

## Review Article

# A critical reappraisal of the definition of cancer cachexia and proposal for a staging system

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**ABSTRACT:** A review of the literature shows that the term *cachexia*, although present in the medical literature for about 2,000 years, has never been given a systematic, widely accepted definition. The current definitions of cancer cachexia are mainly descriptive and focus on the main clinical and metabolic features with the purpose of presenting a complete picture of the syndrome. They often diverge from one another. However, in clinical practice, there is a need for a simple and quick nomenclature which does not require a specialist expertise or laboratory examinations, and which provides a higher degree of specificity. Moreover, a quantification of the degree of cachexia would be extremely useful to differentiate otherwise homogeneous groups of patients as regards clinical characteristics and outcome, to interpret the therapeutic results reported in literature, and to stratify patients when planning randomized clinical trials in comparable groups. We report the SCRINIO Classification and Staging system of cancer cachexia which relies on weight loss and the presence or absence of cachexia-specific symptoms (anorexia, early satiety, and fatigue). The definition of cachexia is the following: a complex syndrome characterized by a severe, chronic, unintentional, and progressive weight loss, which is poorly responsive to conventional nutritional support, and may be associated with anorexia, asthenia, and early satiation. The staging system is as follows: stage I: weight loss < 10% and no symptoms; stage II: weight loss < 10% with symptoms; stage III: weight loss ≥ 10% and no symptoms; stage IV: weight loss ≥ 10% with symptoms. The first 2 stages are referred to as pre-cachexia. This classification correlates with some clinical characteristics (site of primary tumor and cancer stage, performance status, number of symptoms, and nutritional risk score). Moreover, it appears to correlate with the outcome of the randomized clinical trials investigating the effect of nutritional support or specific nutrients on clinical outcome. (*Nutritional Therapy & Metabolism* 2008; 26: 109-17)

**KEY WORDS:** Cancer cachexia, Classification of cancer cachexia, Definition of cancer cachexia, Staging of cancer cachexia

*"The shoulders, clavicles, chest and thighs melt away.  
The illness is fatal..."*

Hippocrates (460-370 BC)

## INTRODUCTION

The word *cachexia* probably dates back to the second century AD, and Tesimone of Leodicea, a Roman physician, is credited with being among the first to use this term. This word, in fact, does not exist in classical Greek and defines a state of progressive, often lethal wasting due to a severe disease. Literally, it means "to be in a bad status" from *κακόσ ἐχειν*. In the past this condition was associated with severe chronic infections, congestive heart failure, chronic obstructive pulmonary

disease, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, human immunodeficiency virus infection and other severe illnesses, and sepsis, whereas in most recent years, it represents the common final outcome of many incurable cancers. In Western industrialized countries only a minority of patients with cachexia are affected by end-stage failure of vital organs such as heart, kidney, and liver.

Cancer cachexia (CC) represents a major problem in oncologic diseases: a quick research in Google.com and in PubMed returns 841,000 hits and 2,655 articles, respectively.

## MAGNITUDE OF THE PROBLEM

Malnutrition (a term often misused as synonymous with CC) or weight loss, which is a prominent feature of CC, has long been recognized as an important prognostic factor in cancer patients. A large body of data has demonstrated that weight loss is a significant predictor of decreased survival in oncologic patients (1-11). More specifically, a shorter survival was reported in cancer patients with depletion of body protein estimated with *in vivo* neutron activation analysis (12) or with a low bio-electrical impedance phase angle, a measure of the integrity of vital cell membranes (13, 14). Quite recently, Bosaeus et al (15) studied body composition by DEXA and reported that loss of skeletal muscle was predictive of survival in males with advanced solid tumors. Moreover, malnourished chemotherapy patients have a reduced quality of life (9, 16), a higher rate of hospital readmission, and a longer duration of hospital stay (17). Finally, 4% to 23% of incurable cancer patients ultimately die because of progressive malnutrition and hypophagia (18-21).

Even if the association between malnutrition and poor survival does not automatically mean that improving the nutritional status translates into a better outcome, there are further data which argue in favor of a vigorous treatment of CC. In fact it has been demonstrated that malnourished chemotherapy patients have a poor response to chemotherapy as regards its rate and duration (9, 16, 22-24), and the availability and administration of the appropriate treatment is the major determinant of prognosis for the potentially curable cancers.

