Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy[1–3]

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ABSTRACT

Background: In our published randomized trial in colorectal cancer, group 1 (n = 37) received individualized nutritional counseling and education about regular foods, group 2 (n = 37) received dietary supplements and consumed their usual diet of regular foods, and group 3 (n = 37) consumed their usual diet of regular foods. Neither group 2 nor group 3 received individualized counseling. Early nutritional counseling during radiotherapy was highly effective at reducing acute radiotherapy toxicity and improving nutritional intake/status and quality of life (QoL). Efficacy persisted for 3 mo after the intervention.

Objective: The objective was to perform long-term follow-up in survivors of that clinical trial to specifically evaluate survival, late toxicity, QoL, and nutritional variables.

Design: Medical data were collected from patients' records, and prescheduled interviews were conducted by dietitians for individualized evaluations. Analyses and comparisons between groups (adjusted for stage) were performed after a median follow-up of 6.5 (range: 4.9–8.1) y.

Results: Patients complied with the Radiotherapy Department's follow-up protocol. Nutritional deterioration was higher ($P < 0.001$) in group 3 (n = 26) and group 2 (n = 29) than in group 1 (n = 34). Adequate nutritional status was maintained in 91% of group 1 patients but not in any of the group 3 patients ($P < 0.002$). Intakes in group 1 were similar to reference values, and the patients adhered to the prescribed recommendations. Intakes in groups 2 and 3 were lower than recommended intakes: group 3 $\simeq$ group 2 $<$ group 1 ($P = 0.001$). Median survival in group 3 was 4.9 y (30% died), in group 2 was 6.5 y (22% died), and in group 1 was 7.3 y (only 8% died): group 3 $>$ group 2 $>$ group 1 ($P < 0.01$). Late radiotherapy toxicity was higher in group 3 (n = 17; 65%) and group 2 (n = 17; 59%) than in group 1 (n = 3; 9%): group 3 $\simeq$ group 2 $>$ group 1 ($P < 0.001$). QoL was worse in groups 3 and 2 than in group 1: group 3 $\simeq$ group 2 $<$ group 1 ($P < 0.002$). Worse radiotherapy toxicity, QoL, and mortality were associated with deteriorated nutritional status and intake ($P < 0.001$). Likewise, depleted intake, nutritional status, and QoL predicted shorter survival and late toxicity (HR: 8.25; 95% CI: 2.74, 1.47; $P < 0.001$).

Conclusions: This study conveys novel information about the effectiveness of nutrition at improving long-term prognosis in colorectal cancer. Overall, the data indicate that early individualized nutritional counseling and education during radiotherapy is valuable for patients. *Am J Clin Nutr* 2012;96:1346–53.

INTRODUCTION

Evidence indicates that intensive individualized nutritional counseling with regular foods, with or without supplements according to patients' requirements, increases nutritional intakes and prevents therapy-associated weight loss and treatment interruptions in cancer patients (1). Individualized counseling and the use of high-protein dietary supplements to increase dietary intake have become the standard recommendation by European Society for Clinical Nutrition and Metabolism guidelines for gastrointestinal and head-neck cancer patients undergoing radiotherapy with or without chemotherapy (1). This evidence is mostly supported by the results of our randomized controlled trials of nutritional therapy, in which a causal pathway between nutritional intervention and quality of life (QoL)[4] and functional and clinical outcomes was shown (2, 3), and subsequently confirmed, by Insenring et al (4, 5), who also used nutritional supplements as necessary.

Despite the expected and experienced acute detrimental effects of radiotherapy in patients with colorectal cancer, we have shown that individualized nutritional counseling, education and monitoring, and timely dietary management of symptoms improved nutritional and nonnutritional outcomes (2). In the original clinical trial, early individualized nutritional counseling during radiotherapy was the most effective regimen at reducing radiotherapy toxicity and improving nutritional intake and status and QoL. After radiotherapy completion and nutritional intervention, the above-mentioned efficacy persisted at the 3-mo follow-up (2).

In this study, we present the long-term follow-up results (updated results) of this clinical trial, aiming to explore whether individualized nutritional intervention during radiotherapy had any long-term influence on disease prognosis and clinical course and whether there was a sustained effect on late radiotherapy

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[4] Abbreviations used: EORTC, European Organization for Research and Treatment of Cancer; PG-SGA, patient-generated subjective global assessment; QoL, quality of life; RTOG, Radiation Therapy Oncology Group.

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toxicity, and possibly on radiotherapy efficacy, and on long-term QoL and survival.

