

REVIEW ARTICLE

Fatigue: A Complex Symptom and its Impact on Cancer and Heart Failure

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Abstract

In chronic diseases like cancer and heart failure (HF), fatigue is a common and complex symptom from an etiological and pathophysiological point of view, thus, a relevant issue in the recent area of oncocardiology. Fatigue is prevalent in 80-90% of the oncological patients treated with chemotherapy and/or radiotherapy and affects approximately 50-96% of the individuals with IC. The toxicity attributed to chemotherapeutic agents can determine the patients' degree of fatigue and may even predict their survival. In recent decades, the advancement of antineoplastic therapies has substantially impacted the survival of patients with cancer, and the risks of harmful effects from these therapies to the cardiovascular system have been increasingly described. Therefore, the cooperation between oncologists and cardiologists has led to the emergence of oncocardiology and the new concept of cardiac surveillance. Cardiotoxicity is one of the clinical complications in the treatment of cancer, and its typical manifestation is left ventricular systolic dysfunction. New diagnostic and therapeutic strategies have been employed in the cardiac surveillance of patients with cancer. Fatigue in these patients has been carefully studied with a multidisciplinary approach and with the development of visual scales to quantify and correlate better its real impact on these individuals' quality of life and survival. The Fatigue Pictogram and Piper Fatigue Scale are tools increasingly used in research and clinical practice. The mechanisms involved in fatigue, from a conceptual point of view, may be of central (central

nervous system) or peripheral (muscular skeletal) origin, both of which may be present in patients with cancer. The present review aims to discuss the new concepts in the assessment of fatigue in oncological patients. These concepts are fundamental to professionals who work in the emerging area of oncocardiology.

Introduction

The survival rate of patients with cancer has improved substantially in recent decades with the emergence of new chemotherapeutic agents and advancement of radiotherapy. However, oncological patients are more susceptible to cardiotoxic effects developed during treatment, which can increase the morbidity and mortality of this population.¹ Within this new scenario, oncocardiology emerged as a new area of specialization based on a multidisciplinary integrative approach. Oncocardiology seeks to improve the quality of cardiologic care offered to patients with cancer, and to study the different dimensions of cardiotoxicity.

Among cardiovascular symptoms, fatigue is a common and very prevalent clinical manifestation in patients with cancer, and its characterization and mechanisms still defy healthcare professionals. Fatigue associated with cancer is a subjective experience characterized by fatigue not relieved by sleep or rest, and is considered a predictor of decreased personal satisfaction and quality of life.² The symptom fatigue varies in duration and intensity, reduces in varying degrees the patient's ability to develop daily activities, and decreases the functional capacity of patients with cancer.³ Fatigue can affect 80-99% of the patients with cancer treated with chemotherapy and/or radiotherapy⁴ and may persist for months to years. Cella et al.⁵ reported that one-third of the patients cured of cancer showed fatigue for 5 years after the end of chemotherapy.

Keywords

Heart Failure / physiopathology; Neoplasms / physiopathology; Cardiotoxicity / complications; Ventricular Dysfunction, Left; Neoplasias / drug therapy.

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The multifactorial nature of fatigue associated with cancer is a crucial point to be considered by professionals dealing with oncological patients. The main causes of fatigue are associated with the cancer effects and treatment on the central nervous system. Other causes include depression and anxiety, anemia, endocrine abnormalities (such as hypothyroidism and diabetes), activation of the immune system, inflammatory mediators, emotional stress, electrolytic disorders, myopathies, pulmonary fibrosis, and heart failure (HF).⁶

HF is a complex and multisystemic syndrome found in elderly patients presenting with the clinical triad fatigue, dyspnea, and edema. The mechanisms associated with fatigue in HF are triggered by inadequate blood perfusion affecting the respiratory and peripheral muscles, leading to decreased oxidative capacity.^{7,8} Fatigue affects 50-96% of the patients with HF and is associated with a reduction in quality of life, restriction of physical activity, and worse prognosis.⁸