Preliminary randomized clinical trials (25, 26) and comparative prospective studies (27) have shown that a nutritional and anticachectic treatment may improve survival in populations of patients, with or without concurrent oncologic therapy.

## A HISTORICAL PERSPECTIVE

For many decades and centuries, cancer cachexia was defined in an imprecise and vague way – something that various specialists talk about, but the nature of which nobody knows very clearly, or what to do about it. The terms *cachexia*, *wasting*, *malnutrition*, and *weight loss* were often used interchangeably. The efforts of clinical researchers focused more on the attempt to determine its prevalence in different types of malignancies and different stages of disease, as well as to point out its debilitating and life-threatening effects, rather than giving a specific definition of this syndrome.

Here we report some of the commonest definitions

of cancer cachexia by different medical specialties and according to some authoritative clinicians and researchers:

—Some internists: CC is characterized by “*weakness, anorexia, depletion and redistribution of host components and, finally a progressive alteration of vital functions*” (28) or by “*progressive weight loss, anorexia, metabolic alterations, asthenia, depletion of lipid stores, and severe loss of skeletal muscle protein*” (29) or by “*a debilitating state of involuntary weight loss complicating malignant diseases and contributing significantly to mortality, anorexia being a major contributor*” (30).

—Some surgeons: CC comprises “*several conditions including anorexia, asthenia, loss of lean body tissues, and the inability to alter some metabolic regulatory functions appropriate to the level of stress and nutritional status*” (31), or CC is “*a complex syndrome characterized primarily by diminished nutrient intake and progressive tissue depletion that is manifest clinically as anorexia and host weight loss*” (32), or CC refers to “*a complex multifactorial syndrome characterized by anorexia or the spontaneous and unintended loss of appetite, generalized host tissue wasting, skeletal muscle atrophy, immune dysfunction, and a variety of metabolic alterations*” (33). More recently CC was defined as “*characterized by a chronic wasting syndrome, involving loss of adipose tissue and lean body mass which is resistant to conventional nutritional support ... the typical patient with advanced cachexia demonstrates severe weight loss, anorexia, early satiety, weakness, anemia, and oedema*” (34).

—Some oncologists: CC is “*a complex syndrome that includes weight loss, anorexia, and muscular weakness, concomitant with a disturbed host metabolism*” (35) or is “*a wasting syndrome involving loss of muscle and fat directly caused by tumours factors, or indirectly by an aberrant host response to tumour presence*” (36). Quite recently the Editor of a prestigious book (38) defined CC as “*a clinical syndrome characterized by anorexia, tissue wasting, loss of body weight accompanied by a decrease in muscle mass, and adipose tissue, and poor performance status that often precedes death*”, or it may be described as a syndrome characterized by “*anorexia, tissue wasting, weight loss and poor performance status, associated with poor compliance to the complications of the disease and to the adverse effects of the oncologic treatment*” (38).

—Some palliativists: “*CC is a complex multifactorial syndrome which combines weight loss, lipolysis, loss of muscle, and visceral protein, anorexia, chronic nausea, and weakness*” (39) or “*CC is an involuntary weight loss of >10% of the pre-morbid weight and is associated with muscle wasting and hypoproteinemia,*

lipid stores are depleted, and serum albumin and prealbumin diminish as serum acute phase reactants increase" (40).

—Some experimental researchers: "CC is characterized by weight loss involving depletion of host adipose tissue and skeletal muscle mass" (41, 42).

If we look at the above-listed definitions, it appears that they are all quite similar in their content, they are poorly specific in differentiating CC from other clinical conditions associated with weight loss, and those from clinicians mainly emphasize some clinical features of CC, while those from basic researchers focus more on metabolic and tissue alterations.

#### THE NEED FOR A COMMON LANGUAGE

Only in the last decade have clinical researchers felt the need for a more scientific definition of CC because of a number of concurrent factors: progress in the development of enteral and parenteral nutrition, both in the composition of their admixtures and in the methodology of their administration and their improved adequacy to deal with different conditions of malnutrition; the availability of new agents targeted as anticachectic (orexigenic, anticatabolic, and anabolic drugs or nutrients); and the growing attention to patients' quality of life, especially when the primary disease cannot be cured.

