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Applied nutritional investigation

Efficacy of ω-3 supplementation on nutritional status, skeletal muscle, and chemoradiotherapy toxicity in cervical cancer patients: A randomized, triple-blind, clinical trial conducted in a middle-income country

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ABSTRACT

Objectives: Supplementation with ω-3 has been shown to favor the preservation of body weight and skeletal muscle. The aim of this study was to evaluate the efficacy of ω-3 supplementation on nutritional status, skeletal muscle quantity and quality, and toxicity for treatment of women with cervical cancer.
Methods: This was a randomized, triple-blinded, placebo-controlled clinical trial in women diagnosed with cervical cancer who underwent chemoradiotherapy between March 2016 and August 2017. The intervention group received four capsules with ω-3 (2.5 g/d) and the control group (CG) received the same number of identical-looking capsules with olive oil, for 45 d. Nutritional status was measured by anthropometry and Patient-Generated Subjective Global Assessment. Body composition was assessed by computed tomography. The skeletal muscle index was calculated using the range −29 to +150 HU. For skeletal muscle quality, the area comprised between −29 and +29 HU was denominated low-radiodensity skeletal muscle index and the range between +30 and +150 HU high-radiodensity skeletal muscle index, representing the skeletal muscle area with high or low intramuscular fat infiltration, respectively.
Results: The study population comprised 40 patients, with an average age 44.53 ± 8.73. The intervention group maintained body weight and showed an improvement in Patient-Generated Subjective Global Assessment score. A significant reduction in skeletal muscle index was observed in both groups. However, in regard to skeletal muscle quality, patients in the intervention group preserved low- and high-radiodensity skeletal muscle index, whereas those in the control group had increased low-radiodensity skeletal muscle index and significantly reduced high-radiodensity skeletal muscle index, reflecting high intramuscular fat infiltration only in the control group. The incidence of chemotherapy toxicity was significantly lower in the intervention group.
Conclusions: The results suggest that ω-3 supplementation is effective in maintaining nutritional status, skeletal muscle quality, and reduced symptoms of chemoradiotherapy among women with cervical cancer.

Introduction

Cervical cancer is the fourth most common cancer type in the female population worldwide and in Brazil [1,2]. Low- and middle-income countries account for ~85% of the cases [1], most diagnosed at an advanced stage. This is attributed to the poor quality of the Pap smear test and the delay in starting treatment [3,4].

Women with cervical cancer often are overweight at diagnosis [5–7]. However, the prevalence of cachexia and weight loss is also high, especially in advanced stages, which may be aggravated after treatment with chemoradiotherapy [8,9]. Loss of weight, as well as skeletal muscle (SM), is associated with unfavorable oncologic outcomes, such as a higher risk for toxicity and shorter length of survival [10–12].

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The quality of SM also has been associated with worse outcomes in patients with cancer [13,14]. This can be evaluated by different methods, but computed tomography (CT) has been gaining prominence in the last decade because it is a commonly performed exam in this population [15] and is capable of assessing the quality of SM by radiologic measurement of muscle density [16].

Interventional strategies, such as ω-3 supplementation, are essential to avoid worsening nutritional state (NS) during oncology treatment. Supplementation with ω-3 has shown to be promising, favoring the preservation of body weight and SM [17–20]. Furthermore, it has been suggested that ω-3 is capable of promoting "selective sensitization" through mechanisms that increase the sensitivity of cancer cells to drugs, which does not occur in healthy cells [21].

Although there is a growing number of studies that indicate the benefits of ω-3 supplementation, few clinical trials have been developed in humans. Studies report the potential benefit of ω-3 supplementation in patients with cancer due to its role in reducing chemotherapy toxicity and enhancing chemotherapy response [20], modulation of the inflammatory response [22], increasing appetite [23], promoting body weight gain [24,25], and preserving SM [17]. An improvement in short-term survival also has been described in patients with lung cancer [20].

However, the studies available to date have some methodological limitations, such as the following:

- Use of electrical bioimpedance to determine body composition, which has low accuracy and reproducibility in patients with cancer [26];
- Lack of sample size calculation, blinding, and randomization; and
- Use of hypercaloric and high-protein industrialized oral supplements, enriched with antioxidant nutrients other than ω-3.

