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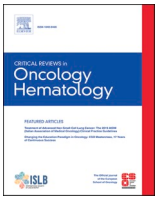

Overcoming barriers to timely recognition and treatment of cancer cachexia: Sharing Progress in Cancer Care Task Force Position Paper and Call to Action

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ABSTRACT

Cachexia is a life-threatening disorder affecting an estimated 50–80% of cancer patients. The loss of skeletal muscle mass in patients with cachexia is associated with an increased risk of anticancer treatment toxicity, surgical complications and reduced response. Despite international guidelines, the identification and management of cancer cachexia remains a significant unmet need owing in part to the lack of routine screening for malnutrition and suboptimal integration of nutrition and metabolic care into clinical oncology practice. In June 2020, Sharing Progress in Cancer Care (SPCC) convened a multidisciplinary task force of medical experts and patient advocates to examine the barriers preventing the timely recognition of cancer cachexia, and provide practical recommendations to improve clinical care. This position paper summarises the key points and highlights available resources to support the integration of structured nutrition care pathways.

1. Introduction

Cachexia is a life-threatening disorder that affects 50–80% of patients with advanced cancer and accounts for up to 20% of cancer deaths (Fearon et al., 2011; Ryan et al., 2016). The hallmark phenotypic feature is a progressive loss of muscle mass that cannot be fully reversed by conventional nutritional support (Fearon et al., 2011). The pathophysiology is characterised by a negative protein and energy balance caused by a variable combination of reduced food intake and metabolic abnormalities (Fearon et al., 2011), including increased catabolism, anabolic resistance, increased energy expenditure, and neurohormonal dysregulation (Prado et al., 2013; Arends et al., 2017; Cederholm et al., 2017).

In contrast to simple malnutrition, cancer cachexia is a physiological adaptation to stress which is driven by a complex interaction between tumour- and patient-related factors (Ryan et al., 2016; Arends et al., 2017; Roeland et al., 2020). Proinflammatory cytokines released by tumour and immune cells activate signalling pathways that induce a

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systemic inflammatory response, leading to increased metabolic demand, depressed appetite, fatigue, increased production of acute phase proteins, and initiation of accelerated muscle protein catabolism (Ryan et al., 2016; Arends et al., 2017; Arends et al., 2017; Muscaritoli et al., 2017). Reduced nutrient intake attributable to tumour-related factors (obstruction, tissue infiltration, malabsorption) or uncontrolled symptoms of cancer or anticancer therapy (pain, nausea, vomiting, diarrhoea, anorexia, dysgeusia) leads to further depletion of body mass (Ryan et al., 2016; Arends et al., 2017; Roeland et al., 2020; Arends et al., 2017). Loss of skeletal muscle mass is associated with reduced physical function (Fearon et al., 2011; Ryan et al., 2016; Prado et al., 2008), poor quality of life (Ryan et al., 2016), increased anticancer treatment toxicity, (Fearon et al., 2011; Ryan et al., 2016; Prado et al., 2007; Prado et al., 2009; Mir et al., 2012; Huillard et al., 2013) increased risk of surgical complications (Lieffers et al., 2012), reduced therapeutic response (Chu et al., 2020; Roch et al., 2020), and reduced survival (Fearon et al., 2011; Ryan et al., 2016; Prado et al., 2008; Peng et al., 2012; van Vledder et al., 2012; Martin et al., 2013; Psutka et al., 2014; Voron et al., 2015; Miyamoto et al., 2015; Blauwhoff-Buskermolen et al., 2016).

Despite the high prevalence and significant adverse clinical consequences of cachexia in patients with cancer, the identification and management of cancer cachexia remains a significant unmet need. Several national and international medical societies have published evidence-based guidelines and expert recommendations aimed at improving nutrition and metabolic care in cancer patients (Box 1) (Fearon et al., 2011; Arends et al., 2017; Roeland et al., 2020; Arends et al., 2017; Muscaritoli et al., 2010; Aapro et al., 2014; Rauh et al., 2018; Jordan et al., 2018; Cederholm et al., 2019; Muscaritoli et al., 2021; Arends et al., 2021); however, integration of nutrition and metabolic care into routine clinical oncology practice has been suboptimal.

In June 2020, Sharing Progress in Cancer Care (SPCC) invited upon suggestion of the two first authors a multidisciplinary task force comprised of experts in medical and surgical oncology, clinical nutrition, palliative and supportive care, cancer rehabilitation, and patient advocacy, all of whom have published in these areas and the majority of whom are members of scientific Societies active in this area to examine the state of the art in the diagnosis and management of cancer cachexia, identify knowledge gaps and research priorities, and provide evidence-based practical recommendations to facilitate early detection and effective management of cachexia in patients with cancer. The aim of the present position paper is to summarise the key points of discussion and highlight available resources to support the integration of structured nutrition care pathways into clinical oncology practice.

2. Definition and Terminology

Several definitions of cachexia have been proposed; however, none has been prospectively evaluated in formal validation studies. An important conceptual foundation was established in a 2010 international consensus guideline committee proposal for an aetiology-based diagnostic framework that distinguished between starvation-related and disease-related malnutrition. (Jensen et al., 2010) The proposed framework established the presence of systemic inflammation as a key distinguishing feature of disease-related malnutrition. Chronic disease-related malnutrition is described as a catabolic state induced by the systemic inflammatory response to disease or trauma, resulting in a rapid depletion of lean body mass that is not amenable to treatment with nutritional intervention alone. According to this aetiology-based definition, cachexia may be considered a form of chronic disease-related malnutrition. Consistent with this view, a European Society for Clinical Nutrition and Metabolism (ESPEN) consensus document on cachexia and precachexia definition stated that “while not all malnourished patients are cachectic, all cachectic patients are invariably malnourished” (Muscaritoli et al., 2010).

In 2011, an international consensus group published a provisional cancer-specific definition that described cancer cachexia as a multifactorial disorder characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. (Fearon et al., 2011) In contrast to the conventional view of cachexia as an end-stage condition in patients with advanced cancer, the 2011 consensus definition described cancer cachexia as a continuum with three clinically distinct stages (Table 1). A limitation of the provisional definition is the lack of criteria related to the underlying pathophysiology, thereby limiting diagnostic sensitivity and specificity.

More recently, a joint task force comprised of representatives from four major clinical nutrition societies (GLIM, Global Leadership Initiative on Malnutrition) published global consensus criteria for the diagnosis of malnutrition in the clinical setting (Table 2). (Cederholm et al., 2019) According to the proposed scheme, the diagnosis is based on three phenotypic criteria (non-volitional weight loss, low body mass index

Box 1
Summary of relevant guidelines, expert recommendations, and position papers from international medical societies and consensus groups.

