


Practical Management of Cancer Cachexia

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ABSTRACT

In cancer patients, delivery of palliative care during anticancer treatment (i.e., concurrent care) leads to enhanced clinical outcome. Nutrition therapy is part of palliative care and, therefore, should be prescribed to prevent or treat cachexia. Effective nutrition therapy is based on a thorough assessment of weight loss history, eating behaviour, changes in appetite, and the presence of nutrition impact symptoms. By identifying a patient's needs, the delivery of nutritional care (i.e., counselling, supplements, enteral or parenteral nutrition according to the “maximal use of supportive therapy” approach) has greater likelihood to be highly effective. However, a careful monitoring programme, which includes periodical check of body weight, energy and protein

intake, quality of life, ensures constant adaptation of nutritional care to the changing needs of cancer patients. Nutrition therapy is becoming a key component of cancer patients management. In this new role, nutrition therapy is key in allowing cancer patients to receive and complete treatments and in improving quality of life. Whether these effects also translate into longer survival remains to be demonstrated but preliminary results are encouraging.

Keywords: Anorexia; Cachexia; Cancer; Clinical outcome; Nutrition therapy; Nutritional outcome

INTRODUCTION

Recently released US statistics show that the incidence of cancer has slowly yet progressively increased over the last 40 years [1]. In the same period, the mortality rate declined consistently [1]. This suggests that available therapies enhance the management of cancer patients. However, a closer look at the US statistics shows that the 5-year survival rate of patients diagnosed with advanced cancer did not improve significantly over the last decade [1]. Therefore, it could be speculated that implementation of early cancer screening programmes significantly contributed to the progressive decline of cancer mortality rate. Also, it appears evident that the

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management of patients with metastatic cancer remains an unresolved clinical issue.

To enhance the efficacy of anticancer therapies, particularly in advanced disease, patient's related factors should be targeted. Consistent evidence shows that the early and simultaneous delivery of chemo-radiotherapy and palliative care results in reduced morbidity and mortality [2]. Palliative care addresses the needs of patients suffering from chronic diseases, and is not related to the timepoint when it is delivered during the clinical trajectory. Considering that malnutrition frequently occurs in cancer patients, nutrition therapy remains a pillar of palliative care, among other patient-centred interventions. Therefore, cancer patients at nutritional risk or already malnourished should receive immediate attention and care, independently from being simultaneously treated or not [3]. This new holistic management of cancer patients receiving treatment is defined as "concurrent care" and has been demonstrated to improve survival by 15% during a follow up of 12 months [4].

This review paper provides the general framework within which nutritional care of cancer patients should be included. Also, based on the available evidence consistent with Ethics guidelines, we suggest a series of procedures to provide timely and possibly effective nutritional care to cancer patients (Fig. 1). This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CACHEXIA AS A RELEVANT TARGET WITHIN THE FRAMEWORK OF CONCURRENT CARE

The clinical journey of cancer patients is frequently complicated by the development of cachexia. Cancer cachexia is defined as the progressive loss of muscle mass [5], although its systemic effects (i.e., on the function of the heart, brain, liver, etc.) should not be overlooked [6]. Although the word "cachexia" is commonly related to extreme malnutrition, it should be reminded that the global obesity pandemic is changing the phenotype of cachectic cancer

patients, since in most western and westernized countries the majority of cancer patients is now overweight or obese according to body mass index [7]. Therefore, the assessment of body composition provides a more precise identification of the cachectic patients. Nevertheless, involuntary weight loss remains a key alert signal prompting nutritional care.

Cancer cachexia, either diagnosed by the presence of muscle mass loss (=sarcopenia) or by involuntary weight loss, is a negative prognostic factor for medical and surgical cancer patients. Its presence is closely related to the development of dose-limiting toxicity, post-operative complications, and shorter survival [8–10]. The aetiology of cancer cachexia is characterized by the variable combination of nutrition-related symptoms (i.e., anorexia, reduced food intake, taste aversion, increased energy expenditure, etc.), whose severity exacerbates during the patient's clinical journey. Over time, cachexia progresses following the "catabolic crisis" model. Although this model is not validated in cancer patients, it was proposed for the progressive decline of function in patients with organ failure [11]. Also, it is common knowledge in clinical practice that nutritional status in cancer patients progressively decline, whereas exacerbations occur at specific therapy-related time points of their clinical journey. Body weight/muscle mass progressively decline, but the rate of loss increases during catabolic events, i.e., radio-chemotherapy or surgery or depression and anxiety, among others. Windows of anabolic opportunity occur during a patient's trajectory, but the patient is almost invariably unable to regain the body weight/muscle mass lost. Therefore, nutrition therapy should be delivered early in the clinical journey of a cancer patient, before muscle mass and function severely deteriorate [12]. Also, nutrition therapy should aim at minimizing the effects of the different catabolic crisis and maximize the anabolic potential during the windows of opportunity [13].

