Module 26.1
Nutritional and Metabolic Consequences of Cancer and its Treatments

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Learning Objectives

- To understand the influence of cancer on nutritional status and body composition;
- To appreciate the phenotypic complexity of nutritional wasting during cancer;
- To appreciate the negative effects of anticancer therapies on nutritional status and body composition;
- To discuss the influence of cancer cachexia on clinical outcomes, including survival and quality of life.

Contents

Key Messages

- Tumour growth is associated with the development of paraneoplastic diseases, influencing the outcome of the patients;
- Nutritional wasting is among the more frequently observed paraneoplastic syndromes;
- Nutritional wasting in cancer is defined as cancer cachexia, a complex syndrome progressing from pre-cachexia to cachexia and ultimately to refractory cachexia;
- The definition of cancer cachexia focuses on muscle loss and lack of response to standard nutritional support, although this definition is being challenged by more recent evidence;
- The diagnosis of cancer cachexia is based on changes in muscle mass, or weight loss/low BMI if body composition analysis is not possible;
- The pathogenesis of cancer cachexia is multifactorial and characterized by a variable combination of alteration of host metabolism and reduced interest in food (i.e., anorexia) and poor food intake;
- Tumour growth triggers the development of cachexia by different means, including increased inflammatory response and mechanical obstruction to food ingestion;
- Anticancer therapies (i.e., surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy) frequently contribute to the development and progression of cancer cachexia;
- Cancer cachexia *per se* has a negative impact on patient outcomes, by impairing response to treatment, increasing therapy-related toxicity and complications, reducing the efficacy of the drugs used.

1. Introduction

Cancer is a systemic disease requiring multi-professional and multi-disciplinary care. During the last decades, the therapeutic options for cancer patients has increased tremendously. Chemotherapy, radiotherapy, surgery, targeted therapy and immune therapy, either as single agents or combined, have significantly improved the likelihood of being effectively treated and even cured. Also, implementation of nationwide screening programmes has yielded an increased likelihood of being diagnosed with an early cancer. When combined, these factors have contributed to reduce the annual toll of cancer deaths. In the US alone, it is estimated that more than 2 million cancer deaths have been averted in the period 1990-2016 (1). Despite this comforting evidence, the number of cancer deaths has increased year after year since 1975 (1). Also, the 5-yr survival rate of patients diagnosed with advanced disease remains poor for many cancers, which suggests that the disease is poorly controllable when it extends beyond the organ of origin and when eradicating surgery is no longer an option (1).

It is now becoming evident that therapeutic strategies exclusively targeting cancer cells may not result in meaningful amelioration of cancer patients' outcomes, i.e., overall survival and quality of life. Also, improvement of progression-free survival is not necessarily associated with improved health-related quality of life (2). This indicates that key needs of cancer patients remain unmet by current oncology care.

During the last decade, solid clinical evidence has shown that combining anti-cancer therapies with pro-active supportive care (i.e., concurrent care) results in improved survival and quality of life (3). Therefore, the nutritional, physical, psychological and social needs of cancer patients (i.e., patient-centred outcomes) are becoming key factors in the comprehensive management of cancer. Consequently, both the American Society of

Clinical Oncology (4) and the European Society of Medical Oncology (5) are now recommending the initiation of supportive therapy, including nutritional care and support, early in the clinical journey of a cancer patient, i.e., not later than 8 weeks after diagnosis. The aim of this module is to discuss the impact of cancer on patients' nutritional status and how this translates into worse clinical outcomes. Also, we will discuss the impact of anticancer therapies on nutritional status and how in turn cancer-associated malnutrition impacts on the efficacy of anticancer therapies.

2. Impact of Cancer on Nutritional Status – Cancer Cachexia

Cancer growth is associated with a number of metabolic and behavioural changes, which are comprehensively defined as cancer cachexia. In the general ESPEN framework of the classification of malnutrition, cancer cachexia is comprehended under the larger umbrella of disease-related malnutrition with inflammation (6).