- 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"(Muscaritoli et al., 2010)
- Definition and classification of cancer cachexia: an international consensus(Fearon et al., 2011)
- Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force (Aapro et al., 2014)
- ESPEN guidelines on nutrition in cancer patients(Arends et al., 2017)
- ESPEN expert group recommendations for action against cancer-related malnutrition(Arends et al., 2017)
- Nutrition in patients with cancer: a new area for medical oncologists? A practising oncologist’s interdisciplinary position paper(Rauh et al., 2018)
- European Society for Medical Oncology (ESMO) position paper on supportive and palliative care(Jordan et al., 2018)
- GLIM criteria for the diagnosis of malnutrition—A consensus report from the global clinical nutrition community(Cederholm et al., 2019)
- From guidelines to clinical practice: a roadmap for oncologists for nutrition therapy for cancer patients(Muscaritoli et al., 2019)
- Management of Cancer Cachexia: ASCO Guideline(Roeland et al., 2020)
- ESPEN practical guideline: Clinical nutrition in cancer(Muscaritoli et al., 2021)
- Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines(Arends et al., 2021)

ASCO, American Society of Clinical Oncology; GLIM, Global Leadership Initiative on Malnutrition; ESMO, European Society for Medical Oncology; ESPEN, European Society for Clinical Nutrition and Metabolism.

Table 1
Diagnostic criteria for cancer cachexia according to Fearon et al.[1].

Precachexia	Cachexia	Refractory Cachexia
▪ ≤ 5% weight loss in the last 6 months ▪ Anorexia and metabolic change	▪ > 5% weight loss in the last 6 months *or* ▪ > 2% weight loss in the last 6 months and BMI < 20 kg/m^2 *or* ▪ > 2% weight loss in the last 6 months and sarcopenia Reduced food intake and systemic inflammation are common	▪ Procatabolic disease, unresponsive to anticancer treatment ▪ Low performance score ▪ Expected survival < 3 months

BMI=body mass index.

[BMI], reduced muscle mass) and two aetiologic criteria (reduced intake or assimilation, inflammation). The combination of at least one phenotypic criterion and one aetiologic criterion is required for a diagnosis of malnutrition. Cachexia is defined as a subtype of disease-related malnutrition, distinguished from simple starvation by an inflammatory aetiology which, in turn, is responsible for metabolic changes. Low BMI is not a mandatory criterion for the diagnosis of cachexia, reflecting the fact that clinically significant changes in body composition can occur even in subjects with normal or elevated BMI.

Since for decades, disagreement on the definitions of malnutrition and subtypes has hampered harmonization of clinical cachexia research, we advise to accept and implement these GLIM criteria in daily practice and research projects. This will allow comparability of observations and of results obtained on a global scale and finally open a path to much needed progress in this area.

While a common limitation of these and other definitions, the absence of criteria that capture the impact of symptoms, decreased quality of life, or impaired physical activity requires further study. (Roeland et al., 2020) Formally evaluating criteria based on quality of life and patient-reported symptoms such as reduced muscle strength, fatigue, and anorexia, may allow refining diagnostic criteria in the future.

In the absence of a globally recognised definition of cachexia, the following concepts provide a useful framework to guide the clinical evaluation of nutritional and metabolic status. First, cancer cachexia differs markedly from starvation-related malnutrition both in terms of aetiology and the typical nutritional and metabolic profiles (Table 3). (Arends, 2008) Second, cancer cachexia is a continuum with stages that range from precachexia to refractory cachexia. In precachexia, early clinical and metabolic signs (e.g., appetite loss, presence of inflammation, glucose intolerance) may precede evidence of weight loss. Finally, assessment of body composition is critically important in the evaluation of metabolic status. Measurement of body weight alone does not account for occult changes in muscle mass or excessive fluid loads and does not allow for a reliable differential diagnosis of cachexia or starvation-related malnutrition (it should be noted that cachexia and starvation-related malnutrition can coexist in certain patients).

We envision exploitation of routinely acquired computed tomography (CT) images to assess body composition in the near future. This will represent a particularly expedient approach, as it provides an opportunity to collect clinically relevant data regarding nutritional and metabolic status in cancer patients—namely, muscle mass and radiodensity as well as visceral and subcutaneous adipose tissue—at little additional cost. (Blanc-Durand et al., 2020; Wochner et al., 2020).

3. Barriers to integration of nutrition and metabolic care in clinical oncology practice

Despite the ubiquity of cancer cachexia and the clear association with poor clinical outcomes, nutrition care in cancer patients remains inadequate because of insufficient awareness among oncologists and other healthcare providers (Muscaritoli et al., 2015; Muscaritoli et al., 2016; Caccialanza et al., 2016; Caccialanza et al., 2016; Muscaritoli et al., 2019). A 2015 survey of Italian oncologists found that only 28% routinely integrated nutrition assessment and support into patient care and 49% indicated that nutrition assessment was either never performed or performed only upon patient request (Caccialanza et al., 2016). More recently, a survey of European cancer survivors found that 73% experienced feeding problems and 70% lost weight during their illness. (Muscaritoli et al., 2019) However, only 35% of respondents reported that weight was regularly measured during oncology visits and more than half indicated that their feeding status was never evaluated. In addition, only 8% of respondents reported receiving information regarding cachexia. Similar observations have been reported from France (Attar et al. Nutr Cancer 2012) and in a recent survey among 300 Italian medical oncologists (Muscaritoli M, Corsaro E, Molfino A. Awareness of Cancer-Related Malnutrition and Its Management: Analysis of the Results From a Survey Conducted Among Medical Oncologists. Front Oncol. 2021;11:682999).

A variety of factors have been identified as barriers to integration of nutrition care in routine clinical oncology practice, including low

Table 3
Distinguishing features of starvation-related malnutrition and cancer cachexia.

	Starvation	Cancer Cachexia
Energy intake	↓	↓
Energy expenditure	↓/=	↑/=
Appetite	↑	↓
Mobility	Maintained	↓
Metabolic pattern	Ketosis	Systemic inflammation
Insulin level	↓	↑
Glucose level	↓	↑
Protein loss	Minimal	↑

Adapted from Arends 2008 (Arends, 2008).

Table 2
Global consensus criteria for the diagnosis of malnutrition. (Cederholm et al., 2019)* .

Phenotype		Aetiology	
Body weight	> 5% within the past 6 months *or* > 10% beyond 6 months	Reduced food intake or assimilation‡	50% of energy requirement for > 1 week *or* any reduction for > 2 weeks *or*
BMI, kg/m^2	< 20 (<70 years) *or* < 22 (>70 years) Asia: < 18.5 (<70 years) *or* < 20 (>70 years)		any chronic GI condition that adversely affects food assimilation or absorption
Muscle mass	Reduced muscle mass† (low appendicular skeletal muscle index or appendicular lean mass)	Inflammation¶	Acute disease/injury or chronic disease-related inflammation

*A combination of at least one phenotypic criterion and one aetiologic criterion is required for a diagnosis of malnutrition.
†Based on validated body composition measurement techniques (dual-energy absorptiometry, bioimpedance analysis, CT, MRI).
‡Symptoms that can impair food intake or absorption (e.g., dysphagia, nausea, vomiting, diarrhoea, constipation) should be considered as supportive indicators.
¶C-reactive protein may be used as a supportive laboratory measure.
BMI, body mass index; GI, gastrointestinal.

awareness (Muscaritoli et al., 2019; Spiro et al., 2006; Martin et al., 2016; Caccialanza et al., 2020), inadequate training in complex nutritional management both at the level of medical schools (Cuerda C, Muscaritoli M, Krznaric Z, et al.; endorsed by the ESPEN Council. Nutrition education in medical schools (NEMS) project: Joining ESPEN and university point of view. Clin Nutr. 2021;40:2754–2761) and postgraduate training (Spiro et al., 2006; Martin et al., 2016), limited institutional resources and time constraints (Caccialanza et al., 2016; Spiro et al., 2006; Martin et al., 2016), lack of standard operating procedures and of clearly defined responsibilities, inconsistent terminology and definitions (Muscaritoli et al., 2019), insufficient collaboration between oncologists and clinical nutrition specialists (Caccialanza et al., 2016), lack of consensus regarding validated diagnostic criteria, (Caccialanza et al., 2016) the misconception that cachexia identifies advanced or even end-of life patients (Muscaritoli et al., 2017), limited evidence from randomised controlled trials to guide therapeutic management (Martin et al., 2016), and a widespread lack of reimbursement for nutrition assessment, counselling, and oral nutrition supplements (ONS).

