Part IX
Gastrointestinal

Chapter 21
Cancer Cachexia and Anorexia

Vickie Baracos[1] & Neil MacDonald[2]

[1]Department of Oncology, University of Alberta, Edmonton, Alberta, Canada, T6G1Z2
Email: vickie.baracos@ualberta.ca

[2]Emeritus Professor, University of Alberta, Emeritus Professor, McGill University

Abstract

Assessment, diagnostic criteria, management, and therapy development in cancer cachexia/anorexia are based on our pathphysiologic understanding of this syndrome Efforts to define and develop diagnostic criteria for cancer cachexia are ongoing in the community of experts in cachexia research. Current concepts of cancer cachexia underscore the central importance of skeletal muscle wasting and its consequent impairment of physical function as well as metabolic impairments (e.g. severe cancer treatment toxicity). Recognition of the complexity of cachexia is also of considerable importance, especially as it presents with a variable combination of reduced food intake (with both primary and secondary etiologies) and abnormal metabolism (including tumor metabolism and host inflammation) in its underlying pathophysiology. These defining characteristics dictate a multifaceted assessment strategy focusing on muscle loss, food intake, nutrition impact symptoms, catabolic drivers including tumor burden, systemic inflammation, altered endocrine status, as well as the clinical, functional and psychosocial consequences. Cancer cachexia treatment is based on multimodal therapy focusing on management of pain, other symptoms and inflammation, treatment of all reversible causes of low food intake, providing a supply of key essential nutrients, and exercise; this therapy entrains the expertise of a multidisciplinary team of health professionals as well as patients and their families.

Key words: cachexia, anorexia, malnutrition, nutrition, inflammation, skeletal muscle, sarcopenia, weight loss

The beginning of wisdom is to call things by their right name

Chinese Proverb

Clinicians and their patients benefit when the condition treated is clearly defined. Alas, this has not been the case for the cancer anorexia–cachexia syndrome. The presence of multiple concurrent but different definitions is an impediment to clinical care and to clinical cachexia research, and this incited a significant recent focus on reaching a consensus definition.

A generic definition encompassing cachexia in all disease conditions was proposed recently by a group of experts [1]. This definition of cachexia notably makes a distinction

I.N. Olver (ed.), *The MASCC Textbook of Cancer Supportive Care and Survivorship*,
DOI 10.1007/978-1-4419-1225-1_21,

between the behavior of skeletal muscle and of adipose tissue: "….cachexia, is a complex metabolic syndrome associated with underlying illness and *characterized by loss of muscle with or without loss of fat mass*"… Importantly, this definition recognizes that skeletal muscle wasting can be hidden within the bulk of body weight and body weight change, and underscores the recent recognition of severe muscle depletion (i.e. sarcopenia) as a clinically important phenomenon [2].

More recently, an international group of experts conducted a Delphi consensus process to provide a definition and conceptual framework specific to cancer-associated cachexia [3]. This consensus definition was "*Cancer cachexia is a multifactorial syndrome [of involuntary weight loss] that is defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and that leads to progressive functional impairment. The pathophysiology of cachexia is characterized by a negative protein and energy balance that is driven by a variable combination of reduced food intake and abnormal metabolism*". This definition underscores the point that loss of skeletal muscle is related to functional impairment, cancer-related mortality, treatment-related complications and poor quality of life. Unlike simple malnutrition, in cachexia the negative energy balance and muscle loss is not solely a result of reduced food intake. Metabolic derangements also contribute (e.g. elevated resting metabolic rate, insulin resistance, excess catabolic drive, lipolysis, proteolysis) to the activation of weight loss. Both host- and tumor-derived inflammatory mediators and catabolic factors my be involved, with the results that cancer cachexia cannot be fully reversed by conventional nutritional support.

The defining features of cancer cachexia:

- Is multifactorial in nature.
- Is characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass).
- It cannot be fully reversed by conventional nutritional support.
- Has as a consequence progressive functional impairment.
- Its pathophysiology is characterized by a variable combination of reduced food intake and abnormal metabolism including tumor metabolism and inflammation.

Management of cancer cachexia depends upon identifying elements contributing to patient wasting. The tumor itself imposes a metabolic demand, which may vary between a negligible value and >800 kcal/day [4], in function of tumor burden and metabolic activity. Aberrant chronic inflammation is generated by interaction of the tumor with the host inflammatory response to the tumor. This harmful inflammatory process is similar to the acute response to infection or injury save here the "the tap is left on', causing enhanced tumor symptoms and increased cancer growth. This is the result of direct tumor stimulation by inflammatory products and interference wth natural killer cells and other elements of an anti tumor immune response. Excess inflammatory mediators generate lipolysis and proteolysis by local action on adipose and muscle tissue; persistent inflammation in the central nervous system has been demonstrated in animal models and this contributes to sustained anorexia as well as catabolic outputs to peripheral tissues [5] Cancer patients are, however, also bedeviled by a plethora of problems that contribute to poor food intake. A list of these are listed in Table 21.1, together with a brief listing of possible 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).