We hypothesized that ω-3 supplementation could reduce muscle loss and prevent fat infiltration in muscles among patients with cervical cancer submitted to chemoradiotherapy treatment. Based on this, the objective of the present study was to evaluate the efficacy of ω-3 supplementation on NS and body composition, focusing on the quantity and quality of SM, and toxicity for treatment of women with cervical cancer who had undergone chemoradiotherapy.

Materials and methods

Data collection

This was a triple-blind, placebo-controlled, randomized controlled trial (RCT), which included women enrolled at the National Cancer Institute of Brazil, ages 19 to 59, with cervical cancer, never treated and who undergone curative chemoradiotherapy during the period of March 2016 and July 2017. Patients with HIV and those with renal disease under dialysis were excluded from the study, in addition to those without oral feeding conditions and with malabsorption disorders. Women over the age of 60 y were excluded to discard the age-related decline in SM on the obtained results.

Additionally, we only included those at nutritional risk or with some degree of malnutrition according to the Patient-Generated Subjective Global Assessment (PG-SGA), that is, PG-SGA B or C. This tool was selected based on its high sensibility and specificity in detecting nutritional risk in patients with cancer [27].

The project was approved by the National Cancer Institute José de Alencar Gomes da Silva Research Ethics Committee and the patients all signed an informed consent form. The study was conducted according to recommendations of the Consolidated Standards of Reporting Trials and a flowchart of patients eligible for the study is presented in Figure 1. The study was also recorded in the Clinical Trials database.

The primary outcomes were the mean changes in SM quantity and quality before and after ω-3 supplementation. Secondary outcomes were the incidence of adverse events during chemotherapy, as well as the mean differences in the serum concentration of polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) before and after the intervention.

For the sample size calculation, the difference observed in total SM (cm^2/m^2) was used, evaluated by CT before and after ω-3 intervention in the study conducted by Murphy et al. [20]. Considering a two-tailed test at a significance level of 5% and a power of 80%, 28 participants were required, with 14 in each group.

The patient's allocation in the control group (CG) or the intervention group (IG) was performed through randomization, using a previously available random table [28], on the first day of chemotherapy. A starting point was selected and the direction from left to right was chosen to follow the further numbers. Odd numbers were denoted as group A and even numbers as group B. Patients, medical and care staff, as well as the researchers, were blinded to the correspondence of groups A and B in relation to the CG or IG. This information was revealed by the pharmacist responsible for the blinding after the data analysis.

On the first day of chemotherapy, before infusion, the first appointment with the lead investigator occurred (T0). The patients were randomized into two groups: Patients in the IG were instructed to take four capsules per day, totaling 2.5 g of ω-3, of which 2 g was EPA and 450 mg was DHA. Patients in the CG were advised to take the same number of capsules, which looked identical to those of the IG but contained only olive oil. The supplements used are registered with the Ministry of Health (Supra Ômega 50 EPA/10 DHA Global Suplementos) and (Azeite de Oliva Extravirgem 1000 MG Global Nutrition).

Because the study included patients at nutritional risk (PG-SGA B and C), both groups received an oral isocaloric nutritional supplement in powder form, offering an additional 430 kcal and 16 g of protein per day. The supplementation occurred for 45 d, corresponding to the average duration of the chemoradiotherapy treatment. After this period, the second appointment with the lead researcher was scheduled (T1).

Assessment of nutritional status and cachexia

The anthropometric evaluation was carried out by measuring weight and height, for body mass index (BMI) calculation and classification, according to the criteria of the World Health Organization [29]. Body weight was measured using a digital platform scale (Filizola® PL; São Paulo, Brazil) and for height, a stadiometer coupled to the same scale was used.

We used the validated Portuguese version of the PG-SGA [30], which classifies NS as A (well-nourished), B (moderately malnourished or suspected of malnutrition), or C (severely malnourished). This instrument also generates a final score, in which a higher score means worse NS [31].

The classification of cancer cachexia followed the recommendations of the international consensus proposed by Fearon et al. [32]:

- Precachexia, when there was weight loss of ≤5% over 6 mo and presence of anorexia; and
- Cachexia, when weight loss was >5% over 6 mo, or a combination of weight loss >2% with a BMI of <20 kg/m^2.