Based on these factors, the SPCC task force identified several opportunities to improve awareness and facilitate integration of cachexia care (in general) and nutrition care (as part of cachexia care) into routine clinical oncology practice:

- Harmonisation of terms and definitions (malnutrition, cachexia, sarcopenia, sarcopenic obesity) by following GLIM criteria
- Incorporation of teaching of clinical nutrition and common nutrition-related comorbidities in medical schools as well as postgraduate oncology training curricula
- Development of clear, practical algorithms for multidisciplinary nutrition care in the oncology setting: screen, assess, intervene, and monitor
- Establishing reliable multidisciplinary, multiprofessional structures within cancer units to ensure implementation of standard operating procedures of nutritional care
- Continued advocacy of multidisciplinary collaboration and organizing continuing training in clinical nutrition and metabolism for all disciplines involved
- Execution of appropriately powered, randomised, controlled trials evaluating the effect of nutritional interventions on well-defined oncological and economic outcomes in patients with precachexia and cachexia

With respect to reimbursement, ICD-10 codes for different grades of malnutrition and cachexia are available, allowing clinicians to specify malnutrition-based diagnoses for billing purposes. However, nutrition interventions such as ONS are generally not reimbursed. Progress in this area is contingent upon demonstrating a clinically meaningful benefit in randomised controlled trials.

4. Early detection

Historically, cancer cachexia has been perceived as a terminal condition and thus a palliative care issue. Coupled with the paucity of evidence of a clinical benefit for specific nutrition interventions, this has led to the common view among oncologists that there is no compelling clinical rationale for routine evaluation for the presence of cachexia at initial presentation or in patients undergoing active anticancer treatment. However, several lines of evidence suggest an urgent need for a contemporary reassessment of this conventional perspective.

4.1. Cachexia as defined above is highly prevalent among cancer patients at the time of initial presentation. (Muscaritoli et al., 2017; Martin et al., 2013)

A prospective multicentre study in 1952 cancer patients showed that 50% had cachexia at the first medical oncology visit, including 46% of patients with non-metastatic disease (Fig. 1) (Muscaritoli et al., 2017). Assessment for precachexia (metabolic derangements and nutrition impact symptoms preceding overt weight loss) in a subset of patients (n = 1085) showed that 17% met the criteria for precachexia based on the 2011 consensus definition, with the prevalence ranging from 3% to 29% across the various primary tumour sites. In a separate study, retrospective analysis of CT images obtained for initial cancer diagnosis or staging in 1473 patients showed that 41% had skeletal muscle index values consistent with sarcopenia and 53% had low muscle attenuation (Martin et al., 2013), both associated with deterioration of clinical outcome.

4.2. Low muscle mass is an independent predictor of dose-limiting treatment toxicity. (Prado et al., 2007; Prado et al., 2009; Mir et al., 2012; Huang et al., 2020).

Studies in patients with a variety of tumour types have demonstrated a significant interaction between low skeletal muscle mass and dose-limiting toxicity.(Prado et al., 2008; Huang et al., 2020; Antoun et al., 2010) The increased toxicity observed in patients with low muscle mass may be attributable in part to the conventional practice of dosing cytotoxic drugs according to body surface area (BSA), which has been shown to be poorly correlated with muscle mass. (Huang et al., 2020; Stobaus et al., 2013) Crucially, dosing based on BSA does not account for variability in the lean tissue compartment or the corresponding effect on drug metabolism, thus leading to possible over-dosing of chemotherapy in patients with low muscle mass. (Prado et al., 2016; Anandavadivelan et al., 2016) Of note, the recent revision of the ASCO guidelines on therapy dosing of obese patients does not discuss the complicating factor of cachexia in obese patients (Appropriate Systemic Therapy Dosing for.

Obese Adult Patients With Cancer: ASCO Guideline Update. Griggs JJ et al.

J Clin Oncol. 2021 Jun 20;39(18):2037–2048. doi: 10.1200/JCO.21.00471. PMID: 33939491).

4.3. Loss of muscle mass is a strong independent predictor of survival (Prado et al., 2008; van Vledder et al., 2012; Martin et al., 2013; Miyamoto et al., 2015)

Evaluation of prognostic variables in 1473 patients with lung or gastrointestinal cancer showed that skeletal muscle depletion is a powerful predictor of survival, regardless of BMI. (Martin et al., 2013) In the same study, a multivariable model comprised of BMI, weight loss, muscle index, and muscle attenuation predicted overall survival better than a conventional prognostic model comprised of age, cancer diagnosis, performance status, and tumour stage. Of note a cancer specific grading scheme for weight loss which incorporates both reduced BMI and loss of body weight has been validated (Martin et al., 2015; J Clin Oncol).

4.4. Early identification of cachexia allows proactive intervention to ensure optimal conditions for anticancer treatment (Minnella et al., 2018; De Waele et al., 2015; Solheim et al., 2017)

Nutritional support combined with exercise training improves perioperative functional capacity during neoadjuvant therapy in patients planned for esophagogastric surgery. (Minnella et al., 2018) In addition, the findings from a randomised controlled pilot study in newly diagnosed cachectic cancer patients suggest that early nutrition-centred support may improve evolution of body weight during anticancer

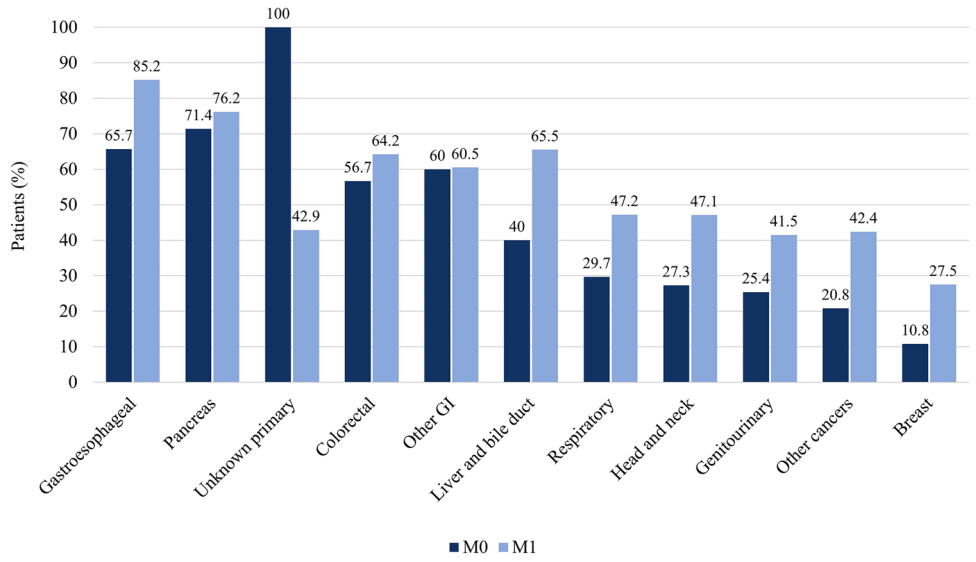

Fig. 1. Prevalence of cachexia by primary tumour type (N = 1952).* Footnotes:*Cachexia defined as weight loss > 5% or weight loss > 2% to ≤ 5% and BMI < 20 kg/m2. BMI, body mass index; M0, stage I–III; M1, stage IV.
Reprinted with permission from Muscaritoli et al. (2017).

