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# Nutrition in Cancer

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**Abstract**

In cancer patients, oral nutrition is the preferred route of feeding since it is a significant part of the patient's daily routine and contributes to the patient's autonomy. It represents a privileged time to spend with family and friends, avoiding the tendency for isolation in these patients. The acknowledgement that the prescribed diet is individualized, adapted and adequate to individual needs empowers the patient with a feeling of control, and thus it is also a highly effective approach of psychological modulation. All these factors may potentially contribute to improve the patient's quality of life and may modulate treatment morbidity. The referral to a nutrition professional responsible for the individualized dietary counseling should always be based on evidence-based decision-making plans. The implementation of individualized nutritional counseling should consider the common causes for a poor nutritional intake in elderly cancer patients. A proper approach through counseling requires professionals with specific experience in both nutrition and oncology. Oral nutritional supplements are a simple and practical way to meet nutritional requirements when normal food intake is compromised. Ideally, oral nutritional supplements should be in addition to and not instead of meals. Supplements should be administered at a time which does not interfere with the appetite of the patient. The administration after the meal theoretically potentiates the anabolic effect on protein metabolism. Supplements with high energy density (>1 kcal/ml) or enriched with ω-3 fatty acid are probably the most effective.


## Malignancy

The word 'cancer' is inclusive and comprises a wide range of different types of malignant tumors, which can develop in virtually every body tissue, thus determining diverse clinical manifestations [1, 2]. Cancer is a major cause of

morbidity and mortality, being the second most frequent cause of death worldwide [2, 3]. However, the advances in early diagnosis and sophisticated treatment modalities increase the possibility of cure or at least may prolong survival. It is thus expectable that most cancer patients will be ambulatory with a desirable 'good' quality of life (QoL); the latter requires a patient-centered multiprofessional management in which nutrition plays a central role [4–8].

*The Wasting Spectrum in Cancer*

Cancer is associated with malnutrition [9–11] that may evolve to cancer cachexia. Cancer cachexia is multifactorial and is defined as 'a multifactorial syndrome with loss of skeletal muscle mass (with or without loss of fat mass), not fully reversed by conventional nutritional support. Its pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism' [12, 13], and cachexia is still an unsolved phenomenon. The prevalence of nutritional wasting in cancer ranges from 8 to 84% depending on the cancer site, e.g. 80% in patients with gastrointestinal (GI) cancer [9, 14–18] and 70% in patients with head-neck cancer [19–23]. Cancer wasting is regarded as a physiological adaptation to stress: the body sacrifices large portions of muscle mass to spare immediate critical functions in visceral organs. But there are limitations to this adaptive response: skeletal muscle mass contraction leads to muscle weakness, and decreased work tolerance and functional capacity [24]. The most frequent manifestation of wasting in cancer is weight loss, which when exceeding 10% is of particular clinical and/or prognostic significance, because weight loss of this magnitude in the setting of any illness may lead to significant increases in morbidity and mortality [24, 25]. Some degree of weight loss has been registered in ~75% of patients before surgery, 57% prior to radiotherapy, 51% prior to chemotherapy and 80% of ambulatory patients [25, 26]. An additional finding is that weight loss is likely to be related to other factors, e.g. cancer aggressiveness (stage and histological characteristics), antineoplastic treatments, age and emotional factors such as depression [5, 8, 27–29].

## Tumor Burden, Metabolic Dysfunction and Symptoms

Anorexia is a common contributor to wasting in cancer [30] and the act of eating may incite a variety of adverse symptoms including 'voluntary anorexia' due to learned food aversions [27, 31]. In addition, the tumor mass alone may preclude adequate ingestion of food. The underlying factors contributing to reduced food intake include decreased central drive to eat, chemosensory

disturbances (dysgeusia and dysosmia), decreased upper GI motility (e.g. early satiety, nausea and vomiting) and distal tract dysmotility (diarrhea and constipation) [26]. On the other hand, the emotional adjustment associated with dealing with cancer is per se a precipitant of depression and anxiety, which are known contributors to anorexia [32, 33]. Of note, wasting and marked nutritional intake deficits have been associated with advanced disease [34, 35] and cancer aggressiveness [8, 28, 29]; all factors are prone to exacerbate every organ/systemic physiological derangements.

Although anorexia frequently accompanies cachexia, the drop in caloric intake alone cannot account for the body composition changes in cachexia; cachexia can occur even in the absence of anorexia. Norton et al. [36] provided evidence for the parabiotic transfer of cachexia into rats, indicating that cachexia must be mediated by some circulating factors: products of host tissues (e.g. TNF-α, IL-1, IL-6 and IFN-γ) and tumor products with a direct catabolic effect on host tissues (e.g. lipid-mobilizing factor acting on adipose tissue and proteolysis-inducing factor acting on skeletal muscle) [37, 38].

