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ORIGINAL REPORT

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 nutritional supplements on outcomes in cancer patients: nutritional, morbidity, and quality of life (QoL) during and 3 months after radiotherapy.

Patients and Methods
A total of 111 colorectal cancer outpatients referred for radiotherapy, stratified by staging, were randomly assigned: group 1 (G1; n = 37), dietary counseling (regular foods); group 2 (G2; n = 37), protein supplements; and group 3 (G3; n = 37), ad libitum intake. Nutritional intake (diet history), status (Ottery's Subjective Global Assessment), and QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0) were evaluated at baseline, at the end, and 3 months after radiotherapy.

Results
At radiotherapy completion, energy intake increased in G1/G2 ($P \leq .04$), G1 more than G2 ($P = .001$), and decreased in G3 ($P < .01$). Protein intake increased in G1/G2 ($P \leq .007$), G1 less than G2 (not significant), and decreased in G3 ($P < .01$). At 3 months, G1 maintained nutritional intake and G2/G3 returned to baseline. After radiotherapy and at 3 months, rates of anorexia, nausea, vomiting, and diarrhea were higher in G3 ($P < .05$). At radiotherapy completion, in G1 all QoL function scores improved proportionally to adequate intake or nutritional status ($P < .05$); whereas in G2 only three of six function scores improved proportionally to protein intake ($P = .04$), and in G3 all scores worsened ($P < .05$). At 3 months, G1 patients maintained/improved function, symptoms, and single-item scores ($P < .02$); in G2, only few function and symptom scales improved ($P < .05$); in G3, QoL remained as poor as after radiotherapy. In G1/G2, respectively, improvement/deterioration of QoL correlated with better or poorer intake or nutritional status ($P < .003$).

Conclusion
During radiotherapy, both interventions positively influenced outcomes; dietary counseling was of similar or higher benefit, whereas even 3 months after RT, it was the only method to sustain a significant impact on patient outcomes.

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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 (eg, anorexia, nausea, vomiting, and diarrhea) is common and may compromise both nutritional status and functional ability,[5,6] which in turn, impacts quality of life (QoL). The latter is a subjective multidimensional construct reflecting functional status, psychosocial well-being, and 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 and QoL in cancer patients.[10]

This study was designed to test the hypothesis of a causal pathway between nutritional intervention and functional and clinical outcomes. Within this framework, we conducted a prospective, randomized, controlled trial in colorectal cancer (CRC) patients referred for RT. 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 QoL) 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 preconstructed 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 before 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, and 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 European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group 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% (ie, an effect size of 0.9) with a significance level of .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] This study therefore included 111 free-living patients (66 males, 45 females), mean age 58 ± 15 years (range, 32 to 88 years): 45 in stage I/II and 66 in stage III/IV. All patients were referred for preoperative RT combined with chemotherapy comprising fluorouracil plus folinic acid–based regimens administered concurrently with the first and the last 5 days of RT.

Patients stratified by cancer stage were randomly assigned at enrollment 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: group 1 (G1; n = 37) received individualized dietary counseling based on regular foods; group 2 (G2; n = 37) were asked to consume two cans per day of a high-protein liquid supplement in addition to their usual diet; in group 3 (G3, n = 37), the control group, patients were instructed to maintain their ad libitum intake. Randomly assigned patients had scheduled visits and identical contact time with the research dietician (P.R.). All parameters and study measures were assessed as described in Table 1

Table 1. Data Collection, Nutritional Intervention, and Visit Schedule

Characteristic	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 (groups 1 and 2)*	X	X	X	X	X	X	X	
Acceptability and compliance		X	X	X	X	X	X	

Abbreviations: RT, radiation therapy; PG-SGA, Ottery's Patient Generated Subjective Global Assessment; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; QoL, quality of life; QLQ-C30, Quality of Life Questionnaire version 3.0.
*Nutritional intervention period from day 1 to 35.

and the use of other medications and dietary supplements and compliance with dietary recommendations were monitored weekly. Overall, the main goal of both nutritional interventions was to enable every patient to achieve his or 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 and protein level to attain, and included 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 20 g protein and 200 kcal. The amount of supplement provided was uniform (two cans per 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 caregiver or relative.

