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ORIGINAL ARTICLE

Oral nutritional supplements containing n-3 polyunsaturated fatty acids affect quality of life and functional status in lung cancer patients during multimodality treatment: an RCT

BS van der Meij[1], JAE Langius[1], MD Spreeuwenberg[2], SM Slootmaker[3], MA Paul[4], EF Smit[5] and PAM van Leeuwen[4]

BACKGROUND/OBJECTIVES: Our objective was to investigate effects of an oral nutritional supplement containing n-3 polyunsaturated fatty acids (FAs) on quality of life, performance status, handgrip strength and physical activity in patients with non-small cell lung cancer (NSCLC) undergoing multimodality treatment.

SUBJECTS/METHODS: In a double-blind experiment, 40 patients with stage III NSCLC were randomised to receive 2 cans/day of a protein- and energy-dense oral nutritional supplement containing n-3 polyunsaturated FAs (2.02 g eicosapentaenoic acid + 0.92 g docosahexaenoic acid/day) or an isocaloric control supplement, during multimodality treatment. Quality of life, Karnofsky Performance Status, handgrip strength and physical activity (by wearing an accelerometer) were assessed. Effects of intervention were analysed by generalised estimating equations. *P*-values <0.05 were regarded as statistically significant.

RESULTS: The intervention group reported significantly higher on the quality of life parameters, physical and cognitive function ($B = 11.6$ and $B = 20.7$, $P < 0.01$), global health status ($B = 12.2$, $P = 0.04$) and social function ($B = 22.1$, $P = 0.04$) than the control group after 5 weeks. The intervention group showed a higher Karnofsky Performance Status ($B = 5.3$, $P = 0.04$) than the control group after 3 weeks. Handgrip strength did not significantly differ between groups over time. The intervention group tended to have a higher physical activity than the control group after 3 and 5 weeks ($B = 6.6$, $P = 0.04$ and $B = 2.5$, $P = 0.05$).

CONCLUSION: n-3 Polyunsaturated FAs may beneficially affect quality of life, performance status and physical activity in patients with NSCLC undergoing multimodality treatment.

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INTRODUCTION

Lung cancer is a leading cause of cancer death worldwide, causing approximately 1.2 million deaths per year.[1] The two major types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer, differentiated by cell type and biological behaviour. NSCLC accounts for 85% of all lung cancers.[2]

Stage IV NSCLC has the shortest survival and is merely treated by palliative chemotherapy. Patients with localised or locoregional disease, such as stage III NSCLC, receive multimodality treatment with curative intent.

This multimodality treatment includes concurrent chemoradiotherapy, followed by surgery.[3–5]

Concurrent chemoradiotherapy increases the length and potential toxic effects of treatment as well as the rehabilitation and recovery process. This treatment frequently extends to 2 months, and the combined side effects can affect all areas of functioning, such as physical, psychosocial and nutritional status.[3]

Yet, little is known about physical, psychosocial and nutritional status in lung cancer patients undergoing multimodality treatment. Anorexia and weight loss are frequently observed, which affects nutritional status and in turn might have an impact on the treatment toxicity, quality of life and survival.[6–9]

Nutritional therapy in cancer patients aims to maintain or improve nutritional status and quality of life during cancer therapy, and to improve tolerance to treatment,[9] but an increase of energy and nutrient intake in cancer has shown to be ineffective because of tumour-derived catabolism.[9–11]

Research currently focuses on therapeutic agents, which modulate catabolism and appetite, for instance pharmaconutrients that are able to inhibit protein degradation and to stimulate protein synthesis.

[1]Department of Nutrition and Dietetics, Internal Medicine, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; [2]Department of Epidemiology and Biostatistics, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; [3]EMGO Institute, Department of Public and Occupational Health, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; [4]Department of Surgery, VU University Medical Center Amsterdam, Amsterdam, The Netherlands and [5]Department of Pulmonary Diseases, VU University Medical Center Amsterdam, Amsterdam, The Netherlands. Correspondence: Professor PAM van Leeuwen, Department of Surgery, VU University Medical Center Amsterdam, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: PAM.vLeeuwen@vumc.nl