SUBJECTS AND METHODS

Subjects

This is the long-term follow-up of a prospective randomized controlled trial of nutritional therapy that was carried out between July 2000 and March 2003 in colorectal cancer ambulatory patients submitted to neoadjuvant radiotherapy (2). This clinical trial was approved by the University Hospital Ethics Committee and conducted in accordance with the Helsinki Declaration, adopted by the World Medical Association in 1964, amended in 1975, revised in 1983, and updated in 2002. In the original trial, throughout the 1.5 mo of radiotherapy, 37 patients received 6 weekly individualized nutritional counseling and education sessions using regular foods (group 1). Group 2 ($n = 37$) received 2 cans/d of a high-protein dietary supplement (20 g protein/can) and consumed their usual diet of regular foods, and group 3 ($n = 37$) consumed their usual diet of regular foods.

All patients were submitted to surgical resection of their tumor between 3 and 5 wk after completion of radiotherapy. Two weeks after surgery, patients received adjuvant 5-fluorouracil– and folinic acid–based regimens. Patients were scheduled and observed at the Radiotherapy Department on periodic appointments according to the Department's protocol: first after the end of radiotherapy, second after surgery and chemotherapy, once every 3 mo until 2 y, once every 6 mo until 5 y, and once a year thereafter, in which patients were evaluated for recurrence and/or disease dissemination (6). For this study, a minimum follow-up period of 5 y was set to concur with the clinically established 5-y control interval.

On every periodic appointment and for every patient, physicians were in charge of performing thorough physical and clinical evaluations, a registry of serum concentrations of carcinoembryonic antigen and cancer antigen 19.9, medications, adjuvant treatment(s), and disease course (progression, remission, and stabilization) determined by local and whole-body imaging methods. In this clinical trial, physicians were blinded for the study groups. Any clinical sign/symptom or rise of carcinoembryonic antigen or cancer antigen 19.9 concentrations prompted further investigations, as appropriate. C-reactive protein concentrations were not available at the time of this study. Overall survival was always registered on patients' records, but only disease-specific survival was later used for censoring in statistical analysis.

Specifically for the long-term follow-up presented in this study, all of the study measures explained below (nutritional variables, radiotherapy toxicity, and QoL) were evaluated by the same research dietitian (PR) after a median follow-up of 6.5 (range: 4.9–8.1) y in interviews prescheduled by the Radiotherapy Department.

Study measures

A nutritional assessment was performed by using the same methods as in the original trial: *1*) Patient-Generated Subjective Global Assessment (PG-SGA) (7), validated for cancer patients, categorized nutritional status as well-nourished or as moderate or severe malnutrition, and *2*) anthropometric data: height was measured by using a stadiometer in the standing position, and weight was determined with a Jofre floor scale. BMI was calculated as weight (kg)/height $(m)^2$ and was classified as undernourished (<18.5) or not undernourished (≥ 18.5) (8, 9). A BMI cutoff of 20 was used for elderly patients (≥ 65 y) (8, 9).

Nutritional requirements and dietary assessment

Given the better performance in predicting resting metabolic rate in comparison with the Harris and Benedict formula, energy requirements were estimated by using the World Health Organization formulae for patients aged ≤ 60 y (10) or by the Owen et al formulae for patients aged >60 y (11–13). To calculate patients' daily energy requirements, basal requirements were multiplied by a 1.5 activity factor (14). Daily protein requirements were determined in comparison with age- and sex-standardized reference values between 0.8 and 1.0 g/kg per day (14). In the same consultation, nutritional intake was derived from a diet history (15, 16) to assess changes in current intake; the primary source of the dietary data were Burke's diet registry, further complemented by a 24-h recall.

Of importance for the readers is the group's practice of individualized nutritional counseling that aimed to educate patients on how to modify their nutritional intake, by making it adequate to individual requirements of energy, macronutrients, and micronutrients and simultaneously to modulate radiotherapy toxicity by reducing foods that would worsen symptoms and/or increase those that might reduce their severity. Dietary counseling consisted of the prescription of therapeutic diets using regular foods, which could be further modified to provide for individual requirements. The diet composition was based on the dietary deficits detected in the individualized and detailed intake questionnaire. Nutritional intervention aimed to achieve an adequate intake, with consideration taken for the digestive and absorptive capacity, symptoms' alleviation and/or arrest, and psychological factors. Therapeutic diets were often further adjusted to patients' usual diet, thereby recognizing personal eating patterns and preferences. The prescription had to specify the type, amount, eating frequency in number of meals, and calorie/protein amounts to achieve daily, all restrictions, limited or increased dietary components, and simultaneously considered the disease stage and progression. To achieve the highest adherence, one had to maintain as close as possible the usual dietary pattern, types of foods, amounts of foods and frequency of eating throughout the day, the disease course, the clinical condition, and the therapeutic goal of each patient.

