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Research Priorities in Cancer Cachexia: The University of Rochester Cancer Center NCI Community Oncology Research Program (NCORP) Research Base Symposium on Cancer Cachexia and Sarcopenia

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Abstract

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Purpose—Cancer cachexia remains understudied and there are no standard treatments available despite the publication of an international consensus definition and the completion of several large phase III intervention trials in the past six years. In September 2015, The University of Rochester Cancer Center NCORP Research Base led a Symposium on Cancer Cachexia and Sarcopenia with goals of reviewing the state of the science, identifying knowledge gaps and formulating research priorities in cancer cachexia through active discussion and consensus.

Findings—Research priorities that emerged from the discussion included the implementation of morphometrics into clinical decision making, establishing specific diagnostic criteria for the stages of cachexia, expanding patient selection in intervention trials, identifying clinically meaningful trial endpoints and the investigation of exercise as an intervention for cancer cachexia.

Summary—Standardizing how we define and measure cancer cachexia, targeting its complex biologic mechanisms, enrolling subjects early in their disease course and evaluating exercise, either alone or in combination, were proposed as initiatives that may ultimately result in the improved design of cancer cachexia therapeutic trials.

Keywords

cachexia; sarcopenia; morphometrics; exercise; ghrelin

INTRODUCTION

Cancer cachexia is a syndrome defined by weight loss and reduced muscle mass (i.e., sarcopenia) with or without loss of fat mass that results in reduced physical performance and functional impairment and correlates with a poor prognosis (1, 2). The underlying pathophysiology is characterized by decreased nutritional intake, a pro-inflammatory state, decreased physical activity, and increased resting energy expenditure (2–4). Cachexia is particularly common in patients with upper gastrointestinal (GI) and lung malignancies. The prevalence of weight loss in patients with cancers of the pancreas, stomach, esophagus and lung is 83%, 83%, 79%, and 60%, respectively (5, 6). Cancer cachexia can have a direct impact on survival; for example, up to a third of patients with pancreatic cancer will succumb primarily due to the adverse effects of cachexia (1, 7).

Development of therapies specific for cancer cachexia has proven difficult and no current standard treatments exist. Successful interventions for cancer cachexia could be very meaningful as studies suggest that the stabilization of weight is associated with improved survival and enhanced quality of life (8). The development of efficacious intervention strategies for cancer cachexia is crucial in order to effectively deliver chemotherapeutic and novel anti-neoplastic therapies to patients.

In September 2015, clinicians and researchers convened for a Symposium on Cancer Cachexia and Sarcopenia at the University of Rochester Cancer Center (URCC) National Cancer Institute Community Oncology Research Program (NCORP) Research Base. In addition to expertise in cancer cachexia, participants (n=25) had diverse backgrounds in multiple fields including sarcopenia research, geriatric oncology, surgical oncology, medical oncology, endocrinology, palliative care, pharmacologic interventions for sarcopenia, and

exercise and muscle physiology. The content and speakers were selected to feature three broad themes: 1) establishing how cachexia and sarcopenia are defined and measured; 2) designing clinical trials with pharmacologic interventions that disrupt the biologic underpinnings of cancer cachexia; and 3) investigating exercise as a therapeutic strategy to improve outcomes.

Defining and Measuring Cancer Cachexia

In the clinic, many terms are used almost interchangeably to describe the loss of muscle and/or fat mass that accompanies weight loss in patients with cancer. Written across a single patient's chart, one may read: 'cachectic,' 'malnourished,' 'frail,' (temporal) 'wasting,' 'muscle atrophy,' or 'sarcopenic.' The many terms used to describe changes in body composition highlights the difficulty in studying cancer cachexia.

The formal definition of cancer cachexia has evolved over the past ten years. At the Cachexia Consensus Conference in 2006, experts defined cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (9)." This conference also laid out specific criteria for the diagnosis of cachexia (Table 1). In 2008, the SCRINIO (Screening the Nutritional Status in Oncology) working group defined cachexia as suffering from greater than 10% weight loss; any degree of weight loss less than 10% was characterized as 'pre-cachexia' (10). Patients were further divided into classes by the presence or absence of fatigue, anorexia, and early satiety. Despite the lack of a measure for muscle or fat mass, the SCRINIO contribution is significant for recognizing pre-cachexia and developing a classification system that illustrates the variability within the cachexia syndrome.

