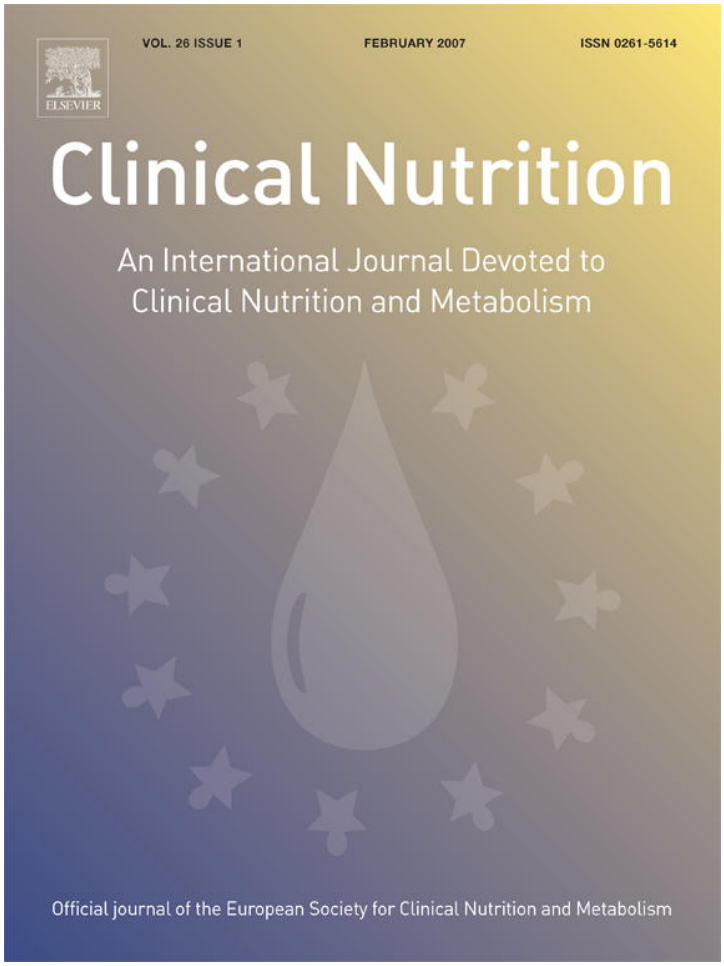

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REVIEW

Cancer wasting and quality of life react to early individualized nutritional counselling! ☆

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Summary
To devise a meaningful nutritional therapy in cancer, a greater understanding of nutritional dimensions as well as patients' expectations and disease impact is essential. We have shown that nutritional deterioration in patients with gastrointestinal and head and neck cancer was multifactorial and mainly determined by the tumour burden and location. In a larger cohort, stage and location were yet again the major determinants of patients' quality of life (QoL), despite the fact that nutritional deterioration combined with intake deficits were functionally more relevant than cancer stage. Based on this framework, the potential role of integrated oral nutritional support on outcomes was investigated. In a pilot study using individualized nutritional counselling on a heterogeneous patient population, the achieved improvement of nutritional intake was proportional to a better QoL. The role of early nutritional support was further analysed in a prospective randomized controlled trial in head and neck cancer patients stratified by stage undergoing radiotherapy. Pre-defined outcomes were: nutritional status and intake, morbidity and QoL, at the end and 3 months after radiotherapy. Nutritional interventions, only given during radiotherapy, consisted of three randomization arms: (1) individualized nutritional counselling vs. (2) ad libitum diet+high protein supplements vs. (3) ad libitum diet. Nutritional interventions 1 and 2 positively influenced outcomes during radiotherapy; however, 3 months after its completion individualized nutritional counselling was the single method capable of sustaining a significant impact on patients' outcomes. The early

☆This paper is based on the presentation given at the III Cachexia Conference (Rome, 8–10 December 2005). During the conference, experts in wasting diseases, both basic scientists and clinical researchers, discussed relevant topics in the anorexia-cachexia field, including pathogenic mechanisms, diagnostic tools, current therapeutic strategies and future options. More details can be found at www.cachexia.org.

