Cancer-associated cachexia

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†It is with sadness we learned of the passing of Professor Kenneth Fearon on 3 September 2016. Ken's research spanned every aspect of cancer cachexia, from experimental models to clinical trials. His landmark paper (Definition and classification of cancer cachexia, an international consensus, *Lancet Oncol.* 12, 489–495 (2011)) will continue to serve as a roadmap for the field, and as legacy for researchers seeking to mitigate cachexia-related suffering.

Competing interests

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Author contributions

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Abstract | Cancer-associated cachexia is a disorder characterized by loss of body weight with specific losses of skeletal muscle as well as adipose tissue. Cachexia is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism and inflammation. Cachexia is most highly associated with cancers of the pancreas, oesophagus, stomach, lung, liver and bowel; this group of malignancies is responsible for half of all cancer deaths worldwide. Cachexia involves diverse mediators derived from the cancer cells and cells within the tumour microenvironment, including inflammatory and immune cells. In addition, endocrine, metabolic and central nervous system perturbations combine with these mediators to elicit catabolic changes in skeletal and cardiac muscle and adipose tissue. At the tissue level, mechanisms include activation of inflammation, proteolysis, autophagy and lipolysis. Cachexia associates with a multitude of morbidities encompassing functional, metabolic, and immune disorders as well as aggravated toxicity and complications of cancer therapy. Patients experience impaired quality of life, reduced physical, emotional and social well-being, and increased use of health-care resources. To date, no effective medical intervention completely reverses cachexia and there are no approved drug therapies. Adequate nutritional support remains a mainstay of cachexia therapy, whereas drugs that target overactivation of catabolic processes, cell injury and inflammation are currently under investigation.

[H1] Introduction

Cachexia is a disorder characterized by the involuntary loss of body weight, with loss of homeostatic control of both energy and protein balance[1]; it has been acknowledged since the earliest written medical treatises. Cachexia occurs in association with multiple chronic non-malignant diseases, including heart failure, kidney disease, chronic obstructive pulmonary disease, neurological diseases, AIDS and rheumatoid arthritis. Cancer-associated cachexia — the focus of this Primer — has distinctive tumour-driven components and leads to progressive functional impairment, cancer-related mortality, treatment-related complications and poor quality of life[2]. The disorder is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism and inflammation. Cachexia is distinct from malnutrition, which is readily reversible by the provision of adequate nutrients.

Consensus is needed regarding the definition of and the specific criteria to adequately describe cancer-associated cachexia, as multiple discordant definitions for cachexia are used in the literature. A single definition widely accepted by clinicians and researchers will aid in the identification and treatment of patients with cachexia as well as the development and approval of potential therapeutic agents[2]. Accordingly, an international Delphi consensus process in 2011 provided a definition and conceptual framework specific to cancer-associated cachexia[2], stating that it is a multifactorial syndrome defined by

an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that can be partially but not entirely reversed by conventional nutritional support.

Half of all cancer deaths worldwide (~8.2 million people per year)[3] are attributed to the cancers most frequently associated with cachexia, namely, pancreatic (0.33 million deaths), oesophageal (0.40 million), gastric (0.72 million), pulmonary (1.59 million), hepatic (0.75 million) and colorectal (0.69 million). Available data from palliative care settings suggest that rates of cachexia are uniformly very high at the end of life, regardless of cancer site[4]. However, in spite of its clear association with advanced-stage disease, cachexia is not an inevitable consequence of cancer. Notable inter-individual variation has been noted with regards to the prevalence and severity of cachexia among patients with the same cancer diagnosis and stage. Indeed, some patients with advanced-stage disease maintain or gain weight, skeletal muscle and fat mass[5,6]. As the nutritional deficits that form an important part of cachexia are preventable and are at least partially reversible, patients with cancer can demonstrate protein anabolic response to feeding[7,8]. Furthermore, some individuals might be resistant to the development of cachexia. For example, patients with a loss of function mutation in the gene encoding the cell adhesion molecule P-selectin (*SELP*), have a low likelihood of developing cachexia[9]. Experimental studies in rodent models also show that even in advanced-stage malignancies, cachexia can be substantially mitigated, independent of tumour progression[10,11].

In this Primer, we describe the unfolding mechanistic insights into cancer-associated cachexia, including imbalances of proteolysis and protein synthesis; imbalances of lipolysis and lipogenesis; and the roles of stem cells, inflammation and the central nervous system (CNS). Individual genetic and tumour-specific factors as well as variations in treatment type might explain the considerable inter-individual variation in cachexia prevalence, phenotype, severity and progression. Each of the patient-specific and tumour-specific elements might be clinically relevant for a small number of individuals, but relevant at the population level when considered all together. An improved understanding of the specific perturbations that occur in a given patient could guide novel, patient-directed therapeutic approaches.

[H2] Prevalence

Cancer is a leading cause of morbidity and mortality worldwide, with ~14 million new cases and ~8.2 million deaths in 2012 (Ref.[3]). Cancer-associated cachexia is not included in national cancer statistics in any country; however, it is mainly associated with incurable disease and is highly prevalent at the end of life. Thus, the rate of cancer death is a plausible upper limit for the number of people affected by cachexia; cachexia seldom if ever appears on certificates of death. Cachexia can also occur in curable cancers, and may be reversed by successful treatment of the underlying cancer.

The diagnosis of cancer cachexia is based on the rate of weight loss as well as attainment of low body mass index (BMI)[2]. Most prevalence data are derived from national point prevalence studies or from systematic screening programs in cancer centres[12–15]. Exact criteria used to define cachexia are not consistent across studies, making it difficult to aggregate data. Regardless of the criteria applied, certain cancers are more prominently associated with cachexia (**Fig. 1**)[12–15]. Additional factors that contribute to the variable prevalence of cachexia include more-advanced cancer stage, sex (men are more susceptible than women), age, genetic risk factors, comorbidities and treatment-related catabolic effects. For example, ~30% of patients with cancer have concurrent cardiac disorders with risk for cardiac cachexia; concurrent cancer-cachexia and cardiac-cachexia are speculated to progressively exacerbate each other[16]. Similarly, several drugs used in cancer therapy (such as sorafenib, a tyrosine protein kinase inhibitor)[17] or in palliation of cancer symptoms (such as glucocorticoids), have specific catabolic effects on skeletal muscle.

Variation in the prevalence of cachexia might also partly be due to genotype. A candidate gene approach has been used to explore inherited genetic variations that could explain inter-individual variations in susceptibility to cachexia[9]. However, this area of research is in its early stages and genome-wide approaches are needed to fully appreciate heritable risk.

[H3] Cachexia in the context of obesity

Current WHO statistics indicate >600 million adults worldwide are obese (BMI of >30 kg/m^2)[18], with national rates as high as 50% in some countries[19]. Accordingly, given that cachexia is partly defined by low BMI, contemporary patients with cancer are increasingly less likely to reach traditionally accepted clinically underweight BMI levels (BMI<18.5 kg/m^2). One-third of cancer diagnoses are attributed to behavioural and dietary risks, including being overweight or obesity, which increases the likelihood of obesity in patients with a cancer diagnosis. By contrast, rates of underweight adults are generally <10% in western countries but 30–40% in developing countries. This upward shift in BMI renders the diagnosis of cachexia increasingly unclear.

For patients who are of normal or low BMI before their cancer diagnosis, the effect of weight loss is magnified. Underweight and severely underweight (BMI <16 kg/m^2) patients are at elevated risk of morbidity and mortality[20]. Additionally, large magnitude weight losses can occur in obese individuals without achieving a low absolute BMI[20]. Importantly, severe depletion of skeletal muscle (sarcopenia) may go undetected in patients with obesity[21] (**Fig. 2**). Importantly, muscle loss can occur in the absence of fat loss, and hence can escape detection in obese individuals. For example, patients with breast cancer may gain weight following diagnosis, sometimes in association with loss of muscle mass, leading to development of sarcopenic obesity[22].

[H4] Mechanisms/pathophysiology

Cancer profoundly alters the normal homeostatic control of energy balance (**Box 1**), of which reduced food intake is an important and in some cases predominant component[23,24]. Decreased muscle protein synthesis has also been documented in weight-losing patients with cancer, and the fact that protein synthesis can be reactivated by the provision of nutrients[7,8,25–27] implies the importance of reduced dietary intake in the aetiology of cancer-associated cachexia.

Additionally, tumour metabolism and a rich tumour secretome are important factors unique to cancer-associated cachexia. Tumours possess an intrinsic metabolic rate, which is related to their mass and degree of oxidative versus anaerobic energy metabolism[28]. Tumours compete with other organs and tissues for energy fuels and biosynthetic substrates, and secrete molecules that directly elicit catabolism in target tissues, including a long list of pro-inflammatory cytokines, eicosanoids and factors with tissue-specific effects such as activin (skeletal muscle) or adrenomedullin (adipose tissue). The enhanced inflammation elicited by the tumour also participates in the generation of catabolic pro-inflammatory factors. These effectors modulate homeostatic controls in the CNS, prompting catabolic neural outputs via the sympathetic nervous system, as well as neuroendocrine outputs (such as the release of adrenal corticosteroids) and sickness behaviour (such as anorexia and fatigue). These humoral, neural and behavioural outputs directly activate proteolysis and lipolysis in target organs, primarily skeletal muscle, adipose tissue and cardiac muscle[29]. It has also been suggested that futile cycling — whereby oxidative phosphorylation is uncoupled from ATP synthesis, resulting in only the production of heat — in brown or browned adipose tissue elicits enhanced and inefficient energy expenditure[30], contributing to cachexia (**Fig. 3**). Moreover, futile metabolism cycles occur not only in the adipose tissue, but as a consequence of the inflammation, insulin-resistance and so on also in other cells, such as the immune cells. Abnormalities of mitochondrial dysfunction have also been noted in skeletal muscles, but these mechanisms have not yet been verified in humans with cancer cachexia [Barreto et al., 2016, PMID:27259276; Brown et al., 2017, PMID:28845591; VanderVeen et al., 2017, PMID:28785374)]

Sarcopenia is a key feature of cancer-associated cachexia[2] and its consequences include increased chemotherapy toxicity, complications from cancer surgery and mortality[68]. Increased mortality in cachexia is suggested to include cardiac arrhythmias, electrolyte abnormalities that enhance the risk of developing arrhythmias, thrombo-embolic events, respiratory difficulties due to diaphragm muscle weakness, aspiration pneumonias due to the bedridden state and swallowing difficulties, gastrointestinal mucosal atrophy leading to endotoxin absorption, poor wound healing and sepsis[69]. The prevailing hypothesis for the association between sarcopenia and toxicity of systemic cancer therapy is that patients with low muscle mass have a reduced volume of distribution in relation to the dose of chemotherapy that they receive[70,71]. For example, when body surface area is used as the basis for dosing cytotoxic chemotherapy, in sarcopenic patients the dose may distribute, be metabolized and be cleared within a

grossly depleted lean compartment. Although few pharmacokinetic data show that sarcopenic patients experience greater drug exposure during cancer treatment, an association of dose-limiting toxicity with sarcopenia in different treatment settings has repeatedly been shown[16].

