



## Nutritional therapy and palliative care in cancer cachexia: a systematic review

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DOI: <https://doi.org/10.54448/jcpmsl23109>

Received: 08-27-2023; Revised: 10-28-2023; Accepted: 11-02-2023; Published: 11-11-2023; JCPMSL-id: e23109

### Abstract

**Introduction:** According to evidence-based clinical practice guidelines, nutritional risk screening and nutritional support are essential for all cancer patients with or without cachexia because inadequate nutritional intake is often observed and associated with weight loss. **Objective:** It was to explore and discuss nutritional therapies and palliative care in cancer cachexia through a systematic review of the literature.

**Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to October 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:**

A total of 134 articles were found, and 38 articles were evaluated in full, and 28 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with  $X^2=51.3\%>50\%$ . It was concluded that the preservation of nutritional status may be a relevant concern during the palliative care phase. In overweight and obese patients with advanced cancer, it was observed that almost 50% of patients are at nutritional risk and 13% are malnourished and have worse outcomes. Measures must be proportionate to the nutritional needs and predominant symptoms of each patient, as part of personalized and adapted nutritional treatment.

**Keywords:** Palliative care. Enteral/parenteral nutritional therapy. Cancer.

### Introduction

According to evidence-based clinical practice guidelines, nutritional risk screening and nutritional support are essential for all cancer patients with or without cachexia because inadequate nutritional intake is often observed and associated with weight loss [1,2]. If inadequate nutritional intake persists despite nutritional counseling and oral nutritional supplements, artificial nutrition and hydration may be indicated. However, there is a growing consensus that artificial nutrition and hydration need to be withheld or withdrawn in patients with imminent death and expected survival of days [2,3].

Several societies and guidelines have recommended parenteral nutrition and hydration (PNH) if patients cannot be fed with other routes of administration and the expected survival is greater than 3 months. Implementation of artificial nutrition and hydration in this population is reasonable, even in palliative care settings, because of nutrition support, including artificial nutrition and hydration [1,3].

Furthermore, previous studies conducted in palliative care settings have suggested that a large number of patients with advanced cancer and their families wish to receive nutritional support when the patients become unable to ingest sufficient food orally [3,4]. In this scenario, it is necessary to increasingly optimize nutritional therapy in these patients, given that estimates from the Global Cancer Observatory indicate that more than 9.0 million cancer-related deaths



occurred in 2018 across the world. Many patients are now cured or living longer with metastatic disease due to advances in diagnostics and treatments [1].

In recent years, patients with advanced cancer have been defined as those with distant metastases, advanced-stage disease, and/or a prognosis of 6 to 24 months. Now, thanks to advances in treatment, these patients live for several years, especially when patients receive precise nutritional therapy, that is personalized and adequate nutrition [2-4].

In this scenario, patients in palliative care have a neoplasm that does not respond to curative treatment or a potentially fatal disease [5]. However, palliative care is not synonymous with end-of-life care or terminal care. By origin, the term "palliative" is derived from the Latin word "pallium" which means "mask" or "cloak". This etymology indicates what palliative care is essentially, covering or masking the symptoms of an incurable disease to alleviate or reduce suffering [6,7].

In this context, the physical symptoms related to cancer, together with the psychological suffering and social and spiritual needs that arise during the disease, seriously affect the lives of the patient and family. Patients with advanced, incurable cancer often experience a burden of symptoms (including pain, dyspnea, fatigue, weight loss, and depression), and emotional, social, existential, and spiritual distress throughout the disease. Cancer symptoms depend on the stage, type of cancer, age, general condition of the patient, and many other factors. These symptoms impair the patient's daily routine and quality of life [2,5].

Also, about the type of cancer, patients receive different types of treatments (chemotherapy, immunotherapy, radiotherapy, surgery, and other anti-cancer treatments) that lead to side effects, toxicities, and, in some cases, permanent disability resulting in disability. Symptom control is an essential part of cancer treatment, and more studies show positive effects of early integration of palliative care and enteral/parenteral nutritional therapy into oncology care to better respond to patient's needs [3,4].

Regarding nutritional support for cancer patients, ESPEN guidelines recommend "In a patient undergoing curative treatment with anticancer medications, if oral food intake is inadequate despite counseling and oral nutritional supplements (ONS), supplemental enteral nutrition or, if this is not sufficient or possible, parenteral nutrition" [2]. However, when curative treatments are no longer available for unresectable locally advanced or metastatic disease, the goal of anticancer treatment is palliative. Chemotherapy is often designed as palliative therapy for patients with advanced cancer due to the expected survival benefit [2-4]. In these patients, nutritional support must be offered and implemented

considering the expected benefit of intolerance to chemotherapy and consequently the potential benefit in survival [4].

