Clinical Nutrition 36 (2017) 1187–1196

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

ESPEN expert group recommendations for action against cancer-related malnutrition

J. Arends [a, b, *], V. Baracos [c], H. Bertz [a, b], F. Bozzetti [d], P.C. Calder [e], N.E.P. Deutz [f], N. Erickson [g], A. Laviano [h], M.P. Lisanti [i], D.N. Lobo [j], D.C. McMillan [k], M. Muscaritoli [h], J. Ockenga [l], M. Pirlich [m], F. Strasser [n], M. de van der Schueren [o, p], A. Van Gossum [q], P. Vaupel [r], A. Weimann [s]

[a] Department of Medicine I, Medical Center – University of Freiburg, Freiburg, Germany
[b] Faculty of Medicine, University of Freiburg, Freiburg, Germany
[c] Department of Oncology, University of Alberta, Edmonton, Canada
[d] Faculty of Medicine, University of Milan, Milan, Italy
[e] Faculty of Medicine, University of Southampton and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK
[f] Center for Translational Research in Aging & Longevity, Department of Health and Kinesiology, Texas A&M University, College Station, TX, USA
[g] Comprehensive Cancer Center, Ludwig-Maximilian-University Hospital, Munich, Germany
[h] Department of Clinical Medicine, Sapienza University, Rome, Italy
[i] Department of Translational Medicine, University of Salford, Salford, UK
[j] Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK
[k] Department of Surgical Science, University of Glasgow, Glasgow, UK
[l] Department of Gastroenterology, Endocrinology and Clinical Nutrition, Klinikum Bremen Mitte, Bremen, Germany
[m] Department of Internal Medicine, Elisabeth Protestant Hospital, Berlin, Germany
[n] Department Internal Medicine and Palliative Care Centre, Cantonal Hospital St Gallen, St Gallen, Switzerland
[o] Department of Nutrition and Dietetics, VU University Medical Center, Amsterdam, The Netherlands
[p] Department of Nutrition and Health, HAN University of Applied Sciences, Nijmegen, The Netherlands
[q] Gastroenterology Service, Hôpital Erasme, University Hospitals of Brussels, Brussels, Belgium
[r] Department of Radiation Oncology and Radiotherapy, Klinikum rechts der Isar, Technical University, Munich, Germany
[s] Department of General, Visceral, and Oncological Surgery, Hospital St Georg, Leipzig, Germany

ARTICLE INFO

Article history:
Received 15 June 2017
Accepted 15 June 2017

Keywords:
Cancer
Malnutrition
Sarcopenia
Cachexia
Anorexia
Nutritional intervention

SUMMARY

Patients with cancer are at particularly high risk for malnutrition because both the disease and its treatments threaten their nutritional status. Yet cancer-related nutritional risk is sometimes overlooked or under-treated by clinicians, patients, and their families. The European Society for Clinical Nutrition and Metabolism (ESPEN) recently published evidence-based guidelines for nutritional care in patients with cancer. In further support of these guidelines, an ESPEN oncology expert group met for a *Cancer and Nutrition Workshop* in Berlin on October 24 and 25, 2016. The group examined the causes and consequences of cancer-related malnutrition, reviewed treatment approaches currently available, and built the rationale and impetus for clinicians involved with care of patients with cancer to take actions that facilitate nutrition support in practice. The content of this position paper is based on presentations and discussions at the Berlin meeting. The expert group emphasized 3 key steps to update nutritional care for people with cancer: (1) screen all patients with cancer for nutritional risk early in the course of their care, regardless of body mass index and weight history; (2) expand nutrition-related assessment practices to include measures of anorexia, body composition, inflammatory biomarkers, resting energy expenditure, and physical function; (3) use multimodal nutritional interventions with individualized plans, including care focused on increasing nutritional intake, lessening inflammation and hypermetabolic stress, and increasing physical activity.

* Corresponding author. University of Freiburg, Department of Medicine I, Hematology, Oncology, and Stem Cell Transplantation, Hugstetter Str. 55, 79106 Freiburg, Germany.
E-mail address: jann.arends@uniklinik-freiburg.de (J. Arends).

http://dx.doi.org/10.1016/j.clnu.2017.06.017
0261-5614/

1. Introduction

Patients with cancer are at particularly high risk for malnutrition because both the disease and its treatments threaten their nutritional status. It is estimated that the deaths of 10–20% of patients with cancer can be attributed to malnutrition rather than to the malignancy itself [1–3]. Thus, nutrition is an important aspect of multimodal cancer care. Yet, recent studies in European hospitals found that only 30%–60% of patients with cancer who were at risk of malnutrition actually received nutritional support (i.e., oral supplements and/or parenteral nutrition and/or enteral nutrition) [4,5]. In another European study, physicians misclassified the severity of cancer-related malnutrition in 40% of cases; as a result, many severely malnourished patients did not get necessary nutritional interventions [6]. Even when physicians recognized cancer-related malnutrition, the patients and their relatives often underestimated its presence [7].

To address cancer-related malnutrition in contemporary practice, the European Society for Clinical Nutrition and Metabolism (ESPEN) recently published evidence-based guidelines for nutrition care in patients with cancer [8]. In further support of these guidelines, an ESPEN oncology expert group met for a *Cancer and Nutrition Workshop* in Berlin on October 24 and 25, 2016. Here, they examined the causes and consequences of cancer-related malnutrition, reviewed currently available treatment approaches, and built the rationale and impetus for clinicians involved with care of the patient with cancer to take actions that facilitate nutrition care in practice. The content of this position paper is based on presentations and discussions at the Berlin meeting.

1.1. Talking about cancer and nutrition: the terminology

Critically important work has been done to build universally accepted definitions for malnutrition, cachexia, and sarcopenia. These definitions are intended to help clinicians identify and treat the underlying metabolic and nutritional issues associated with both aging and with chronic or acute diseases, including cancer (Fig. 1) [9,10]. Despite efforts to clearly differentiate these conditions, there is some overlap in the working definitions, as there is some overlap in the conditions themselves. Notably, the need to be absolute on the definitions is surpassed by the necessity of recognizing the negative impact of cancer on nutrition. While definitions are important, this paper focuses on identifying and treating the metabolic and nutritional alterations that impede recovery and survival of patients with cancer.

Disease-related malnutrition has been defined as a condition that results from the activation of systemic inflammation by an underlying disease such as cancer [9]. The inflammatory response causes anorexia and tissue breakdown that can, in turn, result in significant loss of body weight, alterations in body composition, and declining physical function [9].

Cachexia is a multifactorial wasting syndrome characterized by involuntary weight loss with ongoing loss of skeletal muscle mass with or without loss of fat mass; such wasting cannot be reversed by conventional nutrition care and may lead to functional impairment [10–14].

In **precachexia**, early clinical and metabolic signs precede extensive involuntary loss of weight and muscle. Risk for cachexia and its worsening depends on factors such as cancer type and stage, extent of systemic inflammation, and degree of response to anticancer therapy [10,13].

