Original Article

A Disease-Specific Enteral Nutrition Formula Improves Nutritional Status and Functional Performance in Patients With Head and Neck and Esophageal Cancer Undergoing Chemoradiotherapy: Results of a Randomized, Controlled, Multicenter Trial

Rainer Fietkau, MD[1]; Victor Lewitzki, MD[2]; Thomas Kuhnt, MD[2]; Tobias Hölscher, MD[3]; Clemens-F. Hess, MD, PhD[4]; Bernhard Berger, MD[5]; Thomas Wiegel, MD[6]; Claus Rödel, MD[7]; Marcus Niewald, MD[8]; Robert M. Hermann, MD[4,9]; and Dorota Lubgan, PhD[1]

BACKGROUND: In patients with head and neck and esophageal tumors, nutritional status may deteriorate during concurrent chemoradiotherapy (CRT). The aim of this study was to investigate the influence of enteral nutrition enriched with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on body composition and nutritional and functional status. **METHODS:** In a controlled, randomized, prospective, double-blind, multicenter study, 111 patients with head and neck and esophageal cancer undergoing concurrent CRT received either an enteral standard nutrition (control group) or disease-specific enteral nutrition Supportan®-containing EPA+DHA (experimental group) via percutaneous endoscopic gastrostomy. The primary endpoint was the change of body cell mass (BCM) following CRT at weeks 7 and 14 compared with the baseline value. Secondary endpoints were additional parameters of body composition, anthropometric parameters, and nutritional and functional status. **RESULTS:** The primary endpoint of the study, improvement in BCM, reached borderline statistical significance. Following CRT, patients with experimental nutrition lost only 0.82 ± 0.64 kg of BCM compared with 2.82 ± 0.77 kg in the control group ($P = .055$). The objectively measured nutritional parameters, such as body weight and fat-free mass, showed a tendency toward improvement, but the differences were not significant. The subjective parameters, in particular the Kondrup score ($P = .0165$) and the subjective global assessment score ($P = .0065$) after follow-up improved significantly in the experimental group, compared with the control group. Both enteral regimens were safe and well tolerated. **CONCLUSION:** Enteral nutrition with EPA and DHA may be advantageous in patients with head and neck or esophageal cancer by improving parameters of nutritional and functional status during CRT. ***Cancer* 2013;119:3343-53**. © *2013 American Cancer Society.*

KEYWORDS: head and neck cancer; esophageal cancer; nutritional status; eicosapentaenoic acid; docosahexaenoic acid; nutritional therapy; concurrent chemoradiotherapy; supportive care.

INTRODUCTION

Inoperable tumors of the head and neck region and the esophagus are treated with concurrent chemoradiotherapy (CRT).[1] Patients suffering from these tumor entities often show tumor-related weight loss and cachexia even before the onset of treatment.[2-7]

Moreover, concurrent CRT further worsens the nutritional situation of these patients[8]; a weight loss of 5-10 kg during CRT is a common finding.[9] By use of early enteral nutrition via percutaneous endoscopic gastrostomy (PEG), the weight loss can be reduced at least for some of the patients, preventing them from transition to cachexia.[2,10-15] Nevertheless, the general condition of these patients often deteriorates during concurrent CRT, with a corresponding reduction in nutritional and functional status and quality of life.[2]

Corresponding author: Dorota Lubgan, Department of Radiation Oncology, Erlangen University Hospital, Universitätsstraße 27, D-91054 Erlangen, Germany. Fax: (011) 49-9131-853-3996; E-mail: dorota.lubgan@uk-erlangen.de.

[1]Department of Radiation Oncology, Erlangen University Hospital, Erlangen, Germany; [2]Department of Radiotherapy, University Hospital, Rostock, Germany; [3]Department of Radiotherapy and Radiooncology, University Hospital Carl Gustav Carus, Dresden, Germany; [4]Department of Radiotherapy and Radiooncology, Medical Department, Georg-August University, Göttingen, Germany; [5]Department of Radiooncology, University Hospital, Tübingen, Germany; [6]Department of Radiotherapy and Radiooncology, University Hospital, Ulm, Germany; [7]Department of Radiotherapy and Oncology, University Hospital, Goethe University, Frankfurt/Main, Germany; [8]Department of Radiotherapy and Radiooncology, Saarland University Medical Center, Homburg/Saar, Germany; [9]Centre for Radiotherapy and Radiooncology, Westerstede, Germany

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In tumor patients, it has been shown that the use of special formulae and n-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can have a positive influence on a number of potential mediators of the tumor cachexia and thus possibly reverse or stop the development of cachexia.[16] This has a positive influence on the nutritional status of the patients.

Van der Meij and colleagues[17,18] examined the influence of additional EPA nutritional therapy during chemotherapy or CRT for non-small cell lung carcinoma patients with respect to nutritional parameters and quality of life. We performed a controlled, randomized, prospective, double-blind, multicenter study in which a disease-specific enteral nutrition rich in n-3 fatty acids (EPA+DHA) was compared with an enteral standard nutritional therapy administered via PEG in head and neck and esophageal cancer patients undergoing concurrent CRT.

