CANCER:
METABOLIC DYSFUNCTION, NUTRITION AND QUALITY OF LIFE

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CONTENTS

ABBREVIATIONS

QoL	Quality of Life
RT	Radiotherapy
QV	Qualidade de Vida
NS	not significant
HR	high-risk
LR	low-risk
EORTC QLQ C-30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
HN	head and neck
GI	gastrointestinal
SGA	Subjective Global Assessment
EER	Estimated Energy Requirements
OES	oesophageal
STO	stomach
CR	colorectal
SRHS	self-rated health status
ESO	esophageal
BMI	Body Mass Index
PG-SGA	Patient-Generated Subjective Global Assessment
G1	group 1
G2	group 2
G3	group 3
CRC	colorectal cancer
HNC	head and neck cancer
kcal/d	kcalories/day
g/d	grams/day
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IL-10	Interleukin-10
TNF-α	Tumour Necrosis Factor- α
IFN-γ	Interferon-γ
VEGF	Vascular Endothelial Growth Factor

SUMMARY

Cancer is a major cause of morbidity and mortality worldwide. Cancer is the second most frequent cause of death and is becoming the leading cause of death in an ageing population, as most cancers occur in older adults; of note, cancer-related malnutrition is the immediate cause of death of 20% of the patients with cancer. Notwithstanding that different cancer types or locations may display different nutritional patterns, there is some inconsistency between studies in what concerns nutritional status assessment and cancer/treatment-related variables. A thorough analysis of their interaction is long due, in order to step forward the eagerly awaited evidence to foster the integration of appropriate nutritional therapy. Moreover, although 8 to 84% of cancer patients may present some degree of nutritional deterioration, which has been associated with functional impairment, the interaction between nutritional status and intake, symptoms and other disease/treatment-related factors, is a complex combination which may dictate patients' Quality of Life (QoL). Nevertheless, the multitude of interactions between cancer location and stage, treatments, nutritional status and intervention, morbidity and QoL has never been thoroughly explored. The evidence for these interactions will be demonstrated in this thesis, which results from the collision of data from several prospective studies conducted in cancer patients.

The present Thesis is structured into five sections.

1. Section 1 comprises **Chapter 1** and **Chapter 2**.

Chapter 1 describes the aims and the outline of the thesis. Chapter 2 consists of a general introduction reviewing the main concepts relevant to the studies' design and analyses undertaken in the work ascribed to this thesis; specifically the multifactorial nature of cancer-related malnutrition, its impacts on the patients' disease progress as well as the interactions between nutrition, morbidity and Quality of Life.

2. In **Section 2**, a pilot study conducted in a heterogeneous cancer patient population referred for radiotherapy is presented, which includes a critical analysis of different methods to measure QoL and the effect of nutritional intervention on nutritional parameters and QoL:

- **Chapter 3**. Patients submitted to radiotherapy (RT), particularly of the head and neck or the gastrointestinal tract, are at higher risk of malnutrition, aggravated by the therapy induced toxicity that may further compromise nutrition and functional status. Since patients' QoL reflects functional status, psychosocial well being, health perceptions and disease/treatment-related symptoms, the patients' nutritional status, nutritional intake and symptoms are thus likely to assume a significant role in their QoL. We investigated: 1) the patients' nutritional status, nutrient intake and QoL at the onset and at the end of RT, 2) whether individualised nutritional counselling, despite RT-induced symptoms, was able to enhance nutrient intake over time and whether the latter influenced the patient's QoL and 3) which symptoms may have anticipated poorer QoL and/or reduced nutritional intake. This study showed that in patients prone to develop nutritional

problems and to report the worst QoL during RT, an individualised nutritional counselling did improve nutritional intake which was identified as central to a better QoL. Additionally, from the two QoL instruments tested, the non-specific EUROQOL should be used routinely because its completion is less time consuming; the more comprehensive cancer-specific EORTC QLQ C-30 instrument covers more items and scales, identifies more domains and specific complaints, and although time consuming provides the accuracy required for research. Both instruments were able to assess patients' QoL and both revealed the relevance of nutrition care.

3. Section 3.

- **Chapter 4**. Based on this background, gathering validated objective data on nutritional status and its evolution throughout the disease course is of prime concern. Thus, we conducted a prospective study in head and neck, oesophageal, stomach and colorectal cancer patients, aiming to explore the intricate construct of various disease-related and diet-related factors potentially implicated in the patients' nutritional deterioration. The disease extent was hypothesized as key to current nutritional status, which was assessed by three different methods, further compared in order to disclose their reliability. Regardless of the nutritional assessment method used, nutritional depletion was 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 locations, duration of the disease, protein and energy intake, and previous surgery or chemotherapy, were also significantly associated. Besides the identification of valid nutrition assessment tools, this study provided novel clinical evidence of the complex interactions between cancer and/or treatment-related variables and diet modifications, all of which exerted a combined effect on the patients' nutritional deterioration. Cancer location was the dominant factor influencing the pattern and/or progression of nutritional deterioration; though the tumour burden for the host was of major importance. Our results were consistent with the hypothesized relations between progressive disease and wasting, which purportedly exacerbate every organ/systemic physiological derangement.
- **Chapter 5**. It then became necessary to explore the potential interaction(s) between various disease-related and diet-related factors likely to be implicated in the patients' QoL. A prospective cross-sectional study was thus conducted in head and neck, oesophageal, stomach and colorectal cancer patients; the specific aims were to evaluate patients' nutritional status, nutrient intake and QoL, taking into account the disease stage and previous therapeutic interventions, to determine the potential inter-relations, and to quantify the relative impact of cancer/treatments and/or nutrition-related factors on patients' QoL. This study provided objective evidence that cancer, diet deficits, nutritional deterioration and therapeutic interventions are determinants of

the patients' QoL, but with distinct relative weights. Whilst chemotherapy and surgery were perceived by the patients as of minor relevance, nutritional deficits and/or deterioration were intrinsic to the cancer location and stage, to reduced energy/protein intake and to weight loss, which were independent determinants of QoL. These results concur with seminal landmark data which revealed that semi-starvation impairs functional and psychological abilities, and in addition corroborated our previous study demonstrating the relationship between progressive disease and wasting.

4. Section 4. Based on the knowledge that in the above mentioned cancer patients, the location and stage of the disease as well as nutritional aspects are major determinants of patients' QoL, it remained to be proven whether nutritional intervention might influence outcomes; therefore two prospective randomised controlled trials of nutritional therapy were conducted: 1) in colorectal cancer or 2) head and neck cancer outpatients, in order to address the potential role of adjuvant oral nutritional support on patients' outcomes.

- **Chapter 6**. The study herewith summarised was designed to test the hypothesis of a causal pathway between nutritional therapy and functional/clinical outcomes. A prospective randomised controlled trial, in colorectal cancer patients referred for radiotherapy, was designed to investigate whether, and to what degree, total oral intake was affected by dietary counselling or *ad libitum* intake supplemented with commercial supplements, both provided during RT. Furthermore the impact of nutritional intake on predefined outcomes, nutritional status and QoL, during treatment and 3 months later was examined. Despite the expected and experienced detrimental effects of RT, concurrent nutrition care integrated in the overall patient management allowed proper assessment of nutritional status and nutritional requirements, dietary counselling, education and monitoring of diet compliance and timely management of symptoms. Nutrition intervention was central to the improvement of colorectal cancer patients' nutritional as well as non-nutritional outcomes: nutritional intake and status, QoL and lessened morbidity even in the medium term. Adding oral nutritional supplements to the diet did not appear to be as effective as dietary counselling. The control group showed a progressive deterioration in all items.
- **Chapter 7**. Within a similar framework, with the same goals and an identical study design as in Chapter 6, the results of a prospective randomised controlled trial of nutritional therapy in head and neck cancer patients, referred for radiotherapy, are presented. The results were similar to those registered in colorectal cancer patients: nutritional counselling was indeed central to the improvement of a diversity of patient outcomes in such patients: nutritional intake, nutritional status, QoL and lessened morbidity, even in the medium term, after treatment completion. Adding oral nutritional supplements to the diet did not appear to be as effective as dietary counselling. Indeed, concurrent individualized dietary counselling based on regular foods, was the most effective means of improving patients' nutritional intake, status and QoL during RT

which are sustained 3 months after its completion, thereby lessening RT induced morbidity. The control group showed a progressive deterioration in all items.

5. Finally, **Section 5** comprises **Chapter 8** in which results of the studies ascribed to this thesis are discussed and some guidelines for potential future research are also suggested.

SUMÁRIO

O cancro é causa *major* de morte e morbilidade a nível mundial. É a segunda causa de morte mais frequente, e a mais importante em populações cada vez mais idosas, uma vez que a maioria dos tumores são diagnosticados em indivíduos mais velhos; de notar que a malnutrição associada ao cancro é causa de morte em 20% dos doentes. Apesar de cancros de diferentes tipos e localizações anatómicas determinarem padrões nutricionais diferentes, existe enorme discrepância entre estudos quanto à avaliação do estado nutricional e variáveis associadas à doença oncológica e/ou decorrente do(s) tratamento(s). É de há muito necessária uma análise aprofundada das potenciais interacções entre estas variáveis, com o objectivo de gerar evidência científica que justifique a integração de adequada terapêutica nutricional nos cuidados prestados ao doente. Adicionalmente, embora a prevalência da malnutrição em doentes oncológicos seja de 8 a 84%, e estando associada a limitações da capacidade funcional, a interacção entre estado e ingestão nutricionais, sintomas e outros factores associados à doença/tratamento(s) é uma combinação complexa que pode determinar a Qualidade de Vida (QV) destes doentes. No entanto, a multiplicidade de interacções entre o tumor, sua localização e estadio, tratamentos, estado e intervenção nutricionais, morbilidade e QV nunca foi explorada de forma sistemática. A evidência que consubstancia estas interacções será demonstrada na presente tese, que resulta da compilação de resultados obtidos em diversos estudos prospectivos realizados com doentes oncológicos.

A presente Tese está estruturada em cinco secções.

1. A **Secção 1** contém o **Capítulo 1** e o **Capítulo 2**.

O Capítulo 1 inclui a descrição dos objectivos e o esquema do conteúdo temático desta tese. O Capítulo 2 consiste numa introdução geral que engloba uma revisão dos principais conceitos relevantes para o desenho e análises realizados nos estudos que dão corpo a esta tese; em concreto, a natureza multifactorial da malnutrição associada ao cancro, o seu impacto da progressão da doença, bem como as interacções entre nutrição, morbilidade e Qualidade de Vida.

2. A **Secção 2** contém o **Capítulo 1** no qual é apresentado um estudo piloto realizado numa população heterogénea de doentes oncológicos referenciados para radioterapia; nesse estudo é realizada uma análise crítica de diferentes métodos de avaliação da QV e o efeito da intervenção nutricional em parâmetros nutricionais e de QV:

- **Capítulo 3**. Os doentes submetidos a radioterapia (RT), em particular a cancro da cabeça e pescoço ou tracto gastrintestinal, apresentam maior risco de vir a desenvolver malnutrição agravada pela toxicidade decorrente do tratamento, que pode ainda influenciar a sua alimentação e estado funcional. Porque a QV dos doentes reflecte vários aspectos que englobam: estado funcional, bem-estar psicológico, percepções relativas à sua saúde e a sintomas decorrentes da doença/tratamento(s), também o estado e ingestão nutricionais podem ter um papel significativo na QV de cada doente.

Neste estudo foram avaliados: 1) o estado e ingestão nutricionais e QV dos doentes no início e no fim da RT, 2) se o aconselhamento nutricional individualizado, apesar da sintomatologia decorrente da RT, seria capaz de melhorar a ingestão, e se esta melhoria viria a ter algum reflexo na QV dos doentes, e 3) quais os sintomas que pudessem antecipar uma pior QV e/ou redução da ingestão nutricional. Este estudo mostrou que, em doentes com maior probabilidade de vir a desenvolver problemas nutricionais e pior QV durante a RT, o aconselhamento nutricional individualizado melhorou a ingestão nutricional, identificada como fulcral para uma melhor QV. Para além disso, verificámos que dos dois instrumentos de QV avaliados, o instrumento inespecífico EUROQOL pode ser utilizado na rotina, uma vez que o seu preenchimento é menos moroso; porém, o instrumento mais abrangente e específico para doentes oncológicos EORTC QLQ C-30, engloba mais itens e escalas, identifica mais domínios e sintomas específicos e embora seja mais moroso, tem a precisão e rigor exigidos para uso em investigação. Ambos os instrumentos avaliaram eficazmente a QV dos doentes e ambos revelaram a relevância da terapêutica nutricional.

3. Secção 3.

- **Capítulo 4**. Com base nos resultados antes obtidos, a recolha e análise de dados objectivos e válidos sobre o estado nutricional e sua evolução no decorrer da doença oncológica passou a ser um objectivo necessário. Assim, realizámos um estudo prospectivo em doentes com cancro da cabeça e pescoço, esófago, estômago e cólon/recto com o objectivo de explorar a complexidade decorrente de vários factores associados à doença e/ou à nutrição, potencialmente implicados na deterioração nutricional dos doentes. O estadio da doença foi a hipótese levantada como tendo potencialmente maior influência no estado nutricional; este foi avaliado por três métodos diferentes, posteriormente comparados de forma a analisar a sua validade. Independentemente do método de avaliação nutricional utilizado, verificámos que a deterioração nutricional, "*outcome"* de natureza multifactorial, é determinada por factores associados ao tumor e a aspectos relacionados com a nutrição, quando todos os factores foram avaliados em simultâneo por método linear generalizado. O estadio avançado do tumor revelou claramente ter a associação mais significativa com um pior estado nutricional; a localização anatómica do tumor, a duração da doença, a ingestão calórica e proteica, e a cirurgia ou quimioterapia prévias, também estavam significativamente associadas. Para além da identificação de ferramentas de avaliação nutricional validadas, este estudo contém evidência clínica pioneira e reveladora das complexas interacções entre numerosas variáveis, não apenas associadas ao tumor e/ou tratamentos mas também a modificações na ingestão nutricional; todas, embora com pesos diferentes, exercem um efeito combinado na deterioração nutricional dos doentes. A localização do tumor foi o factor dominante a influenciar o padrão e/ou progressão da deterioração nutricional, mas o estadio avançado do tumor teve uma

importância *major*. Os nossos resultados foram consistentes com as relações anteriormente suspeitadas entre progressão da doença e deterioração nutricional, esta ultima com o potencial de agravar disfunções orgânicas/sistémicas e fisiológicas.

- **Capítulo 5**. Tornou-se então necessário investigar potenciais interacções entre vários factores, relacionados com a doença e com a nutrição potencialmente associados com a QV dos doentes. Foi assim desenvolvido um estudo prospectivo transversal em doentes com cancro da cabeça e pescoço, esófago, estômago e cólon/recto. Os seus objectivos específicos consistiram em avaliar o estado e ingestão nutricionais e QV dos doentes, tendo em consideração o estadio da doença e intervenções terapêuticas prévias, de molde a determinar as potenciais inter-relações e quantificar o impacto relativo para a QV dos doentes, atribuível ao tumor/tratamentos e/ou factores associados à nutrição. Este estudo evidencia que o cancro, défices de ingestão, deterioração do estado nutricional e intervenções terapêuticas, são determinantes da QV dos doentes, apesar de terem pesos relativos distintos. Enquanto os doentes atribuiam uma importância *minor* à quimioterapia e cirurgia, os défices nutricionais e a deterioração do estado nutricional eram mais valorizados e intrinsecamente relacionados com a localização e estadio do tumor, com a reduzida ingestão calórico-proteica e com a perda ponderal, factores determinantes e independentes da QV. Estes resultados, concordantes com anterior demonstração experimental irrefutável de que o semi-jejum prolongado compromete as capacidades funcional e psicológica, corroboram ainda o nosso estudo anterior ao demonstrarem a relação entre doença avançada e depleção nutricional.

4. Secção 4. Tendo como base o conhecimento de que nos grupos de doentes oncológicos supracitados, a localização e estadio da doença bem como aspectos nutricionais são determinantes *major* da sua QV, permanecia a hipótese a testar de que forma a intervenção nutricional poderia influenciar diversos "*outcomes"*. Foram assim realizados dois ensaios clínicos prospectivos randomizados e controlados com terapêutica nutricional, 1) em doentes com cancro colorectal e 2) em doentes com cancro da cabeça e pescoço, de forma a estudar o potencial papel desempenhado pelo suporte nutricional oral adjuvante em diversos "*outcomes"*.

- **Capítulo 6**. O estudo aqui resumido foi desenhado para testar a hipótese da existência de uma relação causal entre terapêutica nutricional e "*outcomes"* funcionais/clínicos. Este ensaio clínico prospectivo randomizado controlado de terapêutica nutricional, em doentes com cancro colorectal referenciados para RT, foi desenhado para investigar se, e de que forma, a ingestão oral total era influenciada por aconselhamento dietético individualizado ou por ingestão *ad libitum* suplementada com suplementos comerciais, ambos administrados apenas durante a RT. Foi também examinado o impacto da ingestão nutricional em "*outcomes"* pré-definidos, estado nutricional e QV, durante o tratamento e 3 meses após o seu *terminus*. Apesar dos esperados, e verificados, efeitos deletérios da RT, a intervenção nutricional integrada na abordagem terapêutica

global permitiu não só a avaliação do estado nutricional e necessidades dietéticas, mas também o aconselhamento e educação nutricionais, a monitorização do cumprimento das recomendações nutricionais, bem como a adequação atempada da nutrição conforme a sintomatologia. A terapêutica nutricional foi essencial para a melhoria de "*outcomes"* nutricionais e não-nutricionais em doentes com cancro colorectal, a saber: estado e ingestão nutricionais, QV e redução da morbilidade mesmo a médio prazo. A adição de suplementos orais à dieta não foi tão eficaz como o aconselhamento nutricional. Todos os itens sob avaliação pioraram significativamente no grupo controlo apenas com ingestão *ad libitum*.

- **Capítulo 7**. Partindo de uma hipótese semelhante, com objectivos e desenho de estudo idênticos ao do Capítulo 6, apresentamos neste capítulo os resultados de um ensaio clínico prospectivo randomizado controlado com terapêutica nutricional em doentes com cancro da cabeça e pescoço referenciados para RT. Os resultados foram semelhantes aos verificados em doentes com cancro colorectal: o aconselhamento nutricional foi de facto essencial para a melhoria de uma diversidade de "*outcomes"* nestes doentes, a saber: estado e ingestão nutricionais, QV e redução da morbilidade, mantidos a médio prazo mesmo após o *terminus* do tratamento. O efeito da adição à dieta de suplementos nutricionais não foi tão benéfico como o aconselhamento nutricional. O aconselhamento nutricional individualizado baseado em alimentos correntes foi realmente a forma mais eficaz de melhorar o estado e ingestão nutricionais e a QV dos doentes durante a RT, melhoria que se mantém 3 meses após o fim do tratamento e com consequente redução da morbilidade decorrente da RT. Todos os itens sob avaliação pioraram significativamente no grupo controlo apenas com ingestão *ad libitum*.

5. Por fim, a **Secção 5** inclui o **Capítulo 8** no qual se apresenta a discussão dos resultados dos estudos que formam esta tese, e são apontadas algumas linhas orientadoras e sugestões para investigação futura.

Section 1

INTRODUCTION

Chapter 1

AIMS AND OUTLINE OF THE THESIS

AIMS

The main goal of the present thesis is to contribute to the understanding and knowledge of the potential interactions between cancer-related variables, nutrition and Quality of Life. The underlying hypothesis to be tested, in sequential prospective studies, is that a multidirectional influence among those variables requires a thorough analysis in order to devise a scientific approach to a comprehensive multiprofessional patient management, and to assert the weight and role of a meaningful nutritional therapy.

The pilot study, **Section 2**, **Chapter 3**, aimed to investigate:

1. The patients' nutritional status, nutrient intake and QoL at the onset and at the end of RT;
2. Which symptoms may anticipate reduced nutritional intake and/or poorer QoL;
3. Whether individualised nutritional counselling improved nutrient intake over time and whether the latter influenced the patients' QoL.

The studies undertaken for the evaluation of potential interactions between various clinical and nutritional variables are presented in **Section 3**.

The aims of the study presented in **Chapter 4** were to explore:

1. The construct of various disease-related and diet-related factors potentially implicated in cancer patients' nutritional deterioration;
2. Different nutritional assessment methods in order to disclose their reliability in this setting.

In the study presented in **Chapter 5** we investigated:

1. Patients' nutritional status, nutrient intake and QoL, taking into account disease stage and previous therapeutic interventions;
2. Potential interaction(s) between the various disease-related and diet-related factors likely to be implicated in the patients' QoL;
3. The quantification of the relative impacts of cancer/treatments and/or nutrition-related factors on patients' QoL.

The randomised controlled trials of nutritional therapy are shown in **Section 4**, **Chapter 6** and **Chapter 7**, aimed to test the subsequent hypothesis: does nutrition influence outcomes, e.g. nutritional status, nutritional intake, radiotherapy-induced morbidity and Quality of Life? Specific questions triggering these studies were:

1. Is there a causal pathway between nutritional intervention and functional/clinical outcomes?
2. Does individualised dietary counselling or *ad libitum* intake supplemented by commercial supplements during RT, affect oral dietary intake, nutritional status and Quality of Life?
3. What is the impact of nutritional intake on predefined outcomes during RT?

4. Does adequate nutritional intervention have the potential to modulate/lessen treatment induced morbidity?
5. Is the latter impact on the various outcomes sustained at 3 months after the nutritional and RT treatment completion?

OUTLINE OF THE THESIS

The present Thesis is structured into five sections.

Section 1 comprises **Chapter 1** and **Chapter 2**.

Chapter 1 describes the aims and the outline of the thesis. Chapter 2 consists of a general introduction reviewing the background concepts fundamental to the working hypothesis and relevant to the design and analyses of the undertaken studies.

Section 2 consists of a pilot study on nutritional intervention and QoL evaluations, **Chapter 3**.

Section 3 displays the results of the studies evaluating the multiple interactions between disease/treatment(s), nutrition and QoL, **Chapters 4** and **5**.

Section 4 contains the randomised controlled trials of nutritional therapy, **Chapters 6** and **7**.

Section 5 includes a global discussion of the data collected in the various studies, their relevance for clinical practice and quality of health care, and suggestions for future research, **Chapter 8**.

Chapter 2

GENERAL INTRODUCTION

I. MALIGNANCY

The word “cancer” is inclusive and comprises a wide range of different types of malignant tumours, which can develop in virtually every body tissue, thus determining diverse clinical manifestations [1]. In 2001, the total number of incident cancer cases in Europe, for both men and women, was 1,480,110 with a 5-year prevalence of 4,049,077 [2]. Cancer is a major cause of morbidity and mortality, being the second most frequent cause of death worldwide [2, 3]. However, the advances in early diagnosis and sophisticated modalities of treatments increase the possibility of cure, or at least prolong survival. It is thus expectable that most cancer patients will be ambulatory with a desirable “good” quality of life, the latter requires a patient-centred multiprofessional management; the potential added value of nutrition remains to be scientifically ascertained [4].

II. THE NUTRITION SPECTRUM IN ONCOLOGY

1. OVERVIEW OF MALNUTRITION IN PATIENTS WITH CANCER

Cancer has been associated with protein-energy malnutrition, or simply malnutrition [5, 6]. A series of studies conducted in patients with cancer, between 1932 and 1974, highlighted the syndrome of nutritional wasting apparently multifactorial in nature [7]. Although many studies were undertaken in the early 20th century, publications in 1980s and 1990s showed that malnutrition is still an unsolved phenomenon. Indeed, estimates of the prevalence of malnutrition in specific groups of cancer patients range from 8% to 84% apparently depending on the cancer site, e.g. 80% in patients with gastrointestinal cancer [5, 8-14] and 70% in patients with head and neck cancer [15-18].

Cancer related wasting is generally regarded as a physiological adaptation to stress: the body sacrifices large portions of the muscle mass to spare more immediate critical functions in visceral organs. There are however limitations to this adaptive response: contraction of the skeletal muscle mass leads to muscle weakness, decreased work tolerance and functional capacity [19]. On the other hand, the most frequent manifestation of malnutrition reported by cancer patients is weight loss [5], which when exceeding 10% is of particular clinical and/or prognostic significance, because weight loss of this magnitude in the setting of any illness may lead to significant increases in morbidity and mortality [4, 20]. At least some degree of weight loss has been registered in up to 75% of cancer patients prior to surgery, 57% prior to radiotherapy, 51% prior to chemotherapy and 80% of general cancer patients living in the community [4]. Despite the suggestion that the presence of malnutrition varies according to the cancer anatomic location, the likelihood that a cancer patient will sustain substantial weight loss is likely to be related to other factors, e.g. the agressiveness of the cancer (stage and histological characteristics), anti-neoplastic treatments (radiotherapy, chemotherapy, surgery), age, and intervening emotional factors such as depression [21].

2. CANCER-RELATED ANOREXIA AND SYMPTOMS

Overall in any disease, clinical practice suggests that loss of appetite is probably the most frequent cause of reduced food intake, deriving from both physical and psychosocial problems; hence, anorexia is a common contributor to wasting in cancer [4]. Particularly in patients with cancers of the head & neck and of the gastrointestinal tract, due to the mechanical dysfunction or concurrent treatments, the act of eating may incite a variety of adverse symptoms: pain, dysphagia, vomiting, diarrhoea, and therefore a "voluntary anorexia" translates the patients' learned food aversions as a means of avoiding such symptoms [22]. Moreover, food aversions may be present unrelated to any other symptom and even before the establishment of the diagnosis [23]. In addition, the tumour mass alone may preclude adequate ingestion of food. On the other hand, the emotional adjustment associated with dealing with cancer is *per se* a precipitant of depression and anxiety, which are known contributors to anorexia [24].