Body composition by CT

For body composition assessment, at T0 we took the CT images used to identify the area to be irradiated before treatment, which were available from the institution's system. All images at T0 had an interval of ≤20 d before the start of treatment. At T1, all patients underwent CT of the upper abdomen. For each patient, an image was selected at the height of the third lumbar vertebra (L3), which was analyzed using the SliceOmatic software version 5.0 (Tomovision, Canada). All the CT scans followed the same parameters, to ensure homogenization in the characteristics of the images. All images were evaluated by the same trained observer and checked by a second observer.

For identification and quantification of SM and adipose tissue, the reference values were used as described previously by Mitsiopoulos et al. [33]. The cross-sectional area representative of SM (−29 to +150 Hounsfield Unit [HU]) was normalized by the $height^2$ and denominated skeletal muscle index (SMI; cm^2/m^2). SMI ≤38.9 cm^2/m^2 was used to classify myopenia, as per the cutoff point established for women [34]. To estimate the total body content of fat-free mass and fat mass, the regression equations developed by Mourtzakis et al., expressed in kg and later normalized by the $height^2$, were used to generate the variables fat-free mass index (FFMI; kg/m^2) and fat mass index (FMI; kg/m^2), respectively [34].

SM quality was determined using the method previously proposed by Paula et al. [35]. This method divides the total density range of SM into two subranges. The SM area in the range of −29 to +29 HU was denominated low-radiodensity skeletal muscle index (LRSMI; cm^2/m^2), representing the area with high fat infiltration in muscle tissue (myosteatosis), and the area in the range +30 to +150 HU was denominated high-radiodensity skeletal muscle index (HRSMI; cm^2/m^2). To evaluate SM quality, the average SM attenuation was obtained by the average of the total SM pixels in the range of −29 to +150 HU.

Evaluation of dietary intake and adherence to supplementation

Dietary intake was assessed at T0 by means of a non-consecutive 3-d food registry. The data was tabulated using the Brazilian Table of Food Composition [36]. To evaluate the adequacy of energy and protein, their values were compared with