Late radiotherapy toxicity and symptoms

Late radiotherapy toxicity was scored in grades (0–4) with a validated self-administered questionnaire according to the European Organization for Research and Treatment of Cancer (EORTC)/Radiation Therapy Oncology Group (RTOG) criteria. The questionnaire assessed specific symptoms of cancer/treatment, in which higher scores indicated higher symptom severity (17, 18). The questionnaire included 22 questions to assess grades of fatigue, anorexia, nausea/vomiting, genitourinary and gastrointestinal complaints, abdominal discomfort, and pain. Genitourinary and gastrointestinal symptoms were evaluated by using

physician's notes, including the need for and use of medication to modulate symptoms.

The pretreatment score was defined as the RTOG score obtained before radiotherapy. Symptoms occurring within 120 d from the start of radiotherapy were, in the original trial, considered to constitute acute toxicity according to RTOG criteria (18). Late toxicity was defined as symptoms occurring 3 mo after the end of radiotherapy and later, as analyzed in the current study. Patients with biochemical relapses or distant metastases were not censored from this analysis but were identified and accounted for in the survival analysis and disease recurrence. The physicians never knew the groups to which the patients belonged.

QoL was assessed with the same method used in the original trial: EORTC Quality of Life Questionnaire version 3.0 (EORTC-QLQ C30)–a 30-item cancer-specific questionnaire including 6 function scales (physical, emotional, cognitive, social, role, and global health/QoL), 3 symptom scales (fatigue, pain, and nausea/vomiting), and 6 single items (symptoms and financial impact of the disease) (19). Higher scores on the function scales indicated better functioning, whereas higher scores on symptom scales and single items denoted increased symptoms or worse financial impairment (19).

Statistical analysis

Statistical analysis was performed by using SPSS 16.0 (SPSS Inc) and EPI-Info 2000 (CDC). For all analyses, within-group and between-group comparisons were conducted with adequate adjustments for disease stage for every patient in the 3 groups. The randomization and stratification performed in the original trial ensured that the 3 groups were comparable. The primary endpoints of the original randomized trial were nutritional status, dietary intake, acute radiotherapy toxicity, and QoL. In the current study, survival (measured as time from randomization to cancer-specific mortality), disease recurrence, and late radiotherapy toxicity were additional endpoints.

Survival was estimated by using the Kaplan-Meier method and was tested with the log-rank test. This analysis was planned at a minimum follow-up of 3 y to have 80% power to detect a 20% absolute difference in all primary endpoints, with a P value <0.05 (2-tailed test). Data related to incidence, prevalence, or frequency (symptoms, disease stages, and nutritional-status categories) were expressed as number and/or percentage and analyzed by using the chi-square test. Age was expressed as the mean $\pm$ SD (range), energy and protein intakes were expressed as the median (range), and patients' QoL scores were expressed as median values. Continuous variables were analyzed by using 1-factor ANOVA or Wilcoxon rank-sum tests as appropriate. Categorical variables and incidence, prevalence, or frequency were evaluated by using the chi-square test. Univariate or between-variables assessments of associations and correlations of multiple variables (nutritional and clinical) were assessed with 2-tailed nonparametric Spearman tests. Outcome analysis and predictive value were analyzed by HRs, multivariate analysis of coded time-dependent variables, and landmark analysis. For all analyses, within-group comparisons and between-variable analyses were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, median survival, and number of patients in each group. Statistical significance was set at a P value <0.05.

RESULTS

Patients complied with the Radiotherapy Department's established follow-up protocol appointments: first after the end of radiotherapy, second after surgery and chemotherapy, once every 3 mo until 2 y, once every 6 mo until 5 y, and once a year thereafter. In this long-term follow-up, the median follow-up time was 6.5 y (range: 4.9–8.1 y), and there were 48 males and 41 females with a mean $\pm$ SD age of 64 $\pm$ 11 (range: 47–77) y.