Nevertheless, anorexia is commonly present even in the absence of the above mentioned factors and may even be the presenting symptom of cancer [25]. In this setting, anorexia is thought to be largely due to the effects of cytokines released by macrophages and lymphocytes of the host, in response to the presence of the neoplasm [26]. In fact, in animal models, a highly reproducible degree of anorexia may be observed with the administration of Tumour Necrosis Factor-α (TNF-α) [27], Interleukin-1 [28] and Interferon-γ [29].

3. TUMOUR BURDEN AND METABOLIC DYSFUNCTION

In order to tackle nutritional deterioration, gathering objective data on nutritional status and its evolution throughout the disease course, appears to be of prime concern. So far, only a few studies have addressed this area of clinical research and did report weight loss either as the most frequent presenting symptom [30] or as a sign of advanced disease stage [31]. Notwithstanding that different cancer types or locations may display different nutritional patterns [32, 33], studies are inconsistent in what concerns the eventual relationship between nutritional status and cancer/treatment-related variables. Indeed, longstanding energy and substrate deficits have not been previously investigated nor adjusted by the patients' cancer stage, though wasting and marked nutritional intake deficits have been hypothesised to be related to advanced disease [5, 15, 34-38]; all factors are prone to exacerbate every organ/systemic physiological derangements.

Besides the tumour burden, symptoms and intake disturbances, cytokines may enhance metabolic dysfunction in various ways. Therefore a wide spectrum of alterations in protein, lipid and carbohydrate metabolism may occur in cancer, **Table 1**.

Table 1 Metabolic mediators potentially involved in cancer anorexia and wasting

Mediator	Wasting-related effects
Tumour necrosis factor-α	• In animal models, injection induces anorexia, weight loss and cachexia [27] • May increase resting energy expenditure [39] • In animal models, has hypothalamic effects in inducing anorexia [27] • Inhibits lipoprotein lipase [40] • Causes hypertriglyceridemia [41] • Depletes body fat stores [39] • Increases skeletal protein breakdown [42] • Increases synthesis of acute phase reactants [42]
Interleukin-1	• In animal models, injection induces anorexia, weight loss and cachexia [43] • May increase resting energy expenditure [44] • In animal models, has hypothalamic effects in inducing anorexia [43] • Causes similar effects on fat metabolism as TNF-α [28] • Causes similar effects on protein metabolism as TNF-α [28]
Interleukin-6	• Induces hepatic gluconeogenesis [45] • Increases synthesis of acute phase reactants [46] • Increases lipolysis [44] • Augments the effects of TNF-α on lipid metabolism -α [28] • Increases anorexia [47]

Adapted from Mutlu et al. [42]

3.1 *Protein metabolism and lean body mass*

Skeletal muscle is the body compartment where most of the contraction of lean body mass occurs [48]. The overriding functional significance of this is underscored by the observation that the extent to which this compartment is diminished correlates with the likelihood of survival [49]. The decrease in skeletal muscle mass appears to be due to both a reduction in muscle protein synthesis and an increase in muscle protein degradation [50]. In cancer-related wasting, TNF-α, Interleukin-6, Interleukin-1 and Interferon-γ appear to play major roles in mediating the dissolution of skeletal muscle [42].

3.2 *Lipid metabolism and adipose tissue*

In the wasting associated with cancer, adipose tissue constitutes the major source of energy and a decrease in fat mass may be observed [48]. The net efflux of glycerol and fatty acids from adipose tissue that is observed in cancer wasting appears to be due to at least three factors: 1) increased lipolysis in adipose tissue, apparently mediated by TNF-α and lipid mobilising factor [41]; 2) a decrease in *de novo* lipogenesis in the adipose tissue, suggested to be mediated by

TNF-α and Interleukin-1 [45]; and 3) diminished activity of lipoprotein lipase [40]. The latter enzyme is necessary for the uptake of fatty acids from circulating lipoproteins and the diminished activity in cancer appears to be mediated by TNF-α, Interleukin-6 and Interferon-γ [40].

3.3 *Carbohydrate and energy metabolism*

The most commonly altered aspects of carbohydrate metabolism include increased rates of gluconeogenesis and glucose flux, and the development of some degree of impaired insulin secretion as well as insulin insensitivity. The latter induces impaired glucose utilisation in peripheral tissues and glucose intolerance [51]. Similar alterations in glucose metabolism are observed in any condition associated with a systemic inflammatory response and are thought to be due to TNF-α [52]. These changes contrast with weight loss unrelated to illness or cancer, where insulin sensitivity is maintained [53].

In summary, if not stopped and ideally reversed, cancer related wasting will progress and lead to what is known as cancer cachexia, a syndrome of progressive weight loss and asthenia, responsible for the death of 20% of the patients with cancer [54-56]. Cachexia does appear to be the end-result of reduced nutrient absorption [57], alterations in the appetite, taste and/or dietary intake [30], metabolic alterations [58] and cancer-related immune activation with cytokine release [59]. **Table 2** summarises the possible causes of cancer related malnutrition.

Table 2 Possible causes of cancer related malnutrition

1. Reduced food intake due to:

- Deterioration in taste, smell and appetite, as a consequence of the tumour and/or therapy [42, 60-64]
- Altered food preferences/food avoidance/food aversion [63, 65-67]
- Eating problems [8, 68]
- Dysphagia, odynophagia or partial/total gastrointestinal obstruction [62]
- Early satiety, nausea and vomiting [61, 62]
- Soreness, xerostomia, sticky saliva, painful throat, trismus [63]
- Oral lesions and oesophagitis [62]
- Radiotherapy/chemotherapy induced mucositis [69]
- Acute or chronic radiation enteritis during and after radiotherapy [70, 71]
- Depression, anxiety [42]
- Pain [42]

2. Malabsorption due to atrophy of the small bowel mucosa, chemotherapy or radiotherapy [62]

3. Metabolic disturbances [42, 62, 72]

4. Humoral and inflammatory responses (e.g. increased or abnormal cytokine activity/production, excessive monocyte and macrophage activation, cancer-specific cachectic factors (Mutlu, 2000 #940; Nitenberg, 2000 #941)

Adapted from Stratton et al. [4]

III. THE IMPACT OF MALNUTRITION

Malnutrition has a diversity of effects, influencing every system of the body, yet it is important to highlight the fact that malnutrition is more than a decline of nutritional status. A prolonged inadequate intake of food results in metabolic, body composition, physical (functional) and psychosocial changes, i.e. a malnutrition status, which is itself a disease and may further increase the risk of disease [4, 73]; there is growing recognition that nutritional intake *per se* may be at least as important as body mass and structure in maintaining normal whole body function. Thus, nutritional intervention studies are necessary to investigate whether or not the provision of nutritional support can reduce or avoid the potential consequences of malnutrition.

Regardless of the underlying mechanisms, cancer-related weight loss and nutritional wasting are multidimensional manifestations that worsen patients' well-being [74], tolerance to antineoplastic therapies and prognosis [5, 15]. Specifically, weight loss decreases immunological responses to tumour cells [75] and resistance to infection [35], enhances susceptibility to postoperative complications [36, 37], and increases disability and overall cost of care [38].

The potential consequences of cancer related malnutrition with obvious clinical implications are listed in **Table 3**.

Table 3 Potential consequences of cancer related malnutrition

1. Reduced muscle function [76]
2. Reduced performance status after chemotherapy [5, 6]
3. Lower general health, lower social functioning, lower outlook/happiness [6, 64]
4. Tendency for greater depression, anxiety, insomnia in weight-losing patients [77]
5. Higher prescription and consultation rates [78]
6. Increased complications after surgery [13, 15]
7. Increased need for reventilation after lung cancer surgery [79]
8. Lower chemotherapy response rates [5, 6]
9. Increased risk of chemotherapy-induced toxicity [6]
10. Shorter duration of remission after chemotherapy [80]
11. Increased mortality, especially in gastrointestinal cancer patients [8], after surgery [12, 13, 15, 79, 81] or after chemotherapy [6]
12. Shorter survival overall [17, 82], after surgery [37, 83] or after chemotherapy [5], and in non-small cell lung cancer [84]

Adapted from Stratton et al. [4]

1. THE FFECTS OF ACUTE AND CHRONIC FOOD DEPRIVATION IN THE PRESENCE OF MALIGNANCY

1.1 *Immunity*

A key deleterious effect of malnutrition in cancer is the potential to impair or reduce the competence of the host's immune system, thus promoting a poorer outcome along with an impaired capacity to arrest and/or recover from the disease. Nevertheless, in cancer patients many other factors, apart from nutritional status, may influence immune function: among others, infection, inflammation, drug therapy, besides the disease itself which may directly influence immunological function [75, 85].

Impairments in immune function associated with nutritional status have long been demonstrated in a variety of cancer patient groups:

- Malnourished patients with inoperable carcinoma of the oesophagus [86];
- Malnourished patients with hepatocellular carcinoma [87];
- Patients with squamous-cell carcinomas of the head and neck displayed a highly significant positive correlation between nutritional status and circulating immune cells [35, 88].

1.2 *Physical activity*

In experimental conditions, both short term starvation (water only) as well as prolonged semi-starvation in healthy volunteers has been reported to reduce physical activity [89, 90]. In the landmark semi-starvation study of Keys et al, in which healthy subjects lost 25% of their body weight over 6 months, there was a reduction in both resting energy expenditure and physical activity [91]. Feelings of tiredness and lethargy can further contribute to impaired physical activity. Marked decreases in physical activity that occur in severe disease-associated malnutrition may predispose to increased morbidity, in parallel to a reduced capacity to maintain daily activities and undertake work [89].

1.3 *Psychological function*

Mental function may be influenced by nutrition in several ways. Starvation and partial food deprivation in adults lead to anxiety, depression and/or other mental changes, which may in part be associated with micronutrient deficiencies [92]. Cognitive function may also be adversely affected. In Keys' et al study, healthy volunteers who underwent partial starvation for 24 weeks, resulting in loss of 25% of body weight had a concomitant increase in their depression score [91].

IV. TUMOUR BURDEN, MORBIDITY AND QUALITY OF LIFE

Since 1948, when the World Health Organisation defined "health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being" [93], Quality of Life (QoL) issues have become increasingly more important in research [94]. Hence Quality of Life was acknowledged as a valid outcome in the growing field of outcomes research to evaluate efficacy, cost-effectiveness, and net benefit of new therapeutic strategies [95]. QoL assessment is able to measure changes in physical, functional, mental and social health in order to evaluate the human and financial costs as well as the benefits of new interventions [95].

It should be widely recognised that psychosocial factors such as pain, apprehension, restricted mobility and other functional impairments, e.g. difficulty in fulfilling personal and family responsibilities, financial burden and cognition decline, must be included in the description of the personal burden of illness [96, 97]. Despite this conceptual knowledge, there still is considerable scepticism and resistance regarding measuring patients' QoL [97, 98]. In general, health-related QoL can be considered as the gap between expectations of health and the actual experience of it [4, 96].

1. PATIENTS' PERCEPTIONS

QoL assessment and, more specifically, "health-related QoL" refer to the physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions [99-101]. QoL assessment aims to

measure general well-being based on objective and subjective changes in physical, functional, mental and social health [97, 102]. Different individuals have different health expectations, though in cancer patients we should bear in mind that when measuring QoL, individuals may be at different time points throughout their illness when measurements are made and expectations may change over time [103]. **Figure 1** shows domains known to contribute to the patients' QoL.

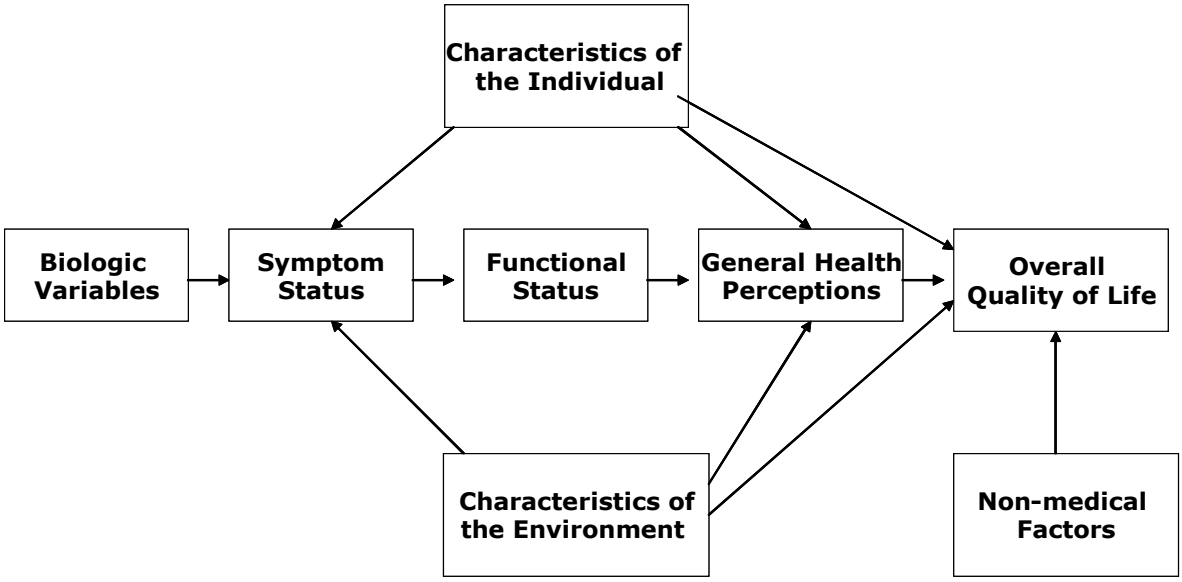

Figure 1 Domains that contribute to the patients' QoL [104].

Hence, accurate assessment of QoL provides important patient information to clinicians and investigators, particularly in oncology treatment and research [105]. A debilitated QoL status can jeopardise the ability or willingness of a patient to complete a treatment regimen [106]. QoL measurement may also assist in establishing a definition of response where any response may be difficult to quantify or where benefits may occur in the absence of conventional endpoints, such as measurable tumour shrinkage [107].

2. NUTRITION AND THE MODULATION OF MORBIDITY AND QOL IN CANCER

QoL depends on physical and psychological well-being, both of which can be influenced by nutrition [108]. Nevertheless, despite the suggested association between worse overall well being/morbidity and nutritional deterioration [109], the interaction between nutrition and QoL remains underestimated [110]. Fatigue, anorexia and emotional stress, so common in cancer patients, may further aggravate and likewise may be worsened by poor nutritional intake and/or QoL [103, 108]. Tumour location and symptoms, e.g. anorexia, taste changes, dysphagia, nausea, vomiting, diarrhoea, may further compromise nutrition and functional ability [30, 37, 111]. Thus, the interaction between nutritional status and intake, as well as nearly all of the experienced symptoms, and/or disease/treatment-related factors, adds up to a complex

combination potentially capable of determining each patient QoL. Indeed, there is the suggestion that poor nutritional status may have an impact in QoL: good nutrition is essential for adequate function and survival, but eating *per se* encompasses other needs, including pleasure, satisfaction, conviviality and provision of a structure to the day [112].

Moreover, it must be emphasised that the nutritional content of the patient's diet, with appropriate dietary and food manipulations, may potentially improve nutritional intake as well as some symptomatic morbidity, derived either from the cancer itself and its anatomic location, or from anti-neoplastic treatments and/or surgery. Nutrition is known to influence various gastrointestinal tract functions, such as motility, enzyme secretion and nutrient absorption; likewise, nutrition modulates the gastrointestinal flora whose ecology is central to the pathogenesis of mucosal injury [113]. Another example is the modification or modulation of the oral cavity ecology, by means of stimulating salivary secretion, and thereby decreasing oral/oropharingeal/oesophageal intolerance to foods [114]. This overview depicts some evidence which supports nutrition as a major issue in QoL in the context of oncology, and that cancer patients should not be left to follow an *ad libitum* intake without adequate orientation.

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Section 2

PILOT INTERVENTION STUDY FOR QUALITY OF LIFE INSTRUMENTS' AND OUTCOMES' EVALUATION

Chapter 3

DOES NUTRITION INFLUENCE QUALITY OF LIFE IN CANCER PATIENTS UNDERGOING RADIOTHERAPY?

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ABSTRACT

Purpose: To investigate in cancer patients referred for Radiotherapy (RT): 1) Quality of Life (QoL), nutritional status and nutrient intake, at the onset and at the end of RT; 2) whether individualised nutritional counselling, despite symptoms, was able to enhance nutrient intake over time and whether the latter influenced the patient's QoL; 3) which symptoms may anticipate poorer QoL and/or reduced nutritional intake.

Material and Methods: One hundred twenty five patients with tumours of the head-neck/gastrointestinal tract (high-risk: HR), prostate, breast, lung, brain, gallbladder, uterus (low-risk: LR) were evaluated before and at the end of RT. Nutritional status was evaluated by Ottery's Subjective Global Assessment, nutritional intake by a 24hr recall food questionnaire and QoL by 2 instruments: EUROQOL and the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30.

Results: Baseline malnutrition was prevalent in HR *Vs* LR, p=0.02; nutritional intake was associated with nutritional status, p=0.007; the latter did not change significantly during RT. In LR, baseline energy intake was higher than EER, p=0.001 and higher than HR' intake, p=0.002; the latter increased, p<0.03 in spite of symptom increase anew and/or in severity, p=0.0001. According to both instruments, QoL was always better in LR *Vs* HR, p=0.01; at the end of RT, QoL improvement in HR was correlated with increased nutritional intake, p=0.001, both remained stable in LR.

Conclusions: Individualised nutritional counselling accounting for nutritional status and clinical condition, was able to improve nutritional intake and patients' QoL, despite self-reported symptoms.

INTRODUCTION

In cancer patients malnutrition is multifactorial and bears a negative prognosis (Cravo, 2000 #492; Van der Schueren, 1999 #460). Patients submitted to radiotherapy (RT), particularly of the head and neck (HN) or the gastrointestinal (GI) tract, are at higher risk of malnutrition [Van der Schueren, 1999 #460]; therapy induced toxicity, e.g. mucositis, xerostomia, taste changes, odynophagia, dysphagia, nausea, vomiting, diarrhoea and anorexia may further compromise nutrition and functional ability (Cosnes, 1988 #461;Deitel, 1987 #462).

Quality of Life (QoL) is a subjective multidimensional construct representing functional status, psychosocial well being, health perceptions and disease/treatment-related symptoms (Ferrell, 1996 #452). Each nutrition related factor, nutritional status, nutritional intake and the above mentioned symptoms are thus likely to assume a significant role in the patients' QoL (Schneider, 2000 #456). Although nutrition management has been proposed as auspicious to cancer patients (Hunter, 1996 #373), to date there is no evidence-based data to support that concept.

Within this framework, we investigated whether individualised nutritional counselling would improve patient's outcomes, nutritional status and QoL in cancer patients undergoing RT. Our specific aims were to investigate: 1) the patients' QoL, nutritional status and nutrient intake, at

the onset and at the end of RT; 2) whether individualised nutritional counselling, despite symptoms, was able to enhance over time nutrient intake and whether the latter influenced the patient's QoL; 3) symptoms which may anticipate poorer QoL and/or reduced nutritional intake.

MATERIAL AND METHODS

Study Design and Patient Sample

This study was designed as a prospective descriptive study to investigate outcomes of nutritional counselling initiated prior to RT and was approved by the University Hospital Ethics Committee. Between July 2000 and February 2001 all consecutive cancer patients referred to the outpatient Radiotherapy Department were considered eligible. Before the decision of RT planning, the medical staff registered the patients' clinical variables, cancer location and TNM staging (8). Exclusion criteria comprised: terminally ill patients, renal failure (creatinine>532μmol/L), congestive heart failure and hepatic failure (bilirubin>21μmol/L). The cohort studied included 125 adult patients, age 63±11 (33-86) years, 83M:42F, proposed for RT: primary, adjunctive to surgery or with palliative intent. Patients with tumours of the HN and GI tract were, on the basis of the expected RT-induced GI symptoms, classified as high-risk patients whilst the remaining were considered as low risk.

Data was recorded in individual sheets preconceived for statistical analysis.

Study Measures

Assessment of nutritional status as described, food intake and dietary advice were performed by a research dietician (PR), at the onset, after 2 weeks and at the end of RT. QoL was evaluated at the onset and at the end of RT.

Nutritional Assessment. Nutritional status was assessed by Ottery's Subjective Global Assessment (SGA), a patient-generated assessment tool validated for cancer patients [Ottery, 1996 #464]. The first four sections address: weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhoea, xerostomia, pain), alterations in food intake and functional capacity. Components of metabolic stress: sepsis, neutropenic or tumour fever, and corticoesteroids, and physical examination: subcutaneous fat (triceps skinfold and at the level of the lower ribs in the midaxillary line), muscle bulk and tone in the temporal, deltoids and quadriceps areas, ankle/sacral oedema, or ascites are added. As a result, nutritional status is categorised in three degrees: normal, moderate and severe malnutrition. Symptoms and side effects determined by therapy toxicity were scored by using a standardised form [Rubin, 1988 #715].

Nutritional Requirements, Dietary Assessment and Counselling. Basal energy requirements were estimated by the World Health Organisation formula [WHO, 1985 #450], for men between 18-30 yrs [64.4 × weight(kg) – 113 × height(m) + 3000], or between 30-60 yrs [19.2 × weight(kg) + 66.9 × height(m) + 3769] and for women between 18-30 yrs [55.6 × weight(kg) – 1397.4 × height(m) + 146], or between 30-60 yrs [36.4 × weight(kg) + 104.6 × height(m) + 3619], or by the Owen *et al* formulas (>60 yrs) [Owen, 1986 #382; Owen, 1987 #383], for men [(879 + 10.2 ×

weight (kg)) × 4.184] and for women [795 + 7.18 × weight (kg)] × 4.184]. These formulas were used due to their higher ability of predicting resting metabolic rate by comparison with the Harris and Benedict formula [Garrel, 1996 #451]. Height was copied from the patient's Identity Card and weight was determined with a Jofre® floor scale. Patient daily estimated energy requirements (EER) were calculated by multiplying basal requirements by a 1.2 activity factor [Food and Nutrition Board, 2002 #646]; protein requirements were estimated by comparison with reference values standardised for age and sex [Panel on Dietary reference values of the Committee on Medical Aspects of Food, 1991 #525].

Nutritional intake evaluation was derived from a 24hr-recall food questionnaire, the nutrient content was analysed by the DIETPLAN5 for Windows software (Forestfield software Ltd 2001, Horsham, UK). Individualised dietary advice was based on current foodstuffs, hence neither nutritional supplements nor enteral tube feeding were used. Nutritional counselling took into account each patient current food habits, actual nutritional status, calculated increase in energy and protein requirements to overcome deficits, known food aversions and reported symptoms. The latter were valued in the context of diet adequacy, which may determine variations in the patients' daily meal plan, diet nutrient content, type and amounts of foodstuffs and food texture.

QoL instruments. Quality of Life was evaluated in every patient by two methods in order to evaluate their relative performance given the significant differences in length of time ascribed to their completion.

The EUROQOL instrument is non-disease-specific and describes and scores health states [Brooks, 1990 #368]. On its first part, health is defined in terms of five dimensions: mobility, self-care, usual activities (work, study, housework, family, leisure), pain or discomfort and anxiety or depression. Each dimension is subdivided into three categories, which indicate whether the respondent has no problem, a moderate problem, or an extreme problem. Combinations of these categories define a total of 243 health states. On the second part, the respondent indicates his/her perception of his/her overall health on a visual analogue scale (0 denoting the worst imaginable health state and 100 the best imaginable health state).

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30, version 3.0) is a 30-item cancer specific questionnaire including five functional scales (physical, emotional, cognitive, social, and role), three symptom scales (fatigue, pain, nausea/vomiting), a global health/QoL scale and six single items assessing symptoms and financial impact of disease [Aaronson, 1993 #503]. The raw scores were linearly transformed to give standard scores in the range of 0 to 100 for each of the scales and single items. Higher scores on the functional and global health scales indicated better functioning, whereas higher scores on the symptom scales represent more symptomatology.

Statistical Analysis

This study was based in the intention to treat principle. Target sample consisted of all consecutive cancer patients referred to the outpatient Radiotherapy Department included between July 2000 and February 2001. Sample size was determined by using the Neyman-Pearson method REF E DETAILS. Based on the therapeutic intervention period, clinically

significant differences were assigned whenever nutritional intake adequacy was accomplished by meeting or overcoming the patients requirements, and an increase of 15-20% in QoL scores was acknowledged [Aaronson, 1993 #503]. Descriptive patient data concerning nutritional status and intake, symptoms and QoL are expressed as number and percentage, mean or median values and are presented for each diagnosis. In order to increase statistical power, patients were grouped as high (HR) or low-risk (LR). Continuous variables were logarithmically transformed before any parametrical tests were performed. Kruskal-Wallis analysis, the Mann and Whitney *U* test and Student's t test were used to analyse associations and/or differences in QoL measures, nutritional intake or nutritional status between patient groups. Frequencies were compared by Chi-Square test. Spearman and Kendal Tau methods were used to determine correlations between nutritional intake or status and QoL dimensions. Multivariate logistic regression analysis was done to identify variables that influence nutritional intake and QoL. For all statistics, significance was accepted at the 5% probability level. SPSS 10.0 (Chicago, USA), EPI–Info 2000 (CDC, Atlanta, USA) and STATISTICA (Statsoft, Tulsa, USA) softwares were used for analyses.

RESULTS

Patients

Patient's diagnoses, tumour staging and RT treatment protocol are shown in **Table 1**.