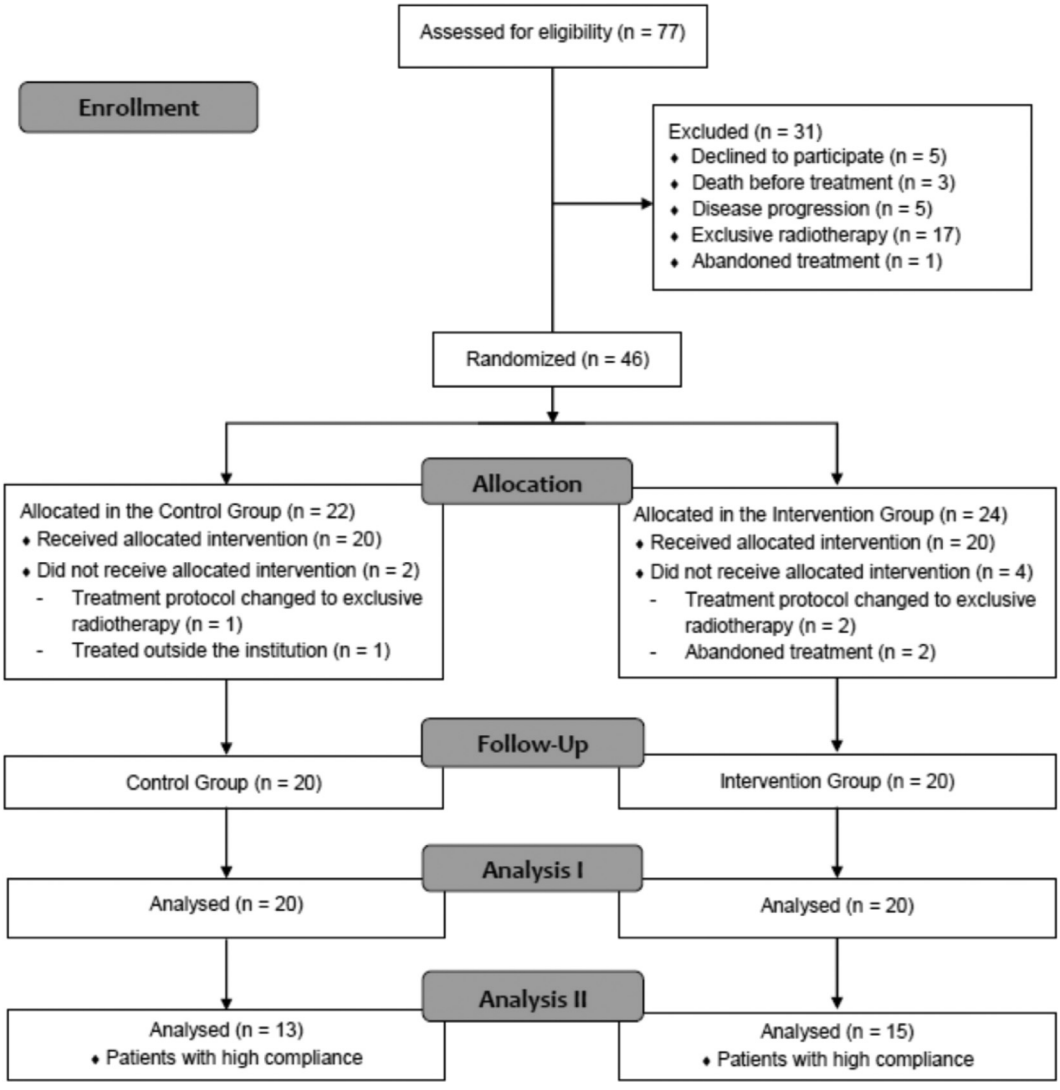

Fig. 1. Flow diagram of the randomized controlled trial.

those recommended for patients with cancer, which is, according to the European Society of Parenteral and Enteral Nutrition (ESPEN) 25 kcal/kg and 1.2 g/kg/d, respectively [18].

The capsule intake of the placebo or ω-3 was evaluated weekly until completion of the 45 d of supplementation. During the T1 appointment at the end of chemoradiotherapy, the amount of supplement taken by each patient was recorded and any unused capsules were returned at the time of patient's visit, to determine the total of capsules consumed. High compliance with supplementation was considered when 80% of the prescribed capsules were ingested.

Toxicity of the chemoradiotherapy treatment

The clinical protocol of the institution for treatment of cervical cancer is based on weekly cisplatin-based chemotherapy at a dose of 40 mg/m^2, for 5 or 6 consecutive wk, concomitant with pelvic radiotherapy (25 sessions). Evaluation of toxicity to the chemoradiotherapy treatment was performed according to the Common Toxicity Criteria for Adverse Events (CTCAE/NCI), version 5.0 [37]. The form was applied twice: once in the middle of cancer treatment (third chemotherapy cycle) and then at the end of supplementation (T1). Dose-limiting toxicity (DLT) was defined as any serious adverse event that resulted in discontinuation, delayed treatment, or the need for a chemotherapy dose reduction [12].

Analysis of plasma long-chain polyunsaturated fatty acids

Blood was collected in heparinized tubes, centrifuged and immediately stored at −80°C until analysis. The long-chain polyunsaturated fatty acid (LCPUFA) contents of the samples were analyzed by gas chromatography using an Agilent Technologies 7890 A CG System equipped with a flame ionization detector coupled to the program EZChrom Elite CDS (Agilent Technologies, Inc., San Diego, CA, USA). The methyl esters of fatty acids (FAs) were obtained by the direct alkaline methylation method AOCS 2 b-11 (adapted) and then separated in a SP-2560 fused silica capillary column of bis-cyanopropyl polysiloxane (Supelco Inc., Bellefonte, PA, USA). The injector and detector temperatures were 250°C. Samples were run in the split-less mode (no split ratio). The methylated FAs were identified based on comparison with the relative retention time of standard peaks (Nu-Chek Prep. Inc., Elysian, MN, USA; methyl esters mixture 463). FAs were then expressed in amount (μg/mL) and percentage of total FAs.

