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Exercise for oncological patients: rehabilitation

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DESCRIPTION OF THE EVIDENCE COLLECTION METHOD:

This study revised articles from the MEDLINE (PubMed) databases and other research sources, with no time limit. To do so, the search strategy adopted was based on (P.I.C.O.) structured questions (from the initials "Patient"; "Intervention"; "Control" and "Outcome". As keywords were used: (Neoplasms OR Carcinogens OR Tumors OR Cancer) AND (Fatigue OR Asthenia OR Lassitude OR Muscle Fatigue OR Fatigue OR Muscles OR specific muscle OR Mental Fatigue OR Fatigue, Mental OR Cancer-related fatigue) AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance); (Neoplasms OR Carcinogens OR Tumors OR Cancer) AND (Fatigue OR Asthenia OR Lassitude OR Muscle Fatigue OR Fatigue OR Muscles OR Specific Muscle OR Mental Fatigue OR Fatigue, Mental OR Cancer-related Fatigue) AND (Chemotherapy, Adjuvant OR Combined Modality Therapy OR Drug Therapy,combination OR Antineoplastic Combined Chemotherapy Protocols) AND (Exercise Tolerance OR Oxigen Consumption* OR Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Physical Fitness OR Physical Conditioning OR Physical Endurance); (Neoplasms OR Carcinogens OR Tumors OR Cancer) AND (Fatigue OR Asthenia OR Lassitude OR Muscle Fatigue OR Fatigue OR Muscles OR specific muscle OR Mental Fatigue OR Fatigue, Mental OR cancer-related fatigue) AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance OR Intensity exercise); (Neoplasms OR Carcinogens OR Tumors OR Cancer) AND (Fatigue OR Asthenia OR Lassitude OR Muscle Fatigue OR Cancer-related fatigue) AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance); Neoplasm AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance) AND Quality of Life ; (Bone Neoplasms OR Neoplasms Metastasis) AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance) AND (Fracture Bone OR Fractures, Bone) AND (Exercise OR Physical Therapy) AND Fracture AND Neoplasm; (Bone Neoplasms OR Neoplasms Metastasis) AND (Exercise OR Physical Fitness OR Exertion OR Exercise Therapy OR Sports OR Exercise Movement Techniques OR Physical Fitness OR Physical Conditioning OR Physical Endurance) AND (Fracture Bone OR Fractures, Bone) AND (Exercise OR Physical Therapy) AND Fracture AND Neoplasm; (Neoplasms OR Carcinogens OR Tumor OR Cancer) AND (Signs and Symptoms Respiratory OR Dyspnea) AND (Breathing Exercise OR Exercise Therapy); (Neoplasms OR Carcinogens OR Tumor OR Cancer) AND (Oxygen Inhalation Therapy OR Positive Pressure Respiration OR PEEP) ; Neoplasms OR Cancer OR Tumor OR Carcinogens AND Terminally ill OR Terminal Care OR Palliative Care AND Oxygen Inhalation Therapy; Neoplasm AND (Muscle OR Muscle Strength OR Muscle Weakness OR Cachexia) AND (Androgens OR Anabolic Agents OR Nandrolone OR Oxandrolone) AND (Exercise OR Physical Therapy OR Rehabilitation); (Anthracyclines OR Trastuzumab OR Ciclofosfamide) AND (Physical Activity OR Exercise) AND (Cardiotoxicity); Neoplasm AND Thrombocytopenia AND (Exercise OR Rehabilitation OR Physical Therapy). With the above keywords crossings were performed according to the proposed theme in each topic of the (P.I.C.O.) questions. After analyzing this material, articles regarding the questions were selected and, by studying those, the evidences that fundamented the directives of this document were established.

LEVEL OF RECOMMENDATION AND EVIDENCE:

A: Strong consistency experimental or observational studies.

B: Fair consistency experimental or observational studies.

C: Case reports (uncontrolled studies).

D: Opinion lacking critical evaluation, based on consensus, physiological studies or animal models.

OBJECTIVES:

Offering information regarding the benefits of physical exercises in the treatment of oncological patients.

CONFLICTS OF INTERESTS:

There are no declared conflicts of interests.

INTRODUCTION

The advancements on cancer diagnosis and treatment have provided an increase in survival in an evergrowing number of people

with oncological diseases. Many of these patients may present several kinds of disabilities and impairments, either temporary or permanent. These may occur due to either the neoplasia's evolution or to consequences originated before, during and/or after treatment. The role of rehabilitation becomes more and more evident in the care of this population, reflecting as a great value intervention in this context, promoting functionality, independence, social inclusion and quality of life of these patients. Therapeutic physical exercises are a valuable tool for cancer patients rehabilitation, hence the importance of evaluating evidence of its effectiveness in the scientific literature as presented in this directive.