Sarcopenia is low lean body mass (mostly muscle); fatigue is common, strength may be lessened, and physical function limited [11,13]. As functionality is lost, patients with cancer may no longer be able to live independently, and they often report lower quality of life [8,13].

Sarcopenic obesity is low lean body mass in obese individuals [9]. In such patients, clinicians frequently overlook muscle loss due to the presence of excess fat and extracellular water [12]. In fact, the presence of sarcopenic obesity is an important predictor of adverse outcome, which can be further worsened by surgical interventions [15].

2. The high prevalence of malnutrition in patients with cancer

Patients with cancer are more likely to be malnourished than patients treated in many other specialties [13]. The prevalence of malnutrition in patients with cancer has been reported to range from about 20% to more than 70% in worldwide studies, with differences related to patient age, cancer type, and cancer stage (Table 1). Patients with gastrointestinal tract, head and neck, and liver and lung cancers are at high risk for malnutrition [2,4,16,17]. Malnutrition is more highly prevalent in older adults than in younger ones, and, and not surprisingly, in those with cancer at

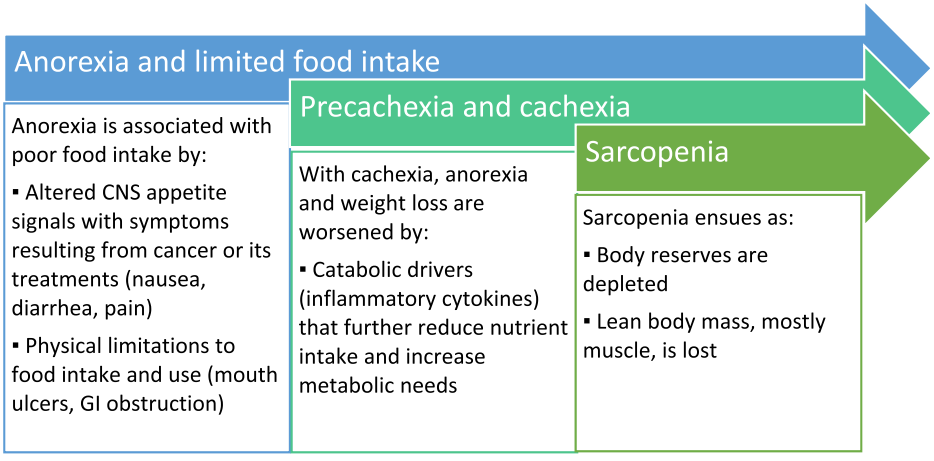

Fig. 1. Malnutrition in patients with cancer: anorexia, cachexia, and sarcopenia. Anorexia, with poor food intake and consequent weight loss, commonly occurs in disease-related malnutrition, especially cancer. These harmful changes are driven by proinflammatory cytokines and tumor-derived factors. The associated conditions of cachexia and sarcopenia may also be present or may develop as cancer advances—cachexia due to inflammation, and sarcopenia due to fatigue and low physical activity and to other causes of declining muscle mass and function. Abbreviations: Central nervous system, CNS; gastrointestinal, GI.

Table 1
Reports of malnutrition prevalence in hospitalized patients with cancer.

Study, country	Cancer type	Malnutrition prevalence
Attar et al., 2016 [6] France	Upper gastrointestinal	52% of patients on chemotherapy
Planas et al., 2016 [5] Spain	Multiple types	34% at hospital admission, 36% at discharge
Fukuda et al., 2015 [20] Japan	Gastric	19% of those hospitalized for gastrectomy
Maasberg et al., 2015 [21] Germany	Neuroendocrine	25% at risk or actually malnourished
Silva et al., 2015 [17] Brazil	Multiple types	71%, with 35% moderate and 36% severe
Hebuterne et al., 2014 [4] France	Multiple types	39% overall prevalence, varying by cancer type
Aaldriks et al., 2013 [19] Netherlands	Advanced colorectal	39% in patients >70 years, prior to chemotherapy
Freijer et al., 2013 [18] Netherlands	Multiple types	30% in patients >18 and <60 years old 39% in patients ≥60 years
Pressoir et al., 2010 [1] France	Multiple types	31%, with 12% rated as severely malnourished
Wie et al., 2010 Korea [2]	Multiple	61% of all patients, varying by cancer type and stage

advanced stages rather than early stages [18,19]. Malnourished patients with cancer may be cared for in hospitals, in nursing homes, or at home, and care must be adjusted to the setting. One report described the general prevalence of malnutrition as 30% in hospitals, 11% in nursing homes, and 23% in home care for adults <60 years old and as 39%, 20%, and 23% respectively for those ≥60 years [18].

3. High health and financial costs of malnutrition in patients with cancer

Numerous studies have highlighted the consequences of malnutrition in patients with cancer, including adverse impact on health and survival and added healthcare costs. We list recent and representative publications to illustrate the wide range of negative effects that have been reported (Table 2). In terms of poor health outcomes, malnutrition was associated with loss of weight and muscle [22], reduced immune competence and more infections [1,20,23], psychosocial stress [24], lower quality of life [25], treatment toxicity [19], and greater risk of mortality [1,21,22]. In terms of outcomes that affect healthcare costs, length of stay in hospital was longer in malnourished patients with cancer [1,5,21], and overall costs were increased by as much as €2000 per hospitalization episode [5]. In the Netherlands, disease-related malnutrition accounts for an excess €2 billion healthcare spending in a year with 1 of every €7 (about €300 million total) attributed to excess healthcare spending on patients with cancer [18].

4. Mechanisms underlying cancer-related impairment of nutritional status

Cancer-related malnutrition is a multimodal process because many factors collude to impair food intake, increase energy and protein needs, decrease anabolic stimuli such as physical activity, and alter metabolism in different organs or tissues. The multimodal drivers of malnutrition form a rationale for use of multiple therapeutic strategies to prevent, delay, or treat malnutrition in people with cancer.

4.1. Immune response, systemic inflammation, and symptoms

Patients with cancer report clusters of symptoms that can be related to poor nutrient intake, weight loss, and declining physical function, as well as fatigue, pain, and depression [26]. Such symptoms have also been associated with reduced quality of life and survival in patients with advanced disease [27,28]. In fact, there is a consistent association between symptoms, the presence of inflammatory markers, and upregulated immune responses (Fig. 2) [26–30]. Poor cancer outcomes are predicted by markers of the systemic inflammatory response—altered acute phase proteins (elevated C-reactive protein, hypoalbuminemia, and their combination as the Glasgow Prognostic Score [29]) and changes in white cell counts (elevated neutrophil counts, low lymphocyte counts, high neutrophil-to-lymphocyte ratio) [26,29,31].

4.2. Spillover of tumor-derived cytokines worsens systemic inflammation

Further systemic inflammation can be provoked by spillover of proinflammatory cytokines produced by the tumor [13,23,32,33]. In turn, these proinflammatory cytokines disrupt metabolism of carbohydrates, fats, and proteins throughout the body (Fig. 3) [32–36]. There is considerable evidence to support the roles of signaling by way of tumor-derived cytokines, e.g., interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) [37,38]. Cytokines can affect the neuroendocrine control of appetite, leading to anorexia [23]. As well, tumor-derived cytokines can cause muscle wasting, resulting

Table 2
Health and financial impacts of malnutrition in patients with cancer reported in selected publications.