In 2011, an international consensus definition of cancer cachexia characterized this syndrome as a loss of skeletal muscle mass "that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" in patients with a cancer diagnosis (2). This international consensus panel established the following diagnostic criteria that are now considered by many as the gold-standard: greater than 5% weight loss over the previous 6 months or at least 2% weight loss with either a BMI <20 or evidence of sarcopenia. These diagnostic criteria have established sarcopenia as an important component of cancer cachexia. Described as a spectrum that patients do not necessarily progress through in its entirety, the international expert panel divided cancer cachexia into 3 stages: pre-cachexia, cachexia, and refractory cachexia (2). Pre-cachexia is described as weight loss that is less than 5 percent accompanied by 'metabolic changes' such as anorexia or impaired glucose tolerance. Cachexia and refractory cachexia, the latter described as an Eastern Cooperative Oncology Group (ECOG) performance score of 3 or 4, a prognosis of less than 3 months and cancer with procatabolic features and not responsive to treatment, are very specific and provide a framework for validation in future trials. Future research should be aimed at providing a more precise definition of pre-cachexia to enable enrollment of pre-cachexia patients in cachexia-directed therapeutic clinical trials.

There is considerable overlap in the definitions of cachexia and sarcopenia as both are characterized by muscle deterioration leading to functional impairment (2, 11). How these two syndromes differ is evident by their Greek word roots. Cachexia, consisting of 'kakos'

meaning *bad* and ‘hexis’ meaning *condition*, implies a debilitating disease process (12). Sarcopenia, conversely, is made up of ‘sarx’ meaning *flesh* and ‘penia’ meaning *loss*, describes a disorder that involves tissue or muscle loss (13). Sarcopenia is not exclusive to chronic illness such as HIV or cancer, and can occur in the context of the normal physiologic processes of aging or deconditioning. In other words, many patients with cancer cachexia suffer from sarcopenia, but many patients with sarcopenia do not suffer from (cancer) cachexia.

Early definitions of sarcopenia focused solely on the loss of muscle mass that assumed loss of function (11). However, muscle strength can be preserved in patients with low muscle mass (14). So, while the reduction in muscle mass is usually associated with loss of strength and function, the relationship is nonlinear, suggesting that reduced strength in sarcopenic individuals is related to both muscle mass and other factors (15). More recent definitions of sarcopenia have incorporated function and physical performance to better characterize this population (see Table 2) (12, 16).

Lack of widely accepted definitions for both cachexia and sarcopenia have, until recently, held back significant progress in evaluating and treating cancer patients who experience weight loss and muscle breakdown (2). Collaboration and consensus in how we define, identify and characterize changes in body composition are crucial to the design and implementation of clinical trials and the development of better intervention strategies.

Measuring Body Composition—The complex relationship between body composition and cancer outcomes, namely overall survival, has been studied using various measurements in clinical research. Body mass index (BMI) is a measure that translates well to the clinic, and offers some utility in identifying cancer cachexia when the BMI is less than 20. More recently, BMI has become less useful in cachexia research as the demographics of body composition are changing in western countries with the advent of the obesity epidemic; only a small minority of cancer patients now present severely underweight (BMI <20) (17). Elevated BMI has been found to be associated with improved survival after patients are diagnosed with cancer when stratifying by BMI alone (17). However, obese patients with cancer who experience some degree of weight loss and have corresponding muscle loss on cross-sectional imaging actually have a similarly poor prognosis when compared to cancer patients who have a BMI less than 20 (17, 18). This ‘obesity paradox’ suggests that studies of cancer cachexia should focus not only on the subject’s height and weight, but also on more precise measurements of fat and muscle mass.

Morphometrics, the study of body shape and form, is a growing area of interest in sarcopenia and cachexia research. Dual energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) are considered the standards for morphometric evaluation as all three can provide quantification of adipose and muscle tissues or distinct body compartments (19). DXA is a less expensive technology, but is not commonly employed in clinical oncology practice. Cross-sectional imaging with CT or MRI is widely used for staging and therapy response assessment and is often performed serially making it an ideal modality to follow changes in muscle or fat mass. A single slice abdominal cross-sectional image, most commonly at the level of the L3 vertebra, can

provide a composite analysis of total body skeletal muscle and fat mass distribution (20). The approach is user-friendly and can be taught to non-radiology clinicians or researchers. Although morphometrics has provided insight into negative associations between cachexia and various cancer-related outcomes like survival and treatment toxicity (17, 21–23), there is scarce evidence demonstrating the use of these measurements in a prospective manner to influence patient care. Studies currently under development are utilizing cross-sectional imaging to direct clinical decision making and hopefully will elucidate the role of morphometrics in daily practice [NCT01624051].

Cancer Cachexia Clinical Trial Design

Patient Selection—Utilizing the clinical spectrum of cachexia could aid in selection of patients for cachexia-specific clinical trials (2). Early intervention is key; the effects of cachexia are likely irreversible at end-stage. In a study of 34 colorectal cancer patients in the last year of life, a logarithmic acceleration in loss of lean muscle mass and adipose tissue was observed during the 2 months prior to death, suggesting changes too rapid to overcome (4). Patients with pre-cachexia may benefit most by interventions aimed to preserve weight, muscle mass and function.