1. Are physical exercises effective in the cancer-related fatigue symptoms?

Fatigue is one of the most frequent manifestations in cancer patients undergoing chemotherapy or chemotherapy combined with radiotherapy treatments. The so-called cancer-related fatigue is associated not only with the treatment's drug effects, but can also be a consequence of the tumor it self or other associated conditions, either metabolical, hematological, or nutritional, that can act as worsening factors. It is a multifactorial condition and its physiopathology is not yet completely known. It leads to physical activity reduction and consequent loss of muscle mass and strength, in addition to worsening the quality of life[1]. Physical exercises are used with the purpose of reducing the fatigue, improving physical capabilities and quality of life of patients undergoing oncological treatment, even faced with evidences of active disease or not[1].

A randomized and controlled study, with 269 cancer patients undergoing chemotherapy, seventy-three male and 196 female, average age of forty-seven years (20-65), comprising of twenty-one different tumors, evaluated this question. The main exclusion criteria was the presence of bone or encephalic metastasis. Two hundred and thirty-five patients completed the follow-up. The exercise program contained high-intensity supervised exercises, preceded by warm-up, resistance training and cardiovascular training, associated with low-intensity training represented by relaxation and body massage, totalling nine hours a week, over the course of six weeks, in addition to traditional care. These activities were distributed along five days a week, with high-intensity training three times a week, with a thirty-minute warm-up, forty-five minutes of resisted training and fifteen minutes of cardiovascular training, alternated with low-intensity training, twice a week, being thirty minutes of relaxation, body consciousness exercises and thirty minutes of massage. The improvement in fatigue was evidenced by the average reduction in -6,6 points (CI 95% -12.3 -0.9; p = 0.02) using the European Organization for Research and Treatment of Cancer Quality of Life Questionarie (FORTC QLQ - C30)[1] **(B).**

The association of high-and low-intensity physical exercises can improve fatigue in patients with several types of cancer during chemotherapy treatment[1] **(B)**.

Another randomized and controlled study, with 103 cancer patients undergoing radiotherapy for advanced cancer, sixty-six male and forty-seven female, aged in average fifty-nine years, comprehending fifteen different types of tumors, in which all 103 completed the follow-up, evaluated the impact of an exercise program on cancer-related fatigue. The program was comprised of trunk and limbs strengthening therapeutic exercises, aiming great muscle groups of upper and lower limbs, as well as providing of educational material. The didactic material was delivered by the physical therapist, with an exercise program three times a week, with ninety-minute duration, of which the initial thirty minutes were performed with the physical therapist. The aerobic training was not included in the program, although the patients were urged to practice it.

In the analog self-evaluation, improvement in the physical wellness was observed in the intervention group (p = 0.04). Fatigue and vigour were not, significantly, different between groups. Although the performance of therapeutic exercises is viable during clinical radiotherapy in advanced cancer patients and having improved their wellness, this benefit was not sustained and exercise did not interfere in their fatigue. Trunk and limbs strengthening therapeutic exercises, aiming great muscle groups of upper and lower limbs, not associated with aerobic training, as well as delivery of educational material, can be beneficial and improve the symptoms of physical wellness in patients with several types of advanced cancer submitted to radiotherapy, but did not result in sustained benefit[2] **(B)**.

In a randomized and controlled study involved fifty-seven prostate cancer patients receiving androgen suppression therapy, aged in average seventy years. Patients with bone metastasis were not included in this study. All patients completed the follow-up. The intervention consisted of an exercise program with resisted and progressive aerobic training, twice a week, for twelve weeks. The resistance exercises consisted of chest press, seated row, shoulder press, triceps extension, leg press, leg extension, and leg curl. Abdominal flexion exercises were also performed. The resisted training consisted of two to four series of twelve to sixteen repetitions. The aerobic training contained fifteen to twenty minutes of cardiovascular training with 65% to 80% of HR max and perceived exertion intensity perceived and maintained between eleven and thirteen on the Borg scale. The patients presented increase in lean mass in comparison with the group that received traditional care: total body, p = 0.047; upper limbs, p = 0.001; lower limbs, (p = 0.019). The exercise group also improved several aspects of quality of life, including overall health (p = 0.022) and fatigue reduction (p = 0.021) and reduction in the C-reactive protein levels (p = 0.008). There were no reports of adverse events during the test with 1-MR or intervention exercise. The exposure to exercise significantly improved physical strength, function and balance in males with hypogonadism in comparison with the control group. The exercise regimen was well tolerated and must be recommended as an effective countermeasure to common adverse effects related to the androgen suppresion treatment[3] **(B)**.