It is especially worthy of note that quite recently oncologists have included maintenance of body weight and control of anorexia in the concept of clinical benefit (43, 44).

The availability of a standard nomenclature for, and classification of, cachexia, which is simple and accepted worldwide, would be clinically very useful: it would make comparisons possible between different therapeutic approaches, as well as to properly stratify patients within different arms of the randomized clinical trials, and it would help to interpret the findings, sometimes conflicting, in the literature, which often mixes patients in a single series who have different degrees of deterioration in their nutritional status.

In the last decade, at least 3 major contributions have appeared in the clinical scenario. Roubenoff et al in 1997 (45) distinguished *wasting* which would mean a decrease in both body cell mass and weight usually associated with poor dietary intake, as opposed to *sarcopenia* which refers specifically to involuntary loss of skeletal muscle mass and consequently of strength, and "cachexia" which is a decrease in body cell mass even in the presence of stable or increasing weight. However, this nomenclature was more focused on defining the alteration in body composition during different health

conditions, and did not gain wide acceptance in the scientific community, because, not only can the assessment of body cell mass not be proposed as a diagnostic procedure in clinical practice but oncologists would also be very reluctant to accept some patients who are not losing weight as being cachectic. Furthermore, the term *cachexia* came into English medical usage in 1541 (46) to describe gross generalized wasting (emaciation) and ill health, usually associated with chronic disease, and this meaning was in textbooks of medicine (47, 48) and in several major medical dictionaries (49-52), so it appears that this word has a well-established and time-honored definition.

Fearon et al (53), on the basis of 170 weight-losing patients with advanced pancreatic cancer, proposed *cancer cachexia as characterized by 3 main factors: body weight loss  $\geq 10\%$ , nutrient intake  $\leq 1,500$  Kcal/day, and level of C-reactive protein  $\geq 10$  mg/L*. This definition is undoubtedly supported by a strong clinical and pathophysiologic rationale, is prognostically validated, and represents the first true attempt to define cachexia according to objective criteria. However, it has some limitations. First, it defines cachexia but does not classify it into different stages of severity. Second, there is an objective difficulty to assessing the calorie content of the diet of cancer outpatients in a nonspecialist setting, and, furthermore, this definition requires a blood examination and, consequently, the need to assess the patient twice.

Finally, after some reports in the literature that even in patients with anorexia nervosa there is a systemic inflammation with increased plasma concentrations of TNF- $\alpha$  and sTNF-RII (54-58), and IL-6 (54, 59), and IFN- $\gamma$  (60), there is some doubt that C-reactive protein level, in spite of its prognostic relevance in cancer patients, is able to discriminate between cancer cachexia and uncomplicated starvation.

More recently, a conference was held in Washington, DC, on December 13 and 14, 2006, where a committee of experts approved the following definition (J.E. Morley, W. Evans, and S. Anker; unpublished communication): "Cachexia is a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults and growth failure in children. Anorexia, inflammation, insulin resistance and increased muscle breakdown are frequently associated with cachexia. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and primary hyperthyroidism and is associated with increased morbidity".

Finally the ESPEN SPECIAL INTEREST GROUP

on Cachexia-Anorexia in Chronic Wasting Diseases during its II Meeting in Istanbul (October 19th 2006) proposed the following definition: “*Cachexia is a multifactorial syndrome characterized by weight loss due to underlying disease(s). It is clinically relevant since it increases patients’ morbidity and mortality. Contributory factors to the onset of cachexia are anorexia and metabolic alterations (i.e., increased inflammatory status, increased muscle proteolysis, impaired carbohydrate, protein and lipid metabolism). Considering the wide range of clinical manifestations of cachexia, the staging of this syndrome is warranted*”.

#### DEFINITION OF CACHEXIA: RATIONALE AND METHODOLOGY

Many of the above-mentioned statements, however, are more qualitative descriptions of a clinical condition, which mainly attempt to include all the clinical and metabolic features and, sometimes, the pathogenetic factors, than true definitions of a pathologic status to be used in practice to assess if a patient is cachectic or not and to what degree. The clinical definition of a pathologic condition should meet the following requirements: it should be simple and quick (that means it should rely on simple clinical features which are easily detected in a clinical examination), it should not require a specific specialist expertise (especially when the condition to be defined is common and not confined to a restricted specialty), and it should not require, if possible, a laboratory examination. Finally, it should be specific enough to be grossly differentiated from similar common conditions. Furthermore, an ideal definition should allow classification into stages which collects in different group patients with different severities by their disease status, different prognoses, probably warranting different therapeutic approaches.