Survival

Cancer-specific survival and recurrence data were always adjusted for disease stage and were determined by Kaplan-Meier analysis (**Figure 1**). The disease-specific median survival in group 3 (control − usual diet of regular foods) was 4.9 y, and 11 of the former 37 patients in this group (30%) died earlier. In group 2 (dietary supplements + usual diet of regular foods), disease-specific survival was 6.5 y, and 8 of the 37 patients (22%) died later than the median for group 3. In group 1 (individualized nutritional counseling with regular foods), disease-specific survival was 7.3 y, and 3 of the 37 patients (8%) died later than the medians for groups 3 and 2. These deaths occurred much later than those of patients in either group 2 or group 3: group 3 $<$ group 2 $<$ group 1 ($P < 0.05$). With respect to disease progression, 9 patients (30%) in group 3 had local recurrence, and 6 (20%) presented liver metastases. In group 2, 6 patients (16%) had positive lymph nodes and 3 (9%) had a single liver metastasis, whereas only 7 patients (19%) in group 1 had local disease recurrence: event frequency was group 3 $>$ group 2 $>$ group 1 ($P < 0.01$).

Nutritional status

Both PG-SGA and BMI showed that the percentage of patients with further nutritional deterioration in comparison with the previous evaluation at the 3-mo follow-up was significantly higher in groups 2 and 3 than in group 1 ($P < 0.001$). Current

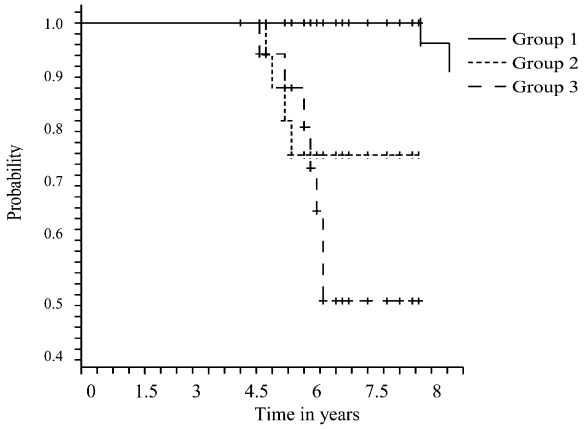

FIGURE 1. Disease-specific survival was calculated by Kaplan-Meier and log-rank tests, and the patients were divided by randomization group: group 1 ($n = 34$), individualized counseling; group 2 ($n = 29$), supplements + usual diet; group 3 ($n = 26$), usual diet. Survival time in group 3 $<$ group 2 $<$ group 1 ($P < 0.05$). For all analyses, within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group.

nutritional deterioration was significantly more severe and had a greater incidence in groups 3 and 2 than in group 1 ($P < 0.002$). Furthermore, the vast majority of patients in group 1 ($n = 31$; 91%) maintained an adequate nutritional status as measured by PG-SGA, and this was never the case in group 3 (**Table 1**).

Nutritional intake

For the 3 groups at the long-term follow-up evaluation, energy intake was compared with current individual basal energy requirements, and protein intake was compared with median reference values. In group 1, median energy (2482 kcal; 95% CI: 2210, 2685) and protein (74 g protein; 95% CI: 69, 77) intakes were similar to the reference values, and patients still adhered to the formerly prescribed individualized dietary recommendations for symptom modulation and diet adequacy. Thus, patients in group 1 maintained an intake similar to that at 3 mo after radiotherapy. Conversely, in both groups 2 and 3, the patients' median energy intakes were 1335 kcal (95% CI: 1150, 1569) and 1332 kcal (95% CI: 1098, 1426), respectively, and median protein intakes were 42 g (95% CI: 39, 44) and 40 g (95% CI: 38, 42.5), respectively; were lower than recommended; and were worse in patients with disease progression ($P < 0.05$). Median energy and protein intakes, comparing the evaluation performed 3 mo after the end of radiotherapy with the long-term follow-up, are depicted in **Figure 2**.

Overall, in comparison with the evaluation at 3 mo after radiotherapy, energy intake decreased by a median of 225 (195–398) kcal/d in group 2 and in group 3 ($P < 0.06$), and protein intake decreased by a median of 3 (2–7) g/d ($P < 0.06$). The dietary intake in group 1 did not change over time during this follow-up. For all groups, patients were questioned at the interviews, and all disclaimed the use of any type of nutritional supplements.