Distinct randomized and controlled study involved forty breast cancer patients, submitted to radiotherapy, aged in average forty-three years. Thirty-seven of the patients completed the study. Patients in the intervention group performed a fifty-minute duration exercise program, three times a week, during five weeks. The training consisted of a ten-minute warm-up, thirty minutes of exercises (with stretching exercises focused in scapular waist; aerobic exercises, such as treadmill walking and bicycle riding; and strengthening exercises), and a ten-minute relaxation. The target heart rate was 50% to 70% of HR max, age-adjusted. The analyzed study showed significant improvement in fatigue (p < 0.001) in the intervention group, against control group[4] **(B)**. The paper analyzed presents a small sample and the patients were evaluated immediately after radiotherapy. Studies with larger samples and longer follow-up time are required to better assess the benefits of exercises in this population. Despite the study's limitations, there was no report of negative effects from the exercises during breast cancer radiotherapy. Physical exercise must be stimulated and must be part of these patients' rehabilitation during radiotherapy[4] **(B)**.

The next study in this directive was randomized and controlled for evaluation of the effects of exercises over fatigue in forty-two

hospitalized patients submitted to bone marrow transplant, twenty-six male and sixteen female. Thirty-four patients completed the follow-up. Patients were submitted to supervised aerobic exercises, daily, using ergometric bicycle for fifteen to thirty minutes (with training heart rate of 75% HR max for their age), fifteen to twenty minutes of trunk, upper and lower limbs resisted exercises (two series of up to twelve repetitions) followed by twenty minutes of relaxation, three times a week, during four to six weeks.

In this study there was improvement in fatigue in the intervention group, however, this difference was not statistically significant (p = 0.405 at the end, p = 0.302 with three months and p = 0.097 with six months)[5] **(A)**.

Randomized, controlled, blind, and larger-sampled studies must be conducted in order to better evaluate the benefits of exercises in the improvement of fatigue in this population. Although this study has not found direct benefit in the improvement of fatigue in patients after bone marrow transplant, we must recommend the performance of physical activity in this population due to the benefits that exercises can, indirectly, provide for their wellness and fatigue **(D)**.

We have found, also, a study that involved twenty-one localized prostate cancer patients, submitted to radiotherapy, aged in average sixty-nine years. The exercise program consisted of a ten-minute warm-up, followed by thirty minutes of aerobic training such as walking, finishing with five to ten minutes of stretching exercises, performed in the morning, before radiotherapy, three times a week, during eight weeks, while the control group did not perform exercises. The intervention group presented statistically significant improvement in fatigue (p = 0.02)[6] **(A)**.

Following that, we verified a study that assessed the effect of an exercise program in 155 prostate cancer patients receiving supressive hormonal therapy, aged in average sixty-eight years. The trunk, upper and lower limbs resisted exercises (two series of eight to twelve repetitions of 60% to 70% of a maximum repetition), three times a week, during twelve weeks, showed to be effective in the reduction of fatigue symptoms in prostate cancer patients during supressive hormonal therapy[7] **(A)**.

Next, a study that involved 121 prostate cancer patients submitted to radiotherapy, aged in average sixty-six years. The patients were divided into three groups: one with aerobic exercises, one with resisted exercises and the last with no exercises, during twenty-four weeks. The resisted exercises (p = 0.010) and aerobic exercises (p = 0.004) showed reduction in fatigue in short-term in prostate cancer patients submitted to radiotherapy[8] **(A)**. Resisted exercise also resulted in improvement in fatigue in long-term (p = 0.002) in comparison with traditional care in this population[8] **(A)**.

Distinct study evaluated the effect of an exercise program in 147 in patients with several types of cancer (most of them breast, hematological, and gynecological), being twenty-four male and 123 female, aged in average forty-nine years. The patients were divided into three groups: physical training, with two hours of individual training (trunk, upper, and lower limbs resisted exercises with training load between 30% to 60% of a maximum repetition, two times a week associated with sports, also two times a week); another performed the same physical training associated with cognitive-behavioral therapy (once a week during two hours); and the third group, no intervention. The physical training (aerobic + resisted), isolatedly, or combined with cognitive-behavioral therapy, obtained significant effects (p < 0.001) in fatigue reduction in patients with several types of cancer when compared to no intervention[9] **(A)**.

Immediate randomized and controlled study involved sixty-nine patients with several types of cancer, fifty-one male and eighteen female. Average age was fifty-seven years. The intervention consisted of stationary bicycle for thirty minutes a day, five days a week. The patients were instructed to maintain a pedaling frequency of about fifty cycles per minute. The training intensity corresponded to a heart rate (HR) of about 80% of maximum heart rate in the exertion test. This intervention was compared to a group that performed stretching exercises. It was observed that the aerobic exercise (training HR = 80% HR max) performed daily over three weeks reduces in a statistically significant manner (p = 0.009) the fatigue symptoms in patients with several cancer diagnoses after surgical treatment[10] **(B)**.