ESPEN guidelines strongly recommend home artificial nutrition (HAN), both enteral and parenteral, in cancer patients with persistent and insufficient oral nutrient intake or malabsorption in appropriate patients [2]. Enteral and parenteral nutrition have specific indications and contraindications. However, many factors can negatively impact the administration of enteral nutrition (EN) in patients with advanced cancer. Specifically, enteral nutrition may not be able to meet nutritional needs in cancer patients with extensive intestinal resections, high-output ileostomy, or intestinal fistula, as well as in the presence of symptoms of nutritional impact (nausea, vomiting, diarrhea, abdominal pain, and constipation) due to carcinomatosis). Orreval et al. [8] showed that nausea, vomiting, and gastrointestinal obstructions were the most common indications for parenteral nutrition in palliative patients.

Therefore, this study explored and discussed nutritional therapies and palliative care in cancer cachexia through a systematic literature review.

## Methods

### Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: 09/28/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 09/28/2023.

### Data Sources and Research Strategy

The literary search process was carried out from August to October 2023 and developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: "Palliative care. Enteral/parenteral nutritional therapy. Cancer" (in English: Palliative care. Enteral/parenteral nutritional therapy. Cancer), and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

### Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons,



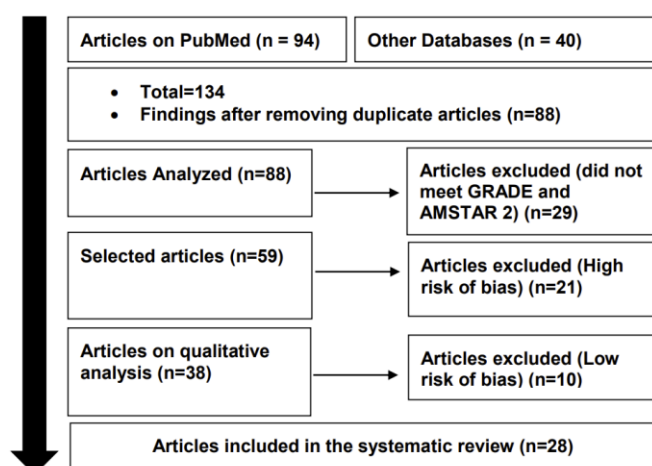
precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

## Results and Discussion

### Summary of Findings

A total of 134 articles were found that were subjected to eligibility analysis, with 28 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with  $X^2=51.3\% > 50\%$ . Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2.

Figure 1. Flowchart showing the article selection process.

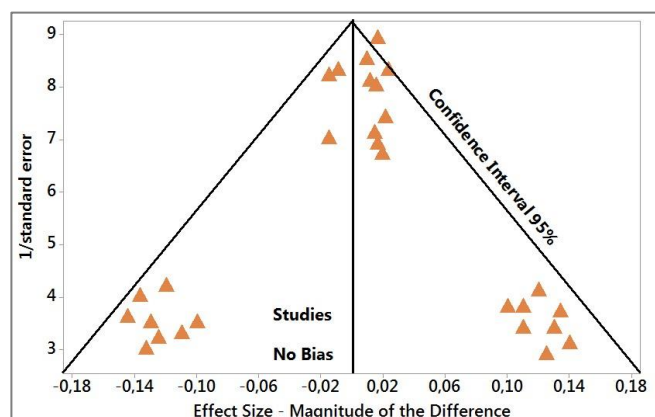


Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the

graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=28 studies).



Source: Own Authorship.

### Main Approaches to Nutritional Therapies and Palliative Care

Regarding cachexia and anorexia, clinical data suggest that approximately 2030% of deaths are attributable to malnutrition rather than cancer. Malnutrition, including muscle loss, on the other hand, is recognized as a common consequence of anticancer treatments. Whether these processes are reversible is a matter of debate, with the pathophysiological mechanisms involved being increasingly studied [2,3].

In this sense, cachexia is a multifactorial syndrome resulting from host factors, type and stage of cancer, and treatment modalities. In preclinical stages, hormonal dysregulation and metabolic abnormalities occur as a result of the cancer microenvironment and chronic inflammatory states, such as insulin resistance, increased proteolytic activity, and lipolysis [9,10]. In later stages, a negative protein and energy balance derived from metabolic disorders results in progressive functional impairment with clinical manifestations characterized by hypophagia, early satiety, fatigue, and wasting.

