# Benefits and Safety of Physical Exercises in Patients with Bone Metastases: Systematic Literature Review and Meta-Analysis

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*Benefícios e Segurança dos Exercícios Físicos em Pacientes com Metástases Ósseas: Revisão Sistemática da Literatura e Metanálise*

Beneficios y Seguridad de los Ejercicios Físicos en Pacientes con Metástasis Óseas: Revisión Sistemática de la Literatura y Metanálisis

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***ABSTRACT***

**Introduction:** The life expectancy of individuals with metastatic cancer is increasing, but this group of patients is at considerable risk of having psychological and physical health problems. In this sense, physical exercise has been an ally in the treatment of patients with bone metastases. **Objective**: Systematic review and meta-analysis on the safety and benefits of physical exercise in patients with bone metastases. **Method:** Meta-analysis with bibliographic investigation carried out in the electronic databases PubMed, LILACS, PEDro and Embase. **Results:** Of the 396 studies, only 10 were included, with a total of 531 subjects. No adverse musculoskeletal effects were observed during the intervention, with exercise being significantly safe in individuals with bone metastases. There was no significant improvement in aerobic capacity, disease progression, quality of life, lean mass and body fat. Three of the studies included assessed pain during and after the intervention, showing an improvement in the pain score, as well as a decrease in use of analgesics in the intervention group. **Conclusion:** Therapy with aerobic and isometric exercises is safe in patients with bone metastases, in addition, it improves pain, but without significant increase of aerobic capacity, disease progression, body mass and quality of life.

**Key words**: physical therapy modalities; exercise; bone neoplasms; neoplasm metastasis; randomized controlled trial.

RESUMO

**Introdução:** A expectativa de vida de pessoas com câncer metastático está aumentando, mas esse grupo de pacientes corre um risco considerável de apresentar problemas psicológicos e de saúde física. Nesse sentido, o exercício físico tem sido um aliado no tratamento de pacientes com metástases ósseas. **Objetivo:** Realizar uma revisão sistemática e metanálise sobre a segurança e os benefícios do exercício físico em pacientes com metástases ósseas. **Método:** Metanálise com pesquisa bibliográfica realizada nas bases eletrônicas: PubMed, LILACS, PEDro e Embase. **Resultados:** Dos 396 estudos, somente dez foram incluídos, com um total de 531 indivíduos. Não foi observado nenhum efeito adverso musculoesquelético durante a intervenção, sendo significativamente seguro o exercício em indivíduos com metástases ósseas. Não houve melhora considerável na capacidade aeróbica, progressão da doença, qualidade de vida, massa magra e gordura corporal. Três dos estudos incluídos avaliaram a dor durante e após a intervenção, demonstrando melhora no escore de dor, assim como a diminuição do uso do analgésico no grupo intervenção. **Conclusão:** A terapia com exercícios aeróbicos e isométricos é segura para pacientes com metástases ósseas, além de apresentar melhora da dor, mas sem evolução relevante na capacidade aeróbica, na progressão da doença, na massa corporal e na qualidade de vida.

**Palavras-chave:** modalidades de fisioterapia; exercício físico; neoplasias ósseas; metástase neoplásica; ensaio clínico controlado aleatório.

RESUMEN

**Introducción:** La esperanza de vida de las personas con cáncer metastásico está aumentando, pero este grupo de pacientes tiene un riesgo considerable de tener problemas de salud física y psicológica. En este sentido, el ejercicio físico ha sido un aliado en el tratamiento de pacientes con metástasis óseas. **Objetivo:** Realizar una revisión sistemática y un metanálisis sobre la seguridad y los beneficios del ejercicio físico en pacientes con metástasis óseas. **Método:** Metanálisis con búsqueda bibliográfica realizada en bases de datos electrónicas: PubMed, LILACS, PEDro y Embase. **Resultados:** De los 396 estudios, solo se incluyeron 10, con un total de 531 sujetos. No se observaron efectos musculoesqueléticos adversos durante la intervención, siendo el ejercicio significativamente seguro en individuos con metástasis óseas. No hubo una mejora significativa en la capacidad aeróbica, la progresión de la enfermedad, la calidad de vida, la masa magra y la grasa corporal. Tres de los estudios incluidos evaluaron el dolor durante y después de la intervención, mostrando una mejoría en la puntuación del dolor, así como una disminución en el uso de analgésicos en el grupo de intervención. **Conclusión:** La terapia con ejercicios aeróbicos e isométricos es segura para los pacientes con metástasis óseas, además presenta mejoría del dolor, pero sin mejoría significativa en la capacidad aeróbica, progresión de la enfermedad, masa corporal y calidad de vida.

**Palabras clave**: modalidades de fisioterapia; ejercicio físico; neoplasias óseas; metástasis de la neoplasia; ensayo clínico controlado aleatorio.

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## INTRODUCTION

Bone metastases are frequent in patients with advanced cancer[1]. Nearly two thirds of the patients with tumor develop bone metastases in the course of the disease and the most frequent site is the spine[2], a major clinical concern due to intense pain, pathological fractures, compression of the bone marrow and significant decline of the quality-of-life[3,4]. It was estimated that 70% of all the patients who die from tumors had bone metastases[5]. The final result of several interdependent metastases, a multifaceted process with a complex interaction between the tumor and the host organism[6].