Late radiotherapy toxicity

Overall, the most common symptoms were permanent flatulence, abdominal distension, and/or diarrhea. These symptoms were more frequent and had a much earlier presentation in groups 3 and 2 than in group 1 (group 3 $\simeq$ group 2 $>$ group 1; $P < 0.001$) (**Figure 3**). Radiotherapy-induced toxicity with symptomatic manifestations was higher in group 3, in whom late symptoms were experienced and/or reported by 17 (65%) patients. In group 2, late symptoms were reported by 17 (59%) patients. In contrast, just 3 (9%) patients in group 1 had late symptoms: group 3 $\simeq$ group 2 $>$ group 1 ($P = 0.002$). Furthermore, the severity of symptoms progressed differently in the 3 groups and was always significantly worse in groups 3 and 2, whereas group 1 had the lowest grades of symptom severity ($P < 0.002$). The incidence of symptoms expressed as number of patients in each study group with permanent flatulence, abdominal distension, and/or diarrhea, classified according to severity, is shown in **Table 2**.

QoL

Median QoL scores for the 3 study groups, evaluated 3 mo after the end of radiotherapy and at long-term follow-up, are shown in **Table 3**. In group 3, QoL scores globally showed deterioration/maintenance in comparison with the results previously

TABLE 1
Changes in nutritional status during the long-term follow-up period categorized according to PG-SGA and BMI[1]

	Group 1 ($n = 34$)				Group 2 ($n = 29$)				Group 3 ($n = 26$)					
	Declined		Maintained/improved		Declined		Maintained/improved		Declined		Maintained/improved			
Methods	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	P^2	P^3
PG-SGA [*n* (%)]	10 (29)	3 (9)	24 (71)	31 (91)	24 (83)	27 (93)	5 (17)	2 (7)	25 (96)	26 (100)	1 (4)	0	<0.001	<0.005
BMI [*n* (%)]	2 (6)	0	32 (94)	34 (100)	6 (21)	23 (79)	23 (79)	6 (21)	17 (65)	25 (96)	9 (35)	1 (4)	<0.002	<0.001

[1] For all analyses, within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group. Group 1 received individualized counseling, group 2 received supplements and consumed their usual diet, and group 3 consumed their usual diet (standard of care). PG-SGA, Patient-Generated Subjective Global Assessment; RT, radiotherapy.

[2] Represents the significance of statistical differences between intervention groups in the nutritional decline between 3 mo after the end of RT and long-term follow-up at a median of 6.5 y (chi-square test).

[3] Represents the significance of statistical differences between intervention groups in the maintenance/improvement of nutritional status 3 mo after the end of RT and in long-term follow-up (chi-square test).

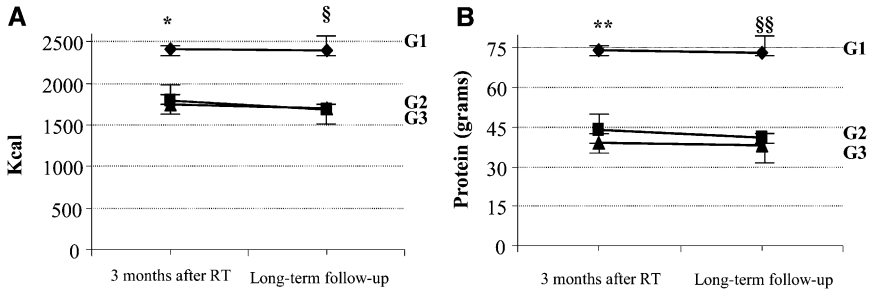

FIGURE 2. Changes in energy (A) and protein (B) intakes during the follow-up period in the 3 study groups: G1 (n = 34), individualized counseling; G2 (n = 29), supplements + usual diet; G3 (n = 26), usual diet. A: *Group 1 > group 2 ≈ group 3 (P = 0.002); [§]group 1 > group 2 ≃ group 3 (P = 0.001). B: **Group 1 > group 2 ≃ group 3 (P = 0.006); [§§]group 1 > group 2 ≃ group 3 (P = 0.001). Wilcoxon rank-sum tests were used for the statistical analysis. For all analyses, within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group. Data shown are medians with minimum and maximum values. G, group; RT, radiotherapy.

reported and were significantly worse than those of group 1. The same pattern was observed for group 2, whose QoL scores were worse than for group 1: group 3 ≃ group 2 < group 1 ($P < 0.002$). By a 2-tailed correlation analysis followed by ANOVA analysis, results on QoL were similar in groups 3 and 2: worse QoL scores in both groups were associated with deterioration of nutritional intake and status ($P < 0.01$). In contrast, QoL scores in group 1 were higher and similar to those reported at the 3-mo follow-up. Plus, greater QoL dimensions in group 1 were associated with the maintenance of an adequate nutritional intake and status ($P < 0.002$).

