Chapter 1

Exercise As Complementary Therapy For Cancer Patients During and After Treatment

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Introduction

Cancer is a disease in which cells in a certain part of the body grow uncontrollably, i.e. a major hallmark of cancer is the rapid proliferation of abnormal cells beyond their normal local region, which then can penetrate adjacent areas of the body and spread to other organs. The latter process is known as "metastasis" and is the leading cause of cancer death, as cancer cells invade and destroy nearby healthy tissues and organs [1,2]. Cancer is the second leading cause of death worldwide, with an estimated 18.1 million new cancers and 9.6 million deaths from cancer in 2018 [3]. It is noteworthy that about one-third of cancer deaths are due to the five main behavioral and dietary risk factors, i.e. lack of physical activity, low consumption of fruits and vegetables, high body mass index (BMI), and tobacco and alcohol use [4]. Since cancer remains a major public health issue worldwide, it is imperative to understand how modifiable behavioral health factors, such as physical activity, can help prevent and control this disease in the general population [5].

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1. The Role of Exercise In Cancer

Current research data show that exercise reduces the risk of cancer development and recurrence, prolonges life of cancer patients and improves their quality of life, while exercise may also limit tumor growth, in terms of histological progression of the disease, at all stages of tumor development [6]. The American College of Sports Medicine (ACSM) and the American Cancer Society (ACS) recommend physical exercise as an intervention strategy that help cancer patients manage their symptoms and improve their physical function and quality of life, both during and after the completion of their treatment [5, 7-9]. Indeed, adequate evidence has led to the general acceptance that exercise is an applicable strategy for enhancing the physical and psychosocial abilities of cancer patients. In addition, solid epidemiological data suggest that exercise reduces the risk of recurrence and mortality from the disease, especially from breast and colon cancer [10]. Interestingly, high-level athletes, who experience the highest exercise loads during their athletic careers, have a much lower risk of overall cancer mortality (-40%) compared with the general population [11,12]. Regarding the effects of exercise in children with cancer, the research evidence is not yet convincing due to the small number of participants and and the insufficient experimental design of the respective studies; however the first findings highlight the positive effects of exercise on body composition, flexibility, cardiorespiratory fitness, muscle strength and the health-related quality of life of children with cancer [13].

The beneficial effects of exercise against cancer development and progression lie in its unique ability to induce various physiological adaptations to many organs and systems of the body, in order to restore and/or enhance its homeostatic balance at cellular, tissue and systemic level. These exercise-induced adaptations are achieved through an integrative coordination between multiple physiological systems and the remarkable biological interactions of those systems due to exercise [14].

The sequence of the various phases in cancer management includes its detection, the therapeutic intervention, the mitigation of the disease symptoms and the patient's survival. Each phase is characterized by different pathological conditions, such as the presence of a tumor, the anticancer therapy, the existence of long-term side effects of treatment, or a combination of these conditions. Exercise can play multiple roles throughout the sequence of cancer development and progression by a) reducing the risk of the disease development, b) improving the body's tolerance to the side effects of anticancer therapy, as well as the effectiveness of drugs, c) limiting long-term side effects after the completion of primary treatment, d) preventing recurrence of the disease, and e) reducing the risk of comorbidities. Interestingly, all these beneficial effects of exercise can occur in patients with advanced cancer [6]. Exercise also reduces inflammation and this effect is vital in oncology, given the relationship between inflammation and tumor development. In addition, the anti-inflammatory effect of exercise can help protect the body from the cardiotoxicity of certain drugs, which is associated with several anticancer therapies and can lead to cardiovascular disease and mortality. Given the complex nature of the various cancer treatment modalities, which also can be given in combination, it is difficult to attribute their possible toxicities to a specific, single treatment, since the therapeutic regimens can act synergistically, resulting in harmful effects caused by two or more treatments.

1.2. Interaction between exercise and anticancer therapy

Anticancer therapy is debilitating for the patient and poses a threat to the body's normal homeostatic function, both during treatment and in the recovery phase. As exercise is also a form of physiological stress for the body, it could worsen the symptoms and the treatment-associated side effects. This view promoted rest as the best strategy for managing the symptoms of cancer patients, until the evidence disputing this recommendation was revealed [10,15,16]. The confirmation of the safety of exercise in cancer survivors further promoted the acceptance of its efficacy in this clinical population [17,18].

As with other clinical populations (eg, patients with diabetes, heart disease, or neurological disorders), moderate-intensity exercise is considered safe, both during and after the completion of anticancer therapy, and the benefits of regular exercise for cancer survivors far outweigh its potential risks. However, the side effects of cancer treatment can affect the ability of these patients to exercise and such limitations should be considered when prescribing (personalized) exercise for cancer survivors [5, 9].

Specifically, a decline of the cardiovascular and respiratory system function is common during cancer treatment and is associated with the reduced levels of physical activity in these patients. However, it seems that the ability of the cardiorespiratory system to adapt to exercise remains intact during treatment. Furthermore, physical exercise appears to be an effective adjunct therapy to compensate for the adverse effects of anticancer drugs on the cardiovascular system (cardiotoxicity) [19, 21].

Muscle fatigue and weakness are also common in anticancer therapy but can be improved through exercise. In addition, cancer cachexia is another multifactorial clinical condition that involves loss of body weight, muscle mass and adipose tissue. In general, changes in body composition are common in these patients during treatment and the combination of exercise with proper nutrition seems to be the most effective way to control these physical changes [17].