treatment. (De Waele et al., 2015) Another randomised controlled study in patients with advanced lung or pancreatic cancer showed that combining metabolic and nutritional interventions improved body weight compared with standard care. (Solheim et al., 2017) Early nutritional assessment and interventions to improve energy and protein intake have been suggestive of improving clinical outcome in cancer patients (Trestini I et al. Eur J Clin Nutr 2018; Bargetzki L et al. Ann Oncol 2021). Finally, evidence suggests that even patients with advanced cancer have exploitable anabolic potential during the early stages of the disease trajectory, creating a window of opportunity for intervention to attenuate or reverse cachexia. (Prado et al., 2013).

Collectively, these findings militate against the prevailing view of cachexia as a mere palliative care issue and demonstrate the need for full integration of nutrition care as a parallel pathway (Muscaritoli et al., 2011), coincident with oncologic therapy from the time of diagnosis. Oncologists should be aware of the profound clinical implications of cachexia and seek to proactively identify the earliest signs. Current evidence-based nutrition guidelines recommend screening for nutrition risk in all cancer patients, followed by a comprehensive nutrition assessment when risk is present (Arends et al., 2017; Arends et al., 2017; Thompson et al., 2017). Comprehensive nutrition assessment should include evaluation of energy and protein intake, potential barriers to intake (including those related to cancer, cancer treatment, and concomitant conditions), body weight, body composition, inflammatory biomarkers, resting energy expenditure, and physical function (Arends et al., 2017; Muscaritoli et al., 2019).

A variety of instruments and techniques may be used to measure body composition, including dual x-ray absorptiometry, bioimpedance analysis, CT imaging, and anthropometry. Analysis of cross-sectional CT images at the third lumbar vertebra has been validated as a measure of whole body skeletal muscle and adipose tissue (Mourtzakis et al., 2008; Shen et al., 2004). Computed tomography scans obtained as part of routine cancer care can therefore be used to assess body composition and inform prognostication and clinical management. While analysis of CT images requires considerable time and technical expertise, automated body composition analysis of CT scans is becoming increasingly available (Lee et al., 2017; van Seventer et al., 2020). Further research is required to validate emerging analytic techniques and identify the thresholds for measures of skeletal muscle mass that define sarcopenia for specific patient populations.

Systemic inflammation is activated frequently in cancer patients [#58: McMillan DC. Cancer Treat Rev 2013] and clinically highly relevant because it is associated with catabolism and anabolic resistance [Baracos V et al. Nat Rev Dis Primers 2018]. The extent of systemic inflammation can be estimated by measuring serum C-reactive protein (CRP) and albumin (Arends et al., 2017). The modified Glasgow Prognostic Score (mGPS) is a practical instrument that quantifies systemic inflammation according to a composite score based on serum concentrations of CRP and albumin (McMillan, 2013; Laird et al., 2013). The mGPS has been extensively validated in medical and surgical oncology patients and has been shown to be highly predictive of morbidity and mortality (Arends et al., 2017; McMillan, 2013; Laird et al., 2013). There are other simple and reliable prognostic instruments which serve as surrogate markers of both nutritional status and systemic inflammation, e.g. the Prognostic Nutritional Index (PNI) based on serum albumin and absolute lymphocyte count (Bruixola et al., 2017; Bossi, 2018). The PNI is an independent predictor of clinical outcomes in patients with various types of cancer, including head and neck (Bruixola et al., 2017) lung, (Gul et al., 2020) liver, (Chan et al., 2015) and colon (Maruyama et al., 2020). as well as of treatment toxicity in patients with head and neck cancer undergoing radiation therapy (Kono et al., 2017). This suggests that simple assessment of the inflammatory state can facilitate identification of patients at risk and allow early intervention with nutritional support and/or modification of the planned treatment regimen to improve clinical outcome.

Optimally, evaluation and monitoring of nutritional and metabolic status should occur as part of an integrated nutrition care pathway and involve routine collaboration with a clinical nutrition specialist. However, the identification of patients with precachexia is within the clinical expertise of oncologists (Muscaritoli et al., 2017; Aapro et al., 2014). In a study evaluating the prevalence of cachexia at the first medical oncology visit in 22 centres, screening and assessment of nutritional status was performed exclusively by oncologists using validated instruments, demonstrating the feasibility of incorporating nutritional and metabolic assessment into routine clinical oncology practice (Muscaritoli et al., 2017).

5. Obesity in cancer

Obesity is a chronic metabolic disease characterised by abnormal adiposity (World Health Organization, 2020) Consistent with trends in the general population, obesity is an increasingly prevalent condition in

patients with cancer. According to published estimates, 40–60% of cancer patients meet the criteria for pre-obesity (BMI 25–30 kg/m^2) or obesity (BMI > 30 kg/m^2) at the time of cancer diagnosis (Ryan et al., 2016; Prado et al., 2016).

There is now a substantial body of evidence establishing a direct link between obesity and several types of cancer (Ryan et al., 2016; World Cancer Research Fund/American Institute for Cancer Research, 2007) While the underlying mechanisms are not fully understood, metabolic patterns play a major role and potential contributing factors include chronic inflammation, elevated oestrogen concentration, insulin resistance, leptin resistance, and altered immune response (National Cancer Institute, 2020.).

Cancer cachexia is an often overlooked condition in patients with obesity, as high adiposity can obscure loss of muscle mass (Prado et al., 2016). The term sarcopenic obesity has been used to describe the combination of low muscle mass and high adiposity. Sarcopenic obesity is an increasingly prevalent abnormal body composition phenotype among cancer patients and a strong independent predictor of poor outcomes (Prado et al., 2008; Prado et al., 2016). Although cachexia is frequently perceived as a condition characterised by weight loss and low body weight, sarcopenia and cachexia can manifest at any given BMI and body weight (Prado et al., 2016). Indeed, marked differences in skeletal muscle mass may be observed between patients with identical weight or BMI. Similarly, patients with substantially different weight or BMI can have an identical amount of muscle mass (Prado et al., 2016).

The variability between muscle mass and body mass underscores the fundamental importance of assessing body composition rather than relying solely on BMI or weight as an indicator of nutritional and metabolic status. In addition, the variability between BSA and lean body mass has important implications for dosing of cytotoxic therapy in patients with sarcopenic obesity (Prado et al., 2016; Anandavadivelan et al., 2016). Low muscle mass and progressively increasing or excess adipose tissue may result in decreased clearance of cytotoxic drugs, leading to an increased risk of dose-limiting toxicity. Future dose-escalation studies should evaluate the effect of individualised dosing of cytotoxic therapy according to lean body mass on tolerability and treatment response.

