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Bridging gaps in cancer cachexia Care: Current insights and future perspectives

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ABSTRACT

Cachexia is characterized by severe weight loss and skeletal muscle depletion, and is a threat to cancer patients by worsening their prognosis. International guidelines set indications for the screening and diagnosis of cancer cachexia and suggest interventions (nutritional support, physical exercise, and pharmacological treatments). Nevertheless, real-life experience not always aligns with such indications. We aimed to review the current state of the field and the main advancements, with a focus on real-life clinical practice from the perspectives of oncologists, nutrition professionals, and radiologists. Pragmatic solutions are proposed to improve the current management of the disease, emphasizing the importance of increasing awareness of clinical nutrition's benefits, fostering multidisciplinary collaboration, promoting early identification of at-risk patients, and leveraging available resources. Given the distinct needs of patients who are receiving oncologic anti-cancer treatments and those in the follow-up phase, the use of tailored approaches is encouraged. The pivotal role of healthcare professionals in managing patients in active treatment is highlighted, while patient and caregiver empowerment should be strengthened in the follow-up phase. Telemedicine and web-based applications represent valuable tools for continuous monitoring of patients, facilitating timely and personalized intervention through effective communication between patients and healthcare providers. These actions can potentially improve the outcomes, well-being, and survival of cancer patients with cachexia.

Background

Cachexia, Greek term indicating "poor physical status", is a life-threatening wasting syndrome whose main manifestations are severe weight loss and skeletal muscle depletion. Cachexia usually emerges in patients affected by inflammatory conditions, including cancer [1,2]. Up to 80 % of patients with advanced cancer experience cachexia. Pancreatic, oesophageal, gastric, head and neck, lung, and liver malignancies are commonly associated to cachexia's risk [3–5].

The pathophysiology of cancer cachexia is marked by a complex interplay between tumour-related factors and patient-specific variables. Prolonged exposure to adverse effects from anti-cancer treatments disrupts endocrine function, impacting both the metabolism and the central regulation of appetite and satiety, worsening cachexia [2,6,7]. In turn, cachexia makes the patients more prone to develop treatment toxicity. The decreased appetite with the consequent reduced food intake accompanied by increased catabolism, results in an overall negative energy balance. In addition, diminished gastrointestinal autonomic function and chronic fatigue, commonly experienced by cancer patients, create a detrimental cycle that exacerbates their clinical condition. This vicious circle leads to a gradual decline in lean body mass and reduced physical activity, further compromising the patients' well-being [8]. Cachexia negatively impacts the quality of life (QoL) of cancer patients [4,8,9], is associated with a worse prognosis and shorter life

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expectancy, and appears to be the primary cause of mortality in 20–30 % of cancer patients [2,4,9,10].

Due to the widespread prevalence of this disorder and the associated poor clinical outcomes, it is crucial to promptly identify individuals at risk of developing cachexia and to optimize nutritional care of cancer patients diagnosed with cachexia [4,9,11–15]. Over the years, many recommendations have been proposed [16,17,4,9].

Recently updated clinical practice guidelines (CPG) from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have provided guidance for the diagnosis, risk assessment, and management of cachexia in cancer patients, which however remain challenging and overlooked in clinical oncology [11–14,17,18,4].

We aim to review the existing knowledge concerning the diagnosis and management of cancer cachexia, highlight the challenges faced in clinical practice, address unmet needs, and explore the recent advancements. Our goal is to identify potential strategies and therapeutic options that can be integrated into clinical practice in the near future.

Definition of malnutrition and cachexia in cancer patients

Malnutrition and cachexia are two conditions commonly occurring in cancer patients [3]. Efforts have been made to discriminate these two overlapping nutritional disorders to facilitate their diagnosis and treatment. Malnutrition, also referred to as undernutrition, is defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease" [19]. The International Consensus Guideline Committee distinguished starvation-related from disease-related malnutrition according to the absence (of the former) and presence (of the latter) of a systemic inflammatory milieu. Anorexia nervosa, a medical condition associated with chronic starvation occurring without inflammation, is an example of chronic starvation-related malnutrition. Disease-related malnutrition can be caused by either acute disease or injury (e.g., infections, burns, trauma, etc.), or chronic diseases (e.g., cancer, rheumatoid arthritis, chronic kidney disease and other end-stage organ diseases), both of which are characterized by an ongoing inflammatory response (mild or sustained, respectively) [19,20]. According to the Global Leadership Initiative of Malnutrition (GLIM) group, the diagnosis of malnutrition is formulated with at least one phenotypical (weight loss $>$ 5 % in 6 months, BMI $<$ 20 kg/m^2, low muscle mass) and one etiological (reduced food intake and/or absorption, increased systemic inflammation and catabolism) criterion [21]. Systemic inflammation should be determined using the modified Glasgow Prognostic Score (GPS), which combining both C-reactive protein (CRP) and albumin serum levels [4,22] gives a reliable prediction of the patient's outcome [22,23]. Should systemic inflammation be the cause of malnutrition, the patient is believed to be affected by cachexia [4], and as recommended by ESMO CPG, cancer cachexia should be defined as "disease-related malnutrition based on the GLIM definition of malnutrition and the presence of systemic inflammation" [4]. More in detail, both ESMO and ASCO CPG adhere to the description of cancer cachexia outlined by an international consensus in 2011 [9]. According to Fearon and colleagues, cancer cachexia is a multifactorial progressive condition characterized by ongoing weight loss (particularly skeletal muscle, but not necessarily fat mass), that leads to functional and physical decline and cannot be fully reversed by conventional nutritional support [9]. In addition, cachexia should be considered as a continuum of three clinically distinct stages: pre-cachexia (involuntary loss of weight lower or equal to 5 %), cachexia (weight loss $\geq$ 5 % within a 6-month period and sarcopenia), and refractory cachexia (advanced cancer, low performance score and $\leq$ 3 months of expected survival). However, not all patients experience the entire spectrum [9]. The recognition of these stages challenges the conventional perceptions of cachexia, offering a window for early intervention and prognosis improvement.

Importantly, starvation-related malnutrition and cancer cachexia have several distinct features, with the latter being characterized by protein catabolism and muscle atrophy that result in sarcopenia [8]. Cachexia is sustained by the elevated level of pro-inflammatory cytokines [24]. Tumour necrosis factor alpha (TNFα), interleukin 1 beta, and interleukin 6 are thought to induce muscle wasting by activating catabolic pathways within skeletal muscle cells [6,25]. Recent studies have highlighted the potential role of non-inflammatory factors, such as activin A, myostatin, growth differentiation factor (GDF) 15, and lipocalin-2, in orchestrating catabolic signalling. This discovery suggests the existence of alternative pathways, opening avenues for innovative translational approaches in the treatment of cancer cachexia [26].

Methods

To assess the current issues of cachexia cancer management in the clinical practice, we performed a systematic literature search on the PubMed database following the PRISMA guidelines [27] [keywords (Title/abstracts): "cancer" and "cachexia" or "malnutrition" and "guidelines" or "guideline", filter 'year 2019-2023']. The search performed on November 8, 2023, retrieved 216 results (Supplementary material). From the identified guidelines, authors independently evaluated the evidence according to their expertise. The selected papers were discussed in depth, with focus on "nutritional screening, risk assessment and diagnosis" and "management". This critical review encompassed an analysis of the existing recommendations, highlighting gaps and challenges, and proposes practical approaches aligned with real-world clinical practices in the "Practical Suggestions" section.

