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EDITORIAL

# NUTRITION IN ONCOLOGY: STATE OF THE ART AND FUTURE PERSPECTIVES

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Malnutrition is a pathological condition resulting from inadequate intake, absorption or utilization of nutrients and/or energy. It frequently arises in patients with various acute and chronic diseases, including cancer, and is associated with adverse outcomes, such as higher morbidity and mortality rates, longer hospital stays, and increased healthcare costs (1, 2). Using various screening tools, malnutrition has been identified in 20-70% of cancer patients, depending on tumor site and disease stage (3). According to a 2019 European report, malnutrition affects approximately 50% of gastrointestinal cancer patients, over 45% of head and neck cancer patients, and over 40% of lung cancer patients (4). In addition, it is estimated that nearly 20% of cancer patients die because of malnutrition rather than from cancer itself (4).

Several metabolic abnormalities, systemic inflammation being the most prominent, are present in 30-75% of cancer patients undergoing active treatment, with prevalence reaching up to 85% in patients with advanced disease (3). Malnutrition and inflammation often coexist and correlate with an increased rate of infectious complications and reduced overall survival. In cancer patients malnutrition is primarily due to a reduction in dietary intake, which may be associated with impaired digestion and absorption. These problems can be a direct consequence of the underlying disease or the result of anti-cancer treatments adverse effects (3).

In response to stress, the local release of pro-inflammatory mediators by neoplastic and immune cells within the tumor microenvironment induces a state of chronic systemic inflammation. This, in turn, drives a series of complex metabolic alterations, including the depletion of muscle mass and fat storages, insulin and anabolic resistance, which collectively shift metabolism towards a catabolic state (3). The association of reduced nutritional intake, chronic inflammation, and metabolic alterations represents the pathophysiological basis of cancer cachexia and of anorexia-cachexia syndrome, both of which are characterized by weight loss and alterations in body composition. The international criteria for identifying this multifactorial

condition are a weight loss exceeding 5% over the past six months, or a 2% weight loss in patients with a body mass index (BMI) below 20 kg/m² or with sarcopenia (5).

Despite the growing evidence about the importance of nutritional interventions as integral parts of a multidimensional approach to cancer patients care, much remains to be done to ensure wider dissemination and standardized practices of malnutrition screening and management. The importance of timely nutritional assessment in oncology is often underestimated by both patients and clinicians, with only one in three cancer patients in Europe receiving nutritional support during treatments (4).

Despite the availability of several validated tools for nutritional screening, including the Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST), the Nutritional Risk Screening 2002 (NRS-2002), the Patient-Generated Subjective Global Assessment-Short Form (PG-SGA SF), and the Mini-Nutritional Assessment Short Form (MNA SF), there is still no international consensus on which is the most suitable in oncology. Nutritional screening remains inadequately implemented in clinical practice within oncology departments, though its systematic use, especially if performed early at diagnosis, could help reducing morbidity rates and hospital stays, yielding not only economic benefits but also the improvement of patients' quality of life (6).

Nutritional care should be provided by clinical nutrition specialists to all cancer patients at risk of or affected by malnutrition, with the objective of targeting nutritional interventions as early as possible in order to optimize caloric and protein intake. Depending on patients' needs, such interventions may include personalized dietary counseling, oral nutritional supplements (ONS), or, if these measures are insufficient to satisfy nutritional requirements, the initiation of artificial nutrition, either enteral or parenteral (7, 8).

Nutritional counseling is a non-invasive procedure that can be easily provided and is now a standard of care in oncology. It is recommended by national and international guidelines and is frequently requested by patients and their families. Nutritional counseling itself offers numerous benefits, particularly in terms of treatment tolerance, especially when initiated early in the care process (7, 8). A recent review has shown a positive effect on increasing caloric and protein intake in patients with stage 4 cancer (9).

