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Original Article

Nutritional Deterioration in Cancer: The Role of Disease and Diet

P. Ravasco*, I. Monteiro-Grillo†, P. M. Vidal*, M. E. Camilo*

*Centre of Nutrition and Metabolism, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon; †Radiotherapy Department, Santa Maria University Hospital, Lisbon, Portugal

ABSTRACT:
Aims: Under-nutrition is a major source of morbidity and mortality in cancer patients. This prospective, cross-sectional study aimed to evaluate the relative contributions of cancer staging, duration and diet on patients' nutritional deterioration.
Materials and methods: We included 205 consecutive patients (133 men and 72 women) with head and neck, gastro-oesophageal, colon and rectum cancer, age 53 ± 12 (33–86) years, referred for radiotherapy (primary, adjunctive to surgery, combined with chemotherapy or with palliative intent). We registered clinical variables, nutritional status (percentage of weight loss, Patient-Generated Subjective Global Assessment and body mass index), nutritional requirements, usual diet intake (diet history) and current intake (24-h recall).
Results: In stage III and IV, we observed a significant decrease of usual and current energy and protein intake (P=0.002), which were not observed in stage I and II. Reduction in nutritional intake was influenced by disease duration (P=0.04), but when the latter was evaluated in a multivariate analysis, current dietary intake was associated only with staging (P=0.004), thus disclosing a distinct pattern of nutritional intake between stages and diagnosis. Using a general linear model, advanced staging showed the most significant association with nutritional depletion (P=0.0001). We also found significant associations for tumour location (P=0.001), disease duration (P=0.002), nutritional intake (P=0.003) and previous surgery or chemotherapy (P=0.02). Percentage weight loss showed a consistently superior performance with regard to clinical variables and ability to detect mild to extreme nutritional changes. Patient-Generated Subjective Global Assessment had a very high sensitivity and specificity, and a strong capacity for detecting patients at nutritional risk compared with body mass index.
Conclusions: Nutritional depletion is multifactorial, dependent mainly on the tumour burden of the host. Percentage weight loss is a sensitive and specific tool that can screen and identify malnutrition effectively. Its joint use with Patient-Generated Subjective Global Assessment, which establishes boundaries for nutritional therapy, will optimise the efficacy of nutritional assessment and support in cancer patients. Ravasco P. *et al.* (2003). *Clinical Oncology* **15,** 443–450

Key words: Cancer staging, diet, nutrition, nutritional assessment, nutritional status, tumour burden, wasting, weight loss

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Introduction

Cancer cachexia, a syndrome of progressive weight loss and asthenia, is the single most common cause of death in the patient with cancer [1,2]. Cancer cachexia is the end result of reduced gastrointestinal nutrient absorption [3], alteration in the diet or appetite [4], hormone-induced metabolic changes [5] and cancer-related immune activation with cytokine release [6]. Regardless of the underlying mechanisms, cancer-related weight loss is a multi-dimensional manifestation that reduces patient well-being [7], tolerance to and prognosis after antineoplastic therapy [8,9], decreases immunological responses to tumour cells [10] and resistance to infection [11], and increases susceptibility to post-operative complications [12,13], disability and overall cost of care [14].

In order to tackle nutritional deterioration, it is important to gather objective data on nutritional status and its evolution throughout the course of the disease. So far, only a few studies have addressed this area of clinical research, reporting weight loss either as the most frequent presenting symptom [4] or as a sign of advanced disease staging [15]. Different cancer types or locations may display different nutritional patterns [16,17]; however, there is some inconsistency between studies comparing nutritional status assessment and cancer or treatment-related variables. A thorough analysis of their interaction may step forward the eagerly awaited integration of appropriate nutritional therapy, as proposed by Ottery [18].

Author for correspondence: Paula Ravasco, Centro de Nutrição e Metabolismo, Faculdade de Medicina de Lisboa, Avenida Prof. Egas Moniz, 1649-028 Lisboa, Portugal. Tel: +351 217 985 187; Fax: +351 217 985 142; E-mail: p.ravasco@fm.ul.pt

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Within this framework, the major goal of this prospective study, in head and neck, gastro-oesophageal and colorectal cancer patients, was to explore the intricate construct of various disease-related and diet-related factors potentially implicated in the patient's nutritional deterioration. The extent of the disease, estimated by staging variables, was hypothesised as key to current nutritional status, which was assessed by three different methods, further compared in order to disclose their reliability.

