had previously been reported in cardiomyocytes.[92,93] The similarity of T-cell and cardiomyocyte responses in this HFpEF model illustrates the emerging importance of cardioimmunology.[94] CAR-T cell therapy for acute lymphoblastic leukaemia and for large B-cell lymphoma is directed against the CD19 target antigen present on B lymphocytes. However, CAR-T cell therapy can also be directed against other antigens, such as proteins responsible for cardiac fibrosis like fibroblast activation protein. In this respect, CAR-T cell therapy has been reported to reduce fibrosis and restore left ventricular function in a mouse model of angiotensin/phenylephrine-induced cardiac fibrosis.[95] A similar overlap between cancer therapy and HFpEF treatment was also evident from the regression of myocardial fibrosis in a metabolic risk-induced HFpEF animal model following administration of chidamide, which is used for the treatment of T-cell lymphoma.[96]

Information on cardiotoxicity of TILs or BiTEs remains limited. Recently a single-centre (Dutch Cancer Institute), retrospective study reported on selected patients who experienced TIL treatment-related cardiac complications.[97] These included myocarditis, myocardial infarction, peri-myocarditis, AF and HF. Specific information on HF phenotypes in TIL-induced cardiotoxicity is, however, missing. Similarly, information on HF phenotypes is also missing for the use of BiTEs, which appear to have a cardiotoxicity comparable to CAR-T cell therapy.[98]

Cardiac wasting in cancer patients and heart failure with preserved ejection fraction

Cardiac wasting or cardiac atrophy (i.e. the loss of left ventricular mass) is observed in up to 50% of patients with advanced cancer.[99,100] The resulting cardiac wasting-associated cardiomyopathy is characterized by thinner left ventricular walls, smaller left ventricular cavity, as well as reduced stroke volume, while LVEF often remains normal.[101] Cardiac wasting when present in patients with cancer, is associated with higher morbidity with impaired physical performance, increased inflammation, and higher mortality. Preclinical models have found that cardiac wasting is linked to fibrosis in the heart and proteolysis.[102] Other factors

that could play an important role in the development of cardiac wasting could be oncometabolites, cytokines, and free hormones circulating in the blood, as well as tissue hypoxia, apoptosis, ventricular remodelling, and diastolic dysfunction.[103] There is a first double-blind, randomized trial currently running in cancer patients in the palliative care setting that also present with cardiac wasting (EMPATICC, NCT05636774).[104] Here patients are randomized to either receive sacubitril/valsartan, empagliflozin, ivabradine, and/or IV iron if possible or placebo. A recently published preclinical trial, demonstrated that empagliflozin prevented cardiac wasting in animals treated with anthracyclines, preserving left ventricular systolic function and mitochondrial structural integrity, function, and dynamics.[105] Further pathophysiological studies and randomized clinical trials are needed to better understand the underlying mechanisms and how to best treat patients with cardiac wasting-associated cardiomyopathy.

Challenges in diagnosing heart failure with preserved ejection fraction in cancer patients and survivors

According to the universal definition of HF, HF is a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality corroborated by at least one of the following: elevated natriuretic peptide (NP) levels or objective evidence of cardiogenic pulmonary or systemic congestion[106] (*Figure 2*). However, the diagnosis of HFpEF in patients with cancer can be difficult given that symptoms of dyspnoea, signs like oedema and reduced functional capacity are common and can be attributable to non-cardiac aetiologies (*Figures 3–4*). For example, anaemia, deconditioning and pulmonary oncologic, inflammatory and thromboembolic disorders, which are common in patients with cancer, can contribute to dyspnoea and reduced functional capacity (*Figure 3*).[107] Several non-cardiac conditions related to cancer and its therapy can contribute to oedema (*Figure 4*). Additional testing is often needed to confirm or refute the diagnosis of HFpEF in such cases. Scores to assess the probability of HFpEF such as the H_2FPEF and the HFA-PEFF, have not been specifically validated in patients with cancer.[108,109] Normal values of NPs may be helpful to rule out HFpEF in non-obese patients as in the general population keeping in mind that up to one third of HFpEF patients can have normal NP values.[110] Elevated levels of NPs can raise suspicion for HFpEF. However, confirmatory tests are necessary. These include echocardiography to assess structural heart disease and estimate filling pressures, or invasive cardiac haemodynamic measurements in certain cases.[111] Interpreting elevated NP levels can be challenging, particularly in individuals with cancer, where NP elevation may occur independently of HF due to an enhanced inflammatory state or production by certain tumours.[112–115] Other associations of elevated NPs such as anaemia and renal dysfunction are also prevalent

