



Definition and classification of cancer cachexia: an international consensus

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To develop a framework for the definition and classification of cancer cachexia a panel of experts participated in a formal consensus process, including focus groups and two Delphi rounds. Cancer cachexia was defined as a multifactorial 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. Its pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. The agreed diagnostic criterion for cachexia was weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body-mass index [BMI] <20 kg/m²) or skeletal muscle mass (sarcopenia). An agreement was made that the cachexia syndrome can develop progressively through various stages—precachexia to cachexia to refractory cachexia. Severity can be classified according to degree of depletion of energy stores and body protein (BMI) in combination with degree of ongoing weight loss. Assessment for classification and clinical management should include the following domains: anorexia or reduced food intake, catabolic drive, muscle mass and strength, functional and psychosocial impairment. Consensus exists on a framework for the definition and classification of cancer cachexia. After validation, this should aid clinical trial design, development of practice guidelines, and, eventually, routine clinical management.

Introduction

Cachexia has been recognised for a long time as an adverse effect of cancer. It is associated with reduced physical function,¹ reduced tolerance to anticancer therapy,² and reduced survival.^{3,4} Weight loss in patients with cancer is rarely recognised, assessed,⁵ or managed actively.^{6,7} Thus, cachexia represents an important unmet need.

Patients with severe muscle wasting, ongoing catabolism, low performance status, and metastatic disease refractory to therapy are unlikely to have clinically important benefits from multimodal treatment intended to result in gain of lean tissue and function. At this stage, the goal of therapy is palliation of symptoms and reduction in distress for both patient and family.⁸ Against this spectrum, there would be merit in recognising the onset of cachexia so that interventions to reduce or delay its effect can be implemented.⁹ However, for this to happen, a definition of the condition and recognition of its diagnostic indicators would be needed.¹⁰

Clinical management of cachexia is currently both limited^{11,12} and complex.⁹ Various different pro-cachectic mechanisms can be involved,^{13–15} which ideally should be assessed and ranked according to importance and reversibility before a management plan is established.¹⁶ However, routine management has not achieved such a level of sophistication.¹⁷ Additionally, most randomised trials have investigated single agents in unselected patients presenting with weight loss of any aetiology.¹⁸ A more sophisticated characterisation would benefit individual patients and improve the robustness of conclusions drawn from trials.

Although our understanding of cachexia has progressed over the past decade,¹⁹ a lack of a definition,

diagnostic criteria, and classification has impeded advancement in both clinical trials and clinical practice.^{20–22} A generic definition for all types of cachexia in both adults and children has been proposed,²³ but the associated diagnostic criteria are not cancer specific and have not been validated.²⁴ Two other definitions of cancer cachexia have also been proposed,^{4,25} but both are based on single-centre experience and do not follow any formal consensus process.

The aim of this study was to develop a definition, diagnostic criteria, and classification system specific to cancer cachexia by use of a formal consensus process. The aim was not to agree on a definitive guideline, because precise cutoffs remain to be determined. The added value of the project derives from its cancer-specific focus linked to clinical management, trial design, education, and policy.

Methods

A Delphi process (brainstorming, narrowing down, and quantification) was applied,²⁶ and it is presented in figure 1. Experts in clinical cancer cachexia research (medical and surgical oncologists, palliative medicine specialists, and nutritionists) were identified on the basis of leadership in publication, clinical cancer cachexia research or phase 3 clinical trials, and participation in clinical cancer cachexia peer review panels. Key individuals in assessment and classification of cancer-associated symptoms,²⁷ the European Palliative Care Research Collaborative (EPCRC),¹⁰ the Society on Cachexia and Wasting Disorders,²³ the National Cancer Research Institute (NCRI) Palliative Care Clinical Studies Group (UK), and the European Society for Clinical Nutrition and Metabolism Special Interest Group on Cachexia contributed to this study.

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In the first step of the process, focus groups (brainstorming and narrowing down)²⁸ discussed the key factors that guide clinical decision making in the management of cachexia in daily practice. In the second step, discussions were based on amalgamated findings from the first round and evidence from literature reviews, with a focus on factors guiding clinical practice and proposed domains for cachexia assessment.