Materials and Methods

Study Design and Patient Sample

The study was approved by the University of Lisbon Hospital Ethics Committee and was conducted in ambulatory patients with cancer of the head and neck, oesophagus, stomach, and colon and rectum. It was designed as a prospective, cross-sectional study to investigate the role of disease staging and duration on the patients' nutritional deterioration. All patients gave their informed consent to participate in the study. Between July 2000 and February 2002, all consecutive patients with cancer of the head and neck, gastro-oesophageal, and colon and rectum referred to the outpatient radiotherapy department were considered eligible. Before radiotherapy planning, the medical staff registered, for each patient, the clinical variables, the duration of the disease, the location of cancer, the presence of distant metastases, and tumour burden according to TNM staging [19], determined by local and whole-body imaging methods. The duration of the disease, always confirmed by histology, was defined as the length of time (in months) between symptomatic manifestations and study entry. The cohort included 205 adult patients (133 men and 72 women), age 53 ± 12 (range: 33–86) years, referred for radiotherapy: primary, adjunctive to surgery, combined with chemotherapy or with palliative intent. Data were recorded on individual sheets designed for statistical analysis.

Study measures

At the onset of radiotherapy, a single trained research dietician (PR) assessed nutritional status as described below.

Nutritional assessment

Height was measured in the standing position using a stadiometer and weight was determined with a Jofre® floor scale. Nutritional status was assessed by (1) calculating the percentage of weight loss compared with the patient's usual weight, classified as severe if >10% in the previous 6 months; (2) Body Mass Index (BMI), classified as malnutrition if $<20\ kg/m^2$, normal if 20–25 kg/m^2, overweight if 25–30 kg/m^2 and obese if $>30\ kg/m^2$ [20]; and (3) Ottery's Patient-Generated Subjective Global Assessment (PG-SGA) [21]. The latter is a validated nutritional assessment tool for cancer patients, which addresses (1) weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhoea, xerostomia, pain), alterations in food intake by comparing current intake with usual intake, and functional capacity; (2) components of metabolic stress (sepsis, neutropenic or tumour fever, corticosteroids); and (3) physical examination: subcutaneous fat (triceps skinfold and at the level of the lower ribs in the midmaxillary line), muscle bulk and tone in the temporal, deltoids and quadriceps areas, ankle/sacral oedema, or ascites. Nutritional status is then categorised as normal, moderate or severe malnutrition.

Nutritional requirements and dietary assessment

Basal energy requirements were estimated by the World Health Organization formula for individuals aged <60 years [22] or by the Owen *et al*. formulae for individuals aged >60 years [23,24] because of their higher ability to predict resting metabolic rate [25]. Patient daily estimated energy requirements were calculated by multiplying basal requirements by a 1.2 activity factor [26]; daily protein requirements were estimated by comparing reference values standardised for age and sex, which ranged between 0.8 and 1.0 g/kg per day [27].

Nutritional intake before diagnosis was derived from dietary history [28] and current intake was assessed by a 24-h recall food questionnaire [29]. The nutrient contents of foodstuffs and meals were analysed by the software DIETPLAN version 5 for Windows (Forestfield software Ltd 2002, Horsham, U.K.).

In order to evaluate differences between cancer stages, patients were clinically and physiologically grouped into two classes: stage I and II (local disease) and stage III and IV (advanced local disease with or without lymph-node invasion) [30].

Statistical Analysis

Statistical analysis was conducted using SPSS 10.0 (SPSS Inc, Chicago, U.S.A.) and EPI–Info 2000 (CDC, Atlanta, U.S.A.). Patients' disease staging and duration, nutritional status and intake were expressed as number and percentage, median and standard deviation values. Between-group comparisons were performed by one-way analysis of variance (ANOVA) for continuous variables, with Bonferroni or Dunn adjustment because of multiple comparisons; categorical variables were compared with Chi-square. Correlations were assessed by non-parametric (Spearman) test. A multivariate general linear model was used to identify the variables that were significantly related to nutritional deterioration. Sensitivity and specificity of the nutritional assessment methods were compared with the Youden index,

Table 1 – Patient diagnosis and disease staging

Location	n*	Stage (n)
Head and neck		
Base of the tongue	7	IV (7)
Salivary gland	5	III (5)
Tonsil	5	II (5)
Nasopharynx	8	III (8)
Oropharynx	15	II (5); IV (10)
Larynx	23	I (5); III (3); IV (15)
Gastrointestinal tract		
Gastro-oesophageal	28	I (1); II (2); III (14); IV (11)
Colorectal	14	II (17); III (72); IV (25)

*n=number of patients; none had distant metastases.

