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REVIEW

Concurrent evolution of cancer cachexia and heart failure: bilateral effects exist

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Abstract Cancer cachexia is defined as a multifactorial syndrome of involuntary weight loss characterized by an ongoing loss of skeletal muscle mass and progressive functional impairment. It is postulated that cardiac dysfunction/atrophy parallels skeletal muscle atrophy in cancer cachexia. Cardiotoxic chemotherapy may additionally result in cardiac dysfunction and heart failure in some cancer patients. Heart failure thus may be a consequence of either ongoing cachexia or chemotherapy-induced cardiotoxicity; at the same time, heart failure can result in cachexia, especially muscle wasting. Therefore, the subsequent heart failure and cardiac cachexia can exacerbate the existing cancer-induced cachexia. We discuss these bilateral effects between cancer cachexia and heart failure in cancer patients. Since cachectic patients are more susceptible to chemotherapy-induced toxicity overall, this may also include increased cardiotoxicity of antineoplastic agents. Patients with cachexia could thus be doubly unfortunate, with cachexia-related cardiac dysfunction/heart failure and increased susceptibility to cardiotoxicity during treatment. Cardiovascular risk factors as well as pre-existing heart failure seem to exacerbate cardiac susceptibility against cachexia and increase the rate of cardiac cachexia. Hence, chemotherapy-induced cardiotoxicity, cardiovascular risk factors, and pre-existing heart failure may accelerate the vicious cycle of cachexia-heart failure. The impact of cancer cachexia on cardiac dysfunction/heart failure in cancer patients has not been thoroughly studied. A combination of serial echocardiography for detection of cachexia-induced cardiac remodeling and computed tomography image analysis for detection of skeletal muscle wasting would appear a practical and non-invasive approach to develop an understanding of cardiac structural/functional alterations that are directly related to cachexia.

Keywords Cancer cachexia · Cardiac atrophy · Cardiac cachexia

1 Introduction

Cancer cachexia is a multifactorial syndrome of involuntary weight loss defined by an ongoing loss of skeletal muscle, fat mass, and progressive functional impairment [1-3]. Cachexia is a major cause of morbidity and mortality, occurring in up to 80 % of patients with progressive cancer, and suggested to be responsible for death in up to 20 % of the patients [4]. Cachexia-associated clinical manifestations include skeletal muscle wasting, anemia, anorexia, and altered immune function which contribute to fatigue, impaired quality of life, and reduced survival [5]. Patients with severe features of cachexia/skeletal muscle wasting are generally unable to react appropriately to stress, and have increased susceptibility to infections, complications during hospitalization, and chemotherapy toxicity [6, 7].

Cachexia can be found in several pathological conditions in humans such as heart failure (HF), chronic obstructive pulmonary disease, acquired immunodeficiency syndrome, cancer, and renal failure, and the presence of cachexia is associated with poor prognosis [8].

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Weight loss in cachexia involves muscle and fat mass as well as multiple organs including liver, kidney, spleen, and lung [9]. A new finding in animal studies is that cardiac dysfunction and atrophy parallels skeletal muscle atrophy in cancer cachexia [10, 11]. Effects of cancer-induced cachexia on cardiac function and structure have not been widely studied in human. Wilens et al. [12] performed necropsies on unselected men (n=1,375) and suggested that weight loss due to disseminated cancer was the most common cause of cardiac atrophy. Wilens appears to have first used the term *cardiac atrophy* in cancer patients. Burch et al. [13] reported that cancer patients have smaller hearts and cardiac dysfunction based on electrocardiogram and X-ray imaging.

Heart failure is by itself and in the absence of any other disease associated with *cardiac cachexia*. Cardiac cachexia is characterized by involuntary weight loss, reduced anthropometric indices of muscle mass, and disturbed homeostasis of several body systems [14]. Since HF is an independent cause of cachexia, cancer cachexia-induced cardiac atrophy and HF may appear as an additional contributing factor to cachexia that consequently exacerbates wasting in the cancer patient.

The purpose of this paper is to review findings which suggest that patients with cancer cachexia may develop a vicious cycle of progressive HF and cachexia (Fig. 1).