Designing clinical trials for patients with pre-cachexia is challenging because there are not specific diagnostic criteria for these patients, there is a lack of reliable biomarkers for pre-cachexia (2), and many patients with cancer are already suffering from overt cachexia at the time of their diagnosis. For example, over forty percent of patients with surgically amenable pancreatic adenocarcinoma were found to have greater than ten percent weight loss prior to surgery (24). In a large cohort study, investigators were able to show that elevations in branched-chain amino acids (BCAAs) were associated with increased risk of pancreatic cancer, particularly between two to five years prior to diagnosis (25). In this same report, in mouse models, the rise in BCAAs in pancreatic cancer was tied to tissue protein breakdown, particularly in fast-twitch muscle fibers. This data suggests that metabolic changes in muscle are an early event in pancreatic cancer development, possibly pre-dating gross evidence of tumor formation. Initiating cachexia directed therapy earlier in the course of disease (i.e. at diagnosis) may translate to improved outcomes or attenuation in the progression of cachexia. Demonstrable positive effects of pre-cachexia interventions may be marginal, however, given the subtle change in weight and mass from a patients baseline; efficacy benchmarks should be adjusted accordingly and focus more on maintenance of weight and function.

Finally, cachexia intervention trials should enroll patients with relevant tumor types. There is a dearth of phase II and phase III trials that specifically focus on GI cancer cachexia (26, 27). Given that cancer cachexia is most prevalent in GI cancers (5), phase II and III intervention trials in the future should include patients with pancreatic, gastric, esophageal and colorectal cancers.

Pharmacologic Interventions for Cancer Cachexia—Clinical trials aimed at stabilizing or improving weight have failed to produce approved therapies for cancer cachexia. Early intervention studies focused on anorexia and weight stabilization through appetite stimulants. Megestrol acetate (MA), corticosteroids and cannabinoids have all been

studied with varying results. Although these agents are shown to increase appetite and aid in weight stabilization, sustained improvements in physical performance and prolonged survival have yet to be demonstrated (28–30). The risk-benefit ratio of these interventions needs to be examined carefully, as all three are associated with significant side effects. In a Cochrane review of 35 trials, edema, thromboembolic disease and death were more frequent in MA-treated groups than comparators (31). Although decreased caloric intake is undoubtedly a contributor to muscle and fat mass loss, repleting nutritional stores alone is unlikely to result in lasting benefits given the metabolic complexities of cachexia.

Promoting anabolic effects on muscle and fat by targeting neuroendocrine pathways is another strategy that has been studied for cancer cachexia. Anamorelin, a ghrelin receptor agonist, and enobosarm, a selective androgen receptor modulator (SARM), were investigated in phase III placebo controlled clinical trials in cancer cachexia. Although neither drug is currently approved for cancer cachexia in the United States, the two strategies serve as examples of cachexia clinical trial innovation.

Ghrelin and Ghrelin Receptor Agonists—The etiology of anorexia in cancer is multifactorial and can be caused by mechanical/tumor obstruction, alterations in taste and smell caused by cancer or cancer therapy, impaired GI tract motility or hormonal changes that result in a decreased central drive to eat (32). Ghrelin is released from the stomach in response to prolonged fasting and binds to ghrelin receptor 1a (GHS-R1a) which is expressed on the orexigenic neuropeptides agouti-related protein (AgRP) and Neuropeptide Y (NPY). Ghrelin has been labeled as “meal initiating;” administration of ghrelin has been shown to increase food intake in healthy volunteers (33) and increase caloric intake in patients with cancer and impaired appetite (34). Ghrelin levels were found to be significantly elevated in human subjects with cancer cachexia when compared to subjects without cachexia. Ghrelin is increased in various cancer diagnoses and across all stages, suggesting that ghrelin may be a specific biomarker for the cancer cachexia syndrome rather than for a specific malignancy (35).

Pre-clinical models also demonstrate the association between ghrelin and cancer cachexia. In both *in vitro* and *in vivo* models, ghrelin inhibits skeletal muscle atrophy (36). Mice treated with cisplatin or implanted with Lewis Lung Carcinoma (LLC) tumors developed weight loss, loss in lean body mass, decreased grip strength, and reduced myocyte cross-sectional area in the tibialis anterior muscle. These changes were prevented by administration of ghrelin and, most notably, ghrelin treatment improved survival (37).

Anamorelin is an orally available, selective ghrelin receptor agonist with a half-life nearly double that of ghrelin (38, 39). In an integrated analysis of two randomized, placebo-controlled phase II trials in patients with cancer cachexia, anamorelin demonstrated an acceptable safety profile and significantly improved lean body mass (40). Two of the largest randomized phase III intervention trials in cancer cachexia to date, ROMANA 1 and ROMANA 2, investigated the use of anamorelin in a 2:1 placebo-controlled, double-blinded fashion. A combined 979 patients with advanced non-small cell lung cancer (NSCLC) with a BMI less than 20 or greater than five percent weight loss in the previous 6 months were enrolled (27). Anamorelin significantly improved lean body mass and appetite, but did not

improve hand-grip strength, the co-primary endpoint; overall survival was similar between groups.