*Acute Phase Responses*

Acute-phase response (APR) refers to various physiologic/metabolic changes in response to tissue injury, infection or inflammation. Liver protein synthesis shifts from synthesizing albumin to producing acute-phase proteins such as C-reactive protein, serum amyloid-A protein, $\beta_2$-macroglobulin and $\alpha_1$-antitrypsin. APR has been associated with more rapid weight loss and reduced survival in patients with lung or pancreatic cancer, and melanoma [39]. APR is activated and modulated by cytokines [24, 40]; moreover, proteolysis-inducing factor activates the transcription of NF-κB, resulting in increased production of proinflammatory cytokines IL-8, IL-6 and C-reactive protein, and decreased production of transferrin [41]. The mechanism underlying the association between APR, weight loss and survival in cancer is not known, but acute-phase proteins have been suggested to scavenge amino acids leading to muscle protein degradation. Yet, APR alone is not sufficient to produce weight loss.

*Hypermetabolism*

In some studies with malnourished cancer patients, food intake failed to correlate with the degree of malnutrition [31, 42, 43]. The use of appetite stimulants, such as megestrol acetate/medroxyprogesterone acetate (acting by downregulating the synthesis and release of proinflammatory cytokines), may be associated with weight gain in some patients; body composition analysis showed that it is due to increased adipose tissue and possibly also an increase in body fluid, but not in fat-free mass [44, 45].

Higher resting energy expenditure (REE) has been observed in patients with lung and pancreatic cancer [29, 46–49]. However, since energy expenditure decreases with a decrease in food intake, even if there is no increase in REE, this could be considered abnormal in the face of progressive anorexia. In addition, not all changes in energy expenditure are increases in REE. Thus, skeletal muscles of patients with GI cancer with weight loss showed a fivefold elevation in mRNA levels for the mitochondrial uncoupling protein (UCP)-3 versus controls and cancer patients with no weight loss, despite the reported lack of an increase in REE [50, 51]. This suggests that either lipid-mobilizing factor or TNF-α may be responsible for the elevation in UCP-3 mRNA in skeletal muscles of cachectic cancer patients, possibly via an elevation in serum lipid levels.

*Wasting, Protein Metabolism and Skeletal Muscle*

Cachexia is characterized by selective skeletal muscle mass loss, which can be reduced by 75% when weight loss approaches 30% [52]. Skeletal muscle is the body compartment where most of the contraction of lean body mass occurs [50, 53, 54]. Loss of skeletal muscle is characterized by decreased protein synthesis and increased protein breakdown. Protein degradation in muscles results in the release of amino acids, namely alanine and glutamine. The former is channeled to the liver for gluconeogenesis and the synthesis of acute phase proteins, whereas glutamine is taken up by tumor cells to sustain energy and nitrogen demands [46]. Changes in total body protein synthesis are often not observed in weight-losing cancer patients, since hepatic protein synthesis is markedly increased (twofold). However, in weight-losing cancer patients, muscle protein synthesis accounted for only approximately 8% of total body synthesis compared with 53% in healthy controls [46]. A number of studies have reported increased whole-body protein turnover, suggesting that degradation rates are also increased. Intracellular protein breakdown is suggested to be due mostly to the ATP-ubiquitin-dependent proteolytic pathway [55– 57]. Low muscle mass in advanced cancer is common and a predictor of immobility and mortality [58, 59]; of note: low muscle mass adversely affects prognosis also in obese patients with advanced pancreatic cancer [60]. Sarcopenic patients are also at higher risk of increased toxicity of antineoplastic treatments [53, 54, 61].

*Wasting, Lipid Metabolism and Adipose Tissue*

Lipids have a high caloric value, and mobilization of lipids is required to meet the increased energy demands of the cachectic patient [11]; as much as 85% of adipose tissue may be lost during the cachectic process [62]. The net efflux of glycerol and fatty acids from adipose tissue in cancer wasting appears to be due to: (1) increased lipolysis apparently mediated by TNF-α and lipid-mobilizing

factor; (2) decreased de novo lipogenesis suggested to be mediated by TNF-α and IL-1 [57, 63], and (3) diminished activity of lipoprotein lipase [11, 64]. The latter enzyme is necessary for the uptake of fatty acids from circulating lipoproteins and the diminished activity in cancer appears to be mediated by TNF-α, IL-6 and IFN-γ [11]. Cancer patients have a high turnover of both glycerol and free fatty acids [65], and the elevated mobilization of lipids is often evident before weight loss becomes established; of note: CT scans showed intra-abdominal fat in cancer patients to be relatively preserved versus intra-abdominal fat in anorexia nervosa patients [66–69].