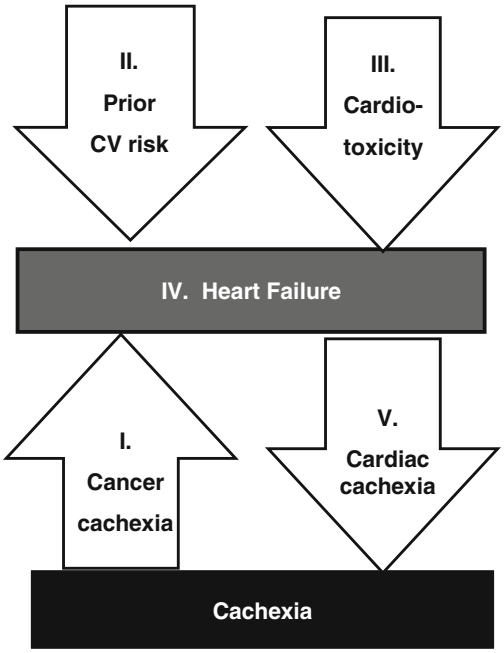

Fig. 1 Bilateral effects of cachexia and heart failure in the cancer context. *I* cancer cachexia is postulated to result in cardiac atrophy/heart failure leading to loss of cardiac function. *II*, *III* pre-existing cardiovascular risk/morbidity as well as cardiotoxic chemotherapy are additional factors that contribute to heart failure in some cancer patients. *IV* heart failure can be initialized/exacerbated by both of cancer cachexia and cardiotoxic chemotherapy. *V* developed heart failure by itself is demonstrated to result in cachexia (cardiac cachexia), augments the severity of the existing cancer cachexia, and potentially increases the susceptibility to chemotherapy-induced cardiotoxicity. These effects could sequentially worsen with cachexia driving heart failure and heart failure contributing to augmented cachexia. *CV* cardiovascular

2 Underlying mechanism of cancer muscle wasting/cachexia

Cachexia is caused by complex interactions between pro-inflammatory cytokines, hypermetabolism, catabolism of muscle protein, neurohormonal changes, and proteolytic and lipolytic factors produced by the host and tumor [1-3]. Cancer cachexia is also associated with a decrease in protein synthesis that might be a consequence of, at least in part, alteration in the activation of the 5′ AMP-activated protein kinase, protein kinase B (Akt), and mammalian target of rapamycin (mTOR) signaling pathways [15, 16].

Activation of the ubiquitin–proteasome system seems to be crucially important in cachexia-induced muscle wasting, resulting in degradation of intracellular proteins including myofibrillar proteins [17]. Several studies showed the importance of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, and tumor necrosis factor-α [TNF-α]), which activate their receptors on muscle and subsequently activate the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB activation up-regulates the ubiquitin-dependent degradation of the myofibrillar proteins [18-20]. Furthermore, increased oxidative stress and reduced activity of antioxidant enzyme contribute to anorexia and cachexia [21, 22].

It is believed that insulin resistance may play a potential role in pathogenesis of cancer cachexia through multiple mechanisms [23, 24]. Overlap exists between insulin signaling and ubiquitin–proteasome pathways in both insulin sensitive and insulin resistant states. Due to the resistance against binding of insulin to its receptor, phosphoinositide 3-kinase activity is decreased, leading to decreased phosphorylation of Akt. Lower levels of pAkt release the inhibition of forkhead box transcription factors O (FoxO) and caspase-3, resulting in increased proteolytic activity [24]. Cancer cachexia substantially impacts on fast twitch skeletal fibers. FoxO and NF-κB affect fast, glycolytic fibers more than slow, oxidative fibers [25].

