Review Article

Cancer cachexia is defined by an ongoing loss of skeletal muscle mass

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Abstract: Since 2007, a quantitative, specific and precise approach to the detection of muscle loss has become accessible with the advent of image-based assessments. Computed tomography images acquired as part of standard cancer care are the serendipitous substrate for these analyses. Three radiologically-determined abnormalities, sarcopenia (severe muscle depletion), catabolic loss of muscle over time, and reduced muscle radiation attenuation associate with progressive functional impairment, treatment-related complications, reduced quality of life, and mortality. Fundamental understanding of muscle wasting in cancer cachexia has been developed on a base of clinical and experimental studies, which have identified alterations in muscle protein synthesis, autophagy and ubiquitin-mediated proteolysis as key contributors to muscle loss. The etiology of cancer-associated muscle wasting is multifactorial. Tumor metabolism captures energy fuels and amino acids, and a suite of tumor-derived molecules elicits catabolic pathways at the tissue level in muscle. Endocrine, neural and inflammatory derangements add further catabolic drive. Antineoplastic agents make a substantial contribution to muscle wasting by directly action on muscle cells, as well as secondarily via their systemic side effects. Encouraging data is emerging as to the potential reversibility of muscle loss and/or reduced muscle radiation attenuation through modulation of specific mechanisms. In the first line, pain and symptom management is a key element of the prevention of catabolic loss of muscle. Intake of intake of high-quality proteins and ω-3 polyunsaturated fatty acids support retention or gain of muscle mass. While there is no approved drug therapy for the indication of cancer-associated muscle wasting, there is preliminary evidence for robust gain of skeletal muscle mass in research studies of new therapeutics including inhibitors of mitogen-activated protein kinase kinases and ghrelin receptor agonists.

Keywords: Cancer; cachexia; skeletal muscle; computed tomography

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A view of cancer cachexia through a radiological lens

While experts agree that the loss of skeletal muscle is a defining feature of cancer cachexia (1), muscle has always been difficult to evaluate in a clinical setting other than by a purely functional or crude anthropometric approach. The 1980's saw the initiation and validation of image-based modalities [computed tomography (CT) and magnetic resonance imaging (MRI)] for the quantification of skeletal muscle (2-4). The precision of measures of skeletal muscle cross-sectional area or volume with these approaches is of the order of 0.4% to 1.5% depending on the model or instrument used and image- or patient- or operator-related sources of variation (3). These methods have allowed us to assess the muscularity of different individuals, to relate muscle mass to disease specific outcomes, to define sarcopenia (severe muscle depletion) in quantitative terms,

to detect catabolic loss or gain of muscle over time, to determine the behavior of specific individual muscles and to define the efficacy of different therapies developed for the treatment of muscle wasting. CT images acquired as part of standard cancer care were identified as a suitable substrate for these types of assessments in ~2008 (5) and have emerged as a particularly rich resource for the study of body composition in relation to oncological outcomes. This approach makes maximal use of existing information, has no incremental impact on the patient and has permitted countless retrospective and prospective studies. Images are particularly abundant in patients on systemic therapy treatment with palliative intent, and are ubiquitously used to plan cancer surgery. Computed tomography methods have been widely adopted by researchers, medical oncologists, surgeons, dietitians and palliative care physicians (6-8). Individual data sets with thousands of patients have started to appear in publications (9-11), and collectively tens of thousands of individuals have been assessed. Many authors have advocated for the extraction of the body composition data from clinical CT records (5,12,13). To date, this information is not yet part of standard radiology reporting, and is being conducted instead by researchers and a variety of health care professionals.

In 2007/2008 early reports showing association between sarcopenia or sarcopenic obesity and two cancer outcomes, chemotherapy-related toxicity and mortality began to emerge (14-16). In the subsequent decade owing to widespread adoption of CT assessments, over 950 publications have catalogued the body composition of different populations of cancer patients. Three radiologically-determined abnormalities, sarcopenia (severe muscle depletion), catabolic loss of muscle over time, and reduced muscle radiation attenuation associate with mortality, complications of cancer surgery, chemotherapy toxicity, physical functioning and quality of life. The reader is referred to the many reviews and meta-analyses of such work, which now increasingly are specific to tumor-site and treatment [e.g., (17)].