Nutritional screening, risk assessment and diagnosis of cachexia in cancer patients

Current recommendations

Risk of malnutrition, nutritional deficiencies and overt malnutrition have been reported respectively in 43 %, 51 % and 9 % of patients with solid cancers when assessed at the first oncological visit in the Prevalence of Malnutrition in Oncology (PreMiO) study. The follow-up study NUTRIONCO revealed that malnutrition severity at baseline was associated with a decreased survival in patients with non-metastatic cancers [28,29]. To assess nutritional risk, ESMO CPG suggest employing the following tools: Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Screening Tool (MST) [4]. In addition, patients at risk should be re-assessed monthly by a nutrition professional, while those that are not, every 3 months (or at the start of chemotherapy) [4]. The Italian Intersociety Working Group for Nutritional Support in Cancer Patients advises regular nutritional screening for cancer patients, including during the first visit, follow-ups, and within 48h of hospitalization [16].

For a standardized differential diagnosis of malnutrition and cachexia, the recent ESMO CPG recommend the criteria established by the GLIM working group [21].

Gaps and challenges

Among the four nutritional screening tests recommended by ESCO CPG (MUST, NRS-2002, SNAQ, MST), none is systematically used for cancer patients in different oncology settings [30].

Despite recommendations, the percentage of cancer patients undergoing an early nutritional assessment is consistently lower than expected [14,15,18,31]. Routine nutritional assessment and standardized diagnosis of malnutrition and cachexia fall short in oncology practice [10,11,13–15,24]. Real-world data from France, Germany and Italy highlighted a lack, or a substantial delay in formulating the diagnosis of

malnutrition [13]. Up to 77 % of cancer patients in France never receives a diagnosis, and only few obtain the necessary nutritional care [13]. The misconception that cachexia only occurs in end-of-life cancer patients fuels this neglectful approach [29].

The lack of a comprehensive nutritional education and training of healthcare professionals (HCPs), along with a scarce collaboration between oncologists and clinical nutrition professionals, are the barriers to the implementation of a standard nutritional care. The absence of clear procedures for oncology HCPs complicates screening and diagnosis [11,24].

The lack of a structured multidisciplinary team and the low number of nutrition experts supporting oncologists, may negatively impact the correct interpretation of the data and hinder screening [16,24]. The Barwon Health Cachexia & Nutrition Support Service (CNSS) suggests that a structured multidisciplinary service would improve the care of personalized approaches [32].

The application of criteria for cachexia definition can yield inconsistent results in patients with specific conditions, such as intestinal insufficiency or failure [33,34]. The investigation of all GLIM criteria in clinical practice is not always feasible. Guidance is essential to identify the best criteria combination for malnutrition diagnosis and to predict the best outcome. Moreover, nutritional screening tools are underutilized or implemented too late for cancer patients, supporting the idea of a lack of awareness about the benefits of an early nutritional intervention. Nutritional parameters are often overlooked in oncology trials, leading to their underestimated value [24].

Staging the progression of the disease is also an unmet need in clinical practice. Several tools have been generated to facilitate the staging through clinical parameters and inflammatory markers. Argiles et al. proposed the Cachexia SCOre (CASCO), followed by a simplified version (miniCASCO) [35,36]. Other examples are the four-group model by Blum et al. [37] and the cachexia staging score (CSS) [38]. While these algorithms hold promise for clinical implementation, they come with certain limitations. These include: i) the inability to distinguish between pre-cachectic and cachectic patients [37]; ii) challenges in completing tests due to the extensive number of measurements required [35]; iii) validation based on a limited patient sample [36,38]. Consequently, a universally accepted, precise, and validated method for staging the progression of cachexia remains elusive.

Body composition and skeletal muscle loss in cachectic cancer patients have greater prognostic value compared to body weight or BMI, as the latter do not necessarily reflect a reduction in lean mass [4,9]. GLIM, ESPEN and ESMO CPG encourage the evaluation of body composition using either computed tomography (CT), dual X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA) [4,39]. CT imaging for body composition assessment is promising, but lengthy analysis, radiation exposure, machine accessibility, and high costs limit its application.

Overall, despite steps forward to improve the definition, diagnosis and staging of cancer cachexia in recent years, more efforts should be made to ensure the standardized and universal application of the recommended approaches. To enhance guidelines' application, malnutrition and cancer cachexia research questions should be addressed in prospective studies, so to increase the quality of evidence.

Recent advances

Current research focuses on innovative scores, digital tools and diagnostic and/or prognostic biomarkers to formulate an early diagnosis of cachexia in cancer patients.

Scores. Wang et al. established a novel cancer cachexia staging index (CCSI) that combines both objective (BMI-adjusted weight loss grade, weight loss, inflammatory markers and prealbumin levels) and subjective (appetite and physical status) measurements. The score was prospectively tested in more than 10,000 patients with gastrointestinal cancers. CCSI categorizes patients in no cachexia, mild or moderate, and severe cachexia subgroups. CCSI also discriminates patients based on their nutritional status, physical function, inflammation, body composition, symptom burden, and QoL. The score showed to predict survival in a multivariate analysis [40].

Digital tools. An online dynamic nomogram based on five predictive factors (age, two nutritional screening tests, QoL, cancer type) has been developed. The study included 4834 cancer patients, randomised to either the development or validation cohort. The nomogram demonstrated a high degree of specificity and sensitivity in predicting cachexia. This easy-to-use online system could be conveniently implemented in routine clinical practice and could offer a valid support to HCPs in evaluating cancer patients at the first visit [41].

Recent advances in artificial intelligence (AI) algorithms have allowed a rapid and automatic analysis of CT metrics (traditionally based on manual or semiautomated segmentation processes) [42]. An example of such progress is the fully automated image-based deep learning platform developed for the assessment of sarcopenia [43]. The authors generated this predictive algorithm based on data obtained from 899 individuals with head and neck squamous cell carcinoma, with available abdomen CT scans and clinical information. Remarkably, skeletal muscle index-based sarcopenia was associated with shorter survival and prolonged feeding tube duration [43]. Once validated, AI tools will hopefully allow the standardized implementation of an exhaustive risk assessment procedure in oncology clinical practice.

Diagnosing cachexia is challenging when patients provide inaccurate historical body weight information. To overcome this, machine-learning methods utilizing baseline clinical characteristics other than body weight are being explored. In a multicenter cohort study with more than 12,000 cancer patients, a 15-variable logistic regression model (including parameters such as cancer type and stage, gastrointestinal symptoms, and serum biochemistry evaluations) was developed. Even in the absence of data on weight loss, the model showed good performance in predicting cachexia in patients with different cancer types, previously diagnosed using Fearons' criteria [44].

Biomarkers. Numerous research groups have recently identified circulating factors that may play a pathogenic role in the disease. Among these, S100A8, S100A9 proteins and S100A8/A9 heterodimer were identified *in vitro* as muscle atrophy inducing factors. Their serum levels correlated with body weight loss and predicted the development of cachexia in pancreatic cancer patients [45]. Other molecules of interest include C-terminal agrin fragment (CAF) [46], ceramides [47] and microRNAs (miRNAs) [48]. Further studies are required to validate these preliminary results.

