



Conference on ‘Nutrition and age-related muscle loss, sarcopenia and cachexia’ Symposium 3: Nutrition for prevention and interventions for sarcopenia and cachexia

The effectiveness of nutritional interventions in malnutrition and cachexia

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Cancer is a common diagnosis and leading cause of death worldwide. Amounts of weight loss vary but it is associated with considerable morbidity, poorer quality of life and reduced survival. Nutritional intervention has the potential to maximise response to treatment and improve functioning and quality of life. The aim of this paper was to review the evidence for oral nutritional interventions in the management of weight loss in patients with cancer. Comparison of studies of nutritional support interventions in people with cancer is complicated by variations in understanding of what constitutes a compromised nutritional status. There are similarities and differences between definitions of both malnutrition and cachexia and studies of oral nutritional interventions have failed to use standard criteria at study inclusion contributing to heterogeneity amongst studies. Meta-analysis of randomised controlled trials has suggested limited evidence of benefit to nutritional and clinical outcomes but some improvements to aspects of quality of life. The presence of cachexia in patients with cancer might explain the limited efficacy of simple oral nutritional interventions, which lack a component designed to address metabolic abnormalities associated with cachexia. Novel strategies combining nutritional support with therapeutic agents designed to down-regulate the metabolic aberrations have failed to demonstrate consistent benefits and the results of multimodal treatments combining several interventions are awaited. There is a need for intervention studies recruiting patients early in the disease course, which underlines the need for definitions which predict poor outcome and hence allow early recognition of vulnerable patients.

Malnutrition: Cachexia: Oral nutritional support: Systematic review: Meta-analysis

The most recent data indicate that worldwide there were about 14 million new cases of cancer diagnosed in 2012 and greater than 330 000 diagnoses being made in the UK in 2011^(1,2). Cancer remains a leading cause of death worldwide and it is estimated that that 8.2 million people died from cancer in 2012 with about 162 000 deaths from cancer in the UK⁽¹⁾. Despite the dismal nature of these data, more than half of people diagnosed with cancer will survive for 10 years or more;⁽¹⁾ therefore efforts to maximise the ability of patients to respond to treatment and to achieve a good quality of life are paramount.

The morbidity experienced by people with cancer arises from the presence of disease and from the side-effects of

treatment. The presence, number and intensity of symptoms are likely to account for a large amount of the suffering experienced by patients. Weight loss is a common symptom in people diagnosed with cancer. A pooled prevalence for any amount of weight loss of 46 (95 % CI 34, 59) % was reported by a systematic review of symptom prevalence in people with incurable cancer⁽³⁾. Amounts of weight loss vary according to the site and stage of disease. A retrospective review of 3047 patients with different cancers entering clinical trials, reported a prevalence varying from 31 % to 87 % with the greatest amounts of weight loss found in patients with cancers of the upper gastrointestinal tract⁽⁴⁾. In a group of patients with advanced

cancer and weight loss, 34 % reported concern about what weight loss meant for them⁽⁵⁾. In addition, pre-illness weight loss of as little as 5 % has been demonstrated to be associated with reduced survival^(4,6). Weight loss is also associated with more adverse reactions and poorer response to treatment as well as reduced quality of life compared with patients with no weight loss⁽⁷⁾.

Taken together, these data provide a rationale for the use of strategies to limit and treat weight loss as part of care for people with cancer and indeed nutritional management is a widely accepted strategy recommended by a number of bodies⁽⁷⁻⁹⁾.