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provision of the appropriate mixture of foods and textures using regular foods may modulate outcomes in cancer patients.

Contents

Introduction

Cancer-related weight loss is known to worsen patients well-being,[1,2] tolerance to antineoplastic therapies[3] and prognosis.[4,5] Specifically, weight loss seems to reduce immunological competence[6] and resistance to infection,[7,8] enhances susceptibility to postoperative complications,[5,9,10] and increases disability and overall cost of care.[11]

Although a few studies were undertaken in the early 20th century,[12–14] malnutrition remained a bewildering syndrome even in relatively recent publications. Indeed, estimates of the prevalence of malnutrition in cancer patients range from 8% to 84%[15] apparently associated with the cancer site, e.g. 80% in patients with gastrointestinal cancer[16,17] and 70% in patients with head and neck cancer.[18] Despite the fact that nutritional deterioration has been associated with patients' functional impairment,[19] neither potential interactions between cancer location and stage, treatments, nutrition, morbidity and quality of life (QoL) nor the impact of individualized nutritional counselling on patients' nutritional, clinical and QoL outcomes have ever been thoroughly explored.[20,21] In fact, there is remarkably little information about the effect of oral nutrition on functional outcome measures and QoL.[15] Innovative and consistent evidence to support integrated nutritional counselling as a major topic in oncology will be illustrated in this overview, which results from the collision of data from prospective studies in cancer patients conducted by our group.[22–26]

Cancer and the nutrition spectrum

Nutritional deterioration, intake deficits and tumour burden

In order to tackle nutritional deterioration, gathering objective data on nutritional status and its evolution throughout the disease course is an absolute necessity. There are indeed studies reporting cancer-related weight loss as the most frequent presenting symptom[27] or potentially associated with advanced disease.[28] Nonetheless, previous data have been inconsistent regarding nutritional status assessment and cancer/treatment-related variables even when addressing similar cancer locations.[29,30] Thus, we performed a thorough investigation of their possible interactions,[22] in order to step forward solid fundamentals to further elaborate on the appropriateness of nutritional therapy, as anticipated by Ottery.[31]

Longstanding energy and substrate deficits have not been previously investigated nor adjusted by the patients' cancer stage. In 205 gastrointestinal and head and neck cancer patients, we have shown that nutritional deterioration is a multifactorial end-result determined by cancer and diet-related factors.[22] The most significant association with worse nutritional status was by far advanced cancer stage; nevertheless, cancer location, duration of the disease, protein and energy intake, and previous surgery or chemotherapy were also significantly associated.[22] This provided novel clinical evidence of the complex interactions between cancer and/or treatment-related variables and diet changes, all of which exerted a combined effect on patients nutritional wasting.[22] Our results were consistent with previously described, though partial, associations between wasting, marked nutritional intake deficits and advanced disease.[4,5,8,9,11,32,33] A subsequent study conducted in a larger patient sample with the same cancer sites, revealed that patients with stage III/IV had markedly lower intakes than stage I/II.[24] Advanced stage was on the whole the common denominator of patients wasting, plus stage III/IV head-neck cancer patients reported the most severe weight loss. Our results thus corroborated prior observations that cancer stage and location are major factors for nutritional deterioration[34–37] and further emphasized the role of nutritional intake deficits, which

may occur early on and will become more severe with disease progression.[22,24]