Finally, cancer patients with obesity warrant special consideration in terms of nutrition counselling. Clinicians should be aware that compliance with nutritional interventions aimed at attenuating cachexia may be poor, as weight loss is often regarded as favourable by patients with obesity. Proactive education regarding the adverse consequences of further depletion of lean body mass and regular monitoring of body composition are vitally important to ensure optimal compliance.

6. Cachexia and Immunotherapy

Cancer immunotherapy is a rapidly evolving field, with advances in technology fuelling a rapid proliferation of novel therapeutic targets and biologic therapies (Marshall and Djamgoz, 2018). While the development of biologic agents targeting pathways involved in immune response has led to marked improvements in outcomes in multiple cancers, the identification of biomarkers that reliably predict response to immunotherapeutic agents has proven to be an elusive goal. Notably, recent studies evaluating potential predictors of treatment response have yielded a growing body of evidence suggesting an interaction between cachexia and immunotherapeutic response. These potentially relevant connections, however, are not yet represented in clinical practice guidelines.

Initial evidence of a potential interaction between cachexia and immunotherapy was reported in an analysis of three trials evaluating pembrolizumab in patients with melanoma or non-small cell lung cancer (NSCLC) (Turner et al., 2018). Analysis of overall survival showed no evidence of a dose response at doses ranging from 2 to 10 mg/kg; however, a strong association was observed between pembrolizumab clearance and overall survival, with a 15-month overall survival advantage among patients with slower baseline catabolic clearance. The relationship between increased pembrolizumab clearance and reduced overall survival paralleled markers of cachexia severity such as weight loss and serum albumin. Similar exposure–response confounding has been reported with other monoclonal antibodies, including trastuzumab (Cosson et al., 2014), ipilimumab (Schadendorf et al., 2015), and nivolumab (Bajaj et al., 2017), raising the possibility of a common source of confounding involving a correlation between cachexia and increased clearance (Turner et al., 2018). Catabolic mediators associated with cachexia constitute the primary elimination route of IgG monoclonal antibodies (Turner et al., 2018; Ryman and Meibohm, 2017); therefore, the hypercatabolic state in patients with cachexia may result in rapid catabolism of monoclonal antibodies, leading to increased clearance and reduced treatment response. (Turner et al., 2018; Ryman and Meibohm, 2017).

Additional evidence of a potential interaction between cachexia and immunotherapy was reported in a recent retrospective study in patients with metastatic melanoma who were treated with ipilimumab (Chu et al., 2020). Multivariable analysis of outcomes showed that low skeletal muscle density on pre-treatment CT images was an independent predictor of poor treatment response. In addition, a significant association was observed between myosteatosis on CT images and systemic inflammation as measured by the neutrophil-to-lymphocyte ratio. A separate study in patients with NSCLC who were treated with either pembrolizumab or nivolumab showed that patients with pre-treatment cachexia had shorter overall survival and a lower probability of achieving disease control than those without pre-treatment cachexia (Roch et al., 2020). Loss of muscle mass during treatment had a similar effect, with shorter progression-free survival and reduced overall survival observed in patients with a $\geq$ 5% decline in skeletal muscle index compared to those with a < 5% decline. Finally, multivariable analysis of data from 300 patients with NSCLC who received immunotherapy found a significant independent relationship between cachexia severity rated according to a validated cachexia scale (0 [precachexia] to 4 [refractory cachexia]) and overall survival (Turcott et al., 2020).

In addition to the potential effect on the pharmacokinetics of immunotherapeutic agents, cachexia may affect immunotherapeutic response by exerting a direct effect on the tumour microenvironment. A prospective study in patients with colorectal cancer showed a significant association between low skeletal muscle density and reduced expression of CD83 and CCR7 on circulating dendritic cells, suggesting a direct relationship between skeletal muscle depletion and impairment of critical signalling pathways involved in the maturation and migration of antigen-presenting dendritic cells (Malietzis et al., 2016).

While immunological therapies are increasingly incorporated into a broadening range of oncological and hematological malignancies, lack of adequate understanding of interactions and dependencies between and among nutritional, metabolic and immunological processes, represents an important and probably highly relevant gap in modern clinical cancer care.

7. Surgical oncology

It is well established that poor nutritional status is associated with an increased risk of surgical complications, including infection, wound dehiscence, anastomotic leak, septicaemia, renal dysfunction, and hepatic failure (Huisman et al., 2016; Lobo et al., 2020). In addition, studies in patients undergoing oncological surgery have shown that radiologically determined preoperative sarcopenia is an independent predictor of both severe postoperative complications and mortality (Weerink et al., 2020).

In oncology, surgical intervention is frequently part of multimodal treatment that includes neoadjuvant and adjuvant chemotherapy and/or radiation therapy. Preoperative nutritional status is often compromised by neoadjuvant therapy, leading to an increased risk of poor surgical outcomes and a reduced ability to tolerate adjuvant therapy

(Eriksson et al., 2017; Motoori et al., 2018; Ishida et al., 2019). In a study evaluating the effect of neoadjuvant chemotherapy in patients with colorectal cancer undergoing surgical resection of liver metastases, skeletal muscle mass decreased by a median of 5.5% during neoadjuvant chemotherapy (Eriksson et al., 2017). Notably, patients with a $>5\%$ reduction in skeletal muscle mass during neoadjuvant chemotherapy were significantly less likely to undergo adjuvant chemotherapy after surgery compared to those with a $\leq 5\%$ reduction. In addition, studies in patients with oesophageal cancer undergoing esophagectomy have shown that depletion of skeletal muscle mass during neoadjuvant chemotherapy is associated with an increased risk of postoperative infectious complications (Motoori et al., 2018; Ishida et al., 2019).

A recent prospective study in patients with gastroesophageal cancer showed that placement of a feeding jejunostomy and provision of enteral nutrition (EN) during neoadjuvant therapy significantly reduced the risk of developing sarcopenia, suggesting that nutritional support during neoadjuvant therapy can improve preoperative nutritional status (Voisinet et al., 2020). Other approaches aimed at optimising the conditions for oncological surgery are currently under evaluation. Multimodal prehabilitation therapy is an emerging strategy based on evidence that postoperative outcomes in surgical oncology patients are influenced by preoperative factors such as functional capacity, nutritional state, psychological state, and smoking behaviour (van Rooijen et al., 2019). This approach employs targeted interventions during the preoperative period to proactively address factors associated with postoperative outcomes. Pilot studies in patients with colorectal and gastroesophageal cancer have shown improvement in postoperative functional capacity following multimodal prehabilitation (Minnella et al., 2018; Minnella et al., 2017). Based on these findings, an international randomised controlled trial is currently underway to evaluate a multimodal prehabilitation programme consisting of exercise training, nutrition supplements, smoking cessation, and psychological support in patients with colorectal cancer (van Rooijen et al., 2019). The results of the trial are eagerly anticipated and will likely inform the design of subsequent trials to determine the optimal type, frequency, and duration of the various interventions.