Lastly, we explained about an additional study, randomized and controlled, with 242 breast cancer patients which assessed the impact of an exercise program during chemotherapy. This program included resisted training, compared with aerobic training and usual care. In this study, a resisted exercise program (trunk, upper, and lower limbs), with two series of eight to twelve repetitions with 60% to 70% of a maximum repetition, during twelve weeks, did not show to be effective in the reduction of fatigue symptoms in breast cancer patients during chemotherapy[11].

Recommendation

Supervised exercises for six weeks, with total duration of nine hours a week, with high-intensity training three times a week, of those thirty minutes of warm-up, forty-five of resisted training, and fifteen minutes of cardiovascular training alternated with low-intensity exercises, twice a week with thirty minutes of relaxation, body consciousness exercises and thirty minutes of massage, allow reduction of fatigue in cancer patients submitted to chemotherapy. The association of high and low-intensity physical exercises can improve fatigue in patients with several types of cancer during chemoterapy treatment[1] **(B)**.

Trunk and limbs strengthening therapeutic exercises, aiming great muscle groups of upper and lower limbs not associated with aerobic training, as well as delivery of educational material, can be viable and improve the symptoms of physical wellness in patients with several types of advanced cancer submitted to radiotherapy[2] **(B)**.

Exposure to exercise has significantly improved physical strength, function and balance in males with hypogonadism in comparison with the control group. The exercise regimen was well tolerated and must be recommended as an effective countermeasure to common adverse effects related to the androgen suppression treatment[3] **(B)**.

Trunk, upper and lower limbs resisted exercises, two series of eight to twelve repetitions of 60% to 70% of 1-MR, three times a week, during twelve weeks, is effective in the reduction of fatigue symptoms in prostate cancer patients during chemotherapy[7] **(A)**. Resisted exercises (p = 0.010) and aerobic exercises (p = 0.004) reduced fatigue in short-term on prostate cancer patients, aged in average sixty-six years, submitted to radiotherapy[8] **(A)**. Resisted exercise also led to long-term fatigue improvement (p = 0.002) in comparison with usual care in this population[8] **(A)**. Physical training, aerobic plus resisted, either isolatedly or combined with cognitive-behavioral therapy obtained significant effects (p < 0.001) in the reduction of fatigue in patients with several types of cancer when compared with no intervention[9] **(A)**. Aerobic exercises with training HR of 80% HR max, performed daily during three weeks, reduces in a statistically significant manner (p = 0.009) the symptoms of fatigue in patients with several cancer diagnoses after surgical treatment[10] **(B)**.

2. What are the best intensity and duration of physical exercises for the reduction of cancer-related fatigue symptoms?

As previously mentioned, cancer-related fatigue presents high prevalence in cancer patients. It is present in, approximately, 65% of all cases, of which 29% present severe fatigue[12]. Thus, it is important to know the exercise modalities and intensities to be used in the treatment.

To do so, we selected a study with 269 cancer patients, seventy-three male and 196 female, aged in average forty-seven years (20-65), with bone or encephalic metastasis. This study evaluated the effect of supervised exercise with cardiovascular high intensity and resistance training, relaxation, and body massage, nine hours a week, during six weeks, in addition to traditional care. Only 235 patients completed the follow-up. It was proved that high and low-intensity physical exercises can improve symptoms of fatigue in breast cancer survivor patients[13] **(B)**. The association of high and low-intensity physical exercises can improve fatigue in patients with several types of cancer[1] **(B)**. Supervised exercises for six weeks, totalling nine hours a week, of high intensity three times a week with thirty minutes of warm-up, forty-five minutes of resistance work and fifteen minutes of cardiovascular training and alternated with low-intensity exercises two times a week with thirty minutes of relaxation, body consciousness exercises and, yet, thirty minutes of massage, allow the reduction of fatigue in -6.6 points (CI 95% -12.3 -0.9 with p = 0.02) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ - C30), with effect size from small[14] **(B)** to moderate[1] **(B)**, but always significant, effect size = 0.13 (CI 95% CI -0.06)[3] **(B)** and 0.33 (CI 95% 0.04-0.61)[1] **(B)** respectively.

By studying only breast cancer women, the performance of exercises could not reduce fatigue[11,15] **(B)**, with (SMD -0.12, 95% CI -0.37 to 0.13)[1] **(B)**, reminding that there is a difficulty in recognizing depression symptoms from fatigue in this population[16] **(B)**.