Moreover, bone loss is also a common clinical manifestation in cancer patients in whom treatment aims to reduce the levels of sex hormones (eg, in breast and prostate cancer). Clinical studies have shown that moderate-intensity exercise can maintain bone health during anticancer therapy but may have limited skeletal benefits beyond those of pharmacological treatment for bone loss. However, exercise should not be overlooked for these patients, as it has multiple other health benefits, including a reduced risk of falls, which further reduces the risk of a bone fracture [17].

In addition to the various pathophysiological side effects of cancer treatment that can be reduced through exercise, psychosocial benefits are also important for cancer patients during their treatment. There is solid scientific evidence that exercise improves a variety of mental health symptoms associated with cancer, such as chronic fatigue, stress, poor quality of life and mood disorders [5,9,20].

Overall, physical exercise appears to be an effective adjunct therapy for cancer patients, both during and after treatment, and several pathophysiological mechanisms may explain the beneficial effects of exercise in preventing the side effects of anticancer therapy. Particularly after the completion of treatment, exercise can reverse the various losses occurred during treatment, reduce the late long-term effects of treatment, and promote the improvement of patients' functional ability, health and survival. Also, the serious psychosocial problems and emotional disturbances faced by cancer survivors can be alleviated through physical exercise [5, 9, 17].

1.3. Acute effects of exercise in cancer

Exercise-induced modifications of the interaction between the body and the tumor microenvironment begins already with an impressive whole-body response triggered by a single exercise session. Specifically, physical exercise requires a synchronized and integrated response of many physiological systems and organs, such as the lungs, heart, blood vessels, liver, pancreas and skeletal muscle, in order to transfer oxygen and energy substrates to metabolically active (exercising) skeletal muscles. In particular, during an exercise session the secretion of numerous factors from the exercising skeletal muscles is activated. Moreover, blood flow is redirected to metabolically active muscles and paradoxically occurs in combination with increased perfusion and decreased hypoxia of a tumor, suggesting a mechanism of exercise-induced regulation of the tumor microenvironment [22-24].

More specifically, a single exercise session leads to sympathetic activation, increased blood flow, increased temperature and endocrine regulation, through the secretion of myokines, catecholamines and other hormones of exercise. This whole-body response causes increased perfusion, oxygen supply and metabolic disorganization of the tumor, as well as production of reactive oxygen species (ROS) and cell damage both inside the tumor and in its microenvironment. Interestingly, exercising at higher intensities may offer more or different benefits than the usual forms of exercise [25], with a possible stronger effect on the tumor microenvironment [22-24]. These exercise-induced acute changes can further induce the activation of signaling pathways that prevent tumor metastasis [6].

1.4. Chronic effects of exercise in cancer

Prolonged physical inactivity is associated with increased levels of many growth factors and hormones in the systemic circulation, which can create a pre-tumorigenic environment. In contrast, the exposure of the body to regular exercise stimulates the exchange of signals between its various tissues and organs, again through the secretion of hormones, cytokines and growth factors into the circulation. These factors can now beneficially regulate an integrated homeostatic network at cellular, tissue and whole-body level.

Specifically, exercise-induced adaptations cause reprogramming of the body's systems, which may be characterized by alterations in availability, mobilization, recruitment and function of specific cell types and molecules, possibly altering their bioavailability in the "remote" microenvironment of a tumor. In other words, changes in physiological systems caused by chronic exercise affect basic regulatory mechanisms, such as angiogenesis, metabolism and immune function, contributing to a cumulative anti-tumorigenic effect [22, 24].

Moreover, changes in communication between the various organs and systems of the body, induced by regular exercise training, promote normal adaptations through a variety of homeostatic circuits. For instance, the maximum degree to which the body can transport and use oxygen to produce work during physical exercise determines its maximum oxygen consumption (i.e., maximal aerobic capacity or VO_2max) and reflects its cardiorespiratory fitness. Regularly repeated exercise sessions can induce significant improvements in VO_2max and this remarkable adaptive capacity of the body allows for a constant redetermination of a new homeostatic "set point", which increases the body's ability, and obviously the ability of its tissues and cells, to withstand subsequent physiological stresses as well as pathological conditions, e.g., the onset of a cancer [22, 24].

2. Implementing Exercise Programs for Cancer Patients

A primary goal of exercise intervention programs in cancer patients is to improve their functional ability and quality of life, both during and after the completion of the treatment [26,27]. Indeed, retaining the independence and self-care, as well as alleviating the symptoms and the side effects of treatment such as fatigue, arthralgia, insomnia, depression, diarrhea, loss of taste, etc. are particularly important in daily life of these patients. Furthermore, cancer patients should take advantage of the acute and chronic beneficial effects of exercise (see above) to reduce the risk of disease recurrence and increase survival rates and, thus, all patients in stable condition should be encouraged to participate in physical activity programs [16, 28].

3. *Contraindications and precautions for exercise testing and prescription in cancer patients*

After cancer diagnosis, the specific therapeutic strategy selected, which may include a combination of different types of treatment, should be accompanied by an overall assessment of the patient's ability to participate in a physical exercise program or exercise testing [8,29]. Specifically, a thorough biochemical and clinical assessment is necessary before a patient's participation in a (personalized) program, in order to recognize potential precautions or contraindications to exercise and ensure patient's safety [30]. Clinical complications that may be encountered are usually related with the cardiovascular, respiratory, musculoskeletal, gastrointestinal or nervous system, as well as with hematological conditions [29,31]. Thus, a regular re-evaluation of several physiological parameters associated with the abovementioned systems' function is necessary in order to ensure the early detection of possible complications and side-effects. In this context, cancer exercise professionals should be able to recognize signs and symptoms related with clinical complications and treatment related adverse effects. In case of absolute contraindications, exercise sessions should be postponed and patient refered to the attendant physician **(Table 1)**. On the other hand, if relative contraindications exist, exercise program(s) and/or testing need to be subjected to modifications **(Figure 1)**.