Tumour burden and QoL

The World Health Organization in 1948 defined "health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being".[38] QoL issues became thereafter increasingly important in research,[39] and have been acknowledged valid instruments in the growing field of outcomes research to evaluate efficacy, cost-effectiveness, and net benefit of new therapeutic strategies.[40,41] QoL assessment, and more specifically "health-related QoL", is able to measure changes in physical, functional, psychological, social domains of health, as well as human and financial costs, seen as distinct areas modulated by a person's experiences, beliefs, expectations and perceptions.[42,43] It must be acknowledged that each individual has different health and performance expectations, hence QoL is highly individualized; moreover, we should bear in mind that when measuring QoL in any patient, particularly in cancer patients, individuals may be at different time points of their illness and expectations are likely to change over time.[44,45] Figure 1 shows domains known to contribute to the patients' QoL.[46] A meaningful QoL evaluation in cancer must include the impact of the disease together with therapeutic interventions, expectations and personal satisfactions; hence the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (EORTC QLQ C-30) is recommended as the most effective tool.[23,24,47]

Nutrition: a key determinant of cancer patients QoL

Multifactorial cancer-related malnutrition[22] is also swayed by experienced symptoms, e.g. anorexia, taste changes, odynophagia, dysphagia, nausea, vomiting, diarrhoea, often subsequent to antineoplastic therapies, may further compromise nutrition and functional ability.[48–51] Thus, the interaction between the reported symptoms and/or disease/treatment-related factors, as well as nutritional status and intake, add up to a complex combination potentially capable of dictating patients' QoL.[23,52–54] Yet, despite the suggested association between worse overall well being/morbidity and nutritional deterioration,[55,56] the interaction between nutrition and QoL did remain underestimated.[57] Fatigue, anorexia and emotional stress are common in cancer patients and may aggravate, and/or be worsened by poor nutritional intake and/or QoL.[52,58] Although nutritional care has been proposed to be integrated in cancer patients' overall management,[22,31,59] to date there is scant evidence supporting a close interaction between nutrition and QoL. Various disease and diet-related factors do have implications in patients' QoL as we have demonstrated.[24]

The weight of nutrition in patients' QoL

Our study comprising 271 patients with cancer of the head-neck, oesophagus, stomach and colon/rectum, provided objective evidence that cancer, diet deficits, nutritional depletion and therapeutic interventions were determinants of the patients' QoL, though with distinct relative weights.[24] Nutritional deficits and/or wasting were inherent to the cancer site and stage, however reduced energy/protein intake and weight loss were independent QoL determinants. Our results concur with Keys et al. landmark study which showed semi-starvation to impair systemic physiological, functional and psychological abilities.[60]

Moving further, it is of major clinical relevance to generate evidence on whether individualized nutritional counselling, education and monitoring integrated in the overall management, do effectively maintain or even improve nutritional intake and status, along with significant improvements in patients overall QoL and outcomes; issues to be focused in the next sections.

Nutrition intervention improves patients outcomes and QoL

Cancer location and its progression are central to nutritional decline.[22] Notwithstanding, nutritional deterioration and intake deficits were shown to be the 2nd most relevant factor (Table 1).[22,24] Our studies were conducted in outpatients referred for radiotherapy and radiation injury is known to aggravate symptoms with nutritional

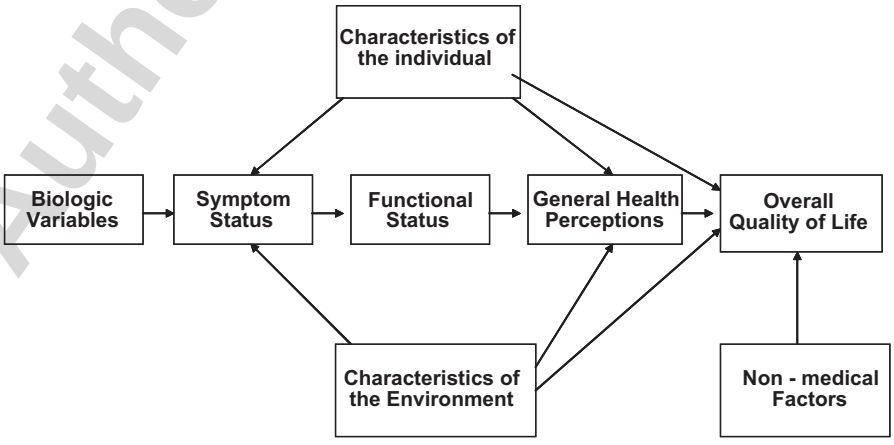

Figure 1 Domains that contribute to the patients' QoL [46].