A successful HF treatment depends on a comprehensive assessment of the symptoms and knowledge of the available approaches to alleviating not only the physical aspects of the patient but also his emotional and spiritual suffering. The "person-centered care" strategy, including a partnership between healthcare professionals and patients with HF, decreases the duration of hospitalization.⁹ The prescriptions are specific to those patients with HF who present with dyspnea at the end of life, with the objective of symptom relief, in addition to full support of the team specialized in palliative care.^{10,11}

In clinical practice, healthcare professionals dedicated to oncology and cardiovascular diseases encounter patients, especially elderly ones, presenting with both conditions. Therefore, the identification and evaluation of fatigue by these professionals is fundamental and must include scientifically validated instruments, as well as a clinical assessment and complementary tests to perform an adequate therapeutic plan.

The objective of this review is to discuss the new aspects of fatigue present in oncological patients and emphasize the importance of early detection of HF and monitoring of cardiac function for more appropriate management of patients undergoing chemotherapy and radiotherapy.

Defining fatigue in clinical practice

There is no consensus in regards to the concept of fatigue. Describing fatigue is a difficult task due to a

large number of synonyms associated with this term. Healthcare professionals attribute different terms to fatigue, such as asthenia, lethargy, exhaustion, feeling of weakness, extreme tiredness, and lack of motivation. Patients with cancer refer to fatigue using different terms, such as weakness, exhaustion, fatigue, depletion, slowness, or weight.¹¹

The scientific literature, in turn, defines fatigue as "a subjective feeling of physical tiredness or exhaustion disproportionate to the level of activity." Additionally, "fatigue may manifest as difficulty or inability in initiating an activity (perception of general weakness); reduced capacity of maintaining an activity (easy tiredness); and difficult concentration, memory problems, and emotional stability (mental fatigue)."¹²

Muscle fatigue, in turn, is regarded by many authors as "an inability to maintain a level of potency or strength during repeated muscle contractions,"¹³ "decreased strength in sustained maximal contraction,"¹⁴ and "reduced availability of energy substrate for the skeletal muscle during exercise."¹⁵

Mechanisms of fatigue

Fatigue originates in the cerebral cortex and may extend up to the cross-bridges of the muscle, induced by a reduction in the number of functional motor units involved in the activity or in the frequency of triggering. The mechanisms responsible for fatigue may be central or peripheral and are investigated through kinesthetic sensations (effort and strength) and by electromyography.¹⁵

Electromyographic signs allow the identification of the manifestation of fatigue of a given muscle through a reduction in the amplitude of the electrical impulse registered, indicative of loss of recruitment or synergic activation of multiple muscles. Another method of study of the physiology of fatigue is the addition of a force by supramaximal electrical stimulation during a maximal voluntary contraction, which translates into impaired muscle activation (at a level proximal to the neuromuscular junction).¹⁶

The central mechanism of fatigue occurs due to changes in the neural input arriving at the muscles, *i.e.*, the recruitment of motor units remains below the ideal one for generation of adequate muscle strength during exercise.¹⁶

Peripheral fatigue stems from homeostatic changes in the skeletal muscle itself and from decreased contractile force. One of the mechanisms inducing muscle fatigue

during exercises influencing the production of force is the depletion of energy substrate required for ATP synthesis and the variation in intracellular concentration of Ca^{++} , H^+ , lactate, phosphate, and ADP. A failure of the muscle in maintaining homeostasis (depending on variations in Ca^{++} and H^+ levels, for example) compromises force production at the cross-bridge level, resulting in the development of fatigue. Another mechanism that contributes to muscle fatigue is the production of free radicals. Current evidence suggests that free radicals can damage the contractile proteins myosin and troponin and decrease the number of cross-bridges, compromising muscle strength. The increased production of free radicals can also compromise the function of the sodium/potassium pump in the skeletal muscle and cause muscle fatigue.¹⁷