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In this respect, n-3 polyunsaturated fatty acids (FAs) from fish oil have presumable immune-modulating effects, partly caused by the formation of 3- and 5-series inflammatory mediators with a lower proinflammatory and immunosuppressive effect.[12,13] In particular, eicosapentaenoic acid (EPA) has been shown to reduce the production of inflammatory cytokines and to treat tissue wasting in patients with cancer.[12,13] Apart from immune-modulating effects of n-3 FAs and indications of preservation of body weight,[14,15] one small trial documented an improved physical activity in a small group of patients with pancreatic cancer.[16]

Up to now, a few randomised controlled trials showed promising effects of n-3 polyunsaturated FAs on quality of life and functional status in cancer patients receiving palliative care, without assessing physical activity.[17,18]

The aim of this paper was to investigate the effects of a nutritional supplement containing n-3 polyunsaturated FAs on quality of life and functional status (performance status, handgrip strength and physical activity) in patients with stage III NSCLC undergoing multimodality treatment.

SUBJECTS AND METHODS

Patients

We included 42 patients with histological or cytological proven stage IIIa-N2 or IIIb NSCLC. Patients 18–80 years of age were included if they were eligible for multimodality treatment, and if their life expectancy was >3 months. Patients who had undergone surgery, chemotherapy or radiotherapy during the previous month and patients with oedema, ascites, severe comorbidities, or using high-dose corticosteroids or fish oil supplements during the previous month were excluded.

Multimodality consisted of concurrent chemoradiotherapy; for the description of the treatment schedule, we refer to our previous publication.

Study design

This study is set up as a randomised, double-blind, placebo-controlled trial. We prescribed two packages per day of either a protein- and energy-dense oral nutritional supplement containing n-3 polyunsaturated FAs (ProSure, Intervention) or an isocaloric control oral nutritional supplement (Ensure, Control) during 5 weeks of chemoradiotherapy. Details on the oral nutritional supplements that are displayed have been previously described.[19] The Medical Ethics Committee of the VU University Medical Center Amsterdam approved the trial and all patients provided written informed consent.

We continuously monitored compliance with the study supplements and adverse events. We assessed quality of life, Karnofsky Performance Status and physical activity at baseline, after 3 and 5 weeks. Patients performed handgrip strength tests at baseline and every week for 5 weeks.

Random assignment

The pharmacist randomised patients, stratified by chemotherapy schedule, in blocks of four to the intervention (I) group ($n=20$) or control (C) group ($n=20$). Independent employees prepared numbered batches of study supplements in the pharmacy. After inclusion of a patient, the pharmacist assigned a batch number. This batch was delivered to the patient concerned. Patients, investigators and study personnel were blind to the treatment group allocation.[19]

Compliance with study supplements

We used two methods to evaluate compliance with study supplements. First, patients were instructed to record supplement intake in a compliance diary. Second, plasma phospholipids EPA levels were assessed at baseline and after 5 weeks, as an objective indicator of study supplement intake, as described previously.[19]

Quality of life

Patients filled out a self-administered questionnaire, the EORTC-QLQC30, a multidimensional validated cancer-specific measure that includes global health status and quality of life, functional and symptom scales.[20]

Global health status implies the patient's own judgment of health status and quality of life. Physical function score expresses the capacity to perform normal daily activities. Other functional scales include role function (the capacity to perform work, daily activities, hobbies or other leisure activities), cognitive function, and emotional and social function.

EORTC-QLQC30 subscales were calculated according to the EORTC-QLQC30 manual and vary from 0 to 100. A high score for a functional or quality of life scale represents a high level of functioning or quality of life. A high score for a symptom scale represents a high level of problems.

The investigator recorded the Karnofsky Performance Status, a valid and widely used instrument to quantify the functional status of cancer patients. The Karnofsky Performance Status ranges from 0 to 100, with a higher score indicating a better ability to carry out normal daily activities and work.[21,22]

Handgrip strength

Handgrip strength was measured in the nondominant hand using a hydraulic hand dynamometer (Baseline; Fabrication Enterprises, White Plains, NY, USA). The patient performed the test in sitting position, with the shoulder adducted and neutrally rotated, elbow flexed at 90°, forearm and wrist in neutral position. Patients were instructed to perform two maximal isometric contractions. Patients took brief pauses between measurements. The maximal value was recorded to the nearest 0.5 kg, and the mean of two measurements was used to compare with age- and sex-dependent reference values for handgrip strength.[23] If patients were unable to perform handgrip strength with their nondominant hand, handgrip strength of the dominant hand was measured.