Management of patients with cancer cachexia

Current recommendations

ESMO and ASCO have provided guidance with the aim to ease cachexia symptoms and preserve sufficient body resources. The main recommendations focus on i) nutritional intervention; ii) physical activity; and iii) pharmacological treatment [4,17].

Interventions should address the eating-related psychosocial distress experienced by cachectic patients. The use of a multimodal approach that combines different strategies to personalize the treatment is endorsed to tackle this heterogeneous disorder [4], and its effectiveness is being explored in clinical trials [49–51]. The CPG specifies the necessity for oncology institutions to establish a specialized cancer cachexia team including dieticians, physiotherapists, palliative care specialists, and psychologists. Additionally, collaboration with other specialists, such as gastroenterologists, head, neck and pain specialists, is emphasized [4].

Nutritional interventions

Over the last decades, several randomized clinical trials have been conducted to evaluate the benefits of nutrition interventions in adults

with cancer. As recently reviewed [52,53], most studies evaluated the effects of dietary supplements, enteral and parenteral nutrition in patients with either gastrointestinal or head and neck cancer. The studies were overall heterogeneous in the type and timing of intervention, observation periods, use of comparator groups, parameters investigated, population characteristics and sample size. Only a small proportion of trials were deemed to be of a medium-to-high quality, but the results were inconsistent, showing varying rates and extent of success. Of note, the start of nutritional intervention also varied across studies, likely being too late to guarantee maximal efficacy.

Despite the lack of strong, high-quality evidence, both ESMO CPG and ASCO agree that all patients with advanced cancer and insufficient food intake should systematically see a registered dietitian. Dietary counselling should advise on appropriate food and improper supplements and fad diets, which could further aggravate their clinical condition [4,17]. The long-chain omega-3 fatty acids, eventually offered as protein-enriched formulations (N3P-ONSs), may be used in patients receiving chemotherapy, radiotherapy, or chemoradiotherapy to increase weight, lean mass and improve QoL [4,54]. Indeed, most studies have indicated that dietary counselling and N3P-ONSs may help improve QoL and prevent body weight loss in patients undergoing anticancer treatment, without effect on overall survival [4,54–59].

In patients unable to eat (due to nausea, dysphagia, or other tumour-related reason), nutritional support should be offered through either enteral tube feeding (ENT) or parenteral feeding (PN). ESMO CPG recommend using ENT in patients retaining lower gastrointestinal function, and PN if ENT is not tolerated or does not guarantee a sufficient nutritional supply [4]. ASCO clarifies that these “invasive” nutritional interventions should be temporary and limited to reasonably fit patients [17]. Those techniques should be interrupted when patients approach the end of life, as the associated risks and/or burden largely overcome the benefits [4,17]. Due to the variable methodology used and the scarce number of high-quality studies, further research is needed to corroborate and/or update these recommendations.

Physical activity

Despite still insufficient evidence that demonstrates the safety and effectiveness of exercise in the treatment of cancer cachexia [60], the effects of physical activity on muscle metabolism and systemic inflammation may help maintaining or improving muscle mass and strength, reduce fatigue and enhance physical ability in cachectic patients. Besides, exercise exerts beneficial effects on mental health and has been found to reduce side effects from anti-cancer treatments [61,62]. A combined exercise and nutritional intervention were recently found to increase the likelihood of achieving the disappearance of invasive tumour in women with breast cancer after completing adjuvant chemotherapy [63]. More specifically, dysphagic patients should be encouraged to perform swallowing exercises, as they have been associated with increased oral intake, solid food intake, lower dysphagia severity and shorter feeding tube duration in a cohort of 595 patients with oropharyngeal cancer [64].

Current ESMO recommendations favour the inclusion of moderate physical exercise within the multimodal program for cancer cachexia, suggesting resistance training two to three times per week in addition to moderate aerobic (endurance) activity. Qualified professional trainers, including physiotherapists, should collaborate in designing a training program based on the individual’s physical abilities. The program should be promptly adjusted or interrupted if clinical contraindications arise [4].

Pharmacological treatment

Current ESMO CPG suggest the use of olanzapine to increase appetite and contrast nausea in patients with advanced cancer [4]. In September 2023, ASCO released a rapid recommendation update endorsing the use of low-dose olanzapine to improve weight gain and appetite in advanced cancer patients [65], based on positive results from a recent trial in chemotherapy-treated patients [66]. Results from another RCT show that olanzapine significantly reduced nausea and improved appetite also in cancer patients not receiving chemotherapy [67]. Interestingly, the combination of olanzapine with megestrol acetate increased appetite and body weight compared with megestrol acetate alone in patients with advanced lung or gastrointestinal cancer [68].

To date, no other pharmacological agents has been formally approved for the treatment of cancer cachexia by either the European Medicine Agency or the Food and Drug Administration. Anamorelin, a ghrelin receptor agonist, is authorized in Japan to treat cachectic patients affected by non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer [69], based on its efficacy in increasing appetite and lean body mass. Further trials elucidating its anti-cachectic effects are ongoing [70].

Because of the multidimensional nature of cancer cachexia, several drugs with different mechanisms of action have been tested over the years: i) inhibitors of inflammatory system; ii) central nervous system/neuroendocrine modulators; iii) anabolic agents/muscle atrophy antagonists. Systemic corticosteroids, inhibitors of pro-inflammatory cytokines and non-steroidal anti-inflammatory drugs (NSAIDs) are the main classes of anti-inflammatory agents evaluated for their potential anti-cachectic effect.

The use of systemic corticosteroids in cancer cachexia is recommended by ESMO and ASCO, providing that the treatment does not last more than few weeks, so to avoid the risk of complications [4,17].

Inhibitors of cytokines, such as anti-TNFα inhibitors and thalidomide, as well as NSAIDs are not recommended due to either conflicting results or poor study methodologies [4,17]. Nevertheless, the use of NSAIDs as part of a multimodal intervention showed positive results in cancer patients and is currently being investigated [4,49].

Progestins, ghrelin receptor agonists, cannabinoids, antipsychotic drugs and prokinetics are the main classes of neuroendocrine modulators explored for the treatment of cancer cachexia.

Medroxyprogesterone acetate and megestrol acetate are the most studied progestins in the context of cancer cachexia and they both exert similar, beneficial effects, increasing appetite and weight gain [4,17]. ASCO and ESMO generally recommend the use of progestins but warn about the potential complications [4,17].

The effects of the tetracyclic antidepressant mirtazapine were assessed in patients with advanced non-small cell lung cancer in a recent trial. Although the appetite score was similar between mirtazapine and placebo-treated patients, mirtazapine treatment increased energy intake through enhanced fat assumption, and decreased the proportion of patients with sarcopenia. Based on these data, mirtazapine could assist patients with advanced non-small cell lung cancer in meeting their energy requirements [71].