Life expectancy of individuals with metastatic cancer is increasing but this group of patients is at considerable risk of psychological and physical problems[7,8]. Despite the increasing evidences of relevant benefits to health, physical exercises declines considerably during cancer treatment and continues as such afterwards[9]. There are evidences that keeping or increasing physical activities in patients with cancer can improve the quality-of-life and well-being as the disease progresses[10,11]. However, patients with cancer and bone metastases typically tend to avoid physical exercises due to insecurity. Physical inactivity is associated with loss of physical function, mobility, balance, protective muscle mass, strength and bone mineral density[12], which not only damages the quality-of-life but increases the risk of comorbidities and fractures.

Globally, the guidelines of exercises for cancer recommend that individuals with bone metastases avoid inactivity and engage in aerobic and resistance exercises[13]. Therapy with exercises is a promising method with potential to reduce the symptoms and side effects of the treatment with patients with cancer. Consequently, improve the physical function and delay or prevent skeletal complications for patients with bone metastases can bring clinically significant benefits to them[14]. However, it is noted that health professionals are uncertain and insecure about the type, frequency and intensity of the exercises, further to risk of bone fracture or musculoskeletal complications for this population.

Therefore, this review had the objective of presenting systematically evidences-based interventions with exercises in individuals with bone metastasis and evaluate the safety and potential benefits for this group.

## METHOD

Systematic review and meta-analysis following the recommendations of Cochrane Collaboration[15] and the Preferred Reporting Items for Systematical Review and Metanalyses: The PRISMA Statement[16]. The study is registered at the base of systematic review of the International Prospective Register of Systematic Reviews (PROSPERO), ID CRD42021288305.

Randomized clinical trials (RCT) published between 2011 and 2021 and complete accessible articles in Portuguese, English and Spanish which met the following criteria were included: (1) individuals diagnosed with bone metastasis independent from the primary site; (2) solid or hematological tumors; (3) 18 years of age or older; (4) addressing interventions with aerobic, resisted or combined exercises (resisted/aerobic/mobility) compared to the control group (did not practice any exercise or performed some activity interfering in the type of exercise tested).

The exclusion criteria were: 1) studies with insufficient information about the results and intervention (no information on the control group, but only of the intervention group, no information of the beginning or end of the intervention, which blocked the meta-analysis, poor results in the charts and no response from authors after contact by e-mail to clarify the results); 2) studies where any of the participating groups had individuals without bone metastasis; 3) studies that did not describe the type of meta-analysis.

The articles were selected in May 2021 from the electronic databases, National Library of Medicine (PubMed), Latin American and the Caribbean Literature on the Sciences of Health (LILACS), Physiotherapy Evidence Database (PEDro) and Embase. The terminology was based in the Medical Subject Headings (MeSH) and the Health Science Descriptors (DeCS). The terms "Neoplasm Metastasis", "Physical Therapy Modalities", "Exercise", "Randomized Controlled Trial" and synonyms were utilized as shown in Chart 1.

Two investigators evaluated the titles and abstracts of all the articles identified independently. The abstracts with no information about the inclusion and exclusion criteria were evaluated in full and selected according to the eligibility criteria. The same reviewers conducted the extraction of the data on methodological characteristics of the studies, patients, intervention and outcome individually. Discrepancies were resolved by consensus or by a third reviewer.

The following six stages to construct the review were followed: elaboration of the research question, literature search of the primary studies based in the inclusion and exclusion criteria, organization of pre-selected studies (extraction of the data of the studies), critical review of the studies selected, synthesis of the results and presentation of the integrative review.

The evaluation of the methodological quality of the studies included consisted in the description of the

**Chart 1**. Strategy of Search – PubMed

| |
|---|
| 1# "Neoplasm Metastasis" [Mesh] or "Neoplasm Metastasis" or "Neoplasm Metastases" or "Metastases, Neoplasm" or "Metastasis, Neoplasm" or "Metastase" or "Metastases" or "Metastasis" |
| 2# "Physical Therapy Modalities" [Mesh] or "Physical Therapy Modalities" or "Modalities, Physical Therapy" or "Modality, Physical Therapy" or "Physical Therapy Modality" or "Physiotherapy (Techniques)" or "Physiotherapies (Techniques)" or "Physical Therapy Techniques" or "Physical Therapy Technique" or "Techniques, Physical Therapy" or "Group Physiotherapy" or "Group Physiotherapies" or "Physiotherapies, Group" or "Physiotherapy, Group" or "Physical Therapy" or "Physical Therapies" or "Therapy, Physical" or "Neurological Physiotherapy" or "Physiotherapy, Neurological" or "Neurophysiotherapy" or Physical Therapy Specialty or "Specialty, Physical Therapy" or "Therapy Specialty, Physical" or "Physiotherapy Specialty" or "Specialty, Physiotherapy" or "Exercise" or "Exercises" or "Physical Activity" or "Activities, Physical" or "Activity, Physical" or "Physical Activities" or "Exercise, Physical" or "Exercises, Physical" or "Physical Exercise" or "Physical Exercises" or "Acute Exercise" or "Acute Exercises" or "Exercise, Acute" or "Exercises, Acute" "Exercise, Isometric" or "Exercises, Isometric" or "Isometric Exercises" or "Isometric Exercise" or "Exercise, Aerobic" or "Aerobic Exercise" or "Aerobic Exercises" or "Exercises, Aerobic" or "Exercise Training" or "Exercise Trainings" or "Training, Exercise" or "Trainings, Exercise" |
| 3# (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) |

following characteristics: random sequence generation, allocation concealment, blinding of outcome assessors, intention-to-treat analysis and losses and exclusions. The Revised Cochrane risk-of-bias tool for randomized trials was applied to evaluate the risk of bias of RCT (RoB 2)[17], which is recommended by Cochrane Collaboration currently in replacement of the Cochrane Risk of Bias Tool. The following domains were considered: randomization bias, deviations from intended intervention (blinding), bias of incomplete data, bias of outcome assessment and bias of outcome reporting.