Study Measures

Nutritional assessment. Nutritional assessment was performed using two methods. The first method, Ottery's Patient Generated Subjective Global Assessment (PG-SGA),[16] is a validated nutritional assessment tool for cancer patients that addresses weight changes, symptoms (anorexia, nausea, constipation, mucositis, vomiting, diarrhea, xerostomia, pain), alterations in food intake by comparison with the usual intake, and functional capacity; components of metabolic stress, including sepsis, neutropenic or tumor fever, and use of corticosteroids; and physical examination, including subcutaneous fat (triceps skinfold and at the level of the lower ribs in the mid/axillary line), muscle bulk and tone in the temporal, deltoids, and quadriceps areas, and ankle or sacral edema or ascites. Nutritional status was thus categorized in three degrees: normal, moderate, and severe malnutrition. The second method used 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 less than 20 kg/m^2 or normal if $\geq$ kg/m^2.[17]

Nutritional requirements and dietary assessment. Basal energy requirements were estimated using the World Health Organization formulas for patients aged $\leq$ 60 years[18] or by the Owen et al[19,20] formulas for patients aged older than 60 years, given their better performance in predicting resting metabolic rate.[21] To estimate patients' daily energy requirements, 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 24-hour–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 weekdays 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 (2003; Forestfield Software Ltd, Horsham, United Kingdom) was used to analyze nutrient contents of regular foods and meals.

QoL instrument. QoL was assessed at the three time points, always using the EORTC Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30). This instrument is a 30-item cancer-specific questionnaire including six function scales (physical, emotional, cognitive, social, role, and global health or QoL), three symptom scales (fatigue, pain, nausea or vomiting), and six single items assessing symptoms and the financial impact of the disease.[7] Higher scores on the function scales indicate better functioning, whereas 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 high statistical significance of the interscale correlations, which were calculated according to EORTC guidelines.[7]

Statistical Analysis

Statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, IL) and EPI–Info 2000 (Centers for Disease Control, Atlanta, GA). 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 $\pm$ standard deviation and range; energy and protein intakes were expressed as the median and range, and patients' QoL scores were expressed as median values. Continuous variables were analyzed using one-way analysis of variance or Wilcoxon rank sum tests as appropriate; categoric variables and incidence, prevalence, or frequency were evaluated by the χ^2 test. Univariate or multiple correlations were assessed by two-tailed nonparametric Spearman's tests. Statistical significance was set for a P value less than .05.

