Learning Objectives

- Understand how the diverse mechanisms of cancer cachexia; mean that a multimodal therapeutic approach is necessary;
- Understand the need to develop more sensitive/robust outcomes for cachexia therapy;
- Understand basic assessment of patients with cancer cachexia;
- Understand the elements that make up a multimodal approach to the management of cancer cachexia;
- Understand the issues of compliance and behaviour modification within a multimodal programme.

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Key Messages

- Although modulation of muscle mass is an important index of therapeutic success, the more relevant outcome is how any change translates into better function. Patient-centred outcomes such as improved appetite or physical function should always be considered along with clinical goals such as improved tolerance of treatment or improved survival;
- Assessment must be linked to treatment strategy;
- The patient must be clinically stable to benefit from cachexia interventions;
- Early intervention is better than late;
- A multimodal approach should take account of nutrition, exercise and inflammation before more specific drugs/interventions are considered.
1. Background to Cachexia and Key Therapeutic Outcomes

Cancer cachexia is a multi-factorial syndrome 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 leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (1). It is caused by complex interactions between inflammation (pro-inflammatory cytokines), neuro-hormonal changes, and potential proteolytic and lipolytic factors produced by the host and the tumour (2). There is no consensus on the optimal treatment for cancer cachexia, however, there is an urgency for improving management. Although there have been several trials examining single therapies for cancer cachexia, overall the results have been disappointing. As multiple factors are responsible for the development of cachexia, it has been argued that optimal cachexia intervention should target all components; multimodal therapy for a multifactorial problem (3) (Fig. 1). Equally, there is no consensus on how to assess cachexia and therefore the choice of therapeutic outcomes is challenging. Based on the knowledge about the consequences of cachexia and cachexia pathophysiology, prevention of cachexia might improve patients’ quality of life (QoL) and survival. However, a new complex intervention first has to be shown to reverse the specific signs and symptoms of cachexia before looking for more general health gain.

![Diagram](attachment:image.png)

**Fig. 1** Patients require optimal medical, oncological and nutritional management in order to benefit fully from a multimodal approach to cachexia management.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are regulatory agencies responsible for scientific evaluation of medicines and licensing of drugs. Until recently, their outcome focus for cancer cachexia has been on simultaneous gain in lean body mass (LBM) and improved muscle strength/power as co-primary endpoints. Unfortunately these goals may not necessarily be applicable to a multimodal treatment programme. For example the end-points considered by regulatory bodies in
chronic obstructive pulmonary disease (COPD) rehabilitation studies are quite different and include patient-centred outcomes such as physical activity level. Furthermore, the results of recent large Phase III trials in the treatment of cancer cachexia suggest that, in the complex clinical environment of patients with advanced cancer (where multiple factors such as tumour progression, effects of therapy and co-incident morbidity can influence clinical status) the close relationship between LBM gain and improved muscle function observed in healthy individuals may not pertain. It also seems logical that if patients are to experience better physical performance it is necessary to have a neutral or positive energy balance and not only improved muscle mass. Therefore to focus exclusively on LBM or muscle gain, rather than weight (LBM plus fat mass [as an index of energy balance]) may be inappropriate in cancer cachexia where significant adverse features include anorexia and reduced food intake.

2. Clinical Assessment

When medical or nursing professionals who have not received specific training are confronted with a patient who requires nutritional assessment the prospect can seem daunting. Moreover, the purpose of such assessment is often muddled since no clear link between assessment and treatment has been provided. The purpose of this section is to provide a clear, logical framework for patient assessment and to link this with a simple treatment algorithm (See section 26.4.3).