Table 2 – Median reduction in energy and protein intake

Diagnosis	Energy*		Protein†	
	Stage		Stage	
	I/II	III/IV	I/II	III/IV
Head and neck	−40	−908	−0.5	−92
Gastro-oesophageal	−37	−812	−1	−81
Colorectal	−20	−648	−0	−67

*Expressed as kcalories/day. †Expressed as grams/day.

which ranks diagnostic tests from −1 (the worst) to +1 (the best).

Results

Individual diagnoses and stages are shown in Table 1; there were 35 staging I or II and 170 stage III or IV patients. Patients' duration of disease was further grouped according to cancer stage (Fig. 1). Overall, patients with advanced disease staging presented with a longer duration of disease (P=0.06). Both usual and current intake was compared with estimated energy requirements, taking into account disease location and staging (Fig. 2). In stage I and II patients, the median usual and current energy intake were not significantly different, unlike stage III and IV patients in whom there was a significant decrease in their usual intake (P=0.002). Furthermore, current energy intake was lower in stage III and IV patients than in stage I and II patients (P=0.001).

Both usual and current protein intake were compared with the median reference value, taking into account disease location and stage (Fig. 3). Usual and current protein intake were not significantly different in stage I and II patients, whereas stage III and IV patients presented a significant decrease in their usual intake (P=0.0001). Overall, current protein intake was lower in stage III and IV than in stage I and II patients (P=0.001). Current nutritional intake was also affected by the duration of the disease, which was negatively correlated with energy (r=−0.31; P=0.04) and protein intake (r=−0.39; P=0.03). Simultaneous analysis of the influence of disease stage and duration on nutritional intake revealed only stage as a significant factor (P=0.004). Table 2 shows that median energy and protein intake decreases for each diagnosis and disease stage; a decrease in energy intake tended to be proportional to a decrease in protein intake (P=0.07), disclosing a global nutritional intake reduction. In stage III and IV patients, protein intake was significantly lower than the reference values (P=0.001); but the decrease in energy intake, although significantly lower than the usual intake (P=0.02), still remained within the estimated requirements. No reduction in energy and protein intake was found in stage I and II patients; furthermore, their intake was significantly higher than the reference values ($P \leq 0.005$). Stage III and IV head and neck and gastro-oesophageal cancer patients showed the worst decreases in energy and protein intake (P=0.03).

Nutritional Status

Weight loss

For each diagnosis, the patients' median percentage of weight loss is shown in Fig. 4. Overall, weight loss was significantly higher in stage III and IV than in stage I and II patients (P=0.001). Among the latter, only two out of 35 (6%) had lost more than 10% of their usual weight, whereas all stage III and IV patients reported weight loss greater than 10%. There was a trend for patients with >10% weight loss to have a longer duration of the disease (P=0.08). Simultaneous analysis of the influence of disease stage and duration on weight loss revealed only stage as a significant factor (P=0.002).

Body mass index

For each diagnosis, the median body mass index (BMI) for each individual is shown in Fig. 5. Overall, BMI was significantly lower in stage III and IV than in stage I and II patients (P=0.04). Among the latter, only two out of 35 (6%) had a BMI below 20 kg/m^2, which was observed in 45 out of 170 (26%) stage III and IV patients (P=0.05); furthermore, 30 (26%) patients with colon or rectal cancer were still obese [20]. We found no association between BMI and duration of the disease, and further multivariate analysis of the latter with disease stage revealed a significant association between BMI and staging (P=0.05).