Through the entire study period, measurements were performed with the same hand.

Physical activity

Physical activity in daily life, assessed by accelerations of the hip, was measured with the physical activity monitor (PAM) accelerometer (model AM101, 28 190 g, $59 \times 43 \times 10\,mm^3$; PAM B.V., Doorwerth, The Netherlands).

The PAM produces a single index score on its display, which accumulates during the day and is a proxy measure of total daily physical activity. Every 3 points of the physical activity score reflects about 10 min of walking.[24] Moreover, the PAM has the ability to register minutes of low and moderate intensity physical activity. Low intensity physical activity corresponded with small in-house movements; moderate intensity corresponded with walking.[25] The reliability and validity of the PAM accelerometer has been tested in a laboratory setting and has shown results similar to the MTI Actigraph for estimating energy expenditure in walking and stair walking.

The PAM was calibrated on a shaking device (2.1 kHz) prior to the study. Patients were instructed to wear the PAM for 7 consecutive days at the following time points: after inclusion (before starting with study supplements) and during the third and fifth week of the study. PAM data were included if the PAM was worn during at least 3 full days during the week before admission to the hospital; average daily PAM scores and minutes of low and moderate intensity were calculated.

Adherence to chemoradiotherapy protocols

The investigator registered acute, nonscheduled hospital admissions, adherence to chemoradiotherapy protocols and chemotherapy delay, using medical records from the departments of pulmonary diseases and radiation oncology.

Statistics

The primary end point of this study and the sample size calculation on body weight have been described previously.[19] The statistical power of remaining parameters was calculated by entering the expected sample

size of 20 and the average within-group differences from baseline to 5 weeks. With a significance level of 0.05, the statistical power of quality of life parameters was 66% (global health status) and 97% (physical function), respectively , and the statistical power of Karnofsky Performance Status, hand grip strength and physical activity were 51, 25 and 55, respectively.

Differences between groups for patient characteristics at baseline for nominal and ordinal variables were analysed by χ^2 tests. For continuous variables, differences between groups at baseline were analysed by linear regression analysis with sex as covariate.

The primary analysis of the effect of n-3 FAs was performed on an intention-to- treat basis of all patients as randomised and allocated to the I or C group.

Generalised estimating equation, a longitudinal linear regression technique, to account for the dependency of the observations in time, was used to analyse the effects of intervention over time for continuous variables. Adjustments were made by addition of baseline values and sex as covariates. Independent dummy variables for group (I or C group) and for separate time points (week 1, 2, 3, 4 and 5) were entered into the generalised estimating equation model. Absolute differences between I and C groups were expressed as B. The generalised estimating equation method is suitable for designs with unequally spaced time intervals.[26,27] We used an exchangeable correlation structure to analyse the data, using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The exchangeable correlation structure assumes the correlation within different time points and is equal for all time points.[28] *P*-values <0.05 were considered as statistically significant.

RESULTS

We included 40 eligible patients with stage III NSCLC, 21 men and 19 women, with median age 57.8 years (range 39–80). In all, 16 patients had stage IIIa NSCLC and 24 patients had stage IIIb NSCLC.

The I group consisted of more men than the C group ($P=0.001$). Other baseline characteristics did not differ between the I and C groups. Quality of life variables did not differ between groups at baseline after adjustment for sex (Table 1).

We assessed 40 patients (I: $n=20$, C: $n=20$) at baseline, 35 patients (I: $n=15$, C: $n=20$) after 3 weeks and 33 patients (I: $n=14$, C: $n=19$) after 5 weeks. Five patients of the I group dropped out within 3 weeks. Reasons for dropout were withdrawal of consent ($n=3$), disease progression ($n=1$) or the occurrence of an adverse event. Compared with patients who did not drop out within 3 weeks, those five patients had a comparable Karnofsky Performance Status, global health status, physical function and stage of disease at baseline.

