INTEGRATIVE REVIEW OF THE LITERATURE

SARCOPENIA IN CANCER PATIENTS UNDERGOING PALLIATIVE CARE: AN INTEGRATIVE LITERATURE REVIEW

Sarcopenia em pacientes oncológicos em cuidados paliativos: uma revisão integrativa

Sarcopenia en pacientes oncológicos en cuidados paliativos: una revisión integradora

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ABSTRACT

Objective: The study's main purpose has been to analyze the scientific production addressing the consequences of sarcopenia in cancer patients undergoing palliative care. **Methods:** It is an integrative literature review. The bibliographic search was performed through electronic search in the following databases available in the Virtual Health Library: PubMed, *LILACS*, and SciELO, using the controlled descriptors "sarcopenia", "palliative care" and "cancer", associated with the Boolean operators "AND" and "OR". **Results:** There were included 18 articles, from which three thematic approaches were elaborated addressing the prevalence and factors associated with sarcopenia, and its influence on survival, quality of life, and symptoms in cancer patients undergoing palliative care. **Conclusion:** Sarcopenia in these patients has a high prevalence, leads to a higher risk of toxicity to palliative chemotherapy with impact on people's survival, furthermore, it is also related to symptoms increased burden, then contributing to undermining the quality of life of such patients. Hence, a further discussion vis-à-vis combating sarcopenia during oncological disease is required.

Descriptors: Palliative care, Neoplasms, Body composition, Survival, Quality of life.

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RESUMO

Objetivo: Analisar a produção científica acerca das consequências da sarcopenia em pacientes oncológicos em cuidados paliativos. **Métodos:** revisão integrativa, sendo realizado o levantamento bibliográfico por meio de busca eletrônica na Biblioteca Virtual de Saúde, Pubmed, LILACS e SciELO, utilizando os descritores controlados "sarcopenia", "cuidados paliativos" e "câncer", associados pelos operadores booleanos "*AND*" e "*OR*". **Resultados:** foram incluídos 18 artigos, dos quais foram extraídas três abordagens temáticas que tratam sobre a prevalência e fatores associados à sarcopenia, e sua influência na sobrevida, qualidade de vida e sintomas em pacientes oncológicos em cuidados paliativos. **Conclusão:** a sarcopenia nestes pacientes possui alta prevalência, leva ao maior risco de toxicidade à quimioterapia paliativa com influência na sobrevida, e, ainda, está relacionada a uma maior carga de sintomas, contribuindo para malograr a qualidade de vida desses pacientes, sendo necessária a discussão sobre o combate da sarcopenia durante o curso da doença oncológica.

Descritores: Cuidados Paliativos, Neoplasias, Composição corporal, Sobrevida, Qualidade de vida.

RESUMEN

Objetivo: Analizar la producción científica sobre las consecuencias de la sarcopenia en pacientes oncológicos en cuidados paliativos. **Métodos:** revisión integradora, y la encuesta bibliográfica se realizó mediante búsqueda electrónica en la Biblioteca Virtual de Salud, Pubmed, LILACS y SciELO, utilizando los descriptores controlados "sarcopenia", "cuidados paliativos" y "cáncer", asociados por los operadores booleanos "AND" y "OR". **Resultados:** fueron incluidos 18 artículos, siendo extraídos tres enfoques temáticos que tratan sobre la prevalencia y factores asociados a la sarcopenia, y su influencia en la supervivencia, calidad de vida y síntomas en pacientes oncológicos en cuidados paliativos. **Conclusión: l**a sarcopenia en estos pacientes tiene alta prevalencia, lleva al mayor riesgo de toxicidad a la quimioterapia paliativa con influencia en la supervivencia, y, aún, está relacionada a una mayor carga de síntomas, contribuyendo para malograr la calidad de vida de eses pacientes, haciendo necesaria la discusión sobre el combate de la sarcopenia durante el curso de la enfermedad oncológica.

Descriptores: Cuidados paliativos, Neoplasias, Composición corporal, Sobrevida, Calidad de vida.