The meta-analysis was conducted through the model of random effects and measures of effect were obtained by post-intervention values. The studies were analyzed separately according to the type of exercise. Value of alpha ≥ 0.05 and confidence interval of 95% (CI 95%) were adopted. The statistical heterogeneity of the effects of the treatment of the studies was evaluated by the Cochran Q tests and inconsistency ($I^2$), where values above 25% and 50% indicated moderate and high heterogeneity, respectively. The software Review Manager, version 5.3 (Cochrane Collaboration) was utilized according to Figure 1.

## RESULTS

386 studies were found at the databases. Of these, 10 were deemed as potentially relevant for the complete analysis of the studies which ensured the meta-analysis. Other ten studies met the eligibility criteria for the systematic review but with insufficient results for meta-analysis. Figure 2 portrays the flowchart of search, and the main characteristics of the studies included are described in Chart 2.

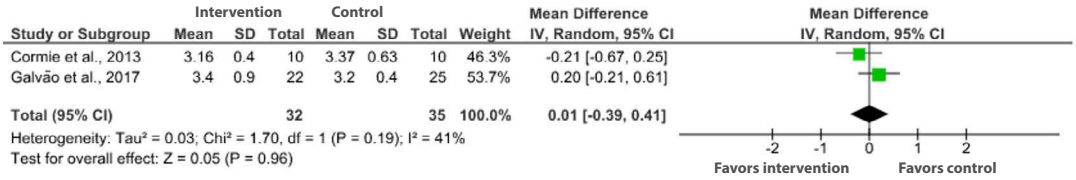
The tool RoB 2[17] was utilized to calculate the risk of bias (evaluation of the methodological quality of the studies) for being highly recommended by Cochrane Collaboration. All the studies (100%) included in the meta-analysis had satisfactory concealment, no loss of follow-up and outcome reporting. However, the randomization process was satisfactory for 40% and the outcome assessment for 60% of the studies, respectively. The final result of the ten RCT included had 20% of low risk of bias and 80% of some concerns with bias as portrayed in Chart 3.

Nine articles[14,18-25] evaluated the safety of physiotherapy and physical exercise during intervention of patients with bone metastasis. The outcomes evaluated were fall, fractures, hospital admission, adverse events and skeletal complications. None of the studies presented any adverse event as falls or musculoskeletal complications after evaluating these outcomes post physiotherapy with combined and isometric exercises.

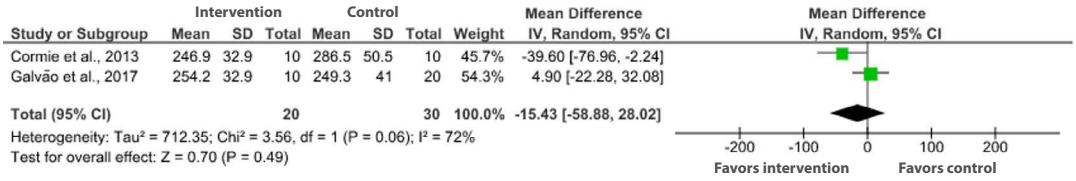
No relevant effect of slowing the progress of the disease through isometric exercises[21,25] was found from the meta-analyzes (relative risk – RR: 0.45; CI 95%: 0.05 to 4.07; $I^2$=64%) and the high heterogeneity can be explained by the bias detected in the articles which revealed their low methodological quality. Aerobic exercise was brought as intervention by Bjerre et al.[18] resulting in more cases of progression of the disease in the control group (16 of 19 patients) compared with the intervention group (9 of 22; $p$=0.009).

Two[14,19] of the nine articles evaluated the aerobic capacity of these patients after combined exercises with no considerable improvement of the outcomes. The outcomes