Table 1. General and baseline characteristics of 40 patients with stage III NSCLC

	I (n = *20*)	*C* (n = *20*)	P[a]
Sex (F), *n* (%)	4 (20%)	15 (75%)	<0.01*
Age (years)	58.4 ± 12.0	57.2 ± 8.1	0.59
Stage of disease, n *(%)*			0.42
IIIa	9 (45%)	7 (35%)	
IIIb	11 (55%)	13 (65%)	
Nutritional status			
BMI (kg/m^2)	24.8 ± 4.1	23.0 ± 2.4	0.42
Weight loss in the previous month (%)	−0.3 ± 2.4	−1.5 ± 4.7	0.56
Body weight (kg)	77.1 ± 14.6	64.7 ± 7.4	0.12
Handgrip strength (kg)	31.3 ± 9.8	26.1 ± 7.8	0.29
Karnofsky performance status	84.0 ± 11.4	80.5 ± 10.0	0.84
60	1 (5%)	0 (0%)	
70	4 (20%)	8 (40%)	
80	4 (20%)	4 (20%)	
90	8 (40%)	7 (35%)	
100	3 (15%)	1 (5%)	
EORTC QLQC30			
Global health status	60.2 ± 24.7	53.8 ± 21.7	0.81
Functional scales			
Physical function	73.6 ± 20.2	68.3 ± 20.8	0.78
Role function	50.9 ± 39.0	50.0 ± 63.3	0.97
Emotional function	70.6 ± 21.8	64.3 ± 29.9	0.73
Cognitive function	81.6 ± 14.6	71.7 ± 26.0	0.75
Social function	63.9 ± 30.4	55.8 ± 28.8	0.59
Physical activity[a]			
Day score (PAM activity score)	7.2 ± 8.7	5.7 ± 5.0	0.84
Low-intensity physical activity (min/day)	46.5 ± 51.5	45.8 ± 27.7	0.73
Moderate-intensity physical activity (min/day)	48.0 ± 67.9	31.0 ± 33.2	0.60

Abbreviations: BMI, body mass index; C, control; EORTC-QLQ, European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire; I, intervention; NSCLC, non-small cell lung cancer. Results are presented as mean ± s.d., unless stated otherwise. [a]*P*-value of difference between groups, with sex included as covariate in the regression model. *$P<0.01$.

Compliance with study supplements

Consumption of study supplements during chemoradiotherapy was approximately one package a day in both the I and C groups ($P>0.05$). After 5 weeks, plasma phospholipid concentrations of EPA and docosahexaenoic acid of the I group were significantly higher than those of the C group. For detailed results on compliance, we refer to our previous publication.[19]

Quality of life

Patients in the I group performed in general better on quality of life scores than patients in the C group (Table 2). After 3 weeks, the I group had a higher Karnofsky Performance Status (B = 5.3, $P=0.04$) than the C group. After 5 weeks, Karnofsky Performance Status did not differ between groups.

After 5 weeks, the I group showed a significantly better global health status (B = 12.2, $P=0.04$), physical function (B = 11.6, $P<0.01$), cognitive function (B = 20.7, $P<0.01$) and social function (B = 22.1, $P=0.04$) on the EORTC-QLQC30 subscales than the C group. In addition, the I group reported less nausea/vomiting (B = −16.0, $P=0.04$) and less financial problems (B = −9.5, $P=0.04$) than the C group after 5 weeks. Other functional or symptom scales of the EORTC-QLQC30 did not significantly differ between groups at any time point.

Physical activity level

Physical activity scores of patients are depicted in Table 2 and Figure 1. Mean daily physical activity score in the patient population amounted 6.3, which is considerably lower than in healthy people (approximately 20).[24] In both groups, at least two-thirds of patients were able to wear the PAM accelerometer, during 5.4 ± 2.4 days at baseline, 5.9 ± 2.2 days during week 3 and 7 ± 3.3 days during week 5, with no significant differences between the I and C groups. Most often mentioned reasons for not wearing the PAM were forgetfulness, taking the PAM off when taking a short bed rest and difficulties with wearing a visible device.

During week 3 and 5, the I group tended to have a considerably higher daily physical activity score (B = 6.6, $P=0.04$ and B = 2.5, $P=0.05$, respectively). There were no differences between the I and C groups in minutes of low and moderate intensity activity during week 3 and 5 (Table 2).