Despite an improvement in lean body mass and an excellent safety profile, the initial report of the ROMANA trials has not yet led to an FDA indication for anamorelin in cachexia. The FDA suggested that either improved survival or significant improvements in physical function may be required in addition to gains in weight and lean body mass to attain approval (41). Despite the mixed outcome of the ROMANA trials, the study of ghrelin agonists for the treatment of cancer cachexia should continue with further investigation in studies utilizing alternative, reproducible endpoints with significant clinical impact.

Selective Androgen Receptor Modulators (SARMs)—Pro-inflammatory cytokines that are elevated in cancer cachexia can influence the gonadal axis. For example, IL-6 administration results in low testosterone (LT) in healthy male subjects (42). To further study this relationship, serum testosterone, inflammatory markers, and symptoms were assessed in males with cancer cachexia, men with cancer without cachexia (CWC) and noncancer controls (43). Subjects with cancer cachexia had significantly lower total testosterone levels than CWC controls. Additionally, cancer cachexia subjects had lower lean body mass, fat mass, grip strength, poorer sexual function, and higher IL-6 levels than controls. Testosterone administration has been shown to increase lean body mass and muscle strength in men, but it can cause adverse side effects on hair, skin, and prostate tissues (44). Selective androgen receptor modulators (SARMs) are non-steroidal anabolic agents that are more tissue-specific (bone and muscle) than testosterone and do not undergo aromatization to estradiol. In rat models, SARMs increased muscle mass while shrinking prostate glands, demonstrating a better safety profile than testosterone supplementation (45).

Enobosarm is an orally bioavailable SARM that was investigated in a randomized phase II, double blinded, placebo-controlled multicenter trial in subjects with at least 2% weight loss in the preceding 6 months and one of the following cancer diagnoses: NSCLC, colorectal cancer, breast cancer, non-Hodgkin lymphoma and chronic lymphocytic leukemia (46). Significant increases in lean body mass, stair climbing power (a surrogate for physical performance), and quality of life were observed in the enobosarm groups (1 mg and 3 mg) with no differences in hair growth or PSA when compared to placebo.

The Prevention and Treatment of Muscle Wasting in patients with cancer (POWER 1 and 2) studies were phase III, nearly-identical (differing chemotherapy regimens), randomized, placebo-controlled studies investigating the safety and efficacy of enobosarm in subjects with advanced NSCLC on chemotherapy (26). Results presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting showed a significant net increase in lean body mass (co-primary endpoint) in both enobosarm trial arms when compared to subjects who received placebo (47). However, the other co-primary endpoint, improved stair climb power, was met in only one of the two trials. Furthermore, this improvement was criticized as it did not represent a change from baseline, but a relative improvement when compared to placebo (48, 49). Subsequently, enobosarm has not received an indication for cancer cachexia and GTx, the Memphis, Tennessee-based, company which developed the drug, has decided not to pursue further use of enobosarm in muscle disorders (49). The

development of enobosarm for cachexia should be recognized, however, as it provides a framework for future cancer cachexia directed therapy trial design.

Trial Endpoints—The ROMANA and POWER trials illustrate the difficulty in achieving improvements in physical performance in patients with advanced cancer and cachexia. The symposium attendees felt that demonstration of stability of weight, lean body mass, and physical performance are clinically relevant and should be considered as viable outcomes, but that other outcomes should be explored as well. Many of the symptoms of cancer cachexia, like fatigue, weakness, sexual dysfunction, and poor quality of life, cannot be objectively measured by imaging or laboratory testing. Patient-reported outcomes (PROs) for ROMANA 1 and 2 were presented at the 2016 ASCO Annual Meeting. Subjects with low BMI (<20) in the anamorelin cohort had significant improvements in anorexia/cachexia symptoms and fatigue (50).

The symposium panel stressed the importance of PROs as valid endpoints in cancer cachexia studies. Although cachexia drug development is managed by the FDA's Division of Metabolism and Endocrinology, there is precedent for approval of oncologic therapies using PROs. In 1996, the FDA approved gemcitabine for treatment of pancreatic cancer on the basis of an improvement in an endpoint termed "clinical benefit:" a composite score of patients' perceived pain and use of analgesia, change in weight, and capability of carrying out activities of daily living (51). The use of this endpoint was applauded for its ingenuity by the Oncology Drug Advisory Committee (ODAC) of the FDA at the time (52).

Given that the cancer cachexia syndrome has multiple underlying contributing factors including systemic inflammation, increased resting energy expenditure, physical inactivity, and anorexia, a combined modality approach may be needed to reach current established endpoints (41, 53). Designing multimodality trials in cancer cachexia will be complex and continued input from the FDA on the approval process will be crucial (41). Despite the completion of several large international phase III trials, it remains important to promote research in cancer cachexia at a smaller scale. Pilot studies with diverse PROs and innovative and widely applicable performance measures are essential to help design the phase III intervention trials of the future.