From the pathogenic point of view, cancer cachexia could be defined as the clinical phenotype resulting from the concerted action of symptoms and signs characterizing sickness behaviour. Sickness behaviour has evolved as a metabolic and behavioural response to external (e.g., trauma) or internal (e.g., sepsis) insults, which confers a survival benefit. Clinically, loss of appetite (i.e., anorexia), lethargy, increased inflammatory response, insulin resistance, and increased muscle proteolysis characterize sickness behaviour. These clinical and metabolic features are triggered by immune and inflammatory responses initiated by the given insult.

Inflammatory and immune responses are similarly involved in originating and sustaining chronic diseases, including cancer. Consequently, sickness behaviour is observed also in patients with cancer, even if the underlying inflammatory and immune responses are in general milder than in acute diseases.

According to an international consensus, cancer cachexia has been defined as "a multifactorial syndrome characterized 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" (7). Although new evidence may now challenge this definition, this remains the most widely accepted and used.

From the pathogenic perspective, cancer cachexia is "characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism" (7), including increased muscle proteolysis, anabolic resistance, hypermetabolism (8). Their contributions vary during the clinical journey of a cancer patient. Therefore, the most effective treatment/prevention of cancer cachexia may also vary considerably across different time points to adapt to the changing metabolic and behavioural needs (9).

2.1 Cancer Anorexia

The loss of appetite and interest in food, i.e., anorexia, is a symptom frequently reported by cancer patients upon diagnosis (10). It is a clinically relevant symptom, since it has an independent negative prognostic influence on the cancer patient's survival, independently of weight loss (11).

The pathogenesis of cancer anorexia involves inflammation-mediated changes in the activity of the brain nuclei controlling energy homeostasis (12). Under physiological conditions, hypothalamic neurons receive information on the metabolic status of peripheral organs and trigger the appropriate feeding response (13). Hyperactivity of hypothalamic

melanocortin neurons has been repeatedly demonstrated to be involved in mediating anorexia in experimental models (14). Melanocortin neurons trigger anorexia by reducing interest in food, by modulating intestinal function, and by simultaneously inhibiting the activity of the prophagic hypothalamic nuclei, i.e., NPY neurons. The pathogenesis of anorexia involves other brain areas as well. Beyond the role of deranged activity of the physiologic homeostatic mechanism (i.e., the concerted action of melanocortin and NPY neurons), cancer anorexia is also triggered by the activation of an anorexigenic pathway located in the brainstem (15), whose main mediator is MIC-1/GDF-15 (16). This pathway should work as an emergency pathway activated during metabolic stress, although recent evidence may suggest that this is the consequence of a nutritional stress (i.e., hypophagia) rather than its cause (17).

Whether changes in the perception of thirst and reduced fluid intake are a part of the cancer anorexia phenotype is a clinical and scientific issue which has not been investigated, but study of this question may yield important therapeutic options since regulation of thirst appears to be modulated at the forebrain level (18).

From the clinical point of view, the diagnosis of cancer anorexia is usually based on the use of validated questionnaires, each exploring a specific dimension affecting food intake (e.g., changes in taste/smell, the presence of early satiety, nausea, meat aversion, etc.) (19). A precise characterization of the symptoms and signs causing cancer anorexia is key to implementation of effective changes in the diet and dietary pattern. ESPEN recommends the use of the FAACT-A/ACS questionnaire to diagnose cancer anorexia (20). More recently, Blauwhoff-Buskermolen et al. derived the FAACT-A/ACS score needed to make the diagnosis of cancer anorexia (21).

2.2 Increased Muscle Proteolysis

Under physiological conditions, the daily turnover of skeletal muscle mass is approximately 1%. The concerted and balanced action of intramuscular anabolic and catabolic pathways allows the preservation of muscle mass over the medium/long period. During cancer growth, the resulting increased inflammatory response disrupts the balance between muscle anabolism and catabolism. In particular, muscle catabolism is increased without a compensatory increase of muscle anabolism (22).