MATERIAL AND METHODS

Study Design

This prospective, randomized, double-blind, controlled multicenter study was approved by the central ethics committee of the University of Rostock (II PV 05/2005) and the institutional review boards of all participating centers. Patients were recruited between September 2006 and October 2009 (last patient out January 2010) from 10 radio-oncological centers in Germany (Erlangen, Rostock, Halle, Dresden, Göttingen, Tübingen, Ulm, Frankfurt/Main, Homburg/Saar, Bremen). The study was conducted in accordance with the current version of the Declaration of Helsinki[19] and according to Good Clinical Practice.[20] Each patient provided written informed consent before participating in the study.

Eligible patients were aged 18 years or older with histologically confirmed inoperable head and neck or esophageal cancer, intended for a concurrent CRT. Further inclusion criteria were body mass index of 16-30 kg/m^2, a Kondrup-score ≥ 3 or subjective global assessment (SGA) B or C, a life expectancy >6 months, start of nutritional therapy via PEG latest at beginning of the CRT.

Exclusion criteria included metastatic disease, second active carcinoma, pregnancy, lactation, significant cardiac disease with cardiac pacemaker. Further exclusion criteria were: severe diarrhea unresponsive to codeine/loperamide, insulin-dependent diabetes mellitus type I and II, allergy to contents of the investigational products, milk protein and fish oil, intake of muscle growth supporting substances (eg, anabolics) and additional fish oil or EPA substitution within the last 4 weeks.

The experimental group received 500 mL of the disease-specific enteral formula Supportan, which is especially designed for tumor patients; contains high amounts of fat (40% of energy [EN%]), protein (27 EN%), and n-3 fatty acids from fish oil (2.0 g EPA and 0.85 g DHA); and is low in carbohydrates (33 EN%).

The control group received 500 mL of the enteral standard nutrition Fresubin energy fibre (protein, 15 EN%; carbohydrates, 50 EN%). Both formulae were provided by Fresenius Kabi Deutschland GmbH and were applied continuously via PEG over a maximum of 14 weeks. Both groups received an additional minimum of 500 mL of standard enteral nutrition (Fresubin) to meet their energy needs of 30-33 kcal/kg. The patients were also allowed to eat and drink during the period of PEG nutrition as required. Neither the attending physician nor the patients knew which diet was applied.

The standard oncologic therapy regimen included concurrent CRT with cisplatin/carboplatin or mitomycin C (with or without 5-FU) and radiation therapy according to the center's current practice. In brief, radiotherapy consisted of a median total dose of 66 Gy in single fractions of 1.8-2.0 Gy daily (Table 1).

OUTCOME MEASUREMENTS

Body cell mass (BCM) was measured by means of bioelectrical impedance spectroscopy[21-23] using BodyScout software (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany).

Fat-free mass, lipid mass, total body water, extracellular water, intracellular water, and lean tissue mass were obtained using the BodyScout software option for water volume analysis. Anthropometric parameters including body weight, body mass index, skin fold thickness, and mid-arm circumference were measured as described previously.[24,25] Nutritional status was assessed using the Kondrup score and the subjective global assessment (SGA) as described previously.[26,27] The Karnofsky index was evaluated by the physician according to the Karnofsky rating scale . The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire was used to assess health-related quality of life[28,29] and was completed by patients themselves. Hand grip strength was obtained by using a hand grip dynamometer according to Jamar.[30] The patient sits square in a chair with feet flat on the floor, the elbows bent at the side and not resting against the body. Three measurements were to be made with the dominant hand in a 30-

TABLE 1. Patient Characteristics

Characteristics	Experimental Group (n = 55)	Control Group (n = 56)	P^a
General data/medical history			
Age, y			
Mean ± SD	55.5 ± 8.9	56.5 ± 10.0	.583
Median (range)	54.0 (32-76)	55.5 (32-85)	
Sex, no. (%)			
Men	45 (81.8)	48 (85.7)	.578
Women	10 (18.2)	8 (14.3)	
Primary cancer diagnosis, no. (%)			
Esophageal carcinoma	4 (7.3)	5 (8.9)	.749
Head and neck cancer	51 (92.7)	51 (91.1)	
Alcohol, no. (%)			
No	21 (38.2)	32 (57.1)	.0455
Yes	34 (61.8)	24 (42.9)	
Anticancer therapy			
Chemotherapy, no. (%)			
Cisplatin/Carboplatin+5-FU or mitomycin+5-FU	30 (54.5)	29 (51.8)	.343
Cisplatin/Carboplatin monotherapy	24 (43.6)	23 (41.1)	
Other therapies	1 (1.8)	4 (7.1)	
Duration of chemotherapy, d, median (range)	33 (1-101)	33 (1-89)	.503
Radiation dose, Gy, median	66.0	66.0	.5665
Study nutrition			
Number of treatment days, d, median (range)	80 (4-149)	77 (2-123)	.361
Total amount of study nutrition, mL, median (range)	35,250 (1000-57,500)	34,500 (500-55,000)	.325
Compliance, %			
Mean ± SD	82.7 ± 17.9	76.9 ± 28.7	.8785
Median (range)	90.5 (37.5-100.0)	87.6 (8.3-100.0)	
Body composition			
BCM, kg			
Mean ± SD	22.32 ± 5.21	24.13 ± 6.03	.118
Median (range)	22.10 (12.7-37.6)	23.65 (12.0-36.3)	
FFM, kg			
Mean ± SD	48.47 ± 7.98	51.30 ± 8.75	.100
Median (range)	49.55 (31.1-68.6)	50.70 (30.1-65.3)	
LM, kg			
Mean ± SD	17.00 ± 8.79	16.67 ± 7.88	.848
Median (range)	14.45 (5.5-51.1)	17.15 (4.4-34.7)	
TBW, L			
Mean ± SD	35.29 ± 5.80	37.35 ± 6.28	.097
Median (range)	35.50 (21.9-49.2)	36.70 (22.0-46.6)	
ECW, L			
Mean ± SD	16.26 ± 2.88	17.37 ± 3.17	.075
Median (range)	16.20 (8.3-22.6)	17.20 (10.2-25.1)	
ICW, L			
Mean ± SD	19.04 ± 3.23	19.99 ± 3.60	.178
Median (range)	19.45 (13.1-27.8)	19.65 (11.8-26.9)	
LTM, kg			
Mean ± SD	40.62 ± 7.79	43.30 ± 8.82	.117
Median (range)	40.15 (27.2-62.9)	42.55 (24.6-60.9)	
Anthropometry			
BW, kg			
Mean ± SD	64.45 ± 13.20	66.99 ± 13.10	.310
Median (range)	62.20 (38.2-107.4)	66.35 (40.0-94.5)	
BMI, kg/m^2			
Mean ± SD	22.0 ± 3.6	22.4 ± 3.3	.573
Median (range)	21.1 (15.7-36.3)	22.3 (16.6-28.7)	
Skin fold thickness, mm			
Mean ± SD	10.05 ± 4.18	10.5 ± 7.40	.817
Median (range)	9.0 (3.0-18.0)	8.0 (3.0-32.0)	
Midarm circumference, cm			
Mean ± SD	25.96 ± 3.46	26.41 ± 3.46	.645
Median (range)	25.0 (18.0-33.0)	26.0 (19.0-33.0)	
Nutritional status			
Kondrup score[b]			
Mean ± SD	3.76 ± 0.86	3.71 ± 0.82	.778
Median (range)	4.00 (2-5)	4.00 (2-5)	