Aim of this review is to provide a bundle of procedures and interventions aimed at preventing and treating cancer cachexia, based on the most recent literature and the recommendations issued by scientific societies.

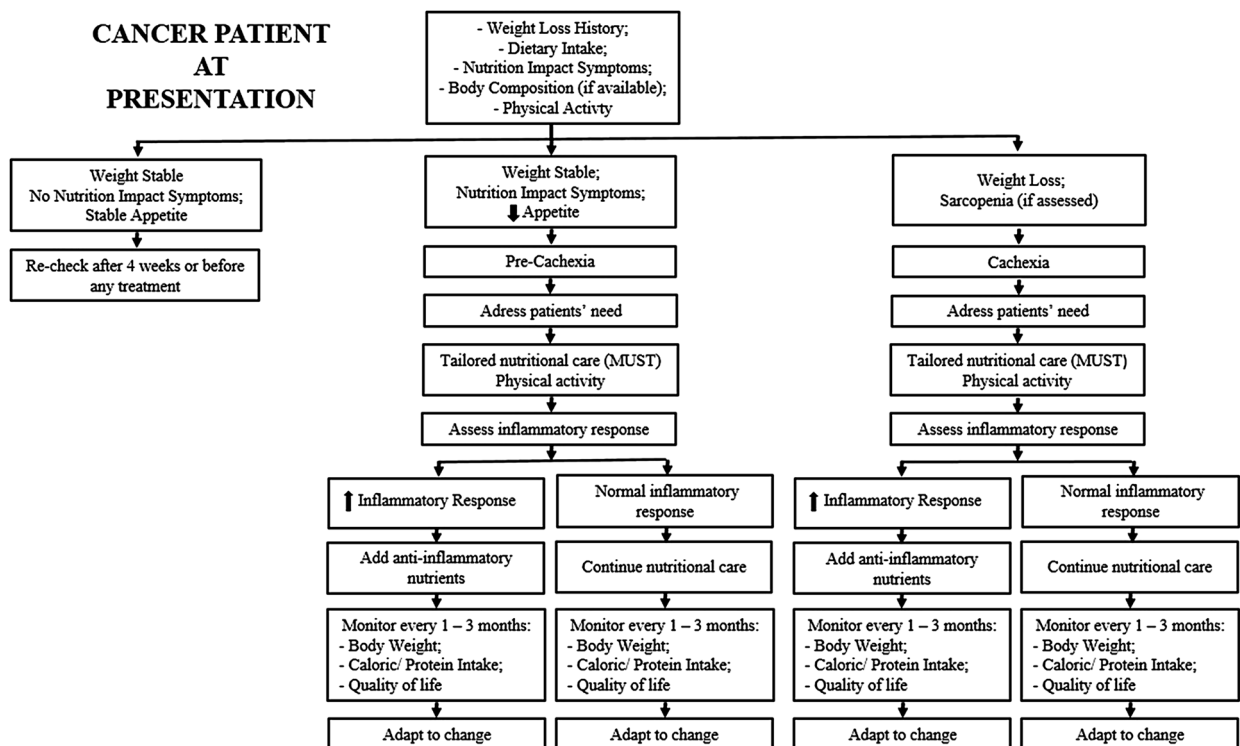


Fig. 1 Upon presentation, cancer patients should be screened for the presence of nutritional risk by using validated screening tools, and those at risk should undergo a thorough nutritional assessment to identify the domains affected by and leading to weight loss/sarcopenia (i.e., appetite changes, early satiety, hyper-metabolism, insulin resistance, dysphagia, physical inactivity, etc.). Cancer patients not at risk should be re-evaluated every 1–3 months and at the beginning of anti-cancer therapies. Cancer patients meeting the definition of pre-cachexia should receive nutritional care targeting their needs (i.e., modified texture of the diet for patients with dysphagia, small and frequent meals/supplements for patients with early satiety, etc.), promoting physical activity, and