Table 2. Quality of life, physical activity and handgrip strength after 3 and 5 weeks for the I and C groups with stage III NSCLC

	Week 3		*Week 5*	
	B	P	*B*	P
EORTC QLQC30				
Global health status	0.4	0.95	12.2	0.04*
Functional scales				
Physical function	−1.7	0.76	11.6	<0.01*
Role function	−14.9	0.21	17.0	0.13
Cognitive function	−0.1	0.99	20.7	<0.01*
Emotional function	−8.6	0.25	6.8	0.30
Social function	2.0	0.87	22.1	0.04*
Symptom scales				
Fatigue	4.8	0.57	0.5	0.95
Pain	2.4	0.79	−2.7	0.79
Nausea/vomiting	−9.9	0.06	−16.0	0.04*
Dyspnoea	−10.4	0.12	−8.7	0.46
Loss of appetite	−5.0	0.64	−2.6	0.82
Insomnia	16.1	0.16	13.0	0.33
Constipation	−1.4	0.86	6.2	0.64
Diarrhoea	−5.2	0.62	1.2	0.90
Financial problems	−6.0	0.29	−9.5	0.04*
Karnofsky performance status	5.3	0.04*	7.2	0.10
Physical activity[a]				
Day score (PAM activity score)	6.6	0.04*	2.5	0.05
Low-intensity physical activity (min/day)	19.4	0.52	−4.0	0.85
Moderate-intensity physical activity (min/day)	26.0	0.26	4.9	0.64
Hand grip strength (kg)[b]	1.8	0.15	1.8	0.25

Abbreviations: B, difference between I and C groups (analysed by generalised estimating equations, corrected for baseline value and sex), B > 0 implies a higher change in the I group than the C group; C, control; EORTC-QLQ, European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire; I, intervention. [a]Week 3: $n = 13$ (I) and $n = 17$ (C), week 5: $n = 8$ (I) and $n = 13$ (C). [b]Week 3: $n = 12$ (I) and $n = 16$ (C), week 5: $n = 10$ (I) and $n = 16$ (C). *$P < 0.05$.

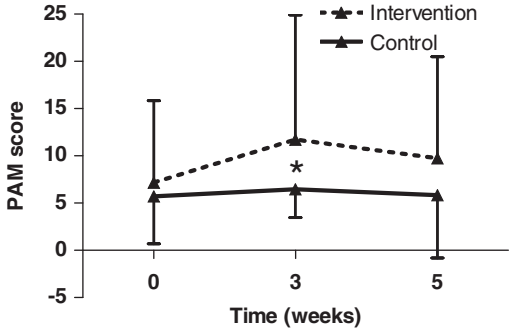

Figure 1. Physical activity (daily PAM score) over time for the I and C groups. Values are mean ± s.d., baseline: $n = 12$ (I), $n = 16$ (C); week 3: $n = 13$ (I) and $n = 17$ (C); week5: $n = 8$ (I), $n = 13$ (C). *$P < 0.05$, difference between the I and C group (analysed by generalised estimating equations, with baseline value and sex as covariate).

Handgrip strength

At baseline, handgrip strength of the study population was on average 92.2 ± 21.2% of age- and sex-specific reference values and not significantly different between the I and C groups. Over time, handgrip strength did not significantly differ between the groups (Table 2).

Adherence to chemoradiotherapy protocols

The number of patients with chemotherapy delays was four in the I group and two in the C group ($P = 0.48$). One patient in the C group needed a chemotherapy dose reduction. The number of patients with nonscheduled hospital admissions was 9 in the I group and 10 in the C group ($P = 0.87$). There were some patients who needed more than one nonscheduled hospital admission (I: $n = 1$: 3, C: $n = 1$: 2, $n = 1$: 3).

In both groups, there were various reasons for hospital admission, most often fever or nausea, vomiting and dehydration after chemotherapy. Other reasons were disease progression, pneumothorax, PEG-tube placement, depression, thrombosis and overall malaise.