Definition and recognition of malnutrition and cachexia

The timely management of patients with weight loss requires their early recognition as well as clear guidelines on the indicators that best identify patients most likely to benefit from nutritional treatment. An audit of the ability of healthcare professionals to recognise weight loss in patients with cancer demonstrated that the staff frequently failed to identify those that met the criteria as suggested by the Malnutrition Universal Screening Tool for being malnourished⁽¹⁰⁾. A survey of knowledge and practice of 337 oncologists in managing nutritional support suggested that 80 % were uncertain about identifying malnourished patients with lack of knowledge being identified as a barrier in 60 % of participants⁽¹¹⁾. These studies underline the difficulties that staff face in meeting the nutritional needs of patients with weight loss and at least in part may result from variations in definitions but also overlap in understanding of the aetiology and clinical basis of observed weight loss. Guidelines and indicators for the identification of patients that are malnourished or at risk of malnutrition vary. The National Institute for Clinical Excellence in their guidance on the nutrition support of adults suggested malnutrition was defined as 'a state in which a deficiency of energy, protein and other nutrients causes measurable adverse effects on body form, function or clinical outcome'⁽¹²⁾. National Institute for Clinical Excellence suggest that indicators based on low BMI (18.5 kg/m²) or unintentional weight loss (>10 %) or a combination of the two (BMI < 20 kg/m² and weight loss >5 %) should be used to identify malnutrition. Other groups have suggested a classification of malnutrition, which is aetiology based and takes into consideration the disease and non-disease-related causes of malnutrition⁽¹³⁾. Operational cut-offs for use in practice are still in development, but have been suggested as including any two of insufficient energy intake, weight loss, loss of muscle, loss of subcutaneous fat, loss or gain of fluid or reduced function assessed by handgrip strength⁽¹⁴⁾.

The situation in patients with cancer may be further complicated by the existence of cachexia. Cancer cachexia was defined as an accelerated loss of skeletal muscle in the context of a chronic inflammatory response and was considered to be a syndrome consisting of combinations of anorexia, weight loss, metabolic alterations, an inflammatory state and anaemia⁽¹⁵⁾. This definition

could be seen to make cachexia different from malnutrition but lacked operational cut-offs to guide recognition in practice. The concept of cachexia has received considerable attention recently and a number of groups have suggested definitions together with operational indicators as summarised in Table 1. The indicators considered to be indicative of the presence of cachexia were different with all definitions including weight loss and five of six including anorexia or a measure of food intake but the cut-offs suggested for each indicator varied. The most recent definition was the consensus view of an international group of experts and relies on combinations of weight loss together with low BMI or low appendicular skeletal muscle loss⁽¹⁶⁾. Notably there was disagreement about the inclusion of systemic inflammatory markers, which have been included by some expert groups but were absent in the consensus definition, although it was recognised that cachexia can exist with or without inflammation⁽¹⁶⁾. Importantly, cachexia is not a single event and has been recognised by many expert groups as representing a spectrum from pre-cachexia to refractory cachexia and death⁽¹⁷⁾. The definition proposed by the expert panel has been widely recognised, but its predictive validity remains to be determined.

Cancer is primarily a disease of older people and in older people three primary categories of muscle loss in association with weight loss have been recognised; starvation, sarcopenia and cachexia⁽¹⁸⁾. In practical terms, the key question is whether all of these entities are similar and should therefore be managed in the same way or whether they are distinct entities, which may be related.

Which nutritional interventions?

In practice, the majority of patients identified as having weight loss and recognised for referral to a dietitian during the course of treatment for cancer will receive oral nutritional support interventions as a first line management strategy. Oral nutritional support consists of a range of options, including food-based interventions, which may include increased size of meals, the use of snacks to supplement intake from meals and fortification of food to increase their nutrient density, as well as the use of proprietary oral nutritional supplements⁽¹⁹⁾. Oral nutritional support options may be provided directly to patients in any care settings, e.g. the provision of nourishing drinks and snacks in residential care or on hospital wards, or may be communicated to patients as dietary advice, to guide patients when at home. Dietary advice has the advantage of being able to be tailored to individual habits, as well as the social and psychological needs of the patient. Conversely, oral nutritional supplements require no preparation and are easy to take.

Each type of nutritional support is associated with different practical considerations. For example advising patients to increase their nutritional intake through the inclusion of additional snacks will allow a patient greater variety compared with a prescription for oral nutritional supplements, but requires the patient to be able to shop, cook and prepare food as well as needing to have