Study, country	Cancer type	Negative impacts of malnutrition
Planas et al., 2016 [5] Spain	Multiple types	Significantly **longer LOS** (>3 days more) and **higher costs of care** (+€2000) for patients with malnutrition risk
Fukuda et al., 2015 [20] Japan	Gastric	Significantly **higher risk of surgical site infections** in malnourished compared to well-nourished patients (36% vs 14%, P < 0.0001)
Gellrich et al., 2015 [25] Switzerland	Oral	Malnourished patients had significantly **lower scores on QoL scales** related to physical function
Maasberg et al., 2015 [21] Germany	Neuroendocrine	Significantly **longer LOS** and **higher risk for mortality** in malnourished patients
Martin et al., 2015 [22] Canada	Multiple types	Weight-stable patients with BMI ≥25.0 kg/m^2 had the longest survival while **high % weight loss values associated with lowered categories of BMI were related to shortest survival**
Aaldriks et al., 2013 [19] Netherlands	Advanced colorectal	Malnutrition predicted **lower tolerance to chemotherapy** and was associated with greater **risk of mortality**
Freijer et al., 2013 [18] Netherlands	Multiple types	Disease-related malnutrition accounted for an excess €2 billion healthcare spending in a year; 1 of every €7 (about €300 million total) could be attributed to **excess healthcare spending on patients with cancer**
Pressoir et al., 2010 [1] France	Multiple types	Compared with adequately nourished patients, malnourished patients required **more antibiotic treatments** (36% vs 23%, P < 0.0001) and had significantly **longer LOS** Severely malnourished patients were at **4-fold higher risk of 2-month mortality** than well-nourished patients

Abbreviations: length of stay, LOS; body mass index, BMI; quality of life, QoL.

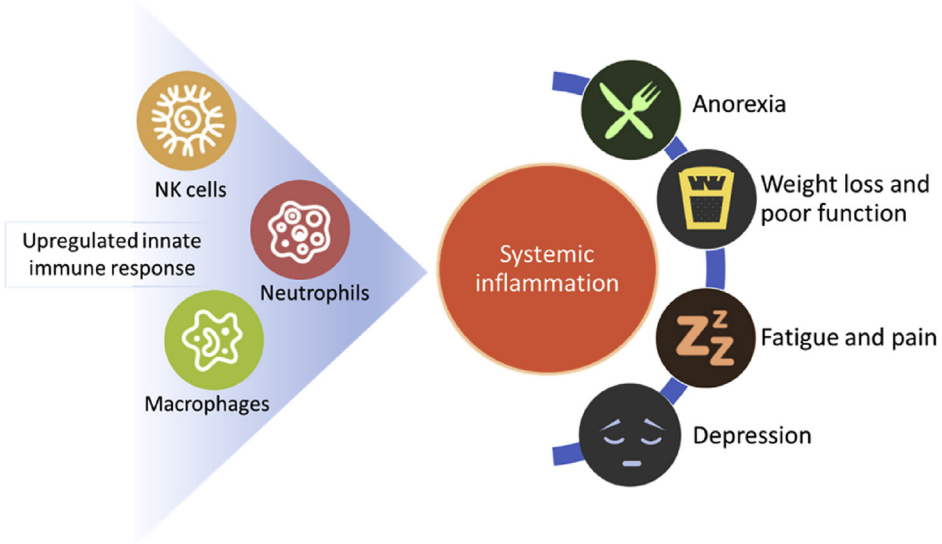

Fig. 2. Association of immunologic, metabolic, and clinical phenomena in cancer. In patients with cancer, systemic inflammation is associated with the host's innate immune response and with clinical symptoms. Abbreviation: natural killer, NK.

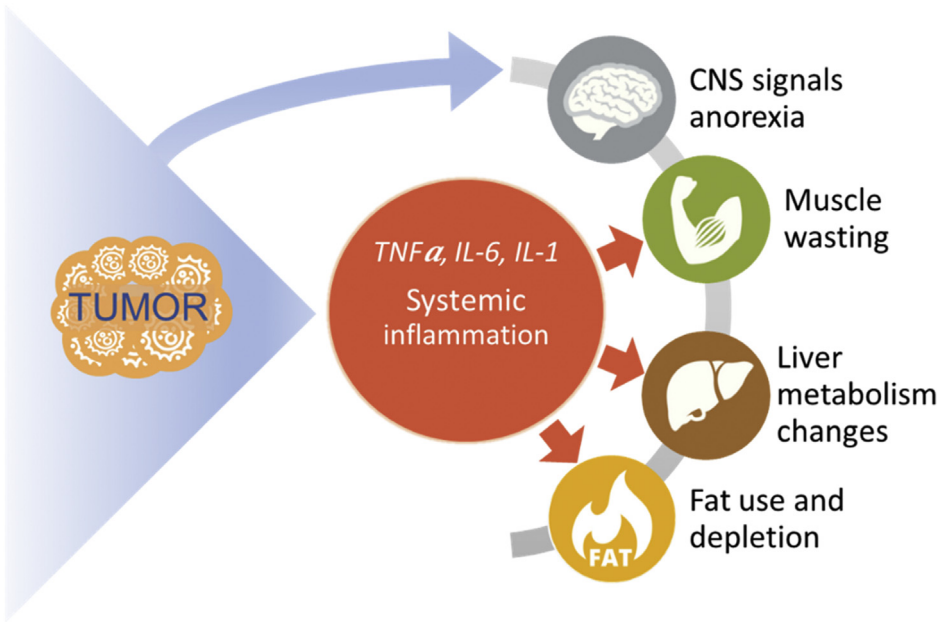

Fig. 3. Pathophysiology and metabolism in the presence of a tumor: the mechanisms. The tumor itself releases inflammatory and other factors that affect the brain, muscle, liver, and fat function. **Brain** – altered appetite signals from the CNS cause anorexia, resulting in reduced caloric intake; **Muscle** – an anabolic/catabolic imbalance leads to muscle wasting, reducing muscle mass and strength, and increasing fatigue; **Liver** – in the liver, acute-phase protein production is stimulated, repressing drug clearance and raising the risk for cancer treatment toxicity; **Fat** – energy stores in fat deposits are depleted as cytokines stimulate increased lipolysis and cause defective lipogenesis, a maladaptive and wasteful response to low food intake. Abbreviations: central nervous system, CNS; IL, interleukin; TNF, tumor necrosis factor.

in fatigue and impaired physical activity [33]. Cytokine-regulated loss of adipose tissue, due to increased lipolysis and defective lipogenesis, depletes fat depots that normally serve as energy reserves [39]. Circulating cytokines can also alter production of acute-phase proteins by the liver, which can suppress drug clearance pathways and lead to risk for toxicity of anticancer agents [36].