In general, cross-sectional analysis of single CT images, typically landmarked at the 3rd lumbar vertebra (L3) (*Figure 1*) is conducted. Muscle cross sectional area (cm^2) in single axial images at this level were shown to have a good correlation with while body muscle volume (r^2 =0.85) by Shen *et al.* (18). Whole body imaging is rare in clinical oncology; an approach using L1 has been suggested for patients with thoracic imaging only (19,20).

Diagnostic imaging allows detailed assessment of the individual cachexia trajectory. The person illustrated in *Figure 1* had a diagnosis of metastatic breast cancer. Compared to time of diagnosis, she lost 10.5% of muscle by year 2 and 29.1% by year 3 (end of life). A transient gain of visceral fat (+93%) and subcutaneous fat (+8%) was seen at year 2, but by end of life 72% of baseline visceral fat and 62% of subcutaneous fat had been lost.

An international consensus of clinical experts (1) defined cancer cachexia as "…being characterized by loss of muscle, with or without loss of fat mass". The concurrent loss of muscle and gain in fat of the patient in *Figure 1* typify this statement. The eventual result of such changes, sarcopenic obesity, is not uncommon in patients with advanced cancer. Sarcopenia and muscle wasting are endemic in patients with advanced cancer in westernized countries, but the same populations are afflicted with epidemic obesity. Literature on sarcopenic obesity in patients with locally recurrent or metastatic cancers was recently summarized (21). The overall prevalence of sarcopenic obesity was 9.3% (range, 2.3–14.6%), and 24% (range, 5.9–39.2%) of patients with a BMI >30 kg/m^2 were sarcopenic. As also summarized by these authors, sarcopenic obesity associates with exceptionally poor clinical outcomes, including complications of cancer surgery, chemotherapy toxicity and mortality.

Each patient's experience of cancer cachexia is uniquely defined by their pre-illness body habitus and their specific trajectory of loss (*Figure 2*). Levels of adipose tissue in subcutaneous and visceral compartments are highly variable among individuals, as is muscularity. Rate of muscle loss over time associates with mortality. For example, Blauwhoff-Buskermolen *et al.* (22) showed that in metastatic colon cancer, the patients with the highest rate of muscle loss (>9%) during a course of palliative chemotherapy, had the highest mortality.

Radiation attenuation is a second radiologic characteristic of muscle that is the subject of recent interest as it is independently related to mortality in melanoma, renal cell carcinoma, lung and gastrointestinal cancers (9,23-25). Considering the entire organ, any given skeletal muscle displays radiation attenuation between –190 to +150 HU. When muscle cross-sectional area and attenuation are reported in the literature, the most common practice is to use predefined HU ranges (5,26). Inter-muscular adipose tissue is separately segmented between –190 and –30 HU. The HU range used for muscle typically extends from –29 to +150 HU. The radiation attenuation of healthy young adults has a prominent peak around +50 and +30 HU is