consequences.[61,62] Thus, such patients were suitable to test whether nutritional therapy would influence outcomes. Therefore, a pilot prospective intervention study was conducted in a heterogeneous patient population,[23] and given the promising results was followed by two prospective randomized controlled trials, one in colorectal cancer[25] and another in head and neck cancer outpatients.[26]

Pilot intervention study

In a heterogeneous cancer patient population submitted to RT, the effect of nutritional intervention in the form of individualized nutritional counselling based on regular foods, on nutritional parameters and QoL was evaluated.[23] Individualized nutritional counselling based on regular

Table 1 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.

Variable	Global function scores			Global symptom scores†			Global single item scores†		
	F-test	Estimates of effect size (%)*	*P*	*F*-test	Estimates of effect size (%)*	*P*	*F*-test	Estimates of effect size (%)*	*P*
Cancer stage	1.6	1	0.18	56.5	22	0.001	103.7	30	0.0001
Cancer 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; *F*-test = test value for the variable; Estimates of effect size = percentage of the overall variance for the dependent variables, determined by the independent variables.

*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.

Table 2 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
Diarrhoea	2	2	0	0	59	78	9	9	6	6
Finance	4	4	1	1	8	8	38	38	5	5

Data are expressed as median value of QoL dimension scores; OES = oesophagus, STO = stomach, CR = colorectal, HN = head-neck, LR = low-risk (breast, prostate, uterus, brain); higher scores on function scales indicate better functioning, higher scores on symptom scales/single items denote increased symptomatology or worse financial impairment.

Table 3 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	<0.002	<0.001

Data are expressed as number of patients; PG-SGA = Patient Generated-Subjective Global Assessment; G1 = individualized dietary counselling based on regular foods; G2 = ad lib intake+supplements; G3 = ad lib intake; 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.

foods, was always designed and prescribed in the form of dietary guidelines in writing, which were given and explained in detail to the patients. The dietary plan (daily meal plan in quantity, type of foods and daily meal distribution) was therefore based on the patients' cancer location, concomitant treatments, surgery, symptoms, nutritional status and weight changes, individual dietary habits and preferences, present intake, food intolerances, taste abnormalities, functional capacity and nutritional requirements.[63] Patients submitted to RT, particularly of the head and neck or the gastrointestinal tract, are at higher risk of malnutrition, aggravated by RT toxicity that may further compromise nutrition and functional status.[64] This study showed that, in patients prone to develop nutritional problems and to report the worst QoL during RT, individualized nutritional counselling did improve nutritional intake which was identified as central to a better QoL, Table 2.[23] Additionally, two QoL instruments were tested, the non-specific EUROQOL[65] could be used routinely because it is less time consuming; the more comprehensive cancer-specific EORTC QLQ C-30 instrument[47] 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 exposed the relevance of nutrition care.[23] Subsequently, nutritional intervention was further evaluated in a prospective randomized controlled trial in head and neck cancer outpatients (submitted to radiotherapy-RT), in order to assess the potential role of adjuvant oral nutritional support on patients outcomes; patients stratified by cancer stage were randomized to receive: individualized dietary counselling based on regular foods (as described above)[63] vs. an ad libitum diet plus high protein supplements vs. ad libitum diet.[26]