Patient-generated Subjective Global Assessment

Nutritional status according to disease location is shown in Fig. 6. Severe malnutrition was not observed in stage I and II, and only four patients (two head and neck, two gastro-oesophageal) presented with moderate malnutrition. Conversely, malnutrition (moderate and severe) was prevalent among stage III and IV patients (79%) compared with stage I and II patients (3%) (P=0.003), and was not significantly associated with the duration of the disease (P=0.09). Simultaneous analysis

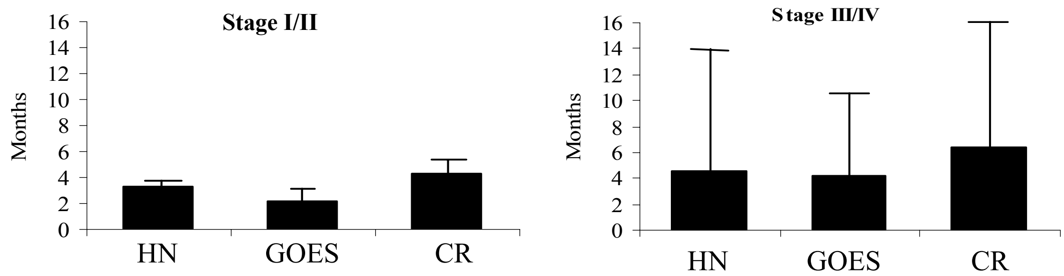

Fig. 1 – Duration of disease, shown as median and standard deviation, for each diagnosis grouped by tumour stage. The duration of disease was longer in stage III and IV patients compared with stage I and II patients (P=0.002). CR, colorectal; HN, head and neck; GOES, gastro-oesophageal.

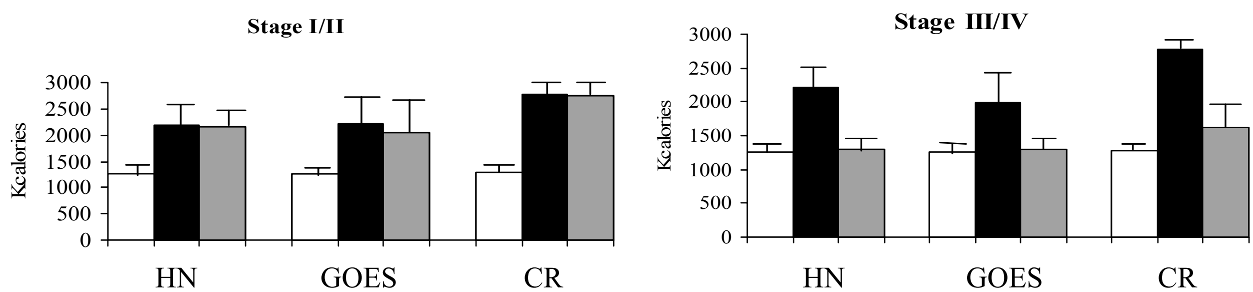

Fig. 2 – Patients' median (and range) estimated requirements □, usual energy intake ■, current energy intake ▨; two HN, two GOES and 15 CR stage I/II patients were in marked positive energy balance. CR, colorectal; HN, head and neck; GOES, gastro-oesophageal.

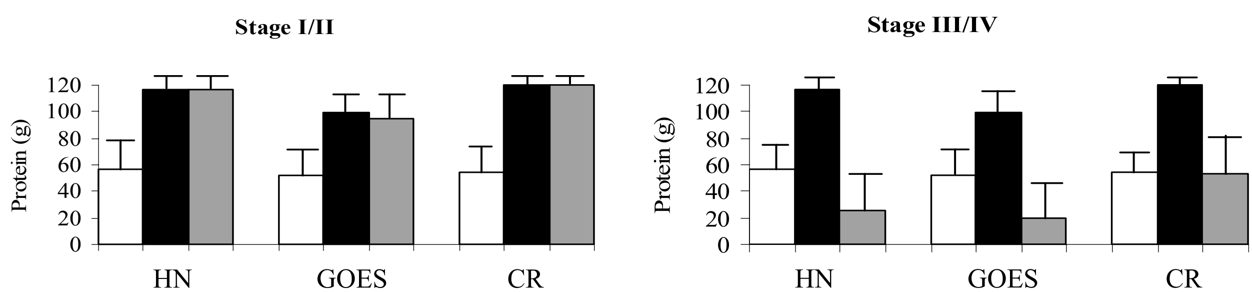

Fig. 3 – Daily total protein intake in grams: patients' median (and range) reference value □, usual intake ■ and current intake ▨. CR, colorectal; HN, head and neck; GOES, gastro-oesophageal.

of the disease stage and duration on nutritional status revealed only staging as a significant factor (P=0.01). Categorisation of numerical variables followed by concordance analysis disclosed a significant agreement between all nutritional assessment methods (k=0.34; P=0.01); percentage of agreement assigned to BMI was the lowest (k=0.12; P=0.06).