In light of their anabolic action, androgens have been explored for their potential to counteract muscle wasting and increase physical function in cancer cachexia. In particular, selective androgen-receptor modulators (SARMs), are a class of compounds that have properties similar to anabolic steroids, but with reduced androgenic effects. SARMs selectively bind androgen receptors in certain tissues, thus stimulating muscle and bone growth [72]. The SARM GTx-024 (enobosarm) has been evaluated in phase II/III trials with mixed results. After a promising phase II study [73,74], a phase III study in non-small-cell lung cancer patients showed an increase in lean body mass but with no associated improved in functional responses, and the compound is currently not approved from the FDA [72].

Gaps and challenges

The main barriers preventing the correct use of a single or multimodal approach in the clinical practice are an inadequate awareness about the beneficial effects associated with the interventions, the lack of

formal protocols and of a multidisciplinary team.

To date, the multimodal approach for the management of cancer cachexia is rarely considered for patients in routine oncology practice. Nutritional, physical and pharmacological interventions do not appear to be used as recommended, even when not as part of a multimodal strategy. Data collected through a survey across German hospitals revealed that nutrition therapy in cancer patients is under-used and nutritional goals (i.e., energy and protein intake) were not set in approximately half of the cases [18]. More dramatically, only 8.4 % Italian metastatic patients received nutritional intervention, consisting of PN in the majority of cases. On average, nutritional intervention was started after 6.6 months from the diagnosis of metastasis and 3.5 months before death. The low percentage of patients being offered nutritional care and the delay of such intervention underline the lack of awareness about this approach in oncology practice [13].

Physical activity intervention also appears to be overlooked: only 19.6 % of German hospitals could offer training sessions within the same facility [18]. On the other hand, too strenuous exercise may require a greater energy demand than the patient's own energy capacity, with the risk of exacerbating rather than improving the patient's cachectic status. This is another reason why patients should be offered individual training and be constantly monitored by dedicated exercise professionals [75].

None of the pharmacological treatments discussed above are approved for the treatment of cancer cachexia. Additional trials with cachexia-specific endpoints are required to strengthen CPG recommendations and obtain regulatory approval of the investigated molecules (alone or in combination).

Recent advances

In recent years, significant progress has been made in understanding the pathophysiology of cancer cachexia. The discovery of novel pathways implicated in the progression of this disease has prompted the development of innovative pharmaceutical agents, including modulators of the transforming growth factor-beta (TGF-β) superfamily and melanocortin-4 receptor (MC4R) antagonists.

Myostatin and growth differentiation factor (GDF)15 are two proteins belonging to the TGF-β superfamily that play a role in muscle growth inhibition. GDF15 exerts anorexigenic effects by signalling through its receptor expressed in the brainstem, which contains appetite regulatory centres [76]. While trials investigating the anti-myostatin antibody LY2495655 have shown weak efficacy on muscle mass and function [77], more expectations are being set on anti-GDF15 compounds. Among those, PF-06946860 (also known as ponsegromab), a monoclonal antibody against GDF15, has been investigated in phase I/IB trials (results not yet published) and is currently entering a large phase II trial involving patients with cachexia, cancer (non-small cell lung, pancreatic or colorectal cancer) and elevated GDF15 serum levels [70,77].

NGM-120, AV-380, and CTL-002 are other anti-GDF15 compounds in early stages of clinical development [78].

Upon activation, MC4R-expressing neurons promote anorexia, whereas inhibition of MC4R signalling is known to increase appetite and food intake [79]. Some MC4R antagonists have been shown to exert anti-cachectic effects in animal models and are currently being investigated [70].

Other molecules such as ruxolitinib, a Janus kinase 1/2 inhibitor, and the NSAID ketorolac are also being tested in phase I trials, on the rationale of their anti-inflammatory effect [78]. Macimorelin, a newly developed orally active ghrelin mimetic, has been tested in a pilot phase II trial with no significant results in body weight improvement [80]. Finally, it is worth mentioning that innovative therapeutic avenues are being explored as alternative approaches to pharmacological agents, such as interventions to manipulate gut microbiota in cancer cachexia patients [81].

Practical suggestions

Strategies to implement cancer cachexia management should point to early identification and referral of the patient at risk to the nutrition specialist for a prompt intervention. Real-world practice imposes a series of limitations (costs, availability of screening tools and nutrition specialists, lack of programs integrating nutrition and physical activity, lack of appropriate pharmacological intervention). Specifically, until a pharmacological option becomes available to target cancer cachexia from a mechanistic perspective, a collaborative approach by a multidisciplinary team is essential to improve the patient's outcome and QoL.

In clinical practice, HCP intervention is mandatory, as emphasized by guidelines [4,65,82]. HCPs can manage cancer cachexia by proactive intervention at first consultation, providing nutritional counselling, assessing and treating symptoms that affect caloric intake, and suggesting a pharmacological approach. However, a patient/caregiver empowerment strategy, is necessary. Interventions must be tailored according to the different phase of treatment (patients in active oncological treatment or in follow-up) and the setting of care (hospital versus home).

Improve patient identification

To implement malnutrition screening, risk assessment and diagnosis of cachexia in cancer patients, the following actions should be prioritized (Table 1):

1) Increase nutrition education. Expanded programs should be offered to medical students, as exemplified by the ESPEN's nutrition education in medical schools' project [83]. HCPs should regularly attend nutrition training, understand the impact of nutritional status on the patient's prognosis, be up-to-date on the most recent recommended approaches [84] and foster a close collaboration with nutrition experts.
2) Establish multidisciplinary teams. Clinical nutrition specialists should be part of all oncology settings, or at least within the oncology teams specialized in cancers associated with high nutritional risk (e.g., gastrointestinal, lung, pancreas, head and neck cancers) [16,24]. If clinical nutrition physicians are absent, the presence of at least one professional figure fully dedicated to offering nutritional support (i.e., dietitians or nurses who received specialised training) should be guaranteed.
3) Immediate referral to nutrition specialists for counselling, regardless of the malnutrition risk assessment. As stated by the Italian

Table 1
Gaps and challenges in the risk assessment and diagnosis of cancer cachexia in the oncological clinical practice, and practical suggestions to optimize guideline implementation.

Gaps and challenges	Practical suggestion
Lack of awareness of benefits of early screening/nutritional risk assessment	Increase nutrition education and training for medical students and HCPs
Lack of multidisciplinary team	Always include clinical nutrition specialists in oncology teams managing cancers types coupled with the highest nutritional risk Immediate referral of patients with cancers types coupled with the highest nutritional risk to clinical nutrition experts, even in absence of risk evaluation
Lack of univocal identification of malnutrition in cancer patients by GLIM criteria	Assess as many GLIM criteria as feasible Monitor weight loss and BMI continuously starting from the first oncology visit
Lack of routine assessment of body composition due to limitations of imaging techniques	Evaluate CT scans already performed for diagnostic purposes

Intersociety Working Group practical recommendations [16], certain subsets of patients (i.e., undergoing specific treatments such as high-dose chemotherapy, curative chemoradiotherapy on the head and neck area, major abdominal surgery, or having types of cancers expected to affect nutritional status) should be directly referred to clinical nutrition specialists, as cachexia is not easily assessed. This would enable a thorough counseling, support, and rigorous monitoring program, ensuring comprehensive care.