3 Cancer cachexia and cardiac alterations: animal models

Mechanisms by which cancer cachexia causes cardiac dysfunction or HF are becoming clearer (Fig. 2). Sjöström et al. [26] investigated a sarcoma model of cachexia in mice and showed significant cardiac atrophy [almost 9 % reduction in heart dry weight (p<0.01)] and a reduced amount of myofibrillar, collagen, and soluble proteins 11 days after tumor implantation, compared to control animals. Tian et al. [27, 28] investigated the effects of colon-26 (C26) tumor-induced cachexia on cardiac

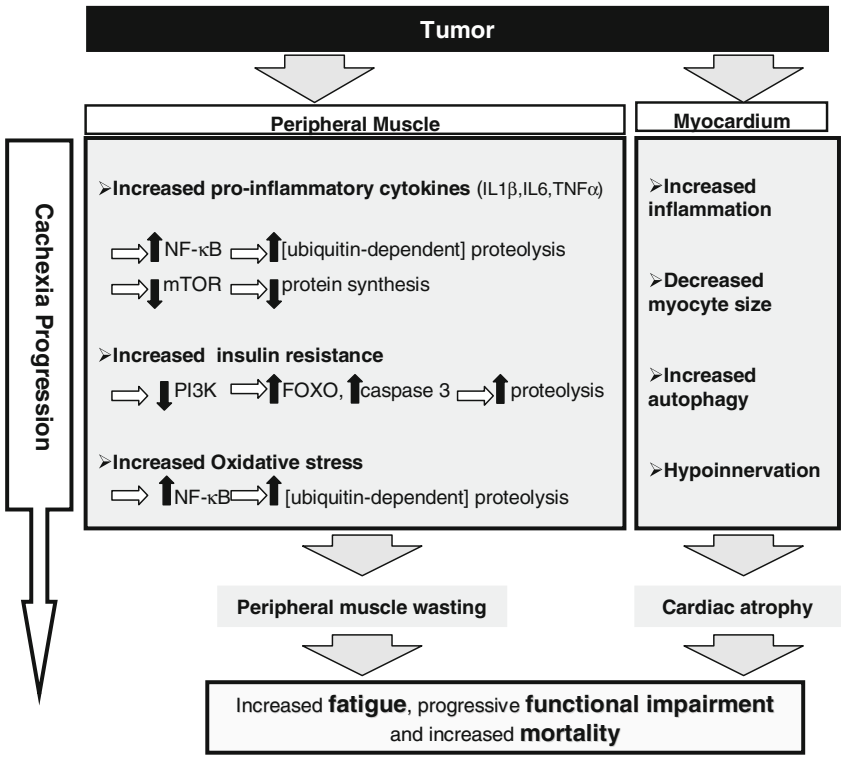

Fig. 2 Cardiac atrophy parallels skeletal muscle wasting occurring in cancer cachexia. *Gray arrow* shows the effects of tumor on peripheral muscle and myocardium which results in peripheral muscle wasting as well as myocardial atrophy, *White arrow* biochemical pathways, *Black arrows* up-regulation and down-regulation. *FOXO* forkhead box O3, *IL* interleukin, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *PI3K* phosphoinositide 3 kinase, *TNFα* tumor necrosis factor α

function and structure. They showed echocardiography-defined evidence of functional impairment [(decreased heartbeat per minute, 528±8 in control mice vs 418±13 in tumor-bearing mice; $p<0.05$) and (decreased fractional shortening [FS], 33 % difference; $p<0.05$)] and decreased posterior wall thickness (PWT) (30 % difference at systole) which is a feature of cardiac atrophy. Gene expression analysis also indicated increased brain natriuretic peptide and c-fos, reduced peroxisome proliferator-activated receptor α, and its responsive gene muscle-type carnitine palmitoyltransferase 1 β. A decreased amount of cardiac myofibrillar proteins and troponin I and increased protein ubiquitination were also consistent with cardiac atrophy and impaired cardiac contractility in cachectic mice. Tian et al. suggested that disturbance in p44/42 mitogen-activated protein kinase plays an important role in initiation and progression of cancer-associated cardiac atrophy [27, 28]. Xu et al. [10] in a similar study reported the significant adverse effect of C26 tumor on systolic function/contractility (decreased %FS, 28.4±4.18 vs 41.2±5.01 in controls, $p<0.01$). They also showed significant decrease in diastolic PWT in tumor-bearing mice (0.5997±0.090 vs 0.7575±0.1147 mm in controls, $p<0.05$) as evidence of atrophy.