TABLE 1. *Continued*

Characteristics	Experimental Group (n = 55)	Control Group (n = 56)	P[a]
Kondrup score impaired nutritional status			
Mean ± SD	1.69 ± 0.81	1.63 ± 0.86	.634
Median (range)	2.00 (0-3)	1.00 (0-3)	
Overall SGA rating, no. (%)			
A (well-nourished)	1 (1.8)	1 (1.8)	.786
B (mildly/moderately malnourished)	48 (87.3)	51 (91.1)	
C (severely malnourished)	6 (10.9)	4 (7.1)	
Functional status			
Hand-grip strength,[c] kg			
Mean ± SD	35.53 ± 10.22	37.75 ± 12.66	.318
Median (range)	35.00 (18.0-60.0)	36.00 (14.0-84.0)	
Quality of life			
Karnofsky index, %			
Mean ± SD	83.3 ± 10.1	84.2 ± 10.4	.688
Median (range)	85.0 (60-100)	82.5 (60-100)	
EORTC QLQ30 global health status/QoL			
Mean ± SD	56.05 ± 18.03	56.78 ± 21.92	.908
Median (range)	58.33 (0.0-83.33)	50.0 (8.33-100.0)	
EORTC QLQ30 appetite loss			
Mean ± SD	17.31 ± 25.13	21.71 ± 33.24	.825
Median (range)	0.0 (0.0-100)	0.0 (0.0-100)	
Laboratory values			
Hemoglobin, mmol/L			
Mean ± SD	7.91 ± 0.94	8.07 ± 0.73	.579
Median (range)	8.05 (6.0-9.60)	8.10 (6.50-9.90)	
Serum triglycerides, mg/dL			
Mean ± SD	129.4 ± 60.1	100.3 ± 46.6	.015
Median (range)	121.0 (46-319)	91.0 (27-275)	
IL-6, pg/mL			
Mean ± SD	10.34 ± 12.97	9.12 ± 8.67	.584
Median (range)	4.80 (2.0-64.0)	5.90 (2.0-44.8)	
TNF-α, pg/mL			
Mean ± SD	33.56 ± 147.41	19.28 ± 50.85	.661
Median (range)	11.20 (4.8-1000.0)	11.70 (4.2-344.0)	

Abbreviations: BCM, body cell mass; BMI, body mass index; BW, body weight; ECW, extracellular water; FFM, fat free mass; ICW, intracellular water; IL-6, interleukin 6; LM, lipid mass; LTM, lean tissue mass; QoL, quality of life; SD, standard deviation; SGA, subjective global assessment; TBW, total body water; TNF-α, tumor necrosis factor α.

[a] Mean ± SD: *t* test. Median: *U* test. Categorial data: chi-square test.

[b] Sum of 3 assessed risk categories: 1) impaired nutritional status, 2) severity of disease, and 3) age-related score (≥3 = severe risk of malnutrition).

[c] Jamar dynamometer.

second rest interval between each trial. The dominant hand was defined as "the hand the respondent would use to cut with pair of scissors or cut bread with a bread knife." Patients were instructed to "squeeze as hard as possible for 3 to 5 seconds." The peak value was considered for data analysis. The time points for each measurement are provided in Figure 1.

Randomization and Statistical Analysis

A stratified block randomization (1:1) with a block size of 4 was used. According to a randomization list provided by an independent statistician, enteral nutrition products were labeled (at the manufacturers). The patients were stratified by study center and by site of cancer (head and neck or esophagus) and were placed into the control group or the experimental group.