Randomized controlled trial of nutritional therapy in head & neck cancer

Nutritional deterioration and intake deficits

Weight loss during RT is an early indicator of potential nutritional decline further on the disease progression.[61] The majority of head-neck cancer patients submitted to a 6–7 week course with ± 70 Gy of RT report weight loss in the absence of nutritional support.[66] In our trial, the nutrition intervention occurred only during RT, whereas the study period comprised a follow-up (3 months after RT completion without any nutrition intervention). At the end of RT, nutritional deterioration was only observed in 20% of the patients receiving individualized dietary counselling based on regular foods (G1), amounting to 76% in those who received supplements (G2), and to more than 96% in the ad libitum (control) patients (G3), Table 3.[26] These findings concur that disease-related malnutrition is frequently caused by reduced dietary intake which may be overcome by the provision of an appropriate nutritional therapy and this generally reflects an improvement in protein-energy status.[15] Indeed, although at baseline the three study groups showed comparable nutritional status, and energy and protein intakes, nutritional intake patterns became quite different according to the type of nutritional intervention. At the end of RT, G1 showed the highest average energy

intake, sustained throughout the 3 months follow-up; the smaller increase in G2 was lost during follow-up when energy intake decreased to/or below baseline; in G3 energy intake never increased but instead decreased to/or below baseline. During nutritional intervention, both dietary manipulation and supplements were effective in restoring protein intake; the increase was just maintained at 3 months in G1, whereas in the other 2 groups the protein intake followed a pattern similar to that observed for energy, Fig. 2.[26] Thus, individualized dietary counselling during RT, taking into consideration each 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.[25]

Symptom induced morbidity

The susceptibility to acute radiation damage on neoplastic and healthy tissues, e.g. head and neck, depend on the tumour histology, total RT dose, fractionation, volume and anatomical location of irradiated area, injury repair mechanisms and concurrent chemotherapy.[61] Indeed, patients with head and neck cancer already have nutritional handicaps ensuing from the tumour location.[23] Further nutritional intake decreases resulting from the direct effects of RT on oral, pharyngeal and laryngeal neoplastic and healthy tissues, accentuate physical discomfort and symptoms,[67] e.g. xerostomia, dysgeusia, odynophagia, dysphagia, anorexia, nausea/vomiting.[8,68,69]

Two randomized controlled trials of enteral nutrition, in gastrointestinal or head and neck cancer patients, showed a possible weight gain or reduced weight loss and reduced mortality, though functional status or global health scores remained unaltered.[70,71] The routine approach however is to maintain an ad libitum oral diet, since comparative studies with dietary manipulation or oral nutrition supplementation, and evaluating functional, clinical and QoL outcomes are lacking.[15] Our study is the first to show that

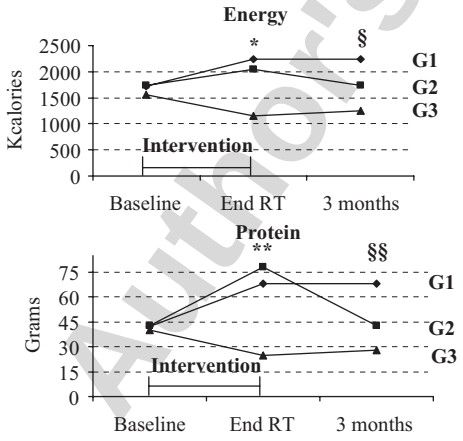

Figure 2 Energy and protein intake patterns during intervention and follow-up for the three study groups; G1 = dietary counselling based on regular foods, G2 = supplements, G3 = ad lib intake. Energy: *G1 > G2 > G3 ($P = 0.005$) and §G1 > G2 > G3 ($P = 0.001$); protein: **G2 > G1 > G3 ($P = 0.006$) and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

Table 4 RT induced morbidity categorized according to severity grades.[67,76]

Symptoms	G1		G2			G3			P^1	P^2	P^3
	Grade 1		Grade 2			Grade 1		Grade 2			
	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	<0.05	<0.12	<0.001
Nausea/vomiting	4	0	1	0	3	2	2	1	3	2	2	1	<0.001	<0.10	<0.05
Xerostomia	12	2	3	0	10	6	6	3	10	5	7	3	<0.04	<0.05	<0.0003
Dysgueusia	10	1	7	2	10	6	11	5	11	5	12	6	<0.04	<0.008	<0.0004
Odynophagia/dysphagia	14	2	8	1	12	3	10	3	12	6	12	6	<0.0001	<0.05	<0.0002

Data are expressed as number of patients; G1 = individualized dietary counselling based on regular foods; G2 = ad lib intake+supplements; G3 = ad lib intake; 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.