Nutritional variables and outcomes

Given the marked differences found in patient outcomes, a thorough analysis of the long-term results and their potential association with nutritional variables was required. To clarify the potential influence of the patients' dietary intakes and nutritional status on late radiotherapy toxicity, QoL, and median survival in the 3 study groups, a 2-tailed multiple correlation analysis was performed, followed by an ANOVA. Worse late radiotherapy toxicity, worse QoL dimensions, and higher cancer-specific mortality were associated with deteriorated nutritional status and inadequate nutritional intake ($P < 0.001$).

To summarize, it is important to highlight the length of dietary counseling: the long-term outcomes shown above were achieved with a mean of 6 individualized dietary counseling sessions offered over ~1.5 mo (radiotherapy treatment). Furthermore, it is worth mentioning that no further dietary sessions were offered to any of the patients in the 3 groups during the subsequent follow-up period.

Moreover, nutritional status, nutritional intake, and global QoL scores at the end of radiotherapy were used as predictors of outcomes: their ability to predict survival and late radiotherapy toxicity was analyzed by a multivariate analysis of coded time-dependent variables and landmark analysis. We found that patients with a poorer dietary intake, worse nutritional status, and poorer QoL scores at the end of radiotherapy had a significantly shorter median survival and an increased incidence of late radiotherapy-induced toxicity (HR: 8.25; 95% CI: 2.74, 11.47; $P < 0.001$). Thereby, poor nutritional intake and status and worse QoL scores had a significant predictive value.

DISCUSSION

This long-term follow-up of a prospective randomized controlled trial in colorectal cancer presents evidence that adjuvant nutritional therapy provided as early and timely individualized nutritional counseling and education had a sustained effect on outcomes, nutritional intake and status, late radiotherapy toxicity, QoL, and prognosis.

With awareness of the limitations associated with the fact that, in this trial, there was one researcher in charge of the intervention and of the assessment of outcome, which can result in detection and performance biases, one cannot ignore that patients spontaneously stated that individualized intervention made them feel better in a variety of QoL dimensions, had improved nutritional variables, and had fewer symptoms. Patients valued greatly the time the dietitian spent with them, explaining the dietary recommendations until patients fully understood the dietary prescription. After complying, patients experienced the benefit of the intervention and education given. They understood what to eat and not eat, which improved their symptoms and most of the QoL dimensions.

Nutritional deterioration may ensue from both cancer and its treatment (20, 21) and is a well-recognized independent risk

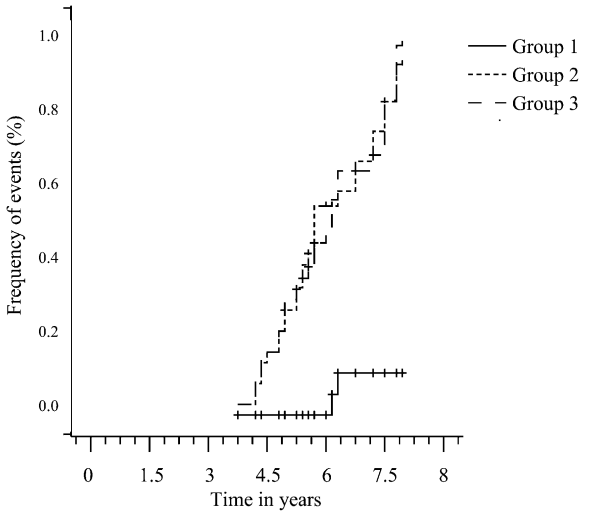

FIGURE 3. Incidence of late radiotherapy toxicity symptoms were calculated with Kaplan-Meier and log-rank tests and by Cox regression: group 1 (n = 34), individualized counseling; group 2 (n = 29), supplements + usual diet; group 3 (n = 26), usual diet. The incidence of late symptoms in the 3 groups was as follows: group 3 ≃ group 2 > group 1 (P = 0.002). For all analyses, within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group.

TABLE 2
Late radiotherapy-induced morbidity categorized according to grade of severity[1]

	Group 1 (n = 34)				Group 2 (n = 29)				Group 3 (n = 26)						
	Grade 1		Grade 2		Grade 1		Grade 2		Grade 1		Grade 2				
Symptoms	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	3 mo after end of RT	Long-term follow-up	P^2	P^3	P^4
Flatulence (n)	6	2	1	0	5	10	3	7	12	10	10	7	<0.02	<0.01	<0.001
Abdominal distension (n)	0	3	0	0	7	8	3	5	9	9	6	5	<0.001	0.17	<0.001
Diarrhea (n)	0	2	0	0	9	10	3	6	15	9	13	8	<0.001	<0.05	<0.001

[1] For all analyses, within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group. Grades 3 and 4 were never observed. Group 1 received individualized counseling, group 2 received supplements and consumed their usual diet, and group 3 consumed their usual diet (standard of care). Data from reference 18. RT, radiotherapy.