Current energy intake was not correlated with BMI (r=−0.17; P=0.24), but was significantly correlated with percentage weight loss (Fig. 7) and was also associated with nutritional status as categorised by PG-SGA (Fig. 8). Patients with adequate nutritional status reported an energy intake ≥1500 kcal, corresponding to ±125% of the estimated energy requirements; on the other hand, in severely malnourished patients, energy intake was ≤955 kcal, which corresponds to about ±80% of the estimated energy requirements.

We further performed a sensitivity and specificity analysis (ROC curve interpreted by comparing areas under the curves and Youden value) for each nutritional status assessment method. Because this is a comparative analysis of one or more methods against a standard, our results flagged percentage weight loss, which showed a consistently superior statistical performance for

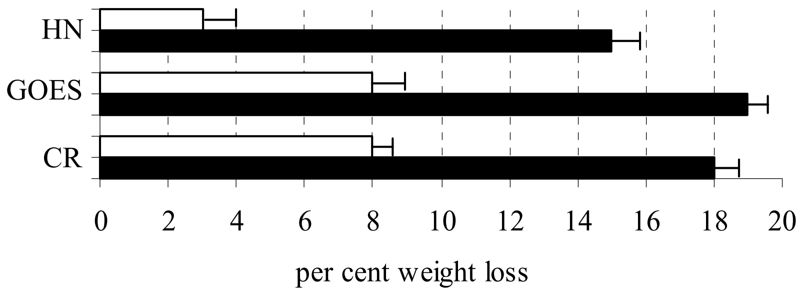

Fig. 4 – Median (and range) percentage of weight loss over the previous 6 months in stage I and II □ and stage III and IV patients ■, according to disease location; CE, colorectal; HN, head and neck; GOES, gastro-oesophageal.

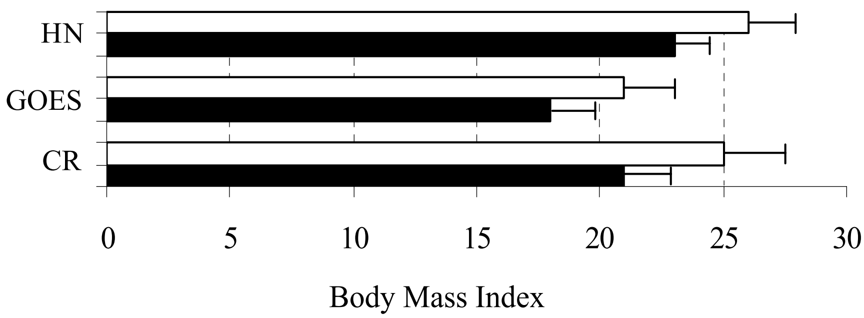

Fig. 5 – Median (and range) Body Mass Index for stage I and II □ and stage III and IV patients ■, according to disease location; CR, colorectal; HN, head and neck; GOES, gastro-oesophageal.

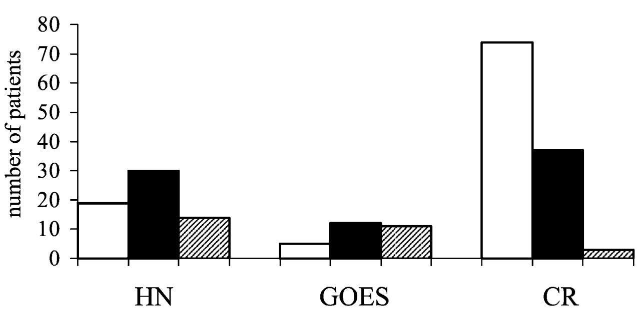

Fig. 6 – Nutritional status categories: normal nutritional status □, moderate malnutrition ■ and severe malnutrition ▨, according to disease location. CR, colorectal; HN, head and neck; GOES: gastro-oesophageal.