4) Include as many GLIM criteria and clinical parameters for the diagnosis of malnutrition. In the authors' opinion, this represents the most pragmatic approach to ensure a precise diagnosis within the clinical practice.
5) Monitor weight loss and BMI, which should be tracked from the first oncology visit, throughout the anti-cancer treatment and during follow-up. Although they do not perfectly mirror metabolic changes or muscle loss, they are easy to measure and may flag a nutritional impairment, prompting more in-depth investigations. Also, there are evidences that BMI may positively impact patients' outcomes [85]. Defining a "critical" weight loss (i.e., $\geq$ 5 % in 1 month or $\geq$ 10 % in 6 months [86] may be useful to prompt proactive nutritional measures.
6) Obtain additional CT scans to determine body composition while assessing tumour growth. As CT scans are performed routinely for oncological purposes, inclusion of CT imaging at the third lumbar vertebra or at the third cervical vertebra as a surrogate represents a validated method to assess body composition and provides precise measurements of skeletal muscle and adipose mass [87,88].

Management of patients in active oncology treatment

While on treatment, the patient is either hospitalized or attends frequent visits to the hospital, being closely monitored by the oncologists' team, which is responsible for detecting early signs of malnutrition and escalating to referral and intervention. The patient should be assessed with the available tools, prioritizing body composition evaluation through additional images, as well as application of feasible GLIM criteria for early referral. At this stage, early nutritional support is essential to ensure the treatments' maximal effect. Physical activity programs may be put on hold if necessary (Fig. 1).

The oncologist should also consider the expected efficacy of anti-cancer treatment and overall prognosis, balancing the following factors:

- anticipated risk of toxicities that impact nutritional status (depending on the primary disease site, presence of baseline dysphagia, emetogenic chemotherapy foreseen, risk of dysgeusia, etc)
- anticipated timing and extent of disease response
- tight balance, time and logistics constraints
- impact of age and comorbidities
- presence of caregiver.

A broader, holistic view on the multifactorial aetiology of malnutrition should be in place especially for head and neck and upper gastrointestinal cancers, including: trismus, chewing and dental problems; swallowing impairment; impact of smell and taste alteration. Behavioral and cognitive interventions focused on nutrition should also be implemented, as they could improve the nutritional status of patients receiving anti-cancer treatment [89].

Patients in follow-up

Patients in follow-up after an active anti-cancer treatment are seen less frequently and are less strictly monitored. As a result, they may feel isolated and more vulnerable.

In this setting, empowering patients/caregivers is essential to ensure adequate nutritional support (Fig. 1). Educating patients about cancer cachexia, its symptoms, and the significance of early detection and

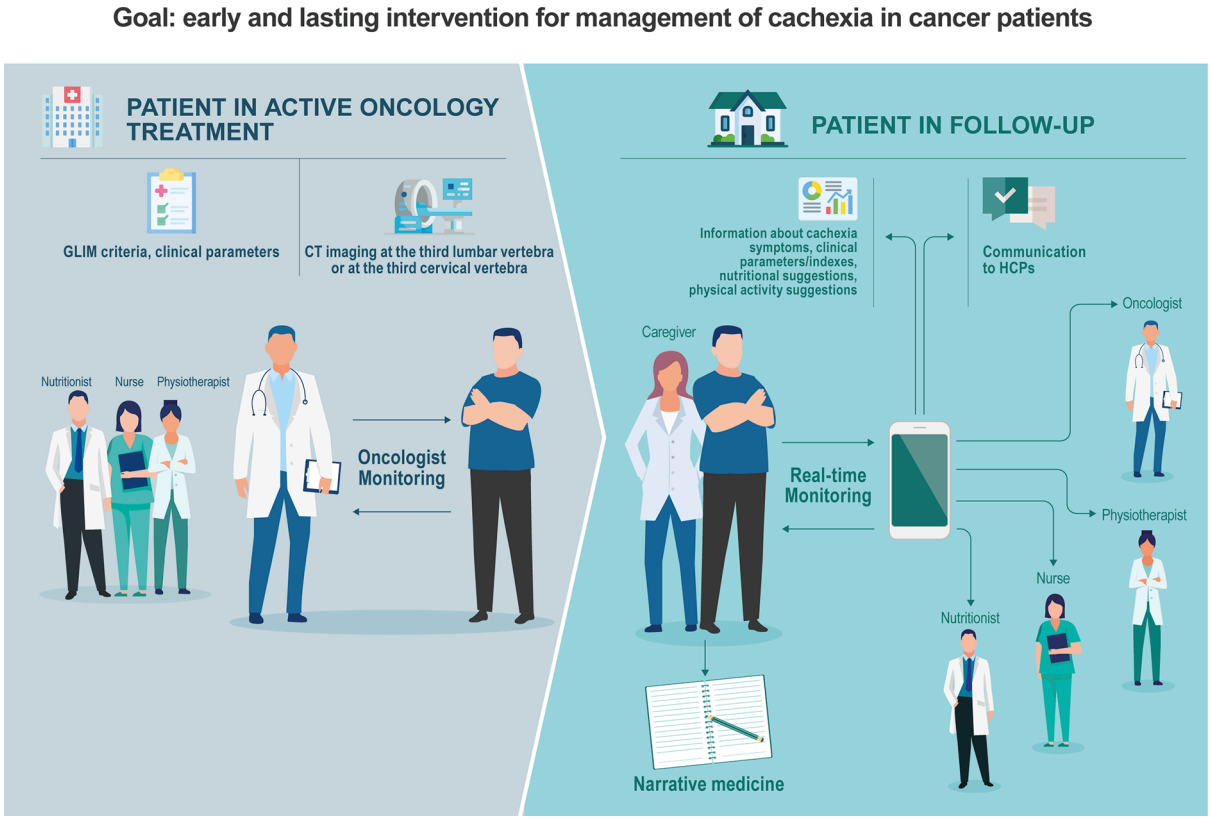

Fig. 1. Holistic approach to cancer cachexia. Increase awareness, multidisciplinarity, early identification, risk assessment and diagnosis, and patient empowerment are necessary to maximize the assistance to both patients in acute phase of treatment and in follow-up.

management is crucial. Encouraging patients to actively engage in their care by setting goals, monitoring progress, and communicating with their healthcare team is also important. In this light, the "Cancer patients' bill of rights to appropriate and prompt nutritional support" and the guidelines on nutritional pathways in cancer elaborated by Italian Ministry of Health are examples of the need to raise the attention of society and institutions about nutritional issues in oncology [90,91].

The value of telemedicine and web-based applications is particularly elevated for patients in follow-up. In-between the visits, the patient/caregiver must be able to recognize and communicate early signs of nutritional decay, changes in physical performance or any other symptoms that may cause concern. The continuous monitoring offered by mobile-based applications would further empower the patient/caregiver. Telemedicine and web-based applications are valuable tools that save resources and accelerate the decision-taking process. Their use should be maximised to improve the interventions that cancer patients require. Telemedicine has been increasingly applied for medical support to oncology patients. By providing an effective method for online patient-clinician communication, telemedicine has also been exploited for nutritional purposes. Although there are examples of successful implementation in oncology nutritional care, to date, telemedicine is not as broadly used as it should be [92,93]. Telematic solutions must be complementary, and not alternatives, to face-to-face interactions between patients and clinicians.