DISCUSSION

This randomised controlled trial investigated effects of an oral nutritional supplement containing n-3 FAs on quality of life and functional status in patients with NSCLC during multimodality treatment. Observed differences between intervention and placebo groups suggest some beneficial effects of the oral nutritional supplement containing n-3 polyunsaturated FAs on quality of life and physical activity. These findings correspond with positive effects of n-3 FAs on nutritional status in the same patient population.[19]

FAs are important constituents of immune cell membranes and precursors of prostanoids and leukotrienes. In contrast to n-6 FAs, n-3 FAs downregulate the production of pro-inflammatory cytokine production and cachectic factors. As a result, n-3 FAs might reduce anorexia, REE, muscle degradation and weight loss in cancer patients.[29-32] Maintenance of body weight and fat-free mass is expected to improve quality of life.[9]

Previous studies showed malnutrition to be associated with a reduced quality of life in patients with head and neck[8,33] and colorectal cancer,[34] and in patients with radiotherapy for different types of cancer.[35] Lung cancer patients with weight loss showed more symptoms, chemotherapy delay, anaemia and fewer symptomatic responses to chemotherapy than those without weight loss.[6] Ravasco *et al.*[8] were the first to show beneficial effects of nutritional counselling on nutritional status, quality of life and outcome in head and neck cancer patients during radiotherapy.

To achieve immune modulation and effects on nutritional status and quality of life, patients' compliance with n-3 FA supplementation is essential. Plasma phospholipids' EPA levels and compliance diaries showed that the overall compliance with the study oral nutritional supplements was lower than expected. There was no significant difference between the I and C groups in the number of study supplements consumed, despite the lower prevalence of nausea and vomiting in the intervention group. Causes for suboptimal compliance of the study supplements, as mentioned by patients of both the I and C groups, were anorexia, palatability and early satiety, and patients' preference to consume normal oral food rather than oral nutritional supplements. As suboptimal compliance with n-3 FA supplements has been reported in other studies, this confirms the need to develop more feasible methods of n-3 FA supplementation for cancer patients, either or not combined with other methods to enhance energy and protein intake.

In addition, some patients showed increased plasma phospholipids' EPA levels at baseline. A number of control patients showed high levels after 5 weeks, indicating abnormal n-3 FA intake from fish or fish oil capsules. As a result, we might

have observed smaller effects of the n-3 FA oral nutritional supplements.

To our knowledge, no other studies reported beneficial effects of n-3 FAs on quality of life in cancer during multimodality treatment. In the current study, observed effects on quality of life variables amounted 10–20 points on a 0–100 scale, indicating clinical significant improvements.[40] Because of the uneven distribution of sex in the I and C groups, these differences might be partly caused by sex, for example, when men are known to be less critical towards their physical status than women. However, after correcting for sex, the I group showed a statistically significant higher physical function and cognitive function than the C group, and tendencies towards a higher global health status and social function.

The physical function score expresses the capacity to perform normal daily activities, such as to carry a heavy bag, to be able to go for a walk, to be bedridden during daytime and to be dependent on help with washing, dressing or eating. The I group also showed a substantially better cognitive function, expressed by reported concentration (for example, when watching television or reading a newspaper) and memory capacity. Polyunsaturated FAs are of importance in human brain development and n-3 FA status might influence cognitive function. A number of studies showed positive effects of docosahexaenoic acid supplementation on cognitive function in Alzheimer disease, elderly and children. Mechanistically, these phenomena have been explained by the anti-inflammatory action of docosahexaenoic acid.[36] Further on, reported problems with family life or social activities in the group receiving n-3 FAs were substantially lower during chemoradiotherapy. The intervention group also reported less nausea/vomiting and financial problems. These subjective findings are unlikely caused by n-3 FAs and may be caused by selection bias or by chance.

Physical activity is an important indicator of quality of life and performance status in patients with cancer.[37,38] Gibney *et al.*[39] showed a reduced physical activity level in a small group of patients with small cell lung cancer. Beneficial effects of n-3 FAs on physical activity level have been shown in one small randomised controlled trial in pancreatic cancer patients.[16] In line with the literature, we also found a reduced physical activity in patients with stage III NSCLC. After 5 weeks of chemoradiotherapy, physical activity in the group receiving the oral nutritional supplement containing n-3 FAs increased, whereas physical activity in the C group remained the same.

Although the statistical power of this study is limited, this is the first randomised controlled clinical trial indicating effects on both objective and subjective functional and quality of life parameters. n-3 Polyunsaturated FAs may beneficially affect quality of life and functional status in patients with NSCLC undergoing multimodality treatment. Yet, more research is required to confirm these findings and to investigate the dose-response effect of n-3 FAs during cancer treatment.

CONFLICT OF INTEREST

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