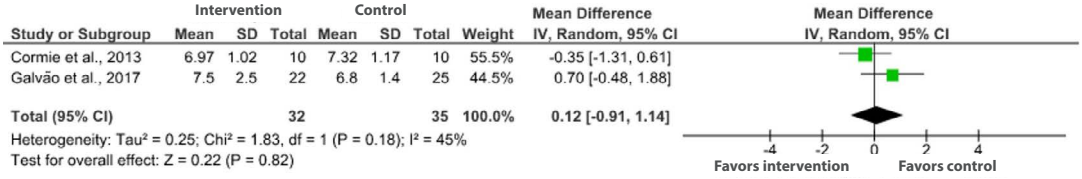
**Six-minute walk test**



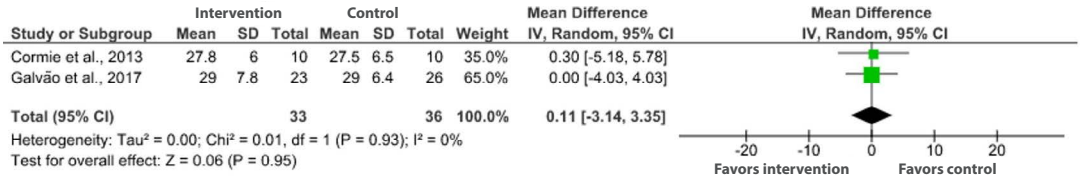

**400 meter walk test**



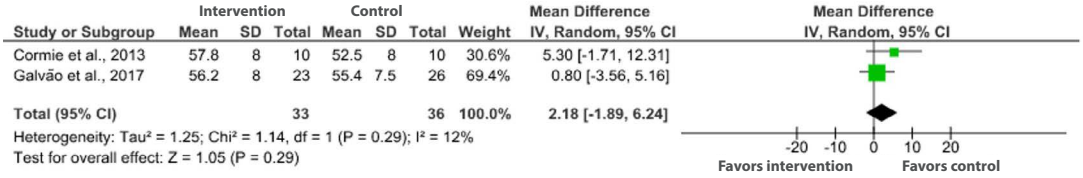

**Timed Up and Go Test**



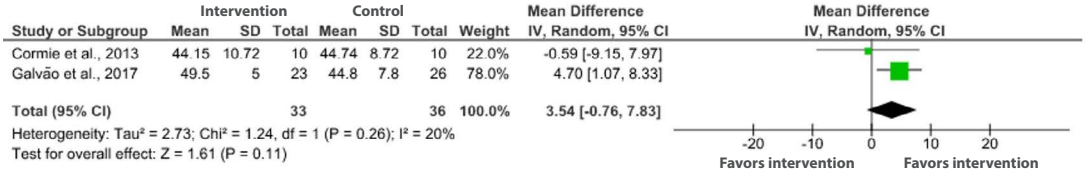

**Total body fat mass**




**Lean mass**




**36-item Short Form Survey (SF-36)**




**Progression of the disease**

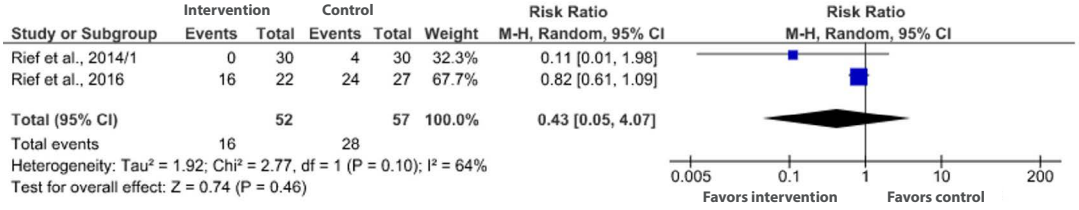



**Figure 1.** Analysis of the outcomes evaluated for patients with bone metastasis comparing control and intervention

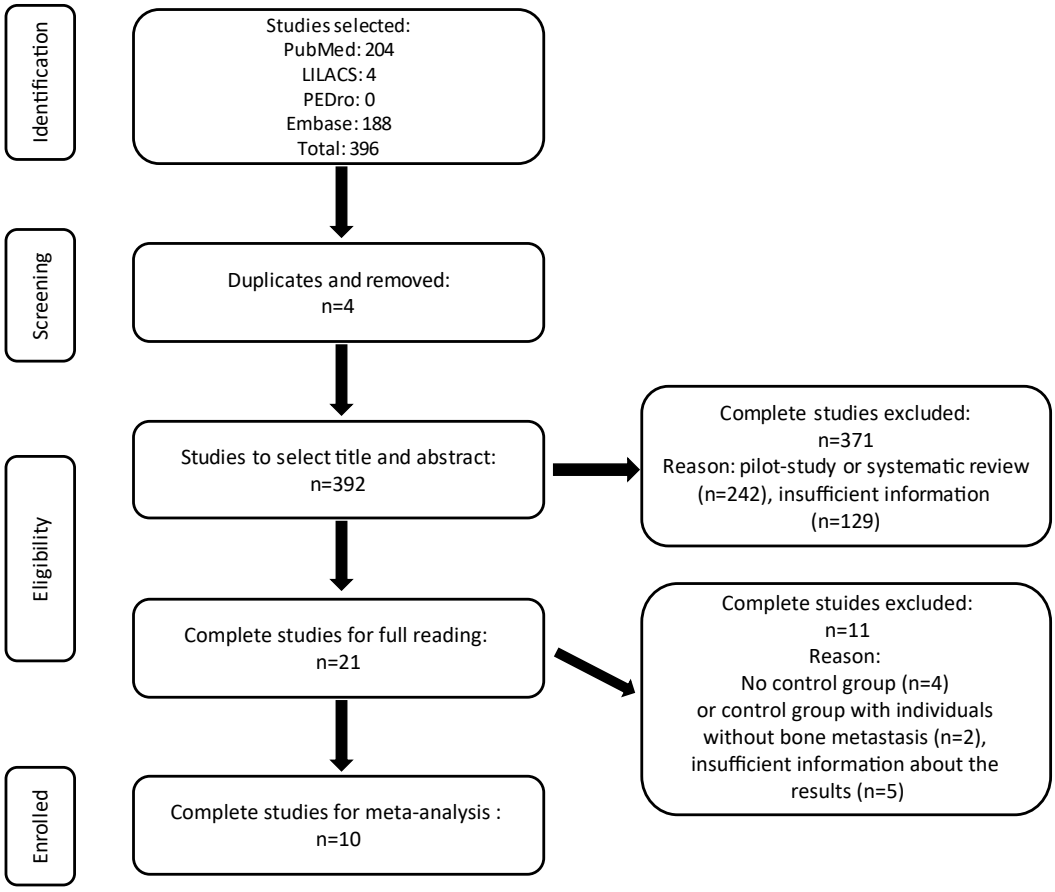



**Figure 2.** Flowchart of the studies identifed according to PRISMA, Rio Grande do Sul, Brazil, 2021

**Chart 2.** Characteristics of the studies selected about exercises of patients with bone metastasis

| Authors | N | Mean Age | Group | Country | Subtype of Exercise | Intervention | Duration | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Bjerre et al.[18] | 41 | 68.9±8.4<br>67.3±7.0 | Intervention (22)<br>Control (19) | Denmark | Aerobic | 20-minute warm-up, 20-minute of football training and 20-minute of regular football game | 1 hour, twice a week for 6 months | Patients with skeletal, metastatic prostate cancer enrolled at a physical exercise program improved the quality of life without adverse events, indicating that high impact aerobic activity for this clinical subgroup is safe |
| Cormie et al.[19] | 20 | 73.1±7.5<br>71.2±6.9 | Intervention (10)<br>Control (10)) | Australia | Resistance+ aerobic+ stretching | Starting with a 5-minute warm-up and ending with 10-minute cooling down (low impact aerobic exercises and stretching). Resistance regimen included 8 exercises targeted to the major muscle groups of the upper and lower parts of the body. The participants were encouraged to complement the sessions with moderate to intense aerobic exercises for 150 minutes weekly | Approximately 60-minute twice a week sessions for 12 weeks | Well-designed and supervised resistance exercises aimed to skeletal areas unaffected by bone lesions can be safe and well tolerated by patients with bone metastatic prostate cancer and may improve physical function, levels of physical activity and lean mass |

to be continued

Chart 2. continuation

| Authors | N | Mean Age | Group | Country | Subtype of Exercise | Intervention | Duration | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Galvão et al.[14] | 57 | 70.0±8.4<br>70.0±8.4 | Intervention (28)<br>Control (29) | Australia | Resistance, aerobic and flexibility | Moderate intensity resistance exercise for the main muscle groups of the chest, lower and upper parts of the body, from 10 to 12 maximum repetitions in 3 sets per exercise. The component aerobic exercise included 20-30 minutes of cardiovascular exercise in several modes as walking on a treadmill, bicycle or paddling in a stationary ergometer with intensity-target of 60%-85% of the estimated maximal heart frequency. Component flexibility involved static stretching, 2-4 repetitions for 30-60 seconds per stretching for all main articulations | Three times a week with sessions of 60-minute exercises during 12 weeks | Exercise improved self-reported physical function in prostate cancer patients with bone metastases without exercise-related adverse events, skeletal fractures or increased bone pain. In addition, the program was well perceived and tolerated by the patients |
| Galvão et al.[20] | 57 | 70.0±8.4<br>70.0±8.4 | Intervention (28)<br>Control (29) | Australia | Resistance, aerobic e flexibility | Moderate resistance exercise targeted to the main muscle groups of the chest and upper and lower limbs, 3 sets from 10 to 12 repetitions maximal per exercise. Aerobic exercise included 20-30 minutes of cardiovascular exercise in several modalities as walking on a treadmill, bicycle or paddling in stationary ergometer at maximal estimated 60-85% of the cardiac frequency. Flexibility component involved static stretching, 2-4 repetitions for 30-60 seconds per stretching for the main articulations | Three times a week, approximately 60 minutes exercises for 12 weeks | The exercise was well tolerated and improved the physical functions but a short-term autonomous exercise program did not influence the rates of sexual function for men with advanced prostate cancer with bone metastases |