RESULTS

As summarized in Table 1, all patients completed the study and none were lost to follow-up. In addition, 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 daily energy requirements 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 ($P = .07$) and protein intake was lower than reference values ($P = .06$). Overall, energy and protein intakes were not significantly different between groups. The median nutritional intake patterns throughout the study are shown in Figure 1. At the end of RT, in comparison with the onset, energy intake showed a net increase of 555 kcal/d (range, 398 to 758 kcal/d) in G1 ($P = .002$) and of 296 kcal/d (range, 286 to 401 kcal/d) in G2 ($P = .04$); G1 more than G2 ($P = .001$). Energy intake decreased in G3 (285 kcal/d; range, 201 to 398 kcal/d; $P < .01$). At the 3-month follow-up, patients in G1 still complied with dietary recommendations as given during RT and maintained their energy intake, whereas in both G2 and G3, patients' energy intake decreased ($P = .05$) either to baseline (stage I/II) or below baseline (stage III/IV). There was a net increase in protein intake of 27 g/d (range, 20 to 35 g/d) in G1 ($P = .007$) and of 30 g/d (range, 20 to 40 g/d) in G2 ($P = .001$). Protein intake in G1 tended to be lower than in G2 ($P = .07$); in both G1 and G2, the increase was always higher in stage I/II ($P = .05$). Protein intake decreased in G3, 10 g/d (range, 7 to 15 g/d; $P < .01$). At the 3-month follow-up, patients in G1 complied with nutritional recommendations as given during RT and maintained their protein intake, whereas both G2 and G3 patients decreased their protein intake ($P = .06$) 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 five malnourished patients in G1, four in G2, and three in G3. The number of patients who presented additional nutritional deterioration both at the end of RT and at the 3-month follow-up was significantly higher in G2 and in G3 relative to G1 ($P < .001$), using both methods. Similarly, nutritional deterioration was significantly more severe and incident in G3 relative to G1 and G2 ($P < .008$), again using both methods (Table 2). Considering PG-SGA specifically, nine of 15 G1 malnourished patients at baseline improved their nutritional status, showing a net average recovery of 4 kg (range, 2 to 7 kg) at the 3-month 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 ($\leq 9\%$), nausea or vomiting ($\leq 8\%$), and/or diarrhea ($\leq 17\%$) 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 listed in Table 3. Additional statistical analyses showed that, overall, both at the end of RT and at 3 months, RT-induced toxicity with symptomatic manifestations was higher in G3 ($P < .05$). Conversely, G1 showed the lowest symptom severity score ($P < .05$). Furthermore, symptom incidence and/or severity improved differently in the three groups throughout the 3-month period between the end of RT and the follow-up visit. The incidence of grade 1 and 2 anorexia decreased in a similar fashion in G1 and G2, and was significantly better than in G3 ($P < .001$). The significance of the reduction of grade 1 and 2 nausea and vomiting was distinctly different between groups: all patients improved in G1, 62% showed improvement in G2, and 51% showed improvement in G3 ($P < .0001$). The incidence and severity of diarrhea was also significantly different between the groups: all patients improved in G1, 59% showed improvement in G2, and 19% showed improvement in G3 ($P < .0001$). In the three groups the different symptomatology pattern occurred despite adequate and appropriate prescription of medications to alleviate symptoms. During RT, antiemetic and prokinetic drugs (metoclopramide and domperidone) were prescribed for 5% of patients in G1, for 49% of patients in G2 and for 68% of patients in G3. Although G1 patients no longer required these drugs, at 3 months, 10% of those in G2 and 32% of those in G3 still needed them. The prescription of antidiarrheal drugs (loperamide)

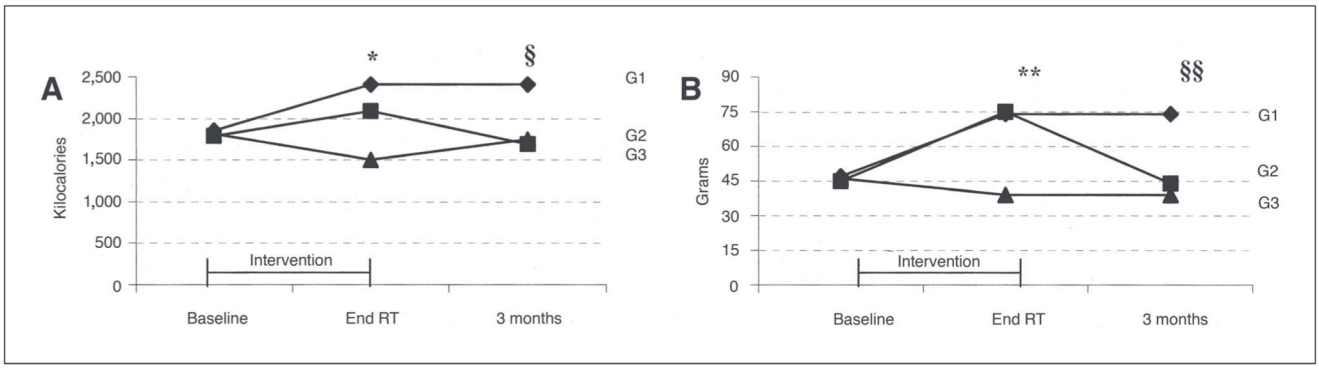

Fig 1. Energy and protein intake patterns during intervention and follow-up for the three study groups; G1, dietary counseling based on regular foods; G2, supplements; G3, ad libitum intake. Energy: *G1 > G2 > G3 ($P = .002$) and §G1 > G2 ≃ G3 ($P = .001$); protein: **G1 ≃ G2 > G3 ($P = .006$) and §§G1 > G2 ≃ G3 ($P = .001$).