As data are limited on the longitudinal changes of whole-body and tissue-specific mechanisms in patients with progressive cancer cachexia, information must be pieced together from separate studies. Collecting data in patients is often difficult because cachexia occurs at a stage in which patient vulnerability limits use of invasive metabolic tests and biopsies, and disease progression limits the number of patients available for follow-up. Accordingly, additional mechanistic insights must be derived from animal models. However, disparities between clinical and animal findings remain difficult to reconcile. In spite of these limitations, measurements of whole-body energy expenditure and metabolic fluxes, lipolysis, gluconeogenesis, protein synthesis and degradation and substrate utilization have been made in patients[27]. Here, we outline the key mechanisms occurring in cancer-associated cachexia, relying on animal data and pointing out where findings have been recapitulated in patient-derived samples.

[H5] Pro-cachexia cytokines and factors

Catabolic pro-inflammatory factors have attracted the most attention as mediators of cachexia, including several interleukins, tumour necrosis factor (TNF), IFNγ, leukemia inhibitory factor (LIF), growth/differentiation factor 15 (GDF15) and TNF ligand superfamily member 12 (TWEAK) (**Fig. 3**). Identified primarily through cell culture conditions and tumour xenograft models, these factors signal through their respective cell surface receptors and activate selective transcription factors, which in turn promote the transcription of ubiquitin proteasome and autophagy components (**Fig. 4**). Synthesized by tumour or immune cells, the activities of these signalling molecules are sufficient to promote catabolism in target organs such as skeletal muscle, but confirmatory patient data have lagged behind[31].

In addition to inflammatory cytokines, other circulating factors have been described that exhibit pro-cachectic activity towards skeletal muscle (**Fig. 4**). Activin A is a member of the TGFβ superfamily of growth factors that is produced by both tumour and immune cells[32]. In cultured myotubes, activin A promotes atrophy and when over expressed in mice promotes weight and skeletal muscle loss with higher potency than IL-6 (Refs[33–35]). Another pro-cachexia cytokine is TWEAK, which belongs to the TNF family. TWEAK acts through the TNFRSF12A receptor (also known as FN14), which when overexpressed in tumours correlates with cachexia; its role was shown via neutralization of TNFRSF12A, which inhibited weight loss and increased the lifespan in a mouse model [36]. Similar to TNF and IL-6, activin A and TWEAK can promote muscle atrophy in non-malignant conditions, making these factors and their respective receptors through which they signal potentially interesting therapeutic targets[37,38]. Clinical trials for intervention studies targeting activin A and TWEAK have been initiated in both cancer and non-cancer

indications (NCT00771329 and NCT01604642). Information gained from these human studies might determine whether single-line therapy against activin A, TWEAK or TNFRSF12A is sufficient to rescue muscle atrophy in patients with cancer or whether, similar to therapies against TNF and IL-6, a combinatorial approach will be needed to ablate the activities of multiple circulating pro-cachexia factors.

In rodent models of cancer cachexia, expression of E3 ubiquitin-protein ligases TRIM63 (also known as MuRF1) and F-box only protein 32 (commonly known as atrogin-1 or MAFbx)[39,40], which are part of the ATP dependent ubiquitin proteasome pathway, are strongly upregulated. Expression of these proteasome components is largely under the control of the transcription factors FoxO1 and FoxO3, whose activities are post-translationally regulated[41,42] and seem to function as a regulatory node between anabolic and catabolic processes. Under physiological conditions, AKT phosphorylates the FoxO proteins, causing their cytoplasmic localization. However, in cachexia, AKT activity is often suppressed, either under the influence of inflammatory cytokines or owing to the decline in insulin-like growth factor-1 (IGF1) levels (which stimulates muscle anabolism). Decreased AKT activity leads to the dephosphorylation and subsequent nuclear translocation of the FoxO proteins, which in turn, enables their nuclear translocation and the transcription of MuRF1 and atrogin-1, the induction of which correlates with the degradation of myofibrillar proteins, in particular thick filament proteins such as myosin heavy chain[43,44]. Inhibition of mechanistic target of rapamycin (mTOR), which also leads to the concomitant decline in protein synthesis. Thus, in cancer, as in other chronic illnesses associated with cachexia, muscle atrophy is likely regulated by an imbalance of anabolic and catabolic processes. However, muscle AKT activity is not always reduced in cancer cachexia models[45] or in patients with cancer[46].

Additionally, inflammatory factors such as cytokines and angiotensin II reduce AKT activity, thereby causing FoxO nuclear shuttling and induction of muscle protein catabolism[47–50]. In addition to the muscle E3 ubiquitin ligases genes, FoxO transcription factors have a vital role in transcribing genes involved in the autophagy system[51]. Under physiological conditions, skeletal muscle homeostasis requires autophagy to eliminate damaged proteins and organelles. However, in cachexia, the upregulation of autophagy genes leads to excessive activation of autophagy pathways that contribute to enhanced breakdown of skeletal muscle. Other transcription factors such as NF-κB, STAT3, and C/EBPβ also contribute to the regulation of the E3 ubiquitin ligases and autophagy genes[52–61] (**Fig. 4**). Given that animal models do not always recapitulate complex events that occur in cancer cachexia in humans[62], it will be important moving forward to validate the significance of these transcription factors by measuring their activities in skeletal muscle in patients with cancer-associated cachexia.

Indeed, when targeted RNA and protein analysis was performed, components of the ubiquitin proteasome pathway and markers of systemic inflammation were associated with weight loss in patients with cancer[63]. Decreases in the AKT pathway as well as myofibrillar proteins were separately described in patients with cancer-associated cachexia[64,65], which collectively are consistent with findings from animal models of cancer cachexia. By contrast, global gene expression analysis studies to this point have not been able to

recapitulate findings in the protein turnover pathways, which have been widely described in animal models[66,67]. Tissue biopsy from patients, usually collected intraoperatively during cancer surgery to minimize invasiveness, has added mechanistic data.

[H6] Homeostatic control in the CNS

Sickness behaviours, which include anorexia and catabolism of lean body tissues, in addition to fever and lethargy, are classic responses in multiple forms of acute and chronic illness, including malignant disease. An increasing body of evidence suggests the CNS exerts overarching control of the pathogenesis of cachexia[72] through the recognition of cytokines as molecular signals of sickness. Existing data support a model wherein peripheral inflammation is amplified and modified within the mediobasal hypothalamus, creating a paracrine inflammatory milieu that in turn initiates and sustains alterations in the activity of neuronal populations that regulate appetite and metabolic processes, including proteolysis and lipolysis[73,74]. Hypothalamic exposure to any of numerous inflammatory stimuli (such as IL-1β and TNF) triggers an acute illness response, leading to anorexia, weight loss and skeletal muscle atrophy. These molecules act acutely by binding to receptors on hypothalamic neuronal populations, such as pro-opiomelanocortin and Agouti-related protein neurons, which trigger a feed-forward loop that involves skeletal muscle protein catabolism and lipolysis[75]. CNS-delimited IL-1β signalling alone can evoke a catabolic program in muscle, rapidly inducing atrophy. This effect is dependent on hypothalamic-pituitary-adrenal axis activation, as CNS IL-1β-induced atrophy is blocked by adrenalectomy or by muscle-specific knockout of glucocorticoid receptors.

Animal studies are particularly germane to the development of understanding of CNS function in cancer cachexia, and these are starting to be complemented by functional MRI brain imaging studies in patients. For example, Molfino *et al.*[76] showed that patients with cancer who have anorexia had low hypothalamic activity on blood-oxygen-level dependent contrast functional MRI; this activity was also poorly responsive to stimulation by oral feeding compared with patients with cancer who did not have anorexia.

[H7] Adipose tissue depletion

In addition to skeletal muscle, a substantial portion of weight loss in patients with cancer derives from the depletion of adipose tissue[5,77]. Studies have shown that this depletion results from a reduction in fat mass due to lipolysis rather than the irreversible degeneration of fat cells due to apoptosis[78,79]. In mouse models of cancer-associated cachexia, fat loss precedes skeletal and cardiac muscle loss[43], potentially reflecting the early phases of the anorexia-cachexia syndrome. Fat and muscle atrophy in cachexia have been considered independent events owing to the fact that cytokines such as TNF can induce catabolism

in both skeletal muscle and adipose cells. However, this concept was challenged by genetic studies performed in mice in which *Atgl*, encoding adipose triglyceride lipase, was ablated; mice bearing Lewis lung carcinoma xenografts were resistant to the lipolysis of white adipose tissue, but surprisingly retained hind limb muscle mass[80]. This finding suggested that fat loss predisposes muscle loss in cancer-associated cachexia. Similar conclusions were reached in a study in which secretion of parathyroid-hormone related protein (PTHrP) from Lewis lung tumours in mice was shown to alter the thermogenesis of adipose tissue via the 'browning' of white adipose cells[81]. Use of an anti-PTHrP antibody inhibited adipose browning, as well as the loss of skeletal muscle mass, suggesting that altered fat metabolism might be a prerequisite for skeletal muscle atrophy. Thermogenesis is regulated by the uncoupling protein 1 (UCP1), the expression of which increases in various mouse models of cancer cachexia, as well as in white adipose tissue from patients with cancer-associated cachexia[82].