Interestingly, current ESPEN guidelines on nutrition in cancer patients indicate that all patients undergoing either curative or palliative surgery should be managed within an enhanced recovery after surgery (ERAS) programme that aims to minimise the metabolic response to surgery through optimised nutritional and metabolic care (Arends et al., 2017). Nutritional components of ERAS include avoiding fasting, preoperative fluid and carbohydrate loading, and commencement of oral intake on the first postoperative day. Efforts should be made in order to overcome barriers to the routine implementation of ERAS in surgical oncology (Hasil L, Fenton TR, Ljungqvist O, Gillis C. From clinical guidelines to practice: The nutrition elements for enhancing recovery after colorectal surgery. Nutr Clin Pract. 2021 Aug 2).

8. Treatment

The clinical management of cancer cachexia represents a distinct challenge owing to the multifactorial aetiology and the limited evidence of a consistent clinical benefit from specific interventions. Moreover, the metabolic component of cachexia makes it substantially different from starvation-related malnutrition. In contrast to starvation-induced nutritional deficits, the metabolic consequences of the systemic inflammatory response induced by tumour- and host-derived factors cannot be fully reversed by nutritional interventions alone (Fearon et al., 2011; Arends et al., 2017; Arends et al., 2017) Nonetheless, a recent international multicentre study clearly demonstrated the association of reduced food intake with cancer-associated weight loss and overall survival (Martin L, Muscaritoli M, Bourdel-Marchasson I, Kubrak C, Laird B, Gagnon B, Chasen M, Gioulbasanis I, Wallengren O, Voss AC, Goldwasser F, Jagoe RT, Deans C, Bozzetti F, Strasser F, Thoresen L, Kazemi S, Baracos V, Senesse P. Diagnostic criteria for cancer cachexia: reduced food intake and inflammation predict weight loss and survival in an international, multi-cohort analysis. J Cachexia Sarcopenia Muscle. 2021 Aug 27). Thus, nutritional support is a vital component of treatment, as further depletion of lean body mass cannot be prevented without adequate intake of energy and protein substrates. While the paucity of high-quality evidence must be acknowledged, existing evidence supports tailored nutritional intervention according to nutritional and metabolic status.

8.1. Treatment goals and principles

A major aim of nutrition care in cancer patients is to optimise the conditions for effective anticancer treatment. The goals of nutrition and metabolic interventions are to maintain sufficient energy and protein intake, mitigate metabolic derangements, maintain physical activity to preserve muscle mass and function, reduce the risk of reduction or interruption of anticancer treatment, and improve quality of life (Arends et al., 2017).

Treatment should be guided by the following principles:

1. *Multimodality*. Given the complex and multifactorial nature of cancer cachexia, it is reasonable to assume that effective management will require a multimodal treatment strategy.
2. *Early intervention*. Because cachexia is characterised by progressive activation of catabolic drivers, initiating diagnosis and treatment as early as possible should be a priority. Progressive anabolic resistance is also a characteristic feature of cachexia; accordingly, early intervention with the aim of preventing muscle loss represents a more logical therapeutic strategy than attempting to regain lost muscle mass (Aapro et al., 2014; Muscaritoli et al., 2019).
3. *Individually tailored management according to the aetiology and severity of malnutrition and cachexia*. Clinical management should be guided by the dominant underlying cause of changes in weight and body composition as well as the stage and severity of cachexia (Aapro et al., 2014).
4. *Comprehensive care*. Integration of nutrition support into routine cancer care facilitates early identification and proactive management of metabolic and nutrition-related conditions that can limit or preclude effective anticancer treatment.
5. *Multidisciplinary collaboration*. Optimal patient care requires routine collaboration between various professional disciplines, including oncology, clinical nutrition, palliative and supportive care, cancer rehabilitation, and patient advocacy (Arends et al., 2017; Muscaritoli et al., 2017; Muscaritoli et al., 2011).

Current ESPEN (Arends et al., 2017) and ESMO (Arends et al., 2021) guidelines on nutrition and cachexia in cancer patients indicate that energy and protein substrate requirements should be met in all cancer patients except those receiving end-of-life care by offering nutrition interventions ranging from counselling to parenteral nutrition (PN) [Arends J et al. ESMO Open 2021] (Arends et al., 2017). In general, patients should receive 25–30 kcal/kg/day and at least 1 g/kg/day of protein. Energy intake should be adjusted to 20–25 kcal/kg/day for patients who are bedridden. Vitamins and minerals should be supplied in amounts consistent with the recommended daily allowances for healthy individuals.

Nutrition care should be accompanied by exercise training to promote anabolism and reduce catabolism and thereby preserve muscle mass and function (Arends et al., 2017). Evidence from randomised trials suggests that physical activity is safe and well tolerated in patients with various types and stages of cancer (Jones and Alfano, 2013; Oldervoll et al., 2011; Lowe et al., 2009). A systematic review of randomised controlled studies evaluating the effect of exercise in patients with cancer concluded that aerobic and resistance exercise improves upper and lower body muscle strength compared with usual care (Stene et al., 2013). Notably, most studies were performed in patients with early stage

disease or in cancer survivors; evidence regarding the effect of exercise in patients with advanced disease is less robust and requires further study.

In general, nutrition care should be tailored according to the stage of cachexia and individual clinical circumstances.

8.2. Precachexia: Nutrition counselling and oral nutrition support

Nutrition counselling by a registered dietician or nutritionist includes ascertainment of energy and nutrient needs, establishment of nutrition goals, discussion of dietary strategies, and management of nutrition impact symptoms such as anorexia, nausea, dysphagia, diarrhoea, constipation, and pain (Arends et al., 2017; Roeland et al., 2020; Arends et al., 2017; Muscaritoli et al., 2017). Nutrition impact symptoms are optimally managed by healthcare practitioners with an expertise in supportive and palliative care with the involvement of a supportive/-palliative care team. Oral nutrition support includes fortified foods as either meals or snacks and ONS to meet any remaining nutritional deficits (Arends et al., 2017; Arends et al., 2017).

Meta-analyses of studies evaluating nutrition counselling and/or ONS in cancer patients have reported evidence of improved quality of life (Baldwin et al., 2012) and increased body weight (de van der Schueren et al., 2018). In addition, a subset analysis of studies evaluating high-protein ONS enriched with omega-3 fatty acids showed that omega-3 enriched ONS were associated with increased body weight and reduced muscle loss compared to isocaloric controls.

8.3. Cachexia: ONS and EN

A systematic literature review of five studies evaluating nutrition counselling in patients with advanced cancer and cachexia reported potential improvements in weight and energy intake (Balstad et al., 2015); however, limitations in study design and data quality precluded meaningful interpretation, highlighting the need for well-designed randomised controlled trials. In patients for whom oral nutrition remains inadequate despite counselling and ONS, current guidelines recommend the use of EN (Arends et al., 2017). If EN is infeasible, intolerable, or insufficient to meet nutritional needs, PN should be considered (Arends et al., 2017).

8.4. Refractory cachexia: Palliative nutrition

Cancer patients with refractory cachexia are unlikely to benefit from nutritional interventions. Accordingly, nutrition care should be tailored to the patient's symptomatic needs and is primarily intended to support comfort and quality of life (Arends et al., 2017). Due consideration should be given to the cultural, personal, and religious practices of patients and their families (Arends et al., 2017; Arends et al., 2017).