INTRODUCTION

Cancer is considered a major public health issue worldwide and is linked to changes in the lifestyle and demographic profile of the population.[1] In 2012, there were 14.1 million new cases of cancer and 8.2 million deaths worldwide. In general, the highest incidence rates were observed in developed countries, with intermediate rates in South and Central America. In Brazil, the incidence of 600 thousand cancer cases was estimated just in the 2018-2019 biennium.[2]

Advanced cancer, either diagnosed late or resulting from the progression of the disease leads cancer patients to be eligible for Palliative Care (PC). According to the World Health Organization (WHO), the PC targets to preventing and relieving suffering, in addition to promoting Quality of Life (QOL).[3]

A common condition that can have a major impact on QOL and the survival of cancer patients is sarcopenia. In 1989, Irwin Rosenberg proposed the term "sarcopenia" (Greek "*sarx*" or flesh + "*penia*" or loss) to describe the decrease in Muscle Mass (MM) related to advancing age,[4] even though its development can be associated with conditions that are not seen exclusively in elderly people, such as inactivity, malnutrition and pathological conditions, including cancer.

Nowadays, sarcopenia is defined as a syndrome characterized by the loss of skeletal muscle strength associated with low muscle quantity or quality, which can compromise physical performance in its severe condition, with the risk of adverse results, such as falls, fractures, functional disability, disorders of immobility, physical dependence, impaired QOL, hospitalization and death.[5]

Given aforementioned issue, the present work meant to analyze the scientific production, both in national and international journals, addressing the consequences of sarcopenia in cancer patients undergoing palliative care

Hence, we understand that the study of this topic is of great relevance to the health field, as it might provide subsidies for health professionals to plan strategies to minimize the adverse effects of sarcopenia in patients without alternative curative treatments, but they require an assistance that provides a better QOL.

METHODS

It is an integrative literature review, whose methodological path was subdivided into six phases: elaboration of the guiding question; literature search; data collection; critical analysis of the included studies; discussion of results and presentation of the review.[6]

Herein, there was applied the following guiding question: What is the scientific production addressing the consequences of sarcopenia in cancer patients undergoing PC?

The bibliographic search was performed through electronic search in the following databases available in the Virtual Health Library (VHL): *Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS)* [Latin American and Caribbean Literature in Health Sciences]; USA National Library of Medicine (MEDLINE/PubMed) and the Scientific Electronic Library Online (SciELO), using, as a research strategy, the controlled descriptors "sarcopenia", "palliative care" and "cancer", associated by the Boolean operators "AND" and "OR".

In regard to the inclusion criteria, complete articles available electronically in Portuguese, English and Spanish between 2009 and June 2019 were included. Letters to the editor, case reports, editorials, duplicate articles and those that did not address the proposed theme were ultimately excluded.

The studies were classified according to the scientific Level of Evidence (LE), as follows:[6] LE I: meta-analysis of multiple controlled and randomized clinical trials;

LE II: studies with experimental design; LE III: quasi-experimental studies; LE IV: descriptive studies or with a qualitative approach; LE V: case or experience reports; LE VI: expert opinions.

The articles were selected, and their relevant information were underlined, described in tables and gathered into thematic categories, then they were interpreted in the light of the literature.

RESULTS AND DISCUSSION

This research found 70 publications according to the search criteria in the databases, of which 18 articles constituted the sample for meeting the inclusion criteria, according to the flowchart Preferred Reporting Items for Systematic Review and Meta-Analyzes (PRISMA)[7] (**Figure 1**). Eight articles (44.4%) date from the years 2017 and 2018, four (22.2%) of each year. Most publications addressing the subject were from the European continent (10 articles, 55.5%), mainly from the Netherlands (five, 27.8%) and Norway (four, 22.2%). Brazil produced only two articles (11.1%) about the object of study. After analyzing the selected studies, the results were presented in **Tables 1** and **2**.

Herein, the studies were classified with relevant LE and had a representative sample number, which demonstrates that the results of this review were consistent with the guiding question.

Figure 1 – Flowchart for identification and selection of the scientific articles according to PRISMA. *João Pessoa* city, *Paraíba* State, Brazil, 2019.
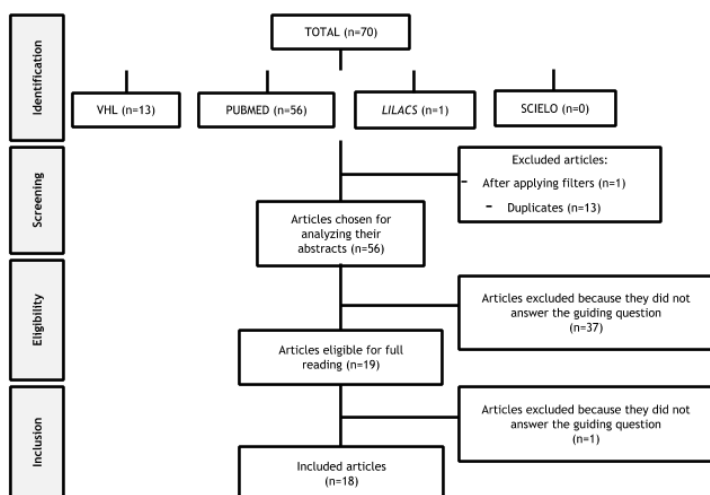

Table 1 – Characterization of the articles included in this integrative literature review, *João Pessoa* city, *Paraíba* State, Brazil, 2019.