The study was planned primarily as a phase 3 study with a 2-stage adaptive design according to Bauer and Köhne.[31] In the first step, 2 × 40 patients were randomized. Depending on the results of the first part of the study, a second confirmatory analysis was planned with recalculation of the required sample size.

The primary efficacy endpoint of the study was the change of BCM over time. These changes were evaluated by means of analysis of covariance (ANCOVA) using the baseline as a covariate and "center" and "additional nutrition" as cofactors and are presented as adjusted changes from baseline.

For the first 80 patients, $P < .0102$ indicated that the study should be stopped, because it would show a superiority of the disease-specific EPA nutrition. A stop was also planned at $P \geq .5$, because it would be assumed that the nutritional therapy with EPA did not differ from the standard nutrition. At $P = .0102 - .5$, the study was to be continued with an adaptive design.

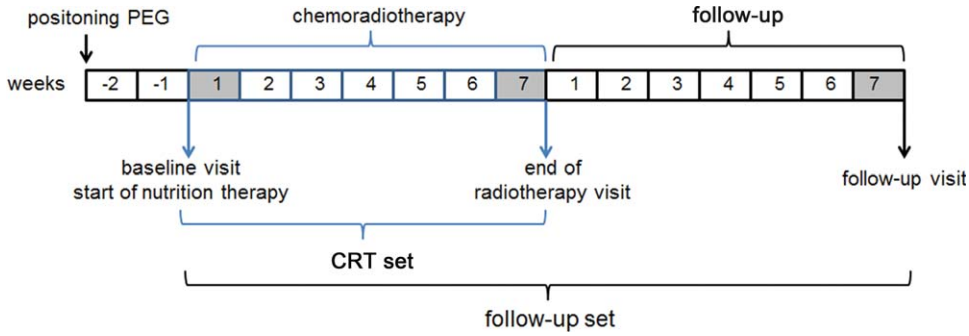

Figure 1. Examination schedule including PEG-percutaneous endoscopic gastrostomy, baseline visit/baseline assessment (start of chemoradiotherapy and nutrition therapy), end of radiotherapy visit/end of radiotherapy (planed cumulative radiation dose is reached), and follow-up visit/closing examination (approximately 6-7 weeks after chemoradiotherapy).

For the analysis of changes from baseline in the secondary endpoints, ANCOVA using baseline as a cofactor was employed. Comparison of categorical variables such as nutritional status (SGA) and quality of life (Karnofsky index) was performed using a chi-square test. Comparison of adverse event indices was performed by means of Fisher exact test and/or chi-square test. For the evaluation of changes in laboratory parameters and the comparison of gastrointestinal symptoms, the Mann-Whitney *U* test and Wilcoxon test were applied.

Continuous variables were evaluated using descriptive statistics, and unless indicated otherwise, results are presented as the mean and/or median ± SD. Standard summary statistics and 2-tailed 95% confidence intervals were calculated as appropriate. All statistical analyses were performed using the statistical software package SAS version 9.1.3 or 9.2.0. The level of significance for all analyses besides that of BCM was set at $\alpha = 0.05$ (2-tailed). Missing data not induced by missing control visits or missing values in a series of measurements were excluded from statistical analysis.

RESULTS

Patient Characteristics

A total of 111 patients (18 women, 93 men) were enrolled in the study. All patients were included in the safety and intention-to-treat analysis (ITT). The CONSORT diagram (Fig. 2) shows numbers of participants who were randomly assigned to treatment and who received intended treatment. A total of 84 patients were included in the efficacy analysis, and the study was completed by 69 patients (experimental group, n = 38; control group, n = 31).

With regard to patients lost to follow-up, resulting in incomplete data records, the study was analyzed in line with the guidance on data analysis by the ICH E9 (Statistical Principles for Clinical Trials) [32] by defining 2 efficacy subsets related to the availability of data, holding on to the intention-to-treat principle as close as possible. The group of patients who were randomized and had a control examination during CRT was defined as the CRT set (n = 84). Those patients who also had an examination in the convalescence period after CRT were defined as the follow-up set (n = 69). Homogeneity analyses for baseline characteristics were performed for all patient data sets (Table 1).

Baseline characteristics (age, sex, body mass index, cancer diagnosis) were well-balanced between groups. However, significantly more patients in the experimental group than in the control group consumed alcohol before the beginning of the study ($P = .045$). The duration and kind of anticancer treatment (CRT) were balanced in both arms, as was the compliance to nutritional therapy during the course of the study (Table 1).

In order to permit adequate analysis, the patients were therefore examined as shown in Table 2.