## The Impact of Cancer Wasting

Regardless of the underlying mechanisms, cancer-related wasting is multidimensional and worsens patients' well-being [39], tolerance to antineoplastic therapies and prognosis [19, 53, 54, 58]. Weight loss decreases immunological responses to tumor cells [70] and resistance to infection [42], enhances susceptibility to postoperative complications [35, 71], and increases disability and overall costs of care [72]. Also, in experimental conditions, both short-term starvation (water only) as well as prolonged semistarvation in healthy volunteers has been reported to reduce physical activity [42, 73, 74]. In the landmark semistarvation study of Keys et al. [75] in which healthy subjects lost 25% of their body weight over 6 months, there was a reduction in both REE and physical activity. Mental function may be further influenced by nutrition in several ways. Starvation and partial food deprivation in adults lead to anxiety, depression and/or other mental changes, which may in part be associated with micronutrient deficiencies. Cognitive function may also be adversely affected. In their study, partial starvation for 24 weeks resulted in loss of 25% of body weight and concomitantly increased their depression score [75].

## Nutrition Intervention

### *Counselling*

In clinical practice, oral nutrition is always the priority. In cancer patients, oral nutrition is the preferred route of feeding because it is a significant part of the patient's daily routine and does contribute substantially to the patients' autonomy [76]. One has to bear in mind that eating is a source of pleasure and is a privileged time to spend with family and friends, avoiding the tendency for isolation in patients. The referral to a nutrition professional responsible for the

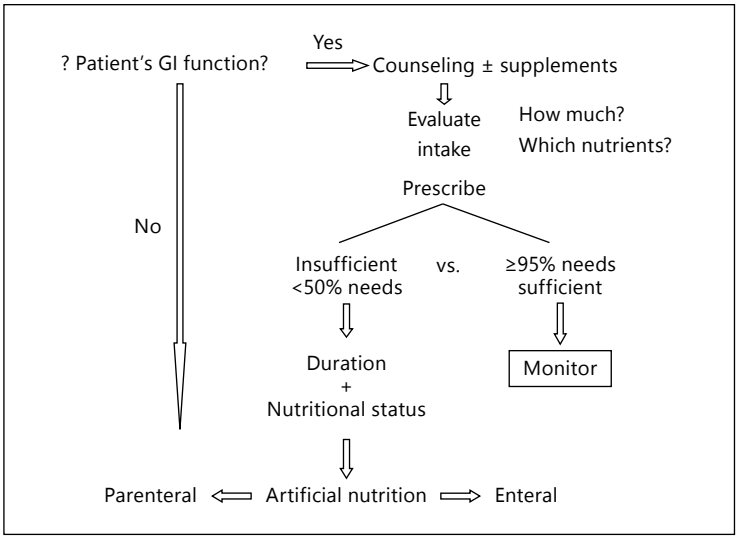


**Fig. 1.** Evidence-based decision-making plan (adapted from ESPEN 2010).

individualized dietary counseling should always be based on evidence-based decision-making plans (fig. 1) [6].

As clinicians, we have to recognize the dimensions that are determinant for patients. An adequate food intake is recognized by the patient as well as by the family and caregivers as essential to maintain the daily activity, energy and functional capacity, and to overcome more successfully the journey of treatment. To be effective, individualized counseling has to be based on a thorough assessment of various nutritional and clinical parameters evaluated in any nutrition consultation [77–80]. A detailed symptom assessment is mandatory (table 1).

Intensive individualized nutritional counseling is the most effective and the most physiologic means of feeding [76–78]. Notwithstanding, one has to acknowledge that this clinical approach requires nutrition professionals specialized in oncology. Due to its worldwide demonstrated efficacy, this integrated intervention should be fostered as the nutritional treatment of excellence in cancer patients.

*Supplementation*

Dietary counseling involves the prescription of therapeutic diets using regular foods; if the patient is unable to achieve his/her nutritional requirements via regular foods, nutritional supplements may be prescribed, the composition of which is based on the dietary deficits detected in the individual and a detailed intake questionnaire. Nutritional supplements can provide energy, protein and nutrients deemed necessary to meet the patient's needs, and represent a useful

**Table 1.** Common causes for a poor nutrient intake in cancer patients

| |
|---|
| Deterioration in taste, smell and appetite as a consequence of the tumor and/or therapy |
| Altered food preferences/food avoidance/food aversion |
| Eating problems (teeth/chewing) |
| Dysphagia, odynophagia or partial/total GI obstruction |
| Early satiety, nausea and vomiting |
| Soreness, xerostomia, sticky saliva, painful throat and trismus |
| Oral lesions and esophagitis |
| Radiotherapy-/chemotherapy-induced mucositis |
| Acute or chronic radiation enteritis during and after radiotherapy |
| Depression and anxiety |
| Pain |

method of support when food intake is a problem. However, the success of supplementation depends on the acceptability of the product by the patient and on patient compliance. Oral supplements, which require an intact and functioning GI tract, can be used as between-meal supplements. If the gut is functioning but oral intake is compromised, tube feeding is often the most feasible means of dietary intervention.