Article	Authors/Year/Country	Design/LE	n	Population
A1	Kurk et al.[8] (2019), Netherlands	Randomized CTr/ LE II	414	Metastatic CRC in two systemic palliative treatments
A2	Silva et al.[9] (2019), Brazil	Cohort, observational/LE III	334	Advanced cancer undergoing PC
A3	Nipp et al.[10] (2018), USA	Randomized CTr/ LE II	237	Incurable either lung or GI cancers
A4	Kurk et al.[11] (2018), Netherlands	Randomized CTr/ LE II	450	Metastatic CRC
A5	Versteeg et al.[12] (2018), Netherlands	Prospective/LE IV	103	Elderly people bearing advanced cancer of breast, prostate or CRC
A6	Queiroz et al.[13] (2018), Brazil	Cross-sectional/LE IV	210	Advanced cancer undergoing PC
A7	Neefjes et al.[14] (2017), Netherlands	Cross-sectional, observational/LE IV	233	Cancers of lung, breast, prostate or CRC undergoing palliative CT
A8	Bye et al.[15] (2017), Norway	Randomized CTr/ LE II	734	Advanced stage IIIB/IV NSCLC
A9	Rier et al.[16] (2017), Netherlands	Retrospective/ LE IV	166	Metastatic breast cancer undergoing CT
A10	Pérez Camargo et al.[17] (2017), Mexico	Longitudinal/ LE IV	628	Palliative cancer
A11	Sjøblom et al.[18] (2016), Norway	Randomized CTr/ LE II	734	Advanced stage IIIB/IV NSCLC undergoing palliative CT
A12	Choi et al.[19] (2015), South Korea	Retrospective/ LE IV	484	Advanced pancreatic cancer undergoing PC
A13	Stene et al.[20] (2015), Norway	Cohort, observational/LE IV	35	Advanced stage IIIB/IV NSCLC undergoing palliative CT
A14	Kilgour et al.[21] (2013), Canada	Longitudinal/ LE IV	203	Advanced stage NSCLC and GI cancer
A15	Thoresen et al.[22] (2012), Norway	Longitudinal/ LE IV	50	Metastatic CRC
A16	Mir et al.[23] (2012), France	Non-randomized CTr/ LE II	28	Advanced biliary tract cancer undergoing palliative CT
A17	Baracos et al.[24] (2010), Canada	Longitudinal/ LE IV	441	Advanced stage III/IV NSCLC
A18	Tan et al.[25] (2009), Canada	Longitudinal/ LE IV	111	Pancreatic cancer undergoing palliative CT

LE: level of evidence; n: sample number; CTr: clinical trial; CRC: colorectal cancer; PC: palliative care; GI: gastrointestinal tract; CT: chemotherapy; NSCLC: non-small cell lung cancer.

Table 2 – Presentation of the main findings considering the articles included in this integrative literature review, *João Pessoa* city, *Paraíba* State, Brazil, 2019.