How fat loss predisposes skeletal muscle atrophy is not known. Although several mechanisms have been proposed to account for tumour-induced lipolysis — including the presence of inflammatory cytokines associated from infiltrating tissue macrophages[83,84], induction of adipose triglyceride lipase[85] and loss of AMP-activated protein kinase (AMPK)[86] —whether one or more paracrine factors are capable of cross-talk between fat and skeletal muscle to mediate the catabolism of myofibrillar proteins in unclear.

In patients with cancer, isotopic tracer methodologies have been used to show that cachexia results in an increase of whole-body lipolysis (mean increase of 50%) and whole-body proteolysis rate (mean increase of 40%). Steady-state amino acid flux measurements — across the leg in patients with cancer suggest that muscle loss is not driven by increased protein degradation, but arises due to decreased protein synthesis rate[87]. Muscle fractional protein synthesis rate has also been specifically measured in an isotopic tracer approach combined with biopsy[88]. Another primary metabolic defect of cancer-associated cachexia is the increased rate of whole-body glycolysis and the concomitantly augmented rate of gluconeogenesis from the lactic acid cycle (mean increase of 300%). Adipose tissue biopsy from patients has added mechanistic data.

[H8] Cardiac muscle atrophy

Little research is available concerning the effects of cachexia on vital organs in those with cancer. Cardiac muscle performs an essential physiological role and was assumed to be spared in cachexia, as it cannot simply be exploited as a repository of amino acids as skeletal muscle can. Although cardiac atrophy remains to be evaluated in human cancer-associated cachexia, research in animal models has shown significant cardiac atrophy in multiple cachexia-inducing tumour models, along with echocardiography-defined evidence of cardiac functional impairment[16]. The mechanisms of cardiac muscle atrophy are also described in animal models and are highly similar to those proposed for skeletal muscle, involving inflammation, proteolysis, apoptosis and autophagy.

[H9] Diagnosis, screening and prevention

Although our understanding of cancer-associated cachexia has progressed, a single unified international set of diagnostic criteria are not available. Indeed, a host of disparate diagnostic criteria, which are a detriment to the identification and treatment of cachexia in clinical practice, have been reported[2,89]. Regardless of which criteria used, weight loss is always included, either weight loss alone or in combination with one or several additional features (such as anorexia, reduced food intake, muscle loss, decreased strength, fatigue and biochemical markers[89]). In addition to the use of different combinations of diagnostic criteria, heterogeneity in data collection and reporting of each individual criterion makes defining cachexia for clinical use difficult.

International consensus groups have begun to address these disparities and have provided a conceptual framework for the classification of cancer-associated cachexia[2]. Any useful classification criteria will define definitive cutoff values for each diagnostic criterion that are determined from large contemporary datasets by determining the values that relate optimally to meaningful patient-centered outcomes. Datasets that include information collected in a standardized fashion are necessary and should be large enough to capture representative distributions of candidate diagnostic criteria, relevant covariates and outcomes for adequately powered statistical analyses, including subset analyses. Inclusion of contemporary patients ensures representation from a variety of populations, body weight demographics and treatment plans.

[H10] Diagnosis

The presence of weight loss is an important clinical sign that can even be the first detectable manifestation of the presence of cancer. After the possibility of intentional weight loss (for example, by dieting) has been excluded, alternative causes of weight loss of unknown origin are investigated. Weight loss is typically the first element of a cachexia diagnosis, and has a distinctive course in each patient. For example, weight loss can occur prior to or after the cancer diagnosis and can be slow, intense, continuous or episodic; it should be monitored over time and referenced to the patient's pre-cancer body weight.

Weight also loss varies in its severity: 5% loss is considered the threshold of significant risk of poor clinical outcome[2], with increasing risk as weight loss cumulatively reaches 10%, 15%, 20% or higher. Cancer-associated cachexia contributes to poor prognosis through progressive depletion of the body's energy and protein reserves; thus, it is relevant to determine the impact of weight loss as a function of initial body reserves[2]. The prognostic significance of weight loss in patients who initially have a low, intermediate or high BMI was determined within an international cancer cachexia data repository including >11,000 patients[20]. This multivariate analysis of the association between BMI, weight loss and mortality was controlled for age, sex, cancer site, cancer stage and performance status[20]. A grading

system based on combinations of BMI and weight loss was developed to differentiate groups with distinct median survival durations (**Fig. 5**)[20]. This grading system has been validated[90] and included in current European clinical practice guidelines[91].

[H11] Other criteria

The diagnosis of cancer cachexia will inevitably include additional information beyond weight loss. Although no consensus is available on the definitions of and methodologies for measuring skeletal muscle depletion, reduced food intake and biological indicators of altered metabolism and catabolism, measurement of these elements is becoming increasingly specific, precise and clinically available.

A key driving mechanism of cachexia is reduced food intake[2]. The gap between energy expenditure and energy intake can be estimated from direct measures of resting energy expenditure (indirect calorimetry; **Box 1**) and records of dietary intake[92]. A variety of validated questionnaires are also available to assess quantity and type of dietary intake (**Box 2**)[93].

No standard clinical assessment of skeletal muscle mass is available; however, most published data have been collected from axial lumbar CT images (**Fig. 2**). Standard oncological CT images, collected for cancer diagnostic purposes, offer a new opportunity to precisely quantify skeletal muscle and fat, and to evaluate their changes over time[21]. Indeed, low levels of muscle mass, associated with treatment complications and mortality, have been characterized[21,68]. CT-defined skeletal muscle mass measurements have been increasingly reported in the literature (including >20,000 cancer patients to date since 2008), with calls for this approach to be used more widely[94]. Data are available in different diseases, cancer sites, cancer stages and regions; some provisional sex-specific cutoff values are available as benchmarks to identify patients with muscle depletion[21,95]. These cutoff values have been determined using statistical methods to identify risks (such as mortality, toxicity and quality of life) that emerge at specific threshold levels of skeletal muscle. As CT data continue to accumulate, these can be aggregated to develop sex-specific and age-specific reference values for skeletal muscle depletion[68], enabling the identification of cachexia in patients with high fat mass.

The specific abnormalities of metabolism that define cachexia in a given individual are not routinely assessed, with the possible exception laboratory measures of the acute phase response (the proteins of which are part of the innate immune system response to neoplasia)[2,92,]. The acute phase response is characterized by leukocytosis, fever and changes in the plasma concentrations of positive acute-phase proteins (namely, fibrinogen, α1-acid glycoprotein serum amyloid A, and C-reactive protein (CRP)) and negative acute-phase proteins (namely, albumin and transferrin)[96]. Typical laboratory values are: albumin (<35 g/L), transthyretin (prealbumin) (<110 mg/L) and CRP (>10 mg/L). The Glasgow Prognostic Score, which provides scores for patients with cancer based on albumin, CRP or both, is established as a

powerful prognostic tool in multiple cancers for tumour progression, survival and symptom burden[97,98]. CRP testing is not routine everywhere, but neutrophil to lymphocyte ratios offer similar prognostic information[99].

Although the production of pro-inflammatory cytokines is understood to be central to the inflammatory response to malignant disease, serum cytokine levels have proven too inconsistent to be useful biological criteria. Various different pro-cachectic mediators suggested by preclinical investigations, are being evaluated in patient populations at risk for cachexia. For example, PTHrP was shown to be independently prognostic of weight loss[100] whereas increased levels of GDF15, IL-6 and IL-8 are correlated with weight loss[101]. In the future, changes of inflammatory markers over time might also be useful as markers of the efficacy of cachexia therapy[102].

[H12] Screening

Cachexia screening is performed with the aim of increasing awareness and enabling early recognition and treatment. To detect cachexia at an early stage and to detect its acceleration, regular evaluation of weight change and BMI is needed, beginning at the cancer diagnosis and repeated depending on the stability of the clinical situation. Cancer sites, stages and treatment plans with higher prevalence of cachexia (pancreatic, oesophageal, gastric, pulmonary, hepatic and colorectal) are a priority for screening.

Height and weight are routine, if not mundane, clinical measures, but the continuity of these measures over time is essential to avoid large cumulative weight loss to go unnoticed. Screening for weight loss is performed as a part of evaluation of nutritional risk within clinical nutrition services of cancer centres, linked with nutrition therapy and monitoring of outcomes. Mandatory screening for weight loss in patients with cancer has been established in some countries[91] under the auspices of screening for malnutrition. Screening can be efficient, brief and inexpensive. Patient-reported outcomes are of value in the assessment of various facets of cachexia; evidence support the reliability of patient self-reported height, weight and weight history[91]. Weight loss history and an index of food intake may be obtained directly, or via validated nutrition screening tools **(Box 2)**[91,103].

Abnormal screening results by themselves do not provide enough information to design individualized cachexia care pathways. Patients with a history of substantial weight loss, therefore, need to be followed-up with specific assessments to determine the origin and severity of food intake impairment and metabolic derangements. Within the conventional organization of cancer care, clinical services might exist that have aspects of the management of cachexia in their charge, but there is no set standard. Only a few institutions possess a dedicated cachexia clinic[104–107]. Otherwise, cachexia can fall in the purview of symptom control or palliative care, but may equally well be attended to by clinical nutrition services insofar

as access to dietitians and medical nutritionists is often available in cancer centres and hospitals. Because of the important role of reduced dietary intake in development of cachexia, presence of this issue can be part of the primary screen, and used to direct further assessments towards identifying needs for nutritional support.

[H13] Prevention

Prevention has not been the standard in the clinical approach to cancer-associated cachexia. Although weight loss can occur early, active treatment of cachexia has often been left to the end stages of the disease and the refractory stage of the cachexia. However, a shift towards considering preventative cachexia therapy (see below) is apparent. Notably, recent trials of cachexia therapeutics[108,109] have been shifted to an earlier time in the disease trajectory and are delivered concurrently with first-line chemotherapy rather than in the end of life phase[110–112]. The earliest possible approach would be contingent on developing a clear understanding of the predictors of cachexia, including the pre-cachexia biomarkers.