enriched with anti-inflammatory nutrients in the presence of increased inflammatory response (i.e., increased C-reactive protein levels). Nutritional goals should be carefully identified and achieved by the “maximal use of supportive therapy” approach (MUST, see text). Similarly, patients with cancer cachexia should receive tailored nutritional care, which encompasses nutritional needs, physical activity and pharmaconutrition. Based on the severity of weight loss or the aggressiveness of anti-cancer therapy, cancer patients should be monitored every 1–3 months to assess efficacy (i.e., quality of life, nutritional parameter, cancer therapy-related toxicity, etc.) and to adapt rapidly to the changing needs

Screening Cancer Patients

Not all cancer patients develop cachexia. Consequently, it is imperative to identify the patients who will benefit the most from nutrition therapy. Screening cancer patients for the presence of cachexia or early stages of cachexia contributes to maximizing the human and financial resources available. Based on the current definition of cachexia [5], documenting a patient’s history of weight loss and BMI may suffice to make the diagnosis of cancer cachexia.

However, assessment of cancer patients’ muscularity by DEXA or CT scans is of greater clinical significance since it may disclose combined obesity and cachexia (i.e., sarcopenic obesity). If reliable body composition analysis is not available, classical nutritional screening tools could be clinically useful to identify the patients at higher clinical risk. As already suggested [14], all cancer patients should be screened for the presence of cachexia or the risk of cachexia upon admission to the hospital, either as in- or out-patient. Validated screening tools (i.e.,

MUST, NRS-2002, PG-SGA) have been demonstrated to identify the patients at higher clinical risk and should be preferred over local, not validated tools [15]. Also, changes in appetite can be used to identify the patients at higher clinical risk [16].

After screening, an action should always follow. In case the patient is negative to the screening procedure, then a new screening should be scheduled within the next 4–6 weeks, possibly before the initiation of any anticancer intervention. In case the patient proves positive to nutrition screening, then a better characterization of his/her nutritional status is necessary.

Diagnosing the Stage of Cachexia and the Attendant Clinical Risk

Nutritional screening allows identifying patients at higher nutritional risk, which is confirmed and detailed by nutritional assessment, i.e., body composition analysis, collection of dietary records, and investigation of the presence of nutrition impact symptoms. Cancer patients at nutritional risk should undergo a thorough nutritional assessment. It is acknowledged that nutrition screening does not require specific nutritional competencies, whereas nutritional assessment can be only performed by experienced healthcare professionals. This may limit the possibility to assess body composition and dietary habits when dietitians or clinical nutritionists or other healthcare professionals with relevant competencies are not available. Nevertheless, staging cancer cachexia is key to devise better nutrition therapy.

Considering muscle loss as the key feature of cancer cachexia, assessing muscle quantity and quality is preferable. The gold standard for body composition assessment remain the analysis of muscle mass and adipose tissue using the CT slice at the level of the L3 vertebra. All cancer patients undergo CT scan for diagnostic purposes, and therefore, CT images can be used to assess muscle mass and quality and to diagnose cachexia. The relevant thresholds have been identified and have been also developed for different populations [17, 18]. When muscle mass is assessed, the stage of cancer cachexia

can be diagnosed. There is general agreement that cancer cachexia can be divided into three stages: precachexia, cachexia, and refractory cachexia (5; Table 1). Unfortunately, the diagnostic criteria for each of these stages are not precisely defined. Thus, these stages appear more a strategy to advocate the early initiation of nutritional care, rather than the definitive answer to the need to identify the severity of cancer cachexia.

Consistent data have demonstrated that long-term survival of precachectic, cachectic and refractory cachectic cancer patients is significantly different between them, and highlight that cachexia treatment should start in its early stage.