Skeletal muscle contraction is a complex process that involves a certain number of cellular proteins and the energy production system, with the interaction of the contractile proteins actin and myosin in the presence of intracellular ATP and Ca^{++} . The process of muscle contraction begins with the arrival of a nerve impulse in the neuromuscular junction. The action potential of the motor neuron causes the release of acetylcholine in the synaptic cleft, which in turn leads to depolarization of the muscle cell. When it reaches the sarcoplasmic reticulum, the action potential promotes the release of Ca^{++} , which binds to troponin and causes a change in the position of tropomyosin. The active sites in actin are then exposed, allowing an “energized” myosin cross-bridge to bind to the actin molecule. When the neural activity ceases at the level of the neuromuscular junction, Ca^{++} is removed from the sarcoplasm and actively pumped into the sarcoplasmic reticulum by the Ca^{++} pump, breaking the cycle of muscle contraction. The term “excitation-contraction coupling” is defined as the sequence of events in which the nerve impulse reaches the muscle membrane and causes shortening of the muscle via cross-bridge activity.¹⁸

Fatigue in chronic diseases

Clinical fatigue is often found in chronic diseases like HF and cancer. Several metabolic, neurological, and myofibrillar adaptations are involved in these conditions and implicated in the onset of fatigue.¹⁹ Ewans & Lambert⁴ have pointed out that cachexia and deconditioning are probably involved in the persistence of fatigue at the end of treatment and after resolution of the disease.

Fatigue in heart failure

Fatigue and dyspnea are cardinal symptoms of HF. Fatigue is triggered by inadequate blood perfusion affecting the respiratory and peripheral muscles and leads to reduced oxidative capacity. Dyspnea, in turn, is caused by an excessive ventilatory demand or a ventilatory disorder arising from sensory systems involved in breathing. The symptom fatigue can be caused by cardiac cachexia and malnutrition that accompany the severe metabolic stage of the disease.⁸ Patients with advanced HF may develop sarcopenia associated with aging and physical inactivity, resulting in worsening of fatigue. The symptom fatigue connected to HF is also related to anemia, sleep apnea, electrolyte disturbance, use of beta-blockers and diuretics, in addition to depression.²⁰

The exercise intolerance present in HF may be associated with central (chronotropic response and reduced ejection fraction) or peripheral (endothelial dysfunction with decreased release of nitric oxide, increased total peripheral resistance and lower vasodilatory response) limitations. The ventilatory muscle weakness present in HF, in turn, is also a limitation that may reflect a greater increase in the work of the diaphragm, triggering a sensation of dyspnea.²¹

Another adaptation found in HF that can contribute to aggravate fatigue is the decrease in contractile function. The myopathy observed in HF clearly reflects the reduction in oxidative phosphorylation with increased type IIb fibers and decreased type I fibers, which are regarded as determinants in the reduction of functional capacity. The administration of drugs used in HF, such as losartan and enalapril, improves exercise tolerance with normalization of the composition of the muscle fibers (i.e., reduction in glycolytic fibers [type IIb] and increase in aerobic fibers [type I]), in addition to improving the maximum energy expenditure (VO_2).²² Similar results have been obtained with exercise training in patients with HF, which resulted in improved endurance, physical activity, and oxidative phosphorylation of the skeletal muscle.²³

The muscle weakness eventually observed in patients with HF can be attributed to changes in function and amount of proteins in the myofilaments and not only to muscle atrophy. These changes are probably secondary and apparent in relation to the deconditioning and/or disuse resulting from the disease and allow the definition of the muscle phenotype in patients with HF.^{24,25}