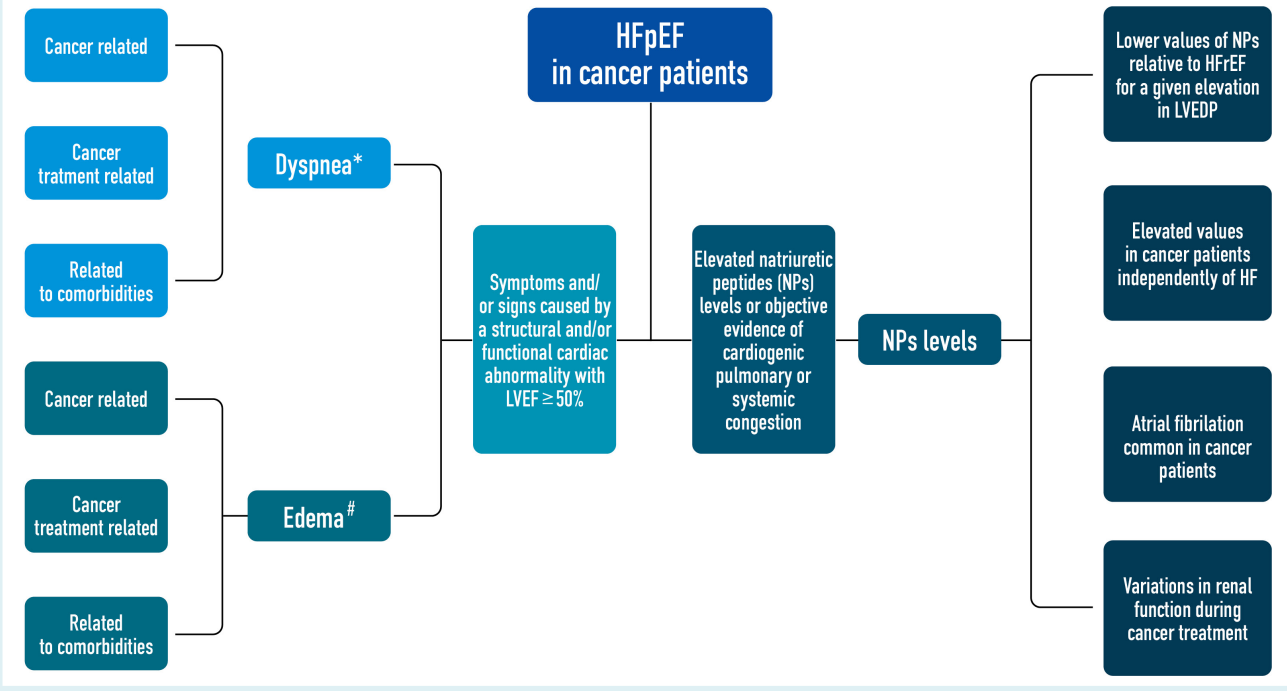

Figure 2 Specific characteristics of heart failure with preserved ejection fraction (HFpEF) universal definition in cancer patients. HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NP, natriuretic peptide. *Causes of dyspnea in cancer patients are depicted in *Figure 3*. #Causes of oedema in cancer patients are depicted in *Figure 4*.