Table 21.1 An approach to identify potentially correctable cause of cancer cachexia

Potentially correctable problems	Possible approaches
Psychological factors	
Anxiety	Anxiolytics
Depression	Antidepressants
Family distress	Social assistance
Spiritual distress	Counseling
Eating problems	
Appetite	Referral to a nutrition clinic or a dietician
Disturbed taste or smell	
Oral	
Dentures, mouth sores	Dental care
Thrush	Antifungal medication
Dry mouth	Oral moisteners ,Change medications
Swallowing difficulties	Related to cause: chewing difficulty, dry mouth, pain Esophageal dilation
Stomach	Regurgitation therapy
Early satiety	Gastric stimulants
Nausea and vomiting	Related to cause
Bowel	
Obstruction	Related to cause
Constipation	Laxatives, especially if on opioids
Diarrhea	
Malabsorption	
Pancreas	Pancreatic enzymes
Fistulas	Related to cause
Fatigue	Exercise protocol
Sleep disturbances	Sleep protocol
Physical limitation	Exercise protocol
Motivation	
Cognitive fatigue	Methylphenidate
Function	Exercise protocol
Home setting	Cause related
Pain	Appropriate analgesics
	Nerve blocks: surgical, percutaneous
	Counseling
Metabolic	As indicated
Diabetes	
Adrenal insufficiency	
Hypogonadism	
Thyroid insufficiency	

Clinical Workup

In concordance with the criteria mentioned above, the clinical workup focuses on:

- The degree and rate of depletion of body weight, muscle protein, and energy stores in adipose tissue.
- Evaluation of muscle mass and degree of functional impairment.
- Anorexia and reduced food intake due to all causes.
- Catabolic drivers including tumor burden, systemic inflammation, and altered endocrine status.
- Psychosocial stress related to food, eating, and altered body image.

Cachexia is not just a late stage phenomenon; patients with some tumors (e.g., pancreas, upper gastrointestinal, and lung cancer) commonly present with weight loss, anorexia and other nutritional issues. Early identification of cachexia may lead to treatments that reverse or prevent, if only for a while, further deterioration. Therefore, it is strongly recommended that oncology clinics employ protocols for screening as well as further detailed assessment, as indicated,of all patients with advanced cancer, at diagnosis and at periodic intervals over the course of their illness. Elements of this protocol include the evaluation of weight and weight loss, level of dietary intake, biological criteria, and nutritional risk factors associated with the underlying pathologies and treatments.

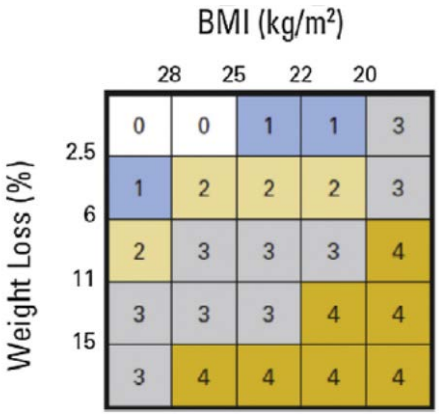
Patient-reported outcomes are of value in the assessment of various facets of cachexia. There is evidence to support the reliability of self-reported height, weight, and weight history [6]. Patient/family generated questionnaires are valuable for the screening process. We use the following battery; however, a variety of similar tools exist that may be used to capture the same information:

- Edmonton System Assessment (ESAS) [7] helps to identify and measure the severity of common symptoms affecting people with advanced cancer, using a 0–10 scale.
- Patient-Generated Subjective Global Assessment (PG-SGA) [8] is an adaptation for oncology patients of the earlier SGA thatwas originally validated as a screening tool for malnutrition in hospitalized patients. The PG-SGA is scored and incorporates questions relating intake, weight, and nutritional risk factors, and is a mixture of patient – report (for weight history, food intake, functional status, and symptoms affecting food intake) and assessments made by health care professionals (comorbid conditions, physical examination, corticosteroid use, and fever).
- Distress Thermometer [9]. This screening tool is used to assess the level of patient distress (on a 0–10 scale) and the specific problems contributing to it by giving them a problem list to indicate their reason(s) for distress. It is an easy way for patients to differentiate between the normal distress and a more significant form of distress that requires help from a health care professional. Patients can fill these questionnaires in a few minutes. Initially, instruction from clinic personnel is desirable.