| Rief et al.[21] | 60 | 61.3±10.1<br>64.1±10.9 | Intervention (30)<br>Control (30) | Germany | Isometric exercises | Isometric exercises to strengthen the paravertebral muscles | For 2 weeks, the session lasted approximately 30 minutes. The patients of the training group were guided to continue the exercises on their own for additional 12 weeks, three times a week | Guided isometric exercises for paravertebral muscles can be practiced safely for patients in palliative care with stable spinal bone metastases, improving their pain score and mobility |

to be continued

Chart 2. continuation

| Authors | N | Mean Age | Group | Country | Subtype of Exercise | Intervention | Duration | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Rief et al.[22] | 60 | 61.3±10.1<br>64.1±10.9 | Intervention (30)<br>Control (30) | Germany | Isometric exercises | Isometric exercises to strengthen the paravertebral muscles | During 2 weeks, the session lasted approximately 30 minutes. The patients of the training group were guided to continue the exercises on their own at home for additional 12 weeks, three times a week | Guided resistance isometric training of the paravertebral muscles can relief pain in 6 months in patients with stable bone metastases of the vertebral column. The intervention was able to reduce the concomitant medication and the equivalent dose of oral morphine. This exercise is a promising and effective therapeutic approach to reduce pain in patients with spinal metastases. |
| Rief et al.[23] | 60 | 61.3±10.1<br>64.1±10.9 | Intervention (30)<br>Control (30) | Germany | Isometric exercises | Isometric exercises to strengthen the paravertebral muscles | During 2 weeks, the session lasted approximately 30 minutes. The patients of the training group were guided to continue the exercises on their own at home for additional 12 weeks, three times a week | Guided resistance isometric training of the paravertebral muscles is able to improve the functional capacity, reduce fatigue and ameliorate the quality-of-life within a 6-month period in patients with stable spinal metastases. The intervention was able to reduce specific fears of mobility loss and dependence of other persons. This exercise is a promising and effective therapeutic approach to reduce emotional stress and anxiety for patients with spinal metastases |
| Rief et al.[24] | 60 | 61.3±10.1<br>64.1±10.9 | Intervention (30)<br>Control (30) | Germany | Isometric exercises | Isometric exercises to strengthen the paravertebral muscles | During 2 weeks, the session lasted approximately 30 minutes. The patients of the training group were guided to continue the exercises on their own at home for additional 12 weeks, three times a week | Guided resistance training for paravertebral muscles can improve bone density of the metastasis as a local response for a 6 months period with stable spinal metastases concomitant to radiotherapy |
| Rief et al.[25] | 60 | 61.3±10.1<br>64.1±10.9 | Intervention (30)<br>Control (30) | Germany | Isometric exercises | Isometric exercises to strengthen the paravertebral muscles | During 2 weeks, the session lasted approximately 30 minutes. The patients of the training group were guided to continue the exercises on their own at home for additional 12 weeks, three times a week | Guide resistance training of paravertebral muscles had no essential impact on bone, global, progression-free survival concomitant to radiotherapy |
| Rosenberger et al.[1] | 56 | 62±9<br>61±9 | Intervention (27)<br>Control (29) | Germany | Spinal stabilization exercises – isometric + flexibility | Spinal stabilization training daily for 10 ± 2 days (min.-max.: 5-17 days) concomitant to radiotherapy | The patients received exercises every day of radiotherapy (approximately 2 weeks) and continued the training program (15-minute/day) at home and unsupervised for 3 months. | The analyzes of the training program suggest that the exercises are well accepted. Given the frequent adjustments due to pain, weakness and immobility, they are feasible for most of the participants and effective to improve the specific muscle strength of the training |