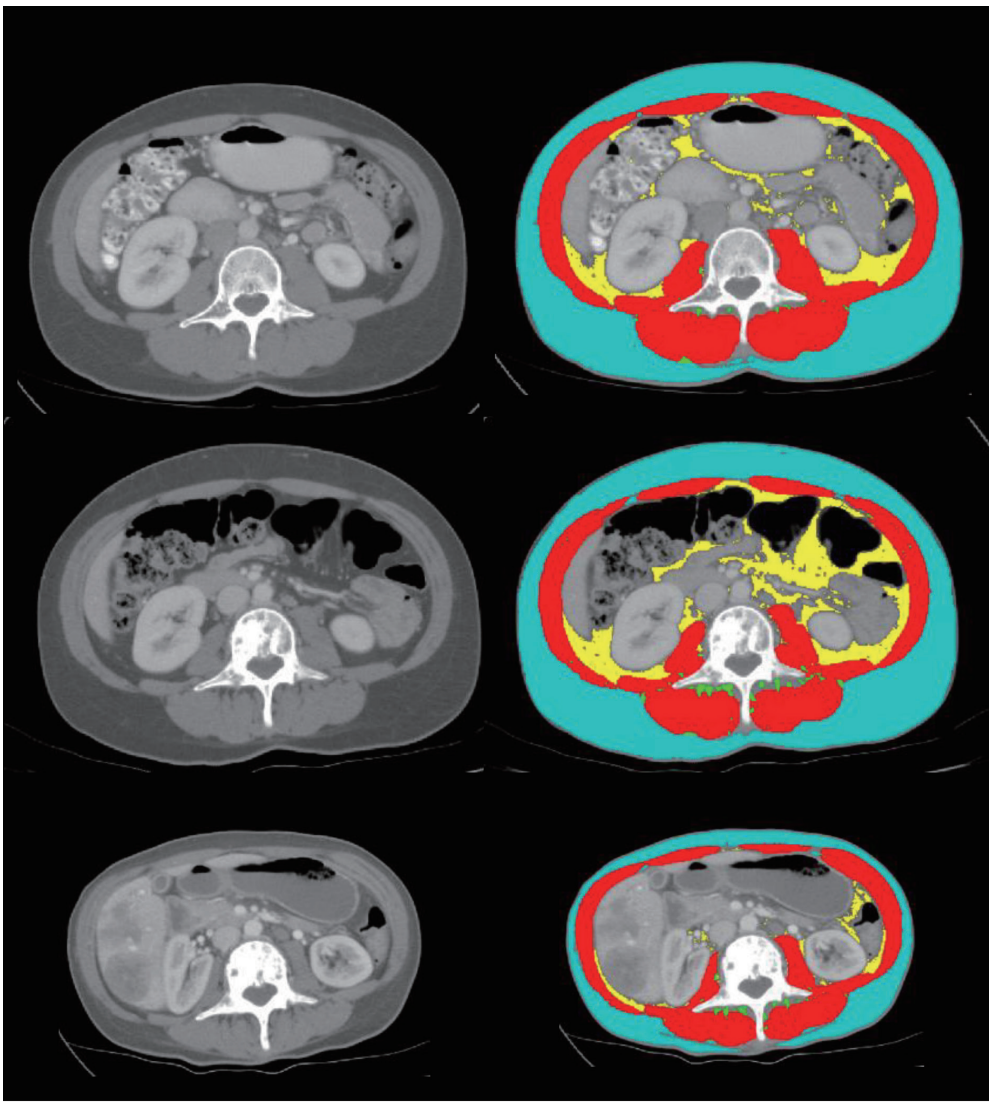

Figure 1 Computed tomography defined progression of cancer cachexia. Left: axial CT images at the 3rd lumbar vertebra are shown for a female patient with metastatic breast cancer. Right: images are annotated for skeletal muscle (red) including the psoas, paraspinal, quadratus lumborum, lateral and oblique abdominal and rectus abdominis, as well as fat [visceral (yellow), intermuscular (green) and subcutaneous (light blue)]. Scans were taken at diagnosis (top), 2 years later at start of year of death (middle), and during the last month of year of death (bottom).

considered to be the lower bound of normal muscle. Older persons typically have a proportion of muscle considered to be of low radiation attenuation (–29 to +29 HU). For discussion of these thresholds, see Aubrey *et al.* (26).

The last 5 years have seen the appearance of multiple publications associating reduced muscle radiodensity (i.e., <25–30 HU) with mortality, and this effect is independent of other clinical covariates and also independent of sarcopenia in patients with solid tumors [e.g., (9,11,17,23)] as well as in hematological cancers (24).

Biological correlates of the radiological findings

Disruption of the anabolic: catabolic balance in skeletal muscle

For a recent review of this area, see Baracos *et al.* (27). Briefly, muscle mass is controlled by the relative rates of