Recommendation

There is benefit in using physical exercises in the reduction of cancer-related fatigue symptoms[1,14] **(B)**, with controversy over this benefit in the population of women undergoing treatment for breast cancer[11,15] **(B)**, even though in the clinical practice there are several reports attesting to these benefits **(D)**. The exercises must be supervised, alternating high-intensity cardiovascular training and resistance work, and low-intensity, relaxation, and massage, totalling nine hours a week for at least six weeks[1] **(B)**.

3. Are unsupervised home physical exercises effective in the reduction of cancer-related fatigue symptoms?

Simple blind study with 119 women with cancer, after chemotherapy, either with or without radiotherapy, and average age of fifty-nine years, analyzed this question. Comprehending three types of tumor: breast, colorectal and ovarian. The patients could read, write and understand English and were capable of signing an informed consent term. Patients with bone marrow transplant, lytic bone lesions, uncontrolled hypertension, diabetes mellitus, pain score over three in a zero to ten scale, orthopedic limitations, major depression history, sleep disorders, chemotherapy in the previous year, acquired immunodeficiency syndrome-related malignancy, leukemia, or contraindications to exercise were excluded. One hundred and six patients completed the study. Those were submitted to an exercise program that consisted of cardiovascular/aerobic training, with one activity modality, e.g., walking, running or riding bicycle, three to five times a week, with intensity of 60% to 80% of maximum heart rate and duration of twenty to thirty minutes of continuous exercise. In addition to monitoring heart rate, the exercise intensity was also measured by the Borg scale to be maintained between twelve and fourteen, until a little difficult. The patients were followed-up via telephone calls. In this specific study, the home exercise program, unsupervised, did not show significant improvement (p = 0.084) in the reduction of fatigue or symptoms related to cancer diagnosis or its treatment, in female patients with cancer diagnosis during or after chemoterapy, either with or without radiotherapy[17] **(B)**, however, it is possible that the patients' adherence to the study may have interfered in the analyzed outcome.

Distinct randomized and controlled study evaluated 119 breast cancer patients during chemotherapy or radiotherapy, aged in average age fifty-one years. One hundred and eight patients completed the study. The participants received written prescription to walk five to six times a day, i.e., moderate intensity walking, with target heart rate of 50% to 70% of maximum heart rate. The regimen was a fast fifteen-minute walk, that later progressed to thirty minutes. This program was performed during the treatment, i.e., six weeks of radiotherapy or three to six months of chemotherapy. In this study, home aerobic physical exercise, moderate-intensity walk, reduced in a statistically significant (p < 0.03) manner the fatigue symptoms in breast cancer patients during the treatment[18] **(A)**.

A new study with sixty-one patients with lymphoma or leukemia post hematopoietic stem cells transplant, aged in average forty-six years, evaluated a supervised aerobic and resisted exercise program, compared with the same program, unsupervised. The training consisted of aerobic exercises such as: treadmill, ergometric bicycle and over ground walking with resistance exercises, e.g.: free weights, machine weights against resistance bands activities. The participants answered the Brief Fatigue Inventory (BFI), both before and after four weeks of training. In this study, the supervised aerobic exercise, as well as the unsupervised training performed in patients with lymphoma or leukemia in the post hematopoietic stem cells transplant period did not prove effective in the reduction of fatigue symptoms[19] **(B)**.

Recommendation

Home aerobic physical exercise such as moderate-intensity walk reduces the fatigue symptoms in a statistically significant (p < 0.03) manner in breast cancer patients during treatment[18] **(A)**. An unsupervised home exercise program, did not prove beneficial in the reduction of fatigue (p = 0.084) or of symptoms related to cancer diagnosis or, even, to their treatment, in female patients diagnosed with cancer during or after chemotherapy and, either with or without, radiotherapy, but it is possible that the patients' adherence to this study may have interfered in the analyzed outcome. We cannot conclude that unsupervised home exercise is not beneficial to this population or to other oncological patients. Additional randomized, controlled and well designed studies are required to demonstrate the benefits of physical exercises in these circunstances.

Knowing the benefits obtained from regular physical activity, we must stimulate and urge these patients to perform physical activities, even unsupervised **(D)**. Supervised aerobic exercise, as well as unsupervised training performed by patients with lymphoma or leukemia in the post hematopoietic stem cells transplant, did not prove effective in the reduction of fatigue symptoms[19] **(B)**. However, this

result does not mean that the exercise is not effective in the reduction of fatigue in this population. Several factors may interfere in the result and the four-week period may have been insufficient to show benefits that could appear in a program of longer duration. We must urge and stimulate patients to perform regular physical exercises as long as their clinical condition so permits **(D)**.