Examples of such classifications are, for instance, the time-honored and currently used determinations of performance status according to the Karnofsky-Burchenal or Eastern Cooperative Oncology Group (ECOG) definitions.

To accomplish this task we utilized a large database of clinical data which were prospectively collected with the Screening the Nutritional Status in Oncologic Patients (SCRINIO) Study and which includes over 1,000 patients. The SCRINIO Study was sponsored by Novartis Medical Nutrition (now HealthCare Nestlé) after a meeting held in Milan in 2003, which involved both oncologists and nutritionists. During the meeting it was clearly appreciated that there was a substantial discrepancy of view between these 2 specialties regarding the

impact that malnutrition might have on the outcome for a cancer patient and the potential role for nutritional support. As a consequence, an open working group was established coordinated by the chairman of the meeting (F.B.), with the aim of establishing a protocol to prospectively screen the nutritional status of oncologic outpatients.

The end points of the study were (a) to define the prevalence and rate of malnutrition and of nutritional risk in cancer outpatients and the need for a nutritional intervention, and (b) to investigate the association of some patient-dependent, tumor-dependent, and therapy-related variables with weight loss and nutritional risk.

The eligibility criteria included adult cancer outpatients presenting for diagnosis or therapy or follow-up to the cancer units of different hospitals, universities, or scientific institutions. Patients were excluded from the study if they were affected by endocrine diseases or they showed a severe impairment of liver or kidney function.

The protocol collects some demographic data (age and sex) of the patients, oncologic data (site of primary cancer, histology, stage, ECOG performance state, and oncologic therapy), and nutritional data, namely percentage of weight loss from the usual body weight and the body mass index (BMI). Systemic and digestive symptoms such as fatigue, anorexia, nausea and/or vomiting, early satiety, dysgeusia and/or dysosmia, odynophagia/dysphagia, diarrhea or constipation were classified semiquantitatively through a 4-point score.

Finally, the risk of complications related to malnutrition was assessed through the Nutritional Risk Screening system. This screening system, endorsed by the European Society for Parenteral and Enteral Nutrition, was validated against over 100 randomized clinical trials comparing nutritional support versus spontaneous intake (61, 62) and proved highly effective in prospective clinical investigations, because patients identified “at nutritional risk” had better outcomes if supported nutritionally.

Briefly, if the patients at the initial screening have a < BMI 20.5, or they have lost weight in the last 3 months, or they have a reduced dietary intake in the last week, or they are severely ill, then they move to the final screening where a quantification of the previous parameters is completed. This is summed up as the severity of the disease. The final scoring ranges from 0 to 7 (0 = no risk, 1-2 = low risk, 3-4 = medium risk, and > 5 = high risk). A score  $\geq 3$  is considered to indicate a requirement for further, more in-depth nutritional assessment for potential nutritional intervention.

The study was proposed to several (mainly Italian) clinicians involved in the care of cancer patients and finally launched in 2004 (see “Appendix” for a list of the

participants in the SCRINO Working Group). Each center got approval for the study and an informed consent form from its own local ethics committee. The central study database was maintained at the Fondazione IRCCS Istituto Nazionale Tumori (Unit of Medical Statistics and Biometry) of Milan, where data collected on each patient were entered, checked for quality and completeness, and analyzed. Further details of this study and preliminary results are to be published in the current year (63).

On the basis of the information available in the database and the consensus reached in the recent “Guidelines on Parenteral Nutrition in Oncology” on behalf the European Society for Parenteral and Enteral Nutrition (64), we propose the following definition of CC: “cachexia” is a complex syndrome characterized by a severe, chronic, unintentional, and progressive weight loss, which is poorly responsive to conventional nutritional support, and may be associated with anorexia, asthenia, and early satiation.”