Assessment of fatigue in heart failure

Several validated scales are available to measure symptoms during care of patients with HF, which allows for individualized treatment to each patient based on his scores. For a better understanding of the symptoms, numerical scales are used with the purpose of evaluating physical, emotional, and cognitive aspects of the patient in relation to the aspects observed by other professionals, for example, the Edmonton Symptom Assessment System (ESAS). The information collected with ESAS helps to measure HF symptoms not traditionally evaluated.²⁶

ESAS is a simple instrument, of easy application, which may be filled out by the patient himself (self-assessment) or by a family member or professional. This scale comprises 10 common symptoms found in patients with cancer receiving palliative care, including lack of appetite, fatigue, nausea, depression, sleepiness, anxiety, pain, dyspnea, malaise, and other symptoms. The scale is graded from 0 to 10, where 0 represents the absence of the evaluated symptom and 10 represents the presence of the evaluated symptom in its strongest intensity.²⁶

A prospective study conducted in Canada assessed the applicability of different questionnaires of palliative care in patients with HF. The study correlated the New York Heart Association (NYHA) functional class and the Kansas City Cardiomyopathy Questionnaire (KCCQ) with the palliative care scales ESAS and Palliative Performance Scale (PPS). The study found a positive correlation of NYHA with PPS and ESAS ($R^2 = 0.57$, $p = 0.001$); however, the KCCQ questionnaire correlated negatively with ESAS ($R^2 = -0.72$, $p = 0.001$). Depending on the difficulty of the identification of patients with HF eligible for palliative care, these tools may be useful in clinical practice.²⁷

Fatigue related to cancer

The symptom fatigue is directly associated with cancer itself and the side effects of its treatment, including toxicity from chemotherapy. Patients with cancer who present severe fatigue during treatment remain fatigued after the end of the therapy or the resolution of the disease. The chronicity of fatigue is implicated in possible metabolic and physiological adaptations, such as deconditioning and cachexia. Increased physical activity is a strategy adopted to reduce the loss of skeletal muscle during chemotherapy.²⁸

Cachexia in cancer is characterized by a continuous loss of skeletal muscle mass and may cause generalized

weakness and fatigue. Roberts et al.²⁹ investigated the weakness of the diaphragm muscle due to cachexia associated with cancer in animal models and observed that muscle weakness was attributed to muscle atrophy and contractile dysfunction.

Lee et al.³⁰ evaluated the difference in physical performance between women and men with and without lymphoma, with the application of the 6-minute walk test (6MWT) and the Brief Fatigue Inventory. The results obtained showed a higher fatigue score in patients who presented worse functional physical capacity.

The multifactorial nature of fatigue associated with cancer hinders the identification of underlying mechanisms involved in the disease. Bower et al.³¹ have confirmed the relationship between increased inflammatory cytokines with worse fatigue in patients with breast and prostate cancer during treatment. Dower et al.³² demonstrated that women with breast cancer and fatigue had reduced levels of cortisol in the morning, suggesting possible abnormalities in the hypothalamic-pituitary-adrenal axis. Fink et al.³³ found that low levels of hemoglobin, depression, and physical limitation may be considered predisposing factors of fatigue.

The diagnosis of fatigue related to cancer is established with the exclusion of reversible causes that can be treated and investigated. Among cited reversible causes are the types of fatigue, hypothyroidism, anemia, sleep disorder, pain, emotional stress, menopause, electrolyte abnormalities, adverse effects of medications, cardiac dysfunction, renal and hepatic failure, myopathy, and pulmonary fibrosis.³⁴ The diagnosis of fatigue can be complemented with information from the patient's clinical history, physical exam, and laboratory tests, with the application by a multidisciplinary team of instruments for the assessment of fatigue.