Efficacy Results

Primary endpoint

The primary endpoint BCM (adjusted changes from baseline of body cell mass) did show a trend toward a smaller decrease in the experimental arm, but the differences in results were not statistically significant:

After adjusting for center, the baseline values for BCM in the experimental arm were 22.32 ± 5.21 kg and 24.13 ± 6.03 kg in the control arm (Table 1). At the end of CRT (CRT set), the BCM in the experimental arm decreased by −0.92 ± 0.65 kg (35 patients) in comparison with the control arm at −2.22 ± 0.69 kg (29 patients, $P = .1835$). At 6-7 weeks after the completion of CRT (follow-up set), the loss of BCM in the experimental arm was −0.82 ± 0.64 kg (31 patients) compared with −2.82 ± 0.77 kg in the control arm (22 patients) and were not

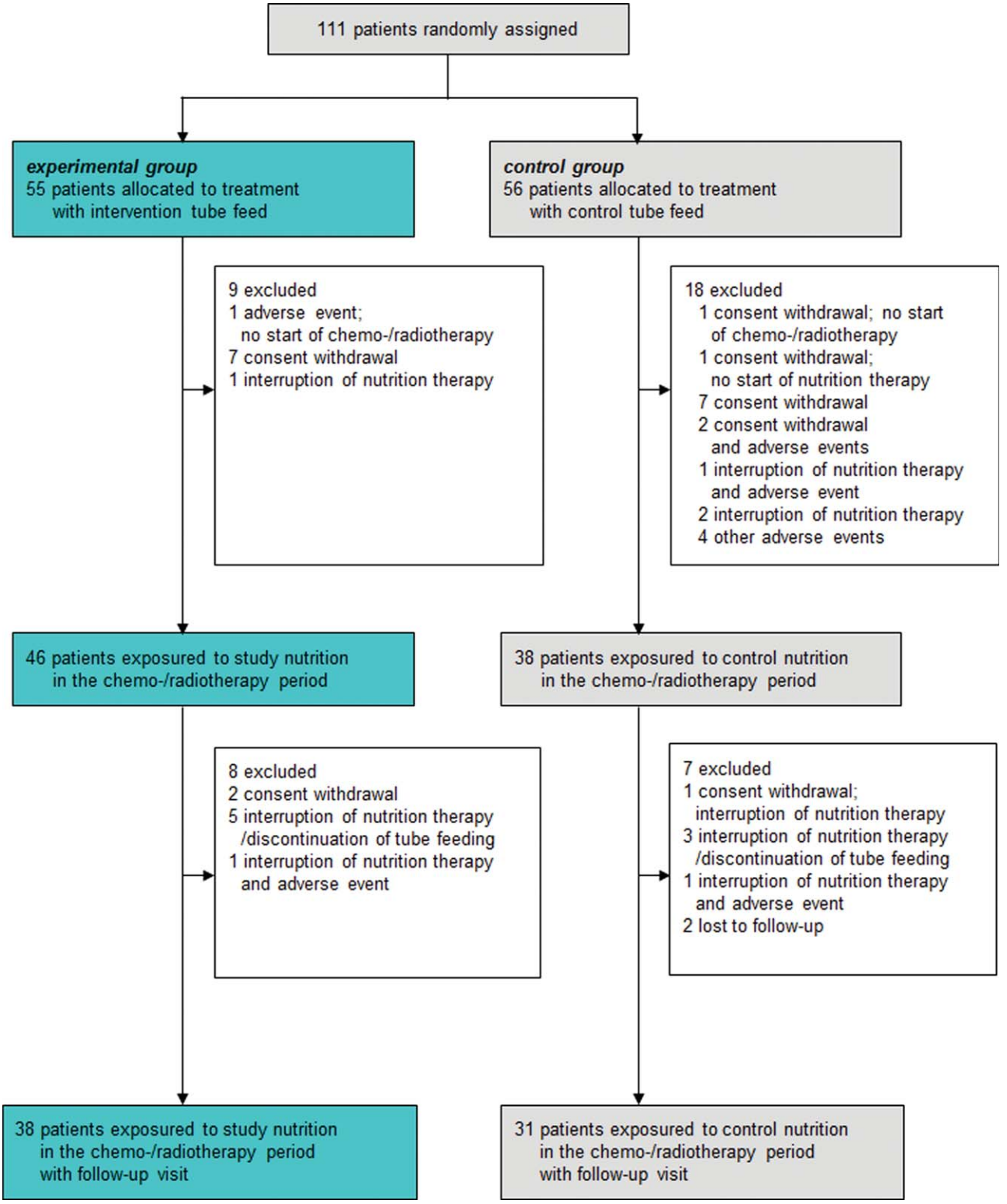

Figure 2. CONSORT diagram.

significant ($P = .055$) (Table 3, Fig. 3). For the head and neck cancer subgroup, the BCM was significant in favor of Supportan ($P = .041$, data not shown).

Based on these results, the study was to continue, and, in the second step, with an assumed P value of .0309 (1-tailed t test; calculation according to Bauer and

TABLE 2. Flow Chart

Examination	Baseline Visit	End of Radiotherapy Visit	Follow-up Visit
General data/medical history	•		
Risk factors	•		
Basis documentation	•	•	•
Rehospitalization, length of hospital stay		•	•
Subjective global assessment	•		•
Kondrup score	•		•
Anthropometry	•	•	•
Bioelectric impedance spectroscopy	•	•	•
Special laboratory parameters	•	•	•
Fatty acids	•	•	•
Hematology	•	•	•
Clinical chemistry	•	•	•
Hand-grip strength[a]	•	•	•
Karnofsky index	•	•	•
EORTC QLQ-C30	•	•	•
Gastrointestinal tolerance	•	•	•

Abbreviation: EORTC, European Organization for Research and Treatment of Cancer.
[a] Jamar dynamometer.

Köhne[31]) at a power of 0.8 and an expected difference of 0.328 kg. At least 138 patients per group would be needed for the confirmatory stage 2 of the adaptive design. Since the recruiting of the first 80 patients already took 4 years, the feasibility of recruiting 276 additional patients in a realistic time frame was questioned and the sponsor decided not to continue part 2 of the study.