Assessment of Weight and Weight Loss

Body weight should be determined and recorded in a consistent fashion, with caution taken to remove footwear, and the contents of pockets at all times patients are weighed. The same scale should be used consistently for follow-up weights, and all scales used in the unit should be regularly calibrated. A measurement of patients' height, determined with a stadiometer, must be

entered into the patient record, to facilitate computation of the common anthropometric descriptor, body mass index (BMI) (kg/m²). Percentage of weight lost is calculated, either relative to premorbid (habitual) weight, or over a defined period of time (e.g., 6 months). Edema, ascites, increased organ volume (e.g., hepatomegaly), constipation, and tumor burden including metastasis, contribute to shifts in body weight in advanced cancer patients [10,11] and should be taken into account in the assessment of weight and weight change over time.



In the past weight loss and BMI cut points have been treated rather heterogeneously in the nutrition screening tools, in the literature, in the Common Terminology Criteria for Adverse Events (CTCAE) and in publications by various health authorities and expert groups. To address this issue, the international group which had earlier provided a consensus framework for cancer cachexia, developed a revised set of diagnostic criteria for the classification of cancer-associated weight loss [12]. Using a risk stratification for overall survival, a robust grading system incorporating the independent prognostic significance of both BMI and % weight loss was developed (Figure 2.1.1).

Figure 21.1. A 5 X 5 matrix representing five weight loss categories within each of five BMI categories was graded 0, 1, 2, 3 or 4 based on median survival. All combinations of BMI and weight loss within the same Grade, have the same survival probability.

This grading scheme is superior to conventional grading systems applied to weight loss in patients with cancer (i.e. CTCAE, cachexia scores, and screening tools for malnutrition) which typically employ simple weight loss cutoffs (e.g. 10%) . Using a single cutoff inappropropriately subgroups patients with disparate degrees of risk. For example, in Figure 21.1, patients with weight loss <10%, includes significantly different subsets of patients including Grade 0 (survival 21.5 months) and Grade 4 (survival 4.7 months).

This system should be considered by oncologists evaluating the risk benefit/analysis of chemotherapy in advanced cancer patients.

Evaluation of Muscle Mass and Degree of Functional Impairment

Wasting of lean tissues and especially skeletal muscle is an important component of cancer-associated weight loss. Muscle wasting can coexist with the depletion of adipose tissue but may also coexist with obesity, and this independent behavior of lean and adipose tissues makes body composition analyses essential. Precise and specific measures of skeletal muscle mass and loss using computed tomography has greatly enabled our understanding of the clinical importance of muscle loss [13]. Cancer patients with significant erosion of skeletal muscle (even if they have large body weights) have an elevated risk of being partially or entirely bedridden and a substantially reduced survival [13]. Sarcopenic patients are also prone to severe toxicity during chemotherapy [14–16], necessitating reductions in the dose of drugs or treatment delays.

Defined sex-specific reference values and standardized body composition measurements are essential to perform assessment of skeletal muscle depletion. There remains a paucity of

reference values related to cancer-specific outcomes. A generally accepted rule is an absolute muscularity below the 5th percentile for normal healthy adults. Assessment of muscularity remains far from routine, although a variety of clinically expedient approaches are available. The following approaches are suggested [3]; sex-specific cut points consistent with sarcopenia are given for each measure:

- Mid upper arm muscle area by anthropometry: men <32 cm^2; women <18 cm^2.
- Appendicular skeletal muscle index determined by dual energy X-ray absorptiometry: men <7.26 kg/m^2; women <5.45 kg/m^2.
- Lumbar skeletal muscle index [12] determined by CT imaging: men <55 cm^2/m^2; women <39 cm^2/m^2.
- Whole body fat-free mass index without bone determined by bioelectrical impedance: men 14.6 kg/m^2; women 11.4 kg/m^2.

It should be noted that these values were determined in Caucasians, and that sex-specific cut points for sarcopenia are emerging for other populations [17].

Function Tests

Simple tests, with minimal patient burden, can be employed. We use a six-minute walk, sit to stand time, gait speed, and the Community Health Activities Model Program for Seniors (CHAMPS) tests. Physician assessment of patient capacity to perform a six-minute walk is necessary prior to testing.