The classification of cancer-related fatigue follows the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) of the National Cancer Institute of the United States and is widely used by Brazilian oncologists (figure 1).³⁵

Dimeo et al.³⁶ concluded that exercises are the only factors with strong evidence in the control of fatigue during and after treatment of tumors of the breast, prostate, and several other solid tumors. Schwartz et al.³⁷ pointed out the effectiveness of therapeutic exercises in improving the patients' fatigue and quality of life, with a reduction of the adverse effects of therapies against cancer. Aerobic training performed during 4 months by women with hypertension, cardiovascular disease,

and breast cancer undergoing treatment resulted in a reduction of systolic and diastolic blood pressure and resting heart rate. A systematic review involving 4,826 participants with cancer, in turn, showed improved quality of life and functional capacity during and after a training program with exercises (tables 1 and 2).³⁸

Risks of cardiotoxicity

The signs and symptoms of HF may be similar to those observed in oncological patients. Fatigue is a common clinical manifestation in both pathologies. In cancer, it can deteriorate due to oncological treatment, which increases the risk of injury to the myocardium, which in turn triggers cardiovascular complications.³⁹

The substantial decline in cardiopulmonary capacity is a consequence of immobility, chronic fatigue, loss

Table 1 - Potential benefits of exercises before and after cancer treatment³⁸

Before treatment	After treatment
Improved cardiorespiratory and cardiovascular function	Improved self-esteem, mood, and self-image
Effects on body composition (preservation or increase in muscle mass, loss of fat mass)	Reduced duration of hospitalization
Improved muscle strength and flexibility	Reduced stress, depression, and anxiety
Improved immune system	Reduced of serious adverse effects including nausea, fatigue and pain