Secondary endpoints

Body composition.For the remaining parameters of body composition (Table 3), there was a similar general tendency for improvement of values in the experimental group compared with the control group. The effect being most pronounced for fat-free mass, total body water, and extracellular water. All nutrition-related effects in favor of the experimental group were more pronounced after convalescence (follow-up set) than directly after CRT (CRT set), yet they remained statistically nonsignificant.

Anthropometric parameters.Similar results were obtained for the anthropometric parameters such as body weight, body mass index, skin fold thickness, and midarm circumference. In general there was a nonsignificant tendency for improvement achieved by the experimental group compared with the control group (Table 3).

Nutritional status.In contrast to the anthropometric and body composition parameters the nutritional status showed significant changes in favor of the experimental group (Table 3). The mean baseline Kondrup score impaired nutritional status was 1.69 ± 0.81 for the experimental- and 1.63 ± 0.86 for the control group. While the mean Kondrup score remained almost unchanged in the control group, there was a significant improvement in the experimental group after follow-up ($P = .0165$).

Compared with baseline, SGA data of the experimental group at the follow-up time point showed an improvement in 10/35 (28.6%) patients and no change in 25/35 (71.4%) patients. The corresponding values for the control group were improvement in 1/30 (3.3%) patients, no change in 26/30 (86.7%) patients, and a deterioration of SGA in 3/30 patients (10%). These results were statistically significant different using a chi-square test ($P = .0065$).

Overall, these results indicate an improvement of the nutritional status in the experimental group compared with the control group.

Functional Status and Quality of Life

After CRT and after follow-up, a slight decrease in hand-grip strength was observed in both trial groups. After convalescence the decrease was more pronounced in the control group compared with the experimental group (−2.72 ± 0.99 kg vs. −1.57 ± 0.96 kg) but statistically nonsignificant (Table 3).

For the Karnofsky performance index, a significant difference between treatment groups was observed after the CRT period (Table 3). The experimental group showed a greater improvement than the control group ($P = .040$, chi-square test). Yet after convalescence (follow-up set), the differences between groups did not remain significant ($P = .662$, chi-square test).

Overall, the parameters of the EORTC QLQ-C30 showed no significant differences between the experimental group and the control group, except for a higher loss of appetite with an experimental tube feed than with a control tube feed ($P = .030$, ANCOVA) (Table 3).

TABLE 3. Baseline Changes After Radiochemotherapy (RCT Set) and 6-7 Weeks After the End of RCT (Follow-up Set)

	End of Radiotherapy			Follow-up		
	Experimental Group	Control Group	P^a	Experimental Group	Control Group	P^a
Body composition						
BCM adjusted for center, kg	−0.92 ± 0.65 (n = 35)	−2.22 ± 0.69 (n = 29)	.1835	−0.82 ± 0.64 (n = 31)	−2.82 ± 0.77 (n = 22)	.055
FFM, kg	−1.32 ± 0.59 (n = 35)	−2.05 ± 0.65 (n = 29)	.417	−0.98 ± 0.66 (n = 31)	−2.67 ± 0.79 (n = 22)	.109
LM, kg	−0.30 ± 0.58 (n = 35)	0.02 ± 0.63 (n = 29)	.7115	−0.32 ± 0.71 (n = 31)	−0.67 ± 0.84 (n = 19)	.757
TBW, L	−0.94 ± 0.41 (n = 35)	−1.44 ± 0.45 (n = 29)	.415	−0.60 ± 0.45 (n = 31)	−1.84 ± 0.53 (n = 22)	.0825
ECW, L	−0.39 ± 0.20 (n = 35)	−0.54 ± 0.22 (n = 29)	.605	−0.06 ± 0.21 (n = 31)	−0.60 ± 0.25 (n = 22)	.1055
ICW, L	−0.56 ± 0.27 (n = 35)	−0.90 ± 0.30 (n = 29)	.407	−0.62 ± 0.34 (n = 31)	−1.22 ± 0.41 (n = 22)	.262
LTM, kg	−1.22 ± 0.75 (n = 35)	−2.15 ± 0.83 (n = 29)	.412	−1.13 ± 0.86 (n = 31)	−2.66 ± 1.02 (n = 22)	.2545
Anthropometry						
BW, kg	−1.64 ± 0.45 (n = 46)	−1.82 ± 0.51 (n = 36)	.787	−1.00 ± 0.67 (n = 38)	−2.73 ± 0.75 (n = 31)	.092
BMI, kg/m^2	−0.53 ± 0.19 (n = 35)	−0.47 ± 0.21 (n = 29)	.839	−0.43 ± 0.27 (n = 31)	−0.86 ± 0.32 (n = 22)	.304
Skin fold thickness, mm	−1.87 ± 1.08 (n = 18)	−0.45 ± 1.23 (n = 14)	.397	−1.45 ± 0.95 (n = 15)	−3.10 ± 1.06 (n = 12)	.258
Midarm circumference, cm	−1.01 ± 0.51 (n = 23)	−0.77 ± 0.61 (n = 16)	.770	0.39 ± 0.67 (n = 17)	−0.83 ± 0.73 (n = 19)	.232
Nutritional status						
Kondrup score[b]	ND	ND	ND	−0.71 ± 0.19 (n = 36)	−0.21 ± 0.20 (n = 30)	.075
Kondrup score Impaired nutrition status	ND	ND	ND	−0.52 ± 0.15 (n = 36)	0.02 ± 0.16 (n = 30)	.0165
Overall SGA rating, no. (%)	ND	ND	ND			
Improvement				10 (28.6)	1 (3.3)	.0065
No change				25 (71.4)	26 (86.7)	
Deterioration				0 (0)	3 (10.0)	
Functional status						
Hand-grip strength,[c] kg	−0.64 ± 0.75 (n = 33)	−0.47 ± 0.81 (n = 36)	.889	−1.57 ± 0.96 (n = 33)	−2.72 ± 0.99 (n = 31)	.411
Quality of life						
Karnofsky index, no. (%)						
Improvement	12 (26.7)	2 (6.1)	.039	7 (20.6)	5 (16.7)	.662
No change	13 (28.9)	16 (48.5)		16 (47.1)	12 (40.0)	
Deterioration	20 (44.4)	15 (45.5)		11 (32.4)	13 (43.3)	
EORTC QLQ30 global health status/QoL	−11.70 ± 2.95 (n = 37)	−15.99 ± 3.66 (n = 24)	.366	−0.33 ± 3.56 (n = 31)	−0.97 ± 4.05 (n = 24)	.906
EORTC QLQ30 Appetite loss	28.66 ± 5.62 (n = 37)	33.60 ± 6.97 (n = 24)	.583	25.11 ± 5.63 (n = 30)	6.11 ± 6.30 (n = 24)	.030
Laboratory						
IL-6, pg/mL	5.25 ± 3.57 (n = 34)	17.15 ± 4.01 (n = 27)	.031	−2.71 ± 1.93 (n = 23)	−4.14 ± 1.86 (n = 25)	.598
TNF-α, pg/mL	−23.93 ± 5.76 (n = 34)	−11.40 ± 6.47 (n = 27)	.154	−30.42 ± 3.92 (n = 23)	−22.52 ± 3.76 (n = 25)	.154