Table 1. Definitions of cachexia recently proposed by expert groups

Parameter for identification	Proposed cut-off for identification of cachexia			Proposed cut-off for identification of pre-cachexia
	Weight loss	BMI (kg/m ²)	Food intake	
Cancer Cachexia study group ⁽⁴¹⁾	≥10 %		<6276 kJ (1500 kcal)	-
Society for Cancer & Wasting Disorders ⁽⁴²⁾	≥5 % in 12 months	<20		The presence of 3 of 5 ↓muscle strength, fatigue, anorexia, low FFM, abnormal biochemistry (CRP, IL-6, Hb, albumin)
American Cancer Society, Screening of the Nutritional Risk of Oncology Patients ⁽⁴³⁾	≥10 %			Complaint of anorexia, fatigue or early satiety used to distinguish symptomatic or asymptomatic cachexia
The European Society for Clinical Nutrition and Metabolism special interest group ⁽⁴⁴⁾	Accepted the definition proposed by the American Cancer Society			
European Palliative Care Research Collaborative ⁽⁴⁵⁾	≥5 %	<20 + weight loss >2 %		Sarcopenia and weight loss >2 %. Often combined with reduced food intake and systematic inflammation
International consensus ⁽¹⁶⁾	>5 % in 6 months	<20 + weight loss >2 %		Sarcopenia and weight loss >2 % Weight loss ≤5 % and anorexia/metabolic change Weight loss ≤5 % and anorexia/metabolic change

CRP, C-Reactive Protein; FFM, fat free mass; kcal, kilocalories.

sufficient money to buy additional snack items. In practice, patient-related aspects are taken into consideration during the dietetic assessment and many patients will receive a combination of oral nutritional support measures to improve their intake.

Assessment of effectiveness of nutritional interventions

Several societies and nutritional guideline bodies have supported the recommendation that patients with cancer and weight loss should receive nutritional support^(7,9,12). The European Society for Clinical Nutrition and Metabolism suggest that ‘nutritional therapy should be started if under-nutrition already exists or if it is anticipated that the patient will be unable to eat for more than seven days. Enteral nutrition should also be started if an inadequate food intake (<60 % of estimated energy expenditure) is anticipated for more than 10 days’⁽⁷⁾. This recommendation, like those of many of the other bodies, is based largely on expert opinion. To understand whether there is an evidence base to support this recommendation, it is necessary to examine the evidence for a benefit of nutritional interventions in people with cancer and weight loss. Before considering whether nutritional intervention resulted in benefits to patients it is necessary to consider which outcomes are most appropriate to assess the benefits of nutritional interventions.

An outcome has been defined as the quantifiable change in the health status of a patient between two or more timepoints⁽²⁰⁾. Traditionally, outcomes have been defined in terms of mortality and morbidity and tended to focus on aspects that are of most concern to researchers. In the past 20 years, the assessment of outcomes has become a multidimensional concept that includes clinical outcomes (mortality and morbidity) as well as broader outcome measures such as quality of life, patient satisfaction, functionality and economic outcomes. Measurement of outcomes can take place at the individual level, organisational level through to the national and international levels and is a developing field with no single measure applicable to all situations⁽¹⁹⁾. The use of Patient-Related Outcome Measures is being developed in some clinical situations and is likely to expand to cover different areas of healthcare⁽¹⁹⁾.

Nutritional interventions are often assessed in terms of nutritional endpoints such as change in nutritional intake and their impact on nutritional status. It is equally valid to consider them in terms of their impact on clinical outcomes, functional endpoints and cost effectiveness. In 1995, The American Society for Clinical Oncology proposed guidelines for outcomes to be used in the assessment of treatment effects⁽²¹⁾. Outcomes were defined in two categories: those relating to the treatment (response to treatment, response duration and time to progression) and patient-related outcomes defined as survival, toxicity and quality of life. These guidelines were reconsidered recently and all working groups were in agreement that overall survival should remain the primary outcome for clinical trials but acknowledged the limitations of this outcome and the need to define clinically meaningful outcomes as well as to balance the risks and benefits of

Table 2. Effectiveness of oral nutritional interventions in the management of weight loss in patients with cancer: findings of a systematic review and meta-analysis (based on the meta-analyses and results presented in⁽²³⁾)