*The Clinical Benefit*

Early individualized nutritional counseling during radiotherapy was the most effective regimen in reducing toxicity, improving nutritional intake and status, as well as QoL [76, 78–80]. After the completion of treatment and nutritional intervention, the efficacy persisted at the 3-month follow-up [78]. Similar results were attained by previous studies, where individualized counseling versus the standard practice did improve the patients' nutritional status, intake, functional capacity and QoL [6, 78, 79, 81]. Of note: these studies were performed in patients with cancers typically associated with nutritional derangements, e.g. head-neck, colorectal and overall GI tract cancers, in all stages of the disease (stage I–IV), in patients submitted to chemotherapy and/or radiotherapy concomitantly, where chemotherapy regimens included 5-fluorouracil and platinum/irinotecan, for example, and in patients in whom median nutritional status was regular at baseline [80].

Hence, individualized nutritional counseling with regular foods, with or without supplements according to patients' requirements, has grade A evidence to increase nutritional intake and prevent therapy-associated weight loss and treatment interruptions [76]. Thus, the right time to start nutritional support is as an adjuvant to antineoplastic treatments, as it should be planned along with the scheduled treatments for the cancer patients. Intensive individualized nutritional counseling became the standard recommendation by ESPEN guide-

lines [76]. This evidence is mostly supported by the results of randomized controlled trials on nutritional therapy, in which a causal pathway between nutritional intervention and functional/clinical outcomes was demonstrated and later confirmed. A comprehensive review of the current literature undertaken by Lis et al. [82] supports the implementation of nutritional screening, assessment and individualized intervention to correct nutritional derangements in cancer patients.

*Timing of Nutrition*

Before Therapy

Individualized counseling with or without supplementation, taking into consideration the patients' clinical condition and symptoms, did assure that a sustained and adequate diet was able to overcome the predictable deterioration subsequent to radiotherapy. Moreover, such nutritional outcomes concur with what has been proposed as the causal pathway, e.g. optimizing nutritional intake may be the most effective method for treating disease-related malnutrition. There is evidence in a range of conditions to support the hypothesis that enabling the provision of the appropriate nutritional therapy leads to improved body weight and fat free-mass, and that this generally reflects an improvement in the protein energy status. This is of particular concern due to the body composition changes and sarcopenia derived from the disease process. We also demonstrated that the nutritional content of the patient's diet based on regular foods with appropriate manipulation is the key to improving GI function and other symptomatic manifestations during treatment and in the medium term. In patients who received dietary counseling and education, treatment-related toxicity, symptom incidence and/or disease severity were lower and their improvement in the medium term was faster. Indeed, dietary modifications may alter bowel functions, such as motility, enzyme secretion and nutrient absorption; likewise, nutrition modulates the GI flora whose ecology is central to the pathogenesis of radiation-induced injury severity. Nutrition is also a key determinant of QoL in cancer patients. Dietary counseling significantly improved all QoL function scores in association with an adequate dietary intake and nutritional status in patients that were able to eat and fit enough to comply with an individualized nutritional plan.

These results emphasize that 'the impairment in structure, function and well-being that form malnutrition, are nutritionally responsive'. Furthermore, the benefits of nutritional intervention on QoL were extrapolated to improved physiological function and overall clinical outcome. In the medium term, in patients that received individualized counseling, all QoL symptom scales reverted to their baseline scores. These results in patients who experience persistent eating diffi-

culties support the concept that increased intake of an appropriate mixture of nutrients using regular foods may be of major benefit in modulating outcomes.

Long-term results of prospective randomized controlled trials with a median follow-up of 6.2 years (range: 4–8.2 years) are currently in press, and do provide novel evidence that adjuvant nutritional therapy, provided as early and timely individualized nutritional counseling and education per se, had a sustained effect on outcomes.

### After Therapy

Individualized nutritional counseling has been proven to induce positive effects on patients' nutritional as well as nonnutritional outcomes: improved nutritional intake and status, increased QoL, decreased late morbidity and probably improved prognosis. Additionally, nutritional status and intake, and global QoL scores at the end of treatment had the ability to predict survival and late toxicity. Patients with poorer dietary intake, worse nutritional status and poorer QoL had a significantly shorter survival and increased incidence of symptoms; thus, poor nutritional intake/status and QoL scores had a significant predictive value. Therefore, all patients should receive nutritional counseling with or without supplements according to their intake at the end of any antineoplastic treatment or surgery. Patients must be taught and educated on what to consume at discharge, so that they can maintain their QoL, nutritional and functional status and overall well-being and autonomy.

## Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

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