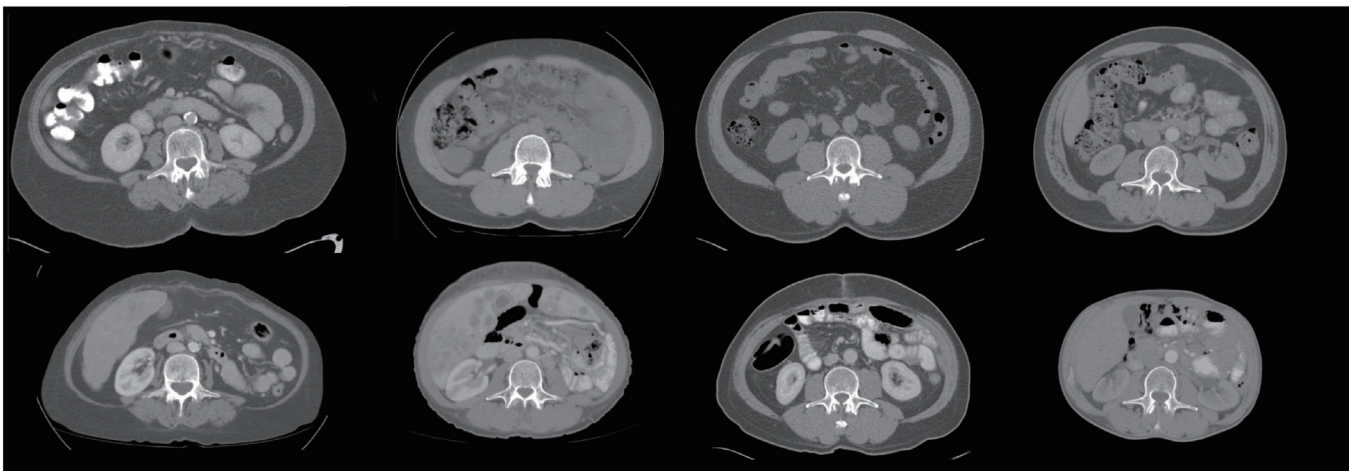

Figure 2 Computed tomography images framing the year of death in four different patients. Axial abdominal images at the 3rd lumbar vertebra. Upper row: 4 unique patients with advanced cancer, initial computed tomography (CT) scan taken in the 1st month of the year of death. Lower row: last CT scan of record in the same 4 patients, taken within the month of death.

protein synthesis and catabolism. A major anabolic pathway is the canonical PI3K/AKT pathway which is activated by insulin, IGF-1 and other growth factors. Downstream of PI3K/AKT, the mammalian target of rapamycin (mTORC1) induces muscle hypertrophy (28,29). Activation of TORC1 stimulates mRNA translation and inhibition of apoptosis, causing an increase in cell size and number (30). Cellular degradation systems in skeletal muscle include the autophagy and ubiquitin-proteasome systems (29,31). Autophagy is a nonselective catabolic pathway through which damaged organelles and proteins are degraded. In the ubiquitin-proteasome system, proteins are targeted for degradation by the 26S proteasome, via protein ubiquitination. Muscle-specific ubiquitin protein ligases are considered the main enzymes responsible for targeting degradation of muscle structural and contractile proteins, and these include Tripartite Motif Containing 63 (TRIM63; also known as Muscle-Specific RING Finger Protein 1) and F-Box Protein 32 (FBXO32; also known as Atrogin-1 or Muscle Atrophy F-Box Protein) (29,31).

In the tumor-bearing host, reduced muscle protein synthesis and activation of catabolism occur, as a result of complex inflammatory, endocrine and nutrition-related effects. Cytokines and other pro-inflammatory molecules generated by host immune system-tumor interactions are thought to play a central role. Pro-inflammatory cytokines activate the hypothalamic-pituitary-adrenal axis, leading to production of catabolic stress hormones (adrenalin, cortisol, glucagon), generating resistance to insulin and growth factors in muscle, increased proteolysis and reduced protein anabolism (27,32). Transcriptional up-regulation of autophagy and ubiquitin-proteasome system is directly activated in muscle cells by a series of pro-inflammatory actors which originate in either the tumor, immune system or both. Prostaglandin (PG) E_2 activates protein catabolism in skeletal muscle (33). Cytokine mediators of muscle catabolism include interleukin (IL)-6, IL-1, tumor necrosis factor-α, interferon γ leukaemia inhibitory factor and TNF ligand superfamily member 12 (TWEAK) (27,34). These factors signal through their respective cell surface receptors and activate the transcription of ubiquitin proteasome and autophagy genes. Nutritional deficits also play a role in the catabolic response of muscle cells. For example, amino acids, particularly the branched chain amino acid leucine, normally stimulate anabolism (and reduce catabolism) of protein in muscle (29,35,36). Low plasma concentrations of amino acids are permissive for activation of the ubiquitin system, autophagy and apoptosis (28,36).