Statistical analysis

Statistical analysis was performed with the aid of SPSS version 22 (IBM, Chicago, IL, USA). Adherence to the normal curve was tested by the Shapiro–Wilk test and a normal distribution was identified for all variables, except for plasma EPA fatty acid; energy, protein, and lipid intake. The continuous variables were expressed as the mean + SD, and proportions for the categorical variables. Associations between the categorical variables were analyzed using the χ^2 or Fisher's exact test.

The comparison of intragroup means between T0 and T1 was tested by the Student's *t* test for dependent variables. To compare the intergroup results, the delta (T1–T0) of each continuous variable was calculated. Intergroup deltas were compared by Student's *t* test for independent variables. In addition to the comparison of means of SM components, the percent change in LRSMI was calculated using the formula: (LRSMI at T1 − LRSMI at T0 / LRSMI at T0) × 100. The percent

change in LRSMI was later classified in distribution quartiles to categorize the percent loss or gain.

The macronutrient intake was expressed in median with minimum and maximum values, and the Mann–Whitney test was used to compare median intergroups in T0.

For all analysis, a significance level of 5% was adopted.

Results

The study population consisted of 40 patients, 20 of whom were randomized in each group (IG and CG). The sociodemographic and clinical characteristics are described in Table 1. Most patients were overweight according to the BMI, whereas ~60% of the women had cachexia and 25% myopenia. No significant difference was observed between groups for any sociodemographic, clinical, and nutritional status variables before chemoradiotherapy treatment (Table 1).

The total number of capsules taken at the end of the intervention was on average 132.68 (±49.92), which corresponds to an average acceptance of 74% of the capsules prescribed. Considering the cutoff point of 80% for high compliance to the intervention, 70% of women met this criterion (13 and 15 patients in the CG and IG, respectively).

Significantly higher intakes of energy, protein, and lipids (kcal/d) were observed in the CG. However, when variables were normalized by body weight at T0, there was no statistical difference between groups (Table 2). Regarding the evaluation of food adequacy, only 53.6% and 57.1% of the population reached the recommended amount of energy and protein, respectively; with no

Table 1
Sociodemographic, clinical characteristics, nutritional status, and body composition at baseline

Characteristic	Total (N = 40)	Control group (n = 20)	Intervention Group (n = 20)	*P*-value*
Age, y†	44.53 ± 8.73	43.90 ± 7.88	45.14 ± 9.67	0.657
Marital status‡				0.739
Single (%)	20 (50)	11 (55)	9 (45)	
Married (%)	17 (42.5)	8 (40)	9 (45)	
Divorced (%)	2 (5)	1 (5)	1 (5)	
Widow (%)	1 (2.5)	0 (0)	1 (5)	
Ethnic group‡				0.478
White (%)	9 (22.5)	3 (15)	6 (30)	
Mixed (%)	28 (70)	15 (75)	13 (65)	
Black (%)	3 (7.5)	2 (10)	1 (5)	
Educational level, y‡				0.451
0–3 (%)	2 (5)	0 (0)	2 (10)	
4–7 (%)	17 (42.5)	9 (45)	8 (40)	
8–10 (%)	13 (32.5)	6 (30)	7 (35)	
≥11 (%)	8 (20)	5 (25)	3 (15)	
Occupation‡				
Housewives (%)	7 (17.5)	4 (20)	3 (15)	0.916
Paid activity (%)	31 (77.5)	15 (75)	16 (80)	
Retired/Unemployed (%)	1 (5)	1 (5)	1 (5)	
Comorbidity‡				0.211
None (%)	29 (72.5)	16 (80)	13 (65)	
Arterial Hypertension (%)	7 (17.5)	2 (10)	5 (25)	
Diabetes Mellitus (%)	4 (10)	2 (10)	2 (10)	
Stage‡,§				0.762
II (%)	23 (57.5)	12 (60)	11 (55)	
III (%)	17 (42.5)	8 (40)	9 (45)	
Histologic type‡				0.486
SCC (%)	36 (90)	17 (85)	19 (95)	
Adenocarcinoma (%)	4 (10)	3 (15)	1 (5)	
Weight, kg†	66.49 ± 15.39	66.99 ± 16.29	65.98 ± 14.83	0.839
BMI, kg/m^2†	26.54 ± 5.71	26.15 ± 6.02	26.92 ± 5.52	0.674
BMI category‡				
Underweight (%)	3 (7.5)	1 (5)	2 (10)	0.083
Normal weight (%)	13 (32.5)	10 (50)	3 (15)	
Overweight (%)	14 (35)	4 (20)	10 (50)	
Obesity (%)	10 (25)	5 (25)	5 (25)	
PG-SGA‡				
A (%)	2 (5)	1 (5)	1 (5)	0.834
B (%)	35 (87.5)	17 (85)	18 (90)	
C (%)	3 (7.5)	2 (10)	1 (5)	
PG-SGA score†	13.62 ± 7.04	15.30 ± 7.94	11.95 ± 5.64	0.134
Classification of cachexia				0.337
Precachexia	17 (42.5)	10 (50)	7 (35)	
Cachexia	23 (57.5)	10 (50)	13 (65)	
Myopenia‡,‖				
No (%)	30 (75)	13 (65)	17 (85)	0.273
Yes (%)	10 (25)	7 (35)	3 (15)	