Table 1: Clinical conditions that indicate potential complications in various physiological systems and constitute absolute contraindications for exercise testing and prescription in patients with cancer [29, 31].

ABSOLUTE CONTRAINDICATIONS FOR EXERCISE TESTING AND PRESCRIPTION
Hematological Conditions
o Do not exercise before blood draw o Absolute platelet count <50,000 o Hemoglobin concentration <10.0 g/dL o Absolute neutrophil count $<0.5 * 10^9/L$
Systemic Conditions
o Fever >37.8°C / 100°F
Cardiovascular Conditions
o Resting Heart Rate >100 bpm, or <50 bpm o Resting Systolic Blood Pressure >145 mmHg, or <85 mmHg o Resting Diastolic Blood Pressure >95 mmHg o Chest pain o Arrhythmias o Swelling of ankles / arms / neck
Musculoskeletal Conditions
o Chest pain o Severe cachexia (weight loss >35% of the body weight before the disease) o Karnofsky performance status <60% o Excessive fatigue and muscle weakness
Respiratory *Conditions*
o Severe Dyspnea o Cough o Wheezing

Gastrointestinal *Conditions*
o Vomiting or Diarrhea persistened for 24-36 hours o Nausea o Dehydration
Neurological *Conditions*
o Peripheral neuropathy o Blurred vision o Significant cognitive impairment

***bpm:** beats per minute*

RELATIVE CONTRAINDICATIONS AND PRECAUTIONS FOR EXERCISE TESTING AND PRESCRIPTION

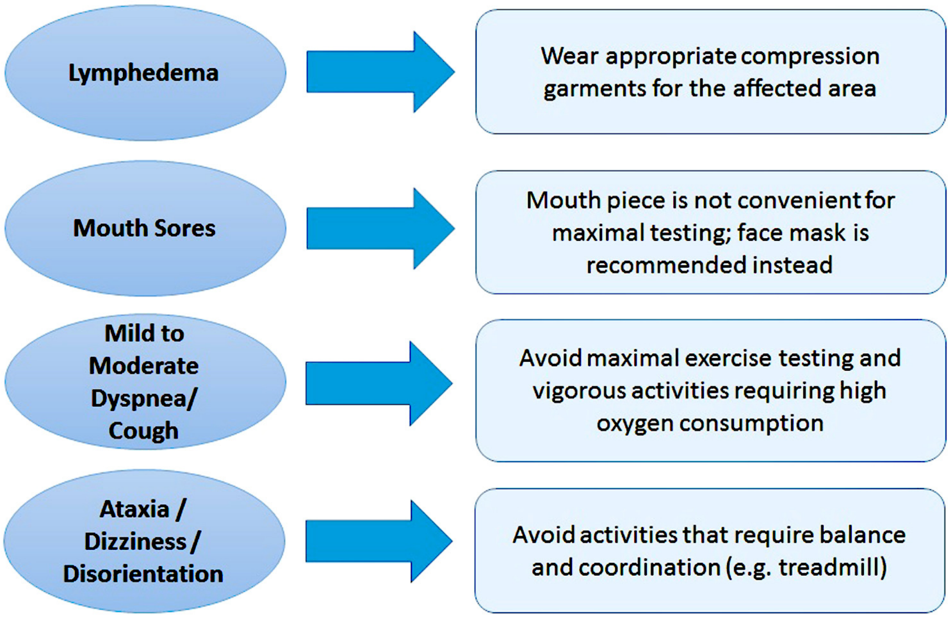

Figure 1: Clinical conditions that constitute relative contraindications requiring modifications of exercise testing and prescription in patients with cancer [29, 31].

4. Special Precautions and Potential Complications Related To The Type Of Cancer And The Treatment Modalities

As already mentioned, physical exercise is a reliable and effective intervention that should be used as a complementary therapy in clinical practice during primary or adjuvant cancer therapy [8,10,11]. Nevertheless, to ensure patients' safety, the risks arising from physical inactivity should be balanced against possible risks associated with exercise in cancer patients [32, 33].

The complexicity of cancer disease and the eterogenity of side effects that individuals with cancer deal with make it difficult to determine a group of evaluation tests for every single type of cancer. Nevertheless, for some types of cancer there are specific precautions and guidelines, related to the tissue and the body area affected by the disease or the treatment modality employed, which should be taken into consideration before the exercise testing and prescription [29,31] **(Table 2; Figure 2)**. Again, it is essential for cancer exercise specialists to be aware of the common symptoms and side effects associated with both the specific type of cancer and the treatment used. Bone fractures, cardiovascular events, neuropathies, fatigue and musculoskeletal disorders are some of the side effects of anticancer therapy that can affect physical performance and increase the risk of clinical complications, both during the evaluation tests and the exercise program [34].

Table 2: Cancer type-specific precautions and guidelines for exercise [29, 31].

SPECIAL PRECAUTIONS RELATED TO SPECIFIC TYPES OF CANCER
Breast Cancer
Before starting an exercise program or testing, it is recommended to assess shoulder mobility and strength, especially if surgery has been performed with simultaneous removal of lymph nodes.
Prostate Cancer
Before participating in exercise programs, it is suggested to assess muscle mass and strength. Moreover, evaluate for muscle atrophy and metastatic bone disease regularly.
Colon Cancer
Patients with ostomies should not engage in water exercise programs and should follow all the physician's instructions for the prevention of infections. Physician's permission is needed for the participation in resistance exercise programs, because there is a high risk of hernia around the ostomy.
Gynecological Cancer
Patients with severe obesity need additional medical evaluation to assess exercise safety. It is also suggested to be assessed for the presence of lower limb lymphedema, before high-intensity aerobic exercise or resistance training.
Multiple myeloma These patients should be treated as having osteoporosis, because they deal with a great risk of bone fractures. Avoid testing procedures and exercises with high risk of falling.