4. Are physical exercises effective in the improvement of quality of life of cancer patients?

Double-blind, randomized and controlled study, evaluated 103 cancer patients submitted to radiotherapy divided into two groups, one control group and the other receiving an interdisciplinary program of physical therapy, trunk and limbs musculature stretchings, and physical activity-related educational material. The parameters of subjective wellness sensation, and the Linear Analog Scale of Assessment, The Profile of Mood States-Short Form, Fatigue-Inertia e Vigor-Activity scales and subscales were evaluated. The resisted exercise program was associated with improvement in wellness of patients with several types of advanced cancer during radiotherapy, even though the benefit was not maintained in long term[20] **(A)**.

A new simple, blind, controlled and randomized study, with a group of fifty-three breast cancer patients, divided into two groups, control and aerobic exercise, three times a week for fifteen weeks, in which fifty-two patients completed the study, evaluated oxygen consumption and found improvement in oxygen consumption peak in the ergospirometry test, and also improvement in the quality of life assessed with the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale. Both aspects presented correlation by the Pearson test, demonstrating the relationship among quality of life, cardiopulmonary function, and physical exercise[21] **(A)**.

Distinct controlled and randomized study evaluated 111 patients aged from eighteen to fifty years, undergoing chemotherapy treatment for lymphoma, breast cancer, gynecological, or testicle cancer, and they were divided into control group or submitted to thirty minutes of supervised aerobic training, two times a week, for fourteen weeks. The study evaluated aspects of quality of life with the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30) and changes in the VO_2 (VO_2 max) consumption peak in ergospirometry test. It found changes in the oxygen consumption peak and in the cardiopulmonary conditioning. However, it did not find changes in the quality of life parameters, maybe due to the variance in the sample used[22] **(A)**.

Another randomized, controlled, simple blind study conducted, evaluated eighty-nine patients with breast cancer using adjuvant therapy after surgery, divided into one control group and the other in use of a multimodal interdisciplinary physical therapy for balance, coordination, flexibility, and relaxation training. It found improvement in the aspects of quality of life assessed by the EQ-5 and EORTC scales, even though the economic cost was high[23] **(A)**.

Recommendation

A strengthening exercises program associated with stretching exercises during oncological treatment (chemotherapy, radiotherapy or hormonal therapy) in breast cancer patients is effective in the improvement of quality of life[20] **(A)**. The aerobic training has beneficial effects in the quality of life of breast cancer survivor patients[20] **(A)**. There is lack of studies to evaluate the improvement of quality of life with physical exercise in other types of cancer, however, reports from less powerful studies demonstrate there are benefits depending on the time of injury, type of cancer, and associated clinical comorbidities **(D)**.

5. Is there added risk of fracture when performing resisted physical exercise in cancer patients with bone metastases?

In our search we could not find studies that evaluated the risk or ocurrence of fracture associated with resisted training exercises in cancer patients with bone metastases.

6. Does resisted-exercise reduce the fracture risk in cancer patients with bone metastases?

We could not find studies that evaluated, specifically, the prevalence of fractures on cancer patients with bone metastasis, submitted to resisted-exercise programs. There are, however, studies that evaluate the influence of the exercises in other risk factors for fracture either associated or not with the presence of metastasis and/or osteoporosis in cancer patients.

A randomized controlled study with 223 post-menopausal breast cancer survivor women evaluated the bone mineral density after twenty months of use of calcium, vitamin D and risedronate isolatedly, or in association with a supervised progressive from moderate to high intensity resisted-exercises program. Around 110 patients completed the study. In this study, resisted physical exercise did not show added benefit to the bone mineral density, but a lower tendendy of bone mass loss over time, in comparison with the drug treatment by itself[24] **(B)**.

A different randomized and controlled study with 106 menopausal patients, sixty-seven of those having completed the study, with breast cancer after radiotherapy or chemotherapy, with only one year of lesion, none of them using drugs for improvement of bone mineral density and free of osteoporosis of any etiology, evaluated the use of a moderate-intensity resisted exercises program during one year, twice a week, regarding the bone mineral density parameters in hip and spine, weight and bone turnover markers. The group that received the physical exercises program showed a lower rate of bone loss with greater preservation of bone mass, thus diminishing the risk of fractures in this population[25] **(B)**.

Another randomized and controlled study, with sixty breast cancer patients using chemotherapy, compared the use of zoledronic acid and oral calcium supplements to an unsupervised home exercise program related to the bone mineral density and found diminished bone mineral density and greater intensity loss of bone mass in the group submitted to exercises[26] **(B)**. Even though, there was no group without any intervention and, therefore, it was not possible to conclude if having physical exercise is better or not than not having any exercise[26] **(B)**.