Cachexia is a multidimensional condition involving a complex interaction between multiple aetiologic factors (Fig. 2) (Arends, 2016). Effective management requires a multimodal approach that employs targeted interventions to address the different components of the disease process, including reduced food intake, systemic inflammation, and muscle loss (Fearon, 2008; Maddocks et al., 2016; Hall et al., 2019). A phase 2 randomised controlled trial evaluating a multimodal intervention comprised of exercise, omega-3 enriched ONS, and non-steroidal anti-inflammatory drugs (NSAIDs) in patients with either lung or pancreatic cancer showed that multimodal therapy was safe and well tolerated and resulted in increased weight compared with standard care (Solheim et al., 2018). The MENAC trial is an ongoing phase 3 randomised controlled trial evaluating the effect of multimodal intervention including dietary counselling, ONS enriched with omega-3 fatty acids, exercise training, and ibuprofen on muscle mass, weight, and physical function in patients with lung or pancreatic cancer (Solheim et al., 2017).

To date, there is no approved pharmacological therapy for cachexia except for progestins and anamorelin, a ghrelin agonist which was recently approved in Japan but is not available elsewhere (a more detailed discussion of pharmacologic therapies is available in the ESPEN guidelines on nutrition in cancer patients (Arends et al., 2017). Further research is required to clarify the potential role of interventions such as immuno-nutrition and experimental therapies such as ghrelin agonists and selective androgen receptor modulators. Additionally, expanding the concept of nutritional and metabolic prehabilitation beyond surgical oncology to the medical oncology setting represents an intriguing approach that warrants further investigation.

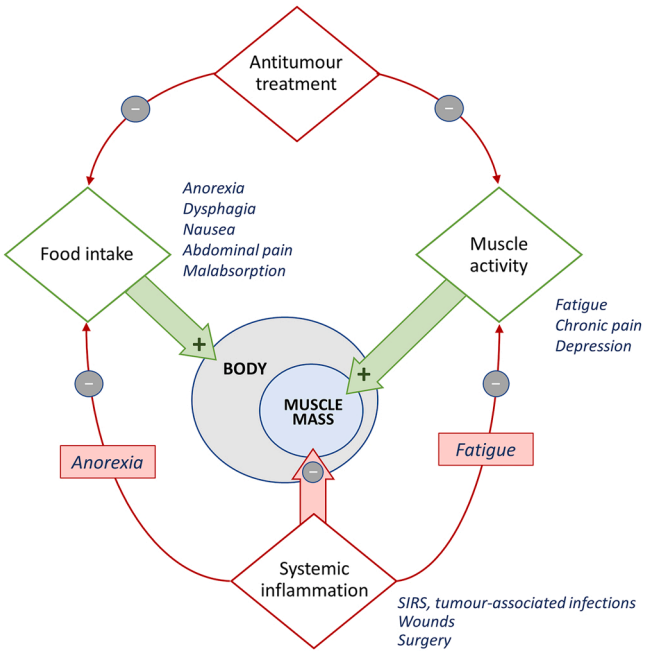

Fig. 2. Multifactorial aetiology of cancer cachexia.Footnotes:SIRS=systemic inflammatory response syndrome.
Modified from Arends (Arends, 2016).

9. Patients' perspective

The European Society for Medical Oncology (ESMO) position paper on supportive and palliative care identified patient-centred care as a cornerstone of comprehensive oncological care (Jordan et al., 2018). Patient-centred care aims to provide integrated, dynamic, and personalised supportive and palliative interventions based on the best available evidence from the time of cancer diagnosis and continuing throughout the patient's cancer journey.

Nutrition support is an integral component of patient-centred care. Nutrition-related issues involve multiple domains of health status, including psychological (uncertainty, anxiety, loss of self-esteem), physical (fatigue, reduced physical activity, nutrition impact symptoms), and social (interpersonal relationships, family tension) domains. Moreover, nutrition-related issues can affect family members and caregivers, as declining nutritional status is a distressing sign and may be misinterpreted by caregivers as a failure to provide adequate care (Roeland et al., 2020; Rauh et al., 2018).

Importantly, nutrition is one of the main areas in which patients can actively contribute to their treatment, giving them a sense of control and supporting mental well-being. Accordingly, patients should actively participate in the development and execution of a nutritional plan, with frequent follow-up to verify actual behaviour. Patients should be asked about nutrition-related conditions, including diabetes, high cholesterol, and obesity, and advised not to continue low-fat and low-sugar diets. Notably, special diets can lead to more social isolation; therefore, it is important for patients to enjoy their food and to integrate with the rest

of the family during routine meals.

Patient organisations play a critical role in assisting patients with the non-clinical aspects of cancer treatment. Many cancer patient organisations have nutritionists or dieticians on staff or available by referral. After diagnosis, patients should be referred to a cancer-specific patient organisation and encouraged to take advantage of the educational resources available through these organisations. Most patient organisations offer educational materials and counselling on a broad range of topics, including nutrition, physical activity, and psychological aspects of living with cancer. In this regard, patient organisations should be considered an extension of the medical team and a vital resource for patients and caregivers.

Despite the fundamental importance of adequate nutrition and patients' commonly expressed need for reliable guidance on diet and nutrition, nutrition support in the typical oncology practice is limited (Caccialanza et al., 2016; Muscaritoli et al., 2019). Patients are commonly advised to eat what they want or to maintain a healthy diet, without any further explanation regarding the principles of a healthy diet or the corresponding effects on anticancer treatment outcomes. In the absence of adequate nutrition counselling, cancer patients often seek information from unreliable sources and may adopt potentially harmful dietary practices based on false or misleading information or dietary recommendations that are unsupported by scientific evidence (Roeland et al., 2020). In a German survey of 1335 cancer patients, the most commonly reported sources for information related to nutrition or problems with food intake were print media (68.5%) and patient groups (58.7%); only 9.8% of respondents reported receiving nutrition information from their physician (Maschke et al., 2017). Proactive nutrition counselling should address patient-specific nutritional needs and clarify the potential harmful consequences of fad diets, unproven supplements, and other extreme dietary measures (Arends et al., 2017; Roeland et al., 2020). Indeed, a potential barrier to the maintenance of nutritional fitness of cancer patients is represented by the exposure to health-related misinformation on social media (Wang Y, McKee M, Torbica A, Stuckler D. Systematic Literature Review on the Spread of Health-related Misinformation on Social Media. Soc Sci Med. 2019 Nov;240:112552). Finally, significant improvements in cancer therapy have led to improved outcomes and a growing population of cancer survivors. Patient-centred nutrition care should encompass the patient's entire cancer journey, including survivorship. Survivor care plans should

Box 2
Barriers to the recognition and treatment of cancer cachexia and possible solutions.