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 improve nutritional intake as well as some local symptomatic morbidity derived from mucosal damage, both during and after RT. Furthermore, RT induced toxicity was more severe and incident in patients with an ad libitum intake and to a lesser extent in the supplemented group, whereas in those patients who received dietary counselling/education, the symptom incidence and/or severity were inferior along with a faster improvement (Table 4).[26] Indeed, dietary modifications may as well modify the ecology of the oral cavity by means of stimulating salivary secretion, and thereby decrease the oral intolerance to foods.[55]

QoL

In clinical trials, QoL assessment of three major dimensions: function, symptom and single item scores, thus measuring patients experiences of the impact of disease/therapy, should be the gold standard as an independent endpoint.[72,73] In this clinical trial, dietary counselling (G1) significantly improved all QoL function scores, in association with an adequate dietary intake and nutritional status, both at the end and 3 months after RT. In G2 patients who received oral supplements, function scores improved during the intervention period, to a lesser extent than in G1, though still proportional to the increase in diet intake; most function scores however deteriorated once the supplementation was discontinued. G3 patients just receiving ad libitum diet, experienced throughout the whole study period a significant deterioration in function scores and fatigue in direct relation to the worsening of their nutritional intake and nutritional status.[26] Therefore, our results emphasize that "the impairment in structure, function and well-being that form malnutrition, are nutritionally responsive".[15] Furthermore, the benefits of nutritional intervention on QoL were extrapolated to improved physiological function and overall clinical outcome. In fact, QoL symptom scores deteriorated in all groups during RT, though more pronounced in the ad libitum group; most of those were also worse in G2 than G1. At the 3 months follow-up, G3 symptom scores 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 QoL scores were then improved and significantly better than at baseline, whereas in G2 only pain showed an improvement, Table 5.[26] These results achieved in patients who experience a variety of persistent and severe swallowing disturbances, sustain the sensible practice of providing the appropriate mixture of foods and textures using regular foods, which may modulate outcomes.[15]

Conclusions

Nutritional deterioration in cancer is a highly complex end-result of multiple interactions which are most likely

Table 5 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
Diarrhoea	7	7	7	6	6	6	7	7	7
Finance	38	38	38	37	37	37	40	40	40

G1: individualized dietary counselling based on regular foods; G2: ad lib intake+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; *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.

individual to each patient and the tumour.[22,62,74,75] In what concerns nutrition and its impact on the patients' QoL, cancer location and stage are the major determinants; nutritional aspects are equally important for QoL functional scores, in which the impact of nutritional deterioration combined with deficiencies in nutritional intake may be from a clinical perspective as relevant as the stage of the disease.[24]

The final question was: does nutrition influence outcomes? Therefore, a prospective randomized controlled intervention trial was conducted in 75 head and neck cancer patients submitted to RT, in order to address the potential role of adjuvant oral nutritional support on patients' outcomes.[26] Nutritional counselling was indeed central to the improvement of a diversity of outcomes: nutritional intake, nutritional status, QoL and lessened morbidity, even in the medium term after nutritional intervention. Adding oral nutritional supplements to the diet was not as effective as dietary counselling.[26]

The body of evidence conveyed in this review demonstrates that nutrition is significant in cancer wasting and QoL, both of which are responsive to early individualized dietary counselling based on regular foods. Cancer patients do benefit from multiprofessional patient management to include a proper early assessment of nutritional status and nutritional requirements, dietary counselling/education, monitoring and timely management of symptoms. Early intensive nutritional intervention and sensible partnerships with patients are key to success.

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