Muscularity assessed at the level of L3 vertebra by CT scan is the gold standard for muscle mass assessment. It is acknowledged that this approach may not be available in all cancer centres worldwide. The reading software may not be available due to financial constraints, or maybe patients do not undergo a CT scan involving L3 vertebra (i.e., head and neck cancer patients). Also, only clinical reasons dictate the prescription of CT scan. Also, it should be highlighted that at this moment there are no agreed thresholds to define cancer pre-cachexia, cachexia, and refractory cachexia. Alternative tools can be used to measure or derive muscle mass in cancer patients. Dual energy X-ray absorptiometry (DEXA) is a reliable procedure

Table 1 Diagnostic criteria for different stages of cachexia. Adapted from Ref. [5]

Pre-cachexia	Cachexia	Refractory cachexia
Weight loss $\leq 5\%$	Weight loss $>5\%$ or BMI <20 or sarcopenia and weight loss $>2\%$	Variable degree of cachexia Cancer disease both
Anorexia and metabolic change	Often reduced food intake/systemic inflammation	procatabolic and not responsive to anticancer treatment
		Low performance score
		<3 months expected survival

for the measurement of muscle mass, although it exposes the patient to ionizing radiation. Estimation of muscle mass can be derived by bioimpedance analysis (BIA), whose reliability is limited by the influence made by water retention. More recently, a parameter derived from BIA, i.e., phase angle, appears to reliably assess body cell mass, and clinical risk of the patients.

In case assessing or estimating body composition is not practical or not possible, the severity of the nutritional deterioration can be assessed by measuring the patient’s body mass index (BMI) and the % of weight loss. Martin et al. recently showed that the clinical risk of cancer patients can be categorized based on the simultaneous assessment of BMI and weight loss (i.e., % vs. usual body weight) [19]. Using a large international database, Martin et al. categorized weight loss of cancer patients in 5 grades. The better survival was observed for patients with weight loss grade 0, which is characterized by high BMI and minimal weight loss. In contrast, the worse clinical outcome was observed for those cancer patients with weight loss grade 4, which is in turn characterized by low BMI and severe weight loss (Fig. 2).

Identifying the needs of the cancer patient

After identifying and characterizing the cachectic or precachectic cancer patients, their specific needs should be assessed. The main

factors determining the progressive onset of cancer cachexia are anorexia and reduction of food intake, reduced physical activity, and inflammation-mediated changes in protein metabolism. Also, it should be remembered that anticancer therapies per se may worsen the deterioration of nutritional status. Anorexia, reduced physical activity and inflammation are variably present in the clinical journey of a cancer patients. As an example, during the diagnostic procedures the patients may well lose body weight and muscle mass because of depression and anxiety leading to reduced food intake. During chemotherapy or surgery, the inflammatory response is often increased yielding to increased energy expenditure. Therefore, the effective treatment of cancer cachexia is based on the precise identification of which factor(s) is contributing the most to its progressive onset. To this end, measuring markers of inflammation (i.e., C-reactive protein) may help, as well as a thorough dietary interview to identify whether the patient has specific or global aversion to food. Also, it is important to assess whether the fluid intake is adequate. This information is key to develop a tailored nutrition programme.

When discussing the nutrition plan with the patient, realistic goals should be set. Patients should realize that the goal of nutrition therapy is to minimize weight loss during catabolic crisis and maximize the anabolic phases which occur during the clinical journey. The European

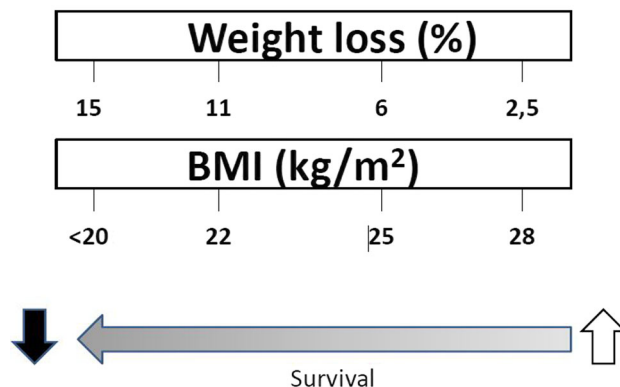


Fig. 2 Using a large database, overall survival of cancer patients has been demonstrated to be a function of body mass index (BMI) and weight loss. Patients with high BMI

and minimal weight loss have longer survival than patients with low BMI and greater weight loss. Adapted from Ref. [19]

Society for Clinical Nutrition and Metabolism (ESPEN) has recently released the guidelines for the use of nutrition therapy in cancer patients [20]. Based on the available evidence, ESPEN recommends that the cancer patient receives 25–30 kcal/kg BW/day and 1–1.5 g/kg BW/day of proteins [20].