4.3. Hypoxic stress in the tumor microenvironment

Tumor hypoxia occurs when tumor cells have been deprived of oxygen. A tumor growing rapidly may outpace its blood supply, resulting in regions of the tumor where the partial pressure of oxygen is significantly lower than in healthy tissues [40]. When such hypoxia develops, complex (mal-)adaptive mechanisms are initiated; tumor metabolism is altered to rely more on glycolysis and less on oxidative phosphorylation, and protection against harmful reactive oxygen species is reduced [41]. These changes are associated with enhanced tumor growth, malignant progression, and even resistance to anticancer therapy [40–45]. Nutritional interventions, by modulating the local generation of reactive oxygen species might potentially interfere with these processes. Given the pathophysiological effects of tumor hypoxia, researchers are seeking new techniques to assess tumor hypoxia (e.g., oxygen electrodes, endogenous markers of hypoxia,

magnetic resonance imaging-based measurements) with hopes that such information can potentially be used to improve the course of treatment [43].

4.4. Indirect effects of cancer or its treatments

Beyond anorexia, poor food intake will often result from side-effects of cancer treatments (drug- or radiation-therapy, surgery) or tumor-related local effects like tissue infiltration or physical obstruction. Such conditions include pain, fatigue, dry mouth or mouth ulcers, difficulty chewing, thick saliva, dysphagia, abdominal pain, nausea, intractable vomiting due to intestinal blockage, constipation, and diarrhea due to infections or malabsorption [8,13,15,24,46,47].

5. Addressing malnutrition in patients with cancer: diagnosis and treatment

ESPEN's evidence-based nutrition guidelines for adult patients with cancer raise awareness by drawing attention to the high prevalence of malnutrition and its adverse impacts on response to treatment, prognosis, and survival [8]. The Academy of Nutrition and Dietetics (AND) has also developed guidelines on nutritional management for patients with cancer in acute care and ambulatory settings [48]. Such updates help clinicians keep pace with advances in the science behind cancer and nutrition, and advise them how to translate information into practice. Of similar importance are well-argued calls for action to effectively couple oncologic and nutritional approaches throughout the patients' journey [49]. As we will discuss in this paper, many strategies are available to update nutritional care in patients with cancer (Box 1). For example, most patients with cancer experience some degree of metabolic stress, which can now be quantified by measures of inflammatory biomarkers. Also, today's patients with cancer may be either underweight or overweight, but both groups are at high risk for cachexia and sarcopenia and its adverse effects. Sensitive new methods facilitate early and accurate measures of body cell and muscle mass [12]. Medical nutrition care strategies have been updated, including recommendations for energy and protein requirements and the use of immune modulators and specialized nutrients to lessen adverse inflammatory and catabolic effects [8].

Box 1
New strategies to update nutritional care in cancer

- Screen each patient's nutritional status early in the course of his or her cancer treatment.
- Identify signs or symptoms of anorexia, cachexia, and sarcopenia as early as possible.
- Measure body cell or muscle mass precisely by sensitive imaging technologies (computed tomography and others) for early detection of malnutrition/sarcopenia.
- Use specific biomarkers to assess severity of cancer-related systemic inflammation, e.g. CRP and albumin.
- Use indirect calorimetry to estimate resting energy expenditure (REE) in order to personalize energy and protein needs.
- Use nutrition and metabolic support as a vital part of cancer care; some new strategies show promise for reducing inflammation and restoring lean body mass.
- Assess physical function routinely to monitor and guide physical rehabilitation.

5.1. Importance of early nutrition screening

For care of patients with cancer, nutritional guidelines consistently advise screening for nutritional risk as soon as the diagnosis of cancer is made, followed by full nutritional assessment when risk is present [8,48]. Specific studies have shown that such screening programs can be implemented for all patients with cancer [50].

5.2. Nutritional assessment and diagnosis of malnutrition

Practice changes for nutritional care in patients with cancer are based on progressing science and technology (Box 1). Identification of patients with cancer who are at risk for malnutrition relied traditionally on low body weight (or BMI) and a history of weight loss. An approach based on body weight alone has become increasingly ineffective in the face of the global obesity epidemic and the new understanding of the metabolic alterations that occur prior to any measurable change in body weight. Anorexia is now recognized as an early risk indicator for malnutrition, and appetite change can occur regardless of a patient's initial weight. Weight loss is a signature sign of advancing malnutrition, thus it needs to be detected and recognized. Inadequate nutritional intake is confirmed if patients cannot eat for a week or if their energy intake is less than 60% of estimated requirements for 1–2 weeks [8].

Evolving definitions of cachexia and sarcopenia aim to identify and quantify signs/symptoms of malnutrition or its risk, including evidence of inflammation as well as loss of muscle mass and function [10,22]. The Glasgow Prognostic Score (GPS), based on serum concentrations of C-reactive protein and albumin as markers of inflammation, is an easy-to-use and highly predictive tool for the assessment of inflammation in patients with cancer [29]. Importantly, GPS has been thoroughly validated in clinical practice to predict prognosis and mortality [29,51]. While imaging techniques have long been used for the diagnosis of cancer, these techniques are becoming forefront strategies for nutritional evaluation. Retrospective reviews of computed tomography images in patients with cancer have shown that such imaging can detect loss of muscle mass as well as fatty muscle infiltration (myosteatosis) [13,52]. It is now recognized that sarcopenia can occur concurrently with obesity [12,53,54]. In under- and overweight patients alike, sarcopenia is associated with higher incidence of chemotherapy-related toxicity, shorter time to tumor progression, physical disabilities, poorer surgical outcomes, and reduced survival [12,53–56]. A recent study found a relationship between loss of physical function and cancer survival [57]; additional studies are needed to identify tools that best assess function in patients with cancer and to use assessment results to guide prescription of physical rehabilitation.

5.3. Treatment: needs, counseling, support, specific ingredients

The form of medical nutrition care depends on the patient's medical history, appetite, type of cancer, stage of cancer, and his or her response to treatment [10]. Some patients with cancer may experience a progression through worsening stages of cachexia, from precachexia to cachexia to refractory cachexia close to end of life (Fig. 4). The burden of cachexia can be lowered or alleviated by comprehensive nutrition care tailored to meet the needs of the patient during different stages of the disease.

5.4. Nutritional needs

Initiating effective nutritional treatment of the patient with cancer depends on an estimation of total energy expenditure

(TEE), which is the sum of resting energy expenditure (REE) plus activity-associated energy expenditure. The use of standard formulas for the calculation of energy needs may be inaccurate given the altered energy metabolism and metabolic differences in patients with different cancer types [35,58,59]. REE tends to be elevated in patients with advanced stages of cancer, but such patients also experience increasing fatigue and decreasing physical activity, thus limiting TEE [60]. Indirect calorimetry appears to be the most accurate in predicting the patient's REE and may be considered for all at-risk patients with cancer [58]. If REE and or TEE cannot be measured directly, 25–30 kcal/kg/day with 1.2–1.5 g protein/kg/day serve as a target range to help maintain or restore lean body mass; it has been proposed that even higher doses of protein may be necessary when depletion is severe [8,61,62]. However, in severely depleted patients, feeding is initiated slowly and over several days (while carefully monitoring phosphate and electrolytes) to avoid potentially harmful refeeding syndrome [63].