For cancer patients undergoing surgery, perioperative nutritional management generally follows the recommendations of the Enhanced Recovery After Surgery (ERAS) protocol. However, given that surgical procedures are often elective and multimodal treatments, such as neoadjuvant chemotherapy, are provided, there is an opportunity for earlier intervention, allowing for nutritional plans to be implemented weeks before surgery (10). Over the past decade, standard oral nutritional supplement formulas have been enhanced with 'immunonutrients' (*e.g.*, arginine, glutamine, omega-3 fatty acids, ribonucleotides, vitamins, and minerals) to stimulate the immune response and counteract inflammation in cancer patients undergoing major surgery. It is hypothesized that these components act by promoting T-cell activation, reducing pro-inflammatory cytokine production, supporting tissue regeneration and wound healing, and modulating inflammation. The available clinical data indicate that the benefits of immunomodulating nutritional interventions may become apparent after approximately seven days. This supports the systematic use of preoperative immunonutrition as an integral part of nutritional care in these patients (11).

The concept of 'prehabilitation', which aims to optimize both physical and psychological suitability for surgery and to counteract muscle loss throughout treatments, is evolving. Through the implementation of multidisciplinary teams, which allow close collaboration among various professionals, patients can receive multimodal interventions including nutritional support, physical activity programs, and psychological support. These interventions are often combined with lifestyle modification plans, which may include smoking and alcohol cessation (10, 11). Despite the lack of consensus on the efficacy of these strategies in improving outcomes and reducing resource utilization, due to inconsistent findings from the available literature, several international organizations are actively investigating the promotion and implementation of prehabilitation programs (12). To date, published trials have exhibited considerable heterogeneity, indicating however an overall positive effect of prehabilitation on functional capacity, suggesting possible reduction in postoperative complication rates and length of hospital stay (12). Additionally, since patients with moderate malnutrition appear to respond better to prehabilitation, additional research is required to ascertain whether and how malnutrition itself may impact the efficacy of these programs (12).

Multidisciplinary collaboration is clearly of key importance within the treatment pathway for cancer patients. Consequently, there is a progressive increase of multidisciplinary tumor boards (MTBs), which include members from various medical and surgical specialties. However, clinical nutrition specialists are seldom included in MTBs, despite the valuable contribution they can bring, particularly regarding decision-making aspects such as timing of nutritional interventions, indication for artificial nutrition and access to home nutritional care (6). In the therapeutic management of patients with cachexia, increase of nutrient intake is of crucial importance, as it also aims to stimulate anabolic pathways. As each case results from a unique combination of pathophysiological, metabolic, endocrine, and psychological alterations, supervised physical activity is also of great importance in stimulating protein anabolism and plays a significant role in improving mood and patient quality of life (QoL), particularly when combined with psychological, social, and spiritual support (3, 13).

Currently, no definitive recommendations can be provided about the use and efficacy of specific drugs and nutrients for the treatment of cachexia. Some studies have suggested a potential role for omega-3 fatty acids in promoting weight gain and attenuating muscle loss in patients undergoing chemotherapy and radiotherapy (3, 14). Concerning pharmacological interventions, according to major European and U.S. oncology societies, only corticosteroids, progestins, and olanzapine may be considered for patients with cancer cachexia to reduce nausea, appetite loss and anorexia and to promote weight recovery, but with limited effects on lean mass and functional capacity, and potentially several adverse effects (3, 13). Moreover, alterations in the gut microbiota have been associated with the onset of cancer cachexia, suggesting that treatments involving prebiotics, probiotics, or fecal transplantation may be effective in reversing the dysbiosis associated with this condition (3).

Recently, two new drugs have emerged as promising options. Anamorelin, an oral ghrelin receptor agonist, in 2021 received approval in Japan, for the treatment of cachectic patients with non-small cell lung cancer and gastrointestinal tumors. In the United States and Europe this molecule is not yet available, despite phase 3 studies demonstrating a statistically significant positive effect on appetite and weight recovery (15, 16). In 2017, the European Medicines Agency (EMA) declined to approve this molecule due to its marginal effects on lean mass and unproven benefits in terms of handgrip strength and quality of life, along with an inadequate safety data collection. Further studies are required to investigate the association of anamorelin with other interventions (primarily nutritional support and physical activity) in order to optimize the treatment efficacy (13).