SPECIAL CONSIDERATIONS RELATED TO ANTI-CANCER MODALITIES

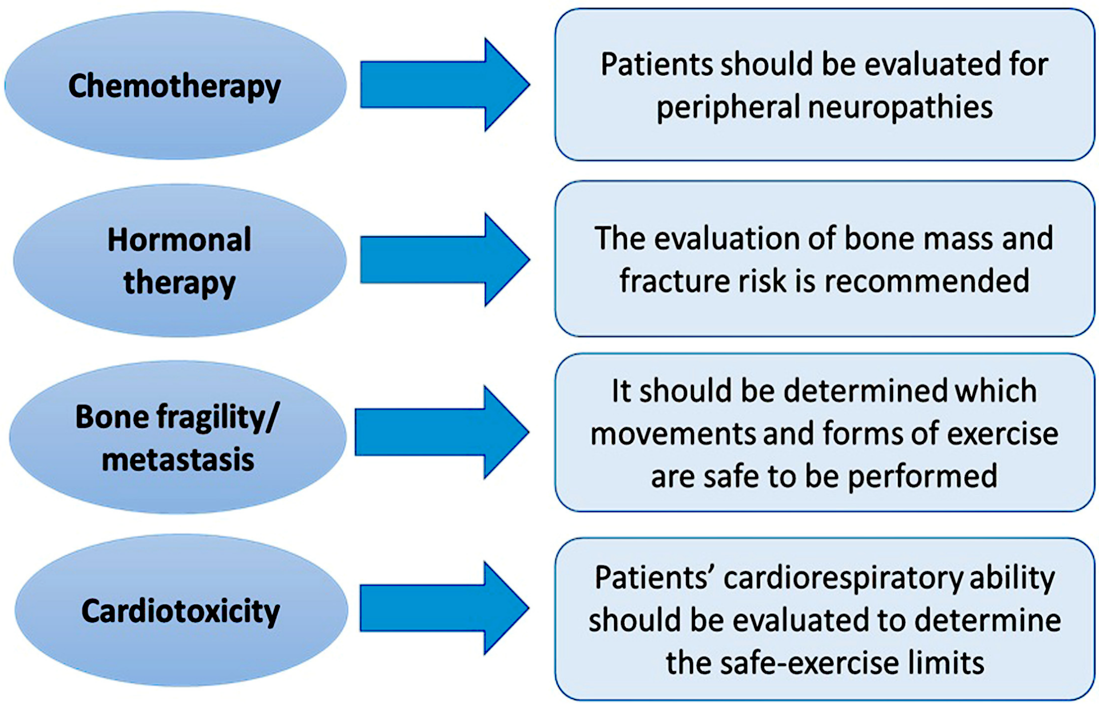

Figure 2: Safety precautions and treatment-specific complications, which should be considered before exercise testing and prescription [29, 31].

5. Exercise Testing

Cancer patients should be thoroughly evaluated for all health-related physical fitness parameters before engaging in therapeutic exercise programs. However, this time-consuming and demanding monitoring could be a barrier to their inclusion in exercise programs, possibly leading to their abstention from physical activity. Thus, according to the recently updated ACSM guidelines [31], for most cancer survivors a previous evaluation is not required to start low-intensity activites like walking, stretching and resistance exercises.

Patients with cancer receive a variety of local and systemic cytotoxic therapies during their active treatment, which often result in several side effects or treatment-induced morbidities and may increase the risk of exercise-associated complications. Thus, before the prescription of an appropriate, personalized exercise program, a detailed medical history is necessary, as well as a clinical, cardiorespiratory, neurological and musculoskeletal examination, in order to assess the exercise safety or the need for further evaluation [35].

Furthermore, in high-risk populations, like older adults or those with a sedentary lifestyle before cancer diagnosis, a thorough assessement of functional ability and health-related parameters is fundamental before joining exercise programs at any phase of their treatment or survivorship [36, 37]. It is worth mentioning that in high-risk patients the possibility to already have, or develop in the future, a cardiovascular disease is 30% to 80% [38-40]. Lastly, during the process of re-evaluating the patient's health condition, it is important to apply the same monitoring procedures under the same conditions performed in the initial assessment, so as the findings to be comparable to each other.

5.1. Cardiorespiratory capacity

Research evidence has documented that cardiorespiratory capacity can be safely assessed in adult cancer patients through both maximal and sub-maximal exercise testing procedures. The American Thoracic Society (ATC) and the American College of Chest Physicians (ACCP) have reported that the risk of death, or the likelihood of life-threatening complications for a patient during the exercise testing is 2 to 5 every 100,000 tests [41].

5.1.1. Cardiorespiratory capacity assessment using a maximal exercise testing

As in other clinical populations, the best choice for maximal exercise testing of cardiorespiratory endurance is an open circuit ergospirometry system using a treadmill or a stationary bike. Ergospirometry is a stress test to continuously and simultaneously monitor the heart function and the respiratory gases exchange during exercise. During a maximal exercise testing, the exercise intensity is increased gradually up to the maximal effort, achieving the maximum oxygen consumption (VO_2max), or the peak oxygen uptake (VO_2peak) [42].