Under physiological conditions, muscle catabolism is sustained by several different pathways. Of great interest for cancer cachexia, the ATP-dependent ubiquitin proteasome system has been extensively investigated. Catabolism is triggered by the ubiquitination of muscle fibres which are then catabolized to amino acids by the proteasome (23). It has been repeatedly shown that mediators of inflammation, including IL-1 and IL-6, increase the activity of this catabolic pathway (23).

The rate of muscle loss is not constantly maintained during the clinical journey of a cancer patient. It appears that proteolysis is accelerated during catabolic stress, e.g., surgery, chemotherapy, immobility, but it may well return to baseline levels, as suggested by imaging evidence showing maintenance of muscle loss of cancer patients over a prolonged period of time (24).

Whether only circulating inflammatory mediators contribute to activating the intramuscular proteolytic systems remains an open question. Nevertheless, suggestive animal and clinical data indicate that cancer-driven inflammation may trigger muscle proteolysis directly and indirectly, by hyperactivating sympathetic tone (25).

2.3 Cancer Cachexia and Comorbidities

In the US, as in many other western countries, the median age at cancer diagnosis is 66 years, so approximately half of new cancer patients are older than 65 years (26). Ageing is closely related to the onset of non-malignant chronic diseases. Consequently, many cancer patients also suffer from other chronic diseases, which in turn could be responsible for quantitative and qualitative changes in body composition. Addressing this clinically relevant issue, Xiao et al. showed in a large sample of cancer patients that pre-existing comorbidities may not significantly impact on skeletal muscle mass, but they influence the structure of muscles as revealed by skeletal muscle radiodensity (27).
In clinical practice, it is almost impossible to assess the specific contributions of cancer and comorbidities to cachexia. However, the effective prevention and treatment of cancer cachexia requires the management of cancer and co-existing comorbidities.

2.4 Obesity and Fat Wasting

The currently acknowledged definition of cancer cachexia focuses on ongoing muscle loss (7). However, studies analyzing large imaging databases are now challenging this definition, and describe a more complex derangement of nutritional status during tumour growth. In particular, it is now evident that cancer cachexia is not restricted to an exclusively quantitative abnormality of muscle mass.
Martin et al. analyzed the muscle mass as measured by CT scan at the level of L3 of more than 1000 colorectal cancer patients undergoing surgery (28). Pure sarcopenia was observed only in 12% of the sample, whereas fat infiltration of muscle mass but no reduction of it (i.e., myosteatosis) was observed in 16% of the sample. Also, combined sarcopenia and myosteatosis was detected in another 16% of the sample. Of great interest, specific changes in fat mass have been reported and they are clinically relevant since they influence clinical outcome. Also, visceral obesity per se increases readmission rate, whereas the association between myosteatosis and visceral obesity extends length of hospital stay (28). Kays et al. showed that fat-only loss in pancreatic cancer patients influences survival similarly to fat and muscle wasting (29). This emerging evidence highlights the complexity of human cancer cachexia, which extends beyond pure and isolated sarcopenia to variable combinations of muscle and fat loss. Whether these body composition changes could represent specific phenotypes and predict tumour biology and responsiveness to therapies remains to be ascertained.

2.5 Anabolic Resistance

The current definition of cancer cachexia includes its lack of response to standard nutritional treatment. Although it is acknowledged that the pathogenesis of cancer cachexia extends beyond mere reduction of energy and protein intake, the issue of anabolic resistance in cancer patients has recently been challenged. Based on repeated assessment of muscle mass in advanced cancer patients, Prado et al. showed that muscle anabolism is maintained until the very late stages of the disease (24). Of great clinical relevance, Engelen et al. showed that the anabolic response of muscle fibres from cancer patients is not different from that of healthy individuals (30), suggesting the possibility of effectively intervening in cancer patients to preserve and treat muscle wasting. Reconciling these opposing positions, it is likely that anabolic resistance could be associated with the degree

of inflammatory response. Therefore, anabolic resistance would be more frequently detected during catabolic stress conditions which may occur only intermittently during the clinical journey of a cancer patient. This assumption translates into the goals of nutrition therapy in cancer, i.e., minimizing weight loss during catabolic stresses and maximizing anabolic recovery during the periods in between.