Patients lose weight as a result of reduced food intake, abnormal metabolic activity or most commonly a combination of the two. Weight loss reflects that the patient has a negative energy balance (resulting in loss of fat mass: the main energy reserve) and a negative protein balance (resulting in loss of skeletal muscle: the main protein reserve). The purpose of nutritional assessment is to determine to what extent stores have been depleted, what contribution has been due to reduced food intake, what impact such changes are having on the patient’s performance, and what potential there is for reversal of the situation? (Fig. 2) In turn, the potential for reversal is partly dependent on the nature of catabolic drivers including such factors as systemic inflammation and tumour progression. Each of these domains can be considered in relation to the patient’s clinical journey (i.e. past, present, and future). The Scored PG-SGA (4) is a validated screening tool designed specifically for patients with cancer and this or similar tools can be used to gather much of the relevant information.

A. Stores (including muscle mass): The primary variables that are assessed readily are weight and weight loss history. Key questions include: height and current weight (kg), previous stable weight, duration of weight loss and calculation of percentage weight loss. Weight loss >10% and/or a BMI <18.5 kg/m² are indicators of depletion of energy and / or protein reserves. In the relatively near future it may be possible in routine practice to derive a direct measure of muscle wasting from diagnostic cross sectional imaging (e.g. CT scans).

B. Intake: Routine clinical assessment with the PG-SGA includes such basic questions concerning type and amount of intake (0, 25, 50, 75, 100% of normal), loss of appetite, presence of early satiety and other symptoms impeding dietary intake. This level of assessment is intended for non-specialists, and is useful for deciding when to refer patients to a nutrition health care professional (dietician or specialist in clinical nutrition). A detailed diet history or diet diary is a specialized assessment which is usually undertaken by a dietician. The information from such assessments can be used to estimate total energy and macronutrient intakes.

C. Performance/psychosocial impact: Every clinical, medical or surgical oncologist is used to assessing the performance status of patients. The functional capacity component of the PG-SGA, is a version of the Eastern Cooperative Oncology Group (ECOG) performance status score; alternatively either the WHO or
Karnofsky scales may be used. Knowledge whether the patient is active and mobile is vital in determining not only how depletion of stores/intake is affecting quality of life but also what the nature of therapy should be. Bed-bound patients suffer from anabolic resistance and in these circumstances it is very difficult to improve muscle mass/function. It is also important to consider the psychosocial impact of cachexia both on the patient and their family (5). Physical activity may be impaired by the loss of muscle tissue, concentration and alertness diminished by fatigue, and mood dominated by lethargy and increasing indifference. Patients may become isolated due to shrinking physical, mental and emotional activity. Some families exhaust themselves by trying to fight the patient’s visible loss of weight and power; urging him or her to eat despite the absence of appetite and finally experiencing frustration, helplessness and fear.

Catabolic drivers (potential for reversal): Knowledge of the patients’ tumour type, stage of disease and purpose of current cancer therapy can give a ready impression of prognosis and the purpose of nutritional intervention. The presence or absence of systemic inflammation (serum C-reactive protein >10mg/L) may also identify the patient who requires early nutritional/metabolic support. For the patient with relatively stable disease and with >2 months to live it is reasonable to plan nutritional intervention. For the patient whose disease is progressing rapidly and has <2-3 months to live, symptomatic management (e.g. steroids) is perhaps more appropriate (refractory cachexia). It is also important to consider carefully the patients’ expectations concerning the future benefits of any intervention. The burden of intervention (e.g. daily intake of oral nutritional supplements) has to match what the patient is willing to consider in the light of possible gains.

![Diagram](image.png)

**Fig. 2** Patients should be assessed according to stores, intake, impact/performance and potential for prevention/reversibility.

### 3. Intervention Strategy

It is important to understand the concept that interventions may be based on groups or tailored to individual patients. This is particularly important when considering the issue of early intervention when the individual patient may not have overt signs of cachexia but rather belong to a group at high risk of developing cachexia in the future (pre-
cachexia). When considering multimodal intervention on a group basis for pre-cachectic patients, assessment might focus on whether the patient has the criteria for that group (e.g. advanced pancreatic cancer undergoing palliative chemotherapy) rather than on the specifics of their cachexia phenotype and the need for a tailored multimodal intervention. To date there have been few studies to evaluate the benefit of uniform versus tailored multimodal programmes for the management of either cachexia or pre-cachexia.