Whether specific nutrients could boost the anabolic potential of standard nutrition support remains to be fully demonstrated. Omega-3 fatty acids, and in particular EPA and DHA, have been repeatedly tested in order to assess their efficacy in improving the nutritional status and possibly the clinical outcome of cancer patients. Unfortunately, the limited quality of the study published in the literature does not allow for a definitive answer. Thus, ESPEN suggests using supplementation with long-chain omega-3 fatty acids to stabilize or improve appetite, food intake, lean body mass and body weight [20]. Whether omega-3 fatty acids may also contribute to clinically relevant outcome measures including survival, this remains to be assessed by well designed, prospective, controlled, randomized clinical trials. However, epidemiological studies seem to suggest that the long-term supplementation with omega-3 fatty acids is associated with a reduction of cancer-specific mortality [21]. Similarly, the supplementation of specific amino acids, i.e., branched-chain amino acids, arginine, glutamine, has not been yet demonstrated to yield to significant nutritional and clinical benefits, and therefore, their use cannot be strongly recommended.

Delivery of Nutrition Therapy (Maximal Use of Supportive Therapy, MUST)

Once devised and discussed with the patient, nutrition therapy should be delivered and implemented. ESPEN guidelines recommend that the oral route should be always preferred, if feasible and tolerated by the patient. Individualized and intensive nutritional counselling has been demonstrated to increase calorie and protein intake significantly, even during catabolic conditions as multimodal anticancer treatment, which in turn translates into better clinical outcome [22]. If the patient cannot meet energy

and protein intake at the recommended level, then oral nutritional supplement should be administered. Consistent evidence demonstrates that oral nutritional supplements are cost effective [23, 24] and improve nutritional status and physical function during chemotherapy particularly if enriched with omega-3 fatty acids [25, 26].

Cancer patients may not be able to achieve nutritional targets via the oral route due to anorexia, gut intolerance, or treatment-related toxicities. At this important clinical turning point, it should be determined whether more aggressive nutritional intervention (i.e., enteral nutrition and parenteral nutrition) should be implemented. A number of factors should be considered, including the willingness, performance status, and prognosis of the patient. Considering that maintaining adequate nutritional intake in cancer patients is associated with a better clinical outcome, it appears that the concern of implementing more aggressive nutritional intervention, i.e., enteral nutrition and parenteral nutrition, should not represent an absolute contraindication. As already demonstrated during the 2014 Ebola virus outbreak in Western Africa, supportive care, including nutrition should be delivered, whatever it takes [27]. This approach is also defined as MUST—maximal use of supportive therapy, not to be confounded with the screening tool MUST, Malnutrition Universal Screening Tool. Preliminary results seem to confirm the importance of delivering nutrition therapy based on the MUST approach. De Waele et al. recently showed in a pilot study that maintaining adequate nutritional intake using all the available tools, i.e., counselling, supplements, enteral or parenteral nutrition, is feasible and safe [28]. Although the study was not powered to detect changes in clinical outcome, De Waele et al. were also able to show that cancer patients receiving nutrition therapy had significantly less day of unexpected hospitalization and longer survival [28]. More recently, Cox et al. showed that malnourished patients with oesophageal cancer and receiving combined anticancer treatment, i.e., chemotherapy + immunotherapy, have significantly shorter survival than adequately nourished patients [29]. Delivery of nutrition therapy to malnourished patients, i.e., counselling,

supplements, enteral nutrition, was associated with a longer survival. Therefore, adequately feeding cancer patients undergoing active treatment appears a key strategy to enhance the efficacy of anticancer treatments, and therefore should be implemented using all the tools available.

A specific role for nutrition therapy and possibly of specific nutrients has been recently proposed in surgical cancer patients. During the perioperative period, nutrition therapy, as well as other interventions including physical exercise, are recommended by the ESPEN guidelines to replenish nutritional stores and pre-habilitate the patient to surgery, even if this requires postponing operation [30]. This approach shares with the enhanced recovery after surgery (ERAS) programme the ability to minimize surgical stress and therefore reduce postoperative complication. However, it is now apparent that such a multidimensional pre-habilitation programme influences not only short-term postoperative complications but long-term clinical outcomes as well. Gustafsson et al. have recently shown that cancer patients receiving at least 70% of the ERAS programme in the perioperative period have a significant 5-year survival advantage [31]. Therefore, the perioperative period is a window of opportunity to influence long-term survival of cancer patients, in which nutrition and particularly omega-3 fatty acids play a role [32]. Therefore, healthcare professionals should be informed that what they are doing, or not doing, today, will have an impact tomorrow.