Article	Evaluation method	Main findings
A1	L3SMI by CAT scans	Sarcopenia: 46 to 54%, related to lower BMI and toxicity to systemic palliative treatment, regardless of BMI.
A2	HGS associated with SMI or AMA or CC	Low SMI: 89.9%; Low AMA: 32.3%; Low CC: 68.3%; Low HGS: 70.4%; Sarcopenia: 27 to 65% depending on the method, being associated with worse nutritional status and lower OS.
A3	L3SMI by CAT scans	Sarcopenia: 55.3%, associated with age, male gender, worse QOL and depression; Lower probability associated with higher BMI.
A4	L3SMI by CAT scans	Sarcopenia: 51%; SO: 6%; MM alternated by periods of loss, stability or gain, being influenced by the intensity of the treatment.
A5	SMD and L3SMI by CAT scans and HGS	Low L3SMI: 66%; Low SMD: 88%; Low HGS: 21%; Correlation between L3SMI and HGS only in males; HGS associated with lower OS.
A6	HGS associated with MAMC	Sarcopenia: 32.4%, associated with lower values of lymphocytes, leukocytes and albumin, worse nutritional status and worse QOL.
A7	L3SMI by CAT scans	Sarcopenia: men 58% and women 61%; Fatigue is related to the loss of MM only in men.
A8	SMD and L3SMI by CAT scans	Low MM associated with fatigue, pain, low QOL in the physical dimension; Low SMD associated with physical disability and dyspnea.
A9	L3SMI by CAT scans and SMD	Low L3SMI: 66.9%; Low SMD: 59.6%; SO: 7.2%; L3SMI showed no association with OS; lower SMD was associated with older age and BMI and lower OS and progression time.
A10	SMI by BIA	Sarcopenia: 46%, associated with males, BMI ≤24.9 kg/m^2, KPS ≤50%, ≥5 clinical symptoms and lower OS.
A11	L3SMI by CAT scans and SMD	Low SMD was found to be associated with worse OS, while L3SMI was not related to OS.
A12	L3SMI by CAT scans	Sarcopenia: 21.3%; SO: 0.6%; Male gender associated with loss of MM and sarcopenia, which are associated with worse OS, regardless of BMI.
A13	L3SMI by CAT scans	Sarcopenia: 74%; Loss of MM: 54%; OS was not associated with sarcopenia, but with loss of MM during CT.

A14	Appendicular SMI with DXA	Low HGS related to worse OS, worse muscle and nutritional markers (BMI, albumin, sarcopenia and muscle strength in lower limbs) and functional (fatigue and QOL).
A15	L3SMI by CAT scans	Sarcopenia: 35.7%, not associated with global QOL, only when adjusted showed worse physical function for women.
A16	L3SMI by CAT scans	Sarcopenia: 35.7%, related to lower progression-free survival and lower OS.
A17	L3SMI by CAT scans	Sarcopenia: 46.8%, being more prevalent among men (61% vs 31%); Loss of MM, regardless of BMI.
A18	L3SMI by CAT scans	Sarcopenia: 55.9%; Sarcopenia with overweight/obesity: 16.2%, being an independent predictor of OS; Increased sarcopenia during palliative CT (45.5% to 61.4%).

L3SMI: L3 skeletal muscle cross-sectional area, cm²/m²; CAT: computerized axial tomography; L3: third lumbar vertebra; BMI: body mass index; HGS: hand grip strength; SMI: skeletal muscle mass index, kg/m²; AMA: arm muscle area, cm²; CC: calf circumference; OS: overall survival; QOL: quality of life; SO: sarcopenic obesity; MM: muscle mass; SMD: skeletal muscle radio-density; MAMC: mid-arm muscle circumference; BIA: bioelectrical impedance analysis; KPS: Karnofsky performance scale; CT: chemotherapy; DXA: dual-energy X-ray absorptiometry.

After analyzing the studies included for the present review as well as the gathered information, it was possible to elaborate three thematic approaches, as follows: I - Prevalence and factors associated with sarcopenia in cancer patients undergoing PC; II - Influence of sarcopenia on the survival of cancer patients undergoing PC; and III - Influence of sarcopenia on QOL and symptoms that affect cancer patients undergoing PC.

I - Prevalence and factors associated with sarcopenia in cancer patients undergoing PC

Sarcopenia is an objective indicator of cancer cachexia. The loss of MM is due to metabolic imbalances, which are caused by systemic inflammation and catabolic factors derived from the tumor, in which catabolism is exacerbated during progressive terminal illness.[26]

Sarcopenia in patients with advanced cancer undergoing palliative treatment is a very prevalent condition. According to the analyzed publications, the prevalence of sarcopenia varied from 21.3 to 74% in the most varied types of cancer.[8–10,13,14,17,19,20,22–25] These values are similar to the prevalence found in non-metastatic cancer patients,[27] evidencing the high prevalence of sarcopenia throughout the oncological disease.

The wide variation in the prevalence of sarcopenia found in publications is the result of several factors, including the following: demographic factors (gender, age and ethnicity), related to cancer (type of primary cancer), different palliative treatments (maintenance medication, more intensive medication, observation), in addition to conceptual differences in sarcopenia and the different methods of measuring MM.