**Captions:** min. = minimal; max. = maximal.

**Chart 3**. Risk of bias of the studies selected

| Author | Randomization | Deviations from intended interventions | Incomplete outcome data | Evaluation of the outcome | Selective reporting of the outcome | Overall result | Outcomes evaluated |
|---|---|---|---|---|---|---|---|
| Bjerre et al.[18] | Low | Low | Low | Low | Low | Low | Safety; functional evaluation quality-of-life; physical and mental health; body composition; bone mineral density |
| Cormie et al.[19] | Low | Low | Low | Low | Low | Low | Safety and tolerance to the exercises program; pain; physical function; body composition; fatigue; quality-of-life |
| Galvão et al.[14] | Low | Low | Low | Some concerns | Low | Some concerns | Functioning and physical function, muscle force; body composition; fatigue; safety |
| Galvão et al.[20] | Low | Low | Low | Some concerns | Low | Some concerns | Sexual health and functioning; adverse effects |
| Rief et al.[21] | Some concerns | Low | Low | Low | Low | Some concerns | Feasibility; mobility; global survivorship; bone survivorship; activity of the patients; local control of metastasis; fatigue |
| Rief et al.[22] | Some concerns | Low | Low | Low | Low | Some concerns | Visual analogue scale, neuropathic pain |
| Rief et al.[23] | Some concerns | Low | Low | Low | Low | Some concerns | Quality-of-life; pain, damages and psychosocial aspects; fatigue; emotional stress |
| Rief et al.[24] | Some concerns | Low | Low | Low | Low | Some concerns | Bone density; pathological fractures |
| Rief et al.[25] | Some concerns | Low | Low | Some concerns | Low | Some concerns | Bone survivorship |
| Rosenberger et al.[1] | Some concerns | Low | Low | Some concerns | Low | Some concerns | Strength; handgrip strength; frequency; adherence; tolerance to exercise |

assessed in these articles were based in the six-minute walk test (RR: 0.01; CI 95%: -0.39 to 0.41; $I^2$=41%), 400-meter walk (RR: -15.43; CI 95%: -58.88 to 28.02; $I^2$=72%) and the Timed Up and Go Test (RR: 0.12; CI 95%: -0.91 to 1.14; $I^2$=45%).

Mean mass and body fat were evaluated by whole body dual-energy X-ray absorptiometry to assess this outcome (Hologic Discovery A, Waltham, MA, USA). Of the ten articles selected, only two[14,19] evaluated the lean mass (RR: 2.18; CI 95%: -1.89 to 6.24; $I^2$=12%) and the body fat (RR: 0.11; CI 95%: -3.14 to 3.35; $I^2$=0%) after physiotherapy with combined exercises. Cormie et al.[19] reported a change of the whole body and significant difference of appendicular lean mass of the groups during 12-week intervention. Galvão et al.[14] did not find changes of total body lean or fat mass. After the meta-analysis, no significant improvement of the outcomes presented was found.

Three articles[19,21,23] reported the evaluation of the pain through the Visual Analogue Scale (VAS) post-intervention, but it was not possible to conduct the meta-analysis of these outcomes because each article described the results differently reaching heterogeneous results even with the same scale.

Rief et al.[21] described that the intervention group of their article improved the pain score (VAS: 0-10) in its course ($p<0.001$) and was better significantly for the groups ($p=0.003$) after three months.

Another study by Rief et al.[23] also listed in the present review found that the course of VAS of the intervention group was significantly lower during and after radiotherapy ($p<0.001$). The utilization of analgesic by the intervention group ($p<0.001$) had the same result significantly lower during and after radiotherapy. Along the time, the concomitant medication and equivalent dose of oral morphine diminished in the intervention group but increased in the control group.

Cormie et al.[19] reported that the severity of the bone pain at each session of exercise was low, mean of 0.6±0.7 in a scale from 0 (no pain) to 10 (very strong) and maximum of 1.4±1.2 in every session. The highest level of bone pain was 3.3 occurred during the exercises program.

The meta-analysis could be completed with two articles[14,19] which evaluated this outcome in the same way. These studies reached the result of quality-of-life with the Short Form Health Survey 36 (SF-36). The utilization of combined exercises did not mean relevant improvement of this outcome (RR: 3.54; CI 95%: -0.76 to 7.83; $I^2$=20%), possibly because of few studies and small sample.