Cosper et al. [11] claimed that cardiac atrophy caused by C26 adenocarcinoma in mice is more prominent in males due to lack of the protective effects of estrogen. Unlike Xu et al. [10], Cosper et al. [11] did not find any significant change in ejection fraction (EF) or %FS. Preserved EF along with increased rate of cardiac fibrosis as reported by Cosper et al. [11] perhaps suggests an association between cancer cachexia and diastolic HF with preserved EF. There is no evidence regarding diastolic cardiac function in Cosper et al.'s study. Cosper et al. [11] also indicated that cardiac atrophy is due to a decrease in myocyte size and not an increase in cell death which was again more prominent in male mice. Based on Cosper et al.'s [11] findings, autophagy especially after a long period of cachexia is the main underlying mechanism of cardiac atrophy in tumor-bearing mice [11]. Manne et al. [29] also confirmed increased autophagy, not protein ubiquitination or cardiomyocyte apoptosis, in cachectic ApcMin/+ mice atrophic hearts.

Muhlfeld et al. [30] studied Lewis lung carcinoma in mice and did not find any significant functional and structural changes in echocardiographic parameters. This inconsistency with other results [27] may be due to different types of tumor (i.e., Lewis lung carcinoma vs C26). However, in this study, only a few parameters of systolic function were reported and diastolic function was not reported. They showed robust metabolic changes of cardiomyocytes in tumor-bearing animals: decreased myofibrillar volume ($p=0.06$), increased sarcoplasmic volume ($p<0.01$), and increased volume of lipid droplets ($p<0.01$). Muhlfeld et al. [30] showed increased lipid content of cardiomyocytes in tumor-bearing mice (triglycerides per unit myocardium (mg/mg), 12.12±3.75 vs 19.5±7.91; $p<0.05$), but markers of lipid peroxidation and apoptosis were not different in tumor-bearing vs control mice. Interestingly, they found a reduction in expression of various innervation-related targets such as neuropeptide Y and nerve growth factor as well as reduced length of axons, in tumor-bearing mice.

This hypo-innervation is suggested to contribute to cardiac atrophy in tumor-bearing mice [30].

There are a variety of potential sources of variation which could contribute to differences in the magnitude of heart structure and functional changes. Skeletal muscle atrophy in rodent cancer models is affected by tumor primary type, degree of tumor burden, tumor-associated metabolic changes, and host animal type and sex, and it seems likewise plausible that these factors influence the heart as well. The specific measures which were made on the hearts in rodent models of cancer have also been somewhat heterogeneous. Finally, it is also noteworthy that the animal models lack the distinctive profiles of comorbidity, including cardiac comorbidity of human cancer patients (Table 1).

3.1 Modulation of cancer-induced cardiac alterations

Wysong et al. [31] confirmed the cardiac atrophy in C26 adenocarcinoma model of cachexia in mice and were able to block it using systemic administration of compounds that can specifically inhibit NF-κB (compound A and NEMO-binding domain (NBD) peptide). Furthermore, Shadfar et al. [32] proved protective effects of resveratrol against C26-induced cardiac atrophy in mice through NF-κB inhibition.

Palus et al. [33] reported overall cardiac atrophy in rats with cancer cachexia, induced by Yoshida AH-130 hepatoma cells, which was seen in the heart weight (752±9 versus 496± 15 mg) as well as a reduction of the end-diastolic diameter compared to sham. They showed that treatment with simvastatin somewhat can improve the cardiac function in cancer rats (cardiac output in untreated sham, 78.9 mL/min vs tumor-bearing rats, 42.4 mL/min and improved by 1, 10, or 20 mg/kg/day simvastatin 62.2, 59.0, and 57.0 mL/min, respectively, all $p<0.05$ vs placebo). Partial normalization of cardiac atrophy due to simvastatin treatment is another interesting finding of Palus et al. [33].

Zhou et al. [34] showed that in both the cachectic C26 tumor-bearing mice and cachectic inhibin-deficient mice, heart weights were decreased by 20–29 % compared to the normal controls (i.e., cardiac atrophy) and a considerable reduction in ventricular wall thickness. They found that treating the mice with ActRIIB antagonist can completely block the cardiac atrophy in both C26 mice and inhibin-deficient mice.

Springer et al. [35] showed that the xanthine oxidase inhibitor, oxypurinol, partially recovered left ventricular (LV) mass ($p<0.05$) and LVEF ($p<0.05$) in Yoshida AH-130 hepatoma cachexia rat model.