Articles which outline their use and precautions include:

- Jones and Eves – Cardiorespiratory exercise testing in clinical oncology research – LANCET Oncology 2008 9 (8): 757-65.
- ATS Statement on six-minute walk test.American Journal of Respiratory Critical Care Medicine (2002) 166:111-117.
- Carli F et al - Analgesia and functional outcome after total knee arthroplasty - British Journal of Anaesthesiology 2010 106: 196-200.

Assessment of Dietary Intake

Prospectively collected dietary records are the gold standard for evaluation of total energy and macronutrient intake. A 3-day collection period seems to be the compromise generally taken between the length of the assessment and the frailty or vulnerability of patients with advanced cancer; 24 h dietary recall and food frequency questionnaires are sometimes used as alternates. Dietary records require the specialized expertise of a registered dietitian and are not commonly used in clinical practice. Nutrition screening tools generally replace dietary records with questions pertaining to the type, number, and frequency of meals or verbal descriptors such as “very little of anything,” “only liquids,” or “little solid food” [7]. Questions related to the patient’s ability to purchase, shop for, prepare food, and eat independently are often included, especially in nutrition assessment tools for the elderly. Dozens of symptoms have the potential to exert a negative impact on food intake (e.g., nausea, vomiting, constipation, early satiety, chemosensory dysfunction, pain, fatigue, difficulty swallowing, mouth sores, dental problems) and should be evaluated.

Biological Criteria

The most clinically useful laboratory measures relate to the acute phase response, a series of

reactions initiated in response to infection, physical trauma, or malignancy. The acute phase response is characterized by leukocytosis, sometimes fever, alterations in the metabolism of many organs as well as changes in the plasma concentrations of acute-phase proteins [17,18]. The positive acute-phase proteins (fibrinogen, α1-acid glycoprotein serum amyloid A, and C-reactive protein) increase and negative acute-phase proteins for both(albumin and transferrin) decrease during an inflammatory disorder. The laboratory values vary according to different authors: albumin (cut points variously <30 to <35 g/L), transthyretin (prealbumin) (<110 or <180 mg/L), and C-reactive protein (>5 or >10 mg/L). The Glasgow Prognostic Score, grading for reduced albumin, increased CRP or both, is established as a powerful prognostic tool in multiple cancers for both tumor progress, survival [19] and symptom burden [20]. Where CRP testing is still not available,neutrophil to lymphocyte ratios offer similar prognostic information on tumor prognosis [21]. The value of both of these indices is supported by meta-analyses in multiple disease sites. While the production of proinflammatory cytokines is understood to be central to the host inflammatory response to malignant disease, serum cytokine levels have proven too inconsistent to be useful biological criteria. Thyroid function and the possible presence of hypogonadism (testosterone screen) may provide additional information on possible causes of weight and muscle loss.

Assessment of Nutritional Risk Factors Associated with the Underlying Pathology(ies) and Treatments

This category is quite heterogeneous and includes any factors likely to drive weight loss or poor food intake. Some examples in this category include old age, poor social support, poor cognition, limited mobility, advanced disease stage, extensive tumor burden and metastases, the presence of fever, and comorbid conditions associated with additional nutritional risk (i.e., compromised organ function, major stress, infection). Depression is a significant independent factor explaining nutritional risks. A variety of medications may contribute to poor food intake or altered metabolism (i.e., high-dose corticosteroid).

General Therapeutic Platform

The management of cancer cachexia is a moving target; new approaches are expected in the near future. While awaiting clinical research advances, much can be done today. Elements include:

1. Evaluate which elements of cachexia are present. If the patient has a high C-reactive protein or unexplained high neutrophil/low lymphocyte count, they are likely to be experiencing inflammation – related catabolic drive.. A low albumin is usually a late feature. All identified secondary issues related to food intake should be addressed. A variety of treatment approaches may be required.
2. Team approach – Adoption of this concept is critical. In addition to the nurse/physician dyad, core members of the team should include a dietitian and a physiotherapist; availability of an occupational therapist, social worker, and a clinical psychologist is also desirable.
3. Our clinics have varying resources. Based on the initial workup, you may establish decision points for the involvement of the Registered Dietitians based on PG-SGA quantitative scores, or physiotherapists based on fatigue/activity scores.
4. Exercise patients within their safe capacity. It is becoming increasingly clear that many categories of cancer patients can benefit from planned physical activity. Physiotherapists and occupational therapists can evaluate and motivate your fatigued, inactive patients to exercise and carry out daily tasks. Fatigue, the most prevalent, devastating symptom encountered by

cancer patients has no established drug therapy however directed exercise can relieve fatigue.