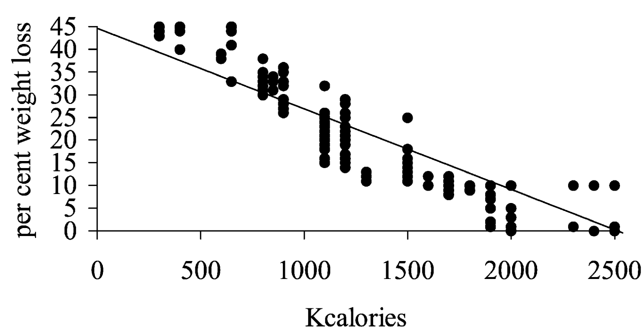

Fig. 7 – Correlation between per cent weight loss and energy intake (r= − 0.67; P=0.002).

clinical variables, as well as the ability to detect mild to extreme nutritional changes. Figure 9 illustrates the sensitivity and specificity relation of per cent weight loss against PG-SGA and per cent weight loss against BMI.

As for PG-SGA, the Youden value of 0.85 (P=0.00001; sensitivity 0.80; specificity 0.89) indicates a high performance compared with the standard, and a strong capacity to detect patients at high nutritional risk effectively; for the BMI, the Youden value of 0.47 (P=0.02; sensitivity 0.27; specificity; 0.27) indicates a poor performance compared with the standard, and a weak capacity to detect patients effectively at high nutritional risk. The influence of energy intake on nutritional depletion was further evaluated by non-parametric correlation stratifying for cancer staging (Fig. 10and Fig. 11). Cancer staging clearly disclosed a distinct pattern of nutritional deterioration between patient groups, thus highlighting the major contribution of advanced cancer staging. By adding cancer location to this analysis, we found a further difference between diagnoses (Table 3). Advanced cancer stage was the common denominator for the patients' nutritional depletion, clearly potentiated by the diagnosis. Patients

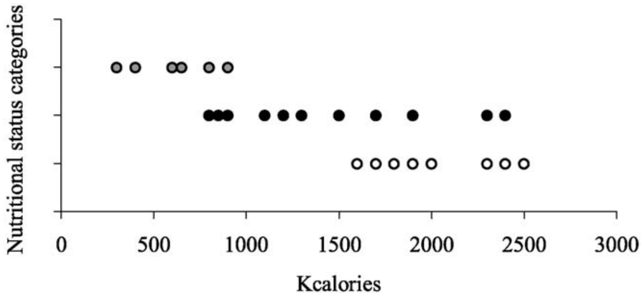

Fig. 8 – Energy intake by PG-SGA categories: normal ○, moderate malnutrition ● and severe malnutrition ◌; a negative association was observed (P=0.003).

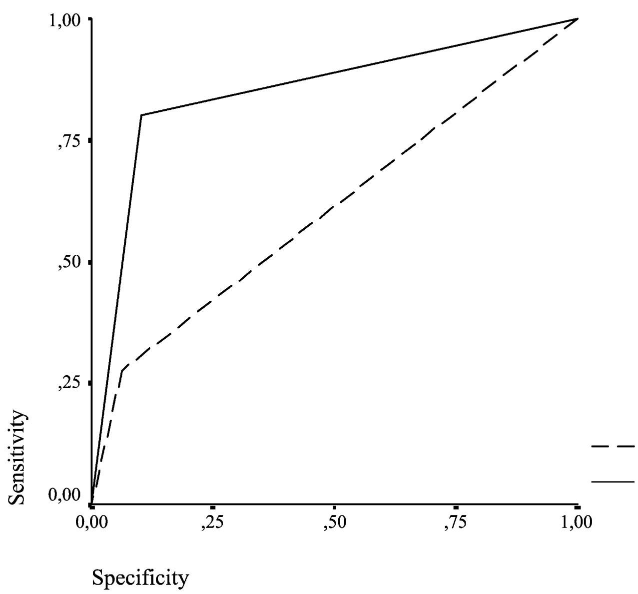

Fig. 9 – ROC curves for per cent weight loss compared with PG-SGA —and per cent weight loss compared with BMI – – –.