In order VO_2max to be achieved, a patient being tested should fulfil specific criteria, such as the stabilization (attainment of a plateau) of maximum oxygen consumption during the last two stages of the exercise testing and the achievement of maximal heart rate. However, many patients with cancer fail to attain the plateau of VO_2max, frequently due to muscle and not cardiorespiratory fatigue, as their muscle function is affected by both the disease and the anti-cancer treatment. In such cases, VO_2peak is used for the evaluation of cardiorespiratory capacity of those patients [43, 44].

5.1.2. Cardiorespiratory capacity assessment using a submaximal exercise testing

When the direct measurement of VO_2max, which is the gold standard method for the determination of cardiorespiratory (aerobic) capacity, is not possible, various sub-maximal tests can be used instead, based on which the VO_2max value is estimated through the appropriate equations.

Specifically, the "6-minute walk test" (6MWT) is a popular, validated and reliable test for the estimation of VO_2max and has also been used in cancer patients [45]; the patient is asked to cover the longest possible distance by walking but not running, during the given time of 6 minutes.

A modification of the 6MWT is the "12-minute walk test" (12MWT), which is performed on a treadmill. After a 2-min warm up, the patient should walk as fast as he/she can for 12 minutes on the treadmill, aiming to cover as much distance as possible. The patient chooses the walking speed and is allowed to change it during the test [46].

Another submaximal testing procedure used in cancer patients for the evaluation of cardiorespiratory capacity is the "1-mile Treadwalk test", which assesses the time required to cover the distance of one mile (1,609 meters) while the patient walks on a treadmill as fast as he/she can [47].

5.2. Muscle strength

Muscle strength is an essential parameter of physical functioning, which is directly influenced by the adverse effects of the anticancer therapies that patients usually experience, such as cachexia, muscle atrophy, and fatigue. Depending on the muscle group assessed and the specific purpose of the assessment, muscle strength can be measured in a variety of ways.

Specifically, muscle strength can be assessed with a dynamometer during an isometric contraction, specifying the evaluation only in the muscle group activated in this specific measurement. Interestingly, however, performance in the handgrip strength assessment, which is a simple and commonly used test, has been associated with the overall strength, functional ability, quality of life and survival rates of cancer patients [48]. In addition, isokinetic dynamometers are widely used to assess muscle strength in either the upper or lower extremities, as isokinetic dynamometry is considered a safe and reliable option for many clinical populations, including cancer patients [49-51].

The measurement of one repetition maximum (1-RM, which corresponds to the highest external load that can be overcome only once when performing a certain movement with perfect technique) is considered the most direct assessment of muscle strength and has been used also in cancer patients [52]. The individual being tested performs consecutive repetitions with a submaximal load, which gradually increases after the appropriate interval, until reaching the maximum load that can be moved to complete only a single repetition (1-RM) [53]. However, as the measurement of 1-RM requires the individual to be familiar with the resistance training, it may be quite demanding for most cancer patients, especially for those who did not participate in exercise programs before the diagnosis of the disease. Therefore, it is better and safer for a cancer patient to perform more repetitions with lower loads [54], e.g., 2 to 10 submaximal repetitions, and muscle strength corresponding to 1-RM can then be estimated using the appropriate prediction equations [55].

5.3. Functional ability

As muscle strength, balance and functional ability are interrelated parameters that affect each other, evaluation tests which activate multiple muscle groups and, at the same time, require balance control can be used to assess the functional ability of a cancer patient. Such tests are the "Sit-to-Stand" and the "Time Up and Go", which are both indicative of patient's functional ability [56].

In particular, the "Sit-to-Stand" test evaluates the number of consecutive repetitions that can be performed within 60 seconds, with each repetition beginning and ending in the sitting position. Similarly, the "Time Up and Go" test evaluates the time that the patient needs to get up from a chair, walk three meters, turn, walk back and sit in the chair, and is mainly intended for older patients who suffer from comorbidities and their dynamic balance has been significantly affected [57]. The height of the chair used in both tests is suggested to be 42-46 cm, considering that the patient's knee angle should be approximately 90^{o} while sitting. Also, the chair should not have armrests and the patient must perform the tests with his/her arms crossed in front of chest [58].

5.4. Flexibility

Flexibility represents an individual's ability to move one or more joints within their normal range of motion without restriction or pain and is one of the physical fitness parameters that affect his/her functional ability and daily life. Flexibility is assessed separately for each joint while there is no specific test to assess overall body flexibility. Cancer treatment modalities such as surgery and radiation therapy possibly affect flexibility in the corresponding region of the body and can result in muscle impalance. Depending on the area that may have been affected, there are specialized flexibility evaluation tests measuring the range of motion in a particular joint with a goniometer [59, 60].

6. Evaluation of Lymphoedema

Lymphoedema is a chronic condition in which lymphatic fluid and proteins accumulate in the interstitial tissue, leading to inflammation, swelling, fibrosis, and adipose hypertrophy. Skin induration and decreased range of motion in the affected area have also been reported [61].

The evaluation of an upper or lower limb lymphoedema through the measurement of the limb circumference is the most widely used method, while its reliability can be ensured if a standardized protocol is followed. Actually, this method does not measure the limb volume but the sequential changes in limb circumference, after the medical diagnosis of lymphoedema [62]. Therefore, when an upper extremity lymphoedema is assessed, e.g. in women who have undergone breast cancer surgery with simultaneous lymph node removal, the percentage difference in circumferences' sum between the upper limbs can be used. The patient should be in a sitting position with the arm in 90^{o} abduction, while the multiple upper limb circumferences are measured with a tape measure at intervals of 5cm from the metacarpophalangeal joints to the base of the axilla. When the percentage difference between the two upper extremities is greater than or equal to 5%, the lymphoedema is considered as clinically significant [63]

Similarly to the assessment of upper extremity lymphoedema, various protocols have been also used for the lower extremities assessment (Leung et al., 2015). For a brief assessment, only three circumferences can be measured, i.e., at the dorsum of foot, mid-calf and mid-thigh [64]. If a more detailed evaluation is needed, again the sum of circumferences at 10 cm intervals from the ankle to the groin can be used [65].