Draft consensus statements were circulated for anonymous rating by use of a scale of 1 (disagree) to 10 (agree), and comments. These inputs were integrated and amended consensus statements prepared with a detailed explanation for each revision. Anonymised results from the first round were then recirculated for scoring, comments, and proposed revisions for statements that scored 7 or less in the first round. Final revisions were derived from this step. A predetermined mean score of 7 or more (with three or fewer outliers: defined as scores less than 4) was used to define consensus.

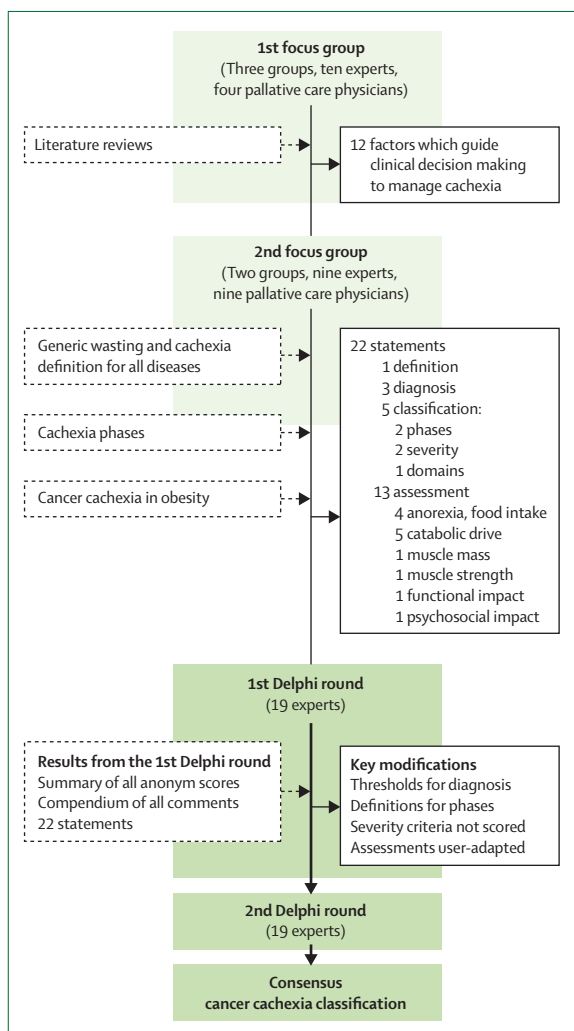


Figure 1: Flow of consensus process

Consensus findings

Definition and diagnosis

Cancer cachexia is defined as a multifactorial syndrome characterised 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 characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism. Consensus statements for diagnosis are presented in the panel.

Classification

Stage

Cancer cachexia is a continuum (with three stages of clinical relevance: precachexia, cachexia, and refractory cachexia (figure 2). Not all patients traverse the entire spectrum. In precachexia, early clinical and metabolic signs (eg, anorexia and impaired glucose tolerance) can precede substantial involuntary weight loss (ie, $\leq 5\%$). The risk of progression varies and depends on factors such as cancer type and stage, the presence of systemic inflammation, low food intake, and lack of response to anticancer therapy. Patients who have more than 5% loss of stable body weight over the past 6 months, or a body-mass index (BMI) less than 20 kg/m² and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2% (for definition see panel), but have not entered the refractory stage, are classified as having cachexia. In refractory cachexia, the cachexia can be clinically refractory as a result of very advanced cancer (preterminal) or the presence of rapidly progressive cancer unresponsive to anticancer therapy. This stage is associated with active catabolism, or the presence of factors that render active management of weight-loss no longer possible or appropriate. Refractory cachexia is characterised by a low performance status (WHO score 3 or 4) and a life expectancy of less than 3 months. The burden and risks of

Panel: Diagnosis of cancer cachexia

- Weight loss >5% over past 6 months (in absence of simple starvation); or
- BMI <20 and any degree of weight loss >2%; or
- Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m²; females <5.45 kg/m²)* and any degree of weight loss >2%†

*Defined reference values (sex-specific) and standardised body composition measurements are essential to undertake assessment of skeletal muscle depletion. Although there is a paucity of reference values related to cancer-specific outcomes,^{29,30} a generally accepted rule is an absolute muscularity below the 5th percentile. This can be assessed as follows: mid upper-arm muscle area by anthropometry (men <32 cm², women <18 cm²);³¹ appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men <7.26 kg/m²; women <5.45 kg/m²);³² lumbar skeletal muscle index determined by CT imaging (men <55 cm²/m²; women <39 cm²/m²);³³ whole body fat-free mass index without bone determined by bioelectrical impedance (men <14.6 kg/m²; women <11.4 kg/m²).³⁴ †A direct measure of muscularity is recommended in the presence of fluid retention, a large tumour mass, or obesity (overweight).

artificial nutritional support are likely to outweigh any potential benefit. Therapeutic interventions focus typically on alleviating the consequences and complications of cachexia—eg, symptom control (appetite stimulation, management of nausea or eating-related distress of patients and families).