[2] Represents the significance of statistical differences between intervention groups in the reduction in incidence of grade 1 symptoms between 3 mo after the end of RT and the long-term follow-up evaluation (chi-square test).

[3] Represents the significance of statistical differences between intervention groups in the reduction in incidence of grade 2 symptoms between 3 mo after the end of RT and the long-term follow-up evaluation (chi-square test).

[4] Represents the significance of statistical differences between intervention groups in the reduction in incidence of grades 1 and 2 symptoms between 3 mo after the end of RT and the long-term follow-up evaluation (chi-square test).

TABLE 3
Median quality-life dimensions scores[1]

	Grade 1 (n = 34)		Grade 2 (n = 29)		Grade 3 (n = 26)	
Items	3 mo	Long-term	3 mo	Long-term	3 mo	Long-term
Function scales						
Global quality of life	82	80	62	50*	35	30
Physical function	79	78	60	42*	22	26
Role function	80	81	58	41*	19	20
Emotional function	83	82	50	35*	28	18
Social function	85	84	51	35*	26	25
Cognitive function	70	73	54	41*	46	40
Symptoms, scales						
Fatigue	26	5*	78	69*	79	75
Pain	15	2*	30	49*	73	70
Nausea and vomiting	10	0*	37	25	68	45
Symptoms, single items						
Dyspnea	8	0	13	5	15	6*
Sleep disturbance	29	2*	75	62	78	65
Appetite	48	2*	72	68	75	69
Constipation	10	0*	8	0*	8	0*
Diarrhea	39	2*	72	76	78	79
Financial impact	14	3*	11	2*	12	7

[1] Higher scores on function scales indicate better functioning, and higher scores on symptom scales/single items denote increased symptoms or worse financial impairment. *Significant differences between 3 mo after radiotherapy and long-term follow-up (1-factor ANOVA; multivariate analysis of coded time-dependent variables and landmark analysis; within-group and between-group comparisons were adjusted for cancer stage, age, follow-up time, disease recurrence, adjuvant treatments, survival, and number of patients in each group). Group 1 received individualized counseling, group 2 received supplements and consumed their usual diet, and group 3 consumed their usual diet (standard of care).

factor for higher mortality in cancer, as shown in the seminal paper from DeWys et al (22): it increases the risk of infections (23), decreases QoL (2, 24), and seemingly decreases life expectancy (22). The basis of the association between nutrition and prognosis shown in this study acknowledges a well-recognized reality by any clinician: poor nutritional status and intake throughout antineoplastic treatments negatively influence their course by determining higher toxicity, treatment interruptions, and consequently unfavorable response and efficacy. As a result, treatment outcomes may be poorer in depleted than in well-nourished patients, as clearly shown in this long-term follow-up of a clinical trial of nutritional therapy. Outcomes research (eg, hard evidence on the effectiveness of adjuvant nutrition) is essential to prove the value of any nutritional intervention (25–27). Research should be action-oriented so that interventions leading to positive outcomes can be determined and ineffective practices phased out or discarded (28). Even so, the role of individualized nutrition intervention on long-term outcomes has been minimally explored.

Nutritional variables

In the current study, we evaluated patients after a median follow-up of 6.5 y and compared results with the previous evaluation 3 mo