[H14] Management

Cancer-associated cachexia evolves over time, and goals of care should be established at each stage of the evolution. The majority of patients with advanced-stage cancers of the lung, pancreas, oesophagus, stomach, colon and liver will experience cachexia[1,12–15], and this foreknowledge should be a basis for early and systematic attention to cachexia management. Although exact diagnostic criteria for 'precachexia' remain undetermined, this is a useful concept that enables preventative intervention at the onset of low-grade weight loss. Recent phase III trials have adopted a strategy of early intervention, moving away from using 5% weight loss as an inclusion criteria and instead including patients with either minimal weight loss (≥2%; see, for example, NCT00467844)[108] or removing a requirement for prior weight loss altogether (see, for example, NCT01355484)[109]. This approach is based on a high and imminent probability of patients in the trial developing cachexia.

The catabolic sequelae of cancer treatments can add substantially to overall weight loss. For example, mean weight losses in patients receiving neoadjuvant chemotherapy for oesophago-gastric cancer (~4.2 kg)[113] or receiving chemoradiotherapy for head and neck cancer (~11.4 kg)[23] are substantial, and these losses are composed of lean tissue in the majority of patients[24,113]. Preventive measures can also be deployed in anticipation of these losses. A multimodal approach targeting the multiple facets of cachexia is likely to be the optimal approach.

[H15] Nutritional and metabolic treatment

Provision of adequate nutrition is a mainstay of cachexia treatment, and up-to-date guidelines for clinical nutrition in oncology are available[91]. First-line approaches include oral nutritional supplements and

consultation with a nutritional health care professional to increase the quantity and quality of the patient's food. In patients in whom the dominant cause of weight loss is deficit of dietary intake (for example, those receiving high-dose chemotherapy ahead of bone marrow transplantation, in whom daily deficits of oral intake can exceed 1,200 kcal/day), active nutritional management leads to better treatment tolerance and better quality of life[95]. For the majority of patients, and particularly for those with advanced-stage cancer, the presence of insufficient dietary intake is not always identified and active nutritional management is not always implemented[15]. Furthermore, compliance to oral nutritional supplements is generally low and in some cases nutritional supplements merely displace food intake at mealtime[114].

If volitional food intake remains insufficient after dietary consultation and oral nutritional supplements have been deployed, escalation to artificial (enteral or parenteral) nutritional support is an option (**Box 3**). Orexigenic drugs (appetite stimulants) have been developed to counteract low appetite in patients with cachexia. Cannabinoids, corticosteroids and progestagens have these actions, but adverse effects constrain their use[115]. For example, corticosteroids increase appetite but result in skeletal muscle atrophy; progestogens have the same effect as well as increasing the risk of thromboembolism[115]. New therapies to enhance food intake under investigation include ghrelin receptor agonists[108,116] and melanocortin receptor 4 antagonists[117]; these agents act on the hypothalamus, which regulates appetite and satiety, but also have systemic effects to promote protein anabolism and energy storage.

Anabolic deficit may be partly addressed by maintenance of physical activity, a notion that is endorsed within European oncology nutrition clinical practice guidelines[91] as well as in the design of clinical trials of multimodal intervention (see, for example, NCT02330926). Patients should be given support to enable them to exercise within their safe capacity[91,118]. Cachexia in chronic non-malignant illnesses such as chronic obstructive pulmonary disease has long been managed by a multimodal approach (including nutrition and exercise)[119]. Indeed, a systematic review of 16 trials in patients with cancer in active oncology treatment, showed that aerobic exercise, resistance exercise and a combination of two improve upper and lower body muscle strength compared to usual care[120]. However, it has been noted that patients with established cachexia might lack the motivation and self-efficacy to undertake regular structured exercise[121]. Others have proposed interventions designed to provide exercise intervention optimized for individual patient activity tolerance[122].

Altered metabolism remains the most challenging aspect of cancer-associated cachexia for therapeutic intervention. Specific therapeutic targets have been proposed for testing in clinical trials (**Table 1**) based on preclinical investigation and covering a broad range of mechanisms. These targets reflect the complexity of cachexia and are drawn from every point of our understanding of cachexia physiology, including tumour-specific factors, pro-inflammatory cytokines and eicosanoids, and mediators of organ-specific or tissue-specific control systems (**Fig. 6**). However, none of these suggested targets has as yet led to approval of a drug for the indication of cancer-associated cachexia. Our understanding of the underlying mechanisms of cachexia in individual patients is crude at best; accordingly, further

characterization of the clinical aetiologies is needed. One approach might be to assess and ‘rank’ different pro-cachectic mechanisms to guide drug development; however, routine management has not achieved such a level of sophistication and aetiology-based diagnostic criteria has not been standardized in clinical care or in clinical trials.

[H16] Symptom control

Cachexia does not occur in isolation; it occurs within a variable terrain of comorbid conditions, cancer treatment response and toxicity, and alongside pain and other symptoms. Symptoms are a considerable source of clinical heterogeneity in weight-losing patients, can change rapidly over the course of the disease trajectory and treatment plan[123] and are most common among patients receiving treatment for advanced-stage cancers[124] — but remain undetected by clinicians in up to half of patients[125]. Symptoms present at any point in time are only a ‘snapshot’ of a longer story that can last several years, with multiple treatments and complications contributing to progressive wasting**.** Cachexia cannot be divorced from these circumstances and good medical management of pain and symptoms is another major principle of cachexia management. Often, multiple causes of potentially reversible weight loss must be assessed and appropriately managed; this is a point for action and immediate benefit to the patient[118].

Causes of weight loss that are amenable to effective management include, but are not limited to, pain, nausea, vomiting, dental problems, dysphagia, early satiety, oesophageal obstruction, malabsorption, endocrine and metabolic disorders, anxiety, depression, distress and inability to sleep. Clinical trials of cachexia therapy have been conducted in the past without a common standard of supportive care elements across centers, which has been suggested to be a source of heterogeneity in individual patient response. A multidisciplinary team approach to supportive care is needed[91], the benefits of which have been reported from prospectively conducted non-randomized studies[126,127]. Clinical services are emerging that operate in partnership between palliative care physicians and the oncology community, as endorsed currently by many cancer agencies including the American Society for Clinical Oncology[128]; these services will be an asset for efficient management of symptoms contributing to cachexia.

[H17] Multimodal care

The inherent complexity of cancer cachexia calls for a multifaceted assessment strategy that focuses on food intake, pain and symptoms, specific losses of muscle and fat, catabolic factors, tumour burden, systemic inflammation and altered endocrine status, as well as the clinical, functional and psychosocial consequences of the condition[129–132]. The rationale is that addressing food intake alone (for example) would be insufficient because this would not necessarily be expected to mitigate excess catabolism (and vice versa). In cancer surgery, a multimodal approach is embraced by multi-component enhanced recovery after surgery protocols[133]. In current clinical practice, multimodal therapy is achieved by a

collaborative approach that engages a multidisciplinary team of health professionals as well as patients and their families. Expertise included in multimodal therapy include clinical oncology, clinical nutrition and palliative care teams as well as the possibility of specialist referral (for example, gastroenterologists). Guidelines and protocols exist, and descriptions of dedicated cachexia services have been reported[104–106]. In ongoing clinical trials (see, for example, NCT02330926), multimodal intervention is formalized and the study design can include nutritional therapy, anti-inflammatory interventions and/or exercise therapy. However, such multimodal interventions remain a minority of available studies (Fig. 6 and Table 1).

A critically important underlying concept is that the driving forces advancing tumour growth and metastases are the same driving forces that underlie cachexia. Accordingly, a combined and collaborative approach to cancer and cachexia therapy, rather than sequential (or parallel) approaches would seem most logical. The potential for a downward spiral, in which cachexia exacerbates treatment toxicity[134,135], which then further exacerbates cachexia, should be acknowledged. This spiral can be interrupted by careful management of cachexia throughout treatment and attention to providing chemotherapy at doses that are within the limits of tolerability for patients already affected by cachexia at the time treatment is initiated. In day-to-day practice, patients who are older or who seem to have a reduced level of fitness are routinely given lower chemotherapy doses or provided a regimen with reduced toxicity, at the treating oncologist's discretion. These approaches may be relevant for patients with manifestations of cachexia.

[H18] Cachexia at the end of life

At the distal end of the cachexia spectrum, the disorder can become refractory to therapeutic intervention; when catabolism intensifies at an exponential pace[5,136], cachexia is driven by progressive disease that no longer responds to antineoplastic therapy, patients frequently become emaciated and death becomes imminent. These blatant manifestations heighten the sense of anguish related to cachexia for patients and their families. Psychological support is key at this point, with lesser emphasis on dietary intake as a therapeutic objective.

Cachexia therapies are associated with risks, burdens and costs that need to be weighed against the expected benefits, with the knowledge and consent of the patient. In refractory cachexia, medical interventions may be futile or inappropriately invasive[91,137]. Artificial nutritional support in the form of parenteral nutrition is a well-known example; clinical practice guidelines in nutrition, oncology and palliative medicine consistently agree that in patients expected to survive <2 months, initiation of parenteral feeding is not recommended[91,137]. Robust predictors of a patient's entry into the end of life phase are needed to limit the potential harm of aggressive anti-cancer therapy and anti-cachexia therapy. Prognostic models for survival have been developed to assist decision-making concerning the use of parenteral nutrition in patients with advanced cancer[138].

A particular weakness of many previous clinical trials of cancer cachexia interventions was to include patients with refractory cachexia or a mixture of these with individuals at earlier stages. Not surprisingly, a substantial proportion of patients died within just a few weeks of random assignment[110–112]. Clinical trials of cachexia therapy often have had inclusion criteria such as 'expected survival' of >6 months. However, in the absence of adequate prognostic algorithms, such criteria have not prevented inclusion of imminently dying patients in trials. High rates of attrition and missing data have created great difficulty in interpreting the results of many investigations.