Low muscle radiation attenuation reflects excess accumulation of lipid

Further studies are needed to identify the specific physiological mechanisms that result in reduced muscle radiation attenuation, as this has been only recently described and the biological findings are sparse. Low radiation attenuation is associated with accumulation of lipid (37) and the term myosteatosis is often used to

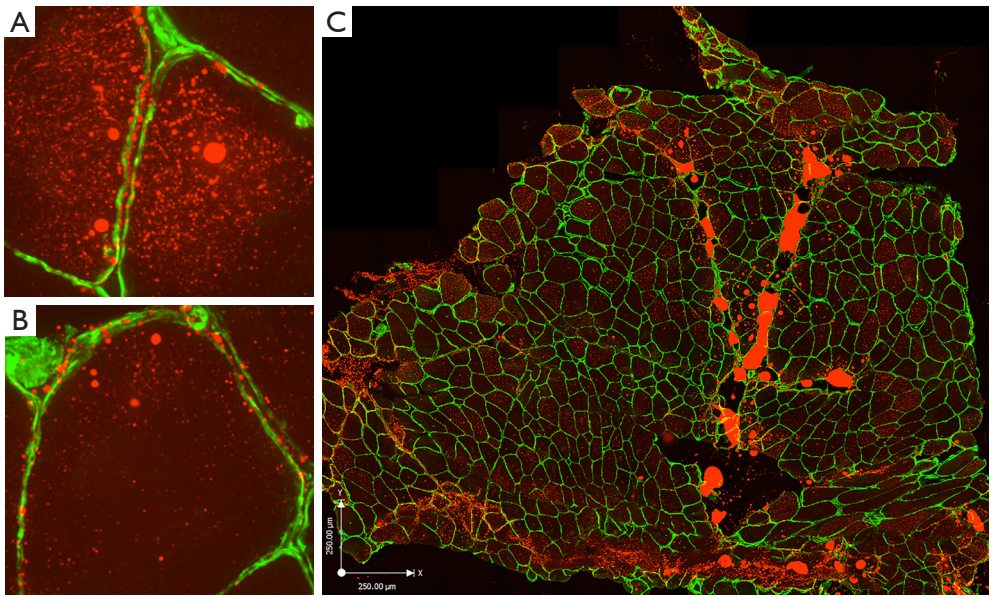

Figure 3 Neutral lipid in skeletal muscle. Rectus abdominis muscle from patient with low muscle radiodensity. Transverse sections stained with laminin-dystrophin (green) to show basal lamina of myofibres and Oil Red O (red) for neutral lipid. (A,B) Intramyocellular lipid droplets in individual muscle fibers. 60× magnification. (C) Large accumulation of neutral lipid in connective tissue planes. 10× magnification. Unpublished results VC Mazurak, AS Bhullar, VE Baracos.

describe it (25,26). In patients with cancer cachexia, rectus abdominis muscle evaluated by transmission electron microscopy showed increased number and size of intra-myocellular lipid droplets compared with non-weight losing controls (38). Preliminary results from our research group also suggest high levels of intra-myocellular lipid in muscles of patients with cancer, revealed by staining rectus abdominis muscle biopsy with Oil Red O (*Figure 3A,B*), used in the morphological examination of neutral lipids (i.e., triglyceride). As well, large aggregates of adipocytes are evident in regions of the perivascular connective tissue (*Figure 3C*).

While mechanisms of excess fatty infiltration are unclear, Stretch *et al.* (39) performed transcriptomic analysis in rectus abdominis muscle biopsies in patients with cancer who had low versus high muscle radiation attenuation values. Differentially expressed genes associated with low muscle attenuation were involved in cell death and survival, cellular function and maintenance, and cell morphology. Oxidative phosphorylation was the most strongly affected canonical pathway. Eighteen differentially expressed genes associated with this pathway (encoding proteins in complex I, II, IV and V of the electron transport chain), had lower expression in muscles from patients with low muscle radiation attenuation. Decreased lipid oxidation would be expected to contribute to lipid accumulation seen in myosteatosis.

Clinically, low radiation attenuation in muscle of patients with cancer has been shown several times to be correlated with the presence of systemic inflammation as assessed by CRP or Glasgow Prognostic Score (25,40,41). Preliminary evidence suggests that myosteatosis is preventable or reversible by the provision dietary ω-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], both clinically (42) and experimentally (43), and this may be due to the well-characterized anti-inflammatory action of these fatty acids.