Web-based applications are effective and accessible tools that can support the care of cancer patients [94]. Indeed, they help monitoring and sharing the patient's data (weight, BMI, quality and quantity of consumed food, physical activity, medications, gastrointestinal symptoms, etc.) with the clinician in real time. In turn, the clinician can easily modulate the intervention. The patient may feel encouraged to adhere to the prescribed interventions by seeing data in real time. Benefits in terms of body weight and skeletal muscle gain have already been shown in patients using mobile phone apps to record their daily diet [95]. The use of electronic narrative diaries allows the patient to document valuable information that may be missed when using mobile phone apps, which often have limited features.

The personalized listening can be strengthened by the introduction of narrative medicine [96], which enriches the point of view expressed in a standardized manner, favoring a *person-centered* approach rather than a *disease-centered* one. The development of digital technologies represents an opportunity for the diffusion of narrative medicine in clinical practice, facilitating sharing subjective needs and demands. The digital platform DNMLAB developed by an innovative non-profit start-up (DNM srl, Rome, Italy) is designed to help implement narrative medicine in clinical practice. This method can provide support to patients in the production of narratives and assist HCPs in interpretating them [96].

This way of capturing patients' needs both in the active therapeutic phase and during follow-up, can help to better follow the pathway between patient and clinician.

Conclusions

An application of standardized treatments for cancer cachexia management in clinical practice remains elusive. Apart from the paucity of resources and economic investments dedicated to oncology nutrition services, insufficient awareness, scarce clinical trials with adequate endpoints addressing the effects of nutrition, physical activity and/or pharmacological intervention, and the absence of a coordinated multidisciplinary collaboration are main obstacles to properly implement guidelines.

Early referral should be pursued for certain categories of patients, even if appropriate screening has not been conducted. Practical tools in follow-up should increase patient/or caregiver empowerment. These preliminary steps prepare the patient for any future pharmacological treatment and maximise its therapeutic effects. Properly tailored measures, aligned with the patient's treatment phase and care, can prevent refractory cachexia and significantly improve outcomes, well-being, and survival.

Author contrirbution

All author conceived the work, performed literature search, analysed the material, drafted and critically revised the manuscript. All author approved the final version to be submitted.

CRediT authorship contribution statement

Carlotta Bianchini: Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Methodology. **Pierluigi Bonomo:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Methodology. **Paolo Bossi:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Methodology. **Riccardo Caccialanza:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Methodology. **Alessandra Fabi:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Validation, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Ni J, Zhang L. Cancer cachexia: definition, staging, and emerging treatments. Cancer Manag Res 2020;12:5597–605.
[2] Law ML. Cancer cachexia: pathophysiology and association with cancer-related pain. Front Pain Res (Lausanne) 2022;3:971295.
[3] Bossi P, Delrio P, Mascheroni A, Zanetti M. The Spectrum of malnutrition/cachexia/sarcopenia in oncology according to different cancer types and settings: a narrative review. Nutrients 2021;13(6).
[4] Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO clinical practice guidelines(☆). ESMO Open 2021;6(3):100092.
[5] Kwon M, Kim RB, Roh JL, Lee SW, Kim SB, Choi SH, et al. Prevalence and clinical significance of cancer cachexia based on time from treatment in advanced-stage head and neck squamous cell carcinoma. Head Neck 2017;39(4):716–23.
[6] Setiawan T, Sari IN, Wijaya YT, Julianto NM, Muhammad JA, Lee H, et al. Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol 2023;16(1):54.
[7] Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia–pathophysiology and management. J Gastroenterol 2013;48(5):574–94.
[8] Peterson SJ, Mozer M. Differentiating sarcopenia and cachexia among patients with cancer. Nutr Clin Pract 2017;32(1):30–9.
[9] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489–95.
[10] von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle 2010;1(1):1–5.
[11] Bossi P, De Luca R, Ciani O, D'Angelo E, Caccialanza R. Malnutrition management in oncology: an expert view on controversial issues and future perspectives. Front Oncol 2022;12:910770.
[12] Caccialanza R, Cereda E, Pinto C, Cotogni P, Farina G, Gavazzi C, et al. Awareness and consideration of malnutrition among oncologists: insights from an exploratory survey. Nutrition 2016;32(9):1028–32.
[13] Caccialanza R, Goldwasser F, Marschal O, Ottery F, Schiefke I, Tilleul P, et al. Unmet needs in clinical nutrition in oncology: a multinational analysis of real-world evidence. Ther Adv Med Oncol 2020;12. 1758835919899852.
[14] Trujillo EB, Claghorn K, Dixon SW, Hill EB, Braun A, Lipinski E, et al. Inadequate nutrition coverage in outpatient cancer centers: results of a National Survey. J Oncol 2019;2019:7462940.