Table 2. Changes in Nutritional Status During RT and at 3 Months Categorized According to PG-SGA and BMI

	Group 1				Group 2				Group 3					
	Decline		Maintained or Improved		Decline		Maintained or Improved		Decline		Maintained or Improved			
Methods	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	*P**	*P*†
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

NOTE. Data are expressed as number of patients.
Abbreviations: RT, radiation therapy; PG-SGA, Ottery's Patient Generated Subjective Global Assessment; BMI, body mass index; NS, not significant.
*Expresses the significance of statistical differences between intervention groups, regarding nutritional decline both at the end of RT and at 3 months.
†Expresses the significance of statistical differences between intervention groups, regarding maintenance or improvement of nutritional status at the end of RT and at 3 months.

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 the drug to control diarrhea.

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 ($r \leq -0.17$; $P \leq .24$), but was significantly correlated with nutritional status as categorized by PG-SGA ($r \leq -0.59$; $P \leq .003$). Similarly, increased overall symptomatology was correlated with worse nutritional status as categorized by PG-SGA ($r \leq -0.63$; $P \leq .002$), but not with BMI.

QoL

Median QoL dimension scores for the study groups at the three evaluation set points are listed in Table 4. At the end of RT in G1, despite RT-induced symptoms ($P < .05$), all QoL function scores improved significantly ($P < .002$) and these were proportional to the increases registered in energy and protein intakes ($r < 0.089$; $P < .001$). There was also a linear positive association with the improvement in the patients' nutritional status ($P < .05$). In considering symptom scales and single items, pain worsened in association with anorexia ($P = .05$), nausea or vomiting ($P = .04$), and diarrhea ($P = .03$). In G2, only three function scores (physical, role, and emotional) improved ($P < .05$), and these were proportional to the increase in protein intake ($P = .04$); the remaining function scales scores did not change significantly. Regarding symptom scales and single items, worse fatigue and pain were associated with anorexia ($P < .001$), nausea or vomiting ($P \leq .04$), and diarrhea ($P < .002$); patients also reported increased severity of sleep disturbance ($P = .02$). In G3 patients, all QoL function scores worsened in association with a deterioration of their nutritional intake ($P < .0001$), as well as of their nutritional status ($P < .002$). All symptom scales significantly worsened: increased fatigue was associated with poorer nutritional intake ($P < .003$) and with nutritional status deterioration ($P < .001$), and pain worsened in association with nausea or vomiting and diarrhea ($P < .001$). Regarding symptoms and single items, sleep disturbance and appetite became worse and were associated with nausea or vomiting and diarrhea ($P < .002$).

Table 3. RT-Induced Morbidity Categorized According to Severity Grades[12]

	G1				G2				G3						
	Grade 1		Grade 2		Grade 1		Grade 2		Grade1		Grade 2				
Symptoms	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	End RT	3 Months	*P**	*P*†	*P*‡
Anorexia	20	6	13	1	19	5	14	3	17	12	17	10	< .02	< .01	< .001
Nausea or 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

NOTE. Data are expressed as number of patients; grades 3 and 4 were never observed.
Abbreviation: RT, radiation therapy.
*Expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 1 symptom incidence between the end of RT and 3 months.
†Expresses the significance of statistical differences between intervention groups, regarding the reduction of grade 2 symptom incidence between the end of RT and 3 months.
‡Expresses the significance of statistical differences between intervention groups, regarding the reduction of grades 1 + 2 symptom incidence between the end of RT and 3 months.

Table 4. Median QoL Dimensions Scores

Items	Group 1			Group 2			Group 3		
	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

NOTE. Higher scores on function scales indicate better functioning; higher scores on symptom scales or single items denote increased symptomatology or worse financial impairment. (———) Highlights overall significant improvement; (– – – –) highlights overall significant deterioration; (· · ·) highlights overall nonsignificant deterioration.