7. Therapeutic Exercise Interventions for Cancer Patients

Research evidence has convincingly revealed that exercise programs can be a supportive intervention for oncology patients, helping them cope with cancer-related complications and treatment side effects. Therefore, the ACS and ACSM suggest physical activity as a complementary therapy during and after the completion of cancer treatment [8, 66] **(Figure 3)**. However, cancer exercise professionals should bear in mind that, evenif patients with cancer receive the same medications, they usually deal with different symptoms, complications and side effects. Thus, each patient is unique and needs a personalised physical exercise program that will be subjected to modifications during the cancer treatment [67].

7.1. Exercise programs after cancer surgery

It is very important for cancer patients not to stay in bed and remain inactive for days after a surgery but, instead, to start exercising as soon as possible. Thus, even on the first postoperative day they can and should be engouraged to start walking inside the hospital or at home, for 5 to 10 minutes twice a day [59]. Indeed, the immediate mobilization of these patients after surgery and their participation in therapeutic exercise programs as soon as after removing the surgical drains is a safe and beneficial practice, if there is not any other contraindication, such as anemia, fever, active infection etc. Specifically, studies have revealed a significant improvement in shoulder mobility, lymphoedema and postoperative complications such as hematoma or infection in women with breast cancer who engaged in exercise programs as early as the first postoperative day compared to control group [68, 69]. In general, in the first two postoperative weeks the exercise programs should include walking and flexibility exercises, while it may take up to eight weeks for a cancer survivor to return to a regular physical activity program [70].

7.2. Aerobic exercise

Exercise programs focused on improving cardiorespiratory (aerobic) capacity are very important, since there is a strong negative correlation between the aerobic capacity of cancer patients and disease mortality. In other words, patients with better cardiorespiratory capacity have a significantly lower risk of premature death from cancer or other comorbidities [71].

Cancer patients should accumulate at least 150 or 75 minutes of moderate- or high-intensity aerobic activity, respectively, per week [9]. As moderate-intensity exercise is defined a physical effort at 40% -59% of the individual's VO_2 reserve, or at 64% - 75% of his/her maximum heart rate (MHR), or at the level 12-13 on Borg's Perceived Exertion Scale (PES). Similarly, high-intensity exercise is defined a physical effort at 60% - 89% of the VO_2 reserve or at 76% - 95% of the MHR, or at level 14-17 on the Borg's PES **(Figure 3)**.

A basic principle of an aerobic exercise program is that exercise intensity should be increased gradually, to be well tolerated by the patient and the aforementioned goals to be achieved. In particular, in the first week of the aerobic program, a cancer survivor can start with three short, 20-minute sessions, which may include low-intensity walking or any other aerobic exercise at 50% – 70% of heart rate reserve (HRR), or at level 14-17 on the PES scale [37]. There is a wide variety of activities that improve cardiorespiratory capacity and can be implemented in several ways, indoors or outdoors, depending on the patient's preferences, his/her previous physical activity levels, the available equipment, and the specific characteristics of the disease. Walking or running is the most preferable form of aerobic exercise for the majority of patients that can be performed either on a treadmill or outdoors [7,12,72]. In addition, bicycle or other fitness equipments can be used for aerobic exercise. However, stationary bike or water exercice may be the most suitable forms of exercise for patients at high risk of falls or fractures [6,73]. Regarding the outdoor exercise programs, which are very popular for the vast majority of this clinical population, the weather conditions, as well as the ground and the overall environmental conditions should be considered, as the risk of infections and falls may be increased [74].

7.3. Resistance exercise

It is well known that resistance exercise training in cancer patients undergoing first- or second-line treatment improves muscle strength, maintains lean body mass, reduces body fat and mitigates the musculoskeletal system-related side effects of treatment [10, 12, 75].

Cancer patients should also be engaged in resistance exercise programs at least two to three times per week in order to improve muscle function and strength of the major muscle groups of the body [9,76,77]. Major muscle groups are considered the core muscles, the quadriceps, hamstrings, gluteus and triceps, which can be trained with elastic bands, dumbbells, resistance machines or the body weight. Similarly to the aerobic physical activities, the intensity in resistance exercise should be gradually increased. At the beginning of a therapeutic exercice intervention, the extrenal load should be lower than 30% of 1-RM, building up slowly with small escalations [12, 53, 78], **(Figure 3)**.

7.4. Flexibility exercises

Flexibility exercises are an integral part of exercise intervention for patients with cancer and should be performed at least two to three times per week, or daily for more health benefits **(Figure 3).** Flexibility exercises could take place during the warmup or the cool down periods of the aerobic or resistance exercise sessions. Treatment modalities, such as surgery or radiation therapy, usually result in muscle imbalances and, hence, stretching exercises at the affected region(s) of the body should be performed, though carefully and gently [79]. Furthermore, muscle stretching exercises can also be performed in all the major muscle groups to prevent muscle shortening, impaired muscle function, cramps and pain.