Concerning the demographic factors, it is observed that sarcopenia in cancer patients undergoing PC is associated with males,[10,17,24] just as men have more frequent loss of MM when going through palliative CT,[19] then demonstrating that the pattern of muscle loss may differ between genders. Advanced age is a factor that correlates with sarcopenia in these patients,[10,18] as well as in the general population, as the elderly are more likely to develop sarcopenia due to reduced physical activity and the nutritional, metabolic and hormonal factors inherent in the advancing age, which can lead to worse clinical outcomes and functional dependence.[5]

It is important to note that most studies, all considering the international framework,[8,10,11,14,17,19,20,22–25] classify sarcopenia only by low skeletal MM.[26] Moreover, these studies used, as a technique for measuring MM the L3-level CAT scans, except Pérez Camargo et al.,[17] whose technique used was BIA, which is also a validated method for assessing MM.[5]

L3-level CAT scanning is a gold standard method for the assessment of MM, as it is related to total body MM.[5] In cancer patients, CAT scans are routinely performed for diagnosis and treatment evaluation and, therefore, are available for the analysis of body composition, without additional costs or patient burden.[8] On the other hand, it is necessary to use specific software for the analysis of images, which have a high cost,[17] which makes its use unfeasible in several services, particularly in either underdeveloped or under development countries.

Only Brazilian studies[9,13] used low MM associated with low muscle strength as a criterion for classifying sarcopenia, as recommended by the most current guideline on sarcopenia.[5] In contrast, these studies were the only ones that used anthropometric measurements as a method of assessing MM, such as AMA, CC[9] and MAMC.[13]

Although anthropometric measurements are considered easily applicable and easily incorporated into the clinical routine, they are subject to measurement variability, and are not considered a priority in the measurement of MM.[5] Nevertheless, they are sensitive to identify nutritional impairment associated with sarcopenia in cancer patients undergoing PC, in addition to being related to adverse clinical results in these patients.[9,13] Lower BMI values were associated with the presence of sarcopenia in various types of cancer in PC,[8,10,16] mainly with BMI values ≤24.9 kg/m².[17]

II - Influence of sarcopenia on the survival of cancer patients undergoing PC

The results of the present review demonstrate that sarcopenia is a relevant indicator for a worse prognosis in cancer patients undergoing palliative treatment, negatively influencing progression-free survival,[23] as well as OS.[9,19,23] Results related to OS were observed including the use of anthropometric measurements (AMA and CC) as a technique for measuring MM.[9] In patients with NSCLC undergoing palliative CT, an L3SMI threshold <47.6 cm²/m² was identified in men related to the lower OS, however, in women, a threshold related to OS was not identified.[18]

During palliative cancer treatment, it is common to observe muscle wasting, increasing the prevalence of sarcopenia during the palliative scenario.[25] Loss of MM during palliative CT is a bad prognostic factor in OS.[19,20] MM reduction by more than 2 cm²/m² is strongly related to the worst OS in patients with pancreatic cancer undergoing palliative CT of both genders, regardless of BMI.[19]

It is important to highlight the difficulty in preserving skeletal muscle during advanced stages of cancer, especially

after extensive weight loss, since the metabolic changes resulting from cancer cachexia might no longer be reversible. Nonetheless, in metastatic disease, especially in the initial phase, patients may still have anabolic potential.[28] Loss of MM in such patients, instead of a continuous process, is considered reversible even in sarcopenic patients and can be influenced by the intensity of systemic treatment palliative.[11] Patients with either increased or stable MM respond better to palliative CT, with a better prognosis.[20]

The approach with multimodal treatment, including aerobic and resistance exercises, orexigenic agents and nutritional support show promising results in the fight against sarcopenia in cancer patients.[29] The decision-making process about the nutritional therapy to be adopted undergoing palliative patients must, however, respect their autonomy, in addition to considering their clinical condition, symptoms and life expectancy, with the primary objective of increasing the QOL of these patients.[3]

It was observed that sarcopenic patients have greater toxicity to palliative CT,[8] being considered a potential risk factor for the reduction of OS, as it results in dose delays, reduction or discontinuation of systemic palliative treatment.