5. Involve the patient and family as members of the therapy team. Almost all cancer therapies call for patients to be passive receptors of care – somebody is doing something to them. Diet and exercise are *their* therapies. We advise but they run the enterprise. We stress that involving care givers is not simply an empty rherorical phrase. They are often more distressed than the patient as they observe a loved one wasting away. Their anxiety can be transferred to the patient leading to conflicts over food intake and preparation. Ideally dietary advice is initially offered to both patient and caregivers. Both patients and caregivers can benefit from an understanding of the biologic factors beyond their control that limit food intaken and enjoyment. This knowledge may help ease their anxiety and enhance the partnership. Follow up protocols are particularly key when patiens have poor social support.
6. Stress must be placed on early detection and management. Meticulous attention to the early onset of weight or muscle loss, inflammation, or other contributing causes can forestall the development of severe wasting.
7. Work from protocols. It is of importance to develop standard practices in the care unit with regard to cachexia and anorexia.
    - What is your screening platform?
    - What is your nutrition platform?
    - How do you identify and manage constipation?
    - What is your policy on appetite stimulants?
    - What is your exercise policy?

Maintaining volitional food intake

Nutrition interventions aim to maintain or improve food intake. Recent evidence-based clinical practice guidelines for nutrition in clinical oncology are available [22] and are a valuable reference. Nutrition counseling is the 1st line approach. Such intervention by an accredited health care professional, aims to support patients with a thorough understanding of their nutritional needs and of the specific eating habits that they can undertake to meet those needs. A dietitian can help patients achieve desirable levels of energy and protein as part of a balanced diet and within the context of their dietary customs. In addition to counseling, oral nutritional supplements are sometimes required. Oral nutritional supplements are nutritionally complete nutrient mixtures intended to supplememt supplement volitional food intake. Research findings indicate that the combination of nutrition counselling with oral nutrition supplements typically support a net increase of intake of ~400 kcal / day. Estimates of daily energy expenditure for cancer patients vary between 24 and 28 kcal/kg body weight per day. If intake remains inadequate despite conseling and supplementation, appetite stimulants, and artificial nutrition by the enteral or parenteral route may be indicated [22].

Therapeutic application of specific micronutrients

1. .Protein intake should be > 1 g/kg/day and, if possible up to 1.5 g/kg/day with emphasis on high quality protein from animal, fish, dairy or plant sources [22]. No specific enhanced amino acid supplements are proven; however, there is current research interest in leucine, branch chain amino acids and glutamine.
2. Omega 3 fatty acids are lipids of proven benefit in maintaining cardiac health. In a wide range of animal studies, they demonstrate antitumor effects, maintain muscle mass in tumor-bearing mice, and protect against chemotherapy injury. A pedigree such as the above makes

them attractive agents in oncology practice, particularly as they are safe components of human diets. In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, are recommended to use supplementation with long-chain omega-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight [22]. Omega-3 fatty acids act as broadly based anti-inflammatory agents that reduce both inflammatory prostanoid and cytokine production; they may particularly benefit the high C-reactive protein group, but studies are lacking. The usual dose is: eicosapentanoic acid (EPA) 2.0–2.5 g daily. Use with caution in those with low platelet counts or bleeding disorders.

3. Vitamins and minerals should be supplied in amounts approximately equal to the recommended daily allowances taken from recommendations of WHO/FAO and national and international nutrition societies [22]. The use of single high-dose micronutrients in the absence of specific deficiencies, is to be avoided. Vitamin deficiencies, notably C, D, and B's, are common in patients following prolonged hospitalization. Although there is only modest research on this topic it may reasonably be assumed that a number of malnourished outpatients may also develop deficiencies. It is our practice to prescribe multivitamin therapy in physiologic doses, plus Vitamin D, based on clinical assessment. While the multivitamin dose is low, some oncologists may prefer that they be withheld during chemo/radiotherapy because of antioxidant properties.
4. Complementary therapy supplements – while it is estimated that half of all cancer patients consume complementary or alternative medical products, none are proven; take care as some may have unknown adverse effects and drug interactions.

Appetite Stimulation

Agents capable of stimulating ingestive behavior in patients with cancer is an active area of investigation. Limited efficacy and side effects are the primary limiations to the currently available choices.

Corticosteroids

These agents have powerful orexigenic action [23]. Their mode of action is not clear, but presumably it relates to their anti-inflammatory properties. Unfortunately, this benefit is purchased at the cost of increasing muscle catabolism, insulin resistance and risk of infection. Consequently, aside from other long-term adverse effects, they are not suitable for continual therapy in mobile patients with reasonable muscle function, other than for restricted periods of time (1–3 weeks) [22]. They are useful in patients whose maintenance of physical function is no longer a high priority. Prednisone and its congeners are the corticosteroids of choice, as dexamethasone, a fluorinated corticoid, is particularly active in stimulating muscle breakdown.