[H19] Quality of life

Cachexia-related quality of life is not currently evaluated by a single agreed instrument. The European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQC30) and Functional Assessment of Anorexia Cachexia Therapy (FAACT) questionnaires are the most commonly used instruments in the literature, whereby the former is not specific to cachexia and the latter has been used but has been criticized as not fully representing all of the relevant domains[139,140]. A new cachexia quality of life instrument is in development within the EORTC paradigm: the QLQ-CAX24 is a cancer cachexia-specific questionnaire comprising 24 items for health-related quality of life assessment in clinical trials and practice[141]. It contains five multi-item scales (food aversion, eating and weight-loss worry, eating difficulties, loss of control and physical decline).

Psychological dimensions of the experience of cancer-associated cachexia from the perspective of patients and their family members is less well explored than the biomedical aspects of the condition[120-128]. Negative interactions with food and eating are described at every stage of cachexia; because of alterations in the taste, smell and texture of food, usual foods and even favourite foods can become unpleasant or even repulsive[123,142,143]. Chewing and swallowing can be painful, and an unpleasant sensation of early satiety makes patients feel too full to continue eating or repelled by the quantity of food served. Furthermore, patients express distress about weight loss and not eating enough and are highly aware of death as the ultimate result of the weight loss[123]. Patients describe laborious efforts to maintain and increase food intake and are often frustrated by emergent pain and symptoms. The wasted appearance of the cachectic patient with cancer is a major source of concern for both patients and families[144,145]. This experience occurs within unique personal, social, historical and cultural contexts.

Loss of control is another major theme in patient narratives about the experience of cancer-associated cachexia. Even the most successful cachexia therapies only slow the rate of weight loss and weight is lost regardless of the level of food intake. Fatigue, weakness and loss of independence compound the sense of helplessness in patients, as does feeling pressured by others with respect to food and eating[123,145,146]. If the patient and his or her family members do not have an equal degree of understanding of disruption in food connections, conflict with family members over food and social

isolation can ensue[144]. For patients, the inability to share food in the manner hoped for by family members can contribute to a larger concern about being a burden.

Psychosocial support to patients and families is recommended as part of cachexia management, especially in the refractory stage[129,130]. The components of such support are in development[147] and include a reduces emphasis on preparing and serving food, enabling family to provide aid without applying pressure and providing information about cachexia and how it will affect the patient and their families.

[H20] Outlook

Cachexia represents a constellation of various phenotypes that require further study from many angles as illustrated in this Primer. Encouragingly, cachexia now has wider recognition as an unmet medical need[148]: its research is supported by an international society — the Society on Sarcopenia, Cachexia and Wasting Disorders (http://society-scwd.org/) — and it has a dedicated research publication (namely, the *Journal of Cachexia, Sarcopenia and Muscle*[149]) as well as a series of international conferences. Cancer research has for many decades been advanced through a system of cooperative research groups that conduct national or international multi-disciplinary research for cancer control; a timely addition to cancer cachexia research would be a cooperative group of researchers, cancer centres and community-based physicians to mount studies that test new ways to screen, prevent, diagnose and treat cancer cachexia.

[H21] Mechanisms/pathophysiology

Emerging mechanistic insights continue to emerge from studies in animal models. For example, new data have surfaced that places attention on skeletal muscle stem cells[150]. Specifically, a resident stem cell population called satellite cells[151], which is marked by the transcription factor Pax7 (Ref.[152]), provides regenerative capacity to this tissue. However, in experimental cancer-associated cachexia, this program lacks key myogenic factors MyoD and myogenin that are needed to repair damaged myofibres[150]. Other muscle progenitor cell populations (such as those expressing non-satellite cell markers, namely NG2 and PDGFRα) also have been shown to be expanded in association with tumour-induced muscle damage. Collectively, these Pax7$^+$ progenitor cells demonstrate activation of NF-κB, which serves to retain a stem cell fate rather than proceed through a differentiating regeneration program. This block in regeneration that contributed to myofiber atrophy, occurred independently from the activation of the ubiquitin proteasome and autophagy pathways that drive muscle loss from within the myofiber.

Another recent report suggested link between muscle weakness and bone metastasis arising from solid tumours such as breast cancer or lytic bone lesions due to multiple myeloma[153]. Lytic metastatic lesions release TGFβ from bone matrix; circulating TGFβ was shown to signal to skeletal muscle through SMAD2 and SMAD3 transcription factors to induce the transcription of *NOX4* (which encodes NADPH oxidase).

NADPH oxidase stabilizes ryanodine receptor I (RyR1) via oxidation, causing aberrant Ca^{2+} 'leakage' from the sarcoplasmic reticulum, resulting in muscle weakness. Muscles from patients with lung and prostate cancer with metastases to bone also exhibited oxidized RyR1. Many solid tumours, including cancers of the stomach, pancreas, breast, colon and rectum[154–157], release TGFβ into the systemic circulation. Using data from The Cancer Genome Atlas (TCGA), a recent study documented the presence of a strong inflammatory gene signature in pancreatic cancer that includes IL-6 and IL-11, occurring in conjunction with a strong TGFβ gene signature[158]. Thus, inflammatory cytokines such as IL-6 and IL-11 possibly cause muscle loss that combines with TGFβ-induced muscle weakness to accelerate cachexia-associated muscle dysfunction.

Despite these advances, a translational gap between human and animal studies of cancer cachexia remains. A large proportion of prior research in rodent models has been conducted on a rather limited repertoire, including models harbouring colon-26 adenocarcinoma, Lewis lung carcinoma, Yoshida hepatoma and Walker 256 carcinosarcoma[159–162]. The original cell lines have become unavailable, cells have been passed between different laboratories and currently available subclones might have deviated no longer provide consistent results[81]. The generation of genetically engineered models of cancer, aligned with the clinical cachexia phenotypes, should offer new avenues for preclinical investigations. For example, a murine model of pancreatic cancer, $KRAS^{G12D/+}$ $P53^{-/-}$ Pdx-Cre (KPC) congenic allografts in C57Bl/6 mice[163] as well as patient-derived orthotopic pancreatic cancer xenografts[164] recapitulate the cachexia features specifically associated with pancreatic ductal adenocarcinoma. Finally, cachexia models do not reflect the clinical complexity of oncology patients, who are generally older and often present with significant concomitant comorbidities and prior, as well as concurrent, treatment with systemic therapies. Solutions to these issues are urgently needed.

[H22] Diagnosis

Aetiology-based diagnostic criteria for cancer-associated cachexia would represent a significant advance. Weight loss 'not otherwise specified' is traditionally used as the basis for a diagnosis of cachexia and the indication for treatment, regardless of aetiology. In past clinical trials, unspecified weight loss was treated with a number of highly specific agents (including the monoclonal antibody infliximab, which targets TNFα[165]) without testing whether the patients expressed the target. As the field continues to advance and patients can be better classified and sub-classified using biomarkers**,** genomics or metabolomics, we will be able to offer a more-personalized, mechanistically derived treatment approach to each patient. Some emerging areas of human biology of cancer-associated cachexia include genetic risk variants[9,166,167], transcriptional variants[168,169] and biological profiling using high dimensional omics approaches[170–172].

[H23] Management

Because cachexia can be divorced mechanistically from the underlying disease[10,11], and anabolic processes can be activated under appropriate conditions in patients, the targeting of anabolic processes

should be possible. For example, patients with locally advanced or metastatic disease demonstrate activation of muscle protein synthesis after intake of high-quality proteins[8,25,26]. Furthermore, drugs that inhibit catabolic processes have been shown to increase both lean and fat mass in kilogram quantities has been achieved in patients with some of the most catabolic diseases, including advanced-stage lung cancer and cholangiocarcinoma[6,7,108]. Optimal conditions for exploiting this anabolic potential are currently under study, with the overall aim of net improvements in muscle mass, functionality, performance status and treatment tolerance.

Another area of growing interest is to use mechanistic insights to develop biomarkers and targeted therapies for cachexia. To achieve this, more information on origins of heterogeneity in the patient-specific aetiology of cachexia is needed. For example, tumour over-production of specific individual mediators that are potently catabolic towards muscle or adipose tissue, such as PTHrP[30,81,82] and adrenomedullin[173] (both of which elicit lipolysis in white adipose tissue), are potential targets. PTHrP is normally absent in the peripheral blood of healthy individuals but mutations that amplify its expression in tumours[174] can promote high systemic concentrations in patients with cancer; this expression is associated with poor prognosis[175]. Adrenomedullin has been shown to be encapsulated in tumour-derived exosomes in pancreatic cancer[173]. It was also demonstrated that microvesicles (which include exosomes) derived from pancreatic cancer cell lines can induce myoblast apoptosis by activating c-Jun N-terminal kinase, and that this effect is mediated through the Toll-like receptor TLR7 (Ref.[176]). These effectors may prove to be actionable targets of cancer cachexia in patients whose tumours overexpress them. However, where complex inflammatory cascades are activated, redundancy between individual mediators is common. Accordingly, the targeting a single mediator will unlikely ‘cure’ the majority of patients with cancer-associated cachexia. Points of targeted intervention must be chosen to maximize impact on the overall syndrome.

Intriguing relationships between cachexia therapy and cancer therapy are also emerging. For example, studies suggest that tumour cell proliferation and the excess muscle protein catabolism characteristic of cachexia might have a common mechanism. Specifically, the mitogen-activated protein kinase kinases MEK1 and MEK2 act downstream of RAS and RAF to induce ERK activation, thereby communicating input from growth factors to promote proliferation of tumour cells. This signalling pathway also seems to be involved in the activation of excess muscle protein catabolism in the tumour-bearing organism[6,177]. MEK inhibitors might, therefore, simultaneously have anti-cachexic and anti-tumour activity. Further exploration of these types of interactions is warranted.