2.6 Hypermetabolism

It is a commonly held opinion that resting energy expenditure is increased in cancer patients, this significantly contributing to the energy gap and thus to nutritional wasting. However, this assumption has not been consistently demonstrated by clinical trials. In particular, Jouinot et al. studied 277 patients, and found that only 51% were hypermetabolic, as defined by a ratio of >1.1:1.0 in measured resting energy expenditure relative to resting energy expenditure predicted by the Harris-Benedict formula (31). More relevant for risk stratification, Jouinot et al. also showed that treatment toxicity was associated with abnormal metabolism. In fact, to predict toxicity, the most sensitive parameter was the resting energy expenditure (31). However, in multivariate analysis, only elevated C-reactive protein was an independent predictor of toxicity (31).

3. Impact of Anticancer Therapies on Nutritional Status

Anticancer therapies may significantly impact on patients' ability to swallow, digest and absorb nutrients. Also, they have a profound impact on patients' metabolism. Consequently, cancer therapies impact on nutritional status. Although it is acknowledged that cancer therapies should not be withdrawn for their potential side effects on nutritional status, it is imperative to consider their side effects for risk stratification, and therefore provide an early and prophylactic nutritional approach to cancer patients.

3.1 Surgery

Eradicative and palliative cancer surgery can be associated with significant impairments of physiological functions. A clear example is given by surgery for foregut tumours, after which swallowing is significantly compromised. In this regard, de Pinho et al. demonstrated that the most important clinical variable presenting the highest risk for moderate/severe malnutrition in a large cohort of Brazilian cancer patients was problems with swallowing (OR 2.8, 95% CI 2.2-3.4, $p < 0.001$), followed by loss of appetite (OR 1.9, 95% CI 1.6-2.3, $p < 0.001$), vomiting (OR 1.8, 95% CI 1.5-2.3, $p < 0.001$), and the presence of more than 3 nutrition impact symptoms (OR 8.3, 95% CI 5.8-12, $p < 0.001$)(32).
Similarly, any major resection of the gastrointestinal tract reduces digestive function and promotes malnutrition. Pancreatic exocrine insufficiency resulting from surgical removal of pancreatic cancer is a negative prognostic factor, which is ameliorated by enzyme replacement (33). Early placement of a feeding tube and initiation of enteral nutrition, or parenteral nutrition when enteral feeding is not possible or tolerated (34), are effective strategies to prevent and treat malnutrition in surgical cancer patients.

3.2 Chemotherapy

Chemotherapy influences nutritional status in different ways. On a short-term basis, chemotherapy induces mucositis, nausea and vomiting, and also activates intracellular

signals that result in the suppression of protein synthesis and activation of a transcriptional programme leading to autophagy and degradation of myofibrillar proteins (35). Also, chemotherapy has more long-lasting effects, which are related to altered sensation in taste and smell. A recent observational study showed that 76% of patients undergoing chemotherapy reported taste disorders and 45% smell changes (36). Xerostomia was the most frequent symptom (63.6%), and it was strongly associated with bad taste in the mouth (OR = 5.96; CI = 2.37-14.94; p value = 0.000) and taste loss (OR = 5.96; CI = 2.37-14.94; p value = 0.000). Anthracyclines, paclitaxel, carboplatin, and docetaxel were the chemotherapy agents producing the highest rates of taste disturbance (36). Logistic regression revealed statistically significant associations between taste loss and carboplatin and docetaxel (OR = 3.50; CI = 1.12-10.90; p value = 0.031), and between cold hypersensitivity and oxaliplatin (OR = 12.14; CI = 4.18-35.25; p value = 0.000). Dysgeusia was produced not only by platin-based drugs such as carboplatin, but also by anthracyclines and paclitaxel (36).