Table 1 Patient groups and treatment protocol

Location	n	**Staging** (n)	**Dose** (Grays)**/Fractionation** (n)/ **Days**
GI tract*			
Oesophagus (OES)	6	II (1); III (5)	45 / 25 / 33
Stomach (STO)	5	I (1); II (2); III (2)	45 / 25 / 33
Colorectal (CR)	46	I (13); III (28); IV (5)	50 / 25 / 33
Head and neck*			
Base of the tongue	3	IV (3)	70-74 / 30-35 / 40-47
Salivary gland	1	III (1)	70-74 / 30-35 / 40-47
Tonsil	2	II (2)	70-74 / 30-35 / 40-47
Nasopharynx	3	III (3)	70-74 / 30-35 / 40-47
Oropharynx	3	II (1); IV (2)	70-74 / 30-35 / 40-47
Larynx	11	I (1); III (3); IV (7)	70-74 / 30-35 / 40-47
Prostate	21	II (15); IV (3)	50 / 25 / 33
Breast	7	II (4); III (2); IV (1)	50 / 25 / 33
Lung	5	II (2); III (2); IV (1)	50 / 25 / 33
Brain	4	I (1); II (2); III (1)	50 / 25 / 33
Gallbladder	6	II (1); IV (2)	50 / 25 / 33
Uterus	2	II (1); III (1)	50 / 25 / 33

n=number of patients or radiation fractions; *defines high-risk (HR) patients due to the expected RT-induced symptoms; remaining diagnoses are classified as low-risk (LR).

Nutritional Status

Patients' nutritional status categories at the onset and at the end of RT, according to the assigned risk level, are shown in **Figure 1**.

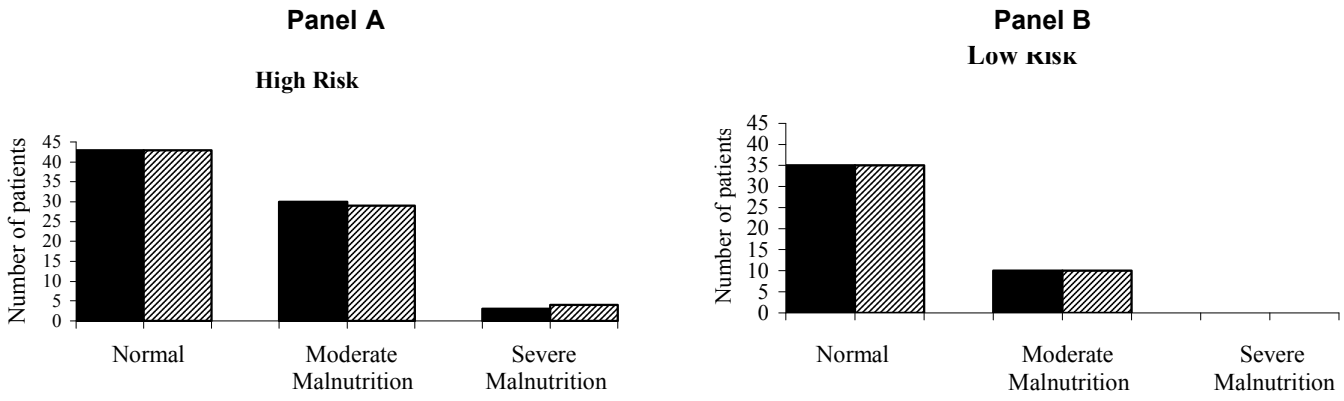

Figure 1 Nutritional status at the onset ■ and at the end of RT ▨.

Before RT, among HR group, only 1 patient with oesophageal cancer was well nourished, all patients with stomach cancer, 52% of HN cancer patients and 6 (13%) patients with CR cancer were malnourished; 6 (13%) patients with CR cancer were obese (body mass index >30 kg/m^2); severe malnutrition was never observed in LR patients. Either at the onset or at the end of RT, malnutrition (moderate + severe) was more often present in the HR group, p=0.02. Nutritional status remained stable in all but one HN cancer patient whose moderate malnutrition deteriorated.

At the onset and at the end of RT, only 1 of the LR patients reported diarrhoea and another anorexia. Throughout RT treatment, only in HR patients did symptoms increase, anew and/or in severity, p=0.0001. **Figure 2** shows the number of patients presenting symptoms at the onset and at the end of RT in HR groups. No patients reported grade 3 or 4 symptomatology.

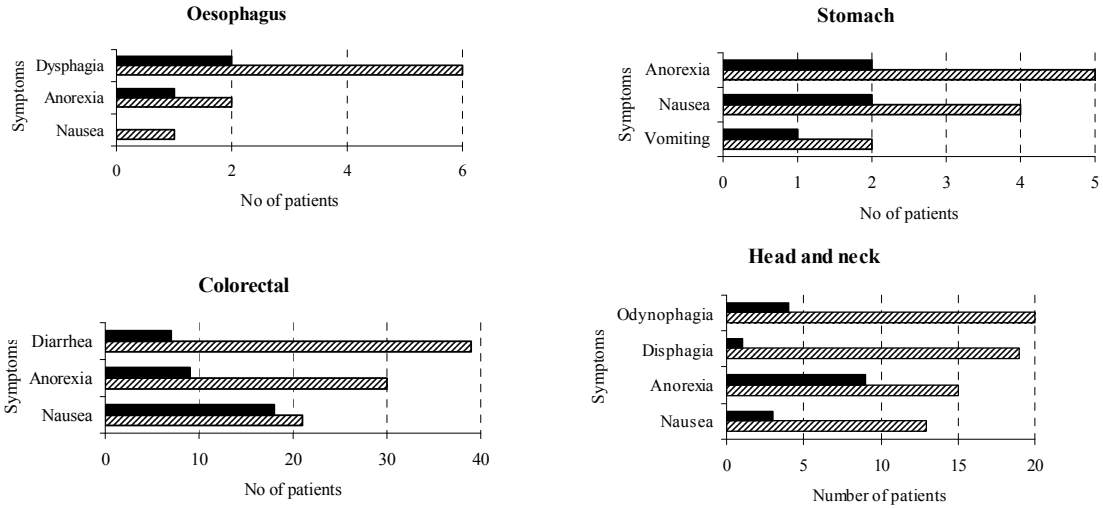

Figure 2 Number of patients presenting symptoms at the onset ■ and at the end of RT ▨ for HR diagnoses. Odynophagia comprised xerostomia, mucositis and taste changes.

Nutritional Intake. Patients' median energy intake and median estimated requirements (EER) are shown in **Figure 3**.

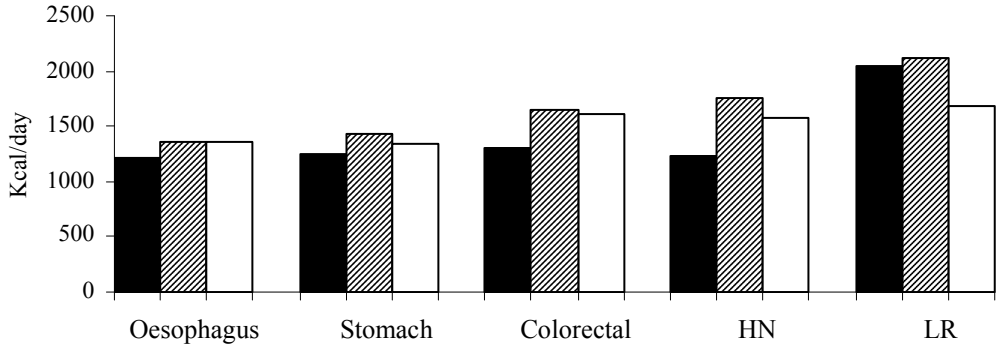

Figure 3 Median energy intake at the onset ■ and at the end of RT ▨; median EER □.

At the onset, the median energy intake of LR patients was higher than their EER, p=0.001, and higher than the median intake of HR groups, p=0.002. In the latter, baseline median energy intake was lower then their EER, reaching significance only in CR and HN cancer, p=0.01. In all diagnoses baseline nutritional status was associated with nutritional intake, p=0.007 (Kruskal Wallis analysis adjusted by tumour staging). Despite the more severe symptoms in HR patients, energy intake did increase significantly, p<0.03, narrowing the gap with their EER; an improvement spontaneously attributed by patients to the individualised nutritional counselling.

Patients with oesophageal and stomach cancer registered similar median increases of 275 kcal (200-425) and 280 kcal (185-400), respectively, a lower increment than in colorectal and HN patients: 410 kcal (352-545) and 510 kcal (358-785), respectively, p=0.03. In the LR group there was a median increase of 70 kcal (NS). Baseline protein intake was similar to requirements in LR patients and higher than in HR patients, p=0.003; in the latter, intake was lower than requirements (NS). Subsequent to counselling, protein intake did increase only in HR patients, p=0.08.

QoL. The number (percentage) of patients that reported moderate or extreme problems regarding each EUROQOL dimension, at both evaluation set points, are summarised in **Table 2**.

Table 2 Patients reporting problems in each EUROQOL dimension at the onset and at the end of RT

EuroQoL	**Problem**																			
Dimension	**Moderate**										**Extreme**									
	OES		STO		CR		HN		LR		OES		STO		CR		HN		LR	
	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End
Mobility	1 (17)	0	0	0	10 (22)	4 (9)	7 (30)	2 (9)	2 (4)	2 (4)	0	0	0	0	7 (15)	0	4 (17)	1 (4)	1(2)	1 (2)
Self care	1 (17)	1 (17)	0	1 (20)	3 (7)	3 (7)	7 (30)	7 (30)	0	0	1 (17)	0	0	0	2(4)	2 (4)	5 (22)	5 (22)	0	0
Usual activities	3 (50)	1 (17)	3 (60)	1 (20)	19 (41)	5 (11)	10 (43)	4 (17)	1 (2)	1 (2)	3 (50)	0	0	0	15 (33)	1 (2)	15 (52)	3 (13)	1(2)	1 (2)
Pain/discomfort	2 (33)	4 (67)	1 (20)	4 (80)	7 (15)	23 (50)	3 (13)	10 (43)	3 (7)	3 (7)	0	1 (17)	0	1 (20)	1 (2)	20 (43)	1 (4)	12 (52)	2 (4)	2 (4)
Anxiety/ Depression	2 (33)	1 (17)	1 (20)	1 (20)	20 (43)	5 (11)	11 (48)	4 (17)	4 (9)	2 (4)	1(17)	0	2 (40)	1 (20)	19 (41)	2 (4)	15 (52)	3 (13)	3 (7)	2 (4)

Data expressed as number (percentage) of patients.

At any stage and for all cancer patients, impaired usual activities, pain/discomfort and anxiety/depression were the most common problems. Overall and for all QoL dimensions, HR patients presented worse scores than LR patients, either at baseline, p=0.001 or at the end of RT, p=0.01. Patients with oesophageal, stomach and head and neck cancer reported the worse QoL, in both evaluations. With the exception of pain/discomfort, all QoL dimension' scores did improve in spite of RT, though only significantly in HR patients, p=0.004; pain/discomfort became worse throughout RT in association with more severe symptoms: anorexia (p=0.001), diarrhoea (p=0.002), dysphagia (p=0.01) and odynophagia (p=0.04). Nevertheless, nutritional intake was improved.

In HR patients, worse mobility was associated with the presence of malnutrition, p=0.01 or reduced energy intake, p=0.0; usual activities were associated in a similar manner (p=0.02/p=0.03) as well as anxiety/depression, p=0.02/p=0.01. Additionally, multivariate analyses identified an association between worse nutritional status and worse mobility (p=0.03) or anxiety/depression (p=0.05), and flagged the association between anxiety/depression and nutritional intake (p=0.02). Nutritional intake improvement was identified as a major determinant of the QoL improvement registered at the end of RT, r=0.78, p=0.001. In LR patients, QoL dimensions were not significantly associated with any nutritional parameter.

Figure 4 shows the mean self-rated health status (SRHS) on the visual analogue scale.

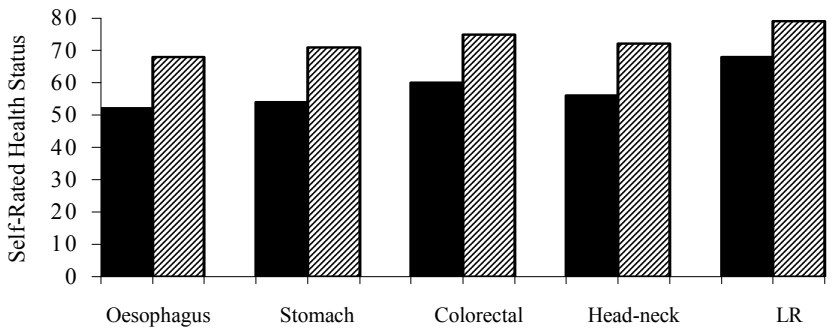

Figure 4 Patients' mean self-rated health status at the onset ■ and at the end of RT ▨.

At the onset, LR patients had a significantly higher mean SRHS when compared to HR patients, p<0.03. At the end, SRHS did increase in all patient groups, though significance was reached only in HR, p=0.01 *Vs* LR, p=0.06; oesophageal, stomach and HN patients reported the highest increase. In HR patients, baseline malnutrition was associated with lower SRHS, p=0.002 and at the end of RT, whilst improved nutritional status was associated with higher SRHS, p=0.03. Unlike LR patients, energy intake in HR was correlated with SRHS, both at the onset (r=0.47, p=0.001) and at the end of RT (r=0.32, p=0.005). At the end of RT, a multivariate analysis considering nutritional parameters and symptoms as the independent variables and SRHS as the dependent variable, highlighted its only association with nutritional intake, p=0.001. The

increase registered in each patients' nutritional intake was correlated with the increase of SRHS, r=0.72, p=0.001 indicating that the patients which improved their energy intake also enhanced their SRHS (Pearson' method).

The average rate of self-reported QoL problems evaluated by the EORTC QLQ C30 instrument, at the onset and at the end of RT, is summarised in **Table 3**.

Table 3 Self-reported QoL problems at the onset and at the end of RT

Items	n=6 OES		N=5 STO		n=46 CR		n=23 HN		n=45 LR	
	Onset	End	Onset	End	Onset	End	Onset	End	Onset	End
Function scales										
Global QoL	52	69	56	70	68	75	50	73	73	80
Physical function	42	65	40	55	69	74	50	80	74	70
Role function	53	68	42	62	62	78	55	75	80	80
Emotional function	58	63	36	45	65	65	74	74	82	82
Social function	68	74	35	58	69	69	66	86	83	83
Cognitive function	54	65	41	55	38	58	53	72	80	80
Symptoms, scales										
Fatigue	59	64	29	19	26	26	67	52	30	30
Pain	22	58	29	52	25	49	13	60	17	17
Nausea and vomiting	25	45	24	72	48	58	43	18	4	4
Symptoms, single items										
Dyspnea	56	58	2	2	5	5	38	38	2	2
Sleep disturbance	45	45	35	35	39	39	53	53	21	21
Appetite	41	79	19	55	68	68	73	19	6	6
Constipation	2	2	1	1	15	4	8	8	12	12
Diarrhea	2	2	0	0	59	78	9	9	6	6
Finance	4	4	1	1	8	8	38	38	5	5

At both evaluation set points, the overall QoL pattern was worse in HR patients, p=0.002; the worse dimensions were reported in patients with oesophageal, stomach and head/neck cancer. At the end of RT, in HR patients, function scales were improved (p=0.001) whilst a deterioration was reported for fatigue (NS), pain (p=0.003), nausea/vomiting (p=0.04) and appetite (p=0.001). In the LR group, global QoL was the only improved item, p=0.05.

In HR patients baseline malnutrition was associated with worse function scales: global QoL (p=0.05), physical (p=0.01), role (p=0.02), cognitive (p=0.02), emotional (p=0.01) and social (p=0.01) as well as with symptoms: poor appetite (p=0.001) or increased fatigue (p=0.03) (Kruskal Wallis). All associations with function scales were also present at the end of treatment: global QoL (p=0.01), physical (p=0.02), role (p=0.02), cognitive (p=0.03), emotional (p=0.01) and social (p=0.04).

Baseline energy intake was correlated with function scales: global QoL (r=0.53, p=0.001), physical (r=0.26, p=0.02) and emotional (r=0.29, p=0.01) as well as with symptoms: anorexia (r=0.52, p=0.001) and fatigue (r=0.60, p=0.001). At the end of RT, energy intake was correlated with global QoL (r=0.50, p=0.001), physical (r=0.35, p=0.01) and emotional (r=0.38, p=0.01) functions. At the end of RT, a multivariate analysis considering nutritional parameters and symptoms as the independent variables and QoL dimensions as the dependent variables, nutritional intake was identified as the only variable associated with global QoL (p=0.001), physical (p=0.03), role (p=0.01) and emotional (p=0.04) functions, and pain/discomfort was only associated with increased severity of symptoms (p=0.001). The increase registered in each patients' nutritional intake was correlated with the increase of global QoL (r=0.78, p=0.001), physical (r=0.68, p=0.002) and emotional (r=0.67, p=0.002) functions (Pearson' method), which indicates that the patients which improved their energy intake also enhanced QoL dimensions.

In LR patients, nutritional parameters were not significantly associated with QoL dimensions.

DISCUSSION

Nutrition is a key issue in oncology; nutritional decline ensues from the disease course and its treatment(s) [Cravo, 2000 #492;Van der Schueren, 1999 #460]. Although the clinical manifestations of radiation injury and its nutritional consequences have been well described [Chao, 1999 #505], to date there are no data on the role of routine adjuvant oral nutritional support in patients' outcomes, e.g. nutritional status and intake or QoL. This prospective study provides evidence that early individualised nutritional counselling improves patients' nutritional parameters and QoL.

Malnutrition was prevalent amongst HR patients, oesophagus, stomach and HN cancer, and rare in LR patients, in whom severe malnutrition was never observed, thus stressing the major role of cancer location, as previously reported [Donaldson, 1984 #528; Liedman, 1999 #529]. Further on, the severity and extent to which patients experience side effects of RT depend on the tumour/treatment site, total dose, fractionation, volume of irradiated organ and injury repair mechanisms; high turnover cells, e.g. GI tract, are the most susceptible to acute radiation damage [Chao, 1999 #505]. In our study, RT-induced symptoms affecting nutrient intake, such as dysphagia, mucositis, xerostomia, taste changes, diarrhea, anorexia and nausea became evident only in HR patients. Our results corroborate that anorexia and nausea occur as a manifestation of the systemic tumour effect but their incidence increase dramatically as a consequence of RT [Mantovani, 2001 #511]. Albeit, although baseline nutritional intake in HR patients was significantly lower than EER it did increase significantly as a result of the individualised nutritional counselling (as patients spontaneously acknowledged), hence overcoming the previous energy deficit; only 2 of the LR patients reported diarrhoea or anorexia, intake remained adequate and stable. Both oesophageal and stomach cancer patients reported a similar increase of $\pm$280 kcal, lower than the observed in CR and HN cancer patients, $\pm$460 kcal, p=0.03. HR patients' baseline protein intake was also lower than requirements (NS) and than LR patients', p=0.003; nutritional counselling did improve protein

intake to a still inadequate amount (NS). These data support the concept of cancer patients' aversion to protein dense foods, namely meat, further aggravated by RT [Mattes, 1992 #534]. Our results clearly show that individualised nutritional counselling based on each patient clinical condition, reported symptoms and nutritional status, is able to overcome the predicted deterioration subsequent to the increased severity of RT side effects; yet only HR patients appear to benefit.

Besides the site-specific RT effects, patients experience fatigue, anorexia and emotional stress, which may influence nutritional intake and QoL [de Graeff, 1999 #532; Padilla, 1992 #533]. QoL assessment measuring the patients' experiences of the impact of disease/therapy, expectations and satisfaction should be the gold standard as an independent end-point in most clinical trials [Testa, 1996 #454; Wasserman, 1995 #466]. In the context of this prospective interventional study, we chose to test two QoL assessment instruments, in order to investigate their feasibility considering time of completion. Both, organised in distinct scales and items but somewhat covering similar dimensions, identified nutrition as one of the patients' major worries, further emphasised by the associations between nutritional parameters and QoL. The EUROQOL instrument disclosed worse QoL in HR patients, namely oesophageal, stomach or HN cancer, both at baseline and at the end of RT, p=0.001. However, with the exception of symptom-induced pain/discomfort, and by contrast with LR patients, HR patients reported a significant improvement in all QoL dimensions at the end of RT. Although some data suggest an association between worse well being/morbidity and poor nutritional parameters [King's Fund, 1992 #415], their relationship with QoL is widely underestimated [Vetta, 1999 #530]; two articles have addressed the value of artificial nutritional support on patients' nutritional status and QoL [Van der Schueren, 2000 #459; Roberge, 2000 #510]. We have shown for the first time that, in HR diagnoses poorer nutritional status and intake were associated with worse mobility, limited usual activities and increased anxiety/depression. The improvement of the patient's nutritional intake, was correlated with the reported improvement of QoL dimensions throughout RT. On the other hand, QoL dimensions scores were always much better in LR patients, likewise nutritional aspects were better, and not different, at both evaluation set points.

Baseline mean self-rated health status (SRHS), i.e. the patients' perception of their overall health [Brooks, 1990 #368] was also better in LR. Worse SRHS in HR patients was associated with poorer nutritional status and intake; although by univariate analysis, a better final nutritional status was associated with higher QoL, p=0.03, the use of multivariate analysis disclosed the single significant association between final SRHS and nutritional intake, p=0.001. Moreover, in spite of marked RT-induced symptoms, all HR patients did show a significant increase in their SRHS, which was correlated with improved nutritional intake, p=0.001. In LR patients, the slight SRHS improvement was independent of nutritional intake. Our findings in HR patients reveal that a successful nutritional counselling and monitoring play an important role in QoL maintenance and/or improvement.

The EORTC instrument [Aaronson, 1993 #503] disclosed overall similar QoL results: HR patients self-reported worse QoL, more evident in oesophageal, stomach and HN cancer, when

compared with LR patients. At baseline, only in the HR group nutritional parameters did affect QoL components; malnutrition was associated with worse function scales as well as with poor appetite and increased fatigue. Poor scores in the latter two, along with worse global QoL, physical and emotional function scales were associated with low energy intake. At the end of RT, HR patients reported a higher QoL improvement, significant for all function scales, whilst LR patients only reported an increase in their global QoL without deterioration in any QoL dimension. HR patients worsened their symptom scales and single items, statistically significant for self-reported pain, nausea/vomiting and appetite; pain/discomfort was only associated with increased severity of symptoms (p=0.001). By multivariate analysis, nutritional intake improvement was the only variable associated with final global QoL (p=0.001), physical (p=0.03), role (p=0.01) and emotional (p=0.04) functions. As observed with the EUROQOL instrument, patients which improved their intake also enhanced their QoL dimensions.

The results of both instruments showed that nutrition care does play a major role in the improvement of HR patients' QoL, despite the expected detrimental effects of RT [de Graeff, 1999 #532; Padilla, 1992 #533]. Our results agree with the Keys *et al* landmark study on human semi-starvation, which clearly demonstrated that psychological and functional improvements are early responses to nutritional intake increase [Keys, 1950 #629].

The EUROQOL instrument describes health-related QoL according to 5 global domains; its completion is significantly shorter and less time consuming, on average 5±2 minutes. EORTC QLQ C-30 instrument covers more items and scales, identifies more domains and specific complaints, hence more comprehensive and time consuming, on average 13±3 minutes. Both instruments were able to assess patients' QoL; in the context of this study both revealed the relevance of nutrition care. The EUROQOL instrument should be used as a routine in such patients, since Quality of Life is a major outcome (25, 26); the QoL instrument to use must be decided within the context of each clinical study/practice.

Cancer patients are at nutritional risk to be evaluated by a health care professional with nutrition expertise (1). His/her integration in the multidisciplinary management allows a proper assessment of nutritional status and requirements, early nutritional counselling and monitoring of diet compliance enables timely adjustments according to symptoms. Our results show that, in patients prone to develop nutritional problems and to report the worst QoL, individualised nutritional counselling during Radiotherapy is feasible, does improve nutritional intake that is identified as central to a better QoL. Early intervention, sensible partnership with patients are the keys to success.

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Section 3

STUDIES OF EVALUATION OF MULTIPLE INTERACTIONS

Chapter 4

NUTRITIONAL DETERIORATION IN CANCER: THE ROLE OF DISEASE AND DIET

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ABSTRACT

Context: Undernutrition is a major source of morbidity and mortality in cancer patients.

Objective: To evaluate the relative contributions of cancer staging/duration and diet on patients' nutritional deterioration.

Design: Prospective cross-sectional cohort study conducted from July 2000-February 2002.

Setting: Ambulatory care.

Patients: 205 (133M:72F) consecutive patients with cancer of the head-neck, esophagus, stomach, colon/rectum, age 53±12 (33-86) years, proposed for radiotherapy (primary, adjunctive to surgery, combined with chemotherapy or with palliative intent) were included. Clinical variables, nutritional status (%weight loss, Patient-Generated Subjective Global Assessment and body mass index), nutritional requirements, usual diet intake (Diet History) and current intake (24hr recall) were registered. ***Results***: In staging III/IV, there was a significant decrease of usual and current energy/protein intake (p=0.002), which was not observed in staging I/II. Nutritional intake reduction was influenced by disease duration (p=0.04), but when the latter was evaluated in a multivariate analysis, current diet intake was associated only with staging, p=0.004, thus disclosing a distinct pattern of nutritional intake between stages and diagnoses. By general linear model, advanced staging showed the most significant association with nutritional depletion (p=0.0001); significant associations were also found for tumor location (p=0.001), disease duration (p=0.002), nutritional intake (p=0.003), previous surgery or chemotherapy (p=0.02). Percentage weight loss showed a consistently superior performance regarding clinical variables and the ability to detect mild to extreme nutritional changes; relative to body mass index, Patient-Generated Subjective Global Assessment had a very high sensitivity/specificity and strong capacity of detecting patients at nutritional risk.