Exercise as a therapeutic intervention in cancer cachexia

Rationale for Exercise—Exercise is an attractive behavioral therapy for cancer cachexia. Patients with cancer experience inhibition of protein synthesis due to inactivity and decreased caloric intake. Reduction in protein synthesis and an enhanced ubiquitin proteasome pathway, which increases protein breakdown, lead to a reduction in muscle force generation by shrinking muscle fiber area and diminishing muscle extensibility (54). Chemotherapy can also contribute to muscle injury, including both skeletal and cardiac muscle, magnifying the clinical effects of cachexia (55, 56).

Exercise results in muscle strengthening and improved physical performance by supporting protein synthesis and muscle growth. Additionally, exercise can reduce inflammation, potentially abrogating catabolic effects that are hallmarks of muscle wasting (57, 58). Building or maintaining muscle mass through exercise training is a safe, low cost, and

scientifically sound adjunct to anti-neoplastic therapy, and can be tailored to reach performance and functional endpoints. As an example, in randomized controlled trials investigating resistance exercise in men (with or without cachexia) receiving radiotherapy for prostate cancer, the exercise group demonstrated significant improvements in quality of life, cancer-related fatigue (59), muscle strength and physical performance when compared to usual care (60). Investigating the utility of exercise in cachexia is a natural next step. However, a recent Cochrane review determined that no randomized control studies have examined exercise interventions specifically in cancer cachexia (61). A lack of a consistent definition of cancer cachexia has made it difficult to assess safety and efficacy of exercise in this population.

Feasibility of Exercise Interventions—Exercise regimens encompass a broad range of activities from low-intensity activities like walking or stretching to high-intensity resistance exercise. This breadth demonstrates that exercise is an intervention that can be utilized by most cancer patients. In a study of 231 cancer patients with a prognosis of less than 2 years, subjects were randomized to exercise versus usual care (62). Physical performance measured by handgrip testing and shuttle walk time significantly improved over an 8-week period. On average, subjects completed 69% of scheduled exercise sessions, demonstrating that an exercise study is feasible in a cohort that carries a terminal diagnosis.

In a multi-site phase III randomized controlled trial examining the efficacy of exercise for improving cognitive impairment and inflammation, 479 non-metastatic cancer patients receiving chemotherapy were randomized to EXCAP®[®], a home-based, low to moderate intensity exercise regimen, or usual care (58). In this study, 75% of patients participated at least 10 minutes per day at a low- to moderate-intensity level for at least five days per week for six weeks. This study also demonstrates that a group can be randomized to no exercise, as contamination was minimal; only 7 of 265 control subjects reported starting resistance training during the study period.

The trials above illustrate feasibility in terms of cost, implementation, safety, and reproducibility of exercise trials in patients with cancer. We expect the role of exercise in cancer cachexia to be further elucidated in the coming years, as several randomized trials are currently investigating exercise either alone or in combination with a pharmacologic agent (Table 3).

Conclusions

For years, clinical investigation of cachexia focused on appetite stimulation and weight gain. Our improved biological and clinical understanding of this syndrome has resulted in innovative trial design and the development of therapeutics that target underlying mechanisms. Standardized definitions and diagnostic criteria established by expert consensus have enhanced our ability to study cancer cachexia. The URCC NCORP Research Base Symposium on Cancer Cachexia and Sarcopenia highlighted these advances and formulated the following research priorities in cancer cachexia: recognizing gaps in using morphometrics in clinical decision making, defining pre-cachexia, capturing patients early in the disease process, difficulty in reaching physical performance endpoints in pharma trials,

and the lack of clinical trials investigating exercise in cancer cachexia either alone or in combination with other nutritional or pharmacologic interventions (Table 4). The panel remains committed to addressing these unmet clinical and research needs and intends to contribute to the work being performed internationally in this effort. Specifically, attendees have developed techniques to measure cachexia and sarcopenia, including PROs, to aid in clinical decision making and have designed and started to accrue patients to a randomized controlled trial investigating exercise as a therapy for GI cancer cachexia (Table 3). Despite past challenges, we remain optimistic that standardized biochemical and clinical measurements will continue to evolve and that FDA-approved intervention strategies for cancer cachexia will be an integral part of standard clinical practice within the next decade.