Involuntary weight loss has been considered the hallmark of cachexia for at least 40 years and has been well-recognized as an independent prognostic factor in cancer patients over the past 15 years [9]. Despite the increasing prevalence of overweight and obesity in advanced cancer, ranging from 40% to 60% [11], it has been observed that almost 50% of patients are at nutritional risk and 13% are malnourished and have worse outcomes [12].



In patients with advanced cancer, preservation of nutritional status may be a relevant concern during the palliative care phase. Even when the disease can no longer be cured, patients can survive for a reasonable period (several months or years). In this context, deficits in nutritional status can impair performance, quality of life, tolerance to palliative antineoplastic treatments, and survival. Therefore, patients with reduced oral intake require nutritional treatment to maintain nutritional status and meet energy and protein needs [2].

Indeed, in the last stages of life, characterized by refractory cachexia with weight loss and deterioration of physical condition, nutritional care should focus on recommending foods that the patient can tolerate and prefer to eat (comfort eating), to ensure a better quality of life and alleviate symptoms [13]. The first goal of nutritional treatment is to preserve oral nutrition by minimizing food-related discomfort and maximizing eating pleasure through strategies that include dietary counseling, food fortification, and oral nutritional supplements [14].

According to ESPEN guidelines, counseling is the first approach within nutritional treatment, aiming to manage symptoms (loss of appetite, nausea, early satiety, changes in taste and smell, constipation, dysphagia, and psychosocial factors) and encouraging the intake of foods and drinks that are better tolerated, considering food intolerances and allergies, dietary history, current eating pattern and any changes in taste or smell that may affect preferences [2].

Dietary recommendations should be provided to optimize energy and protein intake through modifications in food quality, portion sizes, timing and division of meals throughout the day, and adaptation of consistency. In this context, measures must be proportional to the nutritional needs and predominant symptoms of each patient, as part of a personalized and adapted nutritional treatment [13].

Furthermore, patients should be informed that healthy eating guidelines are no longer appropriate for their clinical conditions and that dietary restrictions should be avoided as they limit food intake and enjoyment. Oral nutritional supplementation finds its usefulness when nutritional needs cannot be met by dietary advice and food fortification. High-energy (>1.22 kcal/mL) and high-protein (>20% energy derived from protein) oral nutritional supplementation allow optimization of caloric and protein supply within a reduced volume, and special formulas can be advantageous in selected patients, as semi-elemental products in conditions of malabsorption [15].

According to a meta-analysis by Lee et al. [16], the association of oral nutritional supplement administration

and dietary advice appears to be more effective than oral nutritional supplement alone in nutritional and functional results (gain/maintenance of weight and fat-free mass, improvements in function score quality of life). In the context of oral nutritional supplements, formulas enriched with n-3 fatty acids could provide some results in terms of weight gain and improvement in lean body mass, nutritional intake, and quality of life. However, such evidence appears to be limited by study heterogeneity in terms of stage of cachexia, site, and stage of cancer, concomitant anticancer treatments, and outcome measures [17].

The authors of Oliveira et al. (2023) [18] identified through a prospective cohort study the clinical usefulness of assessing nutritional status using validated tools to indicate enteral nutrition for patients with incurable cancer in palliative care. Patients were assessed for nutritional risk using the Patient-Generated Subjective Global Assessment and for cancer cachexia (CC) using the modified Glasgow Prognostic Score at enrollment and after approximately 30 days. 180 patients participated. The only parameter of nutritional status associated with function was CC. The less severe the CC, the more likely the Karnofsky Performance Status will remain stable or improve over 30 days (non-cachectic: OR = 1.95; 95% CI, 1.01-3.47; malnourished: OR = 1.06; 95% CI, 1.01- 1.42). In addition, white skin color (OR = 1.79; 95% CI, 1.04-2.47), higher education level (OR = 1.39; 95% CI, 1.13-2.78), and inadequate caloric intake (OR = 1.96; 95% CI, 1.02) -2.81) were also associated with the outcome. Therefore, the use of the modified Glasgow Prognostic Score to identify the existence and severity of CC, which is associated with function, has the potential to assist in clinical decision-making regarding the indication of enteral nutrition in patients with incurable cancer undergoing palliative care.

In this context, the role of nutritional support for cancer patients in palliative care is still a controversial topic, in part because there is no consensus on the definition of a palliative care patient due to ambiguity in the common medical use of the adjective palliative. However, guidelines recommend evaluating nutritional deficiencies in all such patients because, regardless of whether or not they are still on anticancer treatment, malnutrition leads to poor performance, impaired quality of life, unplanned hospitalizations, and reduced survival. Given that nutritional interventions tailored to individual needs can be beneficial, the guidelines recommend that if oral food intake remains inadequate despite oral nutritional counseling and supplements, enteral nutrition or if this is not sufficient or feasible, Parenteral nutrition (supplemental or total) should be considered in appropriate patients [19].