Outcome	Number of studies with data in the analysis (number of comparisons)	Summary result	Statistical significance	Heterogeneity
Nutritional				
Energy intake	4 (6)	MD 1807 kJ/d (432 kcal/d) (95 % CI 720, 3000)	$P < 0.001$	$I^2 = 97\%$, $P < 0.001$
Weight	6 (9)	MD 1.3 kJ/d (0.31 kcal/d) (95 % CI -2.5, +5.1)	$P = 0.50$	$I^2 = 0\%$, $P = 0.88$
Clinical				
Mortality	11 (15)	RR 1.06 (95 % CI 0.92, 1.22)	$P = 0.43$	$I^2 = 0\%$, $P = 0.56$
Response to treatment*	6	No difference between groups		
Treatment interruptions*	4	No difference between groups (two studies (n 230)). More days of treatment interruptions in groups receiving routine care (two studies (n 124))		
Treatment toxicity*	7	No difference between groups (two studies). Fewer treatment toxicities in groups receiving nutritional support (five studies)		
Quality of life				
Emotional functioning	3 (5)	MD 5.2 (95 % CI 0.8, 9.7)	$P = 0.02$	$I^2 = 0\%$, $P = 0.61$
Dyspnoea	4 (6)	MD -2.9 (95 % CI -4.0, -1.8)	$P < 0.001$	$I^2 = 17\%$, $P = 0.31$
Loss of Appetite	5 (9)	MD -2.35 (95 % CI -4.48, -0.22)	$P = 0.03$	$I^2 = 8\%$, $P = 0.36$
Global quality of life	3 (5)	MD 5.5 (95 % CI 0.7, 10.3)	$P = 0.02$	$I^2 = 27\%$, $P = 0.24$

RR, relative risk; MD, mean difference; CI, confidence intervals.

* meta-analysis not undertaken, data previously unpublished.

therapies⁽²²⁾. The European Society for Clinical Nutrition and Metabolism in its guidelines on the nutritional management of patients with cancer highlighted the therapeutic goal for cancer patients to be the improvement of function and outcome assessed by the prevention and treatment of undernutrition, enhancement of the anti-tumour effects, reduction of adverse effects of therapy and the improvement of quality of life⁽⁷⁾.

Evidence for effectiveness in patients with cancer

The role of oral nutritional support in managing weight loss in patients with cancer has been examined in a recent systematic review⁽²³⁾. Systematic searches of ten electronic databases identified thirteen randomised controlled trials of oral nutritional interventions in cancer patients who were malnourished or at risk of malnutrition, including 1414 participants. The trials were homogeneous for the interventions given in that all interventions comprised either dietary advice to increase nutritional intake, the provision of oral nutritional supplements or both given together. Included studies varied according to site and stage of tumour, the nature and intent of clinical treatment and the amount of information provided on the nutritional status of patients at baseline. Only four of the thirteen studies defined nutritional status as an inclusion criterion, using recent weight loss as a threshold. Although the inclusion of the remaining participants was justified on the basis of their being at nutritional risk, there was considerable heterogeneity both within and between studies with some studies, including both well-nourished and malnourished patients⁽²³⁾. Despite the considerable attention being given to the definitions of malnutrition and cachexia, no study used a widely

accepted definition for either malnutrition or cachexia to identify patients for inclusion into trials.

Nutritional intake and nutritional status

Data were available on energy intake from ten of the thirteen studies and all reported significant improvements to energy intake. Meta-analysis was only possible on data for this outcome from four studies and the results were too heterogeneous to draw conclusions about the size of any overall effect⁽²³⁾. Data were available on change in body weight from eight of the thirteen studies (twelve comparisons). The meta-analysis of all studies combined suggested a significant benefit of intervention on body weight, but again the heterogeneity between studies was high ($I^2 = 76\%$, $P < 0.0001$). The analysis was repeated with data from three studies that contributed the most heterogeneity removed and there was no difference in body weight between groups (mean difference 0.31 (95 % CI -0.60, +1.21) kg, $P = 0.50$; Table 2).

Effects on outcomes of cancer treatment

Studies included in the meta-analysis assessed three different aspects of treatment outcome; effects on response to treatment, effects on treatment interruptions and effects on treatment toxicity. These data were analysed after completion and publication of the meta-analysis and are therefore reported according to the original studies. Six studies examined the efficacy of nutritional interventions in terms of response to anti-tumour treatment and there were no differences between groups in any study^(24-28,31). Four studies assessed the effects of nutritional interventions on treatment interruptions and

there were no statistically significant differences between groups, although two studies^(29,30) reported more days of treatment interruptions in patients receiving routine care than in those receiving intervention. Seven studies assessed the efficacy of nutritional interventions in reducing treatment toxicity. Two studies reported no difference between groups^(24,31), five studies^(25,29,30,32,33) suggested fewer toxicities in patients receiving nutritional intervention compared with routine care, with two studies reporting significantly fewer symptoms at the end of treatment in groups receiving food-based or supplement-based nutritional support^(32,33).

Effects on mortality

Data were available for meta-analysis from eleven of the thirteen studies on mortality and there were no significant differences between groups and no heterogeneity (relative risk 1.06 (95 % CI 0.92, 1.22), $P = 0.43$; Table 2).