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; PG-SGA, Patient-Generated Subjective Global Assessment; SCC, squamous cervical cancer.
*Statistical analysis between control and intervention groups.
†Mean + SD, *t* test.
‡Absolute number (percentage), χ^2 text.
§Staging according to FIGO.
‖ Myopenia cutoff point established for women by Mourtzaki et al. [34]: ≤38.9 cm^2/m^2.

Table 2
Comparison of dietary intake at baseline

Characteristics*	Total (N = 28)†	Control group (n = 14)	Intervention group (n = 14)	*P*-value‡
Energy, kcal/d	1473.8 (1209.72–1892.21)	1829.2 (1385.52–2093.40)	1369.4 (1044.15–1638.59)	**0.024**
Energy, kcal/kg	24.31 (17.79–31.77)	24.63 (20.41–31.78)	21.44 (15.16–31.33)	0.085
Macronutrients, kcal/d				
Protein	310.40 (207.31–367.39)	320.06 (235.27–450.12)	258.84 (135.77–336.30)	**0.016**
Carbohydrate	828.46 (663.79–1060.28)	911.18 (736.24–1109.86)	748.00 (211.04–960.85)	0.306
Lipids	381.64 (272.72–545.27)	477.67 (325.77–696.92)	324.99 (215.12–399.31)	**0.001**
Macronutrients, g·kg·d^{-1}§				
Protein	1.17 (0.79–1.54)	1.24 (0.90–1.59)	1.11 (0.52–1.40)	0.077
Carbohydrate	3.17 (2.52–4.17)	3.65 (2.83–4.16)	3.21 (2.36–4.45)	0.454
Lipids	0.68 (0.46–0.97)	0.78 (0.53–1.15)	0.68 (0.34–0.78)	0.068

P-values in bold indicate statistically significant values.
*Median (25th–75th percentile).
†Total number of patients who responded to the 3-d food registry.
‡Statistical analysis between control and intervention groups, non-parametric Mann–Whitney test.
§Total amount in grams of protein, carbohydrate and lipids normalized by the body weight of each individual, in kg, at T0.

statistical difference between the groups (χ^2 test, $P = 0.449$ and $P = 0.704$). In relation to plasma concentrations of the LCPUFAs EPA and DHA, there was a statistically significant increase of both FAs after intervention in the IG, which did not occur in the CG (Table 3).

In relation to the changes observed in the NS variables, a significant reduction in body weight and BMI in the CG was observed, whereas patients in the IG did not present significant variation in these parameters. Additionally, a significant improvement in PG-SGA scores was observed only in the group receiving ω-3 supplementation; however, there was no significant intergroup difference (Table 4). For body composition parameters, a significant reduction of SMI, HRSMI, muscle attenuation, and FFMI/m^2 within the groups were observed for both groups. However, although the IG did not present changes in LRSMI, the CG presented a significant increase in this parameter, suggesting an increase in the SM fat infiltration (Table 4).