At a variance with previous definitions, this pragmatic statement mainly focuses on the clinically self-evident features and emphasizes some specific aspects (*chronic, unintentional, and progressive weight loss, unresponsive to conventional nutritional support*). Furthermore, it includes anorexia or early satiety or fatigue, not only for their high prevalence in weight-losing cancer patients but also because their pathogenesis is closely related to the same factors responsible for the derangement in metabolism and weight loss. Hence their presence might reflect the role of some common specific

mechanisms underlying both the clinical appearance and the metabolic picture of CC.

We included anorexia and fatigue in our classification also for other reasons: they are relevant for patients because they are recognized as independent, distressing symptoms (65-67) capable of significantly affecting the quality of life (68-71), and they are also independent predictors of short-term survival (72-74).

Early satiation was also included in the classification because this symptom, albeit less frequently observed in some studies, is characteristic of cancer cachexia and may be responsible for a reduced dietary intake. Early satiation predicts dysmotility and gastroparesis (75) and may be due to a hypothalamic effect of IL-1 which disrupts the migratory motor complexes (76).

#### STAGING OF CACHEXIA

Depending on the degree of the weight loss and the presence/absence of one/all these symptoms, it is possible to stratify the patients into 4 different classes (Fig. 1). These classes (from 1 to 4) represent stages of progressive severity of the cachexia.

Strasser and Bruera (77) have recently reported that authors have quite often used, in prospective protocols, different cutoffs for body weight loss to consider patients cachectic: > 5% compared with stable pre-illness weight, or > 5% during the previous 6 months, or > 2% within a 1-month period, or a decrease of 11 kg in the

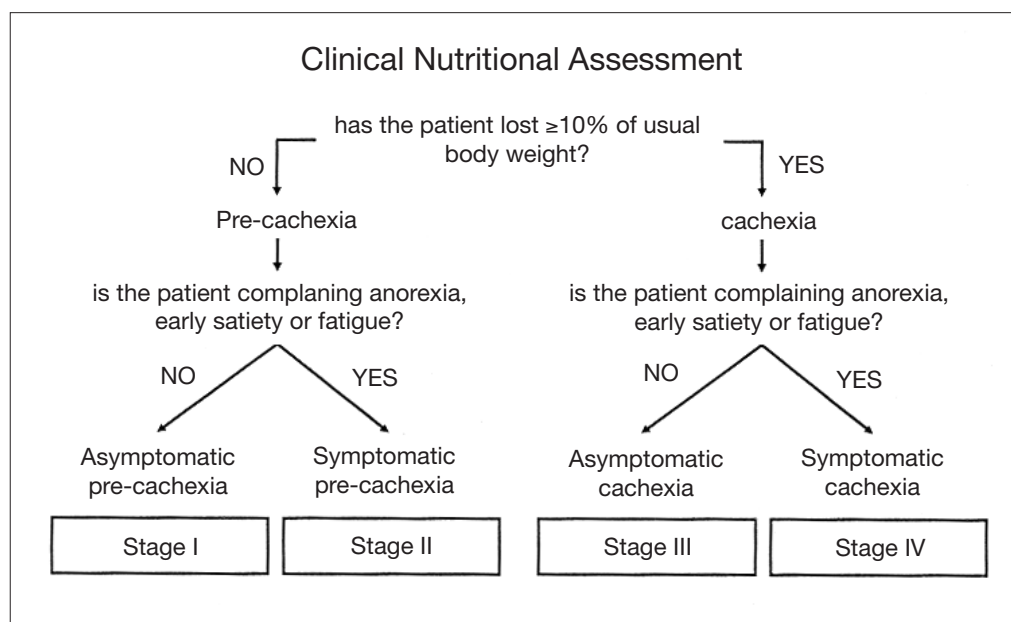


Fig. 1 - SCRINIO Cachexia Staging System.

previous 2 months, or a 6%-9% loss over the past 6 months. Other authors use a > 2-3 kg loss during the last 2 months to accept patients as cachectic and suitable to be enrolled in prospective interventional trials (78).

We have accepted as a cutoff value separating cachexia from pre-cachexia, a weight loss  $\geq 10\%$  of the usual body weight, because this value was deemed clinically significant both in a mixed general patient population (references in (79)) and in oncologic patients (7, 53), and this item is also included in the popular Subjective Global Assessment (80, 81). Recently, Gogos et al (25), in a prospective study in advanced cancer patients receiving n-3 fatty acids, reported a statistically significant difference in survival effect in those with less or more than 10% weight loss.