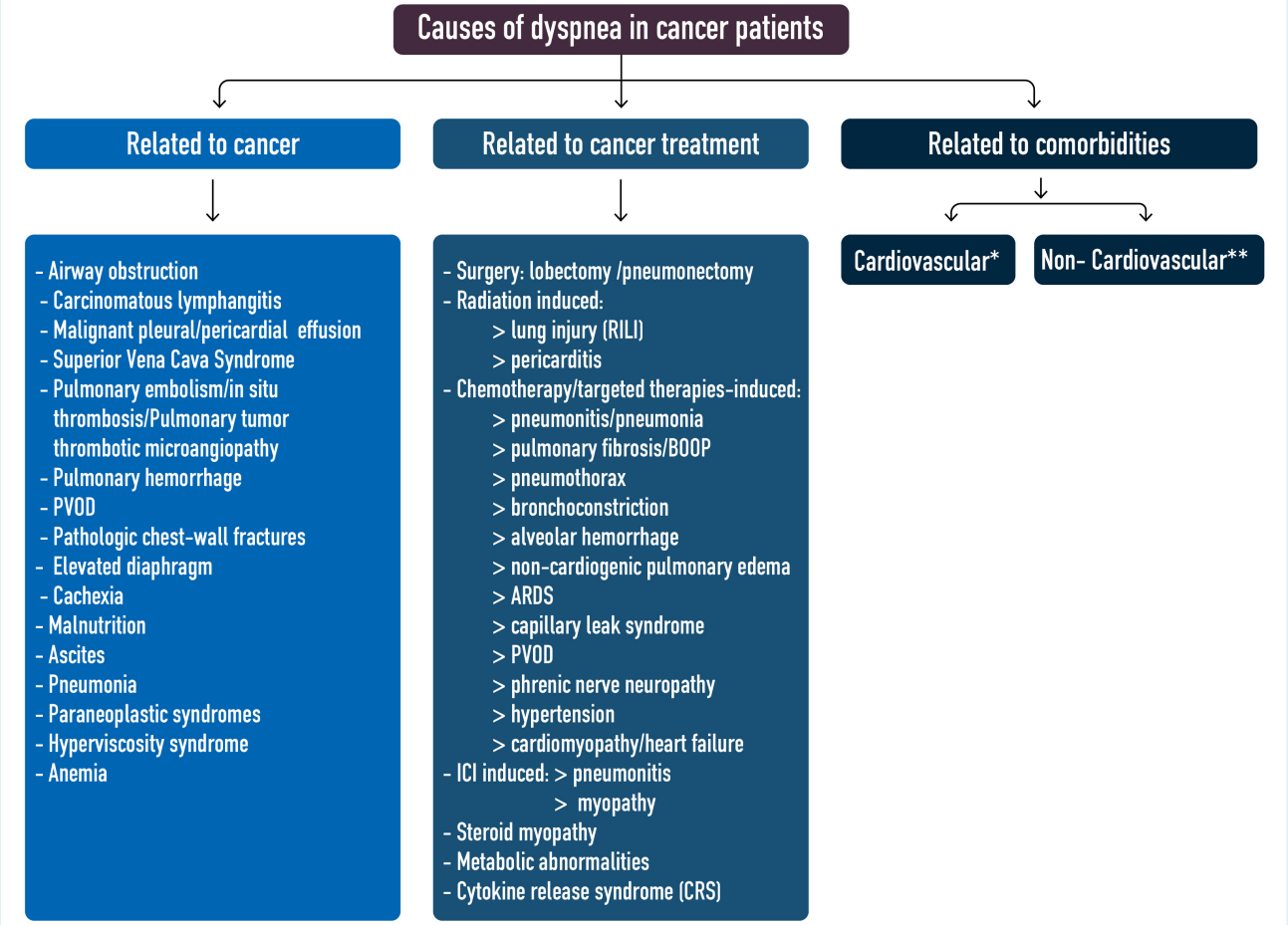

Figure 3 Causes of dyspnea in cancer patients. Modified from Keramida K. *et al* (2023), European Cardiology Review. *Cardiovascular: heart failure, cardiac ischemia, arrhythmias, cardiogenic pulmonary oedema, valvular disease; **Non-Cardiovascular: COPD, asthma, pneumothorax, interstitial lung disease, pulmonary vascular disease, chest wall deformity, arterio-venous malformation, acute respiratory distress syndrome, psychological distress (anxiety/depression/panic attack), psychosocial/spiritual pain, hyperventilation, neuromuscular disorders, retrosternal goiter, thyroid disease, hepatopulmonary syndrome, opportunistic infection, COVID infection, uremia, obesity.

in patients with cancer (*Figure 2*). The diagnosis of HFpEF in cancer is challenging and significant gaps remain, including but not limited to the prognostic value of HFpEF during and after anticancer therapies and optimal biomarkers for diagnosis and monitoring (*Table 1*).

An echocardiographic parameter that can aid in the diagnosis of HFpEF in cancer patients and survivors is left ventricular global longitudinal strain (LVGLS). LVGLS impairment is frequently observed in HFpEF patients, revealing underlying subclinical systolic dysfunction, even if LVEF appears preserved.[116,117] A cut-off value of LVGLS −16% is included in the minor criteria of the HFA-PEFF diagnostic algorithm.[109] Another myocardial strain parameter that can facilitate the diagnosis of HFpEF is left atrial strain and particularly left atrial reservoir strain (LASr). The latter has emerged as a sensitive, non-invasive marker for evaluating left atrial function and estimating left ventricular filling pressures.[118,119] LASr values below 18% have been associated with elevated pulmonary capillary wedge pressure, a hallmark of HFpEF.[120] In the light of these data, the European Association of Cardiovascular Imaging has incorporated LASr in the diagnostic algorithm of HFpEF.[121]

Heart failure with preserved ejection fraction aetiologies-mimics

Patients with specific cardiac (i.e. infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease, pericardial disease, or high-output HF) and non-cardiac causes (liver or kidney diseases) can present with a clinical diagnosis of HF with LVEF ≥50%. The most well-established example of infiltrative cardiomyopathy with a HFpEF clinical phenotype is cardiac amyloidosis.[122] Approximately 13% of patients diagnosed with HFpEF, have cardiac amyloid.[123] Although transthyretin (TTR) cardiac amyloidosis is much more common than light chain (AL) amyloidosis, both are important to keep in the differential given