Source: Adapted from Mishra SI et al, 2012³⁸

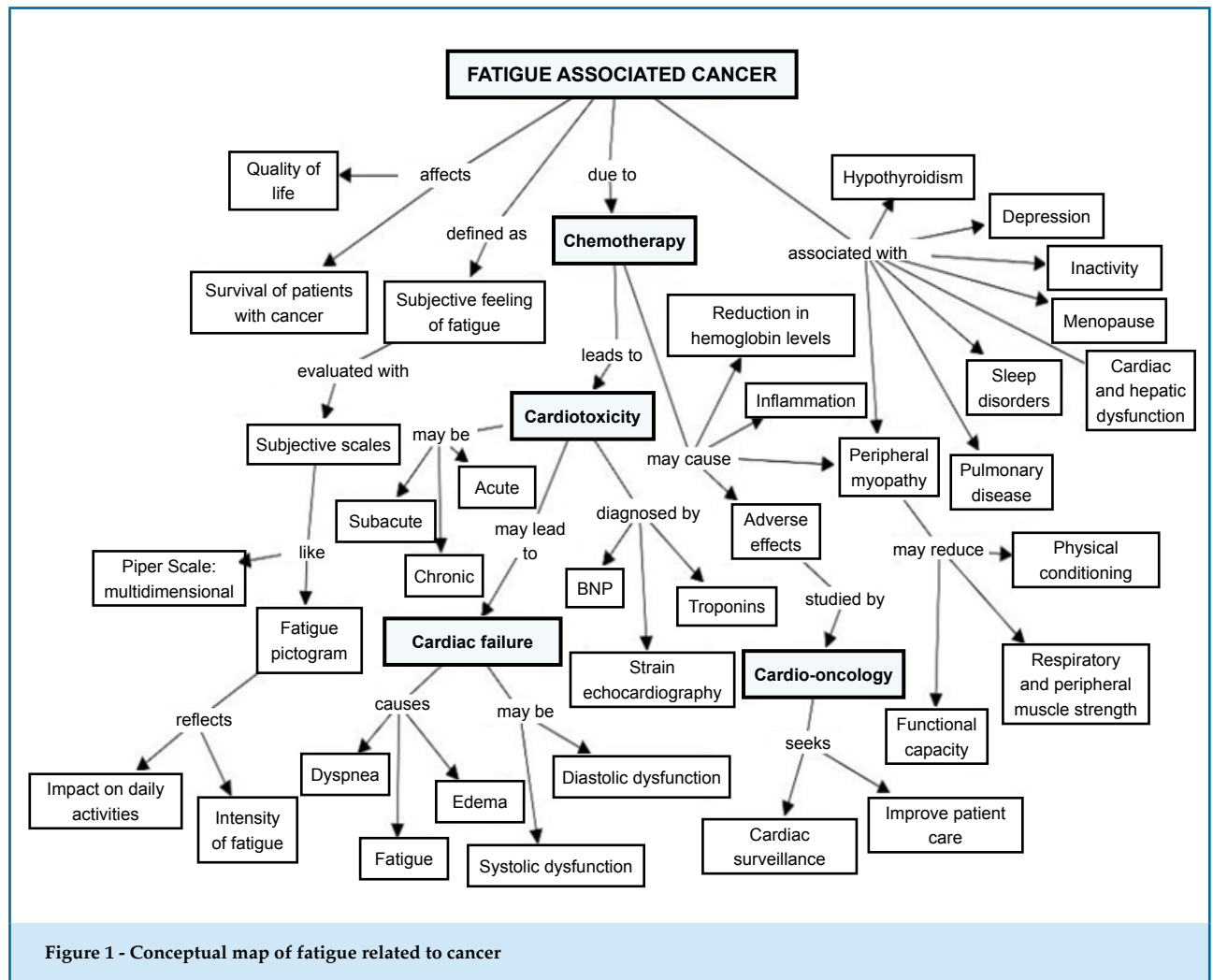


Figure 1 - Conceptual map of fatigue related to cancer

Table 2 - Differences between oncologic fatigue and fatigue related to heart failure

Fatigue associated with cancer	Fatigue related to heart failure
Generalized muscle weakness	Weakness of the peripheral and respiratory muscles
No improvement with rest or sleep	Improves with rest and sleep
Worsens with chemotherapy and radiotherapy	Worsens with corticosteroids and anti-inflammatory drugs
There is no association direct with dyspnea	Associated with dyspnea on exertion
Dysfunction of the central and peripheral nervous system	Dysfunction of the peripheral nervous system
Disuse of muscle fibers and contractile alteration	Atrophy of Type I aerobic muscle fibers
Triggered by low levels of hemoglobin, cortisol, TSH, and free T4	Triggered by an increase in inflammatory mediators
Related with worsening nutritional status	Associated with cardiac cachexia with disease progression
Associated with mild, moderate, or severe pain	

Source: Author, 2017

of muscle mass, anemia, increased inflammatory activity, changes in coagulation, and adverse events from chemotherapy and/or radiotherapy. All these changes consequently lead to worse quality of life among cancer patients.³⁹

Cardiotoxicity induced by chemotherapy has been a major concern among oncologists and cardiologists in search of early identification of cardiac dysfunction and monitoring of cardiovascular function during treatment. Cardiac toxicity is one of the most important complications of cancer therapy and is responsible for considerable morbidity and mortality.⁴⁰

Several drugs used in cancer treatment have been associated with left ventricular dysfunction, in particular, drugs in the anthracyclines group, like doxorubicin. Anthracycline-induced cardiotoxicity manifests early (< 3 months after treatment) or late (3 to 12 months after treatment), but can also occur 1 year after treatment. According to Suter & Ewer,⁴¹

medications can be classified according to the injury that they cause to the myocardium as leading to reversible (type 1) and irreversible (type 2) injury. One of the effects of cardiac toxicity by anthracyclines involves oxidative stress and lipid peroxidation of the cardiomyocytes. Swain et al.⁴² identified 149 cardiac events and reduced left ventricular ejection fraction (LVEF) in 50% of 630 cancer patients treated with doxorubicin.⁴³ A noninvasive hemodynamic evaluation of patients with HF showed an increase of the following variables: cardiac output, stroke volume, heart rate, and blood pressure.⁴³