after radiotherapy: nutritional deterioration was observed in only 9% of patients in group 1 (individualized nutritional counseling), in 93% in group 2 (supplements + usual diet), and in all group 3 control patients (usual diet). Such findings coincide with the differences in nutritional intake between the 3 groups: in group 1, median energy and protein intakes were similar to the reference values, and patients still abided by the formerly prescribed dietary prescription for symptom modulation and diet adequacy during radiotherapy (2). Group 1 patients continued to eat better after the study period, with a consequent improvement in their nutritional status associated with better protein and energy intakes and with an adequate micronutrient intake. Conversely, energy and protein intakes were lower than recommended in patients who did not receive counseling, worsened after treatment, and presented greater nutritional deterioration. These patients had an unfavorable clinical course, with more aggressive disease progression. Thus, individualized nutritional counseling based on the patients' clinical condition and symptoms, provided only during radiotherapy, was also in the long term the most effective means of ensuring a sustained and adequate diet that was able to overcome the expected deterioration subsequent to antineoplastic treatments. This concurs with the pathway of optimal nutritional intake to treat disease-related malnutrition (29, 30). Note that nutritional counseling performed in this clinical trial was always individualized. Dietary counseling was based on a thorough assessment of nutritional and clinical variables: nutritional status and dietary intake was always evaluated with structured, specific, and validated questionnaires: a 24-h dietary recall, a 72-h dietary record (2 weekdays and 1 weekend day) of all meals and foods consumed, and a food-frequency questionnaire including information on food habits. A detailed symptom assessment was made, along with the evaluation of food preferences, habits, intolerances or aversions, and the registry of the diary meal distribution. Patients' psychological status, autonomy, cooperation, and need for support of others in the act of eating were fundamental dimensions that precede any diet prescription.

Late radiotherapy toxicity

Pelvic radiotherapy affects up to 300,000 patients/y worldwide. The subsequent change in bowel habits affects QoL in 5 of 10 patients (31), and complications may appear in 1 of 10 to 1 of 20 patients 10 y after radiotherapy (32). Information on adequate symptom modulation treatments is scant, and clinical research on late toxicity has not been a priority (33). Although a significant proportion of patients may improve with specialized nutritional intervention (34), patients are seldom referred to a specialized dietitian. In our study, permanent flatulence, abdominal distension, and/or diarrhea were always significantly worse in patients in groups 3 and 2, whereas patients in group 1 had the lowest symptom severity. The current study showed that the nutritional content of each patient's diet based on regular foods with appropriate education and manipulation was key in improving gastrointestinal function and acute symptoms during radiotherapy (2) and was sustained in the long term (range: 4.9–8.1 y) beyond the period of nutritional counseling. Dietary modifications may indeed alter bowel functions, such as motility, enzyme secretion, and nutrient absorption (35, 36). Nutrition modulates the gastrointestinal flora, the ecology of which is central to the pathogenesis of radiation injury and its severity. A well-balanced gut flora modulated by adequate foods may thus protect against injury and late radiotherapy toxicity (37, 38).

Survival and quality of life

Of major clinical importance were the results on survival: the highest mortality rate was recorded in the control group, which maintained the standard of care and consumed their usual diet, whereas the longest survival and lowest mortality rate was shown in patients who received nutritional counseling. The truly distinct disease courses may explain those results: 58% of group 3 patients and 31% of group 2 patients had disease progression with distant metastases, local recurrence, and/or lymph node invasion. This aggressive disease pattern did not occur in group 1, in which only local recurrence was observed in 19%. We found that the long-term disease course determined a cancer-specific mortality associated with worse nutritional status and inadequate intake, both present in groups 2 and 3. Longer survival is of utmost importance if accompanied by improved QoL. Indeed, QoL assessment should be the gold standard as an independent endpoint in clinical trials (39, 40). Cancer patients experience functional limitations, cognitive alterations, and emotional stress, and overall QoL depends on psychological, nutritional, and physical well-being (19, 41). Yet, the relation between poor nutrition and QoL remains widely underestimated (21, 42). Our group was one of the first to show that nutrition is a key determinant of QoL in cancer (24), and, in the original clinical trial, we showed that only individualized counseling improved all QoL function scores associated with adequate nutritional status/intake (2). In this long-term follow-up, the results were similar: in groups 3 and 2, deterioration/maintenance of QoL scores was associated with greater deteriorated nutritional intake and status than in group 1. The latter patients complied with the diet prescription and had an adequate nutritional status, and both variables determined a better QoL. With consideration taken that fewer radiotherapy symptoms may allow patients to better tolerate antineoplastic treatments, it is only logical to assume that this factor also contributed to improving patients' survival and QoL.

Undoubtedly, nutrition is an effective adjuvant therapy to any antineoplastic treatment. This study indicates the value of early, prolonged, maintained, and sophisticated individualized nutritional counseling. This approach is paramount for long-term prevention of nutritional and physiologic deficits, for modulation of weight loss and morbidity, and for maintenance of adequate nutritional status, performance status, and QoL. It has the potential to stabilize or improve the patients' clinical status and augment the potential for favorable responses to therapy, a faster recovery, improved prognosis, and longer survival. With the advent of more effective cancer therapies leading to greater numbers of long-term survivors, much more emphasis is urgently required to provide the best care during treatments to improve the clinical course of cancer patients.

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