Finally, clinical trials of cancer-associated cachexia continue to evolve in their design and end points. Until recently, the landscape of clinical trials for cachexia was somewhat limited and the overall quality of the evidence was low[91,115]. However, now trials are no longer conducted in the refractory stage, avoiding

issues of confounding by death, dropout and missing data. Additionally, patient populations and concurrent anti-cancer treatments in current cachexia clinical trials are more homogeneous than in the past. However, regulatory authorities are being challenged with issues in study design and the specific nature of approvable end points[148]. For example, although the consensus is that cachexia therapies should be expected to produce stabilization or gain of radiologically-defined lean mass, skeletal muscle and fat mass, an independent form of clinical benefit associated with these tissue gains is mandated by regulatory authorities. The definition of this clinical benefit is contentious, and several recent randomized phase III studies failed to meet criteria for approval based on the clinical benefit end points of handgrip strength[108] and stair climb test[109]. Alternatives to these end points are under discussion and might include patient-reported outcomes, health care utilization, costs and/or survival. Although these developments are ongoing, creating opportunities for patient participation in clinical trials of emerging drug therapies and nutritional interventions for the indication of cancer-associated cachexia provides a way to access front-line treatments. These investigations are essential to advance the testing and approval of new cachexia therapies.

Display items

Box 1. Energy intake and energy expenditure imbalance in cancer-associated cachexia

Body weight remains stable when there is balance between energy intake (that is, calories provided via oral, enteral or parenteral routes) and the total energy expenditure (TEE) by the body (see illustration). Body weight loss occurs when there is a negative energy balance; a state where TEE exceeds energy intake. TEE is the sum of resting energy expenditure (REE), activity-related energy expenditure (AEE) and the thermic effect of food (TEF). REE is the amount of energy expended by the body at rest, and is the largest contributor to TEE. Accordingly, as TEE is difficult to measure clinically in free-living individuals, REE is typically assumed to represent energy metabolism. REE can be accurately measured using indirect calorimetry or estimated using various widely used equations, which have many limitations. Tumour metabolism and inflammation might increase REE and simultaneously decrease energy intake (through, for example, loss of appetite), shifting the scale toward negative energy balance[178,179]. Additionally, cancer treatments also influence energy balance; for example, energy intake may fall by >50% (~1,200 kcal per day) during chemoradiotherapy in cancers of the head and neck[23]. These factors contribute to the negative energy balance in cancer-associated cachexia.

Box 2. Assessment of dietary intake in clinical practice

Food intake — assessed as a component of clinical questionnaires — is used to screen or assess nutritional status.

- Example tools include the Patient Generated-Subjective Global Assessment (PGSGA), Mini Nutrition Assessment (MNA), Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST), Short Nutrition Assessment Questionnaire (SNAQ), Nutrition Risk Screen (NRS2002).
- Questionnaires are completed by a healthcare provider or the patient, with reponses being categorical in nature. Reductions to food intake are assessed as a ‘yes’ or ‘no’ response, or from a categorical list describing the severity of the reduction (for example, ‘no decrease in food intake’, ‘moderate decrease in food intake’ or ‘severe decrease in food intake’).
- The time frames for assessing reductions in food intake tend to be retrospective and are variable (for example, current intake, recent intake, intake in the past week, past month or past 3 months)
- These tools are clinically practical and expedient, and are obtained from patient reporting.
- The information obtained identifies patients with reduced food intake who might benefit from further dietary assessment and intervention.

Food intake can also be assessed from patient food records.

- Example tools include 24-hour recall (food consumed the previous day) and prospectively collected 1–7-day food diaries.
- Current food and fluid intakes are recorded, entered into a country-specific nutrient database, and macronutrient and micronutrient estimates are calculated.
- Diet records are burdensome to the patient and to healthcare provider who must process the collected information, but are useful for determining food preferences and patterns of consumption, which can aide in the development of a nutrition intervention.

Box 3. Options for nutrition support in patients with cancer

[H1] Volitional nutrition

Volitional nutrition refers to the oral ingestion of nutrients as normal food and/or oral nutritional supplements (ONS). Dietary modification (such as increased calorie or protein density, or texture modifications) and ONS are typical first-line interventions to improve intake in patients with cancer. Management of pain and symptoms is essential to optimize volitional food intake.

[H2] Artificial nutrition

Artificial nutrition is non-volitional feeding and is initiated when an individual cannot meet their nutritional requirements via oral intake. The indications to implement artificial nutrition are either total inability to eat for >1 week or an energy intake <60% of requirement for >2 weeks[91]. Artificial nutrition is provided by the enteral route, unless the gastrointestinal tract is not functional and includes:

- Enteral nutrition (tube feeding), which is any mode of feeding that uses the gastrointestinal tract to deliver all or part of a patient's nutritional requirement. A tube is used to access either the stomach or jejunum. This might be used, for example, owing to tumour obstruction of the oesophagus or dysphagia in pharyngeal cancer).
- Parenteral nutrition (intravenous feeding), which is a mode of feeding that delivers all or part of a patient's nutritional requirements intravenously via a central or peripheral vein, thereby completely bypassing the gastrointestinal tract. This might be used, for example, in patients with gastrointestinal tumours following surgical resection.

Associated risks of artificial nutrition include infections, gastrointestinal adverse effects (such as nausea, vomiting, diarrhoea and hepatic abnormalities), metabolic dysregularities (such as hyperglycaemia) and mechanical complications. High-quality evidence is lacking for the use of artificial nutrition to treat cancer-associated cachexia; however, in settings in which intake is severely impaired primarily owing to tumour location or symptoms of treatment, artificial nutrition can be partially effective and improve outcomes[91].

Figure 1. Cancer cachexia by tumour site. The prevalence of cachexia (defined as >5% weight loss in previous 6 months) by cancer site (panel a) and the average weight loss (%) and its variation (error bars) by cancer site (panel b). Data from Refs[12],[15] .

Figure 2. Severe muscle depletion can occur in patients with cachexia or obesity. CT images from two female patients with sarcopenia are shown; the images on the left correspond to a woman with a BMI of 47 kg/m^2, the images on the right correspond to a woman with a BMI of 17 kg/m^2. Sarcopenia is occult in the woman on the left but obvious in the woman on the right. For both women, the lumbar skeletal

muscle index (SMI, a standardized unit of measure of muscle area normalized for stature), is 36.8 cm^2/m^2. Although both women are 60 years of age, this SMI value is typical for a patient with cancer who is >80 years of age[68]. Axial plane with tissue annotations (panels **a** and **b**). Sagittal plane (panels **c** and **d**). Coronal plane (panels **e** and **f**). **g |** Distribution of SMI in female patients with advanced-stage cancer[68].

Figure 3. Inter-organ relationships in cancer-associated cachexia. On the basis of clinical and experimental findings, tumour-derived catabolic factors have been shown to act on target tissues to elicit excess catabolism. Numerous pro-inflammatory cytokines are generated through tumour cross-talk with the immune system, which act directly on target tissues as well as through alteration of central nervous system (CNS) controls of energy intake and expenditure. Mobilization of adipose tissue results from specific tumour-derived lipolytic molecules (such as adrenomedulin), tumour factors which induce uncoupling and futile cycling in this tissue (such as parathyroid hormone-related protein) and/or by activation of sympathetic neural output. Skeletal and cardiac muscle mobilization is induced by multiple pro-inflammatory cytokines, eicosanoids, and transforming growth factor-β (TGFβ) family effectors (such as activin and myostatin). These effectors might also be responsible for the failure of muscle stem cells to appropriately proliferate and differentiate. Inflammation in the CNS evokes a catabolic programme in muscle, rapidly inducing atrophy. This effect is dependent on hypothalamic–pituitary–adrenal axis activation. GDF15, growth/differentiation factor 15; LIF, leukaemia inhibitory factor; miR; microRNA; PGE_2, prostaglandin E_2; TNF, tumour necrosis factor; TNFRSF12A, TNF receptor superfamily member 12A (also known as FN14); TRAF6, TNF receptor-associated factor 6; TWEAK, TNF ligand superfamily member 12.

Figure 4. Signalling pathways involved in tumour-induced skeletal muscle atrophy. Skeletal muscle atrophy in cancer cachexia is regulated by signaling pathways that are activated by cytokines produced by the immune system or the tumour itself. These factors signal through their respective cell-surface receptors that activate selective transcription factors, which in turn bind to promoters of genes coding for components of the ubiquitin proteasome and autophagy systems. In general, activation of these systems leads to the destruction of selective myofibrillar proteins that form the sarcomere and provide contractile function to skeletal muscles. Loss of these myofibrillar proteins presumably results in muscle atrophy and weakness. Alternatively, growth factors such as and transforming growth factor-β (TGFβ) can signal to alter calcium (Ca^{2+}) handling, leading to the dysfunction of the sarcomere without decaying sarcomeric proteins. In addition to cytokines, growth factors such as insulin-like growth factor-1 (IGF1) signal through AKT to mediate functional repression of the forkhead box proteins (Fox) O1 and FoxO3 transcription factors to inhibit the expression of ubiquitin ligase and autophagy selective genes; in cachexia this activity is often suppressed (indicated by dashed lines), leading to the transcription of genes that encode E3 ubiquitin ligase components. ActRII, activin receptor type-2A; C/EBPβ, CCAAT/enhancer-binding protein-β; GP130R; LIF, leukaemia inhibitory factor; NF–κB, nuclear factor-κB; P, phosphate; R, receptor; SMAD,

mothers against decapentaplegic homolog; STAT3, signal transducer and activator of transcription 3; TNF, tumour necrosis factor; TNFRSF12A, TNF receptor superfamily member 12A (also known as FN14); TWEAK, TNF ligand superfamily member 12.

Figure 5. Grading scheme for weight loss based on risk of mortality in patients with advanced-stage cancer. The grading scheme was developed based on groupings of body mass index (BMI) and weight loss (WL) showing distinct median survival durations. The analysis was laid out in a 5 × 5 matrix representing five different weight loss categories within each of the five different BMI categories and producing 25 possible combinations of weight loss and BMI. Grade 0 was assigned to the subgroups in the matrix with the lowest risk (longest survival), and grades 1–4 were assigned to the subgroups according to decreasing survival rates. Grades were developed based on 8,160 patients and adjusted for age, sex, cancer site, cancer stage and performance status. Adapted from Ref.[20]

Figure 6. Proportional distribution of therapeutic approaches in clinical trials of cancer cachexia therapy. Although not exhaustive, this summary of 134 trials (including published works and ongoing investigations) of the major classes of cachexia therapies includes treatments at phase II–IV clinical trial. The trials are reported in www.clinicaltrials.gov.