Megestrol Acetate

At least 30 randomized studies support the use of Megestrol and other progestational agents for appetite enhancement [24]. These molecules are structurally similar to corticosteroids, and probably increase appetite through their anti-inflammatory actions. These agents also may have catabolic effects on skeletal muscle.Moreover, they may increase the risk of thromboembolism, although this risk seems to be modest at usually employed dose levels in patients without a prior history of thrombotic disease and low risk factors.

Weight gain during therapy with progestational agents is composed of fat, and this can be a

welcome finding in patients with severe weight loss. Concern for muscle function leads many clinicians to limit megestrol use to intermittent schedules, reserving longer term therapy for patients no longer fighting to maintain strength and mobility.

Cannabinoids

Cannabis has a well-defined orexigenic effect in many patients. In some part, this benefit stems from the unique ability of cannabinoids to enhance hedonic appeal of food. This may relate to the central action of cannabinoids on cerebral and hypothalamic centers mediating the sense of pleasure in eating [25]. Cannabinoid receptors are widespread, so they may also enhance appetite through unknown peripheral mechanisms. Their use is limited by real or feared adverse effects and by societal views on marijuana. A virgin user, particularly if elderly, may regard the psychoactive effects as fearful and unpleasant; a view perhaps not shared by younger, experienced patients. At usual doses, psychoactive properties are commonly not expressed while a side benefit, improved sleep, may be noticed.

Cannabinoids are possibly underutilized. They may be helpful in people who are not at risk for cognitive changes (e.g., people with dementia or at risk for becoming demented) or interactive adverse drug effects. What is the best route of administration? A number of oral cannabinoids are available, albeit marketed as antinauseants for chemotherapy patients. It is not clear whether smoked marijuana or tetrahydrocannabinoid aerosols (marketed to relieve muscle spasms in multiple sclerosis and patients with other neurologic symptoms) are superior.

Gastric Stimulants and Laxatives

While not direct appetite stimulants, these agents may reduce gastric atony and constipation, thus making the gastrointestinal tract more receptive to nutrition. In patients complaining of early satiety, after diagnosing and treating constipation, prokinetic agents may be considered. Metoclopromide is widely employed as a gastric stimulant, and tolerability is usually good [22]. The safety profile of metoclopramide, however, includes somnolence, depression, hallucinations, extra-pyramidal symptoms and potentially irreversible dyskinesias.

Without doubt, constipation, which can cause a wide range of symptoms including anorexia, is often overlooked, even in patients not on opioids. A history of a daily stool does not rule out constipation; how much stool is passed and what are its characteristics? A daily stool may be extruded from a column of feces backed up to the ileum. Increasingly, physicians are ordering abdominal films in patients at risk, to determine the presence and severity of constipation, which will guide the patient's laxative protocol.

Anabolic Steroids

There may be a role for physiologic replacement doses of testosterone in hypogonadal male patients [26]. Hypogonadism is common in advanced cancer patients, who are generally elderly, and clinically practical approaches to treatment are available in the gerontology literature. Notably, many chemotherapy drugs and opioids can reduce testosterone production. Screening for this condition as part of the metabolic profile of the cachexia patient is recommended.

Enteral and Parenteral Feeding

Patients with defined limitations to oral intake may benefit from artificial feeding [22,27,28]. Clinical practice guidelines are positive for malnourished cancer patients facing surgery,

encountering severe chemotherapy/radiation therapy, or undergoing bone marrow transplantation. Patients unable to ingest adequate nutrients for extended periods of time are candidates for artificial nutrition. If a decision has been made to feed a patient, enteral nutrition is the approach of choice unless there is severe intestinal insufficiency due to radiation enteritis, chronic bowel obstruction, short bowel syndrome, peritoneal carcinosis, or chylothorax. While there are open questions about the specific indications for starting artificial nutrition, clinical practice, contraindications, complications, and monitoring of enteral and parenteral nutrition do not differ between cancer patients and patients with benign diseases.