Severity

The severity of depletion can be classified according to the rate of ongoing loss of weight in combination with the concurrent degree of depletion of energy stores and body protein mass (which can be compounded by a low initial reserve). Thus, a fall of 5 kg/m² in BMI from an initial value of 22 has more severe implications than the same loss from an initial value of 35. Furthermore, a patient with a BMI of 30 and a history of weight loss is more at risk if muscle wasting has led to sarcopenia, and less at risk if muscle protein mass remains intact.³³

Assessment

The following key features should be assessed to characterise a patient: anorexia or reduced food intake; catabolic drivers; muscle mass and strength; and effect of cachexia on the patient. An individualised management plan can then be based on the patient's baseline characteristics and the mechanisms most likely to contribute to weight loss and their potential reversibility.

Anorexia or reduced food intake

The underlying factors contributing to reduced food intake should be assessed. These include decreased central drive to eat, chemosensory disturbances (eg, in taste and smell), decreased upper gastrointestinal motility (eg, early satiety and nausea), and distal tract dysmotility (after treatment of constipation). Food intake should be assessed routinely (especially protein). At a minimum this might be the patient's own estimate of overall food intake in relation to normal intake. Quantification of protein and calorie intake might sometimes be appropriate. Secondary causes of impaired food intake, such as stomatitis, constipation, dyspnoea, pain, and poor dietary habits should be recognised early, because they might prove readily reversible.

Catabolic drivers

A key but often variable component of cachexia is hypercatabolism caused by tumour metabolism directly, systemic inflammation, or other tumour-mediated effects. The most widely accepted index of systemic inflammation is serum C-reactive protein (CRP). However cachexia can exist without overt systemic inflammation, so indirect indices reflecting the catabolic drive such as responsiveness to chemotherapy and the rate of progression should also be assessed.

No consensus was reached about the usefulness of other factors contributing to catabolism. These include insulin resistance, prolonged high-dose corticosteroid

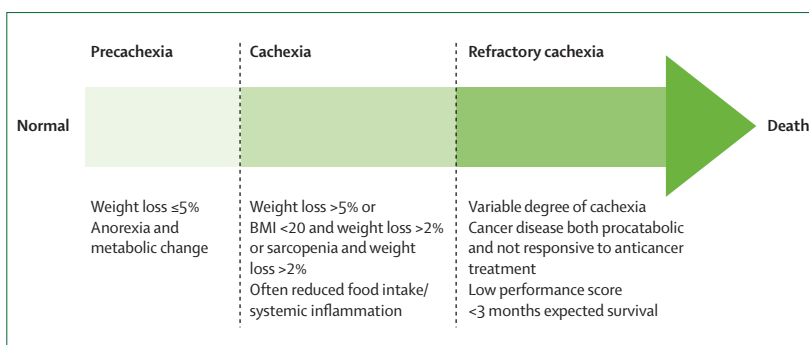


Figure 2: Stages of cancer cachexia

Cachexia represents a spectrum through which not all patients will progress. At present there are no robust biomarkers to identify those precachectic patients who are likely to progress further or the rate at which they will do so. Refractory cachexia is defined essentially on the basis of the patient's clinical characteristics and circumstances. BMI=body-mass index.

therapy, hypogonadism, and increased resting energy expenditure. Disagreement was not related to the relevance of these elements, which was agreed, but rather to the paucity of evidence, clinical practicality, and cost.

Muscle mass and strength

Although routine assessment of muscle mass and strength were advocated there was no clear consensus as to methodology. The order of preference for muscle mass assessment was cross-sectional imaging (CT or magnetic resonance imaging [MRI]), dual energy x-ray imaging (DEXA), anthropometry (mid-arm muscle area), and bioimpedance analysis. This last technique was regarded as only useful for group comparisons in patients without grossly altered body composition. For practical reasons in testing muscle strength, upper-limb hand-grip dynamometry was preferred to lower-limb extension strength testing.