Conclusions: Nutritional depletion is multifactorial, mainly dependent of the tumor burden for the host. Percentage weight loss is a sensitive and specific tool to effectively screen and identify malnutrition. Its joint use with Patient-Generated Subjective Global Assessment, which sets up boundaries for nutritional therapy, will optimize the efficacy of nutritional assessment and support in cancer patients.

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 appears to be the end-result combination 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 multidimensional manifestation that worsens the patients' well-being[7], tolerance to and prognosis after antineoplastic therapy[8,9], decreases immunological responses to tumor cells[10] and resistance to infection[11], and increases susceptibility to postoperative complications[12,13], disability and overall cost of care[14].

In order to tackle nutritional deterioration, gathering objective data on nutritional status and its evolution throughout the disease course appears to be of prime concern. 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]. Notwithstanding that different cancer types or locations may display different nutritional patterns[16,17], there is some inconsistency between studies relative to nutritional status assessment and cancer/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].

Within this framework, the major goal of this prospective study conducted in head and neck, esophageal, stomach and colorectal cancer patients, was to explore the intricate construct of various disease-related and diet-related factors potentially implicated in the patient nutritional deterioration. The disease extent, estimated by staging variables, was hypothesized 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 Hospital Ethics Committee and was conducted in ambulatory patients with cancer of the head and neck, esophagus, stomach and colon/rectum. It was designed as a prospective cross-sectional study to investigate the role of disease staging and/or 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 (HN), esophagus (ESO), stomach (STO) and colon/rectum (CR) referred to the outpatient Radiotherapy Department were considered eligible. Before the decision of radiotherapy planning, the medical staff registered, for each patient, the clinical variables, the duration of the disease, cancer location, the presence of distant metastases, and tumor burden according to TNM staging[19], determined by local and hole-body imaging methods. The duration of the disease was defined as the length of time (in months) between symptomatic manifestations, later confirmed by histology, and study entry. The cohort included 205 adult patients (133M:72F), age 53±12 (range: 33-86) years, proposed for RT: primary, adjunctive to surgery, combined with chemotherapy or with palliative intent. Data was recorded in individual sheets preconceived for statistical analysis.

Study Measures

At the onset of RT, assessment of nutritional status was performed by a single trained research dietician (PR) as described.

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 by comparison 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, that addresses: a) weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhea, xerostomia, pain), alterations in food intake by comparison with the usual intake, and functional capacity; b) components of metabolic stress: sepsis, neutropenic or tumor fever, corticoesteroids, and c) 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 edema or ascites. Nutritional status is then categorized in three degrees: normal, moderate and severe malnutrition.

Nutritional Requirements and Dietary Assessment. Basal energy requirements were estimated by the World Health Organization formula for subjects aged<60 yrs[22] or by the Owen *et al* formulas for subjects aged>60 yrs[23,24], given their higher ability to predict resting metabolic rate[25]. Patient daily estimated energy requirements (EER) were calculated by multiplying basal requirements by a 1.2 activity factor[26]; daily protein requirements were estimated by comparison with reference values standardized for age and sex, which ranged between 0.8 and 1.0 g/kg per day[27].

Usual (prior to the diagnosis) nutritional intake evaluation was derived from the diet history[28] and current intake was assessed by a 24hr-recall food questionnaire[30]. The nutrient contents of cooked foodstuffs and meals, were analyzed by the software DIETPLAN version 5 for Windows (Forestfield software Ltd 2002, Horsham, UK).

In order to evaluate differences between cancer stages, patients were clinically and physiologically grouped in two classes: staging I+II (local disease) and staging III+IV (advanced local disease with or without lymph node invasion[31].

Statistical Analysis

Statistical analysis was conducted using SPSS 10.0 (SPSS Inc, Chicago, USA) and EPI–Info 2000 (CDC, Atlanta, USA). 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 by Chi-square. Correlations were assessed by non parametric (Spearman) test. Multivariate general linear model was used to identify the variables that were significantly related with nutritional deterioration. Sensitivity and specificity of the nutritional assessment methods were compared by the Youden index which ranks diagnostic tests from –1 (the worst) to 1 (the best).

RESULTS

Staging. Patient's diagnoses and cancer staging are shown in **Table 1** there were 35 staging I or II and 170 staging III or IV patients.

Table 1 Patient diagnosis and disease staging

Location	n	**Staging** (n)
Head and neck (HN)		
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)
GI tract		
Esophagus (ESO)	8	II (1); III (4); IV (3)
Stomach (STO)	20	I (1); II (1); III (10); IV (8)
Colorectal (CR)	114	II (17); III (72); IV (25)

n= number of patients; none had distant metastases.

Duration of the disease. Patients' duration of disease was further grouped according to cancer staging, **Figure 1**. Overall, there was as a trend for patients with advanced disease staging to present longer duration of the disease, p=0.06.

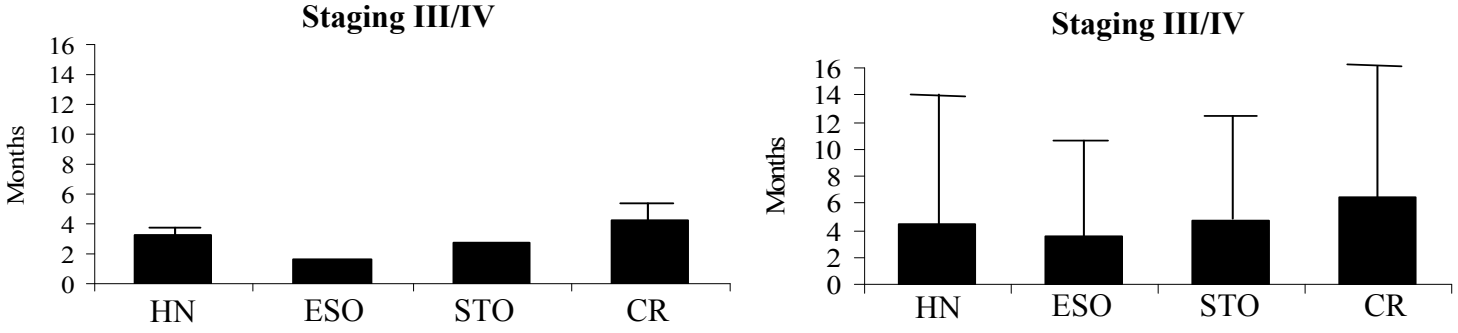

Figure 1 Duration of disease, shown as median and standard deviation, for each diagnosis grouped by tumor staging. The duration of disease was longer in staging III/IV patients *Vs* staging I/II patients, p=0.002.

Nutritional intake. Both usual and current intakes were compared to estimated energy requirements (EER), taking into account disease location and staging, **Figure 2**.

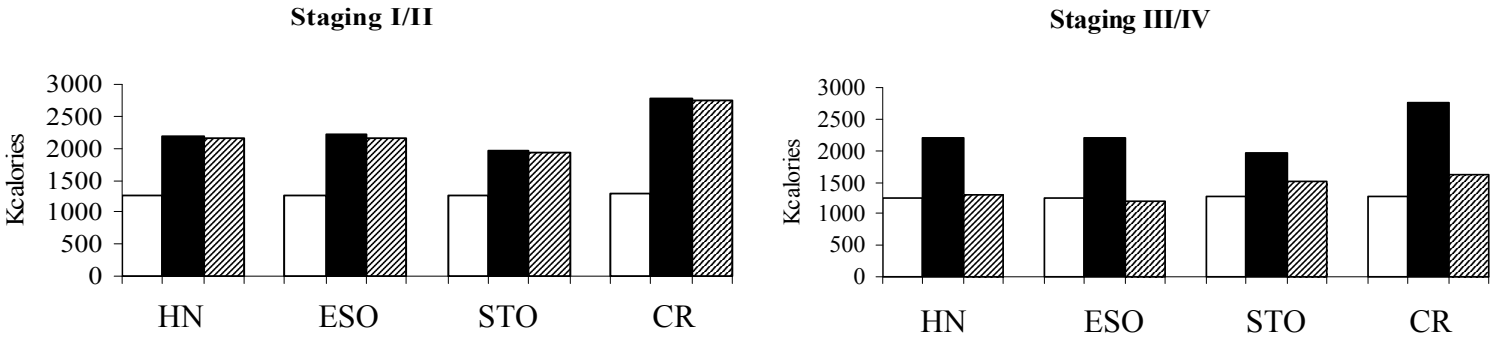

Figure 2 Patients' median estimated requirements □, median usual energy intake ■ and median current energy intake ▨.

In stage I/II patients, the median usual and current energy intake were not significantly different, unlike stage III/IV patients in whom there was a significant decrease of their usual intake, p=0.002. Furthermore, current energy intake was lower in stage III/IV patients than in staging I/II, p=0.001.

Both usual and current protein intake were compared with the median reference value, taking into account disease location and staging, **Figure 3**.

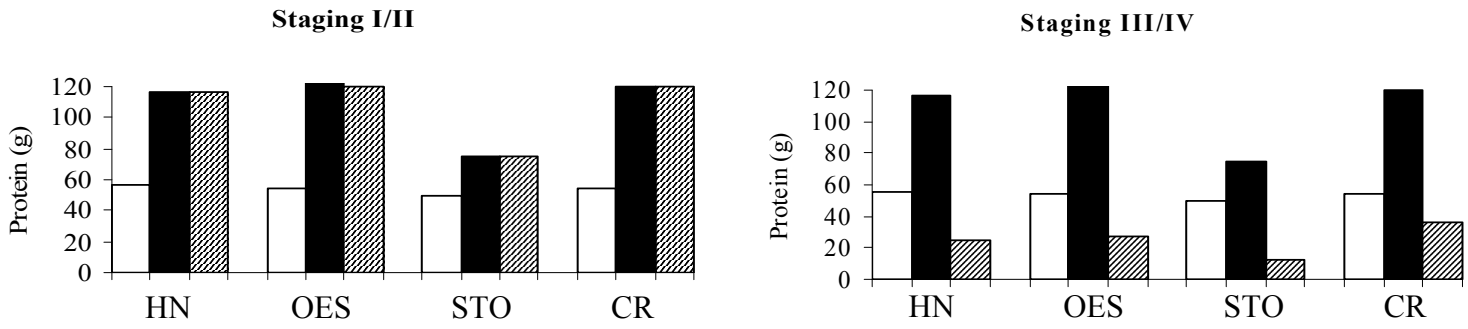

Figure 3 Daily total protein intake in grams: patients' median reference value □, usual intake ■ and current intake ▨.

Usual and current protein intake were not significantly different in staging I/II patients, whereas staging III/IV patients presented a significant decrease of their usual intake, p=0.0001. Overall, current protein intake was lower in staging III/IV *Vs* staging I/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. When the influence of disease staging and duration on nutritional intake were simultaneously analyzed, only staging revealed a significant association, p=0.004. **Table 2** shows the median energy and protein intake decreases for each diagnosis and disease staging; energy intake decrease tended to be proportional to protein intake decreases, p=0.07, disclosing a global nutritional intake reduction.

Table 2 Median reduction in energy and protein intake

Diagnosis	Energy[1]		Protein[2]	
	Staging		Staging	
	I / II	III / IV	I / II	III / IV
Head and neck	– 40	– 908	– 0.5	– 92
Esophagus	– 52	– 1019	– 1	– 96
Stomach	– 20	– 451	– 0	– 62
Colorectal	– 20	– 648	– 0	– 67

[1]Expressed as kcalories/day; [2]expressed as grams/day.

In staging III/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 reference values (p=0.002), still remained within the estimated requirements. No reduction in energy and protein intake was found in staging I/II patients; further, their intake was significantly higher than the reference values, p=0.005. Staging III/IV patients with cancer of the HN or esophagus showed the worst decreases in both energy and protein intake, p=0.02.

Nutritional Status

Weight loss. For each diagnosis, patients' median percentage of weight loss is shown in **Figure 4**.

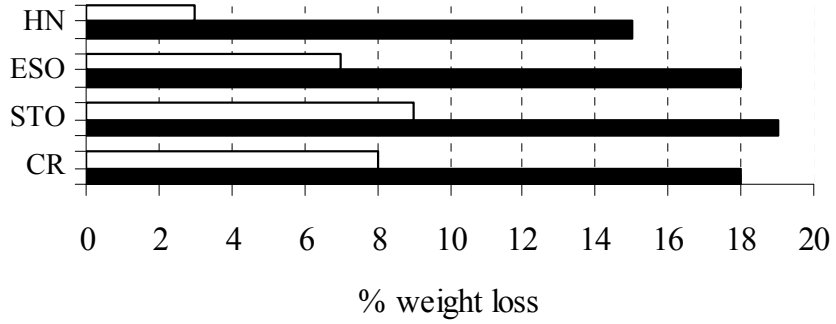

Figure 4 Median percentage of weight loss over the previous 6 months in staging I/II ☐ and staging III/IV patients ■, according to disease location; HN: head-neck, ESO: esophagus, STO: stomach, CR: colorectal.

Overall, weight loss was significantly higher in staging III/IV than in staging I/II patients, p=0.001. Amongst the latter, only 2/35 (6%) had lost more than 10% of their usual weight, whereas all staging III/IV patients reported weight losses greater than 10%. There was a trend for patients with >10% weight loss to have longer duration of the disease, p=0.08. When the influence of disease staging and duration on weight loss were simultaneously analyzed, only staging revealed a significant association, p=0.002.

Body Mass Index. For each diagnosis, patients' median BMI is shown in **Figure 5**.

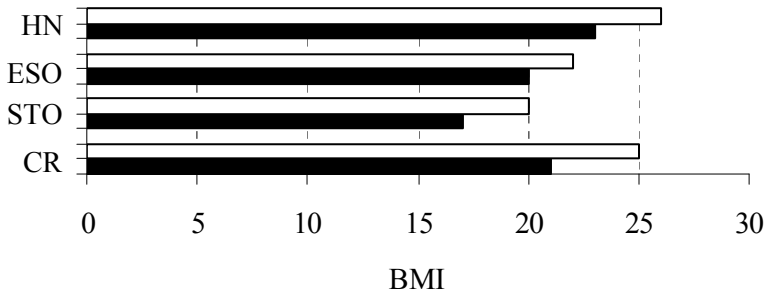

Figure 5 Median Body Mass Index for staging I/II □ and staging III/IV patients ■, according to disease location; HN: head-neck, ESO: esophagus, STO: stomach, CR: colorectal.

Overall, BMI was significantly lower in staging III/IV than in staging I/II patients, p=0.04. Amongst the latter, only 2/35 (6%) had a BMI below 20 kg/m^2, which was observed in 45/170 (26%) staging III/IV patients, p=0.05; further, 30 (26%) patients with CR cancer were still obese (20). No association was found between BMI and duration of the disease and further multivariate analysis of the latter with disease staging, revealed a significant association only between BMI and staging, p=0.05.

Patient-Generated Subjective Global Assessment. Nutritional status according to disease location is shown in **Figure 6**.

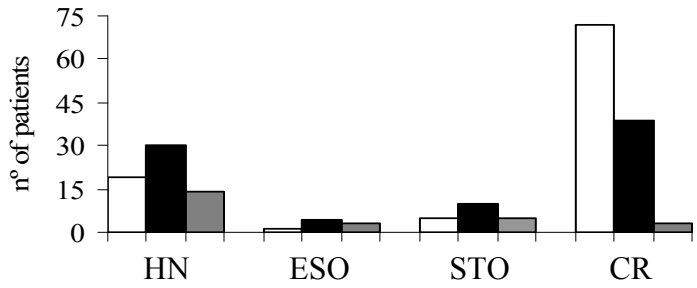

Figure 6 Nutritional status categories: normal nutritional status □, moderate malnutrition ■ and severe malnutrition ▩, according to disease location; HN: head-neck, ESO: esophagus, STO: stomach, CR: colorectal.

In staging I/II severe malnutrition was never observed, and only 4 patients (2 HN, 1 ESO and 1 STO) presented with moderate malnutrition. Conversely, malnutrition (moderate+severe) was prevalent amongst staging III/IV patients (79%) relative to staging I/II (3%), p=0.003, and was not significantly associated with the duration of the disease, p=0.09. When the influence of disease staging and duration on nutritional status were simultaneously analyzed, only staging revealed a significant association, p=0.01. Categorization 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 of weight loss (**Figure 7**) and was also associated with nutritional status as categorized by PG-SGA (**Figure 8**).

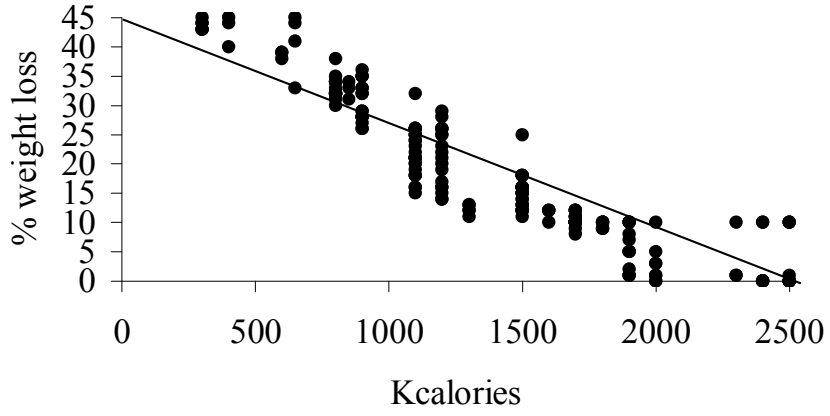

Figure 7 Correlation between % weight loss and energy intake, r=–0.67, p=0.002.

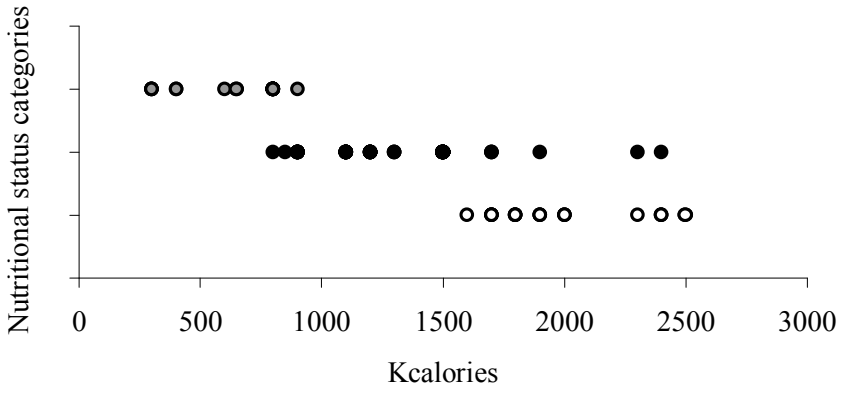

Figure 8 Energy intake by PG-SGA categories: normal ○, moderate malnutrition ● and severe malnutrition ◍; a negative association was observed, p=0.003.

Patients with adequate nutritional status reported an energy intake ≥ 1500 kcal, corresponding to ±125% of the EER; on the other hand, in severely malnourished patients, energy intake was ≤ 955 kcal, which corresponds to about ±80% of the EER.

We further performed a sensitivity and specificity analysis (ROC curve interpreted by relative areas under the curves and Youden value) for each nutritional status assessment method. Because this is a comparative analysis of 1 or more methods *Vs* a standard, our results flagged percentage weight loss which showed a consistently superior statistical performance regarding clinical variables, as well as the ability of detecting mild to extreme nutritional changes. **Figure 9**

illustrates the sensitivity/specificity relation of % weight loss *Vs* PG-SGA and % weight loss *Vs* BMI.

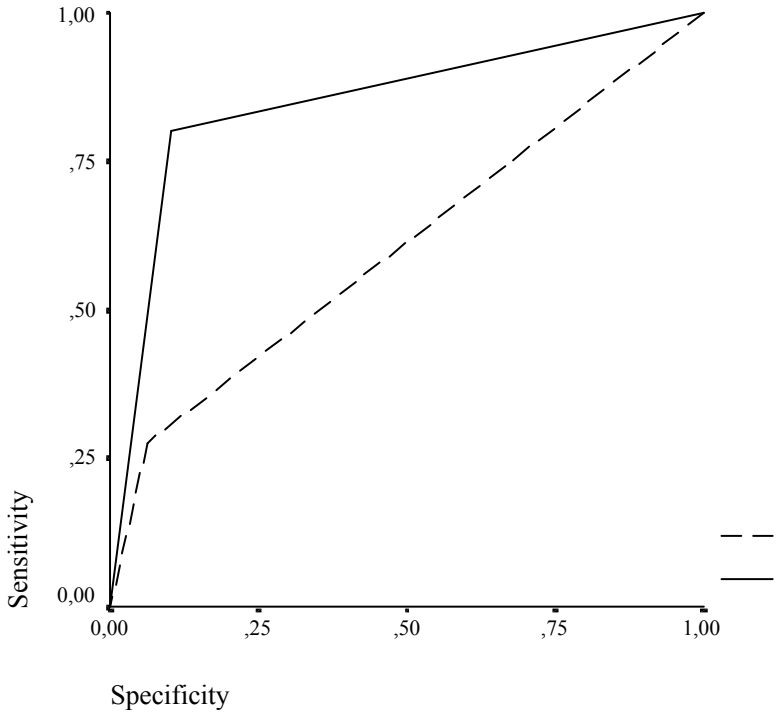

Figure 9 ROC curves for % weight loss *Vs* PG-SGA ____ and % weight loss *Vs* BMI _____.

As for PG-SGA, the Youden value of 0.85, p=0.00001 (sensitivity=0.80, specificity=0.89) indicates a very high performance by comparison with the standard, and a strong capacity to effectively detect patients at high nutritional risk; in what concerns BMI, the Youden value of 0.47, p=0.02 (sensitivity=0.27, specificity=0.27) indicates a poor performance by comparison with the standard, and a weak capacity to effectively detect patients at high nutritional risk. The influence of energy intake on nutritional depletion was further evaluated by non-parametric correlation stratifying on cancer staging (**Figures 10 and 11**).

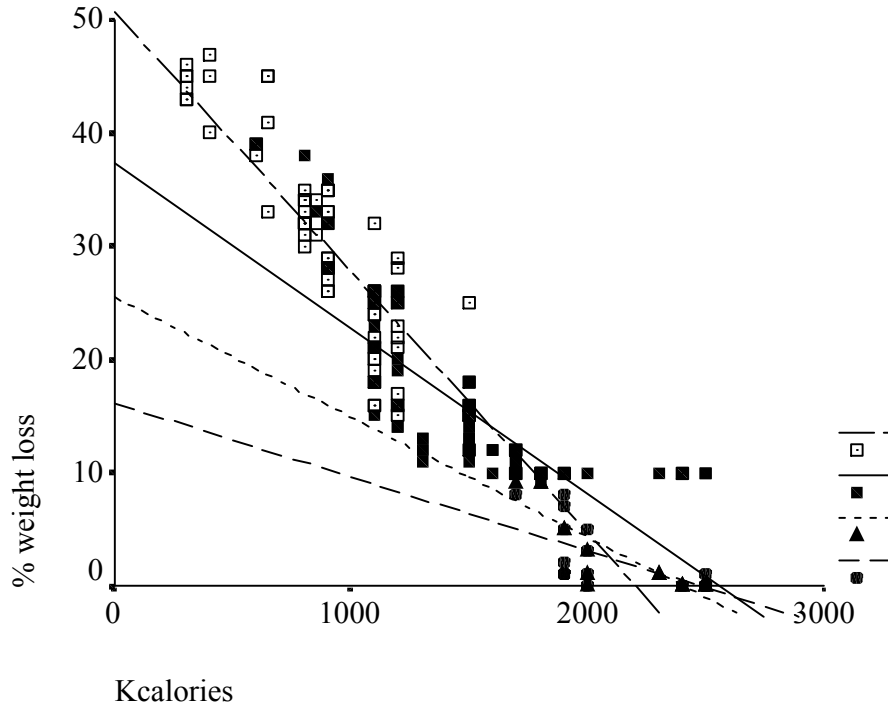

Figure 10 Correlations between % weight loss and energy intake by cancer staging. Staging I ●: r=–0.14, p=0.09; II ▲: r=–0.15, p=0.09; III ■: r=–0.52, p=0.002; IV □: r=–0.72, p=0.001.

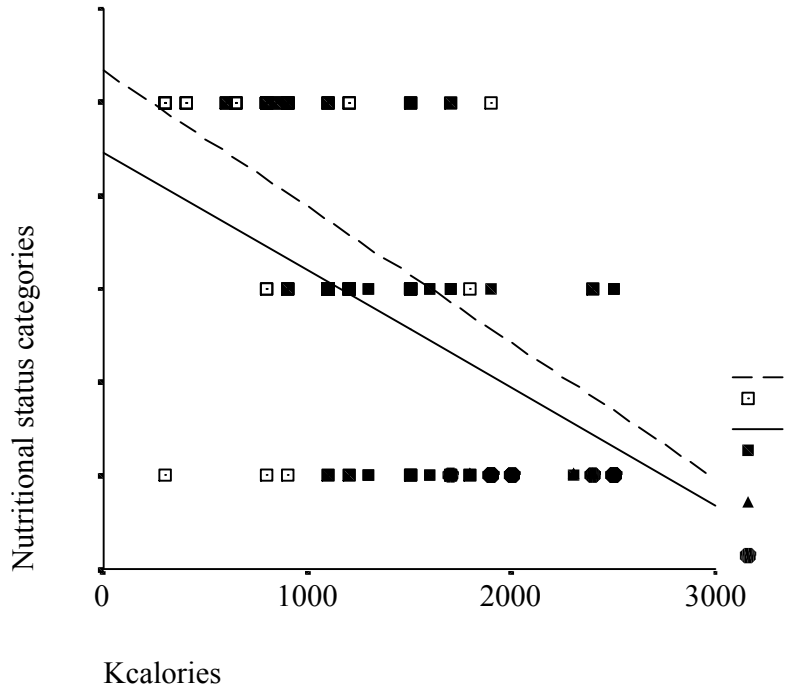

Figure 11 Associations between PG-SGA nutritional status categories and energy intake by cancer staging. Staging I ●: p=0.13; II ▲: p=0.10; III ■: p=0.004;IV □: p=0.003.