[15] Caccialanza R, Lobascio F, Cereda E, Aprile G, Farina G, Traclo F, et al. Cancer-related malnutrition management: a survey among italian oncology units and patients' associations. Curr Probl Cancer 2020;44(5):100554.
[16] Caccialanza R, Cotogni P, Cereda E, Bossi P, Aprile G, Delrio P, et al. Nutritional support in cancer patients: update of the italian intersociety working group practical recommendations. J Cancer 2022;13(9):2705–16.
[17] Roeland EJ, Bohlke K, Baracos VE, Bruera E, Del Fabbro E, Dixon S, et al. Management of Cancer Cachexia: ASCO guideline. J Clin Oncol 2020;38(21):2438–53.
[18] Hardt LM, Herrmann HJ, Reljic D, Jaensch P, Zerth J, Neurath MF, et al. Are guideline recommendations on supportive nutrition and exercise therapy for cancer patients implemented in clinical routine? a National Survey with real-life data. Nutrients 2023;15(14).
[19] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36(1):49–64.
[20] Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the international consensus guideline committee. Clin Nutr 2010;29(2):151–3.
[21] Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr 2019;38(1):1–9.
[22] McMillan DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat Rev 2013;39(5):534–40.
[23] Laird BJ, Kaasa S, McMillan DC, Fallon MT, Hjermstad MJ, Fayers P, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. Clin Cancer Res 2013;19(19):5456–64.
[24] Arends J, Muscaritoli M, Anker S, Audisio R, Barazzoni R, Bosnjak S, et al. Overcoming barriers to timely recognition and treatment of cancer cachexia: sharing Progress in cancer care task force position paper and call to action. Crit Rev Oncol Hematol 2023;185:103965.
[25] Martin A, Gallot YS, Freyssenet D. Molecular mechanisms of cancer cachexia-related loss of skeletal muscle mass: data analysis from preclinical and clinical studies. J Cachexia Sarcopenia Muscle 2023;14(3):1150–67.
[26] Talbert EE, Guttridge DC. Emerging signaling mediators in the anorexia-cachexia syndrome of cancer. Trends Cancer 2022;8(5):397–403.
[27] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[28] Muscaritoli M, Modena A, Valerio M, Marchetti P, Magarotto R, Quadrini S, et al. The impact of NUTRItional status at first medical oncology visit on clinical outcomes: the NUTRIONCO study. Cancers (Basel) 2023;15(12).
[29] Muscaritoli M, Lucia S, Farcomeni A, Lorusso V, Saracino V, Barone C, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. Oncotarget 2017;8(45):79884–96.
[30] van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. Nutrition screening tools: does one size fit all? a systematic review of screening tools for the hospital setting. Clin Nutr 2014;33(1):39–58.
[31] Bian W, Li Y, Wang Y, Chang L, Deng L, Li Y, et al. Prevalence of malnutrition based on global leadership initiative in malnutrition criteria for completeness of diagnosis and future risk of malnutrition based on current malnutrition diagnosis: systematic review and meta-analysis. Front Nutr 2023;10:1174945.
[32] Vaughan VC, Harrison M, Dowd A, Eastman P, Martin P. Evaluation of a multidisciplinary cachexia and nutrition support service- the patient and carers perspective. J Patient Exp 2021;8. 2374373520981476.
[33] Mikkelsen S, Kohler M, Ostergaard T, Rasmussen HH. Different GLIM criteria combinations change prevalence of malnutrition in patients with intestinal insufficiency or intestinal failure. Clin Nutr ESPEN 2021;44:449–57.
[34] Kiss N, Steer B, de van der Schueren M, Loeliger J, Alizadehsani R, Edbrooke L, et al. Comparison of the prevalence of 21 GLIM phenotypic and etiologic criteria combinations and association with 30-day outcomes in people with cancer: a retrospective observational study. Clin Nutr 2022;41(5):1102–11.
[35] Argiles JM, Lopez-Soriano FJ, Toledo M, Betancourt A, Serpe R, Busquets S. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. J Cachexia Sarcopenia Muscle 2011;2(2):87–93.
[36] Argiles JM, Betancourt A, Guardia-Olmos J, Pero-Cebollero M, Lopez-Soriano FJ, Madeddu C, et al. Validation of the CAchexia SCOre (CASCO). staging cancer patients: the use of miniCASCO as a simplified tool. Front Physiol 2017;8:92.
[37] Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, et al. Validation of the consensus-definition for cancer cachexia and evaluation of a classification model–a study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol 2014;25(8):1635–42.
[38] Zhou T, Wang B, Liu H, Yang K, Thapa S, Zhang H, et al. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. J Cachexia Sarcopenia Muscle 2018;9(2):306–14.
[39] McGovern J, Dolan RD, Skipworth RJ, Laird BJ, McMillan DC. Cancer cachexia: a nutritional or a systemic inflammatory syndrome? Br J Cancer 2022;127(3):379–82.
[40] Huo Z, Chong F, Yin L, Li N, Zhang M, Guo J, et al. Development and validation of an online dynamic nomogram system for predicting cancer cachexia among inpatients: a real-world cohort study in China. Support Care Cancer 2022;31(1):72.
[41] Wang J, Tan S, Xu J, Li S, Yan M, Yang F, et al. Development and application of the cancer cachexia staging index for the diagnosis and staging of cancer cachexia. Nutrition 2023;114:112114.
[42] Bates DDB, Pickhardt PJ. CT-derived body composition assessment as a prognostic tool in oncologic patients: from opportunistic research to artificial intelligence-based clinical implementation. AJR Am J Roentgenol 2022;219(4):671–80.
[43] Ye Z, Saraf A, Ravipati Y, Hoebers F, Catalano PJ, Zha Y, et al. Development and validation of an automated image-based deep learning platform for sarcopenia assessment in head and neck cancer. JAMA Netw Open 2023;6(8):e2328280.
[44] Yin L, Cui J, Lin X, Li N, Fan Y, Zhang L, et al. Identifying cancer cachexia in patients without weight loss information: machine learning approaches to address a real-world challenge. Am J Clin Nutr 2022;116(5):1229–39.
[45] Liao WC, Chen CT, Tsai YS, Wang XY, Chang YT, Wu MS, et al. S100A8, S100A9 and S100A8/A9 heterodimer as novel cachexigenic factors for pancreatic cancer-induced cachexia. BMC Cancer 2023;23(1):513.
[46] Monti E, Sarto F, Sartori R, Zanchettin G, Lofler S, Kern H, et al. C-terminal agrin fragment as a biomarker of muscle wasting and weakness: a narrative review. J Cachexia Sarcopenia Muscle 2023;14(2):730–44.
[47] Chakedis JM, Dillhoff ME, Schmidt CR, Rajasekera PV, Evans DC, Williams TM, et al. Identification of circulating plasma ceramides as a potential sexually dimorphic biomarker of pancreatic cancer-induced cachexia. JCSM Rapid Commun 2022;5(2):254–65.
[48] Narasimhan A, Ghosh S, Stretch C, Greiner R, Bathe OF, Baracos V, et al. Small RNAome profiling from human skeletal muscle: novel miRNAs and their targets associated with cancer cachexia. J Cachexia Sarcopenia Muscle 2017;8(3):405–16.
[49] Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8(5):778–88.
[50] Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle 2019;10(1):73–83.
[51] McKeaveney C, Maxwell P, Noble H, Reid J. A critical review of multimodal interventions for cachexia. Adv Nutr 2021;12(2):523–32.
[52] Parsons HM, Forte ML, Abdi HI, Brandt S, Claussen AM, Wilt T, et al. Nutrition as prevention for improved cancer health outcomes: a systematic literature review. JNCI Cancer Spectr 2023;7(3).
[53] Hiatt RA, Clayton MF, Collins KK, Gold HT, Laiyemo AO, Truesdale KP, et al. The pathways to prevention program: nutrition as prevention for improved cancer outcomes. J Natl Cancer Inst 2023;115(8):886–95.
[54] Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. Radiother Oncol 2018;126(1):81–8.
[55] Langius JA, Zandbergen MC, Eerenstein SE, van Tulder MW, Leemans CR, Kramer MH, et al. Effect of nutritional interventions on nutritional status, quality of life and mortality in patients with head and neck cancer receiving (chemo) radiotherapy: a systematic review. Clin Nutr 2013;32(5):671–8.
[56] Garg S, Yoo J, Winquist E. Nutritional support for head and neck cancer patients receiving radiotherapy: a systematic review. Support Care Cancer 2010;18(6):667–77.
[57] de Aguiar Pastore Silva J, Emilia de Souza Fabre M, Waitzberg DL. Omega-3 supplements for patients in chemotherapy and/or radiotherapy: A systematic review. Clin Nutr. 2015;34(3):359–366.
[58] van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA, Brouwer IA, van Leeuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. Am J Clin Nutr. 2011;94(5):1248–1265.
[59] Blackwood HA, Hall CC, Balstad TR, Solheim TS, Fallon M, Haraldsdottir E, et al. A systematic review examining nutrition support interventions in patients with incurable cancer. Support Care Cancer 2020;28(4):1877–89.
[60] Grande AJ, Silva V, Sawaris Neto L, Teixeira Basmage JP, Peccin MS, Maddocks M. Exercise for cancer cachexia in adults. Cochrane Database Syst Rev 2021;3(3). CD010804.
[61] Carayol M, Ninot G, Senesse P, Bleuse JP, Gourgou S, Sancho-Garnier H, et al. Short- and long-term impact of adapted physical activity and diet counseling during adjuvant breast cancer therapy: the "APAD1" randomized controlled trial. BMC Cancer 2019;19(1):737.
[62] Johnsson A, Demmelmaier I, Sjovall K, Wagner P, Olsson H, Tornberg AB. A single exercise session improves side-effects of chemotherapy in women with breast cancer: an observational study. BMC Cancer 2019;19(1):1073.
[63] Sanft T, Harrigan M, McGowan C, Cartmel B, Zupa M, Li FY, et al. Randomized trial of exercise and nutrition on chemotherapy completion and pathologic complete response in women with breast cancer: the lifestyle, exercise, and nutrition early after diagnosis study. J Clin Oncol 2023. JCO2300871.
[64] Barbon CEA, Peterson CB, Moreno AC, Lai SY, Reddy JP, Sahli A, et al. Adhering to eat and exercise status during radiotherapy for oropharyngeal cancer for prevention and mitigation of radiotherapy-associated dysphagia. JAMA Otolaryngol Head Neck Surg 2022;148(10):956–64.
[65] Roeland EJ, Bohlke K, Baracos VE, Smith TJ, Loprinzi CL, Expert CC, et al. J Clin Oncol 2023;41(25):4178–9.
[66] Sandhya L, Devi Sreenivasan N, Goenka L, Dubashi B, Kayal S, Solaiappan M, et al. Randomized double-blind placebo-controlled study of olanzapine for chemotherapy-related anorexia in patients with locally advanced or metastatic gastric, hepatopancreaticobiliary, and lung cancer. J Clin Oncol 2023;41(14):2617–27.