These findings in rodents further support the idea that cancer cachexia results in atrophy of the myocardium by mechanisms similar to those described for skeletal muscle wasting. However, whether cardiac atrophy occurs in humans with cancer cachexia is still a subject of debate. We cannot conclude any relation between the rate of cachexia and severity of cardiac remodeling in rodent studies. It is postulated that based on the rate of cachexia, a range of HF severity can be resulted from diastolic HF with preserved EF to pure systolic HF.

Further research should be performed to investigate the effects of cachexia on the ability of the heart to respond appropriately to physiologic and pathologic stressors. For instance, cachexia effects on a rodent model of pressure overload (transverse aortic constriction [TAC]) may uncover the interaction between TAC model, which results in cardiac hypertrophy, and atrophy which might be the consequence of cachexia.

4 Heart failure and cachexia development: cardiac cachexia

Cardiac cachexia is a frequent finding in classical HF patients with impaired systolic function [14]. Piepoli et al. [36] found cachexia features/marked muscle mass wasting in HF patients compared with matched healthy controls using dual energy X-ray absorptiometry. Significant computed tomography (CT)-defined reduction of muscle cross-sectional area of the thigh as well as impaired maximal quadriceps muscle strength were noticeable signs of cachexia in HF patients compared with age-matched healthy controls [37].

The possible mechanism of cachexia development in HF includes increased energy requirements, decreased nutrient absorption, decreased energy intake, increased inflammatory cytokines, neurohormonal activation, and impairment of skeletal muscle growth hormones [38, 39], similar to mechanisms proposed for cancer cachexia.

Although baseline echocardiographic and cardiac magnetic resonance imaging (MRI) measurements did not show any difference in LV mass between the patients with and without cardiac cachexia, overtime assessments after 6 months (echocardiography) and mean of 15 months (MRI) showed a significant reduction [40, 41]. Both of these studies showed that cardiac atrophy developed as cachexia progressed [40, 41].

5 Bilateral effects of cachexia and heart failure

Heart failure clearly results in cachexia in humans and if, as suggested by animal studies, cancer cachexia leads to HF, then it is possible to hypothesize that there may exist bilateral effects of the two conditions (Fig. 1). The suggestion that cancer cachexia may lead to the development of HF requires new investigations. Some individuals with cancer lose skeletal muscle very intensely (i.e., >5 kg of muscle mass in 90 days) [42], and these would be obvious candidates for developing concurrent cardiac atrophy with development of cardiac dysfunction.

A simple model (Fig. 1) would have a primary interaction between the development of cachexia and HF in cancer patients. There are two additional factors which would serve to exacerbate the primary interaction, the use of cardiotoxic chemotherapy and cardiovascular morbidity that pre-existed the development of the malignancy.

6 Chemotherapy-induced cardiotoxicity: postulated association with cachexia

Different classes of chemotherapy, targeted therapy drugs, and chemoprevention regimens showed cardiotoxic side-effects in a subgroup of patients [43]. Cardiac toxicities are thought to be under-reported [44]. Since cachectic patients are more susceptible to anticancer agent-induced toxicity [6], this may also include increased cardiotoxicity of antineoplastic agents. A wide range of cardiac disorders such as acute coronary syndrome and dysrhythmia have been associated with chemotherapy-induced cardiotoxicity [45]. Anthracyclines and tyrosine kinase inhibitors (TKIs) are two major examples.

New concerns arise regarding the unexpected cardiac events following TKIs, in particular sunitinib therapy. Di Lorenzo et al. [46] conducted a multicenter study and showed a 6.9 % incidence of HF following sunitinib therapy. Apart from LVEF reduction and HF, other cardiac abnormalities are also observed subsequent to sunitinib therapy. Acute coronary syndrome, atrial fibrillation [47], decreased heart rate, and dose-dependent QT interval changes [48] have also been associated with sunitinib therapy. Cho et al. [49] evaluated the cardiac events of 23 patients with renal cell carcinoma (RCC) who received salvage IL-2 therapy and reported severe cardiac events in 6 patients who all had the prior use of TKIs (sorafenib or sunitinib).