When the analysis included only patients with high compliance to supplementation, the reduction in HRSMI was no longer statistically significant in the IG, suggesting an ability in HRSMI maintenance following ω-3 supplementation. On the other hand, there was a significant reduction of HRSMI and an increase in LRSMI in the CG after treatment. In the intergroup analysis, a significant difference was observed only for LRSMI, with a trend toward significance for the HRSMI (Table 5).

The percentage of LRSMI alteration after cancer treatment was classified in distribution quartiles to assess the magnitude of intramuscular fat infiltration (Fig. 2). LRSMI values below the first quartile represented a severe gain; values between quartiles 1 and 2, a moderate gain; between quartiles 2 and 3, a mild gain; and above the third quartile, either loss or maintenance. Therefore, it was observed that 60% of women allocated to the IG presented a mild gain in LRSMI, and only 5% showed a severe gain. On the other hand, among the patients in the CG, 45% presented a severe increase of intramuscular fat infiltration.

The symptoms related to chemotherapy with the highest incidence were dry mouth (72.5%), dysgeusia (72.5%), nausea (70%), anorexia (65%), diarrhea (55%), and fatigue. No statistical difference was observed, in the middle of chemoradiotherapy (cycle 3), in the incidence of adverse events between the allocation groups. However, at the end of treatment (T1), women in the IG presented a significantly lower incidence of anorexia, nausea, dry mouth, and dysgeusia symptoms (Table 6). Among patients with high compliance to supplementation, the results were similar and are described in Supplementary Table 1.

A significant association was found for the presence of moderate to severe toxicity and DLT between the intervention and control groups (Fig. 3), patients supplemented with ω-3 had significantly lower DLT. It should be noted that 80% of patients with DLT were in the CG.

Discussion

Nutritional intervention strategies are poorly evaluated in the oncology setting, which hinders recommendations for this population, especially among patients undergoing chemotherapy and radiotherapy. A randomized, placebo-controlled, triple-blinded study design is considered the gold standard method for evaluation of nutritional interventions. However, as the majority of the RCTs testing the efficacy of the ω-3 intervention in patients with cancer are conducted in high-income countries, we emphasize that it is extremely important to obtain data in other populations. To our knowledge, this is the first RCT evaluating fish oil supplementation in patients with cervical cancer, which is classically related to poverty, and was conducted in a referred center for cancer

Table 3
Plasma phospholipid, EPA, and DHA in control and intervention groups at baseline and after ω-3 supplementation*

	Control group (n = 19)			Intervention group (n = 20)		
	Baseline	End of treatment	*P*-value	Baseline	End of treatment	*P*-value
Amount of EPA, μg/mL*	0.75 (0.40–1.44)	1.08 (0.65–1.57)	0.076†	1.15 (0.50–1.65)	2.02 (0.74–2.76)	**0.025**†
Proportion of EPA, %*	0.48 (0.31–0.56)	0.62 (0.42–0.71)	0.068†	0.47 (0.34–0.76)	1.06 (0.43–1.75)	**0.013**†
Amount of DHA, μg/mL‡	2.15 ± 0.85	2.35 ± 0.81	0.305§	2.14 ± 0.95	2.35 ± 0.88	**0.012**§
Proportion of DHA, %‡	1.27 ± 0.54	1.28 ± 0.34	0.306§	1.21 ± 0.41	1.40 ± 0.41	**0.012**§

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
P-values in bold indicate statistically significant values.
*Results are shows as median (25th-75th percentile).
†Wilcoxon test.
‡Results are shown as mean ± SD.
§Paired sample *t* test.

Table 4
Comparison of nutritional status and body composition parameters between control and intervention groups before and after chemoradiotherapy treatment