3.3 Radiotherapy

The impact of radiotherapy on nutritional status is well acknowledged. Cycles of radiotherapy may limit food intake by triggering local oedema, mucositis, xerostomia, dysphagia and pain when swallowing. Also, radiotherapy impacts on taste (37). All of these symptoms may still exist months after completion of treatment, independently of nutrition support (38). Brown et al. randomized patients to standard care or to early tube feeding (39): following intention-to-treat analysis, linear regression found no effect of early tube feeding on weight loss and this remained non-significant on multivariate analysis (P=0.624). To prevent long-term nutritional effects from side effects of radiotherapy, prophylactic gastrostomy placement has been proposed. Although still controversial, this approach appears to yield clinical benefits (40).

3.4 Targeted Therapy

Cancer with specific molecular aberrations can be treated by targeted therapies, which block the defective molecular pathway. Although highly specific, targeted therapies may well be associated with side effects which potentially threaten nutritional status. As examples, erlotinib delivery is associated with the development of oesophagitis limiting food intake in oesophageal cancer patients (41), and the use of epidermal-growth-factor receptor-targeting antibodies, like cetuximab, for colorectal cancer is associated with hypomagnesaemia (42). Considering these potential side effects of targeted therapy may help in prevention and early recognition of malnutrition.

3.5 Immunotherapy

The new approach to cancer patients is immunotherapy. This approach is based on a different goal from standard anticancer therapies. Immunotherapy is not aiming to destroy all cancer cells or even a majority of them. Immunotherapy aims to unleash the patient's immune system against cancer cells to control their proliferation. Consequently, the aim of immunotherapy is to transform cancer into a controllable chronic disease.

To reach this goal, a specific receptor on immune cells (PD1) and its ligand (PDL1) are targeted. By blocking PD1, immune function against cancer cells is reactivated. Although well tolerated, these drugs have a unique side effect profile and are known to cause

immune-related adverse events. Adverse effects of immunotherapy are most commonly observed in the skin, gastrointestinal tract, liver, lung and endocrine systems. Less common toxicities may include neurological, haematological, cardiac, ocular or rheumatologic involvement (43). Consequently, immunotherapy may induce the onset of nutrition-related symptoms, which in turn contribute to the development of malnutrition.

4. Impact of Cancer Cachexia on Clinical Outcomes

The prevalence of cancer cachexia depends on the diagnostic tools used to assess it and on the type and stage of cancer considered. ESPEN endorsed (20) the definition of cancer cachexia given by Fearon et al in Lancet Oncology in 2011, as well as the proposed diagnostic tools. Therefore, cancer cachexia is defined as a multifactorial syndrome characterized 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. The agreed diagnostic criterion for cachexia is weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI <20 kg/m^2) or skeletal muscle mass (sarcopenia). ESPEN defines sarcopenia as follows (34): mid upper-arm muscle area by anthropometry (men <32 cm^2, women <18 cm^2); appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men <7.26 kg/m^2; women <5.45 kg/m^2); lumbar skeletal muscle index determined from oncological CT imaging (men <55 cm^2/m^2; women<39 cm^2/m^2); whole body fat-free mass index without bone determined by bioelectrical impedance (men <14.6 kg/m^2; women<11.4 kg/m^2).
A panel of experts also agreed that the cachexia syndrome develops progressively through various stages - precachexia to cachexia to refractory cachexia. However, still debate exists on how to set the boundaries between the stages of cachexia, in particular between cachexia and refractory cachexia. In fact, precachexia can be defined with nutrition-alarm symptoms and biochemical signs of increased inflammatory response, whereas cachexia develops when weight loss >5% occurs.
The prevalence of cancer cachexia based on the assessment of muscle loss by CT-scan at the level of the third lumbar vertebra is approximately 50% in advanced colorectal cancer patients (44) but only 12% in colorectal cancer patients with less advanced disease and undergoing surgery (28). In a large cohort of patients with different types of cancer, cachexia as defined by anthropometry was found in 51% of in-patients and 22% of out-patients (45). Recently, it has been proposed that cancer cachexia could be considered an orphan disease, when the different "cachexias" associated with different types of cancer are considered separately (46). This latter proposal appears more provocative than real since it implies that wasting of different cancers recognizes different pathogenic mechanisms, different diagnostic tools and different therapies.
Therefore, the prevalence of cancer cachexia could be estimated at approximately 20-50% of cancer patients, according to the type of tumour and the diagnostic tools used. Such uncertainty highlights the need to reach a consensus on an easily available strategy to diagnose cachexia in cancer.