Effects on patient-centred outcomes

Seven of the thirteen studies reported data on quality of life, of which five included data collected using the European Organisation for Research and Treatment of Cancer-core30 instrument that could be included in a meta-analysis. Data on each of the fifteen scales within the questionnaire were analysed separately and after adjustment for heterogeneity in some analyses, significantly greater benefits to emotional functioning, dyspnoea, loss of appetite and global quality of life were observed in patients receiving oral nutritional interventions compared with routine care. The improvements in quality of life noted were consistent with both small and large differences in scores⁽³⁴⁾ and are likely to be clinically meaningful. The European Organisation for Research and Treatment of Cancer is a generic instrument and it is difficult to assess whether all of the issues relevant to patients have been accounted for with this instrument. There are many tumour-specific versions of the European Organisation for Research and Treatment of Cancer, which have not been used in the present study and it is possible that the other benefits from receiving nutritional interventions were experienced by patients but not identified by these analyses.

Quality of life is not the same as patient satisfaction and many other patient-related outcomes are relevant to consider in the context of examining the efficacy of oral nutritional interventions in patients with cancer and weight loss, but have not been reported in studies. One study included in the review reported higher levels of patient satisfaction with both the nutrition services provided and perceived health benefits in participants receiving nutritional intervention compared with participants receiving routine care⁽³⁵⁾.

Cost-effectiveness

The cost utility of providing oral nutritional interventions to patients with cancer and weight loss was

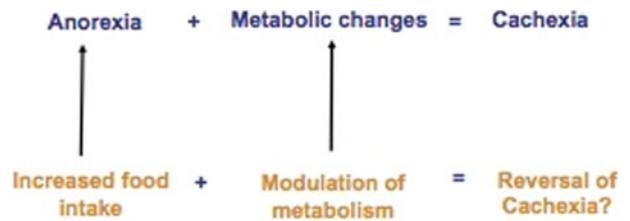


Fig. 1. Diagram to illustrate the suggestion that strategies for the management of cachexia in patients with cancer should include interventions to manage anorexia in combination with strategies to modulate the metabolic changes. ⁽¹⁷⁾ Reprinted from Clinical Nutrition (2012) 31, 577-582, Fearon KCH. The 2011 ESPEN Arvin Wretling lecture. Cancer cachexia: the potential impact of translational research on patient-focused outcomes, with permission from Elsevier).

examined using original data from two studies, mapping data collected using the European Organisation for Research and Treatment of Cancer-core30 instrument onto the EuroQol-5D^(36,37). There was no difference in Quality of Life Years gained between the intervention and control groups in either study. The costs of providing nutritional intervention (estimated from the cost of dietitian time and the cost of oral nutritional supplements) were higher in those receiving oral nutritional interventions, suggesting that usual care may be a more cost-effective approach (M Manzorou, PW Emery, P McCrone and C Baldwin, unpublished results). This analysis is preliminary, based on data only from two studies and not derived from a full cost-effectiveness analysis and should be interpreted with caution.

Overall the findings of this recent meta-analysis suggest that oral nutritional interventions have no effect on survival and that the effect on body weight and energy intake is inconsistent but that statistically significant improvements in some aspects of quality of life may be achieved. In addition, there is a small amount of evidence suggesting that nutritional interventions are associated with greater patient satisfaction and that in some patients reductions in treatment toxicity may be experienced. The data on cost-effectiveness are too preliminary to determine any potential benefits.

The management of weight loss in the context of cachexia

The limited effectiveness of oral nutritional support strategies in managing weight loss in patients with cancer may in part be explained by the aetiology of the underlying condition. It has been suggested that the multifactorial nature of the problem is likely to require a multidimensional solution^(17,38). It is likely that successful strategies will need to address more than the food-related aspects of weight loss and combine strategies to improve nutritional intake with substances that will modulate the metabolic derangements associated with cachexia (Fig. 1). With this in mind a number of potential therapeutic strategies have been trialled and their progress to date is summarised in Table 3. Despite the relatively large number of agents trialled, both with and without additional

Table 3. Summary of information on studies examining ‘novel’ agents with or without nutritional support in the management of weight loss in patients with cancer (based on^(39,40,46))