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 further found a distinct difference between diagnoses, **Table 3**.

Table 3 Non-parametric correlation analysis between energy intake and nutritional depletion stratifying on cancer staging and corrected by diagnosis.

Diagnosis	**Staging**			
	I	II	III	IV
Head-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
Esophagus	–*	–*	r=–0.89, p=0.0001	r=–0.91, p=0.0001
Stomach	–*	–*	r=–0.88, p=0.0001	r=–0.90, 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

*Unable to compute the analysis due to small patient sample size.

Advanced cancer staging was the common denominator to the patients' nutritional depletion, clearly potentiated by the diagnosis. Patients with head-neck and esophageal cancers showed a markedly significant nutritional deterioration.

By using a general linear model, using nutritional status as the dependent variable, the patients' nutritional deterioration was related to the following variables: cancer staging, 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[32], and the production and release of proinflammatory cytokines[6]. The progressive caloric deficit may be exacerbated by anorexia, disphagia, vomiting and malabsorption, associated with cancer itself and/or its treatment[4,33,34]. The relative contribution of the above conditions to nutritional depletion is thought to differ according to cancer type or site[35,36], and has long been suspected to be proportional to cancer extent, a concept mostly based on clinical expertise and observational data[15]. The accurate longstanding energy and substrate deficit has not been systematically investigated nor adjusted by the patients' disease staging.

This prospective analysis of 205 patients with cancer of the head-neck and gastrointestinal tract, demonstrates for the first time that marked deficiencies in nutritional intake are conditioned by the extent of the disease. For all staging 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 markedly lower relative to staging I/II patients, p=0.001. Although the global nutritional intake reduction was negatively correlated with the duration of the disease (p=0.04), which was

longer in advanced stages, by multivariate analysis only cancer staging was significantly associated with dietary changes.

In order to further clarify the relative roles of nutritional intake reduction and cancer staging, the univariate associations between cancer-related variables, diet and nutritional depletion were investigated. Advanced staging was indeed the common denominator to 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-neck and esophageal 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 define nutritional status[37,38], controversy exists regarding 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[39]. In this study, BMI showed low sensitivity and specificity results, which indicate a poor performance and a limited capacity to effectively detect patients at high nutritional risk.

It has become almost a dogma that unintentional weight loss higher than 10% of pre-illness weight, or in the previous 3-6 months, represents a high risk of malnutrition[40-42]. Our analyses corroborated its superior performance regarding all clinical variables, as well as its ability to detect mild to extreme nutritional changes; hence, 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[40-42]. 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 very high performance and a strong capacity to effectively detect patients at high nutritional risk and malnutrition. In cancer patients, the PG-SGA should be used in conjunction with significant weight loss, aiming at establishing a planned overall cancer management and set up boundaries to direct nutritional therapy[18]. This integration should be implemented in clinical practice, group protocols, and nutritional intervention clinical trials, in order to optimize quality of patient care.

It is noteworthy that malnutrition was prevalent in staging III/IV *Vs* staging I/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-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 staging showed by far the most significant association with worse nutritional status; cancer location,

duration of the disease, protein and energy intake and previous surgery or chemotherapy were also significantly associated.

Besides the identification of valid nutrition assessment tools, this preliminary study provides novel clinical evidence of the complex interactions between cancer and/or treatment-related variables and diet changes, all of which exert a combined effect on the patients' nutritional deterioration. The pattern and/or progression of nutritional deterioration is mostly determined by cancer diagnosis; albeit the tumor burden for the host appears to be of major importance. Our results are consistent with the hypothesized relations between wasting and progressive disease, which is likely to exacerbate every organ/systemic physiological derangement.

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Chapter 5

CANCER: DISEASE AND NUTRITION ARE KEY DETERMINANTS OF PATIENTS' QUALITY OF LIFE

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ABSTRACT

Goals of work: 1) to evaluate Quality of Life (QoL), nutritional status and dietary intake taking into account the stage of disease and therapeutic interventions, 2) to determine potential inter-relations, 3) to quantify the relative contributions of cancer/nutrition/treatments on QoL. *Patients and Methods*: In this prospective cross-sectional study conducted in 271 head-neck, oesophagus, stomach and colorectal cancer patients, the following aspects were evaluated, QoL (EORTC-QLQ C30), nutritional status (%weight loss over the previous 6 months), usual diet (comprehensive diet history), current diet (24hr recall) and a range of clinical variables. *Main Results*: Usual/current intakes differed according to the site of the tumour ($p=0.02$). Stage III/IV patients showed a significant reduction from their usual energy/protein intake ($p=0.001$), while their current intakes were lower than in stage I/II patients ($p=0.0002$). Weight loss was greater in stage III/IV vs I/II ($p=0.001$). Estimates of effect size revealed that QoL function scores were determined in 30% by cancer location, in 20% by nutritional intake, in 30% by weight loss, in 10% by chemotherapy, in 6% by surgery, in 3% by disease duration and in 1% by stage of disease. Likewise in the case of symptom scales, 41% were attributed to cancer location, 22% to stage, 7% to nutritional intake, 7% to disease duration, 4% to surgery, 1% to weight loss and 0.01% to chemotherapy. Finally for single items, 30% were determined by stage, 20% by cancer location, 9% by intake, 4% by surgery, 3% by weight loss, 3% by disease duration and 1% by chemotherapy. *Conclusions*: Although the cancer stage was the major determinant of the patients' QoL globally, there are some diagnoses when the impact of nutritional deterioration combined with deficiencies in nutritional intake may be more important than the stage of the disease process.

INTRODUCTION

Malnutrition in cancer is likely to be multifactorial (1, 2), although tumour location and presenting symptoms, e.g. anorexia, taste changes, dysphagia, nausea, vomiting, diarrhoea, may further compromise nutrition and functional ability (2-4). The interaction between nutritional status and intake, and the above-mentioned symptoms and/or disease/treatment-related factors, is a complex combination which may dictate patients' Quality of Life (QoL).

Quality of Life is a subjective multidimensional construct reflecting functional status, psychosocial well being, health perceptions and disease/treatment-related symptoms (5). Despite the suggested association between worse overall well being/morbidity and nutritional deterioration (6), the interaction between nutrition and QoL remains underestimated (7). Although nutritional care has been proposed as auspicious to cancer patients (8), to date there is scant evidence to support an interaction between nutrition and QoL.

Within this framework, this prospective cross-sectional study conducted in head and neck, oesophageal, stomach and colorectal cancer patients was designed to explore the potential interaction(s) between various disease-related and diet-related factors likely to be implicated in such patients' Quality of Life. Our specific aims were 1) to evaluate patients' nutritional status, nutrient intake and QoL, taking into account disease stage and previous therapeutic

interventions, 2) to determine the potential inter-relations, and 3) to quantify the relative impact of cancer/treatments and/or nutrition-related factors on patients' QoL.

PATIENTS AND Methods

Study Design and Patient Sample

This prospective cross-sectional study, approved by the University Hospital Ethics Committee and conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983, was designed to investigate the inter-relations between cancer/treatment, nutrition-related factors and the patients' QoL. Between July 2000 and September 2002, all consecutive ambulatory patients with cancer of the head and neck (HN), oesophagus (OES), stomach (STO) and colon/rectum (CR) referred to the Radiotherapy Department were considered eligible; only patients with other chronic diseases were excluded. All participants gave their informed consent to enter the study. For every patient and prior to radiotherapy planning, the medical staff registered: clinical variables, duration of the disease, cancer location, presence of distant metastases, and tumour burden according to TNM stage (9) determined by local and whole-body imaging methods. The duration of the disease confirmed by histology, was defined as the length of time (in months) between symptomatic manifestations and study entry. In order to evaluate differences between cancer stages, patients were clinically and physiologically grouped in two classes: stage I+II (*in situ* or local disease) and stage III+IV (locally advanced disease with or without lymph node invasion and/or distant metastases) (10). Data were recorded on individual sheets pre-constructed for statistical analysis.

Study Measures

Nutritional Assessment. Weight was determined with a Jofre® floor scale. Nutritional status was assessed by calculating the percentage of weight loss in comparison with the patient's reported usual weight, and classified as severe when >10% had been lost over the previous 6 months (11).

Nutritional Requirements and Dietary Assessment. Basal energy requirements were estimated using the World Health Organisation formulae, patients aged ≤60 yrs (12) or by the Owen *et al* formulae, age >60 yrs (13, 14), given their better performance in predicting resting metabolic rate (15). To estimate patients' daily energy requirements (EER), basal requirements were multiplied by a 1.5 activity factor (16); daily protein requirements were estimated by comparison with age and sex standardised reference values, which ranged between 0.8 and 1.0 g/kg per day (16).

Usual (prior to the diagnosis) nutritional intake was derived from a diet history (17, 18) and current intake was assessed by a 24hr-recall food questionnaire (19). The software DIETPLAN version 5 for Windows (Forestfield software Ltd 2003, Horsham, UK) was used to analyse nutrient contents of foodstuffs and meals.

QoL instrument. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30) was used in all patients to assess QoL. This instrument is a 30-item cancer specific questionnaire including 6 function scales (physical,

emotional, cognitive, social, role, and global health/QoL), 3 symptom scales (fatigue, pain, nausea/vomiting), and 6 single items assessing symptoms and the financial impact of the disease (20). Higher scores on the function scales indicate better functioning whilst higher scores on the symptom scales and single items denote increased symptomatology or worse financial impairment. Original scores were linearly transformed to obtain quantified scores within the range of 0 to 100; in addition, and for better validation in the clinical context, overall scores derived from function scales, symptom scales and single items, were calculated on the basis of the very high statistical significance of interscale correlations according to EORTC's guidelines (20).

Statistical Analysis

Statistical analysis was conducted using SPSS 10.0 (SPSS Inc, Chicago, USA) and EPI–Info 2000 (CDC, Atlanta, USA). Qualitative data, cancer location and stage, were expressed as number and percentage, while age, disease duration, weight loss, nutritional intake and QoL were expressed as median or mean and standard deviation. Between-group comparisons were performed by one way analysis of variance (ANOVA) for continuous variables, with Bonferroni or Dunn adjustment because of multiple comparisons; paired comparisons were performed by Students' t test; categorical variables were compared by Chi-square. Correlations were assessed by non-parametric (Spearman) test. A multivariate general linear model was used to identify variables that were significantly related with the patients' QoL. For all statistics, significance was accepted at the 5% probability level.

RESULTS

Patient sample. This study included 271 free-living patients (173M: 98F), mean age 54±12 (range 32-87) years, referred for radiotherapy (primary, adjuvant to surgery, combined with chemotherapy or with palliative intent). **Table 1** shows location and cancer stages: there were 65 stage I/II and 206 stage III/IV.

Table 1 Patients and disease stage

Location	n	**Stage** (number of patients)
Head and neck		
Base of the tongue	11	II (3); III (4); IV (4)
Salivary gland	6	II (1); III (5)
Tonsil	4	II (4)
Nasopharynx	11	II (2); III (9)
Oropharynx	22	II (5); IV (17)
Larynx	33	I (4); II (3); III (10); IV (16)
Gastrointestinal tract		
Oesophagus	14	II (3); III (6); IV (5)
Stomach	26	I (2); II (4); III (11); IV (9)
Colorectal	144	I (15); II (19); III (76); IV (34)

n= number of patients

Duration of the disease was longer in stage III/IV (6±13 months) *vs* stage I/II patients (3.6±5 months) (p=0.002).

Nutritional intake. Both usual and current energy and protein intakes were respectively compared with EER and the protein median reference values, taking into account the disease location, **Figure 1**.

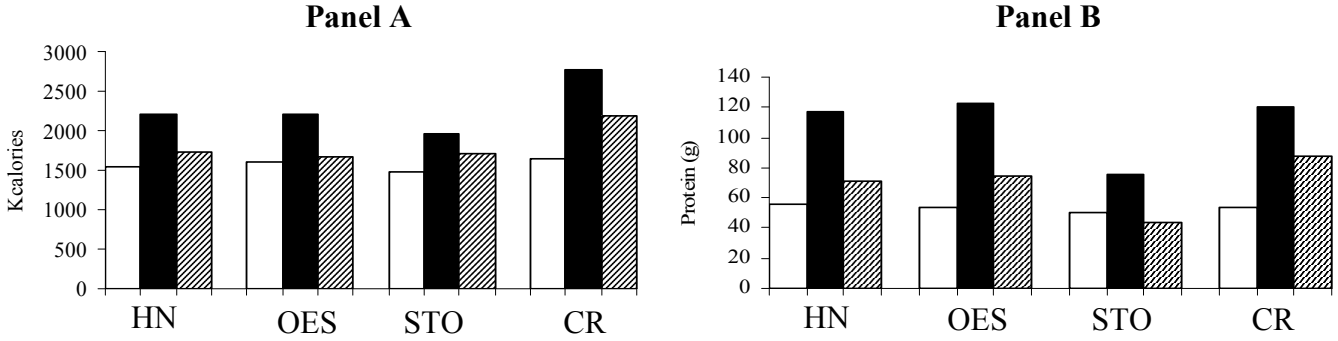

Figure 1 Panel A refers to energy and Panel B to protein intake; patients' median estimated requirements □, median usual intake ■ and median current intake ▨; HN: head-neck, ESO: oesophagus, STO: stomach, CR: colorectal.

In stage III/IV patients, the current protein intake was significantly lower than the reference value (p=0.001) whilst energy intake remained within the EER; conversely, in stage I/II patients, current energy/protein intake was still significantly higher than the reference, p=0.005. Moreover, current energy and protein intakes were lower in stage III/IV (p=0.0002 and p=0.001, respectively). **Table 2** summarises the median intake reductions for each diagnosis and disease stage and shows that decreases in energy and protein intake followed a similar pattern and tended to be proportional (p=0.05).

Table 2 Energy and protein intake: median reduction from usual intake

Diagnosis	**Energy (kcal/day)**		**Protein (g/day)**	
	Stage		**Stage**	
	I / II	III / IV	I / II	III / IV
	n=65	n=206	n=65	n=206
Head-neck (n=87)	– 50	– 910	– 0.8	– 89
Oesophagus (n=14)	– 64	– 1095	– 1	– 94
Stomach (n=26)	– 25	– 491	– 0,2	– 64
Colorectal (n=144)	– 20	– 652	– 0,2	– 68

n= number of patients

The largest decreases, both in energy and protein intake, were shown in HN and OES stage III/IV patients (p=0.02). Stratified analyses further stressed the differences; stage III/IV patients reported a significant decrease from their usual energy (p=0.001) and protein intake (p=0.0002) contrarily to stage I/II patients.

Nutritional status. The patients' median percentage of weight loss for each diagnosis is shown in **Figure 2**; OES and STO cancer patients presented a higher percentage of weight loss compared with HN and CR patients, p=0.04.

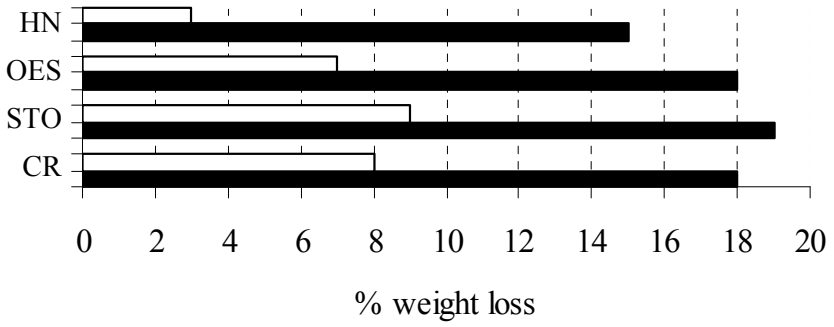

Figure 2 Percentage of weight loss over the previous 6 months (median) in stage I/II □ and stage III/IV ■, according to cancer location; HN: head-neck, OES: oesophagus, STO: stomach, CR: colorectal.

Overall, weight loss was significantly greater in stage III/IV relative to stage I/II patients, p=0.001. In the latter group, only 7/65 (10%) had lost more than 10% of their usual weight, whereas 175/206 (85%) of stage III/IV patients reported weight losses greater than 10%.

Quality of Life. The median QoL dimensions' scores are summarised in **Table 3**.

Table 3 QoL dimensions according to cancer location and stage

Parameters	HN (n=87)		OES (n=14)		STO (n=26)		CR (n=144)	
	I/II	III/IV	I/II	III/IV	I/II	III/IV	I/II	III/IV
Function scales								
Global QoL	73	50	69	52	70	56	75	68
Physical	80	50	65	42	55	40	74	69
Activity	77	55	68	53	62	42	78	62
Emotional	64	51	63	51	45	36	65	65
Social	86	56	74	48	58	55	69	69
Cognitive	72	53	65	54	55	41	58	38
Symptom scales								
Fatigue	52	67	51	64	19	68	26	46
Pain	13	60	22	58	29	52	25	49
Nausea and vomiting	18	43	25	45	24	78	48	58
Symptoms and single items								
Dyspnea	18	25	38	56	2	2	5	5
Insomnia	23	53	25	45	25	35	19	39
Anorexia	19	73	41	55	19	79	28	68
Constipation	2	2	2	2	1	1	4	15
Diarrhoea	2	2	2	2	0	0	44	79
Financial impact	38	38	4	4	1	1	8	8

Results are expressed as median values; HN: head-neck, OES: oesophagus, STO: stomach, CR: colorectal; higher scores on the function scales indicate better functioning, higher scores on the symptom scales and single items denote increased symptomatoloy.

There was a distinct pattern between diagnoses ($p<0.03$) in relation to the QoL function scales which were poorer in HN, OES and STO cancer ($p\leq0.008$). Overall, symptom scales were worse in stage III/IV *vs* stage I/II, $p<0.003$; however, fatigue was significantly higher in HN and OES stage I/II than in STO or CR stage I/II ($p=0.02$), whereas nausea/vomiting was worse in stage I/II CR cancer ($p=0.03$) and pain was not significantly different between diagnoses. In all diagnoses, dyspnea, insomnia and anorexia were worse in stage III/IV *vs* I/II, $p=0.002$. Diarrhoea was more prevalent in CR cancer, $p=0.001$ and more severe in stage III/IV, $p=0.03$. Financial limitations associated with social/economical conditions were prevalent in HN cancer, $p=0.002$.

The analysis of nutrition related factors and their relationships with QoL, showed that energy and protein intake were correlated with function scales: global QoL ($r=0.53$, $p=0.001$), physical ($r=0.26$, $p=0.02$) and emotional ($r=0.29$, $p=0.01$) as well as with some symptoms: anorexia ($r=-0.52$, $p=0.001$), fatigue ($r=-0.60$, $p=0.001$), pain ($r=-0.55$, $p=0.003$), nausea/vomiting ($r=-0.51$, $p=0.003$) and diarrhoea ($r=-0.60$, $p=0.001$). Malnutrition in these patients was associated with poorer function scales: global QoL ($p=0.05$), physical ($p=0.01$), role ($p=0.02$),

cognitive (p=0.02), emotional (p=0.01) and social (p=0.01) as well as with some symptoms: anorexia (p=0.001), increased fatigue (p=0.03), dyspnea, insomnia and diarrhoea (p=0.04).

Given the strong interaction between QoL (dependent variable) and cancer stage and nutrition (independent variables), a non-parametric correlation analysis stratified by diagnosis was conducted. This analysis showed a distinct QoL pattern between diagnoses, and identified which variables were significantly associated with individual QoL global scores (**Figures 3a, 3b, 3c, 3d**, in which the vertical axes denote the global scores of function, symptom scales and single items, derived from inter-patients' median values). **Figures 3a** and **3b** show that functional capacity for all diagnoses was significantly influenced by current nutritional intake deficit and recent weight loss, but it was not affected by the cancer stage; in both instances OES and STO cancer showed poorer global function scores relative to HN and CR, p=0.02.

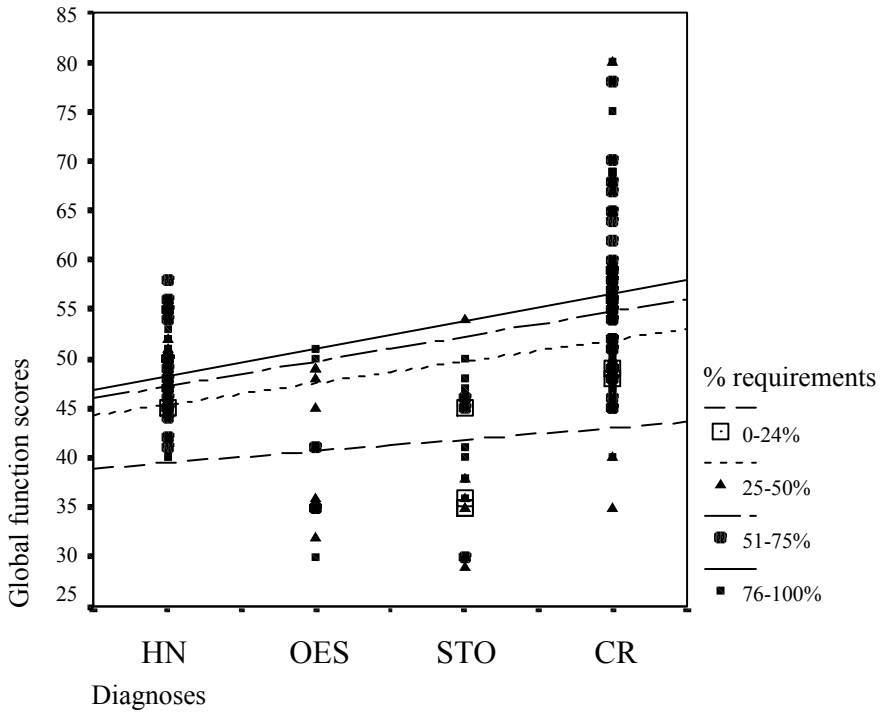

Figure 3a Global function scores according to diagnoses stratified by quartile of energy and protein intake; the vertical axes denote the scores derived from inter-patients' median values; HN: head-neck, ESO: oesophagus, STO: stomach, CR: colorectal. □ 0-24%, p=0.003; ▲ 25-50%, p=0.01; ● 51-75%, p=0.04; ■ 76-100%, p=0.05.

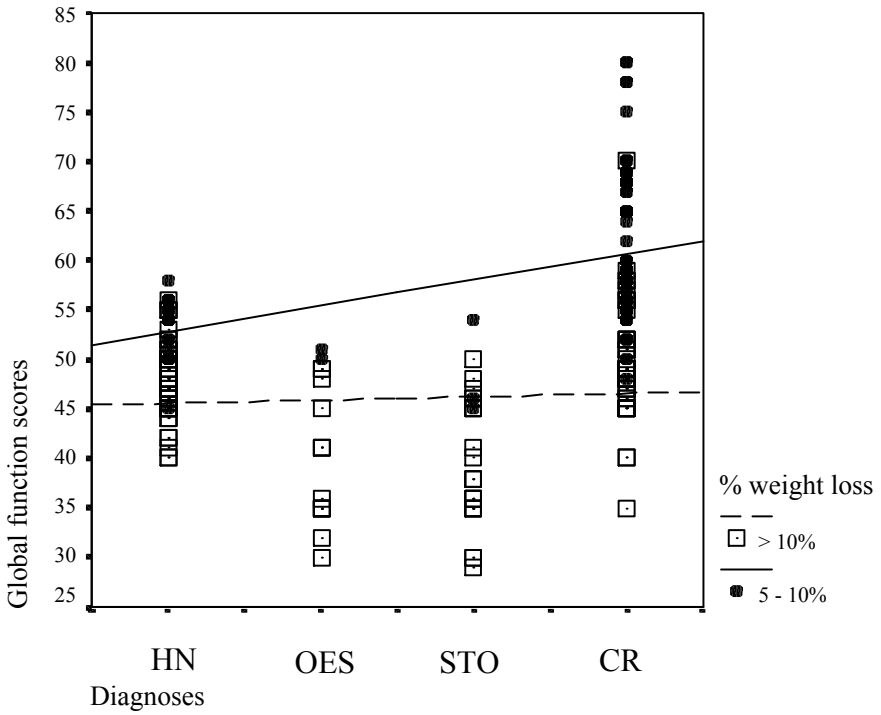

Figure 3b Global function scores according to diagnoses stratified by categories of significant %weight loss; the vertical axes denote the scores derived from inter-patients' median values; HN: head-neck, ESO: oesophagus, STO: stomach, CR: colorectal. ☐ >10%, p=0.001; ● 5-10%, p=0.06.

Figure 3c shows that global symptom scores were strongly associated with the stage of cancer and were not significantly different between diagnoses nor influenced by nutritional parameters.