Data are shown as the mean ± SE unless indicated otherwise.

Abbreviations: BCM, body cell mass; BMI, body mass index; BW, body weight; ECW, extracellular water; EORTC, European Organization for Research and Treatment of Cancer; FFM, fat free mass; ICW, intracellular water; IL-6, interleukin 6; LM, lipid mass; LTM, lean tissue mass; ND, not done; QoL, quality of life; SD, standard deviation; SGA, subjective global assessment; TBW, total body water; TNF-α, tumor necrosis factor α.

[a] Categorial data: analysis of covariance, chi-square test.

[b] Sum of 3 assessed risk categories: 1) impaired nutritional status, 2) severity of disease, and 3) age-related score (≥3 = severe risk of malnutrition).

[c] Jamar dynamometer.

Laboratory Values

Laboratory values did not change significantly during the study, with the exception of interleukin-6 after CRT. The significantly attenuated increase in interleukin-6 after CRT in the experimental group compared with the control group (5.25 ± 3.57 vs. 17.15 ± 4.01 pg/mL; $P = .031$, ANCOVA) (Table 3) suggests an anti-inflammatory effect of Supportan.

Adverse Events

No deaths and no other nutrition-related serious adverse events (AEs) occurred. AEs were reported in 52/55 patients in the experimental group and 51/56 in the control group. The most frequently observed AEs were gastrointestinal disorders in 41/42 patients, followed by general disorders and administration site conditions in 41/35 patients.

Overall, the incidence of AEs suspected to be related to the supplemental nutritional therapy was lower in the experimental group (6/55 [10.9%]) compared with the control group (14/56 [25.0%]), just failing to reach significance ($P = .0535$, chi-square test).

The incidence of AEs suspected to be related to anticancer treatment (CRT) was not significantly different ($P = .093$) between the experimental group (51/55) and the control group (46/56).

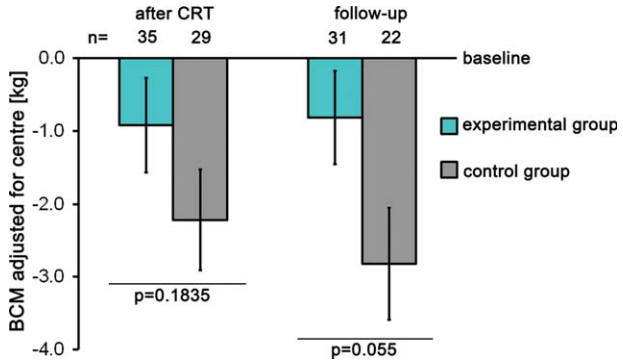

Figure 3. Changes of body cell mass from baseline adjusted for center (mean ± standard error) after chemoradiotherapy and during the follow-up period. Error bars indicate the standard error.