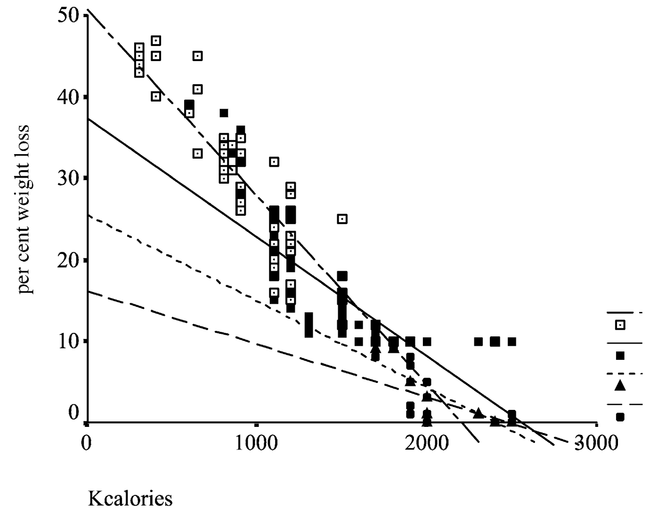

Fig. 10 – Correlations between per cent weight loss and energy intake by cancer staging. Stage I ●: r=−0.14; P=0.09; II ▲: r=−0.15; P=0.09; III ■: r=−0.52; P=0.002; IV □: r=−0.72; P=0.001.

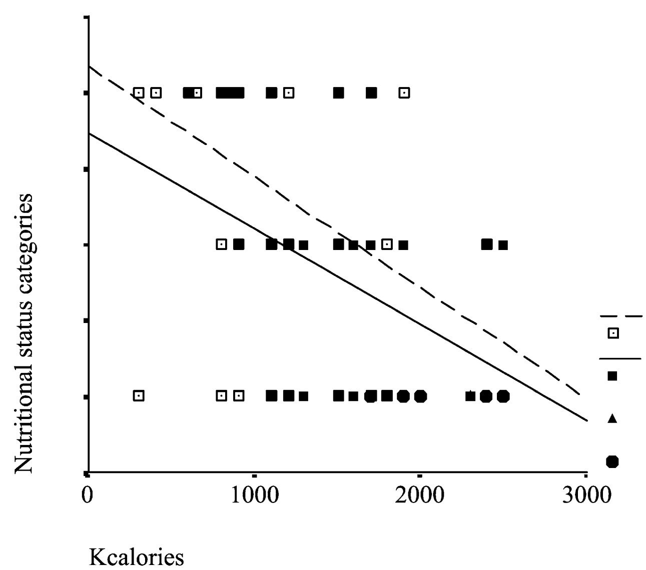

Fig. 11 – Associations between PG-SGA nutritional status categories and energy intake by cancer staging. Stage I ●: P=0.13; IIs ▲: P=0.10; III ■: P=0.004; IV □: P=0.003.

with head and neck and gastro-oesophageal cancers showed a highly significant nutritional deterioration.

By using a general linear model, with nutritional status as the dependent variable, the patients' nutritional deterioration was related to the following variables: cancer stage (P=0.0001); location (P=0.001); duration of the disease (P=0.002); energy intake (P=0.003); protein intake (P=0.003); surgery (P=0.01); and chemotherapy (P=0.02).

Discussion

Cancer-related nutritional deterioration is traditionally attributed to anorexia, continued loss of lean body mass, altered carbohydrate and lipid metabolism [3–6]; the latter may ensue from increased metabolic rates [31], and the production and release of proinflammatory cytokines [6]. The progressive caloric deficit may be exacerbated by anorexia, dysphagia, vomiting and malabsorption, associated with cancer itself, its treatment, or both [4,32,33]. The relative contribution of the above conditions to nutritional depletion is thought to differ according to cancer type or site [34,35], and has long been suspected to be proportional to cancer extent, a concept mostly based on clinical expertise and observational data [15]. An accurate long-standing energy and

Table 3 – Non-parametric correlation analysis between energy intake and nutritional depletion stratified by cancer stage and corrected by diagnosis

Diagnosis	Stage			
	I	II	III	IV
Head and neck	r = −0.42; *P*=0.005	r = −0.48; *P*=0.004	r = −0.78; *P*=0.001	r = −0.84; *P*=0.001
Gastro-oesophageal	r = −0.38; *P*=0.009	r = −0.43; *P*=0.005	r = −0.89; *P*=0.0001	r = −0.91; *P*=0.0001
Colorectal	r = −0.10; *P*=0.12	r = −0.14; *P*=0.09	r = −0.45; *P*=0.005	r = −0.53; *P*=0.002

substrate deficit has not been systematically investigated nor adjusted for the patients' disease staging.