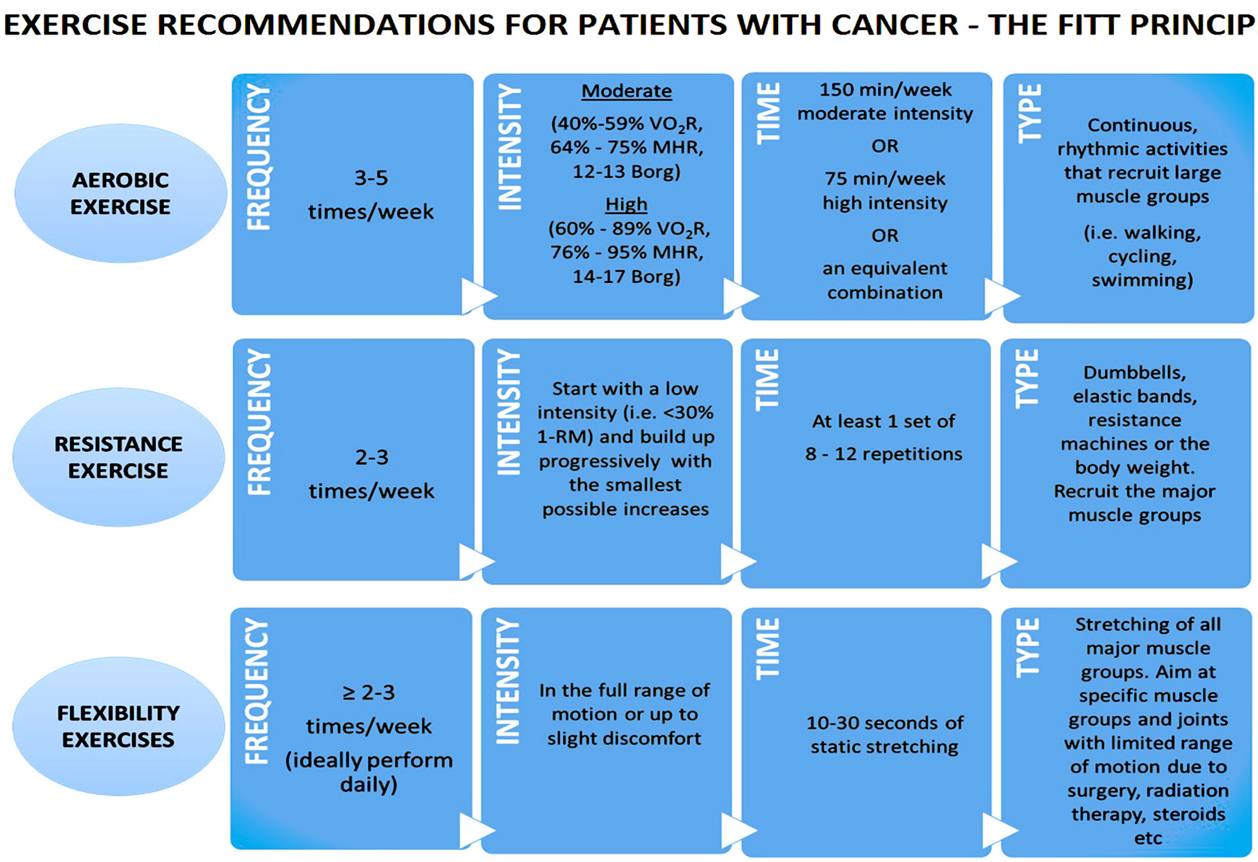

Figure 3: A synopsis of the exercise recommendations for cancer patients based on the Frequency – Intensity - Time – Type (FITT) principle [29, 31].

7.5. Water exercise

Exercise in water or swimming could be an ideal form of exercise for cancer patients with metastastic bone disease. However, it is not suitable for patients with catheters, central lines, feeding tubes or ostomies, as well as for immunocompromised patients, because of the high risk of bacterial infection. In addition, cancer patients subjected to radiation therapy should avoid exercise in water not only because of the high risk of infection but also due to the increased possibility of irritation in the area exposed to radiation [29].

7.6. High impact exercises and contact sports

Bone metastasis is a common form of disease recurrence in many types of cancer (e.g., multiple myeloma, breast, prostate and lung cancer) and, due to the high risk of bone fractures in patients diagnosed with metastatic bone disease, it is important to determine which movements and forms of exercise are safe for them. Specifically, given the increased fragility of the bones in those patients, it is necessary to modify their exercise program by a) limiting the high impact exercises and those with high risk of falling, b) reducing the intensity and the amount of exercises and c) avoiding the participation in sports characterized by physical contact. Thus, stationary bike or walking on a treadmill is more preferred than running or using elliptical machines. The participation in contact sports should be particularly avoided after a cancer surgery in order to protect the surgical wound from further damage [9, 29].

7.7. Pilates and Yoga

The role of cancer exercise specialist is very important not only for engaging patients with cancer in the appropriate, personalized exercise program but also to ensure their adherence to the program. In this context, participation of these patients in popular forms of exercise, such as Pilates and Yoga, may be a strong motivation, thus increasing the possibilities of their long-term compliance in the program.

The Pilates method targets on improving muscle strength and flexibility, and the exercises used in this method are characterized by control, accuracy, concentration and proper breathing [80]. Different exercise protocols focusing on Pilates method have been used, having beneficial effects on women with breast cancer in terms of improving muscle strength and functional ability, and reducing fatigue and lymphoedema. In addition, these protocols have been shown to mitigate the symptoms of pain and depression, thus improving the patients' quality of life [81-83].