The harmful events of chemotherapeutic agents/drugs on the cardiovascular system include HF, hypertension, thromboembolic disease, and myocardial diseases (table 3). The main risk factors for cardiotoxicity associated with chemotherapeutic agents are hypertension, age above 60 years, prior left ventricular dysfunction, and prior thoracic irradiation. According to its clinical presentation, cardiotoxicity may have an acute, subacute, or late presentation.¹

The diagnosis of cardiotoxicity is established using biomarkers (including brain natriuretic peptide [BNP] and troponins) and echocardiographic resources. Approximately one-third of the patients have elevated levels of troponins, which are sensitive and specific markers of myocardial injury with the ability to signal the development of ventricular dysfunction in patients receiving elevated doses of chemotherapeutics.⁴⁴

The European Society of Cardiology currently proposes a discussion about the relevance of the biomarkers and serial evaluations of LVEF in clinical practice and research. The simultaneous use of blood samples for measurement of biomarkers levels and characterization of genetic and epigenetic factors may be useful in identifying patients with cancer susceptible or resistant to cardiotoxicity. With this approach, it is possible to compare the clinically relevant results before and during cancer treatment, allowing the planning of strategies based on evidence through oncocardiology.⁴⁴

Evaluation of oncological fatigue

Standardized questionnaires have been incorporated into the assessment of fatigue. Several instruments for assessment of fatigue are available, seven of which have been validated in Brazil for the evaluation of the impact of fatigue on quality of life of oncological patients.⁵²

Table 3 - Pathophysiological triggers of coronary artery disease in cancer treatment

Agent	Pathophysiological mechanism	Potential coronary events
5- fluorouracil, capecitabine, gemcitabine	Endothelial lesion and vasospasm	Up to 18% of myocardial ischemia and 10% of silent ischemia
Platinum components - cisplatin	Arterial thrombosis and procoagulant	20 years of absolute risk above 8% after testicular cancer
Vascular endothelial growth factor (VEGF) inhibitors: bevacizumab, sorafenib, sunitinib	Procoagulant, arterial thrombosis Endothelial injury	Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, and sunitinib 1.4%
Radiotherapy	Endothelial lesion, platelet rupture, and thrombosis	A 2- to 7-fold increase in the relative risk of myocardial infarction 10% of coronary events in survivors of Hodgkin lymphoma The risk is proportional to the radiation dose

Source: Adapted from the Guideline of the European Society of Cardiology⁶⁴

The Fatigue Pictogram, prepared for the evaluation of the intensity and impact of fatigue in patients with cancer, is a useful tool in clinical practice and research (Figure 2). It is described as a method that is fast, simple, valid, reliable, and applicable to patients with

cancer and low educational level, although it requires adjustments for application to healthy individuals. This instrument was developed and validated in 2007 in four oncology outpatient clinics in the city of São Paulo, with the participation of 584 patients with