The second important concept to understand is that isolated medical intervention for rehabilitation of cancer patients is redundant. As with rehabilitation schemes for other chronic diseases (e.g. COPD), it is important to recognise that patient and carers have more of a role to play than individual medical practitioners, nurses or dieticians. Moreover, the spectrum of support has to cover education, self-management, nutritional rehabilitation and integrated care. Support can be as diverse as a specific multidisciplinary clinic for management of cachexia (rarely available) to a web-site on nutritional advice for cancer patients (universally available).

A simple treatment algorithm is outlined in Fig. 3. For those not at nutritional risk (e.g. weight stable, adequate macronutrient stores, normal appetite/intake, good performance status and stable cancer disease) it would be reasonable simply to review or ask the patients to seek further advice if they lose weight. For patients at nutritional risk (pre-cachexia or cachexia), it is vital to undertake a screen for reversible causes of

![Fig. 3 Patients should be screened for overall risk. If at risk, more detailed assessment should include stores, intake, input and potential reversibility. The overall strategy should be guided by performance status and likely clinical course. (* risk: this can include pre-cachectic patients as well as those identified as at nutritional risk from a screening tool).](image-url)
anorexia/reduced food intake and to ensure that their underlying primary disease and co-morbidities are being managed optimally. Key variables to consider in relation to secondary causes of reduced intake include oral ulceration, intestinal obstruction, constipation, diarrhoea, nausea, vomiting, uncontrolled pain and side-effects of drugs. Metabolism-related variables include the development of diabetes or malabsorption (e.g. both common associations with advanced pancreatic cancer) and which if not managed with insulin/pancreatic enzyme supplements will result in continuing weight loss independent of any nutritional intervention.

The next stage in assessment involves consideration of the patients’ performance status, prognosis and expectations. For patients reaching an end-of-life phase and whose main complaint is anorexia, it would be reasonable to consider the prescription of oral steroids or megestrol acetate. For patients with a better prognosis (including those undergoing palliative chemotherapy/radiotherapy) and who are not bed-bound consideration should be given to the four specific domains, as outlined in section 26.4.2.

4. Basic Components of Multimodal Interventions for Cancer Cachexia

It is important that a multimodal programme addresses at least more than one of the four domains of assessment (stores, intake, performance and potential). The programme can be generic or tailored to individual needs. Programmes may vary according to resources that are available and health economics. Some of the basic components that can make up a programme are given below:

- **Nutrition**

  The main goal of nutritional intervention is to promote energy balance and to ensure optimal intake of protein. Malnutrition is a very common secondary diagnosis for patients with advanced cancer and it is clear that many patients’ dietary intake is insufficient to support energy and protein balance. To date, scientific data behind nutrition support in cancer care remains conflicting, in part due to an overall lack of rigorous randomized controlled trials (RCTs). However, while many valid criticisms exist of the current evidence, it is self-evident that positive energy and protein balance cannot be achieved without a supply of nutrients. The average calorie intake of an advanced cancer patient is about 1,700Kcal/d. Moreover, the average protein intake is about 0.7-1.0 g/kg/day (6). If such a patient is to achieve levels of intake that might support anabolism (recommended intake 1.0-1.5g protein/kg/day), it is evident that food energy intake needs to increase by 300-400 Kcal/day and protein intake increase by up to 50%.