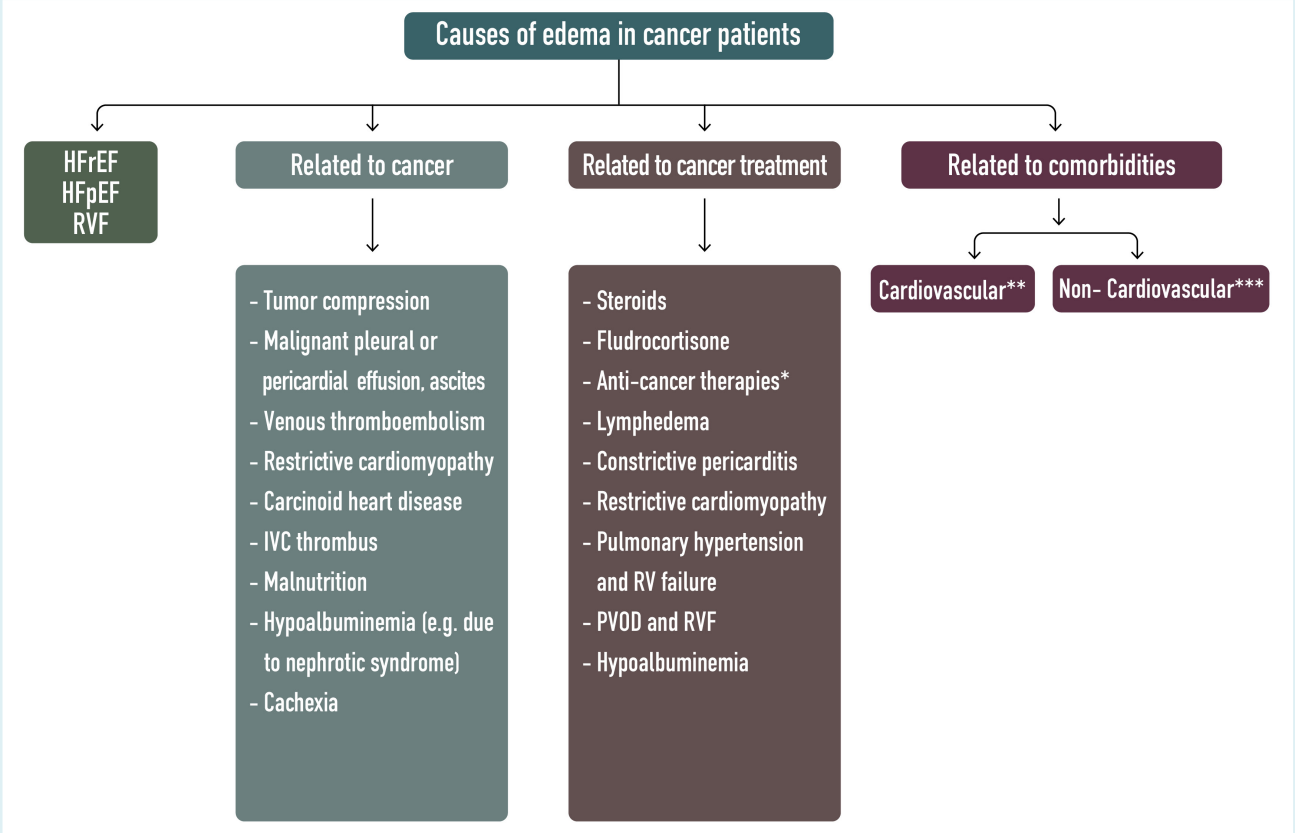

Figure 4 Causes of edema in cancer patients. HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IVC, inferior vena cava; PVOD, pulmonary veno-occlusive disease; RV, right ventricular; RVF, right ventricular failure. *Docetaxel, gemcitabine, aromatase inhibitors, anti-androgenic therapy e.g. as abiraterone, IL-2, Bcr-Abl TKIs e.g. Imatinib; **Cardiovascular: valvular disease, dilated cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, myocarditis, constrictive pericarditis, pericardial effusion, chronic venous insufficiency, deep venous thrombosis, hypertension, pulmonary hypertension, high-output states, vasculitis; ***Non-Cardiovascular: renal causes (nephrotic syndrome, acute kidney injury, chronic kidney disease, glomerulonephritis), hepatic causes (acute liver failure, acute hepatic cirrhosis, endocrine and metabolic causes (hyper- and hypo-thyroidism, Cushing's syndrome, malnutrition), angioedema, systemic lupus erythematosus, sepsis, vasculitis.[107]

Table 1 Main gaps in knowledge concerning heart failure with preserved ejection fraction in cancer patients and survivors

- What is the prognostic value of HFpEF in patients with cancer?
- What are the potential cardiotoxic effects of anticancer therapies in cancer patients with pre-existing HFpEF?
- Which are the optimal biomarkers for monitoring of patients with pre-existing HFpEF diagnosed with cancer?
- Is the concept of 'permissive cardiotoxicity' applicable to cancer patients with pre-existing or with newly diagnosed HFpEF during antineoplastic treatments?
- Should the development of HFpEF modify cancer treatment?
- Are there medications that could prevent the development of HFpEF in patients diagnosed with cancer?
- What treatments are effective for anticancer therapy–induced HFpEF, and do they vary according to the specific etiology?
- What is the prognostic value of HFpEF developed during or after antineoplastic therapies for patients' outcome?
- Is the risk of developing HFpEF higher during or after anticancer treatments?