Yoga is an ancient Indian practice that trains both mind and body [84]. So far, several studies have used Yoga as a form of exercise intervention in patients with lymphoma, breast, lung and ovarian cancer. Overall, evidence from those studies suggests that Yoga can improve muscle strength and flexibility and reduce some of the adverse effects of cancer treatment, which impair patients' functional ability and quality of life, such as cancer-related fatigue, anxiety and depression [85-88].

8. Special Considerations for Exercise In Cancer Patients

Cancer patients undergoing chemotherapy may occasionally experience nausea and fatigue during the treatment cycles and, as a result, frequent modifications of their prescribed exercise may be needed. Thus, when such symptoms are present the exercise intensity and/or duration should be scaled down.

Moreover, there are evidence suggesting that HRR may be a less reliable variable in monitoring the intensity of aerobic exercise in cancer survivors during or immediately after their treatment, due to treatment-induced changes in the values of resting and maximum heart rate. Hence, it is recommended to use Borg's scale (PES), instead, for monitoring exercise intensity and physical effort during and immediately after the phase of active treatment.

Furthermore, for immunocompromised patients, e.g., because of receiving an immunosuppressive medication after a bone marrow transplantion, exercising in a controlled health care environment or at home is a better option than exercise in a public center or gym. If this is not feasible, care should be taken to reduce the risk of possible infection.

In addition, in high-risk cancer patients, the participation in supervised exercise programs, when this is feasible, should be preferred, while they certainly should not remain physically inactive for long periods of time [89]. For instance, in cancer patients with comorbities such as metabolic disease or type 2 diabetes, along with a high risk for, or already diagnosed, cardiovascular disease, exercise is strongly recommended to be performed under supervision. Similarly, when cancer is at an advanced stage, the patient has bone metastases, or develops dementia, exercise should also be supervised [29, 31].

Research evidence indicates that exercise benefits related to quality of life and cardiorespiratory or musculoskeletal health of cancer patients are increased when physical activity programs are performed under the supervision of a specialist rather than without supervision [4, 56, 90, 91]. Similarly, the level of patients' adherence to the exercise programs is higher when exercise is performed under supervision [92].

On the other hand, when exercise is not possible to be closely supervised, the surveillance of exercise programs through modern telecommunication and information technologies is a useful alternative, which can be very efficient on improving the functional ability and quality of life of cancer patients (93). In particular, exercise programs overseen from distance, utilizing appropriate telecommunication tools in patients with breast, lung and colon cancer, have been found to have positive effects on cardiorespiratory endurance, BMI, cancer-related fatigue, sleep quality and overall quality of life [94, 95].

9. Conclusions and Future Perspectives

Adequate scientific data have shown that regular physical activity or exercise training can play an important role in prevention and control of cancer. Indeed, regular physical activity is associated with reduced risk of developing cancer and, while the mechanisms that mediate this role of exercise in cancer prevention remain to be further characterized, the existing data are strong and compelling, especially for certain types of cancer. Moreover, despite the effectiveness of various anti-cancer therapies, many of them cause adverse events and have side effects such as fatigue, anxiety, depression and poor quality of life, which can be alleviated through exercise. In general, exercise both during and after treatment improves the function of many physiological systems in the body, resulting in a variety of beneficial, physical and psychosocial, effects for patients with cancer.

However, further research is needed to reveal the optimal dose of physical activity or exercise for minimizing the risk of cancer, alleviating the side effects of treatment and improving functional ability of patients with cancer. Thus, targeted clinical trials are required to investigate the relationship between exercise dose and clinical responses. Revealing the effectiveness of specific therapeutic exercise programs, depending on their particular characteristics (in terms of intensity, frequency and duration), would make a decisive contribution to establishing an interdisciplinary consensus for the integration of therapeutic exercise into clinical practice for both the prevention and treatment of cancer.

More specifically, future research needs to answer key questions such as whether there is a minimum and maximum limit for physical exercise to benefit the patient with cancer and what those potential limits are; Also, whether the type of cancer or the time during which the exercise is used, depending on the stage of the disease (i.e., for prevention, after diagnosis, during treatment, or after the completion of treatment), affects those limits of the beneficial effect of exercise. Thus, these studies could contribute to the necessary enrichment of scientific data particularly regarding the relationship between exercise dose and specific outcomes of the disease, such as its relapse, patient survival, and progression-free survival [5].

It is also important to emphasize that physical exercise, in addition to the need of being a constant general recommendation for the patients with cancer, must be further examined in the context of its individualized utilization, depending on the health status and the treatment regimen of each patient [6, 96]. In particular, the exercise prescription should be adjusted according to the individual characteristics of the patient and his/her medical history, medication and response to exercise, utilizing the different types of exercise according to the patient's preferences. In other words, prescribing exercise for a cancer patient could be characterized by such a degree of personalization that, actually, exercise oncology would have the same targeting as the personalized (precision) oncology, according to which treatment is adapted to specific characteristics of the cancer in each individual patient [9, 19, 96].

It is noteworthy that, despite the fact that several scientific and public health organizations worldwide have published guidelines for the use of physical exercise as a complementary therapeutic intervention for cancer patients, in order to mitigate the adverse effects of anti-cancer therapy but also to prevent the disease, however the majority of patients and cancer survivors are not regularly physically active. Hence, it is very important clinicians to evaluate the health status of their patients and advise/refer them accordingly, either for further evaluation of their ability to exercise, or directly to participate in personalized exercise programs, at home or in properly organized centers [8, 96]. Certainly, this will require the coordination of the health services provided, through the interdisciplinary collaboration of properly trained health and exercise professionals, as well as the adoption of a joint strategy, by the attendant physicians, patients and cancer exercise specialists that will integrate exercise as part of the clinical practice for cancer [5, 96, 97].

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