Anthracyclines such as doxorubicin can also lead to cardiomyocyte injury. Roughly 10 % of patients treated with doxorubicin or its derivatives will present with cardiac side-effects up to 10 years after the cessation of chemotherapy [23]. Several underlying mechanisms have been proposed for doxorubicin cardiotoxicity; however, no clinically proven treatment has been found for doxorubicin cardiomyopathy [50].

Generally, cardiotoxicity of any kind and its severity due to anticancer therapy is multifactorial in nature, determined by the interaction between genetic and environmental factors [43]. Individual genetic background is known to be important in anthracycline cardiotoxicity [51]. Several predisposing factors have been mentioned to be related to chemotherapy-induced cardiotoxicity. For instance, a history of hypertension [46], coronary artery disease [46, 52], and HF [52] seem to be associated with sunitinib-induced cardiotoxicity. Cochet et al. [53] reported that impaired LV diastolic function before treatment is an independent predictor of trastuzumab-induced cardiotoxicity after adjuvant anthracycline therapy in the patients with breast cancer, while Serrano et al. [54] confirmed that age, history of cardiac disease, and/or diabetes are risk factors for trastuzumab-related cardiotoxicity in breast cancer patients.

Severe muscle wasting is suggested to predispose patients to dose-limiting toxicity (DLT) characteristic of different chemotherapies and regimens. Antoun et al. [6] reported a significant association between low body mass index and skeletal muscle wasting and sorafenib DLT in patients with RCC. Similar associations were found for fluoropyrimidines in metastatic breast and colorectal cancer, adjuvant multidrug regimens in breast cancer, and sorafenib in hepatocellular carcinoma settings [55]. One question that needs to be asked, however, is whether any relation exists between cancer cachexia and cardiotoxicity specifically. No study so far specifically investigated the impact of cachexia on the degree and progression of cardiac dysfunction/cardiotoxicity following potentially cardiotoxic chemotherapy agents. More extensive research in regard to chemotherapy-induced cardiotoxicity is required, including its potential interaction with cachexia.

Generally, a wide range of chemotherapy-induced HF has been reported: acute HF, chronic HF with impaired systolic function, and diastolic HF with preserved EF.

Currently, there is no robust evidence of any association between diastolic HF with preserved EF and cancer cachexia. Cardiac follow-up for the cancer patients undergoing chemotherapy should definitely include the techniques which can elucidate diastolic function (e.g., tissue Doppler imaging [TDI]). TDI to complement conventional echocardiography has been shown to be beneficial in recent studies regarding chemotherapy-induced cardiotoxicity follow-up [56, 57]. Furthermore, adding strain and strain-rate measurements are highly sensitive in early precise detection of diastolic HF with preserved EF [58]. Strain imaging is highly sensitive for early detection of chemotherapy-induced cardiotoxicity [59, 60].

In conclusion, patients with cachexia could thus be doubly unfortunate, with both cachexia-related HF and increased susceptibility to cardiotoxicity during treatment.

7 Cachexia and pre-existing cardiovascular risk

A preliminary report suggests that cancer and HF patients both have clinical manifestation of tachycardia and reduced LVEF, dyspnea, fatigue, and reduced exercise capacity [61]. Indeed, it has been suggested that cancer fatigue syndrome may reflect a presentation of non-overt HF [62]. However, beyond studies looking specifically at cardiotoxic chemotherapy, there is a lack of detailed assessment of cardiac function in cancer patients. Von Haehling et al. [63] reported that patients with cancer tend to have higher values for blood pressure, stroke

Table 1 The prevalence of cardiac disorders in a population of 16,500 patients who died of cancer in Alberta, Canada

Cardiac disorder	ICD-9	Most responsible diagnosis for the hospital stay	Percentage	Any diagnosis of cardiac disorder	Percentage
Ischemic heart disease	410.x–414.x	228	0.7	3,914	12.2
Cardiomyopathy	425.x	8	0.0	169	0.5
Conduction disorders	426.x	18	0.1	652	2.0
Cardiac dysrhythmia	427.x	129	0.4	3,127	9.7
Heart failure	428.x	262	0.8	2,428	7.5
Total		645	2.0	10,290	32.0

ICD-9 International Classification of Diseases-Ninth Revision

volume, cardiac output, and dP/dtmax at rest which may represent a higher cardiovascular risk in cancer patients compared to control subjects. A recent cross-sectional analysis of data of 93,663 patients (Gourin et al.) who had head and neck cancer surgery showed that after controlling for all other variables, patients with weight loss (i.e., evidence of cachexia) had an increased risk of acute cardiac events compared with patients without weight loss (relative risk ratio, 1.32; $p=0.016$) [64].