This prospective analysis of 205 patients with cancer of the head and neck and gastrointestinal tract shows for the first time that marked deficiencies in nutritional intake are conditioned by the extent of the disease. For all stage III and IV diagnoses, there was not only a significant decrease of the usual energy and protein intakes (*P*=0.002), but current intakes were also significantly lower compared with stage I and II patients (*P*=0.001). Although the global reduction in nutritional intake was negatively correlated with the duration of the disease, which was longer in advanced stages (*P*=0.04), multivariate analysis showed that only cancer stage was significantly associated with dietary changes.

In order to further clarify the relative roles of a reduction in nutritional intake and cancer staging, we investigated the univariate associations between cancer-related variables, diet and nutritional depletion. Advanced staging was indeed the common denominator for the patients' nutritional deterioration, by contributing to a worse nutritional status as well as disclosing a distinct pattern of nutritional intake between cancer stages. It should be stressed that cancer location further strengthened the association between advanced staging and depletion, and was simultaneously able to identify major differences between diagnoses; in fact, patients with head and neck and gastro-oesophageal cancer were already at early stages severely depleted and showed significant dietary reductions.

Severe nutritional deterioration has been reported in patients with cancer of the stomach, pancreas, lung and colon [8]. Although nutritional assessment is key to defining nutritional status [36,37], there is still no consensus on which is the most appropriate in a specific clinical setting. In this study we compared the widely used clinically significant weight loss, Ottery's PG-SGA [21] and body mass index [38]. In this study, BMI showed low sensitivity and specificity results, which indicate a poor performance and a limited capacity to detect patients at high nutritional risk effectively.

It has become almost a dogma that unintentional weight loss greater than 10% of pre-illness weight, or in the previous 3–6 months, represents a high risk of malnutrition [39–41]. Our analyses confirm that weight loss was certainly the best indicator of nutritional deterioration and should be used to identify patients at nutritional risk or with recent onset undernutrition [39–41]. PG-SGA, a combination of weight changes, indicators of functional status, clinical aspects of nutritional intake and its impediments determines nutritional risk and depletion [21]. Our results revealed high sensitivity and specificity for PG-SGA, indicating a high performance and a strong capacity to detect patients at high nutritional risk and malnutrition effectively. In cancer patients, the PG-SGA should be used in conjunction with significant weight loss, aiming to establish a planned overall cancer management and set up boundaries to direct nutritional therapy [18]. Indeed, the combination of weight loss and PG-SGA would allow the detection of 18% more 'true positive cases' (moderate/severe malnourished patients), thus increasing its sensitivity and predictive positive value; to detect severe malnutrition, the added value from using PG-SGA and weight loss as a screening tool would be 9%. Hence, this integration should be implemented in clinical practice, group protocols and nutritional intervention clinical trials, in order to optimise quality of patient care.

It is noteworthy that malnutrition was prevalent in stage III and IV compared with stage I and II patients, whether defined by a BMI below 20 kg/m^2 (*P*=0.05), >10% weight loss in the previous 6 months (*P*=0.001) or according to PG-SGA (*P*=0.003). Although some head and neck cancer patients were already malnourished at early stages, weight loss was never the presenting symptom.

Regardless of the nutritional assessment method used in this study, we have shown that nutritional depletion is a multifactorial outcome determined by cancer and diet-related factors, all of which were simultaneously evaluated in a general linear model. Advanced cancer stage showed by far the most significant association with worse nutritional status; cancer location, duration of the disease, protein/energy intake and previous surgery, chemotherapy, or both, were also significantly associated.

Conclusion

In addition to the identification of valid nutrition assessment tools, this preliminary study provides new clinical evidence of the complex interactions between cancer treatment-related variables, diet changes, or both, all of which exert a combined effect on the patients' nutritional deterioration. The pattern and progression of nutritional deterioration is mostly determined by cancer diagnosis, and the tumour burden for the host seems to be of major importance. Our results are consistent with the hypothesised relation between wasting and progressive disease, which is likely to exacerbate physiological derangement.

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