2016 ESPEN Oncology Nutrition Guidelines [22] states "*Ethical considerations for artificial nutrition relate to its use during the last weeks and days of life in advanced malignancies. The risks and detriments as well as the possible futility of artificial nutrition must be weighed against possible physiologic and or psychological benefits, for a given patient and family. As a general rule, the risks of PN are regarded to outweigh its benefits for patients with a prognosis of less than 2 months.*" These views are espoused in other international clinical practice guidelines on parenteral nutrition. Clearly, this advice concerns patients with far-advanced illness. Some authors developed prognostic indices to assist in the decision – making process for parenteral nutrition in advanced cancer [28] and further refinements of survival prediction for this context would be welcomed. Lastly, it should be noted that clinical practice regarding artificial nutrition differs due to religious, cultural and ethnic background of patients as well as social, emotional and existential aspects of each individual. In some cultures, active feeding in any form is regarded as essential.

THE FUTURE

Progress in Drug Therapy

To advance treatment, we strongly hold that clinics with research capacity for randomized clinical trials of cachexia and anorexia therapy, should ensure that the opportunity to participate in these trials is available to patients in their setting. The introduction of new agents will stem directly from our growing understanding of the pathophysiology of cachexia. Intriguing ideas centred on controlling inflammation and unbalanced autonomic activity are coming to the fore. Agents of special interest in the authors' opinion are listed below; this is not an all-inclusive list and may reflect author bias.
:

Anti-Inflammatory Agents

- Cytokine inhibitors directed toward Il-6; Il-1β
- NSAIDS alone and in combination with other agents.

Effectors of Muscle Anabolism

- Selective androgen receptor modifiers (SARMS), a class of specific ligands for the skeletal muscle androgen receptor. These non-steroidal compunds enhance muscle synthesis without androgenic effects.
- Anti-myostatin compounds. Monoclonal antibodies or peptibodies neutralizing myostatin activity.

Autonomic Nerve Modulators

- B_2 antagonists and agonists.
- A seeming paradox – the antagonists (beta blockers) can regulate wasteful increased resting energy expenditure and excess sympathetic lipolytic output, while some agonists (e.g., clenbuterol, formaterol) have direct effects enhancing muscle synthesis. How can they both be potential helpful drugs? The answer is not clear and may depend upon the primacy of an increased REE in a given patient .or on selective activity of certain second messenger systems in muscle.

Hypothalamic Neurotransmitters

- Melanocortin receptor 4 (MCR4) inhibitors acting centrally may influence all elements of cachexia. While demonstrated in mice, human data are awaited.
- Ghrelin is is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract which functions as a neuropeptide in the central nervous system. The physiological actions of ghrelin include stimulation of appetite, food reward, gastrointestinal motility, pancreatic secretion, lipogenesis and anabolism. Recent Phase III clinical trials indicate a robust anabolic response to small molecular weight orally active ghrelin analogs in patients with non-small cell lung cancer [29].

Cachexia Therapy Integrated With Cancer Treatment

Within the conventional organization of cancer care there may exist clinical services that have aspects of the management of cachexia in their charge, but there is no set standard. For example, cachexia may 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 available in cancer centers and hospitals. While we earlier stressed the importance of multidisciplinary involvement in cachexia management, we do not believe that many examples of purposefully organized cachexia care teams, in practice, exist. There are a few recently published models for cachexia care integrated within a supportive multidisciplinary team approach [30-33]. The benefits of this care have been reported from prospectively conducted non-randomized studies [30-33]. We foresee that clinical services operated in true partnership between palliative care physicians and the oncology community will emerge, as endorsed currently by many cancer agencies e.g. American Society for Clinical Oncology [34]. A critically important underlying concept is that the driving forces of pain and symptoms, including cachexia are the same driving forces advancing tumor growth and metastases. Our past separate approaches to symptom research and anti-tumor research is not logical. This concept may be particularly important for trials on immune modulators as these compounds theoretically may also alter immune mediators that stimulate cachexia and other cancer symptoms. It is notable in this context that the most recent trials of cachexia therapeutics [29] have been shifted forward in the disease trajectory and are delivered concurrently with 1st line chemotherapy rather than in the end of life phase [23-25]. We strongly favor the development of integrated structures to provide cachexia therapy and overall pain and symptom management integrated with anti-cancer therapy. This is in accordance with the current view that patients with advanced cancer should receive dedicated, early palliative care concurrently with standard oncology treatment [34] based on evidence that it improves quality of life, reduces depression and improves satisfaction with care.