  The best way to increase overall intake is with normal food. However, dietary goals may be difficult to achieve in populations affected by old age, frailty, comorbidity and the side effects of anti-cancer therapy. Individual dietary counselling and the use of ONS, alone or in combination, are two main strategies used to enhance overall dietary intake (7, 8). Counselling aims to educate patients on how to modify their diet, to achieve individual requirements for energy, macronutrients and micronutrients and to reduce foods that would worsen symptoms and increase foods which might reduce the severity of symptoms. A systematic literature review evaluating the effect dietary counselling in treating weight loss and improving energy intake in patients with cancer cachexia was reported recently (9). Five studies were retrieved, and three were RCTs. Counselling included increased intake of energy dense foods, increased meal frequency and/or use of oral liquid nutritional supplements (ONS). Most studies showed some effect on body weight, stabilization or increase, during the intervention either in subgroups or at some given time point. The review showed that dietary counselling can have some beneficial effect on body weight and energy intake. The efficacy of oral nutritional interventions (advice and supplements) in malnourished
patients with cancer was recently the subject of a meta-analysis which identified 13 studies and included 1414 patients (8). There was considerable variation in the quality of the studies and in the statistical heterogeneity. Nevertheless, nutritional intervention was associated with a significant increase in energy intake (430 Kcal/day), a weight gain of 1.9 kg and a beneficial effect on some aspects of QoL but not survival. The changes in weight and energy intake were not significant after the removal of the main sources of heterogeneity.

- Exercise
In cancer patients, there is evidence that physical exercise can reduce fatigue, improve QoL of life and relieve many of the adverse side-effects experienced both during and after treatment (10). Physical exercise is considered to be well-tolerated, feasible and safe during and following cancer treatment (10, 11), and even cancer patients with advanced stages of disease are willing to engage in physical exercise (11). Thus, based on current knowledge, it is considered clinically sound to advise most cancer patients to perform physical exercise.
Physical exercise may be of particular importance for cancer patients with advanced disease in a pre-cachectic or cachectic stage because of its potential effects on muscle mass and strength (12). Animal models have demonstrated that physical exercise might have a possible anti-inflammatory effect in cancer cachexia, by reducing the release of pro-inflammatory cytokines (13). Furthermore, a trial comparing healthy mice with tumor-bearing mice, demonstrated that physical exercise induced a partial rescue of muscle mass and strength when combined with EPA (14). In humans, one study including cachectic patients with COPD reported a 7 % increase in muscle mass (Central Surface Area) after eight weeks of high intensity endurance exercise (15).
A systematic review of 16 RCT’s on the effect of physical exercise on muscle mass and strength in cancer patients undergoing cancer treatment has been reported recently (16). Improvements in muscle strength were demonstrated more or less equally in favour of both aerobic and resistance exercise and interventions combining the two types. Based on one trial there is some indication that resistance exercise might improve muscle mass more than aerobic exercise (17). The evidence on the effect of exercise on muscle strength and mass in cancer patients with advanced disease and cachexia is limited. Thus, prescription of exercise must be based on evidence extrapolated from the general cancer population. At the practical level it is likely that an intervention will consist of a home-based exercise programme delivered via an initial interview with a trained health professional and supported by a standardised booklet. The prescription might consist of three times a week functional resistance exercises in addition to aerobic training two times weekly. Dependent on patient preference and centre service provision, exercises may be supervised on occasion. Clearly, exercises should be modified to fit the patient in question.

- Anti-inflammatory treatment
It is believed that inflammation is one of the main pathophysiological drivers in cachexia (2). There is no ideal anti-inflammatory for use in cancer patients and little clear evidence to support their use. Until such time as adequate trials become available, the recommendations in this section can only be general in nature.
NSAIDs are blockers of cyclooxygenase (COX) that convert arachidonic acid (AA) to prostaglandins and cause inflammation and pain (COX-2 pathway). COX-1 is a constitutive enzyme present in most tissues in the body and blockade of this can increase the risk of gastrointestinal haemorrhage due to reduction of mucosa-protective prostaglandins. NSAIDs also block the formation of thromboxane A2 (TXA2) in platelets and might therefore prevent platelet aggregation (COX-1). It is appealing to use NSAIDs in the treatment of cachexia as they counteract an upstream mechanism for inflammation and thus might influence several pathways (e.g. IL-1 that reduce appetite, and TNF-α that might influence muscle and fat atrophy). Furthermore, NSAIDs are inexpensive and easy to administer.
A systematic review examining NSAID treatment in cancer cachexia has been reported recently (18). Thirteen studies were retrieved, of which six were comparative trials. Patients receiving NSAIDs had significantly improved body weight compared with controls, with differences ranging from 2.5 kg and 2.9 kg at 6 weeks and 5.1 kg at 12 weeks. There is also some evidence that NSAIDs may improve performance status, self-reported QoL, and inflammatory parameters. Major limitations of the different studies were that several had small sample sizes and some had a multitude of outcomes.