Tumor- and treatment-driven muscle catabolism

Tumor-generated catabolism: how do we counteract it?

Malignant tumors contribute prominently to muscle wasting by merit of their direct capture of energy fuels and amino acids and their consequent ability to deprive other tissues of these substrates (44). Tumor cells also generate numerous catabolic factors that directly activate proteolysis in skeletal muscle. These include but are not limited to eicosanoids, cytokines (see above), members of the transforming growth

factor (TGF)-β superfamily [activins, myostatin, TGFβ 1 and 2, growth and differentiation factor (GDF)-11 and GDF-15] (27,34). Muscle response to these effectors is via cell surface receptors, which are linked to transcriptional activation of ubiquitin, proteasome and autophagy genes.

The degree to which tumor-generated muscle catabolism is modifiable is not clear. Muscle gain does occur in patients with advanced cancer, and this seems to occur in the context of disease response to anticancer treatment (45). There is clinical evidence that muscle anabolism can be activated under appropriate conditions. Patients with locally advanced or metastatic disease demonstrate activation of muscle protein synthesis after intake of high-quality proteins (46,47). We do not yet possess a means of eliminating the chorus of catabolic effectors noted above, although several of those molecules are the targets of investigational new therapies. Several drugs have been shown to induce increases in muscle mass, even in patients with some of the most catabolic diseases, including advanced lung cancer and cholangiocarcinoma. These include anamorelin® (a growth hormone secretagogue receptor type 1 (ghrelin receptor) agonist) (48), as well as selumetinib® which targets mitogen-activated protein kinase kinases (49). Optimum conditions for exploitation of this anabolic potential are currently under study, with the overall aim of net improvement in the muscle mass, functionality, performance status and treatment tolerance by the patient (50).

Dietary ω-3 polyunsaturated fatty acids have been proposed as therapeutic agents for treatment and prevention of muscle loss (51,52). The main studied effect of ω-3 fatty acids is to down—regulate the synthesis of catabolic pro-inflammatory eicosanoids (PGE_2), cytokines (TNF-α, IL-6, IL-1β), and their downstream effectors such as NF-κB, that induce muscle proteolysis (53-55). Clinically ω-3 fatty acids increase the rate of muscle protein synthesis in older adults (56) and in a recent meta-analysis (51) high-protein ω-3 polyunsaturated fatty acid-enriched oral nutritional supplements supported weight gain (+1.89 kg, 95% CI, 0.51–3.27, P=0.02) and provided attenuation of lean body mass loss in patients with cancer on chemotherapy, versus an isocaloric control.

When cancer is unresponsive to treatment and showing rapid growth, loss of muscle mass occurs at high rates (45). In disseminated metastatic disease, the mass and high metabolic activity of the tumor relentlessly drive muscle and fat loss and this accelerates during the last 3 months of life (45,57). There is a point in the trajectory of incurable cancer where this intense catabolism is unstoppable. The term "refractory cachexia" (1) was coined to describe a rapidly progressive cancer unresponsive to anticancer therapy, and a corresponding state of highly active catabolism, to a point that renders active management of muscle loss impossible.

Chemotherapy-induced muscle catabolism: a treatment side effect that can be mitigated?

The radiological approach to the assessment of muscle wasting has provided new quantitative information regarding the involvement of cancer treatments on muscle wasting. Cancer treatments often elicit losses of weight and of muscle, and these effects can be substantial. Weight loss of 4–12 kg easily occur during a standard course of neoadjuvant chemotherapy or chemo-radiotherapy (58-60). Diagnostic imaging reveals that these losses are often composed mostly of muscle (22,58,60).

To at least some extent cancer treatments induce loss of muscle mass via gastrointestinal side effects such as anorexia, oral mucositis, dry mouth, early satiety, malabsorption, diarrhea, nausea and vomiting. During cancer treatment patients experience additional problems that contribute to poor food intake, such as pain, anxiety, depression, altered sleep, fatigue and endocrine disorders. For many of these side effects there are therapeutic options. The management of these issues should be prioritized, as they may be readily reversed by appropriate treatments (e.g., pain, nausea, reduced bowel motility, mood disorders). A team approach, involving oncologists, palliative care physicians, dietitians, patients and families is required to optimize this approach. Pain and symptom management is crucial to maintain or improve food intake during treatment. Updated evidence-based clinical practice guidelines for nutrition in clinical oncology are available (52). Nutrition counseling by an accredited health care professional working within the supportive care team provides patients with a thorough understanding of their nutritional needs and of the specific eating habits that they can undertake to meet those needs.