4.1 Post-operative Complications

The presence of cachexia negatively impacts on postoperative complications and on long-term outcomes. In patients with locally advanced rectal cancer sarcopenia and visceral obesity were identified in initial staging CT by measuring the muscle and visceral fat area

at the third lumbar vertebra level (47). Among the 188 included patients, 74 (39.4%) patients were sarcopenic and 97 (51.6%) patients were viscerally obese. Sarcopenia and high levels of preoperative carcinoembryonic antigen were significant prognostic factors for overall survival (P = 0.013, 0.014, respectively) in the Cox regression multivariate analysis. Visceral obesity was not associated with overall survival.
In patients with resectable pancreatic cancer, sarcopenia showed a negative impact on overall survival (14 vs. 20 months, p = 0.016). Sarcopenic yet obese patients showed higher incidence of major postoperative complications (p<0.001). In addition, sarcopenia proved an independent prognostic factor for overall survival (p = 0.031) in the multivariable Cox regression model (48).
In 153 patients with gastric cancer, sarcopenia was present in 24 of 153 patients (15.7%). Thirty (19.6%) patients developed postoperative complications, 20 (13.1%) of which were infectious complications. Sarcopenia was significantly associated with age, body mass index, serum albumin, comorbid pulmonary disease, operative time, surgical approach, and postoperative complications (49).
The sum of these data recommends preoperative assessment for cachexia and possibly starting nutritional support before surgery in order to improve early and long-term clinical outcomes.

4.2 Toxicity

Cancer cachexia is uncontroversially associated with chemotherapy-related toxicity. Among the different components of cancer cachexia, skeletal muscle loss is considered the main factor predisposing to increased toxicity and dose-limiting toxicity. In colorectal cancer patients, sarcopenia at the start of chemotherapy was not associated with dose-limiting toxicity, whereas patients with >2% drop in skeletal muscle index had a significantly higher risk of dose-limiting toxicity (44). At the start of subsequent chemotherapy regimens, the risk of dose reduction was significantly higher for patients with a preceding drop in their skeletal muscle index (44). By contrast, BMI (loss) at the start of or during either treatment was not associated with an increased risk of dose-limiting toxicity (44). Similar results have been obtained in patients with other gastrointestinal cancers (50), as well as in patients receiving targeted therapy (51). The likely explanation for the strong relationship between muscle loss and toxicity may lie in the distribution volume of chemotherapy agents, which is not captured by the standard dosing system based on body surface area. Therefore, patients may receive excessive doses of chemotherapy resulting in increased toxicity (52).
Beyond muscle loss, other factors may influence the risk of developing toxicity. Hypermetabolism has been shown to predict toxicity (31), as well as low BMI (53), although it should be highlighted that low BMI is not a common presenting feature of cancer patients, at least in the western world. In fact, the average presenting BMI is within the overweight range (54).

4.3 Survival

The negative impact of malnutrition on cancer survival has been repeatedly demonstrated, independently of the parameter used to assess poor nutritional status (i.e., low BMI, involuntary weight loss, low muscle mass, low fat mass, etc.). As mentioned in the previous section, malnutrition is associated with increased postoperative complications, low immune