Recommendation

Studies that evaluate the incidence of fractures and the use of resisted training in non-oncological patients, with mild to moderate osteoporosis, found improvement in the bone mineral density of these patients **(B)**. It is possible that physical exercise promotes a bone loss reduction and maybe a bone density increase in patients with bone metastasis and/or osteoporosis after cancer, leading to a possible reduction in the risk and prevalence of fractures in this population **(D)**. In addition to this, it is possible that there is an increase in muscle tone and that this reflects in improvement in gait and balance, and in the consequent reduction of incidence of falls

and other accidents, thus diminishing the fracture incidence **(D)**. Randomized and controlled studies are required to evaluate the incidence of fractures in cancer patients with bone metastases and/or osteoporosis performing resisted physical exercises, comparing them also to the conventional drug treatment, as well as related to their side effects and the best use parameters **(D)**.

7. Does physical exercise improve respiratory symptoms in cancer patients?

Multicentric study conducted with patients submitted to allogeneic hematopoietic stem cell transplant (HSCT), with a partially supervised program of exercises performed in general from one to four weeks before hospital admission, during the internment period, and that remained in follow-up up to six to eight weeks after hospital discharge showed benefits in the reduction of physical fatigue, dyspnea and improvement to physical performance in the study group when compared to the control group **(A)**. The intervention in the study group consisted of the tolerance of three series and two sessions of resistance a week - light aerobic activity for a few minutes and stretching, resistance (with and without elastic bands with different degrees of resistance from eight to twenty repetitions; two to three series) and aerobic training (walking, twenty to forty minutes or bicycle) during internment. The training intensity was adapted using the Borg scale and they were evaluated in relation to pain, fatigue, emotional state and, depending on the outcome, categorized in three different groups regarding tolerance to exercise: green group, with greater demand in the exercise series performed from thirty to forty minutes; yellow and red groups, with moderate degree of demand in the exercise series performed from twenty to thirty minutes or from fifteen to twenty minutes, according to the patients' clinical conditions. However, regardless of recommendation, the patients should walk without interruption whenever physically possible. The physical exercises were contraindicated in case patients presented signs and symptoms of infection (temperature > 38°), severe pain, nausea and dizziness, thrombocytopenia (lower than 20 thousand) and hemoglobin < 8g/dL. The exercise sessions should be interrupted in case of pain, dizziness or other contraindications[27].

A different study conducted in lung cancer patients with minimum walking capacity of fifty meters, no cognitive deficits or severe heart disease showed improvement in the physical capacity measured with theIncremental- and Endurance Shuttle Walk Test (ISWT AND ESWT) after completing an intervention program, however, no changes were observed in pulmonary function and quality of life. The intervention in this study consisted of seven weeks of training, two times a week, focused in the walk training, circuit training, dosed according to the dyspnea intensity to be performed daily at home. The ISWT test showed improvement in the maximum aerobic capacity in twelve of the seventeen patients who completed the seven-week intervention period despite the low adherence to the program. The authors demonstrated that there was no change in the pulmonary function of fifteen out of seventeen patients before and after intervention[28] **(B)**.

Recommendation

Supervised exercises are beneficial to patients who undergo an allogeneic hematopoietic stem cell transplant when performed before, during, and after the internment period with a three series and two resistance sessions a week program - light aerobic activity for a few minutes and stretching, resistance (with and without elastic bands with different degrees of resistance from eight to twenty repetitions, two or three series) and aerobic training (walking, twenty to forty minutes or bicycle) during internment. The training intensity must be adapted using the Borg scale assessing the presence of pain, fatigue, and emotional state, and patients must be oriented to keep the walking exercise without interruption whenever physically able[27] **(A)**.

A physical therapist-supervised exercise program focusing respiratory exercises (pursed lip breathing, resting positions and dyspnea coping) and walking exercises in ninety-minute sessions (fifteen minutes for each exercise series) may benefit the improvement of lung cancer patients with minimum walking capacity of fifty meters, no cognitive deficits or severe heart disease[28] **(B)**.

8. Is the use of steroids (nandrolone is the most studied) associated with exercises effective in helping muscle mass gain and muscular strength in cancer patients?

In a study comparing several doses of megestrol acetate to achieve weight gain in cancer patients it was found that the greater weight gain occurs with a 240 mg dose, leading to an average gain of 0.448 kg (CI 95% 0.21-0.874). In the same follow-up period, patients not using the medication had an average weight loss of 1.090 kg (CI 95% 0.561 - 1.620)[29] **(B)**.

A different randomized, controlled, and double-blind study, with forty esophageal cancer patients, divided in two groups, control with twenty-one patients and treatment group with nineteen patients, receiving nandrolonedecanoate for three months, evaluated the increase in weight, apetite, and forearm circumference. No improvement was found in any of the parameters[30], however, the authors suggest that in higher doses other benefits could be attained.