5.5. Nutritional counseling and nutritional support

Nutritional counseling is the first and most commonly utilized intervention for the management of malnourished patients with cancer and a functioning gastrointestinal tract [64]. A dietitian-nutritionist can provide individualized advice to achieve energy and nutrient balance based on the patient's estimated REE, lifestyle, disease state, current intake, and food preferences. Counseling needs to address the presence and severity of symptoms such as anorexia, nausea, dysphagia, abdominal bloating or cramping, diarrhea, and constipation. Critical components of nutrition counseling are to: (1) convey to the patient the reasons and goals for nutritional recommendations, and (2) motivate the patient to adapt to altered nutritional demand of their disease.

Oral nutrition support includes regular food or fortified foods as meals or snacks and oral nutritional supplements (ONS) to fill nutritional gaps when patients are at nutritional risk. Some studies evaluating nutrition counseling with and without the use of ONS have shown improvements in nutrition outcomes when including ONS: weight gain, BMI increase, and improved scores on a validated nutrition assessment test (Patient-generated subjective global assessment, PG-SGA) [65]. Studies have been limited, however, and remain inconclusive with respect to the effectiveness of oral nutrition strategies for the management of weight loss in patients with cancer [66]. The limitations are likely due to the wide range of pathophysiological alterations that occur in cancer, which require complex and individually targeted strategies such as adaptations to gastrointestinal deficiencies and modulations of metabolic components of cachexia in order to allow nutrition interventions to be effective [23].

5.6. Anti-catabolic and anti-inflammatory ingredients

In patients with cancer, systemic inflammation inhibits nutrient utilization and promotes catabolism, thus leading to muscle breakdown. Calorie and protein fortification of regular foods, even with standard ONS, does not reduce systemic inflammation. Updated nutritional strategies now suggest considering nutrition with anti-catabolic and inflammation-suppressing ingredients.

Studies have indicated that ONS with addition of essential amino acids (EAA) or high-dose leucine may improve muscle protein synthesis even within the context of inflammation, although results have not been fully consistent [67,68]. More research is needed in this area to confirm roles of nutrition with EAA and leucine in the management of patients with cancer.

Fish oil, a source of long chain omega-3 fatty acids, is currently suggested to improve appetite, oral intake, lean body mass, and body weight in patients with advanced cancer and at risk of malnutrition [8]. The mechanism of fish oil to downregulate the systemic inflammation related to cancer cachexia is still under investigation. Results of a randomized study in patients with advanced colorectal cancer who were given 2 g fish oil daily during the first 9 weeks of chemotherapy showed time-to-tumor-progression was significantly longer for patients receiving fish oil [69]. Two studies with a complete oral nutritional supplement containing the omega-3 fatty acid eicosapentaenoic acid (EPA) given to patients with lung cancer showed improvement in quality of life and physical function [70,71]. While studies are still needed to confirm improvement in clinical outcomes, fish oil remains promising as an important part of overall nutrition management.

Arginine and nucleotides are being studied as immune-supporting ingredients in enteral feeding formulas in surgical and radiation patients. When immunomodulatory enteral formulas were given to patients undergoing cancer surgery, there were positive trends toward enhancing the immune response and reducing post-operative infections [72–77]. A study in cancer patients receiving radiation therapy showed enhanced immune

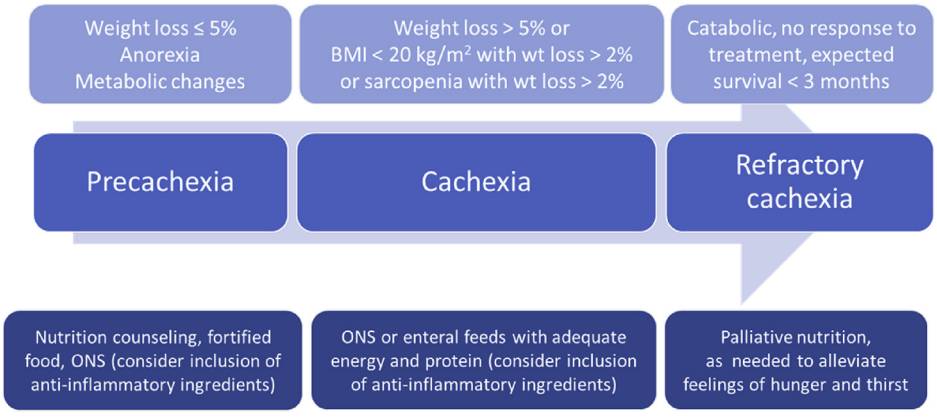

Fig. 4. Medical nutrition care depends on a patient's nutritional and metabolic needs, which are related to cancer stage and nutritional status. Some nutritional strategies can be used across multiple cancer stages. In general, worsening cachexia (with intensifying inflammation) necessitates adjustments in nutritional care. Abbreviations: oral nutritional supplements, ONS; weight, wt.

cell responses in the group treated with immune-enhancing enteral therapy [74]. Meta-analyses of randomized controlled studies have shown that patients undergoing major surgery (including for cancer) have reduced infectious complication rates and lengths of stay in hospital when given an immune enhancing feed rather than a standard isocaloric, isonitrogenous feed [78–81]. This is a promising area of nutritional research; however, further study is needed to provide definitive and clinically meaningful results.

5.7. Realizing the importance of exercise training and physical rehabilitation

Physical activities are included in the new ESPEN guidelines on nutrition and cancer [8]. Endurance and resistance exercises of varying intensities are increasingly recognized as essential anabolic stimuli for maintaining body resources in patients undergoing anticancer treatment, as well as for recovery in survivors of cancer. Activities may be in the form of usual daily grooming, chores, and errands as well as aerobic exercise and resistance training. A systematic review reported evidence supporting aerobic and resistance exercise as effective strategies to improve upper and lower body muscle strength more than usual care [82]. Most of the reviewed studies were done in patients with early stage cancers, in breast and prostate cancers or in tumor-free survivors, so further work is needed to examine effects in more advanced stages.

5.8. Multimodal therapy: putting it all together

Body resources in patients with cancer are endangered by a complex and varying pattern of physical and functional derangements. Therefore, nutritional therapy by itself could be clinically ineffective if other current needs are not addressed. Nutritional therapy should be part of a more comprehensive supportive care, including psychological counseling, optimal pain control, among others. Following this understanding, Fearon et al. introduced the concept of multi-modal therapy for optimal care in patients with cancer [23]. The adverse nutritional effects of tumors (and their treatments) represent potential primary sites for therapeutic intervention—(1) increasing and optimizing nutritional intake, limiting systemic inflammation, and engaging in exercise and activities (Fig. 5) [23]. In the future, nutrition programs will need to be merged with metabolic concepts, exercise programs and other approaches. As multi-modal strategies evolve, we anticipate interactions that will enhance individual effects of each individual treatment modality.