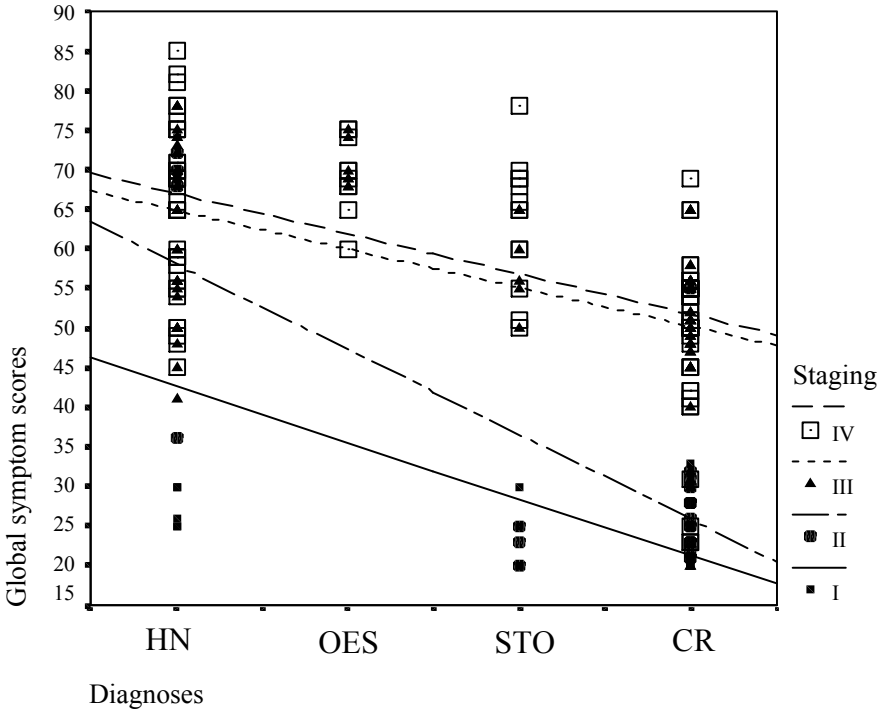

Figure 3c Global symptom scores according to diagnoses stratified by cancer staging; the vertical axes denote the scores derived from inter-patients' median values; HN: head-neck, ESO: oesophagus, STO: stomach, CR: colorectal. □ IV, p=0.001; ▲ III, p=0.002; ● II, p=0.04; ■ I, p=0.04.

Figure 3d shows that, similarly to the global symptom scores, poorer global single item scores were only associated with stage III/IV; although there were no significant differences between HN, CR and OES cancer, the latter showed the worse single item scores by contrast to STO cancer, p=0.03.

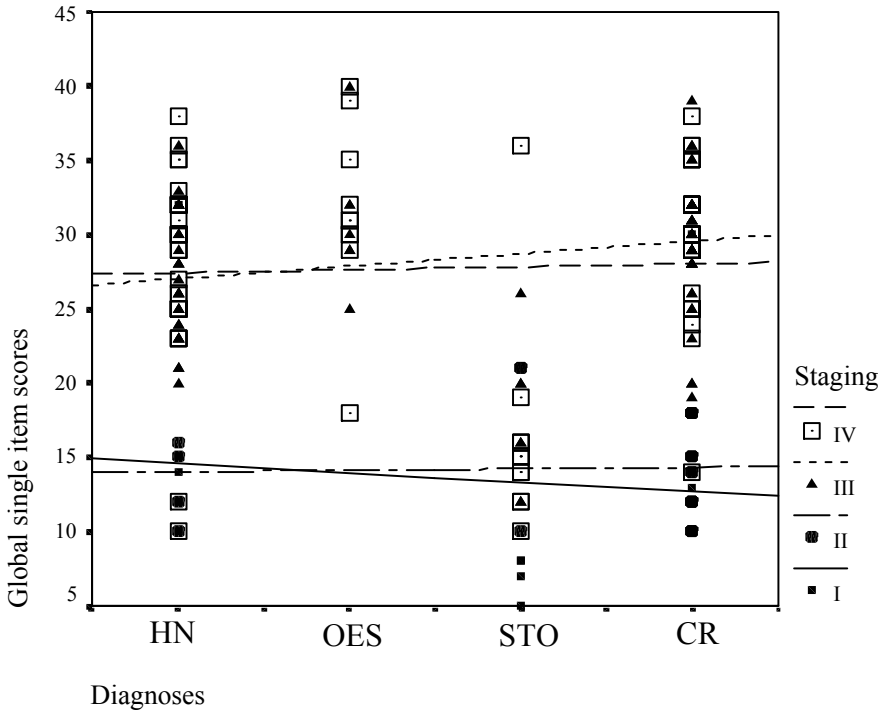

Figure 3d Global single item scores according to diagnoses stratified by cancer staging; the vertical axes denote the scores derived from inter-patients' median values; HN: head-neck, ESO: oesophagus, STO: stomach, CR: colorectal; □IV+ ▲ III, p=0.001; ● II+■ I, p=0.05.

Table 4 shows the results of a general linear model that included global QoL scores, nutritional parameters and cancer/treatment-related variables in order to calculate the estimates of effect size and the respective statistics.

Table 4 Inter-relationships and estimates of effect size (relative weights) of nutritional parameters and cancer/treatment related variables on QoL: results from general linear model analysis

	Global function scores			Global symptom scores‡			Global single item scores‡		
Variable	F-test	Estimates of effect size*	p	F-test	Estimates of effect size*	p	F-test	Estimates of effect size*	p
Stage	1.6	1%	0.18	56.5	22%	0.001	103.7	30%	0.0001
Location	111.2	30%	0.0001	77.2	41%	0.0001	49.2	20%	0.001
Energy intake	27.2	10%	0.01	1.0	3%	0.35	3.9	4%	0.07
Protein intake	27.2	10%	0.01	1.0	4%	0.25	4.2	5%	0.07
Weight loss	133.7	30%	0.0001	0.05	1%	0.82	1.2	3%	0.10
Duration of the disease	1.5	3%	0.14	10.0	7%	0.06	1.2	3%	0.30
Chemotherapy	35.3	10%	0.001	2.1	4%	0.22	1.3	1%	0.25
Surgery	6.1	6%	0.01	1.4	1%	0.86	3.0	4%	0.09

Columns denote dependent variables, and rows independent variables; each of the scales and single items were linearly transformed and grouped to obtain global scores before inclusion in the analytical model; *the sum of percentages may not equal 100% due to the corrected error size; ‡due to the potential association between symptoms and diagnoses, associations were adjusted for cancer location.

Cancer location, chemotherapy and surgery were significantly associated with all QoL scores whilst stage was only associated with symptom scores and single item scores. Nutritional intake and weight loss were significantly associated only with function scores, although there was a trend for an association with symptom scores and single items (p=0.06).

In order to evaluate which diagnosis was most strongly associated with poorer QoL, individual dimensions were grouped and valued according to their relative weights. STO cancer patients had the worst QoL although not significantly different from OES cancer; HN and CR cancer patients had a better QoL (p=0.02), CR>HN (NS). Overall, the stage of disease was identified as the major determinant of the patients' QoL (p=0.002), closely followed by deterioration in nutritional status (p=0.005) and dietary intake (p=0.007).

DISCUSSION

To be meaningful, QoL assessment must include the impact of the disease together with therapeutic interventions, expectations and personal satisfactions hence the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire was chosen as the most effective tool (20). The present study clearly shows that cancer patients' QoL is multifactorial and that it is distinctively influenced by the disease, therapeutic interventions and various nutritional parameters.

Cancer-related nutritional deterioration has been traditionally attributed to anorexia and metabolic derangements (3, 21, 22). Despite the fact that nutritional deterioration is associated with functional impairment (6), the interaction between nutrition and QoL is as yet unexplored (7). Artificial nutrition in cancer patients has been suggested to maintain nutritional status and

QoL (23, 24). Indeed, fatigue, anorexia and emotional stress, common in cancer patients, may further aggravate, but also be worsened by, poor nutritional intake and QoL (25, 26).

This study focuses on the evaluation of the potential and relative weight of nutritional baseline data amongst other potential QoL determinants. In cancer, longstanding energy and substrate deficits were not previously investigated nor adjusted by the patients' disease stage. Our results demonstrated marked nutritional intake deficits in the advanced stages of disease; there was not only a significant decrease from the usual energy and protein intake in stage III/IV, but current intakes were also markedly lower than in stage I/II. Stage III/IV HN and OES cancer were shown to be the most severe energy and protein depleted.

An advanced stage of disease was, indeed, the common denominator of patients' nutritional deterioration. Weight loss and reduced energy/protein intake were associated ($p=0.06$) although there was no consistent pattern. Our results corroborate and expand previous observations that progressive nutritional intake deficit may be associated with cancer location (3, 4, 27, 28), and may eventually be proportional to the extent of the disease (29).

In what concerns QoL dimensions, cancer stage mainly influenced the severity of symptom scales and single items, while energy/protein intake deficits and weight loss were detrimental to QoL function scales. Overall, patients' functional capacity was affected by cancer location and nutritional factors with a similar quota of 40% each, and by the stage of disease in only 1%; the relative contributions ascribed to chemotherapy, surgery and duration of the disease were 10%, 6% and 3%, respectively, as previously suggested in different patient groups (30-32). The symptom scales had an inverse pattern by comparison with function scales: 41% were attributed to cancer location, 22% to stage, 7% to nutritional intake, 7% to the duration of the disease, 4% to surgery, 1% to weight loss and 0.01% to chemotherapy. Likewise, cancer stage and location were the major determinants of QoL single items, which were worse in stage III/IV. Altogether, although the stage of disease was the major determinant of the patients' QoL, in some diagnoses the impact of nutritional deterioration combined with deficient intake may be more clinically important.

This study of 271 patients with cancer of the head-neck, oesophagus, stomach and colon/rectum, provides objective evidence that cancer, diet deficits, nutritional depletion and therapeutic interventions are determinants of the patients' QoL, but with distinct relative weights. Whereas chemotherapy/surgery were viewed by the patients as of minor relevance, our data are consistent with the hypothesised relationship between wasting and progressive disease (29). Although nutritional deficits and/or deterioration were intrinsic to the site and stage of disease, reduced energy/protein intake and weight loss were independent determinants of QoL. Our results concur with *Keys et al* landmark study which showed semi-starvation to impair functional and psychological abilities (33). It is of clinical relevance that individualised nutritional counselling and education appears to effectively maintain/improve nutritional intake/status, along with a significant improvement in the patients' overall QoL (34, 35).

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CONFLICT OF INTEREST STATEMENT

All authors hereby disclose any financial and personal relationships with other people or organisation that could inappropriately influence our work.

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Section 4

RANDOMISED CONTROLLED TRIALS OF

NUTRITIONAL THERAPY

Chapter 6

DIETARY COUNSELING IMPROVES PATIENT' OUTCOMES: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL IN COLORECTAL CANCER PATIENTS UNDERGOING RADIOTHERAPY

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ABSTRACT

Purpose: To investigate the impact of dietary counseling or oral nutrition supplements on outcomes in cancer patients: nutritional, morbidity and Quality of Life (QoL), during and 3 months after radiotherapy. *Patients and Methods*: 111 colorectal cancer outpatients referred for radiotherapy, stratified by staging, were randomized: G1(n=37) dietary counseling (regular foods), G2(n=37) protein supplements and G3(n=37) *ad lib* intake. Nutritional intake (diet history), status (Ottery's Subjective Global Assessment) and QoL (EORTC-QLQ-C30) were evaluated at baseline, at the end, and 3 months after completion of radiotherapy. *Results*: At radiotherapy completion, energy intake increased in G1/G2 ($p \leq 0.04$), G1>G2 ($p=0.001$) and decreased in G3 ($p<0.01$). Protein intake increased in G1/G2 ($p \leq 0.007$), G1<G2 (NS) and decreased in G3 ($p<0.01$). At 3 months, G1 maintained nutritional intake, G2/G3 returned to baseline. After radiotherapy and at 3 months, anorexia/nausea/vomiting/diarrhea were higher in G3 ($p<0.05$). At radiotherapy completion, in G1 all QoL function scores improved proportionally to adequate intake/nutritional status ($p<0.05$); whereas in G2 only 3/6 function scores improved proportionally to protein intake ($p=0.04$) and in G3 all scores worsened ($p<0.05$). At 3-months, G1 patients maintained/improved function, symptoms, single item scores ($p<0.02$); in G2, only few function and symptom scales improved ($p<0.05$); in G3, QoL remained as poor as after radiotherapy. In G1/G2, respectively, improvement or deterioration of QoL correlated with better or poorer intake/nutritional status ($p<0.003$). *Conclusions*: During radiotherapy, both nutritional interventions positively influenced predefined outcomes, dietary counseling was of similar/higher benefit, whilst even 3 months after RT, it was the only method to sustain a significant impact on patient' outcomes.

INTRODUCTION

Cancer related malnutrition is multifactorial (1) and bears a negative prognosis (2, 3). The risk of nutritional deterioration, particularly in cancers of the gastrointestinal tract, increases during radiotherapy (RT) (4). RT induced morbidity, e.g. anorexia, nausea, vomiting and diarrhea, is common and may compromise both nutrition as status and functional ability (5, 6), which in turn, impacts upon Quality of Life (QoL). The latter is a subjective multidimensional construct reflecting functional status, psychosocial well being, health and disease/treatment-related perceptions (7, 8). Preliminary data support evidence-based benefits from oral nutritional intervention (9) and recently our group demonstrated the association between nutritional parameters and worse overall morbidity/QoL in cancer patients (10).

This study was designed to test the hypothesis of a causal pathway between nutritional intervention and functional/clinical outcomes. Within this framework, we conducted a prospective randomized controlled trial in colorectal cancer (CRC) patients referred for radiotherapy. The study was designed to investigate whether dietary counseling or oral nutrition commercial supplements during RT affected oral intake. Furthermore the impact of nutritional intake on predefined outcomes (nutritional status and Quality of Life) during treatment and at 3 months was examined.

PATIENTS AND METHODS

This prospective randomized controlled trial was approved by the University Hospital Ethics Committee and was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. All patients gave their written informed consent to participate in the study. Data were recorded on individual forms pre-constructed for statistical analysis. Between July 2000 and March 2003, all consecutive CRC ambulatory patients referred for RT were considered eligible, regardless of whether the proposed RT was primary, adjuvant to surgery, combined with chemotherapy or with palliative intent.

For every patient and prior to RT planning, the medical staff registered the following: clinical variables, recent medications and chemotherapy, duration of the disease, cancer location, presence of distant metastases, and tumor burden according to TNM stage (11) determined by local and whole-body imaging methods. The duration of the disease, confirmed by histology, was defined as the length of time (in months) between symptomatic manifestations and study entry. Inclusion criteria were referral for RT treatment of 50.4 Gy administered in 28 fractions, absence of renal disease and/or diabetes *mellitus*. Throughout RT, all medication and concurrent chemotherapy was registered, and acute RT induced morbidity was scored from 0 to 4 according to the EORTC/RTOG criteria, in which higher scores indicate increased symptom severity (12).

Study Design

A minimum sample size of 58 patients was calculated to detect a difference in body weight of 1.9 kg, in nutritional intake of 25% and in QoL scores of 20% (that is, an effect size of 0.9) with a significance level of 0.01 between groups and a power of 0.85. Statistical power was based on the changes observed in weight, nutritional intake and QoL from a pilot study conducted in 46 patients with CRC (13, 14). The present study therefore included 111 free-living patients (66M: 45F), mean age 58$\pm$15 (range 32-88) years: 45 in stage I/II and 66 in stage III/IV. All patients were referred for pre-operative RT combined with chemotherapy comprising 5-Fluorouracil + Folinic Acid based regimens administered concurrently with the first and the last 5 days of RT.

Patients stratified by cancer stage were randomized at enrolment in permutation blocks of three, using a sequential series of numbered opaque sealed envelopes containing computer generated random assignments. A copy of the randomization sequence was kept separately from the study personnel. Randomization envelopes were opened before the first appointment with the patients by a person blind to the study procedures.

Patients' distribution after randomization was as follows: G1 (n=37) received individualized dietary counseling based on regular foods, G2 (n=37) were asked to consume two cans per day of a high protein liquid supplement in addition to their usual diet, in the control group G3 (n=37) patients were instructed to maintain their *ad lib* intake. Randomized patients had scheduled visits and identical contact time with the research dietician (PR). All parameters and study measures were assessed as described in **Table 1** and the use of other medications and dietary supplements and compliance with dietary recommendations were monitored weekly.

Table 1 Data collection, nutritional intervention and visit schedule

Visit	**Baseline**	**RT treatment period**					**End RT**	**3 months**
Study day	1	7	14	21	28	35	42	132
Demography	X							
Medical history	X							
Informed consent	X							
Randomization	X							
Concomitant medications	X	X	X	X	X	X	X	X
Nutritional status with PG-SGA	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Diet history	X							X
24-hour recall		X	X	X	X	X	X	X
RT induced morbidity with EORTC/RTOG			X	X	X	X	X	X
QoL with EORTC QLQ-C30	X						X	X
*Nutritional intervention (G1, G2)	X	X	X	X	X	X	X	
Acceptability and compliance		X	X	X	X	X	X	

*Nutritional intervention period from day 1 to 35.

Overall, the main goal of both nutritional interventions was to enable every patient to achieve his/her calculated energy and protein requirements. Dietary counseling involved the prescription of a therapeutic diet using regular foods, which was further modified to provide for individual requirements. This was based on the need for an adequate intake and also took into consideration other relevant factors, including digestive and absorptive capacity, the need for alleviation or arrest of symptoms, and psychological factors. The therapeutic diet was additionally adjusted to the individual's usual diet, thereby recognizing personal eating patterns and preferences, which formed the basis for individualized dietary counseling. The prescription identified the type, amount and frequency of feeding, specified the caloric/protein level to attain, together with any restrictions and limited or increased individual dietary components (15).

Oral nutrition supplements, selected on the basis of the pilot study (13, 14) that identified protein as the main nutritional deficit, were ready to use, high protein, energy dense liquid polymeric formulations, intended to act as a supplement to the patients' usual diet. Supplements were offered to patients who were able to select their preferred flavors and were instructed to use them as drinks in addition to any other meal. Supplements used throughout the study were always of the same commercial brand. Each 200 mL can provides 20g protein and 200 kcal. The amount of supplement provided was uniform, 2 cans/day and this covered the calculated requirements. Compliance was ensured by using a supplement consumption record which was kept daily by patients, and verified by a carer/relative.

Study Measures

Nutritional Assessment was performed using 2 methods: 1) Ottery's Patient Generated Subjective Global Assessment (PG-SGA) (16), a validated nutritional assessment tool for cancer patients that addresses: a) weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhea, xerostomia, pain), alterations in food intake by comparison with the usual intake, and functional capacity; b) components of metabolic stress: sepsis, neutropenic or tumor fever, corticosteroids, and c) 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 edema or ascites. Nutritional status was thus categorized in three degrees: normal, moderate and severe malnutrition. 2) Anthropometric data: height was measured in the standing position using a stadiometer and weight was determined with a Jofre® floor scale. Body Mass Index (BMI) was then calculated according to the formula weight(kg)/height(m)^2, classified as malnutrition if <20 kg/m^2 or normal if ≥20 kg/m^2 (17).

Nutritional Requirements and Dietary Assessment. Basal energy requirements were estimated using the World Health Organization formulae for patients aged ≤ 60 yrs (18) or by the Owen *et al* formulae for patients aged > 60 yrs (19, 20), given their better performance in predicting resting metabolic rate (21). To estimate patients' daily energy requirements (EER), basal requirements were multiplied by a 1.5 activity factor (22); daily protein requirements were estimated by comparison with age and sex standardized reference values, which range between 0.8 and 1.0 g/kg per day (22).

Nutritional intake was derived from a diet history (23, 24); to assess changes in current intake during the RT treatment period a 24hr-recall food questionnaire was used (25). In detail, the primary source of the dietary data was Burke's diet history, which was further complemented by multiple and sequential 24-hour recall evaluations (2 week-days and 1 weekend day) undertaken at every scheduled visit. Both energy and protein intakes were always analyzed together. The software DIETPLAN version 5 for Windows (Forestfield software Ltd 2003, Horsham, UK) was used to analyze nutrient contents of regular foods and meals.

QoL instrument. QoL was assessed at the 3 time-points, always using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30). This instrument is a 30-item cancer specific questionnaire including 6 function scales (physical, emotional, cognitive, social, role, and global health/QoL), 3 symptom scales (fatigue, pain, nausea/vomiting), and 6 single items assessing symptoms and the financial impact of the disease (7). Higher scores on the function scales indicate better functioning whilst higher scores on the symptom scales and single items denote increased symptomatology or worse financial impairment. Original scores were linearly transformed to obtain quantified scores within the range of 0 to 100; in addition, and for better validation in the clinical context, overall scores derived from function scales, symptom scales and single items, were calculated on the basis of the very high statistical significance of the interscale correlations, which were calculated according to EORTC's guidelines (7).

Statistical Analysis

Statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, USA) and EPI–Info 2000 (CDC, Atlanta, USA). All analyses were conducted on an-intention-to-treat basis, and therefore available data from all study patients were used. If any missing data were observed, the missing value(s) would be replaced by the average of the study group, which would have no effect on the estimators. Study groups were assessed for comparability at study entry. Data related to incidence, prevalence or frequency (symptoms, cancer stages and nutritional status categories) were expressed as number and/or percentage; age was expressed as the mean ± standard deviation (range); energy and protein intakes were expressed as the median (range), and patients' QoL scores were expressed as median values. Continuous variables were analyzed using one-way analysis of variance (ANOVA) or Wilcoxon rank sum tests as appropriate; categorical variables and incidence, prevalence or frequency were evaluated by the Chi-square test. Univariate or multiple correlations were assessed by two-tailed non parametric Spearman tests. Statistical significance was set for a p value < 0.05.

RESULTS

As summarized in **Table 1,** all patients completed the study and none were lost to follow-up. Additionally, none were taking any other dietary supplements, either prior or throughout the period under scrutiny.

Nutritional intake. At baseline, current energy and protein intakes for the three study groups were compared with EER and the protein median reference values. Patients' median baseline estimated requirements and median nutritional intake were similar in all groups; energy intake tended to be higher than estimated requirements (0.07), protein intake was lower than reference values, p=0.06. Overall, energy and protein intakes were not significantly different between groups. The median nutritional intake patterns throughout the study are shown in **Figure 1**.

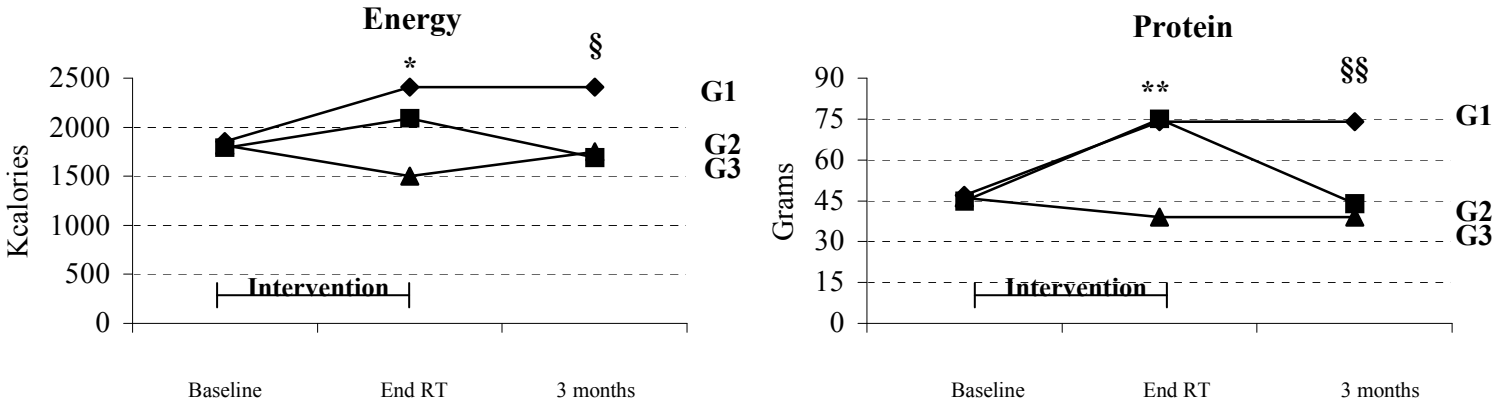

Figure 1 Energy and protein intake patterns during intervention and follow-up for the three study groups; G1=dietary counseling based on regular foods, G2=supplements, G3=*ad lib* intake. Energy: *G1>G2>G3 (p=0.002) and §G1>G2~G3 (p=0.001); protein: **G1~G2>G3 (p=0.006) and §§G1>G2~G3 (p=0.001).

At the end of RT by comparison with the onset, energy intake showed a net increase of 555 (398-758) kcal/d in G1 (p=0.002) and of 296 (286-401) kcal/d in G2 (p=0.04); G1>G2, p=0.001. Energy intake decreased in G3, 285 (201-398) kcal/d (p<0.01). At the 3 months follow-up, patients in G1 still complied with dietary recommendations as given during RT and maintained their energy intake, whilst in both G2 and G3 patients' energy intake decreased (p=0.05) either to baseline (stage I/II) or below baseline (stage III/IV). There was a net increase in protein intake of 27 (20-35) g/d in G1 (p=0.007) and of 30 (20-40) g/d in G2 (p=0.001); intake in G1 tended to be lower than in G2 (p=0.07); in both G1 and G2, the increase was always higher in stage I/II (p=0.05). Protein intake decreased in G3, 10 (7-15) g/d (p<0.01). At the 3 months follow-up, patients in G1 complied with nutritional recommendations as given during RT and maintained their protein intake, whilst both G2 and G3 patients decreased their protein intake (p=0.06) either to baseline (stage I/II) or below baseline (stage III/IV).

Nutritional status. According to both PG-SGA and BMI, the prevalence of malnutrition at baseline was similar between the three study groups and was only observed in stage III and IV. At baseline, PG-SGA identified 15 malnourished patients in G1, 14 in G2 and 13 in G3, whereas BMI identified 5 malnourished patients in G1, 4 in G2 and 3 in G3. The number of patients that presented further nutritional deterioration both at the end of RT and at the 3-months follow-up was significantly higher in G2 and in G3 relative to G1 (p<0.001), using both methods. Similarly, nutritional deterioration was significantly more severe and incident in G3 relative to G1 and G2 (p<0.008) again using both methods (**Table 2**).