References

1. Evans WJ, Morley JE, Argilés J *et al.* Cachexia: a new definition. Clin Nutr. 2008;27(6):793–9.
2. Rolland Y, Czerwinski S, Abellan Van Kan G *et al.* Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives.J Nutr Health Aging. 2008;12(7):433–50.
3. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus framework. Lancet Oncol 2011;12:489-95.
4. Friesen DE, Baracos VE, Tuszynski JA. Modeling the energetic cost of cancer as a result of altered energy metabolism: implications for cachexia. Theor Biol Med Model. 2015;12(1):17
5. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90-9
6. Perry GS, Byers TE, Mokdad AH *et al*. The validity of self-reports of past body weights by U.S. adults. Epidemiology. 1995;6:61–6.
7. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15–9
8. Nekolaichuk C, Watanabe S, Beaumont C. The Edmonton Symptom Assessment System: a 15-year retrospective review of validation studies (1991–2006). Palliat Med. 2008;22(2):111–22.
9. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer. 2008;113(4):870–8.
10. Honnor A. Classification, aetiology and nursing management of lymphoedema. Br J Nurs. 2008;17(9):576–86.
11. 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;89(4):1173–9.
12. Martin L, Senesse P, Gioulbasanis I *et al*. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015;33(1):90-9
13. 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;9(7):629–35.
14. Prado CM, Baracos VE, McCargar LJ *et al.* Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res. 2007;13(11):3264–8.
15. Sjøblom B, Grønberg BH, Benth JŠ *et al.* Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer. 2015;90(1):85-91.
16. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol. 2016;54:2-10.
17. Fujiwara N, Nakagawa H, Kudo Y et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol. 2015;63(1):131-40.
18. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340(6):448–54.
19. Douglas E, McMillan DC. Towards a simple objective framework for the investigation and treatment of cancer cachexia: the Glasgow Prognostic Score. Cancer Treat Rev. 2014;40(6):685-91.
20. Laird BJ, Fallon M, Hjermstad MJ, Tuck S, Kaasa S, Klepstad P, McMillan DC. Quality of Life in Patients With Advanced Cancer: Differential Association With Performance Status and Systemic Inflammatory Response. J Clin Oncol. 2016;34(23):2769-75
21. Wei B, Yao M, Xing C et al. The neutrophil lymphocyte ratio is associated with breast cancer prognosis: an updated systematic review and meta-analysis. Onco Targets Ther. 2016;9:5567-75.
22. Arends J, Bachmann P, Baracos VE et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2016 Aug 6. pii: S0261-5614(16)30181-9. doi: 10.1016/j.clnu.2016.07.015. [Epub ahead of print] .
23. Behl D, Jatoi A. Pharmacological options for advanced cancer patients with loss of appetite and weight. Expert Opin Pharmacother. 2007;8(8):1085–90.
24. Madeddu C, Macciò A, Panzone F *et al.*. Medroxyprogesterone acetate in the management of cancer cachexia. Expert Opin Pharmacother. 2009;10(8):1359–66.
25. Pisanti S, Bifulco M. Endocannabinoid system modulation in cancer biology and therapy. Pharmacol Res. 2009;60(2):107–16.
26. Hugh Jones T. What should I do with a 60 year old man with a slightly low serum total testosterone concentration and normal levels of serum gonadotrophins. Clin Endocrinol (Oxf). 2010;72:584–8.

27. Bozzetti F, Arends J, Lundholm K *et al.* ESPEN Guidelines on Parenteral Nutrition: non-surgical oncology. Clin Nutr. 2009;28(4):445–54.
28. Bozzetti F, Cotogni P, Lo Vullo S, et al. Development and validation of a nomogram to predict survival in incurable cachectic cancer patients on home parenteral nutrition. Ann Oncol. 2015;26(11):2335-40.
29. Temel JS, Abernethy AP, Currow 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;17(4):519-31.
30. Feldstain A, Lebel S, Chasen MR. An interdisciplinary palliative rehabilitation intervention bolstering general self-efficacy to attenuate symptoms of depression in patients living with advanced cancer. Support Care Cancer. 2016;24(1):109-17.
31. Chasen M, Bhargava R, MacDonald N. Rehabilitation for patients with advanced cancer. CMAJ. 2014;186(14):1071-5.
32. Gagnon B, Murphy J, Eades M, Lemoignan J, Jelowicki M, Carney S, Amdouni S, Di Dio P, Chasen M, Macdonald N. A prospective evaluation of an interdisciplinary nutrition-rehabilitation program for patients with advanced cancer. Curr Oncol. 2013;20(6):310-8.
33. Chasen MR, Feldstain A, Gravelle D, Macdonald N, Pereira J. An interprofessional palliative care oncology rehabilitation program: effects on function and predictors of program completion. Curr Oncol. 2013;20(6):301-9.
34. Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, Ferrell BR, Loscalzo M, Meier DE, Paice JA, Peppercorn JM, Somerfield M, Stovall E, Von Roenn JH. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol. 2012;30(8):880-7