Distinct randomized study with 475 patients with post-cancer cachexy or anorexia (where 311 completed the study) receiving dexamethasone and megestrol or fluoxymesterone, evaluated improvement in apetite, with no significant improvement in any of the groups[31] **(B)**.

Recommendation

There is indication of therapeutical use of steroids in the cachexia anorexia syndrome in cancer patients. The use of megestrol (in variable doses, generally, between 160-480 mg, but may reach 1600 mg) leads to increase in appetite, with AR = 3.86 (CI 95% 3.13-4.59), providing NNT = 3 (CI 95% 2-3) and weight increase with AR = 1.41 (CI 95%0,88-1,94), providing NNT = 7 (CI 95% 5-11)[29] **(B)**. This benefit in the increase in appetite and weight is confirmed both in cancer patients and in acquired immunodeficiency syndrome[32] **(B)**. One must not forget that megestrol presents deep venous thrombosis rate of up to 5%[31] **(B)**. There is benefit in the use of steroids in the cachexia anorexia syndrome in cancer patients[29,32] **(B)**. Megestrol acetate (160-480 mg) leads to an increase in appetite in one out of three patients treated[29] **(B)**. The best dosage for increase in weight is 240 mg, being capable of increasing weight between 200-870 g[33] **(B)**. Caution is required in the follow-up due to the increased risk of deep venous thrombosis[31] **(B)** and other yet unidentified medium-term side effects **(D)**. There is a lack of studies in the analysis of nandrolonedecanoate, but in high doses, a few case reports suggest benefits **(D)**, although no medium-term side effects are known **(D)**. There is controversy regarding the use of nandrolone for weight loss reduction in lung cancer patients, a few papers show possible benefits[34] **(D)**, whereas others do not[35,36] **(B)(D)**. Steroids are contraindicated for prostate and breast cancer patients[37,38] **(D)**.

9. Is the use of an aerobic physical exercise program effective in reducing cardiac insufficiency in cancer patients using cardiotoxic chemotherapeutic agents (anthracyclines, trastuzumab, cyclophosphamide)?

Cohort study with seventeen cancer patients, receiving chemotherapy and using trastuzumab and with aerobic training, thirty to sixty minutes a day, three times a week during four months, did not observe reduction neither in the left ventricle dilatation nor in the cardiac ejection fraction associated with the use of trastuzumab[39] **(B)**.

A different simple blind, controlled and randomized study, with a sample of fifty-three breast cancer patients, divided into two groups (control and in use of aerobic exercises three times a week during fifteen weeks), in which fifty-two patients completed the study, n the oxygen consumption and found changes in the oxygen consumption peak in ergospirometry test, and also improvement in the quality of life with assessment by the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale. Both aspects presented correlation by the Pearson test, demonstrating a relationship between quality of life, cardiopulmonary function and physical exercise[21] **(A)**.

Distinct controlled and randomized study evaluated 111 patients aged eighteen to fifty years, using chemotherapy, with lymphoma, breast cancer, gynecological or testicle cancer, divided into control group or submitted to thirty-minute sessions of supervised aerobic training, twice a week during fourteen weeks, evaluated aspects of quality of life with the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30) and changes in the VO_2 (VO_2 max) consumption peak in ergospirometry test. It found changes in the oxygen consumption peak and in the cardiopulmonary conditioning. However, it did not find changes in the quality of life parameters, maybe due to the variance in the sample used[22] **(A)**.

Recommendation

The Trastuzumab start is associated with the left ventricle dilatation and reduction in cardiac ejection fraction despite aerobic training in cancer patients[39] **(B)**. A supervised aerobic training significantly improves cardiorespiratory conditioning in cancer patients using chemotherapeutic agents[21,22] **(A)**. Although there is controversy and few studies in the literature, the use of aerobic physical training can improve cardiopulmonary conditioning in cancer patients undergoing chemotherapy, even related to other cardiotoxic chemotherapeutic agents, as long as it is controlled, supervised and respects the clinical limits of each individual patient.

10. Is kinesiotherapy safe for patients with severe chemotherapy-induced thrombocytopenia (below 30.000)?

A study with a twelve-patient group (eight completed the study), aged between twenty-five and sixty-six years, with chemotherapy-induced hematological disorders and with blood platelets count > 20.000 without use of platelet concentrate or with thrombocytopenia below 10.000 with platelet replacement, were all submitted to the same three-month period of aerobic training, three times a week, for fifteen to thirty minutes, and as outcome the platelet count was 27.000 with a minimum of 8.000. None of the patients presented bleeding with platelets over 10.000[40] **(B)**.

Recommendation

Supervised ergometric training can be safe in cancer and chemotherapy-induced severe thrombocytopenia patients, in patients with over 10 thousand platelets **(B)**.

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