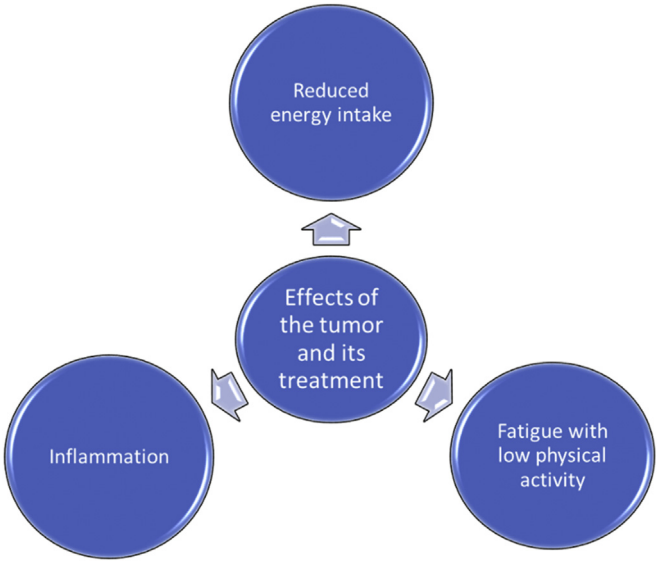

Fig. 5. Three major negative effects of tumors and their treatment. The 3 principal adverse effects represent 3 potential targets for interventions by (1) nutritional support, (2) physical rehabilitation, and (3) anti-inflammatory nutrients or medications.

5.9. Specific nutritional strategies for cancer subgroups

Two subgroups of patients with cancer pose specific nutritional challenges, which call for additional treatment strategies—those undergoing surgery and those nearing end-of-life.

For all patients with cancer who are undergoing either curative or palliative surgery, the perioperative period should be “exploited” to improve long-term outcome [83]. The surgical management of choice follows the strategy of an enhanced recovery after surgery (ERAS) program [84]. Within this program, every patient should be screened for malnutrition, and if deemed at risk, given nutritional therapy [84]. Compliance to the ERAS protocol has been shown to improve survival in patients with colorectal cancer [85]. A special risk group are those with upper gastrointestinal cancer [86]. While early oral feeding is the preferred mode of nutrition, additional nutritional therapy avoids the risk of underfeeding during the postoperative course. Preoperative nutritional therapy is mandatory in patients with severe metabolic risk and can be recommended even for non-malnourished patients, as it has been shown to maintain better nutritional status and reduce the number and severity of postoperative complications [86,87]. With special regard to functionally impaired patients at nutritional risk with neoadjuvant cancer treatment the time period before surgery should be used for “prehabilitation” with physical and nutritional therapy [88].

For patients with cancer who are nearing end of life, dedicated palliative care is appropriate [89]. In end-of-life care, nutrition is tailored to the patient's symptomatic needs and is primarily intended to support comfort and quality of life. While many earlier goals for care are no longer valid (e.g., maintaining energy intake, physical activity), patient feelings of hunger and thirst must still be met [90]. In some settings, patients feel connected to others by the thread of sharing food and drink, even if only in small or in a symbolic way. Optimal patient management in these settings requires sensible education and respectful counseling for patients and families. To this end, meaningful interactions between the patient, caregivers, and the medical team are important to help fulfill each patient's specific needs and thus improve quality of life. There are many ethical considerations concerning food and hydration, so feeding decisions are made with and for each patient in the context of cultural, personal, and religious practices for the patient and his or her family members [90].

6. Take-home messages for cancer nutrition practice and research

Despite numerous advances in treatments and care for people with cancer, malnutrition remains an unresolved issue. In recent guidelines on nutritional care in patients with cancer, ESPEN experts advised practice updates and summarized evidence supporting such advice [8]. At the *Cancer and Nutrition Workshop*, Berlin 2016, our ESPEN expert study group underscored the importance of putting the guidelines into full practice and offered key recommendations for improving nutrition care (Box 2).

Box 2
Call-to-action: improved nutritional care for patients with cancer

- Screen all patients with cancer for nutritional risk early in their course of care, regardless of body mass index and weight history; regularly rescreen nutritional status.
- Increase nutrition assessment to include measures of anorexia, body composition, inflammatory biomarkers (e.g., Glasgow prognostic score), resting energy expenditure, and physical function.
- Use nutritional intervention with individualized plans, including care focused on increasing nutritional intake, decreasing inflammation and hypermetabolic stress, and increasing physical activity.

Statement of authorship

All authors participated in the *Cancer and Nutrition Workshop* in Berlin on October 24 and 25, 2016. The content of this manuscript is based on presentations made and discussions held at that workshop. DNL, PCC, and JA acted as primary reviewers; all authors approved the final version of this article.

Funding source

This work received funding from ESPEN; no other funding was used.

Conflict of interest statement

No authors have direct conflicts of interest to declare in the preparation of this manuscript. The following authors report personal fees, speakers' honoraria (payable to themselves or their institution), expert testimony, research grants, or membership on advisory boards as follows:

- JA: Baxter, B.Braun, Chugai, Fresenius-Kabi, Helsinn, and Nutricia
- HB: Baxter, Nutricia, B.Braun, Hipp Germany, and Fresenius-Kabi
- ND: Abbott Nutrition
- NE: B.Braun, CSL Behring, and Freseius-Kabi
- AL: Abbott Nutrition, B.Braun, Fresenius-Kabi, Nestlé Health Science, Nutricia, and Baxter
- DNL: B.Braun; and personal fees from Baxter Healthcare, Fresenius-Kabi, AbbVie, and Nutricia
- JO: Fresenius-Kabi, Braun Melsungen, and Nutricia Pfrimmer
- MP: Nutricia, Fresenius-Kabi and Berlin Chemie
- FS: Helsinn Healthcare, Mundipharm Medical, PrIME Oncology, Novelpharm, Grünenthal, ISIS Global, Danone Trading, Psioxus Therapeutics, medac, Vifor, Sunstone Capital A/S, Ono Pharmaceutical, Helsinn, Novartis
- AW: Baxter, Danone, BBraun, Berlin Chemie, Fresenius Kabi, Medtronic, Lilly, Nestlé Healthcare Nutrition

Acknowledgments

The authors thank Cecilia Hofmann, PhD, Western Springs, Illinois, USA, for her helpful editorial assistance in preparation of this manuscript.