Abbreviations: QoL, quality of life; RT, radiation therapy.

*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 3-month follow-up and in comparison with the end of RT, all G1 patients maintained or improved their overall QoL ($P < .02$), which was positively and proportionally associated with maintenance or improvement of nutritional status ($P < .02$) and adequate dietary intake ($P < .01$). Function scales scores also improved or were maintained ($P < .04$), and symptom scales or single items were similar to baseline scores. G2 patients maintained or worsened their overall QoL ($P < .03$) and patients also reported worse physical, role, emotional, and cognitive functions ($P < .05$). This deterioration was associated with poor dietary intake ($P < .003$) and depleted nutritional status ($P < .002$). Notwithstanding the improvement of pain, nausea or vomiting, and diarrhea ($P < .04$), sleep disturbance and anorexia worsened ($P < .03$), whereas the remaining scores were unchanged in 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 ($P < .004$). This deterioration was significantly associated with inadequate dietary intake ($P < .001$) and deficient nutritional status ($P < .002$). Symptom scale scores, apart from diarrhea, remained as poor as those reported at the end of RT, and were significantly worse than at baseline ($P < .001$); the worst scores were associated with inadequate dietary intake ($P < .005$).

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 RT-induced morbidity.

Weight loss during RT is an early indicator of nutritional decline.[26] A 6-week course with ± 50 Gy of RT to the abdomen or 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 entire study period, including intervention and follow-up, nutritional deterioration was only observed in 18% of patients in G1 (dietary counseling), in 50% of patients in G2 (supplements), and in more than 90% of the G3 control patients. These findings are concordant with the fact that disease-related malnutrition frequently is 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 RT, G1 showed the highest average energy intake sustained during the follow-up; the smaller increase in G2 was lost at follow-up when energy intake decreased to or below baseline, as was always the case in G3. During the nutritional intervention phase, both dietary manipulation and supplements were effective in restoring protein intake; similarly, the increase was just maintained in G1 at 3 months, whereas in the other two groups the protein intake followed a pattern similar to that observed for energy (Fig 1).

Thus, within the context of this clinical trial, individualized dietary counseling during RT, taking into consideration the patients' clinical condition and symptoms, was the most effective nutrition intervention, ensuring a sustained and adequate diet that was able to overcome the predictable deterioration subsequent to RT. Moreover, such nutritional outcomes concur with what has been proposed as the causal pathway (ie, 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 RT-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 or 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 libitum oral feeding, although comparative studies of functional, clinical, and QoL outcomes that 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 RT and in the medium term. In this trial, 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 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, the ecology of which is central to the pathogenesis of radiation injury severity.[33]

QoL assessment measuring the patients' experiences of the impact of disease and 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 of 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 (G1) significantly improved all QoL function scores in association with an adequate dietary intake and nutritional status. In patients who received oral supplements (G2), only three of six 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 (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."[28]

Furthermore, the benefits of nutritional intervention on QoL were extrapolated to improved physiologic function and overall clinical outcome. During RT, QoL symptom scales and single-item scores deteriorated in all groups, and these were significantly more pronounced in the ad libitum group. These scales were also significantly worse in G2 versus G1. In the medium term (eg, at 3 months or for a longer period), G3 symptom scales and single items remained as poor as those reported at the end of RT and worse than at the onset; worsening scores were again associated with inadequate nutritional intake. Conversely, in G1 patients all of the above-mentioned scales reverted to their baseline scores, whereas in G2 there was an improvement in pain, nausea or vomiting, and diarrhea, although 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 RT, multiprofessional patient management allowed proper assessment of nutritional status and nutritional requirements, dietary counseling, education, monitoring of diet compliance, and timely management of symptoms.

Nutrition intervention was central to the improvement of CRC patients' nutritional as well as non-nutritional outcomes (nutritional intake, status, and QoL) and lessened morbidity even in the medium term. The addition of 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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The authors indicated no potential conflicts of interest.

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