HFpEF, heart failure with preserved ejection fraction.

that TTR amyloidosis can co-exist in patients with cancer, especially the elderly, and AL amyloidosis can occur as a result of plasma cell dyscrasias, such as multiple myeloma.

In patients with cancer, valvular heart disease may be pre-existing or may be induced or exacerbated by chemotherapy or RT. Although the most likely complication of chemotherapy is mitral and tricuspid regurgitation secondary to atrial and/or ventricular remodelling and dysfunction,[124] it may also affect the valves directly. A prospective trial in breast cancer patients treated with anthracyclines showed a significant increase in the development of new mitral regurgitation with normal left ventricular function and independently of exposure to left-sided RT or trastuzumab therapy.[125] Most of the data for RT-induced valvular disease comes from patients with lymphoma or left-sided breast cancer, treated with older RT techniques.[126–129] The prevalence of valvular disease in cancer survivors increases with the time from RT (1% at 10 years, 5% at 15 years and 6% at 20 years develop severe valvular disease).[127] The risk of valvular disease induced by RT increases with the dose of radiation to the heart, the interval from irradiation and sequential chemotherapy.[130]

Cancer patients may also present with the clinical presentation of HFpEF due to pericardial effusion or constrictive pericarditis, necessitating prompt investigation for targeted treatment. Pericardial involvement occurs in 5–20% of autopsy cases,[131–133] mostly caused by direct or metastatic spread. One third of them is related to chemotherapy, RT, infection during immunosuppression, or metabolic derangement.[134] Chemotherapy agents associated with pericardial toxicity include anthracyclines, cyclophosphamide,[135] cytarabine, and TKIs (e.g. dasatinib).[136–138] ICIs may induce early pericarditis in 7–14% of cases.[139,140] Progression to constrictive pericarditis is uncommon after chemotherapy but may increase with newer therapies. While early RT-induced pericarditis has decreased with modern protocols,[141] constrictive pericarditis can appear months to decades later.[142]

High-output HF is characterized by low systemic vascular resistance. In patients with cancer this condition is very rare and can be seen in various clinical settings mainly due to vasodilatation and/or arterio-venous shunting (e.g. in renal carcinoma,[143–147] primary plasma cell leukaemia,[148] multiple myeloma,[148] or carcinoid syndrome[149]).

Treatment of heart failure with preserved ejection fraction during and after cancer treatments

According to the 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF,[150] treatment of HFpEF in general includes diuretics for fluid retention, an SGLT2 inhibitor (empagliflozin or dapagliflozin) to reduce the risk of HF hospitalization or CV death and specific treatments according to the phenotype, the aetiology and the CV and non-CV comorbidities. Since these guidelines, the publication of four landmark randomized controlled trials (RCTs) with finerenone, semaglutide and tirzepatide provided significant new data for the management of patients with HFpEF. In the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF), finerenone reduced a composite of total worsening of HF events and CV deaths in patients with HF with mildly reduced or preserved LVEF.[151] Semaglutide led to significant reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo in patients with obesity-associated HFpEF with or without diabetes enrolled in STEP-HFpEF.[152,153] In the recently published SUMMIT trial, tirzepatide compared to placebo led to lower risk of a composite endpoint of death from CV causes or worsening HF, as well as improved health status in patients with HFpEF and obesity.[154]