Table 2 Changes in nutritional status during RT and at 3-months categorized according to PG-SGA and BMI

Methods	**G1**				**G2**				**G3**				***p*[1]**	***p*[2]**
	Decline		Maintained/improved		Decline		Maintained/improved		Decline		Maintained/improved			
	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months		
PG-SGA	3	10	34	27	19	24	18	13	34	36	3	1	<.002	<.001
BMI	1	2	36	35	3	6	34	31	5	8	32	29	NS	NS

Data are expressed as number of patients; NS = not significant; p^1 expresses the significance of statistical differences between intervention groups, regarding nutritional decline both at the End RT and at 3 months; p^2 expresses the significance of statistical differences between intervention groups, regarding maintenance/improvement of nutritional status at the End RT and at 3 months

Considering PG-SGA specifically, 9/15 Group 1 malnourished patients at baseline improved their nutritional status, showing a net average recovery of 4 (2-7) kg at the 3 months follow-up. Conversely, none of the patients in G2 and G3 ever improved their nutritional status.

Symptom induced morbidity. At the onset of RT, the prevalence of anorexia (≤9%), nausea/vomiting (≤8%) and/or diarrhea (≤17%) did not differ between the groups. After RT, more than 90% of the patients in the three study groups experienced RT induced toxicity, the severity and incidence of which are presented in **Table 3**.

Table 3 RT induced morbidity categorized according to severity grades (12)

Symptoms	**G1**				**G2**				**G3**				***p*[1]**	***p*[2]**	***p*[3]**
	Grade 1		Grade 2		Grade 1		Grade 2		*Grade1*		Grade 2				
	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months			
Anorexia	20	6	13	1	19	5	14	3	17	12	17	10	<.02	<.01	<.001
Nausea/ Vomiting	27	0	7	0	23	7	10	3	18	9	16	6	<.001	.17	<.0001
Diarrhea	32	0	2	0	25	9	9	3	18	15	17	13	<.0001	<.05	<.0001

Data are expressed as number of patients; grades 3 and 4 were never observed; p^1 expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 1 symptom' incidence between the End RT and 3-months; p^2 expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 2 symptom' incidence between the End RT and 3-months; p^3 expresses the significance of statistical differences between intervention groups, regarding the reduction of grades 1+2 symptom' incidence between the End RT and 3-months.

Further statistical analyzes showed that, overall, both at the end of RT and at 3 months, RT-induced toxicity with symptomatic manifestations was higher in G3 ($p<0.05$). Conversely, G1 showed the lowest symptom severity score ($p<0.05$). Furthermore, symptom incidence and/or severity improved differently in the three groups throughout the 3 months period between the end of RT and the follow-up visit. The incidence of grade 1+2 anorexia decreased in a similar fashion in G1 and G2, and was significantly better than in G3 ($p<0.001$). The significance of the reduction of grade 1+2 nausea and vomiting was distinctly different between groups: all patients improved in G1 *vs* 62% showing improvement in G2 *vs* 51% in G3 ($p<0.0001$). The incidence and severity of diarrhea was also significantly different between the groups: all patients improved in G1 *vs* 59% showing improvement in G2 *vs* 19% in G3 ($p<0.0001$). In the 3 groups the different symptomatology pattern occurred despite adequate and appropriate prescription of medications to alleviate symptoms. During RT, anti-emetic/pro-kinetic drugs (metoclopramide/domperidone) were prescribed for 5% of patients in G1, for 49% in G2 and for 68% in G3. Whilst G1 patients no longer required these drugs, at 3 months, 10% of those in G2 and 32% in G3 still needed them. The prescription of anti-diarrheal drugs (loperamide) was also significantly different between groups: during RT they were prescribed to 7% of patients in G1, to 53% in G2 and to 78% in G3. At 3 months, there was no need for loperamide in G1, but 15% of patients in G2 and 54% in G3 still needed it to control diarrhea.

In order to clarify the influence of dietary intake and RT induced symptoms on patients' nutritional decline, a two-tailed multiple correlation analysis was performed. In all study groups, dietary intake was not correlated with BMI ($r \leq -0.17$, $p \leq 0.24$), but was significantly correlated with nutritional status as categorized by PG-SGA ($r \leq -0.59$, $p \leq 0.003$). Similarly, increased overall symptomatology was correlated with worse nutritional status as categorized by PG-SGA ($r \leq -0.63$, $p \leq 0.002$), but not with BMI.

Quality of Life. Median QoL dimension scores for the study groups at the three evaluation set points are presented in **Table 4**.

Table 4 Median Quality of Life dimensions' scores.

Items	G1			G2			G3		
	Onset	End	3-months	Onset	End	3-months	Onset	End	3-months
Function scales									
Global QoL	48	75*	82#§	46	70*	62#	47	35*	30#
Physical function	49	74*	79#	48	65*	60#	45	25*	22#
Role function	50	78*	80#	52	65*	58	48	20*	19#
Emotional function	55	79*	83#	50	48	50	51	38*	28#§
Social function	52	82*	85#	51	48	51	49	30*	26#
Cognitive function	64	73*	70#	62	62	54	62	55*	46#§
Symptoms, scales									
Fatigue	30	55*	26§	31	75*	78#	29	78*	79#
Pain	25	63*	15#§	22	74*	30#§	23	78*	73#
Nausea and vomiting	15	50*	10§	14	71*	37#§	12	72*	68#
Symptoms, single items									
Dyspnea	5	8	8	6	7	13	5	6	15
Sleep disturbance	30	40*	29§	28	55*	75#§	32	60*	78#§
Appetite	45	57*	48§	40	59*	72#§	42	65*	75#§
Constipation	12	10	10	11	9	8	9	8	8
Diarrhea	38	45	39	35	81*	72#§	33	92*	78#§
Finance	14	14	14	11	11	11	12	12	12

Higher scores on function scales indicate better functioning, higher scores on symptom scales/single items denote increased symptomatology or worse financial impairment. ___ Highlights overall significant improvement, _ _ highlights overall significant deterioration, ... highlights overall non-significant deterioration; *significant differences between baseline end of RT; #significant differences between baseline and at 3-months; §significant differences between end of RT and at 3-months.

At the end of RT in G1, despite RT induced symptoms ($p<0.05$), all QoL function scores improved significantly ($p<0.002$) and these were proportional to the increases registered in energy and protein intakes ($r<0.089$; $p<0.001$). There was also a linear positive association with the improvement in the patients' nutritional status ($p<0.05$). In considering symptom scales and single items, pain worsened in association with anorexia ($p=0.05$), nausea/vomiting ($p=0.04$) and with diarrhea ($p=0.03$). In G2, only 3 function scores (physical, role and emotional) improved ($p<0.05$) and these were proportional to the increase in protein intake ($p=0.04$); the remaining function scales scores did not change significantly. Regarding symptom scales and

single items, worse fatigue and pain were associated with anorexia ($p<0.001$), nausea/vomiting ($p\leq0.04$) and diarrhea ($p<0.002$); patients also reported increased severity of sleep disturbance ($p=0.02$). In G3 patients, all QoL function scores worsened in association with a deterioration of their nutritional intake ($p<0.0001$), as well as of their nutritional status ($p<0.002$). All symptom scales significantly worsened: increased fatigue was associated with poorer nutritional intake ($p<0.003$) and with nutritional status deterioration ($p<0.001$), pain worsened in association with nausea/vomiting and diarrhea ($p<0.001$); as far as symptoms and single items were concerned, sleep disturbance and appetite grew worse and were associated with nausea/vomiting and diarrhea ($p<0.002$).

At 3-months follow-up and by comparison with the end of RT, all G1 patients maintained or improved their overall QoL ($p<0.02$), which was positively and proportionally associated with maintenance/improvement of nutritional status ($p<0.02$) and adequate dietary intake ($p<0.01$). Function scales scores also improved or were maintained ($p<0.04$), and symptom scales/single items were similar to baseline scores. G2 patients maintained or worsened their overall QoL ($p<0.03$) and patients also reported worse physical, role, emotional, and cognitive functions ($p<0.05$). This deterioration was associated with poor dietary intake ($p<0.003$) and depleted nutritional status ($p<0.002$). Notwithstanding the improvement of pain, nausea/vomiting and diarrhea ($p<0.04$), sleep disturbance and anorexia worsened ($p<0.03$), while the remaining scores were unchanged by comparison with the end of RT and were worse than at baseline. In G3, function scores further deteriorated both in relation to the baseline and to the end of RT ($p<0.004$). This deterioration was significantly associated with inadequate dietary intake ($p<0.001$) and deficient nutritional status ($p<0.002$). Symptom scale scores, apart from diarrhea, remained as poor as those reported at the end of RT, and were significantly worse than at baseline ($p<0.001$), the worst scores were associated with inadequate dietary intake ($p<0.005$).

DISCUSSION

Nutrition is a major issue in oncology and nutritional decline may ensue from both disease course and its treatment(s) (1). This carries a negative prognosis (2). Although symptomatic manifestations of radiation injury and their nutritional consequences have long been recognized (26), the potential role of adjuvant oral nutritional support on patients' outcomes has not yet been explored. This prospective randomized controlled trial is the first to demonstrate that concurrent individualized dietary counseling, based on regular foods, is the most effective means of improving patients' nutritional intake, status and QoL, thereby lessening radiotherapy induced morbidity.

Weight loss during radiotherapy is an early indicator of nutritional decline (26). A 6-week course with $\pm$ 50 Gray of radiotherapy to the abdomen/pelvis, has been associated with an average weight loss of 3.4 kg, and 59% of the patients lost 10% of their baseline weight (27). In our trial and throughout the whole study period, including intervention and follow-up, nutritional deterioration was only observed in 18% of patients in Group 1 (dietary counseling), amounting to 50% in Group 2 (supplements) and to more than 90% of the Group 3 control patients. These

findings are concordant with the fact that disease-related malnutrition is frequently caused by reduced dietary intake (28). Indeed, although the three study groups showed comparable energy and protein intakes at baseline, nutritional intake patterns became quite different according to the type of nutritional intervention. At the end of radiotherapy, Group 1 showed the highest average energy intake sustained during the follow-up; the smaller increase in Group 2 was lost at follow-up when energy intake decreased to/or below baseline, as was always the case in Group 3. During the nutritional intervention phase, both dietary manipulation and supplements were effective in restoring protein intake; similarly the increase was just maintained in Group 1 at 3 months, whereas in the other 2 groups the protein intake followed a pattern similar to that observed for energy (**Figure 1**). Thus, within the context of this clinical trial, individualized dietary counseling during radiotherapy, taking into consideration the patients' clinical condition and symptoms, was the most effective nutrition intervention assuring a sustained and adequate diet which was able to overcome the predictable deterioration subsequent to radiotherapy. Moreover, such nutritional outcomes concur with what has been proposed as the causal pathway, i.e. optimizing nutritional intake may be the most effective method for treating disease-related malnutrition. There is evidence in a range of conditions to support the hypothesis that enabling the provision of the appropriate nutritional therapy leads to improved body weight and fat free-mass and that this generally reflects an improvement in protein-energy status (28).

The severity and extent to which patients experience radiotherapy induced toxicity, depend on tumor histology, total dose, fractionation, volume of irradiated area, injury repair mechanisms and concurrent chemotherapy, which dictate susceptibility to acute radiation damage, during which high turnover cells of the intestinal tract are at higher risk (26). The resulting nutritional sequelae occur through direct effects on neoplastic and healthy tissues, which may induce anorexia, nausea/vomiting and diarrhea leading to physical discomfort and a variety of malabsorption syndromes (29-31). So far, the routine clinical approach is to maintain *ad lib* oral feeding, although comparative studies of functional, clinical and QoL outcomes which can be achieved via dietary manipulation or through oral nutrition supplementation, are lacking (28). Our study is the first to demonstrate that the nutritional content of the patient's diet based on regular foods with appropriate manipulation, and not just protein and calorie supplementation, is the key to improving gastrointestinal function and other symptomatic manifestations during radiotherapy and in the medium term. In this trial, radiotherapy induced toxicity was more severe/incident in patients with an *ad lib* intake and to a lesser extent in the supplemented group, whereas in those patients who received dietary counseling and education, symptom incidence and/or severity were lower and their improvement in the medium term was faster (**Table 3**). Indeed, dietary modifications may alter bowel functions, such as motility, enzyme secretion and nutrient absorption (32); likewise, nutrition modulates the gastrointestinal flora whose ecology is central to the pathogenesis of radiation injury severity (33).

QoL assessment measuring the patients' experiences of the impact of disease/therapy, expectations and satisfaction should be the gold standard as an independent end-point in

clinical trials (34, 35). Patients experience functional limitations, cognitive alterations and emotional stress, and overall QoL depends on both physical and psychological well-being (7, 36, 37). All these aspects may influence or be influenced by nutrition although the relationship between poor nutritional parameters and QoL remains widely underestimated (38, 39). Our group was the first to show that nutrition is a key determinant of QoL in cancer patients (10). In this clinical trial, both at the end and at 3 months after RT, dietary counseling (Group 1) significantly improved all QoL function scores in association with an adequate dietary intake and nutritional status. In patients who received oral supplements (Group 2), only 3/6 function scores improved during supplementation, and these were proportional to the increase in dietary intake; however, once the supplementation was discontinued most function scores deteriorated. Patients not submitted to any nutritional intervention (Group 3) experienced, throughout the whole study, a significant deterioration in function scores and fatigue in direct relation to the worsening of their nutritional intake and nutritional status. Therefore, our results emphasize that "the impairment in structure, function and well-being that form malnutrition, are nutritionally responsive" (28).

Furthermore, the benefits of nutritional intervention on QoL were extrapolated to improved physiological function and overall clinical outcome. During radiotherapy, QoL symptom scales and single item scores deteriorated in all groups and these were significantly more pronounced in the *ad lib* group. These scales were also significantly worse in Group 2 *vs* Group 1. In the medium term, Group 3 symptom scales and single items remained as poor as those reported at the end of radiotherapy and worse than at the onset; worsening scores were again associated with inadequate nutritional intake. Conversely, in Group 1 patients all the above mentioned scales reverted to their baseline scores, whereas in Group 2 there was an improvement in pain, nausea/vomiting and diarrhea, although not as relevant as the improvement observed in Group 1. These results in patients who experience persistent eating difficulties support the concept that increased intake of an appropriate mixture of nutrients using regular foods will be of major benefit in modulating outcomes.

Despite the expected, and experienced, detrimental effects of radiotherapy, multiprofessional patient' management allowed proper assessment of nutritional status and nutritional requirements, dietary counseling, education and monitoring of diet compliance and timely management of symptoms. Nutrition intervention was central to the improvement of colorectal cancer patients' nutritional as well as non-nutritional outcomes: nutritional intake, status, QoL and lessened morbidity even in the medium term. Adding oral nutritional supplements to the diet did not appear to be as effective as dietary counseling. Early intervention and sensible partnerships with patients are key to success.

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Chapter 7

THE IMPACT OF NUTRITION ON OUTCOME: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH HEAD & NECK CANCER UNDERGOING RADIOTHERAPY

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ABSTRACT

Background: We aimed to investigate the impact of dietary counseling or oral supplements in cancer patients outcomes: nutritional, morbidity and Quality of Life (QoL), during and 3-months after radiotherapy. *Methods*: 75 head-neck cancer patients referred for radiotherapy were randomized: G1(n=25) dietary counseling with regular foods, G2(n=25) supplements and G3(n=25) *ad lib*. Nutritional intake (diet history) and status (Ottery's Subjective Global Assessment), QoL (EORTC-QLQ-C30) were evaluated at baseline, end of radiotherapy and at 3-months. *Results*: After radiotherapy, G1/G2 increased energy ($p \leq 0.05$) and protein ($p \leq 0.006$) intakes whereas both decreased in G3 ($p<0.01$). At 3-months, G1 maintained intakes, G2/G3 returned to or below baseline. After RT, >90% patients experienced RT toxicity, not significantly different between groups with a trend for reduced syptomatology in G1 *vs* G2/G3 ($p<0.07$). At 3-months, the reduction of incidence/severity of grade 1+2 anorexia, nausea/vomiting, xerostomia, dysgeusia was different: 90% of the patients improved in G1 *vs* 67% in G2 *vs* 51% in G3 ($p<0.0001$). After radiotherapy, QoL function scores improved ($p<0.003$) proportionally to improved nutritional intake+status in G1/G2 ($p<0.05$), and worsened in G3 ($p<0.05$); at 3-months, G1 patients maintained/improved overall QoL which was maintained/worsened in G2+G3. *Conclusions*: During radiotherapy, both nutritional interventions positively influenced outcomes, counseling was of similar/higher benefit; in the medium term only counseling exerted a significant impact on patient' outcomes.

INTRODUCTION

Cancer related malnutrition is multifactorial [1] and bears a negative prognosis [2, 3]. The risk of nutritional deterioration, particularly in cancers of the head and neck, increases during radiotherapy (RT) [4]. RT induced morbidity, e.g. mucositis, odynophagia, dysphagia, xerostomia, dysgeusia, nausea, vomiting and anorexia, is common and may compromise both nutrition as status and functional ability [5, 6], which in turn, impacts upon Quality of Life (QoL) [7]. The latter is a subjective multidimensional construct reflecting functional status, psychosocial well being, health and disease/treatment-related perceptions [8, 9]. Preliminary data support evidence-based benefits from oral nutritional intervention [10], and we have recently demonstrated the association between nutritional parameters and worse overall morbidity/QoL in cancer patients [11].

This study was designed to test the hypothesis of a causal pathway between nutritional intervention and functional/clinical outcomes. Within this framework, we conducted a prospective randomized controlled trial in head-neck cancer (HNC) patients referred for radiotherapy. The study was designed to investigate whether and to what extent dietary counseling or oral nutrition commercial supplements during RT affected oral intake. Furthermore the impact of nutritional intake on predefined outcomes (nutritional status and Quality of Life) during treatment and at 3 months was examined.

MATERIALS AND METHODS

This prospective randomized controlled trial was approved by the University Hospital Ethics Committee and was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. All patients gave their written informed consent to participate in the study. Data were recorded on individual forms pre-constructed for statistical analysis. Between July 2000 and March 2003, all consecutive HNC ambulatory patients referred for RT were considered eligible, regardless of whether the proposed RT was primary, adjuvant to surgery, combined with chemotherapy or with palliative intent.

For every patient and prior to RT planning, the medical staff registered the following: clinical variables, recent medications and chemotherapy, duration of the disease, cancer location, presence of distant metastases, and tumor burden according to TNM stage [12] determined by local and whole-body imaging methods. The duration of the disease, confirmed by histology, was defined as the length of time (in months) between symptomatic manifestations and study entry. Inclusion criteria were: referral for RT treatment of 70 Gy administered in 35 fractions, absence of renal disease and/or diabetes *mellitus*. Throughout RT, all medication and concurrent chemotherapy was registered, and acute RT induced morbidity was scored from 0 to 4 according to the EORTC/RTOG criteria, in which higher scores indicate increased symptom severity [13].

Study Design

A minimum sample size of 40 patients was calculated to detect a difference in body weight of 1.9 kg, in nutritional intake of 25% and in QoL scores of 20% (that is, an effect size of 0.9) with a significance level of 0.01 between groups and a power of 0.85. Statistical power was based on the changes observed in weight, nutritional intake and QoL from a pilot study conducted in 36 patients with HNC [14, 15]. The present study therefore included 75 free-living patients (60M: 15F), mean age 60±11 (range 36-79) years, with cancer of the base of the tongue, nasopharynx, oropharynx, larynx: 30 in stage I/II and 45 in stage III/IV. All patients were referred for pre-operative RT, having been previously treated with chemotherapy (5-Fluorouracil + Cisplatin + Folinic Acid based regimen).

Patients stratified by cancer stage were randomized at enrolment in permutation blocks of three, using a sequential series of numbered opaque sealed envelopes containing computer generated random assignments. A copy of the randomization sequence was kept separately from the study personnel. Randomization envelopes were opened before the first appointment with the patients by a person blind to the study procedures.

Randomized patients had scheduled visits and identical contact time with the research dietician (PR). All parameters and study measures were assessed as described in **Table 1**, and the use of other medications and dietary supplements and compliance with dietary recommendations were monitored weekly.

Table 1 Data collection, nutritional intervention and visit schedule

Visit	**Baseline**	**RT treatment period**						**End RT**	**3 months**
Study day	1	7	14	21	28	35	42	49	139
Demography	X								
Medical history	X								
Informed consent	X								
Randomization	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Nutritional status with PG-SGA	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Diet history	X								X
24-hour recall		X	X	X	X	X	X	X	X
RT induced morbidity with EORTC/RTOG			X	X	X	X	X	X	X
QoL with EORTC QLQ-C30	X							X	X
*Nutritional intervention (G1, G2)	X	X	X	X	X	X	X	X	
Acceptability and compliance		X	X	X	X	X	X	X	

*Nutritional intervention period from day 1 to 42; RT: radiotherapy; PG-SGA: Ottery's Patient Generated Subjective Global Assessment; G1: dietary counseling based on regular foods; G2: supplements.

Overall, the main goal of both nutritional interventions was to enable every patient to achieve his/her calculated energy and protein requirements. Dietary counseling involved the prescription of a therapeutic diet using regular foods, which was further modified to provide for individual requirements. This was based on the need for an adequate intake and also took into consideration other relevant factors, namely the need for alleviation or arrest of local symptoms, as well as psychological factors and digestive and absorptive capacity. The therapeutic diet was adjusted to the individual's usual diet, thereby recognizing personal eating patterns and preferences, which forms the basis for individualized dietary counseling. The prescription identified the type, amount and frequency of feeding, specified the caloric/protein level to attain, together with any restrictions and limited or increased individual dietary components [16].

Oral nutrition commercial supplements, selected on the basis of the pilot study that identified protein as the main nutritional deficit [14, 15], were ready to use, high protein, energy dense liquid polymeric formulations, intended to act as a supplement to the patients' usual diet. Supplements were offered to patients who were able to select their preferred flavors and were instructed to use them as drinks to be consumed in-between meals, in addition to any other meal. Supplements used throughout the study were always of the same commercial brand. Each 200 mL can provides 20g protein and 200 kcal. The amount of supplement provided was uniform, 2 cans/day and this covered the calculated requirements. Compliance was ensured by using a supplement consumption record which was kept daily by patients, and verified by a carer/relative.

Study Measures

Nutritional Assessment was performed by using Ottery's Patient Generated Subjective Global Assessment (PG-SGA) [17], a validated nutritional assessment tool for cancer patients that addresses: a) weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhea, xerostomia, pain), alterations in food intake by comparison with the usual intake, and functional capacity; b) components of metabolic stress: sepsis, neutropenic or tumor fever, corticosteroids, and c) 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 edema or ascites. Nutritional status was thus categorized in three degrees: normal, moderate and severe malnutrition.

Nutritional Requirements and Dietary Assessment. Basal energy requirements were estimated using the World Health Organization formulae for patients aged ≤60 yrs [18] or by the Owen *et al* formulae for patients aged >60 yrs [19, 20], given their better performance in predicting resting metabolic rate [21]. To estimate patients' daily energy requirements (EER), basal requirements were multiplied by a 1.5 activity factor [22]; daily protein requirements were estimated by comparison with age and sex standardized reference values, which range between 0.8 and 1.0 g/kg per day [22].

Nutritional intake was derived from a diet history [23, 24]; to assess changes in current intake during the RT treatment period a 24hr-recall food questionnaire was used [25]. In detail, the primary source of the dietary data was Burke's diet history, which was further complemented by multiple and sequential 24-hour recall evaluations (2 week-days and 1 weekend day) undertaken at every scheduled visit. Both energy and protein intakes were always analyzed together. The software DIETPLAN version 5 for Windows (Forestfield software Ltd 2003, Horsham, UK) was used to analyze nutrient contents of regular foods and meals.

QoL instrument. QoL was assessed at the 3 time-points (**Table 1**), always using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30). This instrument is a 30-item cancer specific questionnaire including 6 function scales (physical, emotional, cognitive, social, role, and global health/QoL), 3 symptom scales (fatigue, pain, nausea/vomiting), and 6 single items assessing symptoms and the financial impact of the disease [8]. Higher scores on the function scales indicate better functioning whilst higher scores on the symptom scales and single items denote increased symptomatology or worse financial impairment. Original scores were linearly transformed to obtain quantified scores within the range of 0 to 100; in addition, and for better validation in the clinical context, overall scores derived from function scales, symptom scales and single items, were calculated on the basis of the very high statistical significance of the interscale correlations, which were calculated according to EORTC's guidelines [8].

Statistical Analysis

Statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, USA) and EPI–Info 2000 (CDC, Atlanta, USA). All analyses were conducted on an-intention-to-treat basis, and therefore available data from all study patients were used. If any missing data were observed,

the missing value(s) would be replaced by the average of the study group, which would have no effect on the estimators. Study groups were assessed for comparability at study entry. Data related to incidence, prevalence or frequency (symptoms, cancer stages and nutritional status categories) were expressed as number and/or percentage; age was expressed as the mean ± standard deviation (range); energy and protein intakes were expressed as the median (range), and patients' QoL scores were expressed as median values. Continuous variables were analyzed using one-way analysis of variance (ANOVA) or Wilcoxon rank sum tests as appropriate; categorical variables and incidence, prevalence or frequency were evaluated by the Chi-square test. Univariate or multiple correlations were assessed by two-tailed non-parametric Spearman tests. Statistical significance was set for a p value < 0.05.