Monitoring

As previously mentioned, the aetiology of cancer cachexia is variable and depends on the specific clinical setting in which it develops and/or worsens. Consequently, healthcare professionals should monitor the efficacy of their nutritional therapy in achieving the planned nutritional and clinical goals, and should be ready to modify it according to the changing needs of the patients. As an example, shifting from oral nutritional supplements to enteral nutrition or parenteral nutrition if the patients is unable to take food per os, and then becomes

intolerant to enteral feeding. Also, the patient may need to add specific nutrients, including omega-3 fatty acids, when the inflammatory response increases.

Of great importance, in all the different phases of nutrition therapy across the clinical journey of cancer patients, is the inclusion of physical exercise. As previously mentioned, the goals set with physical exercise should be realistic and achievable by the patient. A combination of aerobic and resistance exercise is advisable, although no intervention nor observational trial is currently available to assess the exact type and amount of physical exercise needed to counteract cachexia and promote muscle anabolism. At this stage, cancer patients should be encouraged to increase their physical activity by at least taking daily 15–30 min walks and to perform approximately 10 lifts/day of mild weight (i.e., books, 500 mL bottles, etc.) with both arms and legs.

The monitoring of cancer patients receiving nutritional care should be based on the goals that the healthcare professionals set at baseline. Considering that weight loss is an independent negative prognostic factor in cancer patients during either active anticancer treatment and during palliative care, body weight, and possibly muscle mass, should be regularly controlled. Also, in patients with anorexia and/or dysphagia receiving nutritional care, the amount of calories and proteins taken with the diet should be monitored every 1–3 months, in order to prove the efficacy of nutritional care. In patients with established inflammatory response (i.e., C-reactive protein levels > normal values), measurement of proinflammatory mediators should be checked every 3 months. Either during active treatment and palliative phase, cancer patients' quality of life, as assessed by validated questionnaires, i.e., EORTC-QLQ-C30) should be regularly monitored.

NUTRITION IN THE ADVANCED CANCER PATIENT

Nutrition therapy plays a key role in cancer patients receiving anticancer therapy, either surgical or medical, since it preserves or

ameliorates nutritional status, which in turn contributes to allow initiation and completion of the planned therapies. Also, recent studies suggest that feeding may be beneficial per se in cancer patients [33]. However, nutrition therapy plays an important role also for those cancer patients for whom therapeutic options are not available any more.

In palliative cancer patients, the role of nutrition therapy is to ameliorate or stabilize quality of life, but it may also allow longer survival in aphagic cancer patients. However, it is acknowledged that the identification of those cancer patients who will benefit the most from nutrition therapy, particularly parenteral nutrition, in the palliative phase is not easy. In fact, it may occur that nutrition therapy is initiated in patients who die in a few days, or withdrawn in patients whose actual survival is much longer than the few weeks estimated at baseline. Consequently, practical tools to identify the patients with greater likelihood to benefit from nutrition therapy have been developed. Bozzetti et al. recently developed a nomogram to predict survival of cancer patients, based on which an informed decision on whether feeding or not feeding could be made [34]. Based on a large database of more than 500 cancer patients, Bozzetti et al. identified Glasgow Prognostic Score, Karnofsky Performance Status, tumour site and spread as determinants of survival and developed a predictive nomogram.

CONCLUSIONS

Cancer is a deadly disease when lately diagnosed and treated. Available cancer therapies significantly improved the clinical management of cancer patients, yet tumour immune evasion remains a major risk for treatment failure. Recent results show that favouring adequate nutrition intake and status enhances the efficacy of anticancer therapies. Therefore, it is now becoming an ethical imperative to identify cancer patients at nutritional risk or already cachectic and deliver the more appropriate nutrition therapy. All healthcare professionals involved in cancer patient management should then remember that what is done, or not done, today has an influence tomorrow.

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