The recognition of comorbidity-induced inflammation as a driver of HFpEF triggered testing of anti-inflammatory therapy. Specific targets consisted of proinflammatory cytokines such as IL-1 or IL-6 and of myeloperoxidase, which is abundantly present in neutrophil granulocytes and released upon exposure to urate crystals. Blockade of IL-1 with anakinra led to higher peak oxygen consumption (VO2) in a pilot trial and lower NTproBNP in a subsequent randomised trial.[155,156] An intriguing follow-up study demonstrated anakinra to have a larger effect on peak VO2 in HFpEF patients with LVEF > 60%.[157] The IL-1 antibody canakinumab reduced HF hospitalizations in the CANTOS trial, which unfortunately failed to discriminate between HFpEF and HFrEF.[158] Nevertheless, many patients of the CANTOS trial likely suffered from HFpEF as they were old with a high prevalence of obesity and diabetes. Use in HFpEF of the IL-6 antibody ziltivekimab is currently being tested in the HERMES trial (NCT05636176) and the results are eagerly awaited, as IL-6 also impairs natriuresis because of increased reabsorption of sodium in the distal renal tubule.[159] Blockade of myeloperoxidase or reduction of uric acid production have also been tested as potential anti-inflammatory therapy in HFpEF but the results have been inconsistent. The SATELLITE trial[160] investigated the use in HFpEF of mitiperstat, a myeloperoxidase inhibitor and showed a trend for symptomatic improvement. The ENDEAVOR trial[161] also evaluated mitiperstat and a preliminary report revealed less CV events and HF hospitalizations but no evidence of symptomatic improvement. Finally, the AMETHYST trial[162] tested in HFpEF patients the combined use of verinurad, a novel uric acid transporter 1 inhibitor and allopurinol but also failed to improve exercise tolerance. Emerging therapeutic strategies are reshaping the management of HFpEF by emphasizing a multifaceted approach that integrates novel pharmacologic interventions with personalized treatment plans tailored to specific HFpEF phenotypes.[163] However, since recent or active cancer is an exclusion criterion of most of RCTs in HF, specific data are not available for such patients. It seems reasonable to treat patients who develop HFpEF during or after cancer therapies in accordance with relevant guidelines in the general population, although the safety and efficacy in the various clinical contexts (including different cancer drugs and different cancer populations) is untested. Dedicated RCTs of therapies in these populations with HFpEF are needed but may be difficult to conduct in large numbers, especially in patients with active cancer.