The Ω-3 fatty acids EPA and docosahexaenoic acid (DHA) are found in fish oil and may have a role as a ‘natural’ alternative or adjunct to the use of NSAIDs. EPA is a competitive substrate with AA for the COX-pathway, and is converted to prostanoids which are less inflammatory than the prostanoids derived from AA. The use of Ω-3 fatty acids as a nutritional intervention for cancer remains an area of intense interest particularly as it relates to the potential to improve response to cytotoxic treatments and reduce associated side effects, particularly muscle wasting. EPA and DHA are well recognized for anti-inflammatory properties (19) and these actions, together with EPA’s ability to inhibit muscle protein breakdown, probably account for EPA’s favorable effect on preventing cancer cachexia in patients undergoing chemotherapy (20, 21). EPA can be given in combination with a nutritional supplement. The optimal dose of EPA is estimated between 1.5-2 g daily.

- Anti-cancer Therapy
The best way to manage cancer cachexia is to treat the cancer. In incurable cancer, anti-cancer therapy (e.g. chemotherapy) is given with the aim of delaying disease progression, and/or treating symptoms. It is acknowledged increasingly that to manage cachexia optimally, treatments need to be initiated at an early phase of cachexia. At this point early in the disease, concomitant treatment with chemotherapy is very common. There is some evidence for benefits in improving tumour-related outcomes or toxicity in trials looking at anti-cancer treatment and the concomitant treatment with both EPA (20), NSAID (22), nutrition (23) and physical exercise individually.

5. Compliance with Multimodal Treatment/Behaviour Change
In general, about 70-80% of patients comply with drug treatment as prescribed. Compliance with oral nutritional supplements is reported to be as high as 70% in highly motivated patients assisted by a highly motivated clinical team, but can be as low as 10-15%. Compliance with exercise may be better with aerobic exercise (0-75%) than with resistance exercise (0-50%). Patients’ reasons for non-compliance include poor motivation, disinterest, or not being used to exercise. In addition, some feel too weak to comply or find the exercises too demanding or difficult. It is a challenge implementing new lifestyle changes in patients previously not used to regular exercise and it requires close follow up and continual re-motivation. Nevertheless, getting at least a substantial proportion of patients to eat more, take exercise and take their anti-inflammatory drugs is much better than systematic nihilism. The symptom burden, altered function and reduced quality of life experienced by cancer patients with cachexia is not simply the result of their cancer or nutritional deficit but also depends on their adaptation to the illness and its treatment. Thus, the educational element of any rehabilitation scheme needs to include a significant component promoting behavioural change and self-management (including goal setting, problem solving and taking action based on a predefined action plan). For example, if a cancer patient has sarcopenic obesity as their dominant phenotype and is unwilling to take any exercise, then the possibility of significant rehabilitation is extremely limited.

6. Programme Duration, Structure and Staffing
There remains no consensus on the optimal duration or content of programmes for the management of cancer cachexia. It is vitally important that the evidence-base for multimodal therapy is broadened such that Management becomes standardised, can be evaluated in terms of health economics and funded appropriately.

7. Summary

- Cancer cachexia is a complex clinical syndrome for which there can be no single solution;
- Cachexia needs to be managed as an integral part of the patient’s multi-disciplinary cancer management;
- Clinicians, nurses and patients need to feel empowered and knowledgeable enough to address key nutrition and exercise issues;
- Early intervention during active cancer therapy is probably the ideal time to initiate cachexia management;
- Goals should be realistic and recognise that not everyone will be 100% compliant;
- Assessment should be linked to treatment;
- Treatment pathways are still to become fully evidence-based but should contain elements that address at least nutrition, exercise, inflammation and optimal medical, oncological and psychological management.

8. References


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