[67] Navari RM, Pywell CM, Le-Rademacher JG, White P, Dodge AB, Albany C, et al. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. JAMA Oncol 2020;6(6):895–9.
[68] Navari RM, Brenner MC. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Support Care Cancer 2010;18(8):951–6.
[69] Wakabayashi H, Arai H, Inui A. The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. J Cachexia Sarcopenia Muscle 2021;12(1):14–6.
[70] Kadakia KC, Hamilton-Reeves JM, Baracos VE. Current therapeutic targets in cancer cachexia: a pathophysiologic approach. Am Soc Clin Oncol Educ Book 2023;43:e389942.
[71] Arrieta O, Cardenas-Fernandez D, Rodriguez-Mayoral O, Gutierrez-Torres S, Castanares D, Flores-Estrada D, et al. Mirtazapine as appetite stimulant in patients with non-small cell lung cancer and anorexia: a randomized clinical trial. JAMA Oncol 2024.
[72] Christiansen AR, Lipshultz LI, Hotaling JM, Pastuszak AW. Selective androgen receptor modulators: the future of androgen therapy? Transl Androl Urol 2020;9(Suppl 2):S135–48.
[73] Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle 2011;2(3):153–61.
[74] Dobs AS, Boccia RV, Croot CC, Gabrail NY, Dalton JT, Hancock ML, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol 2013;14(4):335–45.
[75] Allan J, Buss LA, Draper N, Currie MJ. Exercise in people with cancer: a spotlight on energy regulation and cachexia. Front Physiol 2022;13:836804.
[76] Emmerson PJ, Wang F, Du Y, Liu Q, Pickard RT, Gonciarz MD, et al. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. Nat Med 2017;23(10):1215–9.
[77] da Fonseca GWP, Sato R, de Nazare Nunes MJ, Alves S, von Haehling. Current advancements in pharmacotherapy for cancer cachexia. Expert Opin Pharmacother 2023;24(5):629–39.
[78] Nishie K, Nishie T, Sato S, Hanaoka M. Update on the treatment of cancer cachexia. Drug Discov Today 2023;28(9):103689.
[79] Tao YX. The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. Endocr Rev 2010;31(4):506–43.
[80] Herodes M, Anderson LJ, Shober S, Schur EA, Graf SA, Ammer N, et al. Pilot clinical trial of macimorelin to assess safety and efficacy in patients with cancer cachexia. J Cachexia Sarcopenia Muscle 2023;14(2):835–46.
[81] Panebianco C, Villani A, Potenza A, Favaro E, Finocchiaro C, Perri F, et al. Targeting gut microbiota in cancer cachexia: towards new treatment options. Int J Mol Sci 2023;24(3).
[82] Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. Clin Nutr 2021;40(5):2898–913.
[83] Cuerda C, Muscaritoli M, Krznaric Z, Pirlich M, Van Gossum A, Schneider S, et al. Nutrition education in medical schools (NEMS) project: joining ESPEN and university point of view. Clin Nutr 2021;40(5):2754–61.
[84] Murphy JL, Munir F, Davey F, Miller L, Cutress R, White R, et al. The provision of nutritional advice and care for cancer patients: a UK national survey of healthcare professionals. Support Care Cancer 2021;29(5):2435–42.
[85] Pfeiler G, Hlauschek D, Mayer EL, Deutschmann C, Kacerovsky-Strobl S, Martin M, et al. Impact of BMI in patients with early hormone receptor-positive breast cancer receiving endocrine therapy with or without palbociclib in the PALLAS trial. J Clin Oncol 2023. JCO2300126.
[86] Jager-Wittenaar H, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer–prevalence and risk factors at diagnosis: an explorative study. Support Care Cancer 2007;15(9):1045–50.
[87] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33(5):997–1006.
[88] Swartz JE, Pothen AJ, Wegner I, Smid EJ, Swart KM, de Bree R, et al. Feasibility of using head and neck CT imaging to assess skeletal muscle mass in head and neck cancer patients. Oral Oncol 2016;62:28–33.
[89] Britton B, Baker AL, Wolfenden L, Wratten C, Bauer J, Beck AK, et al. Five-year mortality outcomes for eating as treatment (EAT), a health behaviour change intervention to improve nutrition in patients with head and neck cancer: a stepped-wedge, randomised controlled trial. Int J Radiat Oncol Biol Phys 2024.
[90] Caccialanza R, De Lorenzo F, Gianotti L, Zagonel V, Gavazzi C, Farina G, et al. Nutritional support for cancer patients: still a neglected right? Support Care Cancer 2017;25(10):3001–4.
[91] Salute Md. Accordo Stato-Regioni su "Linee di indirizzo sui percorsi nutrizionali nei pazienti oncologici"(rep. atti n. 224/csr; 14/12/2017) 2017 [Available from: https://www.salute.gov.it/portale/documentazione/p6_2_{21.jsp?lingua=italiano&id=2682.
[92] Bas D, Sonmez O, Koc ES, Celayir OM, Hajhamidiasl L, Tontas E. Is virtual nutritional counseling efficacious for cancer patients during the COVID-19 pandemic? J Telemed Telecare 2023. 1357633X231158831.
[93] Lobascio F, Caccialanza R, Monaco T, Cereda E, Secondino S, Masi S, et al. Providing nutritional care to cancer patients during the COVID-19 pandemic: an italian perspective. Support Care Cancer 2020;28(9):3987–9.
[94] Lazar DE, Postolica R, Hanganu B, Mocanu V, Ioan BG. Web-based nutrition: a useful resource for cancer patients? Front Nutr 2023;10:1134793.
[95] Jimoh F, Lund EK, Harvey LJ, Frost C, Lay WJ, Roe MA, et al. Comparing diet and exercise monitoring using smartphone app and paper diary: a two-phase intervention study. JMIR Mhealth Uhealth 2018;6(1):e17.
[96] Cercato MC, Colella E, Fabi A, Bertazzi I, Giardina BG, Di Ridolfi P, et al. Narrative medicine: feasibility of a digital narrative diary application in oncology. J Int Med Res 2022;50(2). 3000605211045507.