Functional and psychosocial effects

Both physical functioning and components of the psychosocial effect should be assessed. To estimate the effect on physical functioning, routine assessment of physical activity is recommended. The method of choice was patient-reported physical functioning (eg, European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30 or patient-completed Eastern Cooperative Oncology Group questionnaire). The order of preference for other methods was physician reported activity (eg, Karnofsky score) followed by objective methodologies, such as activity meter and checklists of specific activities. The psychosocial effect of cachexia should also be assessed routinely by questions such as: "how much do you feel distressed about your inability to eat" or "have you experienced feelings of pressure, guilt or relational stress with regard to food intake and weight-loss".

Figure 3 is a management algorithm based on the consensus. Established tools, such as the Patient-Generated Subjective Global Assessment Instrument,³⁵ can provide

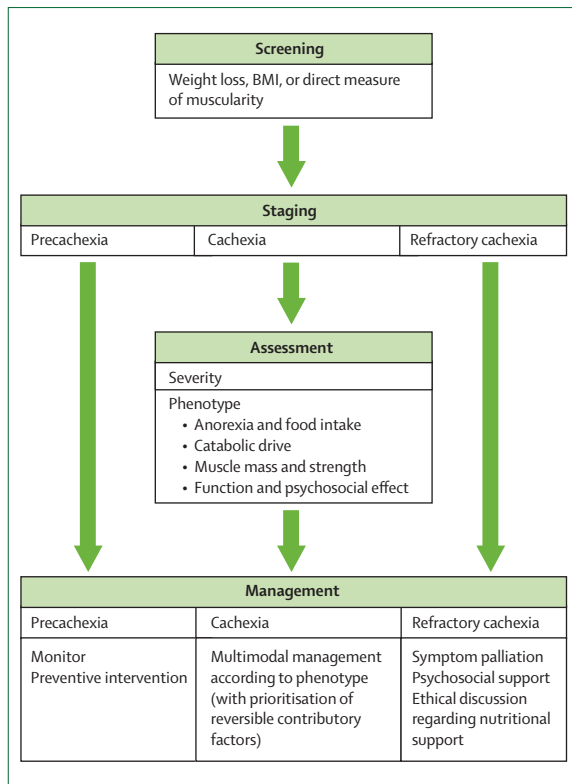


Figure 3: Management algorithm for cancer cachexia
 Patients should be screened for cachexia, then undergo detailed assessment. All patients require optimum oncological and general medical management. Once patients with cachexia have been phenotyped, a detailed multimodal management plan (including nutrition, exercise, anti-inflammatory strategies, and other adjuncts) can be established. BMI=body-mass index.

some, but not all, of the information needed for a detailed assessment. A comprehensive, yet simple, framework for the clinical assessment of patients is a further aim of the present working group.

Conclusion

Cachexia remains a challenging clinical syndrome, the importance of which lies in its prevalence and profound adverse effect on patients’ quality and length of life.¹⁻³ The present consensus definition focuses on the complex interplay between reduced food intake and abnormal metabolism and identifies loss of skeletal muscle as key in patients’ functional impairment. Such emphasis supports the concept that skeletal muscle mass can be both a marker for the syndrome and an important therapeutic target. Hence the consensus diagnostic criteria attempt to extend beyond simple weight loss to include (where available) direct measures of muscularity. The consensus classification of stages in cachexia provides context for early multimodal intervention (precachexia) or symptom-control intervention (refractory cachexia). The consensus severity classification emphasises the concept that loss of weight (or muscle) can be compounded by a low starting point. Finally, the

consensus domains for assessment emphasise the importance of anorexia, tumour progression, systemic inflammation, reduced muscle mass and function, and the psychosocial sequelae of the cachexia syndrome.

The present cancer-specific definition of cachexia is broadly comparable with the recent generic definition proposed by Evans and co-workers.²³ However, key differences relate to the need to be specific for entry criteria or outcome measures for future clinical trials; hence, the current emphasis on loss of skeletal muscle mass and associated functional impairment.