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References

1. Fearon KC, Voss AC, Hustead DS, Grp CCS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr*. 2006 Jun; 83(6):1345–50. [PubMed: 16762946]
2. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011 May; 12(5):489–95. [PubMed: 21296615]
3. Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. *Eur J Cancer*. 2008 May; 44(8):1124–32. [PubMed: 18375115]
4. Lieffers JR, Mourtzakis M, Hall KD, et al. A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. *Am J Clin Nutr*. 2009 Apr; 89(4):1173–9. [PubMed: 19244378]
5. Laviano A, Meguid MM. Nutritional issues in cancer management. *Nutrition*. 1996 May; 12(5):358–71. [PubMed: 8875522]
6. Stewart GD, Skipworth RJ, Fearon KC. Cancer cachexia and fatigue. *Clin Med (Lond)*. 2006 Mar-Apr; 6(2):140–3. [PubMed: 16688969]
7. Bachmann J, Ketterer K, Marsch C, et al. Pancreatic cancer related cachexia: influence on metabolism and correlation to weight loss and pulmonary function. *BMC cancer*. 2009; 9:255. [PubMed: 19635171]
8. Davidson W, Ash S, Capra S, Bauer J. Cancer Cachexia Study G. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr*. 2004 Apr; 23(2):239–47. [PubMed: 15030964]
9. Evans WJ, Morley JE, Argiles J, et al. Cachexia: a new definition. *Clin Nutr*. 2008 Dec; 27(6):793–9. [PubMed: 18718696]
10. Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIO Working Group. *JPEN J Parenter Enteral Nutr*. 2009 Jul-Aug; 33(4):361–7. [PubMed: 19109514]
11. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Epidemiol Rev*. 1998 Apr 15; 147(8):755–63.
12. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and ageing*. 2010 Jul; 39(4):412–23. [PubMed: 20392703]

13. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997 May; 127(5 Suppl):990S–1S. [PubMed: 9164280]
14. Wang X, Miller GD, Messier SP, Nicklas BJ. Knee strength maintained despite loss of lean body mass during weight loss in older obese adults with knee osteoarthritis. *J Gerontol B Psychol Sci Soc Sci.* 2007 Aug; 62(8):866–71.
15. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci.* 2006 Oct; 61(10):1059–64. [PubMed: 17077199]
16. Morley JE, Abbatecola AM, Argiles JM, et al. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc.* 2011 Jul; 12(6):403–9. [PubMed: 21640657]
17. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol.* 2013 Apr 20; 31(12):1539–47. [PubMed: 23530101]
18. Tan BH, Birdsell LA, Martin L, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res.* 2009 Nov 15; 15(22):6973–9. [PubMed: 19887488]
19. Mourtzakis M, Prado CM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab.* 2008 Oct; 33(5):997–1006. [PubMed: 18923576]
20. Shen W, Punyanitya M, Wang ZM, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol.* 2004 Dec; 97(6):2333–8. [PubMed: 15310748]
21. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res.* 2009 Apr 15; 15(8):2920–6. [PubMed: 19351764]
22. Miyamoto Y, Baba Y, Sakamoto Y, et al. Sarcopenia is a Negative Prognostic Factor After Curative Resection of Colorectal Cancer. *Ann Surg Oncol.* 2015 Aug; 22(8):2663–8. [PubMed: 25564158]
23. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* 2008 Jul; 9(7):629–35. [PubMed: 18539529]
24. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, et al. Cachexia worsens prognosis in patients with resectable pancreatic cancer. *J Gastrointest Surg.* 2008 Jul; 12(7):1193–201. [PubMed: 18347879]
25. Mayers JR, Wu C, Clish CB, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. *Nat Med.* 2014 Oct; 20(10):1193–8. [PubMed: 25261994]
26. *Crawford J, Prado CM, Johnston MA, et al. Study Design and Rationale for the Phase 3 Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER Trials). *Curr Oncol Rep.* 2016 Jun. 18(6):37. This article provides important insight on how cancer cachexia trials are designed, including a robust discussion on selection of study endpoints. [PubMed: 27138015]
27. **Temel JS, Abernethy AP, Curott DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol.* 2016 Feb 19. This study describes two of the largest cancer cachexia pharmacologic intervention trials to date.
28. Lesniak W, Bala M, Jaeschke R, Krzakowski M. Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome--a systematic review and meta-analysis. *Polskie Archiwum Medycyny Wewnetrznej.* 2008 Nov; 118(11):636–44. [PubMed: 19140567]
29. Jatoti A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol.* 2002 Jan 15; 20(2):567–73. [PubMed: 11786587]
30. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol.* 1999 Oct; 17(10):3299–306. [PubMed: 10506633]