References

[1] Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. Br J Cancer 2010;102(6):966–71.
[2] Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. Nutrition 2010;26(3):263–8.
[3] Sesterhenn AM, Szalay A, Zimmermann AP, Werner JA, Barth PJ, Wiegand S. [Significance of autopsy in patients with head and neck cancer]. Laryngo-rhinootologie 2012;91(6):375–80.
[4] Hebuterne X, Lemarie E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. J Parenter Enteral Nutr 2014;38(2):196–204.
[5] Planas M, Alvarez-Hernandez J, Leon-Sanz M, Celaya-Perez S, Araujo K, Garcia de Lorenzo A, et al. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES study. Support Care Cancer 2016;24(1):429–35.
[6] Attar A, Malka D, Sabate JM, Bonnetain F, Lecomte T, Aparicio T, et al. Malnutrition is high and underestimated during chemotherapy in gastrointestinal cancer: an AGEO prospective cross-sectional multicenter study. Nutr Cancer 2012;64(4):535–42.
[7] Gyan E, Raynard B, Durand JP, Lacau Saint Guily J, Gouy S, Movschin ML, et al. Malnutrition in patients with cancer. J Parenter Enteral Nutr 2017. http://dx.doi.org/10.1177/0148607116688881 [Epub ahead of print].
[8] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36(1):11–48.
[9] 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.
[10] 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.
[11] Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010;29(2):154–9.
[12] Prado CM, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. Proc Nutr Soc 2016;75(2):188–98.
[13] Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuachalla E, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc 2016;75(2):199–211.
[14] Dev R, Hui D, Chisholm G, Delgado-Guay M, Dalal S, Del Fabbro E, et al. Hypermetabolism and symptom burden in advanced cancer patients evaluated in a cachexia clinic. J Cachexia Sarcopenia Muscle 2015;6(1):95–8.
[15] Tewari N, Awad S, Lobo DN. Regulation of food intake after surgery and the gut brain axis. Curr Opin Clin Nutr Metab Care 2013;16(5):569–75.
[16] Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980;69(4):491–7.
[17] Silva FR, de Oliveira MG, Souza AS, Figueroa JN, Santos CS. Factors associated with malnutrition in hospitalized cancer patients: a cross-sectional study. Nutr J 2015;14:123.
[18] Freijer K, Tan SS, Koopmanschap MA, Meijers JM, Halfens RJ, Nuijten MJ. The economic costs of disease related malnutrition. Clin Nutr 2013;32(1):136–41.
[19] Aaldriks AA, van der Geest LG, Giltay EJ, le Cessie S, Portielje JE, Tanis BC, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol 2013;4(3):218–26.
[20] Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Maeda S, Haraguchi N, et al. Prevalence of malnutrition among gastric cancer patients undergoing gastrectomy and optimal preoperative nutritional support for preventing surgical site infections. Ann Surg Oncol 2015;22(Suppl 3):778–85.
[21] Maasberg S, Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C, et al. Malnutrition predicts clinical outcome in patients with neuroendocrine neoplasias. Neuroendocrinology 2017;104(1):11–25.
[22] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol 2015;33(1):90–9.
[23] Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol 2013;10(2):90–9.
[24] Farhangfar A, Makarewicz M, Ghosh S, Jha N, Scrimger R, Gramlich L, et al. Nutrition impact symptoms in a population cohort of head and neck cancer patients: multivariate regression analysis of symptoms on oral intake, weight loss and survival. Oral Oncol 2014;50(9):877–83.
[25] Gellrich NC, Handschel J, Holtmann H, Kruskemper G. Oral cancer malnutrition impacts weight and quality of life. Nutrients 2015;7(4):2145–60.
[26] Roxburgh CS, McMillan DC. Cancer and systemic inflammation: treat the tumour and treat the host. Br J Cancer 2014;110(6):1409–12.
[27] Laird BJ, Fallon M, Hjermstad MJ, Tuck S, Kaasa S, Klepstad P, et al. Quality of life in patients with advanced cancer: differential association with performance status and systemic inflammatory response. J Clin Oncol 2016;34(23):2769–75.

[28] 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.

[29] 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.

[30] Dantzer R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur J Pharmacol 2004;500(1–3):399–411.

[31] Costa MD, Vieira de Melo CY, Amorim AC, Cipriano Torres Dde O, Dos Santos AC. Association between nutritional status, inflammatory condition, and prognostic indexes with postoperative complications and clinical outcome of patients with gastrointestinal neoplasia. Nutr Cancer 2016;68(7):1108–14.

[32] Tsoli M, Moore M, Burg D, Painter A, Taylor R, Lockie SH, et al. Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice. Cancer Res 2012;72(17):4372–82.

[33] Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 2014;14(11):754–62.

[34] Fukawa T, Yan-Jiang BC, Min-Wen JC, Jun-Hao ET, Huang D, Qian CN, et al. Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. Nat Med 2016;22(6):666–71.

[35] Martinez-Outschoorn UE, Peiris-Pages M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. Nat Rev Clin Oncol 2017;14(1):11–31.

[36] Tsoli M, Robertson G. Cancer cachexia: malignant inflammation, tumorkines, and metabolic mayhem. Trends Endocrinol Metab 2013;24(4):174–83.

[37] McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nat Cell Biol 2014;16(8):717–27.

[38] Patel HJ, Patel BM. TNF-alpha and cancer cachexia: molecular insights and clinical implications. Life Sci 2017;170:56–63.

[39] Bing C. Lipid mobilization in cachexia: mechanisms and mediators. Curr Opin Support Palliat Care 2011;5(4):356–60.

[40] Vaupel P, Höckel M, Mayer A. Detection and characterization of tumor hypoxia using pO_2 histography. Antioxid Redox Signal 2007;9:1221–35.

[41] Renner K, Singer K, Koehl GE, Geissler EK, Peter K, Siska PJ, et al. Metabolic hallmarks of tumor and immune cells in the tumor microenvironment. Front Immunol 2017;8:248.

[42] Vaupel P, Mayer A. The clinical importance of assessing tumor hypoxia: relationship of tumor hypoxia to prognosis and therapeutic opportunities. Antioxid Redox Signal 2015;22(10):878–80.

[43] Walsh JC, Lebedev A, Aten E, Madsen K, Marciano L, Kolb HC. The clinical importance of assessing tumor hypoxia: relationship of tumor hypoxia to prognosis and therapeutic opportunities. Antioxid Redox Signal 2014;21(10):1516–54.

[44] Vaupel P, Mayer A. Tumor hypoxia: causative mechanisms, microregional heterogeneities, and the role of tissue-based hypoxia markers. Adv Exp Med Biol 2016;923:77–86.

[45] Curtis KK, Wong WW, Ross HJ. Past approaches and future directions for targeting tumor hypoxia in squamous cell carcinomas of the head and neck. Crit Rev Oncol Hematol 2016;103:86–98.

[46] Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One 2012;7(5):e37563.

[47] Cushen SJ, Power DG, Teo MY, Maceneaney P, Maher MM, McDermott R, et al. Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. Am J Clin Oncol 2017;40(1):47–52.

[48] Thompson KL, Elliott L, Fuchs-Tarlovsky V, Levin RM, Voss AC, Piemonte T. Oncology evidence-based nutrition practice guideline for adults. J Acad Nutr Diet 2017;117(2):297–310.

[49] Muscaritoli M, Molfino A, Gioia G, Laviano A, Rossi Fanelli F. The "parallel pathway": a novel nutritional and metabolic approach to cancer patients. Intern Emerg Med 2011;6(2):105–12.

[50] Dupuis M, Kuczewski E, Villeneuve L, Bin-Dorel S, Haine M, Falandry C, et al. Age Nutrition Chirugie (ANC) study: impact of a geriatric intervention on the screening and management of undernutrition in elderly patients operated on for colon cancer, a stepped wedge controlled trial. BMC Geriatr 2017;17(1):10.