Low muscle mass in advanced cancer is common and is an independent predictor of immobility and mortality.³³ It is not restricted to patients who appear thin. For example, low muscularity is an independent adverse prognostic indicator in obese patients with advanced pancreatic cancer.³⁶ Patients with sarcopenia seem prone to toxic effects during chemotherapy,^{29,30,37} requiring dose reductions or treatment delays (which could then reduce treatment efficacy).³⁷ The present consensus relies on expressing measured levels of muscularity in relation to a standard norm. Whether a given loss of muscle mass or a defined level of low body muscularity is the best index for cancer cachexia remains to be determined. Clearly, the lean body mass or body-cell mass is made up of various tissues that can be affected differentially by the cachectic process. While focusing on skeletal muscle, it is important not to forget the potentially vital parts played by other tissues, such as cardiac muscle, the immune system, and the liver.

Previous diagnostic criteria for cancer cachexia have focused on an arbitrary minimum degree of weight loss (5–10%). The extent to which such weight loss acts as a surrogate marker for active muscle wasting or a defined level of low muscle mass is not known. Definitive cutoffs for such variables could be determined from large contemporary datasets by determining the values that relate optimally to meaningful patient-centred outcomes, such as loss of function or decreased survival. Alternatively, the evidence base for diagnostic criteria might be derived from the entry criteria of drug trials that have shown clear therapeutic efficacy. Unfortunately, no such trials up to now pertain to cancer cachexia and so the criteria suggested in the present consensus remain arbitrary. Clearly there are special populations for which the definition and diagnostic criteria might need specific modification (eg, sex, age, and ethnicity) and this would have to be part of the general validation process.

The present consensus attempts to develop a clear classification of the distal ends of the cachexia trajectory, its initial and often barely perceptible beginning (precachexia) and refractory cachexia. It is obvious that weight loss, which has culminated in a state of emaciation, is a different entity than the initially subtle early manifestations of cachexia. However, there has been a remarkable paucity of attention to these distinct states in the cancer cachexia research. A single publication in

early 2010 attempted a definition of precachexia³⁸ whereas the concept of refractory cachexia is proposed, to our knowledge, for the first time by the present consensus group. The early manifestations of cachexia must be defined to identify individuals at risk and to allow preventive interventions. Low-grade weight loss is an initial clue. However, the key biological signs predicting cachexia development remain to be determined exactly.

At the other end of the spectrum, it is worthwhile identifying those who are unlikely to benefit from interventions aimed at reversing muscle and weight loss; these patients should be managed actively with symptom control and the alleviation of cachexia-related suffering, hence the concept of refractory cachexia. The development of more specific diagnostic criteria for refractory cachexia is awaited. For the moment, definition of this stage of cachexia is essentially clinical, with an emphasis on unresponsiveness to anticancer therapy, duration of survival less than 3 months, and the presence of ongoing catabolism at an exponentially increasing rate. These considerations resonate with most clinical practice guidelines pertaining to aggressive nutritional support (eg, parenteral nutrition) in patients with very advanced cancer as contraindications to the initiation of treatment. The high rate of attrition of muscle and adipose tissue concurrent with uncontrolled growth of treatment-resistant metastatic disease has been characterised in patients with metastatic colorectal cancer during 100 days preceding death;³⁹ during this timeframe patients had a 91% chance of undergoing rapid muscle loss, a 6% chance of stable muscle mass, and only a 2% chance of gaining skeletal muscle mass. The term refractory delineates cachexia of varying severity in patients who are entering a stage of their cancer journey in which medical and ethical considerations change the pace and focus of intervention.⁴⁰ Identification of such patients can be aided by early and repeated consultation with end-of-life care teams. It is important to appreciate that often it can be the overall medical condition of the patient rather than the severity of cachexia that will render them refractory.

A particular weakness of many previous cachexia intervention trials was to include patients in terminal stage alongside earlier stage individuals. Inclusion criteria of clinical trials of cancer cachexia^{41,42} usually allowed for any degree of weight loss greater than a single cutpoint, and this served to group together patients with extremely wide ranges of weight loss as if these were a single entity. An acknowledgment of the problem of refractory cachexia can be inferred from inclusion criteria based on an expected survival of more than 6 months. However, such prognostication is very unreliable and has not prevented the participation of a substantial proportion of patients who died within just a few weeks of randomisation.⁴¹

The present consensus underscores the need for a severity system for cancer cachexia classification.