31. Ruiz Garcia V, Lopez-Briz E, Carbonell Sanchis R, et al. Megestrol acetate for treatment of anorexia-cachexia syndrome. The Cochrane database of systematic reviews. 2013; 3:CD004310.
32. Fearon KC, Voss AC, Hustead DS. Cancer Cachexia Study G. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr*. 2006 Jun; 83(6):1345–50. [PubMed: 16762946]
33. Akamizu T, Takaya K, Irako T, et al. Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. *Eur J Endocrinol*. 2004 Apr; 150(4):447–55. [PubMed: 15080773]
34. Neary NM, Small CJ, Wren AM, et al. Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004 Jun; 89(6):2832–6. [PubMed: 15181065]
35. Garcia JM, Garcia-Touza M, Hijazi RA, et al. Active ghrelin levels and active to total ghrelin ratio in cancer-induced cachexia. *J Clin Endocrinol Metab*. 2005 May; 90(5):2920–6. [PubMed: 15713718]
36. Porporato PE, Filigheddu N, Reano S, et al. Acylated and unacylated ghrelin impair skeletal muscle atrophy in mice. *J Clin Invest*. 2013 Feb; 123(2):611–22. [PubMed: 23281394]
37. Chen JA, Splenser A, Guillory B, et al. Ghrelin prevents tumour- and cisplatin-induced muscle wasting: characterization of multiple mechanisms involved. *J Cachexia Sarcopenia Muscle*. 2015 Jun; 6(2):132–43. [PubMed: 26136189]
38. Pietra C, Takeda Y, Tazawa-Ogata N, et al. Anamorelin HCl (ONO-7643), a novel ghrelin receptor agonist, for the treatment of cancer anorexia-cachexia syndrome: preclinical profile. *J Cachexia Sarcopenia Muscle*. 2014 Dec; 5(4):329–37. [PubMed: 25267366]
39. De Vriese C, Gregoire F, Lema-Kisoka R, et al. Ghrelin degradation by serum and tissue homogenates: identification of the cleavage sites. *Endocrinology*. 2004 Nov; 145(11):4997–5005. [PubMed: 15256494]
40. Garcia JM, Boccia RV, Graham CD, et al. Anamorelin for patients with cancer cachexia: an integrated analysis of two phase 2, randomised, placebo-controlled, double-blind trials. *Lancet Oncol*. 2015 Jan; 16(1):108–16. [PubMed: 25524795]
41. Fearon K, Argiles JM, Baracos VE, et al. Request for regulatory guidance for cancer cachexia intervention trials. *J Cachexia Sarcopenia Muscle*. 2015 Dec; 6(4):272–4. [PubMed: 26675232]
42. Tsigos C, Papanicolaou DA, Kyrou I, et al. Dose-dependent effects of recombinant human interleukin-6 on the pituitary-testicular axis. *J Interferon Cytokine Res*. 1999 Nov; 19(11):1271–6. [PubMed: 10574620]
43. Burney BO, Hayes TG, Smiechowska J, et al. Low testosterone levels and increased inflammatory markers in patients with cancer and relationship with cachexia. *J Clin Endocrinol Metab*. 2012 May; 97(5):E700–9. [PubMed: 22419719]
44. Bhasin S, Calof OM, Storer TW, et al. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nat Clin Pract Endocrinol Metab*. 2006 Mar; 2(3):146–59. [PubMed: 16932274]
45. Narayanan R, Coss CC, Yepuru M, et al. Steroidal androgens and nonsteroidal, tissue-selective androgen receptor modulator, S-22, regulate androgen receptor function through distinct genomic and nongenomic signaling pathways. *Mol Endocrinol*. 2008 Nov; 22(11):2448–65. [PubMed: 18801930]
46. Dobs AS, Boccia RV, Croot CC, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. *Lancet Oncol*. 2013 Apr; 14(4):335–45. [PubMed: 23499390]
47. Crawford J, Johnston MA, Taylor RP, et al. Enobosarm and lean body mass in patients with non-small cell lung cancer. *J Clin Oncol*. 2014; 32(5s) ASCO Annual Meeting suppl abstr 9618.
48. Ebner N, von Haehling S. Unlocking the wasting enigma: Highlights from the 8th Cachexia Conference. *J Cachexia Sarcopenia Muscle*. 2016 Mar; 7(1):90–4. [PubMed: 27128291]
49. Garber K. No longer going to waste. *Nat Biotechnol*. 2016 May 6; 34(5):458–61. [PubMed: 27153267]

50. Currow DC, Temel JS, Giordano R, et al. Anamorelin in cachectic patients with non-small cell lung cancer (NSCLC) and low BMI (<20 kg/m²): A pooled efficacy data analysis of two phase 3 studies. *J Clin Oncol*. 2016; 34(15s) ASCO Annual Meeting suppl; abstr 10119.
51. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997 Jun; 15(6):2403–13. [PubMed: 9196156]
52. ODAC recommends full approval for Gemzar for pancreatic cancer. *Oncology*. 1995 Sep; 9(9): 799–800. [PubMed: 8562322]
53. Muscaritoli M. Targeting cancer cachexia: we're on the way. *Lancet Oncol*. 2016 Feb 19.
54. Schneider CM, Hsieh CC, Sprod LK, et al. Cancer treatment-induced alterations in muscular fitness and quality of life: the role of exercise training. *Ann Oncol*. 2007 Dec; 18(12):1957–62. [PubMed: 17804476]
55. Gilliam LA, St Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antioxid Redox Signal*. 2011 Nov 1; 15(9):2543–63. [PubMed: 21457105]
56. Chicco AJ, Hydock DS, Schneider CM, Hayward R. Low-intensity exercise training during doxorubicin treatment protects against cardiotoxicity. *J Appl Physiol*. 2006 Feb; 100(2):519–27. [PubMed: 16210442]
57. Maddocks M, Murton AJ, Wilcock A. Therapeutic exercise in cancer cachexia. *Crit Rev Oncog*. 2012; 17(3):285–92. [PubMed: 22831159]
58. Mustian KM, Janelins MC, Peppone, et al. EXCAP exercise effects on cognitive impairment and inflammation: A URCC NCORP RCT in 479 cancer patients. *J Clin Oncol*. 2015; 33 ASCO Annual Meeting (suppl; abstr 9504).
59. Mustian KM, Peppone LJ, Palesh OG, et al. Exercise and Cancer-related Fatigue. *US oncology*. 2009; 5(2):20–3. [PubMed: 21853012]
60. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009 Jan 20; 27(3): 344–51. [PubMed: 19064985]
61. Grande AJ, Silva V, Riera R, et al. Exercise for cancer cachexia in adults. *The Cochrane database of systematic reviews*. 2014; 11:CD010804.
62. Oldervoll LM, Loge JH, Lydersen S, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncologist*. 2011; 16(11):1649–57. [PubMed: 21948693]