function, and dose-limiting toxicity, which in turn reduce the efficacy of anticancer therapies.
Similar results have also been reported for patients receiving immunotherapy. In particular, low muscle mass and low subcutaneous fat mass are negative prognostic factors for the efficacy of immunotherapy (55, 56). The mechanisms explaining the low efficacy of immunotherapy in cachectic cancer patients are not clear. However, it could be hypothesized that the increased proteolytic drive of cachexia may also contribute to degrade immunotherapy agents. Supporting this hypothesis, low albumin levels and on-study rate of weight change were reported as negative predictive factors for overall survival in pembrolizumab treated melanoma and lung cancer patients (57).
Although it is evident that cachexia impacts on survival of cancer patients, its quantitative contribution remains a matter of debate. It has frequently been stated that 20% of cancer deaths are due to cachexia. This is an imprecise assessment since the figure is derived from a study published almost 100 years ago and which mainly enrolled hospice patients (58). In a more recent analysis, cachexia was the immediate cause of death of 1 out of 30 pancreatic cancer patients, but was a contributing cause in 5 other cases (59). Similarly, cachexia was the cause of death in 10% of head and neck cancer patients receiving an autopsy (60). A different scenario is observed when the immediate cause of death of cancer patients is not assessed by autopsy, but is derived from the patients' charts. In such cases, cachexia is not reported as the immediate cause of death (61). However, since infection and sepsis are largely contributing to the death of cancer patients, and since malnutrition has a role in predisposing to infections, it could be speculated that cachexia per se is a trigger of the progressive decline of many cancer patients ultimately leading to death.

4.4 Quality of Life

Patients with cancer cachexia have severely impaired quality of life. Low muscle mass has been shown to impair different domains, i.e., physical function, role function and global quality of life, possibly more so in men than in women (62). In a recent study, patients with advanced cancer, referred for the management of cachexia by a specialised multidisciplinary clinic were studied (63). Quality of life was assessed at visits 1-3 using a dedicated quality of life tool for cachexia, and the change in quality of life was calculated for each patient. The correlation between clinical features and quality of life at baseline and subsequent change in quality of life was analysed, to determine what factors predict improvements in quality of life during the intervention. Approximately 350 patients assessed at visit 1 had a mean weight loss of 10.2% over the preceding 6 months. Baseline quality of life scores were severely impaired but clinically important improvements were observed over visits 1-3 to the clinic. Improvements in quality of life were not determined by baseline characteristics and were similar in all patient subgroups. However, those patients who gained weight and increased their 6 min walk test had the greatest improvements in QoL (62). Therefore, all facets of the cancer cachexia syndrome affect quality of life. Nonetheless, the multimodal approach to management of cancer cachexia results in clinically important improvements in quality of life.

5. Summary

Tumour growth is associated with profound modifications of body mass and composition, which directly and negatively influence clinical outcome. This paraneoplastic syndrome (i.e., occurring with the development of the tumour, its severity being related to the

aggressiveness of the cancer, and ameliorating simultaneously with tumour regression) is characterized by skeletal muscle loss, although recent evidence shows more complex features of nutritional deterioration during tumour growth. Factors other than the metabolic impact of cancer cells contribute to cachexia, including concurrent comorbidities, as well as anticancer therapies.

Since cancer cachexia is a relevant and robust predictor of outcome, it is key that its presence or the increased risk of development should be included in the comprehensive baseline assessment of all cancer patients, as recommended by international scientific societies (4, 5, 34). However, it is acknowledged that it can sometimes be difficult to measure muscle mass in oncological centres worldwide. However, it is imperative that nutritional wasting is diagnosed based on alternative tools, including anthropometry, weight change history, feeding behaviour and low BMI. In this regard, Martin et al. showed that combining the degree of involuntary weight loss with the baseline BMI allows for a robust risk stratification of patients suffering from cancer of different organs (64).

For decades it has been proposed that cancer cachexia is unresponsive to standard nutritional support. It is now becoming more evident that cancer cachexia accompanies the whole clinical journey of cancer patients. Therefore, cachexia rapidly progresses during catabolic periods (e.g., chemotherapy, radiotherapy, surgery, etc.), but windows of opportunity do exist in the trajectory of a cancer patient. During these periods, muscle anabolism is restored, and recovery of muscle mass is possible, at least partially. Therefore, the fight against cancer cachexia is a long-term effort during which the aim is to minimize muscle loss during catabolic periods and to maximize anabolism during recovery phases.

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