Table 1. Example phase III clinical trials for cancer-associated cachexia, anorexia and muscle wasting

Study	*n*	Therapy (mechanism)	Therapeutic approach	Results
Temel et al.[108] (NCT01395914 and NCT01387269)	979	Anamorelin (ghrelin receptor agonist)	Appetite-modifying and anabolic	• Increased lean body mass • No effect handgrip strength
Crawford et al.[109] (NCT01355484 and NCT01355497)	651	Enobosarm (selective androgen receptor agonist)	Anabolic	Increased lean body mass, stair climb power and stair climb speed in those receiving taxane chemotherapy versus non-taxane chemotherapy
Bourdel-Marchasson et al.[180] (NCT00459589)	341	Dietary advice	Nutritional	• No change in survival at 1 year and 2 years • No change in chemotherapy toxicity • No change body weight
Sánchez-Lara et al.[181] (NCT01048970)	96	ω-3 fatty acids (oral nutritional supplement)	Nutritional	• Increased weight • Increased lean body mass • No change in chemotherapy response
Madeddu et al.[182]	60	L-Carnitine, celecoxib and megestrol acetate versus L-carnitine and celecoxib (nutritional supplement and COX2 inhibitor with or without appetite stimulant)	Multimodal	Non-inferiority of two-agent versus three-agent combination with respect to lean body mass and total daily physical activity
NCT02330926	240	Ibuprofen, physical activity, dietary advice and ω-3 fatty acids	Multimodal	In progress; assessing body weight, muscle mass and physical activity
NCT02138422	276	Xilonix™ (anti-IL-1α)	Anti-inflammatory	In progress; assessing disease response rate, muscle mass and appetite
NCT02553187	160	Kanglaite (coicis oil)	Herbal or alternative	In progress; assessing body weight and lean body mass
NCT02802540	78	Nabilone (synthetic cannabinoid)	Other	In progress; assessing anorexia, weight loss and caloric intake

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Figure 1

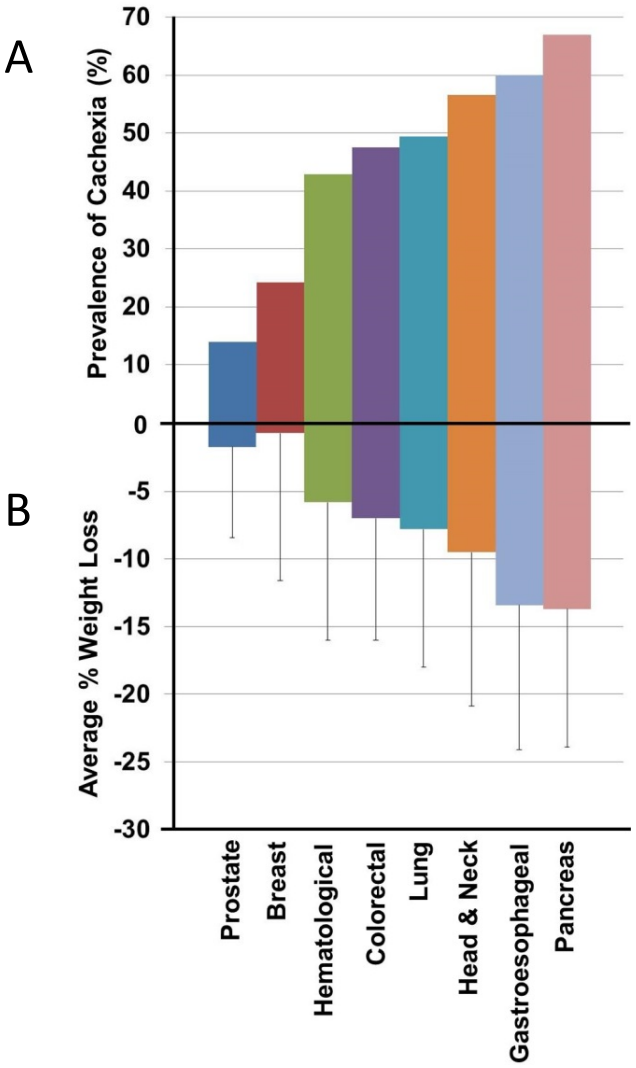
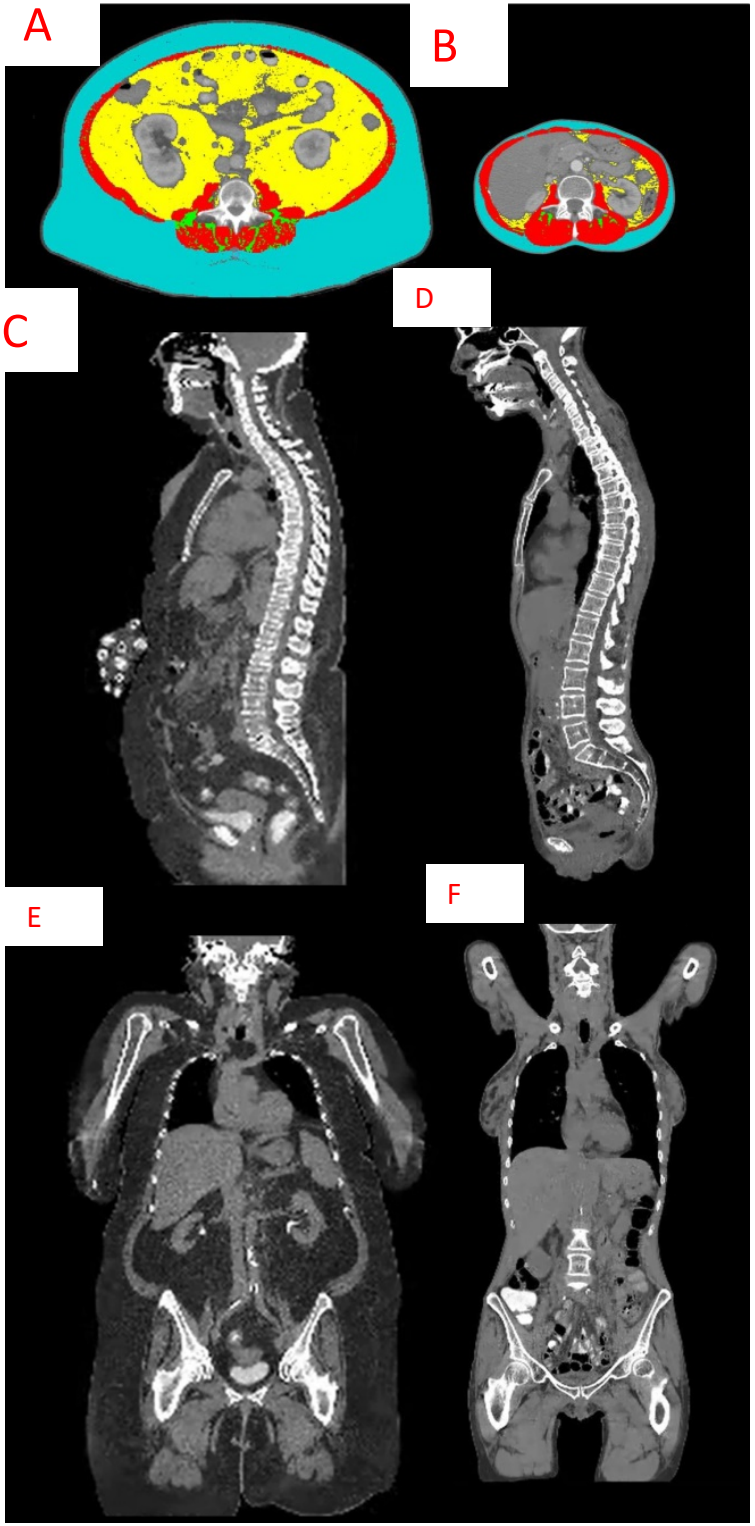
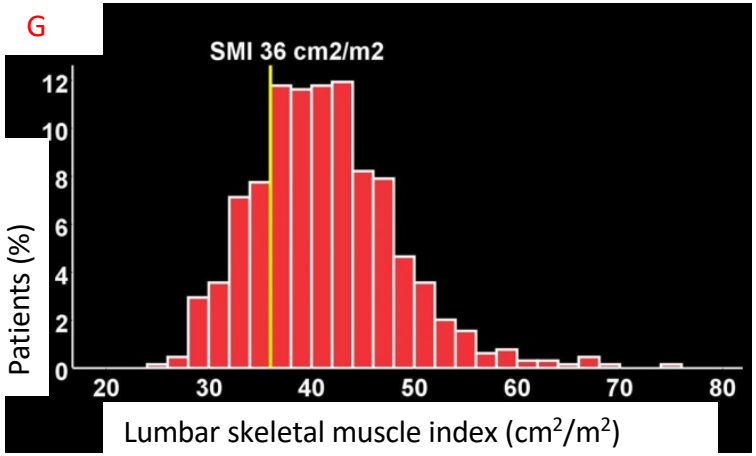

A
B
Prevalence of Cachexia (%)
Average % Weight Loss
70
60
50
40
30
20
10
0
-5
-10
-15
-20
-25
-30
Prostate
Breast
Hematological
Colorectal
Lung
Head & Neck
Gastroesophageal
Pancreas

Figure 2





Yellow: visceral adipose tissue
Red : skeletal muscle
Blue: subcutaneous adipose tissue
Green: intermuscular adipose tissue