Heart disease is one of many categories of comorbidity that affect cancer patients. Table 1 shows the prevalence of cardiac disorders in a population of 16,500 patients who died of cancer in Alberta, Canada, 1993–2000. These disorders were noted in administrative health data (hospital discharge abstracts) encompassing all hospitalizations occurring in the 365 days preceding the death of each patient. This time encompasses the part of the disease trajectory when cachexia is the most prominent [42]. Overall, a diagnosis of HF was noted in 7.5 % of patients; however, this was especially prevalent in certain subsets (14.4 % in multiple myeloma, 10.4 % in leukemia, 9.7 % in lymphoma, 8.9 % in male genital in urinary system cancers, 8.5 % in lung cancer, and 7.6 % in female breast cancer). By contrast, relatively few (1.5–3 %) patients with cancers of the brain, endocrine system, oral cavity, pharynx, and skin had a diagnosis of HF. Smoking and cardiovascular atherosclerotic diseases in some cancer types may exacerbate consequent cardiac complications. This variation in cardiac comorbidity as well as the inherent individual and tumor-specific variation in the evolution of cachexia will contribute to variation in the cachexia–cardiac interactions.

Although the association between HF and cancer has been established, there has been little discussion about the effects of cachexia on cardiac alterations in the presence of cardiovascular risk factors and morbidity. In other words, the effects of cachexia on the heart of the patients with either pre-existing risk factors or HF need to be studied in the near future. Likewise, in non-malignant disease, researchers are beginning to probe the complex interactions among HF, cachexia, and co-morbid conditions [65].

8 An argument for more detailed assessments in cardio-oncology research and practice

A global guideline of assessments (imaging or biomarkers) for the early detection, management, and prevention of cancer-induced cardiac disorders does not currently exist. Cardiac management may have been ignored in part owing to the poor prognosis of some patients. However, with improvement in the management of cardiac comorbidity and tolerance of cancer therapy, research in cardio-oncology is needed.

In animal studies, development of cardiac atrophy subsequent to cancer cachexia is clearly proven [10, 11, 26-34]. Prospective studies are needed to uncover the possibility of association between cachexia and HF in human patients. It may be somewhat complicated to separately evaluate the effects of cardiotoxicity and the effects of cancer cachexia on cardiac function and structure. Also, coexistence of cardiovascular morbidities (e.g., hypertension) makes the interpretation problematic.

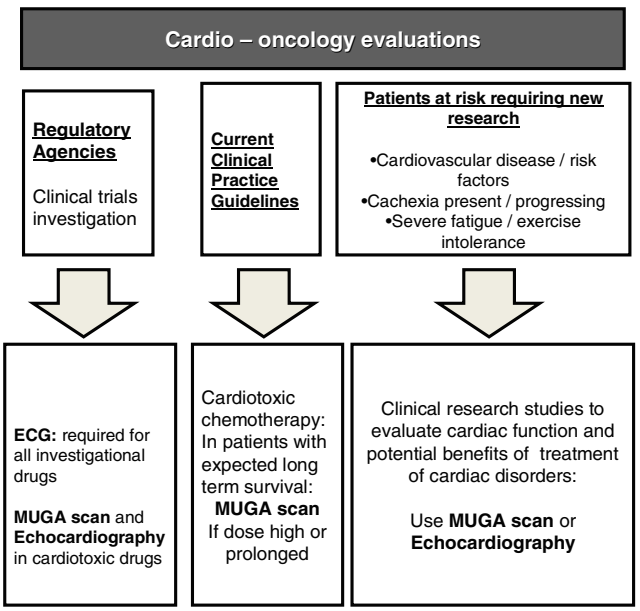

Fig. 3 Suggested cardio-oncology evaluations for cancer patients undergoing cardiotoxic treatment or are at high risk of cardiac disorder development. *ECG* electrocardiogram, *MUGA* multi gated acquisition scan