Key Points

- The study of body composition, or morphometrics, using cross-sectional imaging or DXA has helped characterize outcomes in cancer cachexia though its utility in clinical decision-making is unknown and warrants further study.
- Intervention trials in cancer cachexia should focus on well-vetted biologic targets and be evaluated by standardized, clinically meaningful outcomes, including patient-reported outcomes.
- Though relatively understudied in this field, there is strong pathophysiological rationale to evaluate exercise as an intervention for cancer cachexia; multiple studies are on-going.

Table 1

Definitions of cachexia.

(Cancer) Cachexia	
Cancer Cachexia Study Group (2006)	10% weight loss, anorexia (<1500 kcal/day), and systemic inflammation (CRP ≥ 10 mg/L)
Cachexia Consensus Conference (2006)	>5% in previous 6 months with three of the following: 1) Reduced Muscle Strength 2) Fatigue 3) Anorexia 4) Low Fat-Free Mass 5) Abnormal biochemistry (elevated IL-6 or CRP or low albumin)
SCRINIO Working Group (2008)	Cachexia: > 10% weight loss Pre-Cachexia: <10% weight loss
International Consensus on Cancer Cachexia Classification (2011)	>5% in previous 6 months or >2% weight and: BMI <20 kg/m ² or sarcopenia

Table 2

Definitions of sarcopenia.

Sarcopenia	
European Working Group on Sarcopenia in Older People (2010)	Reduced muscle mass and: Reduced muscle strength or Reduced physical performance
The Society of Sarcopenia, Cachexia, and Wasting Disorders (2011)	Lean appendicular mass < 2 SDs below average for age and ethnicity and: Walking speed < 1 m/s or Unable to walk 400 M in 6-minute walk test

Table 3

RCTs investigating exercise in cancer cachexia.

Randomized Controlled Trials Investigating Exercise in Cachexia					Status
NCT Identifier	Tumor Type (s)	Location (s)	Description	Outcomes	
01136083	Lung, on targeted therapy	Taiwan	UC vs. 8-week high aerobic treadmill interval training	Exercise capacity *, blood VEGF-A and myostatin, QOL, body composition, nutrition	complete
01419145	Lung or Pancreas, on chemotx	Norway, United Kingdom	UC vs. 6-week home-based resistance exercise and walking program + celecoxib and protein supplements	Feasibility of recruitment and retention *	complete
02330926	Lung, Pancreas or Biliary, on chemotx	Canada, Norway, United Kingdom	UC vs. 6-week home-based exercise program + ibuprofen and nutritional advice/supplements	Change in body weight *	recruiting
00196885	Lung or GI Cancer	Germany	resistance exercise program +/- n-acetyl/cysteine	muscle area * and peak forces *, muscle fiber composition (cytokines, myostatin, Akt activity)	complete
	Upper GI Tract Cancers, on chemotx	Rochester, NY	UC vs. 12-week low- to moderate-intensity home-based resistance exercise and walking program (EXCAP®)	SPPB *, SCPT, weight, aerobic capacity, muscle strength and force, lean body mass, QOL, inflammatory cytokines	recruiting

* denotes primary outcome

Abbreviations NCT: national clinical trial, chemotx: chemotherapy, UC: usual care, EXCAP®: exercise for cancer patients, QOL: quality of life, SPPB: short physical performance battery, SCPT: stair climb power test

Table 4

Research priorities in cancer cachexia.

Research Priorities in Cancer Cachexia
Development of strategies to implement morphometrics into clinical decision making
Specify and validate diagnostic criteria for pre-cachexia
Identify biomarkers for pre-cachexia
Expand patient selection in cancer cachexia trials (Earlier enrollment, GI Cancers)
Identify tangible and realistic endpoints in cancer cachexia trials
Investigate exercise as an intervention for cancer cachexia