Figure 3

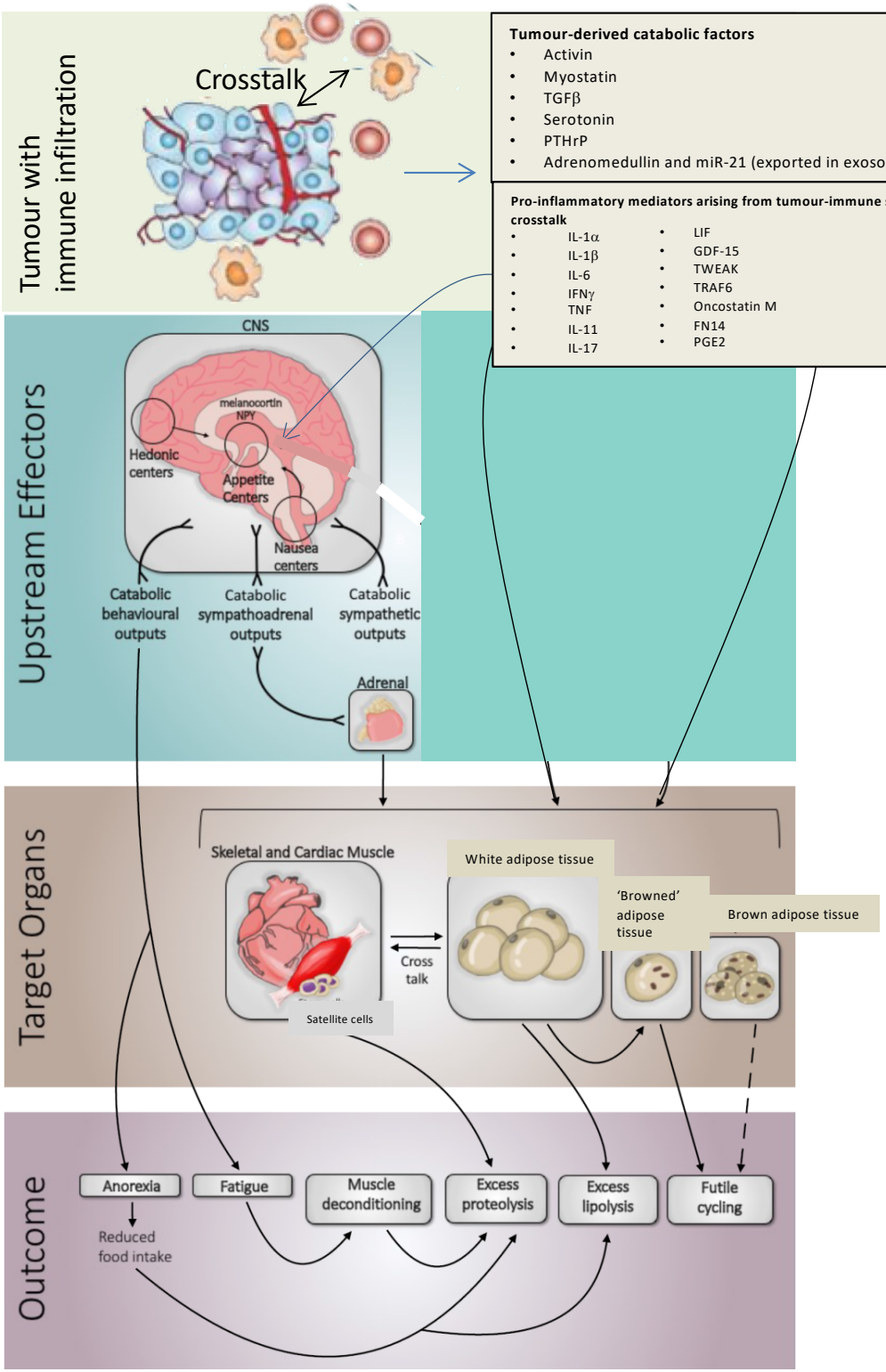

Tumour with immune infiltration
Crosstalk
Tumour-derived catabolic factors
Activin
Myostatin
TGFβ
Serotonin
PTHrP
Adrenomedullin and miR-21 (exported in exosomes)
Pro-inflammatory mediators arising from tumour-immune system crosstalk
IL-1α
IL-1β
IL-6
IFNγ
TNF
IL-11
IL-17
LIF
GDF-15
TWEAK
TRAF6
Oncostatin M
FN14
PGE2
Upstream Effectors
CNS
melanocortin
NPY
Hedonic centers
Appetite Centers
Nausea centers
Catabolic behavioural outputs
Catabolic sympathoadrenal outputs
Catabolic sympathetic outputs
Adrenal
Target Organs
Skeletal and Cardiac Muscle
Satellite cells
Cross talk
White adipose tissue
'Browned' adipose tissue
Brown adipose tissue
Outcome
Anorexia
Fatigue
Muscle deconditioning
Excess proteolysis
Excess lipolysis
Futile cycling
Reduced food intake

Figure 4

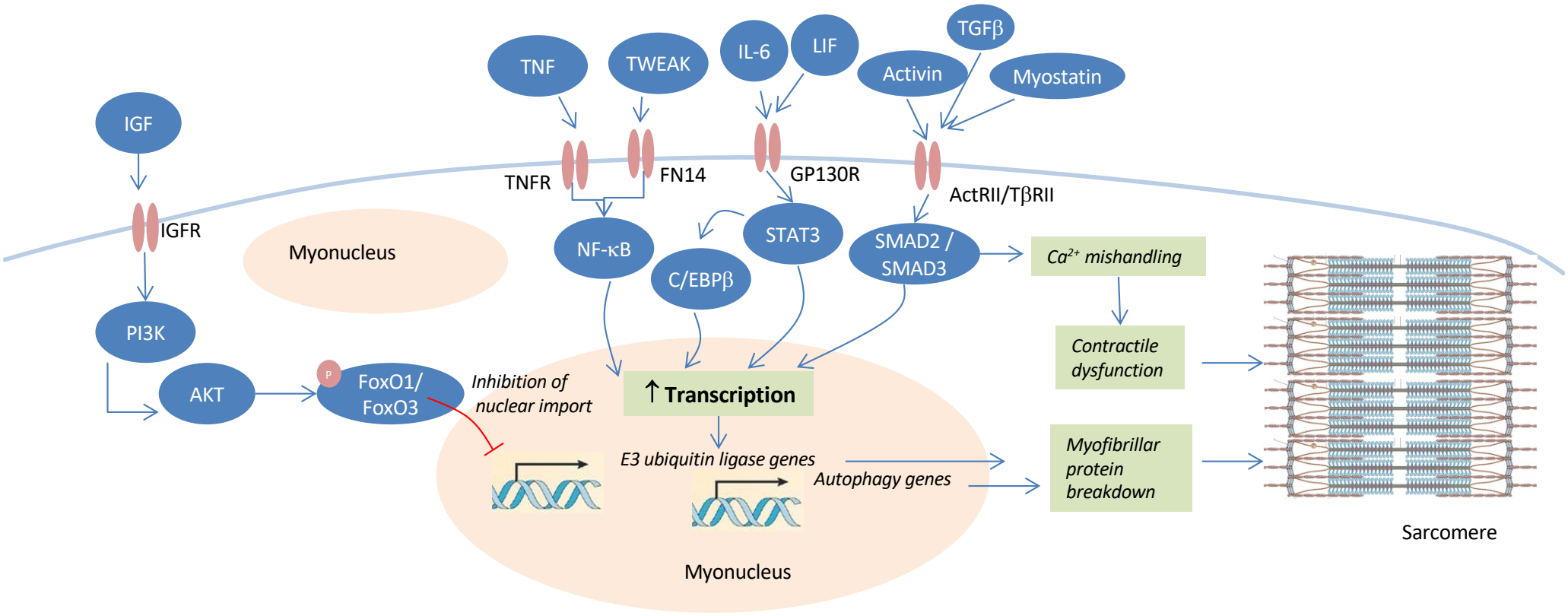
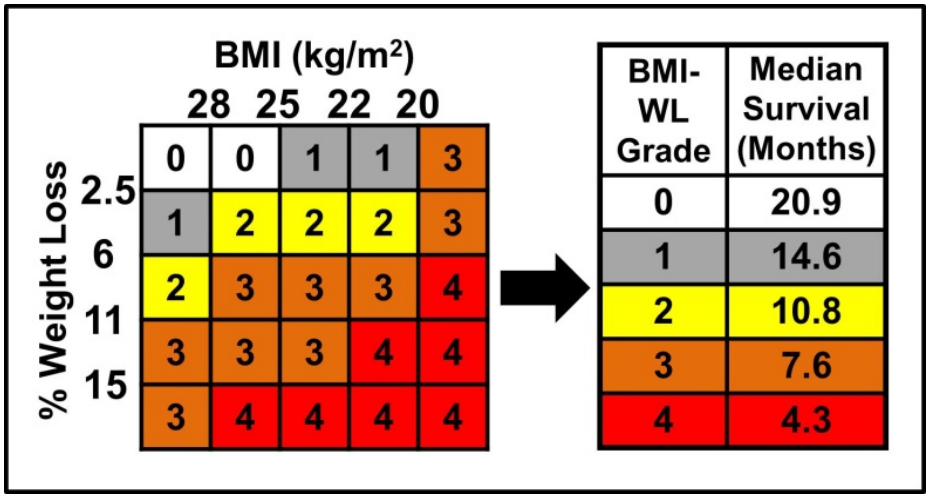

TNF
TWEAK
IL-6
LIF
TGFβ
Activin
Myostatin
IGF
TNFR
FN14
GP130R
ActRII/TβRII
IGFR
Myonucleus
NF-κB
STAT3
C/EBPβ
SMAD2 / SMAD3
Ca2+ mishandling
PI3K
AKT
P
FoxO1/ FoxO3
Inhibition of nuclear import
↑ Transcription
Contractile dysfunction
E3 ubiquitin ligase genes
Autophagy genes
Myofibrillar protein breakdown
Myonucleus
Sarcomere

Figure 5


BMI (kg/m²)
28 25 22 20
% Weight Loss
2.5
6
11
15
0 0 1 1 3
1 2 2 2 3
2 3 3 3 4
3 3 3 4 4
3 4 4 4 4
BMI-WL Grade
Median Survival (Months)
0 20.9
1 14.6
2 10.8
3 7.6
4 4.3