Further investigations should be undertaken to clarify the association between cancer cachexia and cardiac structural and functional alterations in human patients. Application of cardiac imaging techniques combined with skeletal CT scan in longitudinal studies may elucidate the parallel wasting of skeletal and cardiac muscle. CT is extensively used for routine oncology-related clinical assessments, and these images can be efficiently used to detect skeletal muscle wasting/cachexia as well as other features of clinical importance (accumulation of visceral adipose tissue, pathological accumulation of lipids in tissues) [66-68]. A detailed treatment of methods can be found elsewhere [67-73]. For assessment of cardiac functional and structural alterations, advanced echocardiographic methods appear to be suitable. Magnetic resonance imaging offers better image quality in some patients and would also provide additional structural information of the myocardium. But the limited availability and the relatively high costs would not allow serial measurements in larger cohorts of patients.

It will be of interest to evaluate plasma biomarkers in detection of cardiac alterations in cancer patients. The utility of brain natriuretic peptide (BNP) and pro-BNP in detection of HF patients has been proven [74]. Promising evidence exists in regard to high sensitivity troponin I (hs-TnI) and BNP in detection of chemotherapy-induced cardiotoxicity [75, 76]. Some inflammatory biomarkers including C-reactive protein, TNF-α, and IL-6 seem to be acceptable predictors of cancer cachexia/muscle wasting [77, 78] as well as HF progression in cardiac (i.e., non-cancer) patients [79, 80]. Hs-TNI and BNP suggested to be tested in further longitudinal cancer studies with both cardiotoxic and non-cardiotoxic agents.

We are proposing that there is a group of cancer patients who have elevated risk of cardiac impairments that reduce their fitness to tolerate treatment, reduce their quality of life, and potentially limit their survival. This group of patients is not currently receiving cardiac investigations as part of standard care, and thus, their cardiac problems could be underestimated. Oncologists have existing indications for cardiac investigation and follow up; however, these are restricted to investigational new drugs and drugs in current use that are cardiotoxic (Fig. 3). Regulatory agencies require electrocardiogram in all cancer patients in all clinical trials, and multi gated acquisition (MUGA) scan and echocardiography are used in trials of new drugs with potential cardiotoxicity. For doxorubicin and epirubicin, which have established cardiotoxicity, cardiac evaluation is part of clinical practice guidelines [81]. MUGA scan is a standard of care for patients receiving these agents at specified doses. Aside from these specific instances, there is no mandated cardiac investigation in cancer patients and no basis to make recommendations without new evidence. Collaboration between medical oncologists and cardiologists is essential to develop this area [43]. We must develop a clearer idea of which cancer patients could benefit from cardiac therapies. The new clinical investigations should be focused in patients with multiple risk factors as discussed here (comorbidity, sarcopenia, cachexia risk factors, cardiovascular risk factors, presenting with severe fatigue/exercise intolerance) but whose quality and quantity of life over the disease trajectory is likely to be significantly compromised if their heart condition remained untreated. The deployment of interventions is at this time entirely speculative, but it is of interest in rodent studies that HF medications such as statins, beta blockers, and aldosterone antagonists could attenuate both skeletal and heart muscle wasting in cancer cachexia models [33, 82].

9 Conclusion

It is postulated that over time, during development of cancer cachexia, significant cardiac dysfunction and progressive cardiac muscle wasting may occur. Also, developed HF as a consequence of cachexia itself or pre-existing cardiovascular disease and/or anticancer drug cardiotoxicity may play a role as a further source of cachexia. Possible bilateral effects between cancer-induced cachexia and subsequent HF require investigation in human studies. Although a large and growing body of literature has investigated the cardiotoxic effects of several types of chemotherapy agents, whether cachexia aggravates chemotherapy-induced cardiotoxicity requires investigation. Moving forward, identification of skeletal muscle loss in cancer patients with regular CT scan as well as parallel cardiac assessments with feasible tools (i.e., echocardiography) will contribute to development of novel knowledge in human patients.

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