Sarcopenic patients might have altered chemotherapy drug concentration and clearance time parameters, and to reduce toxicity in these patients, the dose of CT must be adjusted to body composition, since most chemotherapeutic agents are metabolized in the muscle.[8] Currently, CT prescription is based on body surface area, which holds a low correlation with lean mass, remarkably in obese people.[30]

Sarcopenia concomitant with the presence of obesity is less prevalent in patients with palliative cancer, ranging from 0.6 to 7.2%,[11,16,19] not having a significant association with OS and the time of disease progression in cancer patients metastatic breast cancer undergoing palliative CT.[16] In patients with pancreatic cancer undergoing palliative CT, sarcopenia associated with overweight and obesity was identified as an independent predictor of OS.[25]

When going through palliative treatment, although patients usually present muscle loss, there may be an increase in body weight.[11] BMI is not a good prognostic factor in these patients, consequently, a detailed assessment of body composition is necessary to assess muscle changes, as well as the muscle strength assessment.

According to the studies scrutinized, it has been shown that the loss of muscle strength measured by HGS is associated with lower MM and lower OS in palliative patients with NSCLC and gastrointestinal cancer,[21] as well as in the elderly bearing breast, prostate and colorectal cancers.[12] Muscle weakness has a strong association with negative outcomes and has been related to worse muscle quality, being represented by low SMD, whose measure reflects the increase in fat deposits in skeletal muscle.[18]

Low SMD was associated with higher BMI, advanced age and lower OS in patients undergoing PC with breast cancer,[16] NSCLC[18] and metastatic renal carcinoma,[31] whereas OS was not associated with MM in these studies. Sjøblom et al.[18] found an SMD threshold <28 Hounsfield Units (HU) for men and <23.8 HU for women related to the lowest OS. This demonstrates that not only muscle size, but also strength and muscle quality are considered significant prognostic factors for cancer patients undergoing PC.

III - Influence of sarcopenia on QOL and symptoms that affect cancer patients undergoing PC

After scrutinizing the publications, it is observed that sarcopenia, regardless of the diagnostic criterion, can affect the global QOL of cancer patients undergoing PC, with a larger impact on the physical dimension.[13,15,22] Discrete reductions in skeletal MM might not affect the QOL, accordingly, MM must be below a threshold before the effects on physical function and other QOL scores can be detected. Marked reductions in these scores have been observed in patients with NSCLC undergoing palliative CT with decreased L3SMI below about 42-45 cm^2/m^2 for men and 37-40 cm^2/m^2 for women.[15]

Physical function depends not only on MM, but also on muscle strength. In the study carried out by Kilgour et al.,[21] a pronounced relevance of muscle strength was observed as a predictor of QOL, where patients with NSCLC and advanced gastrointestinal cancer with low HGS had worse QOL, demonstrating that HGS is an independent factor associated with functionality. The low MM, as well as the loss of muscle strength, lead to deterioration of physical function and a greater likelihood of dependence to perform activities of daily living.[13]

Muscle strength holds direct correlation with SMD. Muscle quality is considered more important for muscle function than absolute MM.[16] The larger infiltration of fat into the muscle might increase the risk of immobility in elderly people.[15]

Sarcopenia is related to the symptoms increased burden of cancer patient undergoing PC. In sarcopenic patients, the most common clinical symptoms are fatigue,[14,15,17] pain,[15,17] and depression,[10,17] which have an impact on such patients' QOL.

Cancer-related fatigue in patients undergoing PC is a highly prevalent symptom and has been associated with loss of MM, assessed by L3-level CAT scans,[14] and muscle weakness measured by the HGS,[15] with the greatest influence on males, indicating that, in women, other factors may have a bigger impact on fatigue.

Anorexia and dyspnea are frequent symptoms, which affect the QOL of such patients. Anorexia was associated with low MM, which might indicate that low food intake can compromise the maintenance of MM, whereas dyspnea was associated with worse muscle quality and not low MM in patients with NSCLC undergoing palliative CT.[15]

CONCLUSIONS

Sarcopenia in cancer patients undergoing PC is a particularly pertinent subject, given its high prevalence in such population. Its presence, as well as the loss of MM during palliative treatment, are related to the shorter time for disease progression and susceptibility to palliative CT toxicity, which contributes to lower OS. Furthermore, sarcopenia is related to a series of clinical symptoms, which contribute to the worsening of QOL, especially in the physical dimension, directly interfering in the functionality and independence of these patients.

Nonetheless, the results of this review should be interpreted with caution, as the present study has limitations, since most of the analyzed articles did not use muscle strength as a diagnostic standard for sarcopenia, whose measurement is considered an important parameter of sarcopenia.

Bearing the aforesaid in mind, both assessment and monitoring of body composition and muscle strength during the course of the advanced oncological disease are essential, as joint interdisciplinary approaches can contribute to minimizing the impact of sarcopenia on OS and QOL of patients undergoing PC.

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