Barrier	Possible solution
- The still limited awareness among oncologists of the impact of cancer on metabolic and nutritional status	- Including clinical nutrition and nutrition-related comorbidities in oncology training curricula
- Terminological confusion between cachexia, malnutrition, sarcopenia	- Dedicated training programs for team and staff members
- The often unclear therapeutic differences between cachexia and "simple" malnutrition	- Responsibilities assigned to dedicated professionals in each oncologic institution to organize and monitor nutritional and metabolic support
- Relatively low esteem still associated with nutritional support in clinical oncology	- Incorporation of relevant structural elements into accreditation procedures for oncologic centers of excellence
- Financial incentives to limit nutritional support	Implementation of a quality control system to highlight and improve deficits
- Lack of nutrition topics in medical and oncology specialist training	- Implementing nutrition education in medical schools and residency training programs (esp. oncology)
- Low utilization of drugs in nutritional treatments	- Fostering good quality multicenter clinical trials on nutritional therapy in oncology
- Ease of application of nutritional support, including oral or intravenous nutrition	- Establishing dedicated structures and standard operating procedures
- Relatively large therapeutic index of supplementary enteral or intravenous nutrients	- Ensuring follow-up visits and monitoring nutritional and metabolic outcome
- Lack of specific malnutrition symptoms	- Routine screening for malnutrition in all cancer patients
- Dearth of acute and generally rather unspecific effects of nutritional care	- Involvement of patients and patient associations in educational activities on nutrition in oncology
- Sparsity of high-quality evidence supporting diagnostic and therapeutic nutritional and metabolic interventions	- Participation in clinical research projects targeting treatments in areas of "low evidence"

Estimated costs associated with nutritional support

Goal	*fraction of all patients*	*time required per patient (5)*	*total time per patient admitted*
Screen (1)	100%	0.15 h	0.15 h
Assess (2)	40%	0.50 h	0.20 h
Nutrition support (3)	35%	1.00 h	0.35 h
Exercise training (4)	30%	1.00 h	0.30 h
Total			1.00 h

(1) Assuming to screen every patient admitted to a clinical oncology institution for the risk of malnutrition
(2) Assuming screening to result in findings of 'at-risk' situations in 40%
(3) Assuming 85–90% of all assessed patients to require and consent to nutritional support, that is 35% of all patients
(4) Assuming 75% of all assessed patients to require and consent to exercise training, that is 30% of all patients
(5) Assuming average time requirements of professional work for screening, nutritional assessment, nutrition management, and exercise training to be 0.15 h, 0.5 h, 1.0 h, and 1.0 h, respectively per patient screened, assessed or treated.

Points taken from ESPEN guidelines on nutrition in cancer patients (Arends et al., 2017; Lobo et al., 2020).

include practical guidance on maintaining proper nutritional intake and adequate exercise after completion of cancer therapy.

10. Discussion

Cancer cachexia is a complex and challenging condition and a significant impediment to achieving optimal outcomes in patients with malignant disease. While considerable progress has been made in understanding the aetiology and consequences of cachexia, progress in clinical management has been comparatively modest owing to factors ranging from low awareness to limited high-quality evidence to inform therapeutic intervention (see Box 2.). As a consequence, the early detection and effective management of cancer cachexia remains a significant unmet need.

In an effort to address this urgent need, the ESPEN expert group recommendations for action against cancer-related malnutrition highlighted three specific steps that clinical oncologists can implement to improve nutritional care (Arends et al., 2017):

1) screen all cancer patients for risk of malnutrition early in the course of care, with routine monitoring thereafter;
2) expand assessment of nutritional status to include measures of anorexia, body composition, inflammation, and physical function; and
3) use multimodal nutritional interventions aimed at increasing nutritional intake, reducing inflammation and hypermetabolic stress, and increasing physical activity.

The SPCC task force on nutrition and cachexia in cancer patients endorses these practical recommendations and joins the ESPEN expert group in urging immediate implementation. Mandatory screening and periodic rescreening of all cancer patients for nutrition risk, followed by comprehensive assessment of nutritional and metabolic status in those at risk facilitates detection of cachexia at a stage that is more likely to be responsive to therapeutic intervention. A diversity of opinion was expressed among members of the task force regarding specific diagnostic criteria for cachexia; however, there was broad general agreement on the need for practical, reliable, and prospectively validated criteria.

Efforts to promote early detection of cancer cachexia will be further aided by harmonisation of terms and definitions, establishment of validated diagnostic criteria supported by international consensus, mandatory collection of body composition data in oncology clinical trials, and formal integration of supportive and palliative care in the training curriculum for medical oncologists in accordance with the ESMO/ASCO Recommendations for a Global Curriculum in Medical Oncology (Dittrich et al., 2016).

Clinical management should be guided by the stage of cachexia and individual clinical circumstances and informed by the best available evidence. Evidence for nutrition interventions in patients with cachexia remains limited; however, attenuation of losses in lean body mass cannot be achieved without adequate protein and energy intake. Accordingly, nutritional requirements should be met in all cancer patients except those receiving end-of-life care through individually tailored nutrition interventions. Integration of nutrition care into a continuum of cancer care that includes ongoing multidisciplinary collaboration to review and adapt treatment plans as necessary facilitates timely intervention and optimises the conditions for successful cancer treatment.

Patients should be empowered to actively participate in the development of a nutritional plan and advised to avoid low-fat, low-sugar diets, unproven supplements, and other extreme dietary measures. Cancer patient organisations are a vital source of information on the non-clinical aspects of treatment; patients should be referred to a cancer-specific patient organisation for further education and guidance on topics such as nutrition, physical activity, and psychological aspects of living with cancer.

Important areas for future research are summarised in Box 3. Priority research topics include prospective validation of diagnostic criteria, including patient-reported symptoms and measures of physical function; evaluation of nutrition interventions in prospective, randomised, controlled trials; investigation of the effects of multimodal nutritional prehabilitation in medical oncology patients; and further exploration of the potential interactions between cancer cachexia and immunotherapy.

11. Conclusion

Cancer cachexia is a pernicious disorder that profoundly affects patients and caregivers and significantly compromises the ability to achieve an optimal response to cancer treatment. Quite unfortunately, cultural barriers still exist preventing its effective prevention and treatment. Clinicians responsible for the care of cancer patients have an obligation to ensure that all patients receive comprehensive care. Early detection of cancer cachexia allows timely intervention at a stage that is more likely to be responsive to therapeutic intervention, thereby minimising the adverse effects of cachexia on anticancer therapy. Prompt recognition and effective management of cachexia is best achieved through integration of all patient-directed interventions (nutritional, pharmacologic, psychosocial, exercise) from the time of diagnosis and continuing throughout the course of care in parallel with oncologic treatment and follow-up. The unmet needs and research priorities identified in the present position paper are intended to serve as an urgent call to action to researchers, educators and clinicians to take immediate steps aimed at reducing the burden of cachexia in patients with cancer.

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Box 3
Priority topics for future research.

- Prospective validation of diagnostic criteria for cachexia, including patient-reported symptoms and measures of functional status
- Identification and validation of a standardised biomarker that is sensitive to changes in the stage of cachexia and responsive to therapeutic intervention(s)
- Validation of emerging techniques for automated body composition analysis of CT images
- Evaluation of nutrition interventions, including multimodal therapy, in prospective, randomised, adequately-powered, controlled trials in well-defined populations stratified by cachexia stage
- Investigation of the effects of multimodal nutritional prehabilitation in medical oncology patients
- Further exploration of the potential interaction between cachexia and antineoplastic monoclonal antibodies
- Evaluation of the effect of modifying body composition and systemic inflammation on the metabolism of immunotherapeutic agents and immunotherapeutic response
- Evaluation of the effect of dosing cytotoxic drugs according to body composition rather than BSA in dose-escalation studies

BSA, body surface area; CT, computed tomography.

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