Bjerre et al.[18] evaluated the quality-of-life with the Functional Assessment of Cancer Therapy – Prostate

(FACT-P), specific for prostate cancer and the results were better for the intervention group than the control group in 12 weeks with a difference of 7.6 points (CI 95%: 0.5 to 15.0; $p$=0.038). Rief et al.[23] evaluated this outcome with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases Module (EORTC QLQ-BM22), however, except psychosocial aspects, the difference was not statistically significant due to the small size of the study sample of 60 patients.

## DISCUSSION

This study included ten RCT[1,14,18-25] whose frequency of exercises was six months, from 15 minutes to one hour of intervention totaling 531 patients randomized, 265 assigned to the intervention group and 266 to the control group. Three RCT[14,19,20] adopted combined exercise (resistance + aerobic + stretching and flexibility), five RCT[21,22-25], only isometric exercises, one[1], isometric plus flexibility exercises and one[18], only aerobic exercises.

The study limitations were the difficulty to obtain a homogeneous sample and poor methodology of the articles for presenting different descriptions of the results and failing to describe the standard-deviation and mean of the variables. Another limitation was the unsatisfactory clarification of the results, which blocked the interpretation and meta-analysis.

Nine of the studies analyzed[14,18-25] evaluated the safety of physical exercise in patients with bone metastases; the results are positive since none of them had any adverse effect or musculoskeletal complications or fracture. In addition, four admissions occurred in the control group and none in the intervention group[18].

Typically, individuals with bone metastases are immobilized due to the risk of pathological fractures and risk of compression of the bone marrow. Rosenberger et al.[1] investigated the feasibility of isometric exercises to stabilize the spine concomitant to analgesic palliative radiotherapy in patients with unstable spinal metastases (with high risk of fracture, Taneichi score ≥ D)[26]; the exercises have been shown safe and given individual adjustments, feasible and effective for specific muscle strength.

However, patients with metastatic bone cancer tend to not practice physical exercises for safety reasons, mostly. Due to few studies addressing safety and efficacy of exercises in the oncology environment, the lack of this activity is highly damaging because physical activity is associated with loss of physical function and consequently additional decline of musculoskeletal structure and function, more risk of comorbidities, fractures and poor quality-of-life[1,19].

Bjerre et al.[18] and Cormie et al.[19] suggest that well designed and supervised aerobic and resistance exercises are safe and tolerated by patients with bone metastases and can improve the physical function. A training effort of up to 20% to 30% of the maximal power does not increase or reduce the strength and can match the daily load of induced muscle tensions. The muscles of the immobilized patient are activated at less than 20% which can lead to atrophy. The training range is within 30%-40% of the maximal muscle strength, above which the training can have positive results[27], the level of power utilized by Cormie et al.[19] in their intervention exercises. For this population, the isometric training of paravertebral muscles can be practiced safely in palliative patients with unstable spinal bone metastases, improving their pain score and mobility.

The 6-minute walk, the 400-meter walking and the Timed Up and Go tests were utilized to evaluate the aerobic capacity through which the meta-analysis of these outcomes was possible in two studies[14,19]. The study by Cormie et al.[19] concluded there was improvement of the submaximal aerobic exercise with favorable changes of the physical function verified for the intervention group in comparison with the control group of usual care. However, Galvão et al.[14] concluded otherwise, no changes of the physical function were detected. The evidence-based meta-analysis of these two RCT which compared combined exercise (38 individuals of the intervention group) *versus* control (39 individuals) found that combined exercise failed to significantly improve this outcome.

However, clinically relevant improvement of post-training functional capacity as muscle strength submaximal aerobic capacity and ambulation involving combined and resistance aerobic exercises were found by other studies[19,28].

The body fat and lean mass did not differ significantly between the groups in the current review. Heterogeneous results were found in two studies[18,19] which reported reduction of the body fat and improvement or maintenance of the lean body mass and of the hip's bone mineral density. Galvão et al.[14] concluded there was no change of total lean or fat body mass. These results show that aerobic exercise diminishes body fat and keeps appendicular lean mass protecting against falls and skeletal complications that cause significant morbimortality; however, combined exercise failed to present considerable difference for these outcomes.

Rief et al.[24] have reached findings with combined exercises which significantly improved the bone density for all the metastases in 28.3% and 80.3% after three and six months, respectively for the intervention group, concluding that resistance training concomitant to

radiotherapy can ameliorate bone density. For hip bone mineral density, the intervention group with aerobic exercises in the study of Bjerre et al.[18] had a slight improvement (0.008 g/cm$^2$).

The mechanism responsible for bone neoplasms is complex and involves the tumor stimulation of the osteoclast and osteoblast and the response of the bone microenvironment. Rief et al.[24], in their study, obtained interesting data after evaluating the bone density of post-intervention osteolytic and osteoblast metastases. After three and six months of intervention, the analysis of the subgroup of osteolytic metastases concluded that bone density significantly improved when compared to the control group. Bone density of osteolytic metastases of the intervention group reached 179.3% after six months but the osteoblastic metastases failed to significantly improve after three and six months for both groups.

The VAS was the tool most utilized by the articles selected for meta-analysis to assess pain, but each article reported the result differently which blocked the analysis of this outcome. Nevertheless, post-intervention positive results for pain were found for this population and also without expressive increase of the pain during the exercise at the end of the review.

According to Rief et al.[22], the pain score was significantly better after three months of isometric exercises as intervention. Similarly, the severity of bone pain reported at each session of exercise was low, mean of 0.6±0.7 in a 0 (painless) to 10 (very strong) scale and maximum of 1.4±1.2 in all sessions[19]. No incidence of change of bone pain during the exercise interfering in the activities of daily life was found post-intervention.