DISCUSSION

This randomized controlled study examined the effect of a disease-specific enteral diet high in fat, protein, and EPA+DHA on nutritional status and quality of life in patients with head and neck and esophageal tumors during multimodal therapy. Therefore, this study has a fundamentally different design to comparable studies with eicosapentaenoic acid.[33-36] These studies evaluated the influence of n-3 fatty acids or EPA on the cachexia of tumor patients, but had several important shortcomings, including different palliative chemotherapy regimens or no tumor specific therapy at all, small sample sizes, lack of randomization, or no nutrition support in the control arm.[33-36]

Mazotta and Jeney[35] and Ries et al[36] concluded that there is no conclusive data from randomized studies that favors the use of n-3 fatty acids for tumor patients. In contrast, Colomer et al[33] reported that the use of n-3 fatty acids for tumors of the pancreas and the upper gastrointestinal tract led to an improvement in weight status, appetite, and quality of life when EPA was applied at a dosage of 1.5 g/day for 8 weeks. The study groups of Murphy et al. and van der Meij et al. examined the influence of additional EPA nutritional therapy during chemotherapy or CRT for non-small cell lung carcinoma patients with respect to nutritional parameters and quality of life.[18,37,38] Both groups found that the additional EPA nutritional therapy led to patients gaining more weight, improved quality of life, and, in part, it even improved the response of the patients to the oncologic treatment.

The study presented here differs from these studies. First, at baseline of our study, no advanced signs of cachexia as in the above-mentioned studies were observed; nevertheless, the nutritional status of patients according to the Kondrup score and the SGA score was reduced compared with the general population . Moreover, patients in the above-mentioned studies received the usual standard-of-care support in the control arm, which did not necessarily include primary enteral nutritional therapy. As in patients with tumors in the head and neck region, it is well known that nutritional therapy intervention can improve nutritional status, quality of life, and possibly the therapeutic results as well, both during radiation therapy alone or CRT,[39] we considered it necessary to initiate nutritional therapy even in the standard arm by means of enteral nutrition. Thus, in the current study, both arms included supplemental enteral nutritional therapy via PEG, which was supported in the experimental arm through the additional administration of EPA+DHA. The current study thus permits quantification of the effects of adding fish oil to supplemental nutritional therapy.

The difference over time in the primary endpoint of our study, improvement in BCM, did not reach statistical significance. Both in follow-up and after completion of CRT, the loss of BCM was reduced through the cancer-specific nutrition including EPA+DHA, but the *P* values of .055 and .1835 did not confirm a significant difference. Nevertheless, patients have experienced significant subjective benefits (Kondrup score, SGA score) from the improvement in objective parameters of body composition. It also needs to be taken into consideration that this study cohort only represents the first part of an adaptive design based on the procedure of Bauer and Köhne.[31] In order to achieve a significant effect, it would have been necessary to have a further 138 patients per group. Based on the slow recruiting, it seemed improbable that enough patients could have been included in the study in a reasonable time. Nevertheless, this study confirms the analyses of Murphy and van der Meij[18,37,38] that EPA-enriched nutritional therapy distinctly reduces the loss of weight or lean body mass and helps to maintain BCM in comparison with supportive standard treatment during tumor-specific therapy.

The secondary endpoints showed a different picture: The objectively measured nutritional parameters, such as body weight and fat-free mass, showed a tendency toward improvement through the disease-specific nutrition enriched with EPA, but the differences were not significant. In contrast, the subjective parameters, in particular the Kondrup score (NRS 2002) and the SGA score, improved significantly. This also applies to the Karnofsky index after completion of CRT. For the EORTC score, only the patients with additional EPA administration

showed an increased loss of appetite. The latter finding was presumably related to higher fat (40 vs. 35 EN%) and protein (27 vs. 15 EN%) content of the cancer-specific tube feed as compared with the standard tube feed.

NRS 2002 is presently considered the best-validated screening tool for measuring the nutritional risk in hospitals, with a high predictive validity of the Kondrup score regarding improvements in outcome.[40,41] The fact that the subjective nutritional parameters (Kondrup score, SGA rating) change significantly before the objective nutritional parameters do, was quite a surprise for us, and it once again points out the particular significance of the Kondrup and SGA scores in assessing the nutritional status of patients. This screening system has been shown to enable the distinction between trials with a positive effect versus trials with no effect.[26] Therefore, the results of subjective parameters in the present trial strongly indicate that benefits with regard to improvements in nutritional status and disease severity will be greater with the metabolically adapted cancer-specific tube feed than with a standard enteral regimen in cancer patients undergoing CRT.

Interestingly, the rate of AEs related to study CRT was distinctly lower in patients treated with experimental nutrition than in controls, as were the rate of premature discontinuations due to AEs or adverse drug reactions and the rate of AEs suspected to be related to CRT, suggesting that the application of the experimental nutritional therapy may also be associated with a better tolerance of CRT.

In conclusion, enteral nutrition with a metabolically adapted cancer-specific enteral formula high in fat, protein, and EPA+DHA may be advantageous in patients with head and neck or esophageal cancer, improving parameters of nutritional and functional status during CRT. These beneficial effects may be related to the provision of EPA+DHA and to the specific nutrient profile adapted to the tumor-induced alterations in substrate metabolism by increasing the fat/carbohydrate ratio. Both enteral nutrition regimens were safe and well tolerated.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Fietkau is supported by a grant to Strahlenklinik Erlangen, Erlangen, Germany from Fresenius Kabi Deutschland GmbH (Bad Homburg, Germany) and has acted as a member of the Speakers Bureau, received honoraria, and support for travel from the company. Dr. Niewald has received a grant from Fresenius Kabi Deutschland GmbH for the inclusion of patients and documentation. Dr. Holscher has received honoraria from Fresenius Kabi Deutschland GmbH and has offered expert testimony in regional court and for EqualEstro (Neully-sur-Seine France). Dr. Herman has received honoraria for lectures.

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