Weight-related abnormalities, like other conditions, are normally graded, and in this context the lack of a grading or severity classification system for cancer cachexia seems quite a notable omission. There are widely accepted grades of abnormally high bodyweight and a severity system for obesity was recently proposed to aid decision making in routine clinical practice.⁴³ Weight loss is also graded, and an example well known to oncologists is the Common Terminology Criteria for Adverse Events (CTCAE), which has three grades defined by overall weight loss cutpoints of 5%, 10%, and 20%. The present consensus suggests that severity should be graded according to degree of weight loss and concurrent BMI. Severity classification of cancer cachexia should be developed further around the predictive value of the system for outcomes such as treatment toxicity, quality of life, hospitalisation, and survival. Prospective collection of new data will be needed and this will be advanced by international collaboration to access representative populations. Data acquisition might include the elements identified in the present consensus evaluation (ie, weight history, body composition, and inflammatory markers), relevant demographic and disease-related features, and outcomes. A repository of biological samples (eg, blood, urine, and DNA) would be a valuable addition.

The present consensus identified certain overall domains for assessment: anorexia or reduced food intake,⁴⁴ catabolic drivers,^{40,45,46} muscle mass and strength,⁴⁷ and the functional and psychosocial effect of cachexia.⁴⁸ There was consensus that taste and smell abnormalities can limit food intake and that these can be independent of treatment side-effects; that management of early satiety and distal gastrointestinal dysmotility is important in optimising food intake; and that the assessment and maintenance of an adequate protein intake is important. Serum CRP was agreed to be an important biomarker, but it was recognised that cachexia can be present in the absence of overt systemic inflammation. There was consensus that measurements of muscle mass had to be interpreted in relation to function and that although strength might only be related indirectly to overall function, this was often a useful prognostic marker. Finally, an agreement was made that the effect of cachexia should not only be considered in terms of overall physical function, but that psychosocial effects should be assessed routinely.

Although it was possible to reach broad agreement about assessment variables, there was diversity of opinion regarding the local availability of different techniques, the time allotted for assessment, and the different focus required for routine care versus research. The development of a more practical classification approach for routine clinical use and a more sophisticated classification for rigorous research purposes²⁷ is anticipated.

In summary, a new system for diagnosis and classification of cancer cachexia has been presented, for which a parallel can be drawn with the TNM staging

Search strategy and selection criteria

This Review on items and domains associated with involuntary weight loss in cancer applied two search strings conceptualised around weight loss (including cachexia, anorexia, and wasting) and cancer. A search was done of the Medline, Cochrane, Embase, PsychINFO, and CINAHL databases for papers that included either a comparison of groups of patients with or without weight loss or patients with various degrees of weight loss. Only papers published between 1976, and 2007, in English or German were included; these papers informed the start of the Delphi process. Quality criteria for including papers were applied. The following search terms were used: "cachexia", "anorexia", "weight loss", "loss of appetite", "loss of weight", "wasting syndrome", "eating problem", "protein malnutrition", or "energy malnutrition" and "neoplasm" or "cancer". Paper retrieval was done stepwise from citations to abstracts to full papers. The inter-rater reliability for raters' performance was checked, and a hand search of practice guidelines, editorials, and letters was done to search for further references and cachexia experts, who were invited to accompany the review process and provide additional publications, upto July, 2010. Data extraction was done independently by at least two researchers (consensual approach), and was standardised for measurement of items, absolute differences in comparisons, and characterisation of patients (sex, age, weight loss, tumour type, and survival).

system for cancer. As in the TNM system, the importance of the present proposal does not lie in being definitive, but in providing a framework that can evolve over time. A period of validation should allow this new classification system to be modified. This should provide a mechanism for the introduction of new interventions aimed at improving the outlook in cancer cachexia.

Contributors

KF, FS, SK, VEB were responsible for the conception and design of the Delphi Consensus rounds, the collection and compilation of the responses, and drafted the report. All authors participated in the Delphi Consensus process and the interpretation of the results. The sponsor of the consensus had no role in the study design, data collection, analysis, or writing of the report. All authors had access to the raw data. KF had full access to all the data and had final responsibility for the decision to submit for publication.

Conflicts of interest

MM has received speaking honoraria from Abbott, Baxter, Fresenius Kabi, Nestlé, and Nutricia. NM has received honoraria from Abbott, Millennium Pharmaceuticals and Tofis Epsom, and grant funding from Immunotec Solvay. SDA has received honoraria for advisory board membership from Novartis, and consultancy fees from Myotec Therapeutics. All other authors declared no conflicts of interest.

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