RESULTS

Patients' distribution after randomization was as follows: G1 (n=25) received individualized dietary counseling based on regular foods, G2 (n=25) were asked to consume two cans per day of a high protein liquid supplement in addition to their usual diet, patients in the control group G3 (n=25) were instructed to maintain their *ad lib* intake. All patients completed the study as outlined in **Table 1** and there were no patients lost to follow-up; none was taking any other dietary supplements, either prior or throughout the period under scrutiny.

Nutritional intake. At baseline, current energy and protein intakes for the three study groups were compared with EER and the protein median reference values, intakes were not significantly different between groups, **Figure 1**.

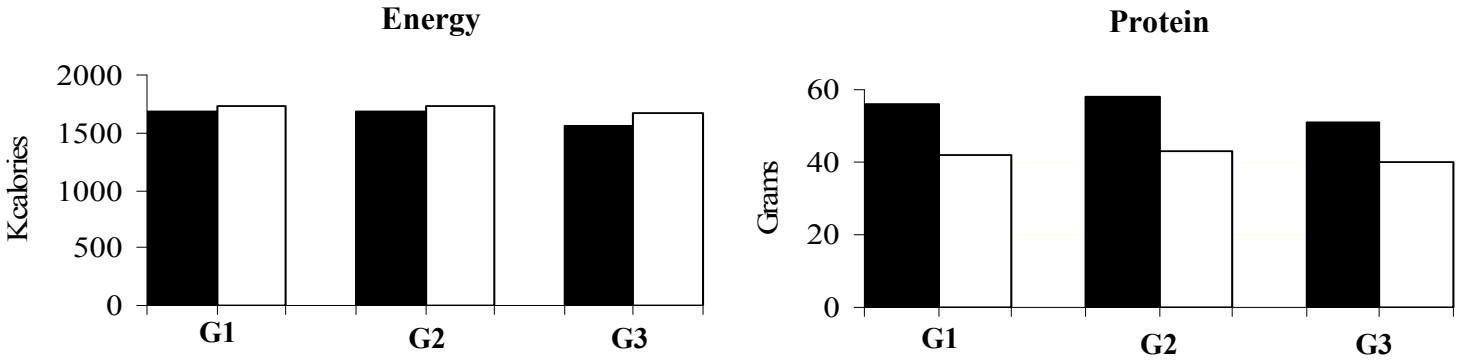

Figure 1 Patients' median baseline estimated requirements ■ and median intake □, nutritional intake was similar in all groups; energy intake was not significantly different from estimated requirements, protein intake was lower than reference values, p=0.05; G1=dietary counseling based on regular foods, G2=supplements, G3=*ad lib* intake.

The median nutritional intake patterns throughout the study are shown in **Figure 2**.

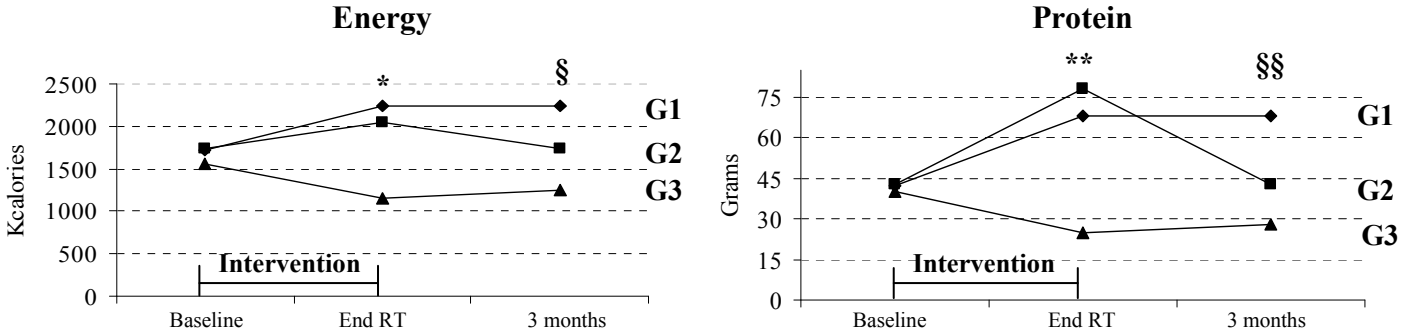

Figure 2 Energy and protein intake patterns during intervention and follow-up for the three study groups; G1=dietary counseling based on regular foods, G2=supplements, G3=*ad lib* intake. Energy: *G1>G2>G3 (p=0.005) and §G1>G2>G3 (p=0.001); protein: **G2>G1>G3 (p=0.006) and §§G1>G2>G3 (p=0.001).

At the end of RT by comparison to the onset, energy intake showed a net increase of 521 (358-732) kcal/d in G1 (p=0.002) and of 322 (286-412) kcal/d in G2 (p=0.05); G1>G2, p=0.005. Energy intake decreased in G3, 400 (201-502) kcal/d (p<0.01). At the 3 months follow-up, all patients in G1 still complied with dietary recommendations as given during RT and maintained their energy intake, whilst in both G2 and G3 patients' energy intake decreased (p=0.005) either to baseline or below baseline. In what concerns protein intake, there was a net increase of 26 (20-34) g/d in G1 (p=0.006) and of 35 (20-44) g/d in G2 (p=0.001); G1<G2, p=0.06; in both G1 and G2, the increase was always higher in stage I/II, p=0.05. Protein intake decreased in G3, 15 (9-21) g/d (p<0.01). At the 3 months follow-up, patients in G1 complied with nutritional recommendations as given during RT and maintained their protein intake, whilst both G2 and G3 patients decreased (p<0.05) their protein intake either to baseline or below baseline.

Nutritional status. The prevalence of malnutrition at baseline was similar between the three study groups (16 in G1, 14 in G2 and 15 in G3); 56% of the malnourished patients were in stage III and IV and 4% in stage I and II. The number of patients that presented further nutritional deterioration, both at the end of RT and at the 3-months follow-up, is shown in **Table 2**.

Table 2 Changes in nutritional status during RT and at 3-months categorized according to PG-SGA

Methods	**G1**				**G2**				**G3**				***p*[1]**	***p*[2]**
	Decline		Maintained/improved		Decline		Maintained/improved		Decline		Maintained/improved			
	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months		
PG-SGA	5	3	20	22	19	24	6	1	24	25	1	0	<.002	<.001

Data are expressed as number of patients; NS = not significant; p^1 expresses the significance of statistical differences between intervention groups, regarding nutritional decline both at the End RT and at 3 months; p^2 expresses the significance of statistical differences between intervention groups, regarding maintenance/improvement of nutritional status at the End RT and at 3 months.

In G1, 8/16 malnourished patients at baseline improved their nutritional status with a net average recovery of 4 (2-6) kg at 3 months; conversely, none of the patients in G2 and G3 ever improved their nutritional status.

Symptom induced morbidity. At the onset of RT, the prevalence of anorexia (≤7%), nausea/vomiting (≤10%), xerostomia (≤20%), dysgeusia (≤22%) and/or dysphagia/odynophagia (≤25%) did not differ between the groups. At the end of RT, overall more than 90% of the patients experienced RT-induced toxicity, the severity and incidence of which are presented in **Table 3**: the incidence of the above designated symptomatic manifestations was not significantly different between groups ($p<0.08$); though there was a trend for reduced syptomatology in G1 *vs* G2, G3 ($p<0.07$). Nevertheless, the incidence and/or severity of the symptoms improved differently in the three groups after RT.

Table 3 RT induced morbidity categorized according to severity grades (12)

Symptoms	**G1**				**G2**				**G3**				p^1	p^2	p^3
	Grade 1		Grade 2		Grade 1		Grade 2		*Grade1*		Grade 2				
	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months	End RT	3 months			
Anorexia	10	1	2	0	9	4	5	3	9	5	7	3	<.05	<.12	<.001
Nausea/ Vomiting	4	0	1	0	3	2	2	1	3	2	2	1	<.001	<.10	<.05
Xerostomia	12	2	3	0	10	6	6	3	10	5	7	3	<.04	<.05	<.0003
Dysgueusia	10	1	7	2	10	6	11	5	11	5	12	6	<.04	<.008	<.0004
Odynophagia/ dysphagia	14	2	8	1	12	3	10	3	12	6	12	6	<.0001	<.05	<.0002

Data are expressed as number of patients; grades 3 and 4 were never observed; p^1 expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 1 symptom' incidence between the End RT and 3-months; p^2 expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 2 symptom' incidence between the End RT and 3-months; p^3 expresses the significance of statistical differences between intervention groups, regarding the reduction of grades 1+2 symptom' incidence between the End RT and 3-months.

At 3 months, the reduction of incidence and severity of grade 1+2 anorexia, nausea/vomiting, xerostomia and dysgeusia was distinctly different between groups: 90% of the patients improved in G1 *vs* 67% in G2 *vs* 51% in G3 ($p<0.0001$); G1 > G2, G3 ($p<0.07$). The reduction of grade 1+2 dysphagia/odynophagia incidence and severity remained not significantly different between groups ($p<0.09$).

In the 3 groups the different symptom pattern occurred despite adequate and appropriate prescription of medications to alleviate symptoms. During RT, oral anti-fungal solutions (nistatine), local anesthetics (lidocaine) and/or anti-inflammatory drugs were prescribed to 57% of patients in G1, to 61% in G2 and to 68% in G3 (NS).

In order to clarify the influence of dietary intake and RT induced symptoms on patients' nutritional decline, a two-tailed multiple correlation analysis was performed; dietary intake was significantly correlated with nutritional status in all study groups ($r \leq -0.59$, $p \leq 0.002$).

Quality of Life. Median QoL dimension scores for the study groups at the three evaluation set points are presented in **Table 4**.

Table 4 Median Quality of Life dimensions' scores

Items	G1			G2			G3		
	Onset	End	3-months	Onset	End	3-months	Onset	End	3-months
Function scales									
Global QoL	48	75*	82$^{\#\S}$	46	70*	62$^{\#}$	47	30*	30$^{\#}$
Physical function	49	74*	79$^{\#}$	48	69*	60$^{\#}$	45	21*	22$^{\#}$
Role function	50	78*	80$^{\#}$	52	68*	58$^{\#}$	48	20*	19$^{\#}$
Emotional function	55	79*	83$^{\#}$	50	66*	62$^{\#}$	51	28*	28$^{\#}$
Social function	52	82*	85$^{\#}$	51	66*	61$^{\#}$	49	19*	20$^{\#}$
Cognitive function	38	58*	60$^{\#}$	35	51*	54$^{\#}$	37	20*	20$^{\#}$
Symptoms, scales									
Fatigue	30	55*	26§	31	75*	78$^{\#}$	29	78*	79$^{\#}$
Pain	25	63*	15$^{\#\S}$	22	74*	45$^{\#\S}$	23	78*	73$^{\#}$
Nausea and vomiting	15	50*	10$^{\#\S}$	14	71*	60$^{\#\S}$	12	72*	73$^{\#\S}$
Symptoms, single items									
Dyspnea	15	39*	8$^{\#\S}$	14	40*	38$^{\#}$	18	38*	38$^{\#}$
Sleep disturbance	30	55*	29$^{\#\S}$	28	55*	75$^{\#\S}$	32	60*	78$^{\#\S}$
Appetite	45	68*	48$^{\#\S}$	40	59*	72$^{\#\S}$	42	65*	75$^{\#\S}$
Constipation	12	10	10	11	9	8	9	8	8
Diarrhea	7	7	7	6	6	6	7	7	7
Finance	38	38	38	37	37	37	40	40	40

G1: dietary counseling based on regular foods; G2: supplements; G3: *ad lib* intake; higher scores on function scales indicate better functioning, higher scores on symptom scales/single items denote increased symptomatology or worse financial impairment. ___ Highlights overall significant improvement, _ _ highlights overall significant deterioration, ... highlights overall non-significant deterioration; *significant differences between baseline end of RT; $^{\#}$significant differences between baseline and at 3-months; §significant differences between end of RT and at 3-months.

At the end of RT in G1, despite RT induced symptoms, all QoL function scores improved significantly ($p<0.003$) and these were proportional to the increases registered in energy and protein intakes ($r<0.83$; $p<0.001$). There was also a linear positive association with the improvement in the patients' nutritional status ($p<0.05$). In G2, all function scores improved ($p<0.009$) although these were only proportional to the increase in protein intake ($r<058$; $p<0.05$). In considering symptom scales and single items for both G1 and G2, pain worsened in association with odynophagia/dysphagia ($p<0.04$), and fatigue (more severe in G2) was

associated with anorexia ($p<0.05$); patients also reported increased severity of sleep disturbance and dyspnea ($p<0.05$). In G3, all QoL function scores worsened in association with a deterioration of their nutritional intake ($p<0.0001$), as well as of their nutritional status ($p<0.002$). All symptom scales significantly worsened ($p<0.004$): increased fatigue was associated with poorer nutritional intake ($p<0.003$) and with nutritional status deterioration ($p<0.001$), pain worsened in association with odynophagia/dysphagia ($p<0.001$); as far as symptoms and single items were concerned, sleep disturbance, appetite and dyspnea also grew worse ($p<0.002$).

At 3-months follow-up and by comparison with the end of RT, all G1 patients maintained or improved their overall QoL, which was positively and proportionally associated with maintenance/improvement of nutritional status ($p<0.008$) and adequate dietary intake ($p<0.01$). Function scores improved or were maintained, and symptom scales/single items were now significantly better than baseline scores ($p<0.002$). G2 patients maintained or worsened their overall QoL ($p<0.03$) further reporting worse physical, role, emotional, and social functions ($p<0.07$); deterioration was associated with poor dietary intake ($p<0.003$) and depleted nutritional status ($p<0.002$). Notwithstanding the improvement of pain ($p<0.06$), the remaining scores were unchanged by comparison with the end of RT and were worse than at baseline ($p<0.002$). In G3, function scores further deteriorated both in relation to the baseline and to the end of RT ($p<0.004$), deterioration significantly associated with inadequate dietary intake ($p<0.001$) and deficient nutritional status ($p<0.002$). Symptom scores, with the exception of pain, remained as poor as reported at the end of RT and significantly worse than at baseline ($p<0.003$); the worst scores were associated with inadequate dietary intake ($p<0.005$).

DISCUSSION

Nutrition is a major issue in oncology; nutritional decline may ensue from the disease location and stage and its treatment(s) [1] and bears a negative prognosis [2]. Although symptomatic manifestations of radiation injury and their nutritional consequences have long been recognized [26], the potential role of adjuvant oral nutritional support on patients' outcomes has not yet been explored. This prospective randomized controlled trial is the first to demonstrate that even in HNC, concurrent individualized dietary counseling, based on regular foods, is the most effective means of improving patients' nutritional intake, status and QoL, thereby lessening radiotherapy induced morbidity.

Weight loss during RT is an early indicator of nutritional decline [26]; in the absence of nutritional support, the majority of head-neck cancer patients submitted to a 6-7 week course with $\pm$ 70 Gy of RT reported weight loss [4]. In our trial and throughout the whole study period, including intervention and follow-up, nutritional deterioration was only observed in 20% of patients in G1 (dietary counseling), amounting to 76% in G2 (supplements) and to 96% of the G3 control patients. These findings are concordant with the fact that disease-related malnutrition is frequently caused by reduced dietary intake [27]. Indeed, although the three study groups at baseline showed comparable energy and protein intakes, nutritional intake

patterns were quite different according to the nutritional intervention. At the end of RT, G1 showed the highest average energy intake sustained at the 3 months follow-up; the smaller increase in G2 was lost at follow-up when energy intake decreased to/or below baseline, as always registered in G3. Both dietary manipulation and supplements were effective protein intake restorers during the nutritional intervention phase; at 3 months the increase was just maintained in G1, whereas in the other 2 groups protein intake followed a pattern similar to the one observed for energy (**Figure 2**). Thus, within the context of this clinical trial, individualized dietary counseling during radiotherapy, taking into consideration the patients' clinical condition and symptoms, was the most effective nutrition intervention assuring a sustained and adequate diet which was able to overcome the predictable deterioration subsequent to radiotherapy. Moreover, such nutritional outcomes concur with what has been proposed as the causal pathway, i.e. optimizing nutritional intake may be the most effective method for treating disease-related malnutrition. There is evidence in a range of conditions to support the hypothesis that enabling the provision of the appropriate nutritional therapy leads to improved body weight and fat free-mass and that this generally reflects an improvement in protein-energy status [27].

The severity and extent to which patients experience radiotherapy induced toxicity, depend on location, tumor histology, total dose, fractionation, volume of irradiated area and injury repair mechanisms, which dictate susceptibility to acute radiation damage, during which high turnover cells are at higher risk [26]. The resulting nutritional sequelae occur through direct effects on oral, pharyngeal and laryngeal neoplastic and healthy tissues, accentuating physical discomfort and symptoms, e.g. xerostomia, disgeusia, odynophagia, dysphagia, anorexia, nausea/vomiting, which further decrease nutritional intake [28-30]. So far, the routine clinical approach is to maintain *ad lib* oral feeding, although comparative studies of functional, clinical and QoL outcomes which can be achieved via dietary manipulation or through oral nutrition supplementation, are lacking [27]. Our study is the first to demonstrate that the nutritional content of the patient's diet based on regular foods with appropriate manipulation, and not just protein and calorie supplementation, is the key to improving nutritional intake as well as some local symptomatic morbidity derived from mucosal damage, during radiotherapy and in the medium term. Indeed, dietary modifications may modify the ecology of the oral cavity by means of stimulating salivary secretion, and it is possible to decrease the oral intolerance to foods, both central to the pathogenesis of radiation injury severity [31].

QoL assessment measuring the patients' experiences of the impact of disease/therapy, expectations and satisfaction should be the gold standard as an independent end-point in clinical trials [32, 33]. Patients experience functional limitations, cognitive alterations and emotional stress, and overall QoL depends on both physical and psychological well being [7, 8, 34]. All these aspects may influence or be influenced by nutrition although the relationship between poor nutritional parameters and QoL remains widely underestimated [35, 36]. Our group was the first to show that nutrition is a key determinant of QoL in cancer patients [11]. In this clinical trial, both at the end and at 3 months after RT, dietary counseling (Group 1) significantly improved all QoL function scores in association with an adequate dietary intake and

nutritional status. In patients who received oral supplements (G2), function scores improved during supplementation, but to a lesser extent than in G1, and also proportionally to the increase in diet intake; however, once the supplementation was discontinued most function scores deteriorated. Patients not submitted to any nutritional intervention (G3) experienced, throughout the whole study, a significant deterioration in function scores and fatigue, in direct relation to the worsening of their nutritional intake and nutritional status. Therefore, our results emphasize that "the impairment in structure, function and well being that form malnutrition, are nutritionally responsive" [27].

Furthermore, the benefits of nutritional intervention on QoL were extendable to improved physiological function and overall clinical outcome. During RT, QoL symptom scales and single items' scores deteriorated in all groups, though more pronounced in the *ad lib* group; most of these scales were also worse in G2 *vs* G1. In the medium term, G3' symptom scales and single items remained as poor as those reported at the end of RT and worse than at the onset; worse scores were again associated with inadequate nutritional intake. Conversely, in G1 patients all the above mentioned scales were now improved and significantly better than their baseline scores, whereas in G2 there was an improvement in pain, though not as relevant as the improvement observed in G1. These results in patients who experience persistent eating difficulties support the concept that increased intake of an appropriate mixture of nutrients using regular foods will be of major benefit in modulating outcomes.

Despite the expected, and experienced, detrimental effects of radiotherapy, multiprofessional patient' management allowed proper assessment of nutritional status and nutritional requirements, dietary counseling, education and monitoring of diet compliance and timely management of symptoms. Nutrition intervention was central to the improvement of head-neck cancer patients' nutritional as well as non-nutritional outcomes: nutritional intake, status, symptoms and QoL even in the medium term. Adding oral nutritional supplements to the diet did not appear to be as effective as dietary counseling. Early intervention and sensible partnerships with patients are key to success.

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Section 5

CONCLUSIONS

Chapter 8

DISCUSSION AND FUTURE PERSPECTIVES

DISCUSSION AND FUTURE PERSPECTIVES

Nutrition is clearly and consistently associated with cancer. It constitutes one of the most significant risk factors for the development of oncological diseases [1], and later on throughout the disease course, 8-84% of the patients will suffer from undernutrition [2] which will be the immediate cause of death of 20% of the patients with cancer [3]. The present Thesis was driven by the complexity of this multidirectional interrelation.

Overall, the studies herewith presented were conducted in the difficult and diverse clinical setting of patients with cancers of the head and neck, oesophagus, stomach and colon/rectum. The results represent a breakthrough in demonstrating, beyond any doubt, the major importance of nutrition in cancer and its key role in patients' well-being, Quality of Life and tolerance to treatments, in a disease whose aggressiveness bears a heavy burden that patients have to carry, adapt to and live with. These findings were followed by a clear scientific demonstration in the two prospective randomised controlled trials of nutritional therapy, conducted in two very distinct diagnoses such as head and neck cancer and colorectal cancer. Both clearly argue for the integration of Nutrition as part of a team approach for cancer treatment and patient' management and do recognise the importance and necessity of good nutrition as therapy. Altogether the evidence produced definitely constitutes a step forward, which should strengthen the recognition of patients' right of expecting adequate nutrition care, mandatory to sustain life throughout the disease journey.

EVALUATION OF MULTIPLE INTERACTIONS STUDIES

Nutritional deterioration in cancer is a highly complex end-result of multiple interactions which are most likely individual to the unique combination of each patient and the tumour [4]. Some of the implicated factors have been addressed in this Thesis.

Greater understanding of factors contributing to nutritional deterioration in cancer, as well as patients' expectations and the personal impact of the disease, are required to devise meaningful nutritional therapy. Despite the major importance of the tumour burden for the host, the pattern and/or progression of nutritional deterioration are also highly influenced by the cancer location [4]. In what concerns nutrition and its impact on the patients' Quality of Life, although the location and stage of the disease are globally the major QoL determinants, nutritional aspects are equally important for functional scores, mainly for some diagnoses: head-neck, oesophageal cancer, in which the impact of nutritional deterioration combined with deficiencies in nutritional intake may, from a clinical perspective, be as relevant as the stage of the disease process [5, 6]. Specifically, in the cross-sectional study of 205 patients with cancer of the head-neck, oesophagus, stomach, colon/rectum, nutritional deterioration was multifactorial and mainly determined by the tumour burden [4]. In a larger cohort of 271 patients, although cancer stage and location were the major determinants of the patients' Quality of Life, nutritional deterioration combined with deficiencies in nutritional intake were functionally more relevant than cancer stage [5].

RANDOMISED CONTROLLED TRIALS OF NUTRITIONAL THERAPY

Based on this background, we tested the potential role of nutritional therapy on patient predefined outcomes: nutritional status, diet intake, morbidity and Quality of Life. Two prospective randomised controlled trials were conducted in patients with cancer of the colon/rectum (n=111) [7] or head-neck (n=75) [8]; in both instances patients were stratified for cancer stage. In order to compare nutritional therapy during radiotherapy, each study had 3 arms: individualised dietary counselling *vs ad libitum* intake supplemented with commercial supplements *vs ad libitum* intake; outcomes were analysed at the end and 3 months after radiotherapy, the latter period without nutritional intervention.

During radiotherapy and in both trials, only patients who received any form of nutritional intervention had a positive improvement in all outcomes; 3 months after the combined treatment period, only individualised nutritional counselling had a carry-over effect central to the improvement of various patient outcomes: nutritional intake, nutritional status, QoL and lessened morbidity. Oral nutritional supplements in addition to the *ad libitum* diet were not as effective as dietary counselling. Both clinical trials demonstrated that concurrent individualised dietary counselling based on regular foods, was the most effective means of improving patients' nutritional intake, status and QoL during RT, which were sustained 3 months after its completion, thereby lessening RT induced morbidity [7, 8].

Cancer patients do really benefit from multiprofessional patient management; it must include a proper assessment of nutritional status and nutritional requirements, dietary counselling, education and monitoring of diet compliance and timely management of symptoms. Nutrition is central to the improvement of a diversity of patient outcomes in colorectal and head-neck cancer patients. The integration of early intensive nutritional intervention and sensible partnerships with patients is key to success.

FUTURE PERSPECTIVES

Still many doubts persist in what concerns the dynamics that may lead to or be the cause of cancer-related wasting [9, 10].

We are currently exploring potential mechanisms implicated in cancer-related metabolic dysfunction and nutritional wasting, namely, the measurement of resting energy expenditure and its possible association with various clinical variables (cancer stage, histology), circulating concentrations of inflammatory cytokines and their genetic polymorphisms, and to investigate whether an interrelationship among all these variables exists. Some of the specific questions are:

1. What are the major determinants of patients' resting energy expenditure?
2. Does radiotherapy has any effect on the circulating concentrations of inflammatory cytokines (IL-1ra, IL-6, IL-10, TNF-α, IFN-γ and VEGF) and if so, how does that effect may be reflected on wasting components (resting energy expenditure, weight loss, nutritional intake)?

3. Are the concentrations of inflammatory cytokines correlated with each other and with cancer-related variables (stage, histology)?
4. Is there a relationship between the presence of polymorphisms and the clinical/nutritional outcome of the patients?
5. Is there a relationship between the presence of polymorphisms, the circulating concentration of inflammatory cytokines, cancer-related variables and wasting components?

Indeed, much needs to be investigated in cancer wasting and the putative involved components; our preliminary, yet unpublished, data on this topic (data not shown) do suggest that the composite wasting syndrome appears to ensue from a complex construct in which tumour histology and invasiveness along with released pro-inflammatory cytokines, namely IL-1ra, IL-6, TNF-α, IFN-γ, bear different burdens in the various wasting components with a maladaptive response to weight loss [11, 12]. Undoubtedly, cancer and nutrition provide a wide range of possibilities for future relevant research.

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