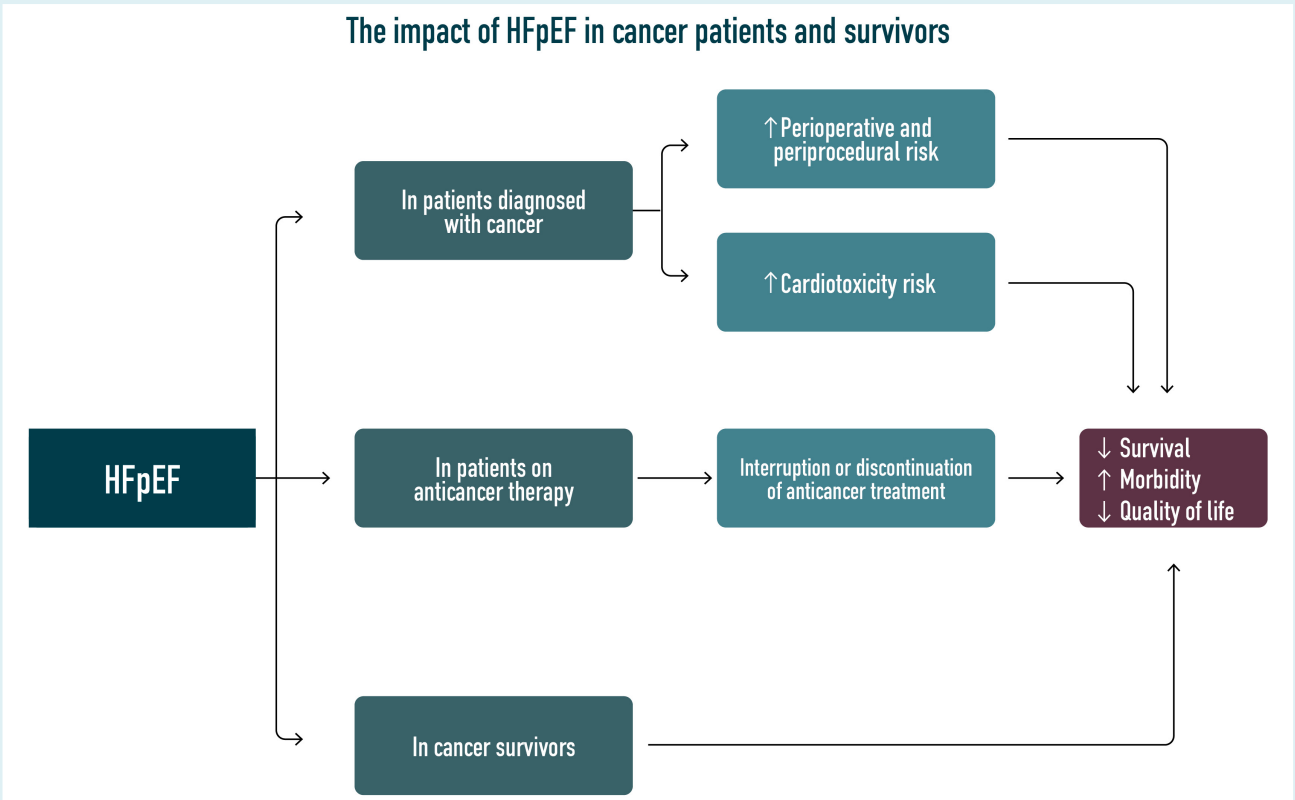

Figure 5 The impact of heart failure with preserved ejection fraction (HFpEF) in cancer patients and survivors.

Notably, specific aspects need to be highlighted in patients with cancer and HFpEF. Onco-haematological therapies may cause stomatitis, loss of appetite, vomiting, and diarrhoea, with decreased intake and increased loss of fluid, potentially leading to hypovolaemia, while for some procedures fasting is needed. Patients should be instructed to withhold SGLT2 inhibitors on 'sick days' or before the relevant procedures, e.g. before a surgery, in order to minimize the risk of euglycaemic ketoacidosis, especially in those with diabetes mellitus.[164] In cancer patients undergoing myelosuppressive chemotherapy and at high risk of intermittent neutropenia and neutropenic sepsis, the safety of SGLT2 inhibitors needs to be determined. In addition, the safety and efficacy of weight loss with antiobesity medications such glucagon-like peptide-1 (GLP-1) agonists or dual GLP-1/glucose-dependent insulinotropic polypeptide agonists in patients with active cancer is not known, given that loss of weight including significant loss of muscle mass may occur during the course of cancer. Furthermore, the possibility of unfavourable pharmacological interactions between HFpEF and anticancer therapies should not be overlooked.

Prognostic value of heart failure with preserved ejection fraction in cancer patients and survivors

Cancer survivors with preserved LVEF and prior exposure to anthracyclines have lower exercise capacity and peak oxygen consumption,[165,166] which are associated with intramuscular fat accumulation.[167] This reduced exercise tolerance is central in the phenotype of patients with HFpEF and it is prognostic for survival in patients with cancer.[168–170] In fact, the survival of cancer patients who develop HFpEF is generally poorer compared to those without HF, but also compared to those with HFrEF.[5] Breast cancer survivors with HFpEF have a higher risk of HF–related hospitalizations compared with those with HFrEF, along with significantly increased mortality[5] (*Figure 5*).

Conclusion

This scientific statement highlights the growing importance of HFpEF in cancer patients and survivors. While sharing common risk factors with cancer and contributing to increased morbidity and mortality, HFpEF epidemiology, pathophysiology, and optimal management in this vulnerable population remain understudied. The complex interplay of cancer therapies, pre-existing CV conditions, and systemic inflammation contributes to the development of HFpEF. Several gaps in knowledge must be addressed through research to improve our understanding, enhance diagnostic accuracy, and optimize prevention and management strategies of HFpEF in the context of cancer.

Conflict of interest: The declaration of interest review has been done according to the ESC Scientific Documents policy and the DOIs of the authors are available online.

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