Galvão et al.[14] evaluated bone pain through the Functional Assessment of Cancer Therapy – Bone Pain – FACT-BP and as a result of this outcome, no change of bone pain with combined exercises as intervention occurred. Simultaneous to this result, Rief et al.[22] reported that the use of analgesic medication was quite low during and after radiotherapy of the intervention group; the concomitant medication and the equivalent dose of oral morphine declined in the intervention group but raised in the control group. Six months post-radiotherapy, the utilization of analgesic medication declined in the intervention group and significantly increased in the control group.

Three of the articles submitted to meta-analyzes[18,21,25] had information about the progression of the disease; post meta-analysis of this outcome, two of these studies led to the conclusion that physiotherapy with isometric exercises failed to present relevant effect. Rief et al.[21] did not observe progression of other spinal metastases three months after intervention in the respective group, but progression was noted in 17.4% of the patients of the control group (n=4). Bjerre et al.[18] adopted aerobic exercises as intervention and the results about the progression of the disease were more expressive in the control group (16 of 19 patients) *versus* the intervention group (9 of 22; $p$=0.009), post-intervention with aerobic exercises during one hour twice a week. Aerobic exercise is a robust tool to prevent the progression of the disease.

The review by Knols et al.[29] showed that the positive effects of therapy with exercises are contingent upon the tumor type and stage, pharmacotherapy, therapeutic procedures and patient's lifestyle. Delrieu et al.[30] concluded that moderate or intense physical exercise continued statistically associated with better global survivorship only for HER2-positive metastatic breast cancer. On the other hand, patients' survivorship for luminal and triple-negative cancer remained unaffected by physical exercise. These results reveal that, beyond the importance of a correct selection of the type of physiotherapy treatment, some aspects are very relevant as the stage or type of tumor and lifestyle.

The antitumor effect of physical exercise can be explained by different biological mechanisms. It improves insulin sensitivity, reduces the levels of fasting insulin which can minimize the risk of breast cancer[31,32], and can also reduce circulating estrogen levels[33,34]. In addition, physical exercise has been shown to have immunomodulating effects, increasing the immunity and promoting cancer surveillance. Studies have shown that aerobic exercises can reduce the oxidative stress and improve the mechanisms of DNA repair, diminishing carcinogenesis[32,35].

Jones et al.[36] showed that women with metastatic breast cancer who reached peak oxygen uptake ($VO_{2peak}$) <1.09 L/min had median survivorship of 16 months (CI 95%: 7 to 27 months) and those who reported more than 1.09 L/min at the cardiopulmonary exercise test (CPET), 36 months of survival (CI 95%: 24 to 75 months). Similar conclusions were presented by Guercio et al.[37] in a study with 1,218 patients with metastatic colorectal cancer whose physical training (18 or more hours of metabolic equivalent of task – MET/week) was characterized by a lower general mortality compared with a group with less than 3 MET hours/week (hazard ratio – HR=0.85; CI 95% 0.71-1.02; p=0.06). In addition, a study with advanced breast cancer women reports that one additional hour of moderate physical exercise reduced the risk of mortality in 23%[38]. These results indicate that physical exercises with correct frequency and intensity and high peak $VO_2$ can have positive effect on survival of metastatic oncological patients.

The analysis of the quality-of-life could be completed with two articles[14,19] through the SF-36 scale and the

results indicated that the combined exercises did not mean significant improvement, possibly due to few studies and small sample. However, Bjerre et al.[18] evaluated the quality-of-life through the FACT-P, specific for prostate cancer and the result was considerably better for the intervention group compared to the control group in 12 weeks post aerobic exercises.

Rief et al.[23] utilized the evaluation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Fatigue Assessment (EORTC QLQ-FA13) and concluded that an improvement of the patients' psychosocial aspects occurred as well as reduction of the emotional stress of the intervention group after six months. Hayes et al.[39] and Guercio et al.[37] described that the physical exercise is associated with a benefit during and after the oncologic treatment like the reduction of the frequency of complications of chemotherapy (neutropenia, anemia, diarrhea, dehydration, vomit, nausea, cachexia and neuropathy) and, in fact, is able to reduce the impact of side effects and symptoms of the disease. Interventions with exercises can potentially modulate the immune response and genic expression, in addition to reducing the systemic inflammation and oxidative stress or change the tumor[40] vascularization. For this population, the exercise reduced the anxiety, the depressive symptoms and fatigue during or after therapy[41].

Every patient with metastatic disease should be encouraged to practice exercises. Within the perspective of rehabilitation, frequency, intensity, type and time of exercise must be chosen if adjusted to the specific activities of daily life or target-symptoms the intervention intends to improve. Some authors of the present review[1,19] extended the time and maximum repetitions gradually according to the personal response; the selection of specific exercises was based on the site of the bone metastases to avoid the affected areas and reduce the mechanic strength.

With increased evidence supporting the safety and efficacy of physical training, it became an important field of clinical investigation in oncology. The benefits of physical exercise are not seen only in patients at initial stage but also in metastatic populations. Individual exercises planning can improve the prognosis and quality-of-life of patients with advanced cancer and play a significant role as tool of supportive care. Therefore, supervised physical exercise by skilled professionals should be defined as a standard component of the oncologic treatment with patient-centered approach and good communication among professionals to reduce the complication-related risks of physical exercises to the minimum, remaining only their innumerous benefits.

## CONCLUSION

Therapy with aerobic and isometric exercises is safe for patients with bone metastases without any adverse effect, being viable and recommended for this population. Scientific evidences are necessary for different forms of exercises in individuals with bone metastases because it is important in their recovery process and maintenance of the quality-of-life effectively and safely.

### CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

### DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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