#### VALIDATION OF THE SCRINIO STAGING SYSTEM

We approached the problem of validating this new system staging in two ways. First, we analyzed whether the classes we have determined could actually discriminate between groups of patients with different clinical and prognostic characteristics, and, secondly, we briefly reviewed the evidence-based literature to determine whether the outcome of treatment with nutritional support and/or special nutrients depended on the stage of cachexia (82).

The first analysis was carried out with SAS software, by using the Cochran-Mantel-Haenszel test for count data and analysis of variance (ANOVA) for continuous data, and using 5% two-sided *p* values for assessing statistical significance. We found, in 1,300 patients included in the database of SCRINIO, that in moving from asymptomatic pre-cachexia (class 1) to symptomatic cachexia (class 4), there were statistically significant trends ( $p < 0.0001$ ) in the percentage of gastrointestinal versus nongastrointestinal tumors, severity of cancer stage, percentage of weight loss, number of symptoms per patient, ECOG performance status, and nutritional risk score.

When we looked at the evidence-based literature, we found that a benefit in outcome was reported in stages of pre-cachexia in patients randomized to individual nutritional support (83) or intensive individualized nutrition counseling by a dietitian using a standard protocol and oral supplements (84), or to intensive individualized nutrition counseling by a dietitian using a standard protocol and oral supplements (26, 85), compared with patients receiving standard care. It is noteworthy that these positive results in patients with pre-cachexia were all achieved through an oral

nutritional support, and this would suggest that this group of patients was not so severely compromised to require a more aggressive and invasive nutritional approach.

The therapeutic results in cachectic patients (class 3 or 4) are by far less encouraging. Lundholm et al (27) provided home parenteral nutrition (20-25 Kcal/kg per day; 0.6-0.9 g amino acid/kg per day) for 46 days to initially cachectic patients (weight loss  $\sim 10\%$ ), and only with as-treated analysis (but not intention-to-treat analysis), they could observe a benefit in metabolism, function, and survival, when compared with randomized control patients. A small study including patients with head and neck cancer and weight loss > 10% (class 3 or 4) showed that 7-10 days of enteral nutrition only achieved a small benefit in some indexes of physical and emotional functioning by the EORTC QLQ-C30 questionnaire, but no other major clinical advantage in comparison with patients randomized to no tube feeding (86).

The supplementation of specific nutrients or anti-inflammatory nutraceuticals, albeit promising in preliminary studies, was not supported by large randomized clinical trials.

Three RCTs (87-89) investigating the effects of eicosapentaenoic acid (EPA), as single preparation or enriched supplement, in severely weight-losing patients did not show any benefit in an intention-to-treat analysis with regards to body weight gain (87-89), survival (88, 89), and fatigue (87), a result in keeping with the conclusions of a recent Cochrane systematic review (90).

Only in 1 study (91), where the authors supplemented an adequate diet (23 Kcal/kg per day and  $\sim 1$  g amino acid/kg per day) with L-glutamine (14 g/day), L-arginine (14 g/day), and  $\beta$ -hydroxy- $\beta$ -methylbutyrate (3 g/day) for 24 weeks in cachectic patients ( $\sim 18\%$  weight loss), it was possible to achieve an increase in the body mass and the fat-free mass whereas there was a decrease in the randomized controls.

#### CONCLUSIONS

In conclusion, this review has shown that the time-honored definitions of cachexia are mainly qualitative descriptions of this pathologic condition and the recent proposals in the literature are not specific enough and practical to be easily used in clinical practice. In addition, they lack any scoring of severity.

In contrast, the clinical definition and classification of cachexia we are proposing relies on weight loss and some specific cachexia-related symptoms, is

simple and quick, may be performed by every physician or nurse, and may be used to better interpret, retrospectively, the results of different treatments of cachexia. Prospectively, it may prove useful in planning a rational approach to therapy for weight-losing cancer patients, or for selecting the appropriate patient population to be enrolled in future trials.

We think that the SCRINIO classification should be tested in larger series, within a comprehensive oncologic approach to weight-losing cancer patients, until more sophisticated or specific techniques of analysis of body composition or determination of specific mediators of weight loss become available in the routine clinical examination of patients.

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