Based on the observation that high levels of growth differentiation factor 15 (GDF-15) in cancer patients are associated with weight loss, skeletal muscle mass loss, and decreased strength and survival, a recent study have investigated the potential of ponsegromab, a humanized monoclonal antibody that selectively binds to circulating GDF-15, preventing it from binding to its receptor glial cell-derived neurotrophic factor (GFRAL). The GDF-15-GFRAL pathway appears to be involved in appetite modulation and body weight regulation (5). In a preliminary phase Ib study including 10 patients with cancer cachexia and elevated GDF-15 levels, ponsegromab was associated with improved appetite, body weight, and physical activity, with a low incidence of adverse events (17). Subsequently, in a phase II study involving 187 cancer patients, the administration of ponsegromab for 12 weeks resulted in a significant weight gain, with a recovery of over 5% of initial weight in the treatment group with ponsegromab 400 mg compared to the placebo group, showing significant effects even in patients with more severe weight loss. Additionally, positive effects were observed on body composition, appetite, quality of life, and physical performance (5). Nevertheless, a significant limitation of the existing studies is the absence of any nutritional intervention in association with the administration of the drug. This even though cancer cachexia, as previously stated, is a condition that is inherently associated with malnutrition. The integration of ponsegromab into a comprehensive therapeutic strategy, that includes personalized nutritional support and a structured physical activity program, is likely to further enhance its positive effects.

Furthermore, it's important to be aware of the rising popularity, in recent years, of anticancer restrictive diets (fasting mimicking diets and ketogenic diets being the most studied), driven in part by dissemination of information on social media platforms (18). Many patients often self-administer these diets based on nutritional advice found on the internet. However, despite the promising results observed in experimental models, findings in humans remain

inconclusive, and currently no studies have demonstrated the effectiveness of these diets in terms of clinical and prognostic outcomes in cancer patients (18). Conversely, restrictive regimens could be detrimental, especially if not supervised by specialists in Clinical Nutrition, as they may result in weight loss and malnutrition. Moreover, the prolonged exclusion of specific food categories (*e.g.*, dairy or animal products) can result in vitamin and mineral deficiencies in the absence of adequate supplementations, potentially worsening rather than improving patients' prognoses (18). For these reasons, such dietary regimens are not recommended in the latest guidelines for the management of cancer patient (7, 8), and further studies are needed to clarify the impact of their use in this field (18).

Finally, nutritional intervention plays a pivotal role throughout the whole therapeutic process of cancer patients, and it should be considered also in patients eligible for palliative care, despite the controversy surrounding this topic. Artificial nutrition may be incorporated into a palliative care program if it is expected to improve/maintain quality of life or if the risk of death from malnutrition is deemed to exceed that from disease progression (8, 19). Once again, nutritional interventions in end-of-life care should be individualized and focused on comfort and improvement of QoL and are more effective when integrated into a comprehensive and timely multidimensional approach.

Thus, it is imperative to promote the diffusion of nutritional screening and assessment practices to enable prevention, early identification and treatment of malnutrition in cancer patients at all the disease stages. From this perspective, the provision of personalized nutritional support would not only confer benefits to the patients but would also help to reduce the economic burden of malnutrition, which is estimated around 12 billion/year in Italy (4, 20).

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### Authors' contributions

AT: conceptualization (equal); writing and original draft; VDP: writing, review and editing (equal); EM: writing, review and editing (equal); FDS: writing, review and editing (equal); LP: writing, review and editing (equal); FS: writing, review and editing (equal); PP: supervision (equal); writing, review and editing (equal); RC: conceptualization (equal); supervision (equal); writing, review and editing (equal).

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N/A.

### Publication ethics

#### *Plagiarism*

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

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All the data corresponds to the real.

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