More recently, it is becoming clear there are direct effects of cytotoxic and targeted cancer therapies on muscle cells, including altered contractile properties, insulin resistance and atrophy. These side effects of cancer treatments are worrisome and for the moment are incompletely understood. Many cancers show aberrant activation in pathways upstream of the mammalian target of rapamycin (mTORC1). For this reason, "targeted" cancer therapies, by design, are directed at the mTORC1 complex (e.g., sirolimus, everolimus and ridaforolimus) (30).

Unfortunately muscle protein synthesis is activated by insulin and amino acids via the same (mTORC1-dependent) pathways that tumor cells rely on for proliferation (28,29), so the predicted effect of such agents is muscle atrophy. Furthermore, several cytotoxic agents (e.g., oxaliplatin, cisplatin, anthracyclines, 5-fluorouracil, irinotecan) appear to be taken up by muscle cells and induce proteolytic and apoptotic signaling, mitochondrial dysfunction, oxidative damage, cellular energy depletion and apoptotic or necrotic cell death (summarized in 34). In mice on gemcitabine + cisplatin therapy, skeletal muscles showed induction of TGFα family ligands myostatin and activin A, pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, as well as the expression of ubiquitin ligases TRIM63 and FBXO32 and proteasome activity (61). These direct effects of cancer therapeutics on muscle suggests that debilitating muscle atrophy is a significant (and under-appreciated) adverse effect of cancer treatment.

Post scriptum: limitations and opportunities

Cancer-associated loss of skeletal muscle sits at the center of our current conception of cancer-associated cachexia (1). With the advent of secondary analysis of standard oncologic images, muscle mass and muscle loss are now precisely quantifiable, and this approach is being used to generate detailed assessments in different cancer types and treatment plans. There have been extensive studies in animal models, but one of the main limitations has been the sparsity of our knowledge of the human biology of cancer-associated muscle wasting. We lack understanding of molecular mechanisms underlying the heterogeneity of cachexia in individual patients with the same pathologic type of cancer. A positive development is that tissue-level investigations are accessible through collaboration with surgeons to obtain intraoperative muscle biopsy during cancer surgery [e.g., (38,39)]. These types of approaches will provide much-needed mechanistic insights.

It is becoming increasingly clear that an important part of the muscle loss experienced by cancer patients is iatrogenic. Paradoxically, two of the major long-standing treatments for cancer anorexia and cachexia, corticosteroids and progestational agents, have among their major side effects, atrophy of skeletal muscle (62). A wide variety of systemic antineoplastic agents generate muscle loss directly by expressing direct catabolic actions on muscle cells, as well as secondarily via their systemic (gastrointestinal) side effects that impair food intake during treatment. Muscle wasting deserves consideration as a potential adverse effect in the use of current cancer therapies and the development of new ones. Where muscle wasting is most profound, consideration might also be given to adding preventative measures to limit the toll of this side effect.

While we know that some patients with cancer have sarcopenia at diagnosis [e.g., (10)], the year of death is the period in which the most striking catabolic losses of muscle ensue (45,57). This is illustrated by CT images (*Figures 1*,*2*); images from the end of life show that some patients have become frankly emaciated. In our setting, about one in five patients with advanced cancer reach this body habitus. In current paradigms of care, a patient entering the year of death is likely to be an outpatient at a cancer center or hospital, in the charge of an oncologist, receiving chemotherapy and have access to referral for supportive care in various forms within the institution. Towards the end of the year of death, treatment may or may not still be ongoing (63), and referral for palliative care is likely to have occurred. Muscle wasting and cachexia are not generally a primary focus of oncologists, and the opportunity for early identification and intervention can easily be lost. Referral to palliative care still occurs late in the disease trajectory for many patients, at which time cachexia and its associated muscle wasting may have reached the refractory stage. There are current calls for the integration of oncology and palliative care (64): the year of death trajectory of cancer cachexia is but one example of the need for integration, in this case of diagnostic imaging, human and experimental biology, supportive and palliative care, clinical nutrition, clinical pharmacology and oncology.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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