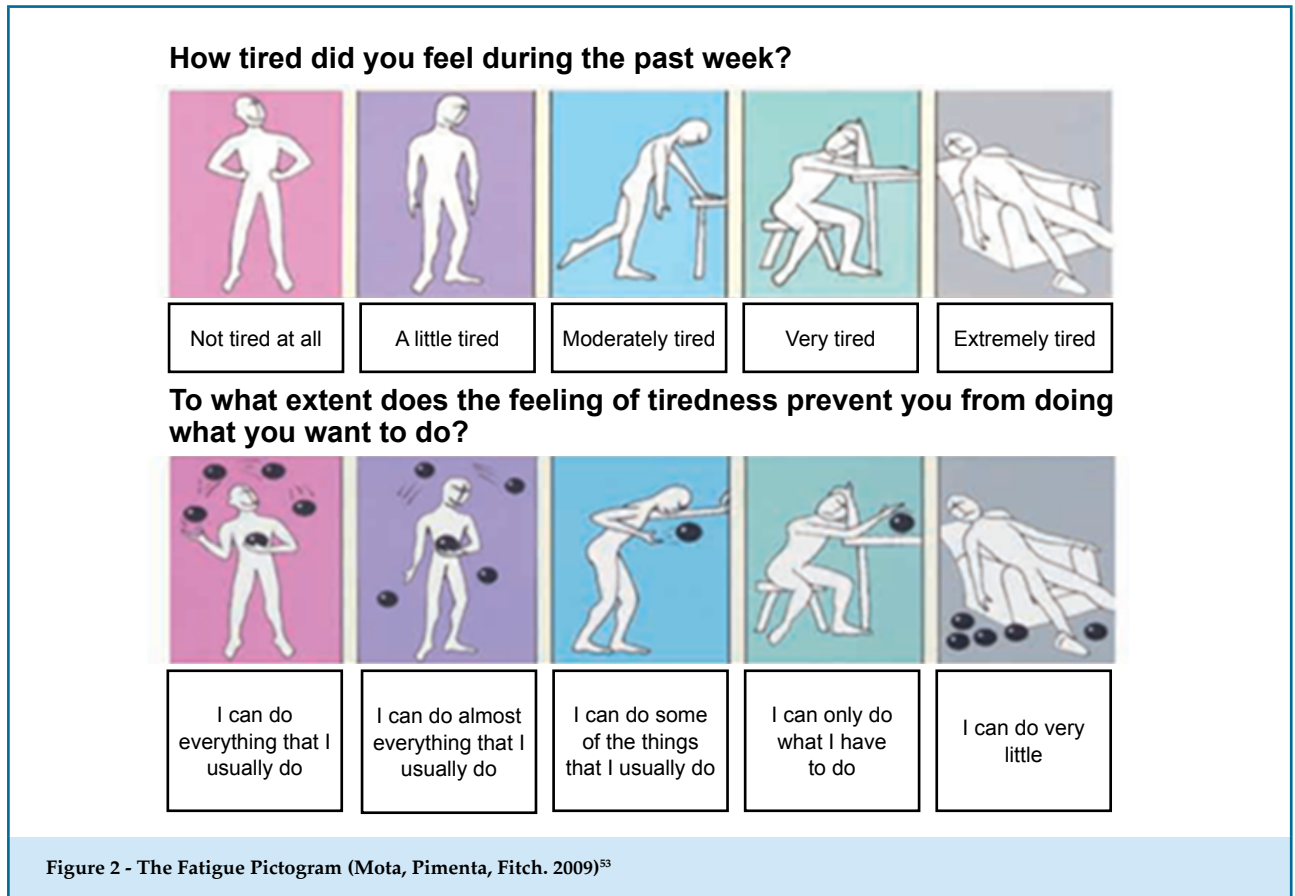


Figure 2 - The Fatigue Pictogram (Mota, Pimenta, Fitch. 2009)⁵³

different types and stages of cancer receiving or not treatment with radiotherapy.⁵³

Fatigue may also be assessed with the Piper Fatigue Scale. Revised and validated in Brazil in 2009, this scale covers all dimensions of fatigue and can be applied to cancer patients at all stages of the disease. This scale establishes a cutoff point from which the individual should be regarded as fatigued.⁵⁴ Another widely used questionnaire is the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), which was validated and applied in a study carried out at the Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) in 2008 and showed a negative impact of fatigue on the quality of life of patients with breast cancer undergoing chemotherapy.⁵⁵

Conclusion

Although fatigue is a common symptom in patients with cancer, it receives little attention in daily clinical practice. In recent decades, fatigue has been progressively recognized by its impact on the patients' quality of life and survival. Fatigue is also one of the cardinal symptoms of HF. Cardiac surveillance and oncocardiology are concepts that are being incorporated by multidisciplinary teams caring for patients with cancer. Therefore, the identification of fatigue and its pathophysiological mechanisms, as well as its correct stratification and therapeutic approach, are fundamental steps to be met by healthcare professionals involved in the care of patients with cancer.

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