[51] McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr 2017. http://dx.doi.org/10.1016/j.clnu.2017.05.017 [Epub ahead of print].

[52] Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clin Nutr 2016;35(5):1103–9.

[53] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9(7):629–35.

[54] Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: current concepts and imaging implications. AJR Am J Roentgenol 2015;205(3):W255–66.

[55] Baracos V, Kazemi-Bajestani SM. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. Int J Biochem Cell Biol 2013;45(10):2302–8.

[56] Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. Eur J Clin Nutr 2015;69(10):1079–86.

[57] Brown JC, Harhay MO, Harhay MN. Patient-reported versus objectively-measured physical function and mortality risk among cancer survivors. J Geriatr Oncol 2016;7(2):108–15.

[58] Purcell SA, Elliott SA, Baracos VE, Chu QS, Prado CM. Key determinants of energy expenditure in cancer and implications for clinical practice. Eur J Clin Nutr 2016;70(11):1230–8.

[59] Bozzetti F, Pagnoni AM, Del Vecchio M. Excessive caloric expenditure as a cause of malnutrition in patients with cancer. Surg Gynecol Obstet 1980;150(2):229–34.

[60] Ferriolli E, Skipworth RJ, Hendry P, Scott A, Stensteth J, Dahele M, et al. Physical activity monitoring: a responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? J Pain Symptom Manag 2012;43(6):1025–35.

[61] Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14(8):542–59.

[62] Bozzetti F. Tailoring the nutritional regimen in the elderly cancer patient. Nutrition 2015;31(4):612–4.

[63] Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice-the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr 2008;62(6):687–94.

[64] Guinan EM, Doyle SL, O'Neill L, Dunne MR, Foley EK, O'Sullivan J, et al. Effects of a multimodal rehabilitation programme on inflammation and oxidative stress in oesophageal cancer survivors: the ReStOre feasibility study. Support Care Cancer 2017;25(3):749–56.

[65] Lee JL, Leong LP, Lim SL. Nutrition intervention approaches to reduce malnutrition in oncology patients: a systematic review. Support Care Cancer 2016;24(1):469–80.

[66] Baldwin C. The effectiveness of nutritional interventions in malnutrition and cachexia. Proc Nutr Soc 2015;74(4):397–404.

[67] Engelen MP, Safar AM, Bartter T, Koeman F, Deutz NE. High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. Ann Oncol 2015;26(9):1960–6.

[68] Deutz NE, Safar A, Schutzler S, Memelink R, Ferrando A, Spencer H, et al. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. Clin Nutr 2011;30(6):759–68.

[69] Camargo Cde Q, Mocellin MC, Pastore Silva Jde A, Fabre ME, Nunes EA, Trindade EB. Fish oil supplementation during chemotherapy increases posterior time to tumor progression in colorectal cancer. Nutr Cancer 2016;68(1):70–6.

[70] Sanchez-Lara K, Turcott JG, Juarez-Hernandez E, Nunez-Valencia C, Villanueva G, Guevara P, et al. Effects of an oral nutritional supplement containing eicosapentaenoic acid on nutritional and clinical outcomes in patients with advanced non-small cell lung cancer: randomised trial. Clin Nutr 2014;33(6):1017–23.

[71] van der Meij BS, Langius JA, Spreeuwenberg MD, Slootmaker SM, Paul MA, Smit EF, et al. Oral nutritional supplements containing n-3 polyunsaturated fatty acids affect quality of life and functional status in lung cancer patients during multimodality treatment: an RCT. Eur J Clin Nutr 2012;66(3):399–404.

[72] Hamza N, Darwish A, O'Reilly DA, Denton J, Sheen AJ, Chang D, et al. Perioperative enteral immunonutrition modulates systemic and mucosal immunity and the inflammatory response in patients with periampullary cancer scheduled for pancreaticoduodenectomy: a randomized clinical trial. Pancreas 2015;44(1):41–52.

[73] Song GM, Tian X, Liang H, Yi LJ, Zhou JG, Zeng Z, et al. Role of enteral immunonutrition in patients undergoing surgery for gastric cancer: a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;94(31):e1311.

[74] Talvas J, Garrait G, Goncalves-Mendes N, Rouanet J, Vergnaud-Gauduchon J, Kwiatkowski F, et al. Immunonutrition stimulates immune functions and antioxidant defense capacities of leukocytes in radiochemotherapy-treated head & neck and esophageal cancer patients: a double-blind randomized clinical trial. Clin Nutr 2015;34(5):810–7.

[75] Yildiz SY, Yazicioglu MB, Tiryaki C, Ciftci A, Boyacioglu Z. The effect of enteral immunonutrition in upper gastrointestinal surgery for cancer: a prospective study. Turk J Med Sci 2016;46(2):393–400.

[76] Manzanares Campillo MD, Martin Fernandez J, Amo Salas M, Casanova Rituerto D. A randomized controlled trial of preoperative oral immunonutrition in patients undergoing surgery for colorectal cancer: hospital stay and health care costs. Cir Cir 2016. http://dx.doi.org/10.1016/j.circir.2016.10.029 [Epub ahead of print].

[77] Qiang H, Hang L, Shui SY. The curative effect of early use of enteral immunonutrition in postoperative gastric cancer: a meta-analysis. Minerva Gastroenterol Dietol 2016 [Epub ahead of print].

[78] Osland E, Hossain MB, Khan S, Memon MA. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. J Parenter Enteral Nutr 2014;38(1):53–69.

[79] Braga M, Wischmeyer PE, Drover J, Heyland DK. Clinical evidence for pharmaconutrition in major elective surgery. J Parenter Enteral Nutr 2013;37(5 Suppl.):66S–72S.

[80] Cerantola Y, Hubner M, Grass F, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. Br J Surg 2011;98(1):37–48.
[81] Marimuthu K, Varadhan KK, Ljungqvist O, Lobo DN. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. Ann Surg 2012;255(6):1060–8.
[82] Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment – a systematic review. Crit Rev Oncol Hematol 2013;88(3):573–93.
[83] Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol 2015:213–26.
[84] Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg 2017;152(3):292–8.
[85] Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is associated with 5-year survival after colorectal cancer surgery: a retrospective cohort study. World J Surg 2016;40(7):1741–7.
[86] Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr 2017;36(3):623–50.
[87] Kabata P, Jastrzebski T, Kakol M, Krol K, Bobowicz M, Kosowska A, et al. Preoperative nutritional support in cancer patients with no clinical signs of malnutrition – prospective randomized controlled trial. Support Care Cancer 2015;23(2):365–70.
[88] Minnella EM, Bousquet-Dion G, Awasthi R, Scheele-Bergdahl C, Carli F. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol 2017;56:295–300.
[89] Prevost V, Grach MC. Nutritional support and quality of life in cancer patients undergoing palliative care. Eur J Cancer Care (Engl) 2012;21(5):581–90.
[90] Druml C, Ballmer PE, Druml W, Oehmichen F, Shenkin A, Singer P, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. Clin Nutr 2016;35(3):545–56.