Furthermore, the nutritional management of patients in palliative care can raise ethical questions, especially when enteral nutrition is prescribed through a nasogastric tube (NGT). The authors Sánchez-Sánchez et al. (2021) [20] analyzed, through a systematic review, the current state of management of enteral nutrition through NGT in patients under palliative care and its effect on their well-being and quality of life. The use of NGT caused fewer episodes of diarrhea and more restrictions than the group that did not use NGT. Additionally, the use of tubes increased emergency department attendance, although there was no contrast between NGT and percutaneous endoscopic gastrostomy (PEG) devices. No statistical difference was found between the use of tubes (NGT and PEG) or non-use, regarding symptom treatment, comfort level, and satisfaction at the end of life. However, it improved hospital survival compared to other procedures, and differences in hospitalizations were found with the use of other probes or devices.

Furthermore, artificial nutrition can be integrated into a palliative care program when a positive influence on the quality of life is expected and the risk of dying from malnutrition is greater than from the progression of cancer. ESPEN guidelines suggest that enteral nutrition should be considered first whenever the gastrointestinal tract is functional and oral nutrition remains inadequate despite nutritional interventions [21].

In this aspect, enteral nutrition is most often used in patients undergoing palliative care with head and neck or upper gastrointestinal tract cancer. In these patients, the main indication for starting enteral nutrition is oropharyngeal/esophageal dysphagia or gastric obstruction/dysmotility, due to mechanical and functional factors related to the disease, but also to palliative side effects induced by chemotherapy and/or radiotherapy [22].

In patients with a life expectancy of several weeks or months who are unable to meet more than 60% of their long-term daily energy needs through oral intake, it is a useful strategy to obtain early gastrointestinal access. Among gastric devices, PEG is the gold standard, while radiologically inserted gastrostomy or eventually surgical gastrostomy must be performed when an endoscopically guided tube cannot be placed. Long-term jejunal access (endoscopic or surgical jejunostomy) may be an option in the case of gastric obstruction/dysmotility. Placement of an NGT or nasojejunal tube may be considered when short-term enteral nutrition is expected (usually up to 6 weeks) and/or survival is uncertain [23].

In addition, in patients with head and neck cancer who are unable to swallow, the use of an enteral route

via NGT or gastrostomy may be an appropriate strategy to obtain nutritional support in the home care environment [23]. According to a study, evaluating the impact of home artificial nutrition (HAN) on performance status and survival in palliative oncology patients, enteral nutrition, with dysphagia as the main indication, can maintain/improve KPS and prolong median survival within 22.1 weeks (considering that death from starvation usually occurs within 2 months in healthy individuals, or even sooner in advanced cancer patients without nutritional support) [24,25].

In patients with esophageal cancer, PEG provides a better nutritional status than a self-expandable metallic stent and is an independent factor associated with overall survival [26]. In these patients, endoscopically assisted NGT is also a viable palliative option, with a low rate of complications and for nutritional support, as it allows us to increase energy intake, serum albumin, median survival, and reduce hospitalization compared to zero orally [27]. However, Yu et al. [28] indicate a slightly worse quality of life in esophageal cancer patients using NGT feeding compared to the percutaneous route during chemoradiotherapy. In a comprehensive evaluation, it is reasonable to consider PEG as the preferred choice for long-term nutritional support in palliative patients with esophageal cancer.

When enteral nutrition is contraindicated or unfeasible, due to stenosis, subobstruction/obstruction, dysmotility, peritoneal carcinomatosis, malabsorption, abdominal pain or intolerance, and severe discomfort, parenteral nutrition should be considered [21]. Therefore, to choose the ideal nutritional access, a multidisciplinary clinical evaluation is strongly recommended, taking into account not only the primitive and secondary location of the tumor (gastrointestinal vs. extragastrointestinal) and its direct/indirect effects on the digestive tract, but also the patient's general situation, clinical condition including cancer prognosis, nutritional status, performance status, quality of life, potential effects of nutritional support, and the wishes and expectations of the patient and their family [21].

## Conclusion

It was concluded that the preservation of nutritional status may be a relevant concern during the palliative care phase. In overweight and obese patients with advanced cancer, it was observed that almost 50% of patients are at nutritional risk and 13% are malnourished and have worse outcomes. Measures must be proportionate to the nutritional needs and predominant symptoms of each patient, as part of personalized and adapted nutritional treatment.



## Acknowledgement

Not applicable.

## Ethics approval

Not applicable.

## Informed consent

Not applicable.

## Funding

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

## Similarity check

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## Peer Review Process

It was performed.

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