Drug/intervention category	Therapeutic action	Summary of information
Appetite stimulants		
Progestagens (megestrol acetate)	Downregulation of synthesis and release of pro-inflammatory cytokines	Dose range 160–1600 mg/d. Effective at increasing appetite and promoting weight gain. No effect on lean body mass. No overall conclusion on quality of life. Use limited by side effects
Corticosteroids (medroxyprogesterone)	Not well understood, possible inhibition of TNF- α , IL-1 and PG	Associated with rapid improvements to appetite, food intake, nausea and sensation of well-being but no effects on weight. Side effect profile limits long-term use
Anti-cytokine agents		
Anti-TNF (thalidomide, melatonin)	Downregulation of TNF	Thalidomide: benefit to weight, muscle mass and strength demonstrated in small trial but meta-analysis concluded insufficient evidence and more trials needed. Melatonin: small trials and no evidence of benefit
Anti-IL-6	Downregulation of IL-6	Phase I and II trials suggested well tolerated and effective. Phase III trial needed
Anti-inflammatory agents		
Indomethacin and ibuprofen	Reduction of systemic inflammation associated with cachexia by inhibition of PG production (by limiting COX enzymes)	Recent systematic review of thirteen trials demonstrated benefit to QOL, PS, inflammatory markers and weight but trials poor quality and small size. Overall insufficient evidence to recommend use
COX-2 inhibitors		Phase II trial demonstrated reduction in cytokines and improvements to body composition, QOL, strength and PS with no severe toxicity. Recommend can be included in combined treatment approaches
<i>n</i>-3 Fatty acids		
EPA capsules	<i>n</i> -3 Fatty acids: inhibition of TNF- α , IL-1 by blockage of COX and lipoxygenase pathways. EPA: downregulation of acute phase response and effects on proteolysis-inducing factor and lipid mobilising factor	Small non-randomised studies suggested benefits
Oral nutritional supplements with added (EPA)		Meta-analyses suggested insufficient evidence of effect but many trials small, poor quality and in patients with advanced disease. Recently suggested future trials should consider: (1) offering EPA capsules as an alternative to oral nutritional supplements and (2) earlier intervention
Anabolic agents		
Testosterone derivatives (nandrolone and oxandrolone)	Synthetic derivatives of testosterone with anabolic effects	Phase III trial demonstrated increased LBM, reduction in fat mass and fewer self-reported anorectic symptoms. Associated with hepatic toxicity, reduced HDL and interactions with anticoagulants, oral hypoglycaemics, adrenal steroids and hypogonadism
Selective androgen receptor analogues (ostarine and andarine)	Anabolic effects via tissue-selective modulation of androgen receptors	Phase I and II trials ostarine demonstrated increased LBM, and function and safety. Phase III trial needed
Insulin and GH	Involved in metabolic processes which regulate body composition	Some positive effects on nitrogen balance and LBM but safety concerns related to increased mortality with GH in critically ill patients and the frequent presence of insulin resistance in cachexia

COX, cyclo-oxygenase; QOL, quality of life; PS, performance status; GH, growth hormone; LBM, lean body mass.

nutrition, and either singly or in combination with one another, there remains no standard accepted treatment for the management of cancer cachexia available. Prostagens are currently the only approved drug for the management of cachexia but they have limited efficacy

in clinical practice with their benefits being limited to gains in appetite and fat mass and heterogeneous effects on quality of life⁽³⁹⁾. The majority of reviews and recommendations now point to the potential of multimodal therapies^(7,39,40). Although some trials in this area have

already demonstrated superiority to single- and dual-agent strategies, the tablet burden was large and understanding and acceptance by patients were limited⁽³⁸⁾. The findings of a multicentre trial, incorporating exercise with nutritional and pharmacological interventions, is awaited⁽⁴⁰⁾.

Summary and conclusions

Nutritional interventions in the management of weight loss in cancer continue to be recommended as the preferred strategy but their efficacy as a single modality intervention in terms of nutritional, clinical and patient-centred outcomes remains doubtful. Future management needs to take into consideration the likely aetiology of weight loss in people with cancer and will probably involve multiple strategies that target the nutritional deficit as well as the metabolic derangements associated with cachexia. It is also likely to be important to begin treatment for cachexia in the early stages of development of the syndrome. In order for this to happen, there needs to be a widely accepted definition of cachexia, validated to predict successful and meaningful outcomes, that can be used to identify those patients most likely to benefit from early intervention.

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