Nutritional status and body composition parameters		Control group (n = 20)	Δ*	Intervention group (n = 20)	Δ*	*P*-value†
Weight (kg)	T0	66.99 ± 16.29	−1.93 ± 2.82	65.41 ± 14.82	−1.58 ± 2.66	0.685
	T1	64.06 ± 17.26		64.48 ± 15.33		
	P-value‡	**0.001**		0.098		
BMI (kg/m^2)	T0	26.15 ± 6.01	−0.75 ± 1.11	26.92 ± 5.52	−0.45 ± 1.13	0.752
	T1	25.39 ± 6.39		26.58 ± 5.69		
	P-value‡	**0.001**		0.098		
PG-SGA score	T0	15.30 ± 7.99	−2.35 ± 10.05	12.95 ± 5.64	−2.95 ± 7.75	0.876
	T1	12.95 ± 8.91		9.00 ± 5.49		
	P-value‡	0.203		**0.031**		
SMI (cm^2/m^2)	T0	44.60 ± 8.11	−3.17 ± 2.23	45.11 ± 6.15	−3.43 ± 2.68	0.741
	T1	41.44 ± 7.01		41.67 ± 6.53		
	P-value	**0.000**		**0.000**		
HRSMI (cm^2/m^2)	T0	28.87 ± 7.33	−5.06 ± 4.43	27.60 ± 3.72	−3.45 ± 3.38	0.209
	T1	23.81 ± 3.80		23.87 ± 4.72		
	P-value‡	**0.000**		**0.000**		
LRSMI (cm^2/m^2)	T0	15.73 ± 6.39	1.90 ± 3.08	17.50 ± 6.89	0.10 ± 2.09	**0.040**
	T1	17.63 ± 5.51		17.80 ± 5.74		
	P-value‡	**0.013**		0.551		
Average skeletal muscle attenuation (HU)	T0	35.54 ± 6.78	−3.20 ± 3.60	34.46 ± 6.19	−2.67 ± 3.10	0.632
	T1	32.34 ± 4.68		31.26 ± 5.55		
	P-value‡	**0.001**		**0.020**		
FMI (kg/m^2)	T0	9.23 ± 2.45	−0.15 ± 0.70	10.06 ± 2.72	−0.06 ± 0.45	0.612
	T1	9.08 ± 2.62		10.00 ± 2.71		
	P-value‡	0.337		0.559		
FFMI (kg/m^2)	T0	15.75 ± 2.43	−0.95 ± 0.67	16.02 ± 1.87	−1.03 ± 0.80	0.742
	T1	14.80 ± 2.14		14.98 ± 1.95		
	P-value‡	**0.000**		**0.000**		

BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index; HRSMI, high-radiodensity skeletal muscle index; LRSMI, low-radiodensity skeletal muscle index; PG-SGA, Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.
P-values in bold indicate statistically significant values.
*Mean difference between T1 and T0.
†Two independent sample *t* tests between the different groups.
‡Dependent *t* test between the same group.

Table 5
Comparison of nutritional status and body composition parameters between control and intervention groups of patients with high compliance of the prescribed capsules (≥80%)

		Control group (n = 13)	Δ*	Intervention group (n = 15)	Δ*	*P*-value†
Weight (kg)	T0	70.44 ± 16.54	−1.83 ± 3.18	67.73 ± 14.83	−1.27 ± 2.21	0.885
	T1	67.61 ± 13.54		66.63 ± 14.99		
	P-value‡	**0.011**		0.061		
BMI (kg/m^2)	T0	27.29 ± 6.04	−0.71 ± 1.25	27.47 ± 5.15	−0.37 ± 0.92	0.934
	T1	26.05 ± 6.43		26.99 ± 5.18		
	P-value‡	**0.013**		0.062		
PG-SGA Score	T0	14.92 ± 8.62	1.93 ± 7.65	12.07 ± 4.82	2.46 ± 9.93	0.875
	T1	12.96 ± 9.69		9.93 ± 5.59		
	P-value‡	0.389		**0.040**		
SMI (cm^2/m^2)	T0	45.84 ± 8.45	−3.40 ± 2.17	45.34 ± 5.33	−2.76 ± 2.19	0.445
	T1	42.64 ± 7.23		42.59 ± 5.58		
	P-value‡	**0.000**		**0.000**		
HRSMI (cm^2/m^2)	T0	30.22 ± 8.05	−5.97 ± 4.87	27.65 ± 3.35	−3.05 ± 3.51	0.067
	T1	24.66 ± 3.85		24.60 ± 3.37		
	P-value‡	**0.002**		0.060		
LRSMI (cm^2/m^2)	T0	15.61 ± 6.53	2.57 ± 3.33	17.70 ± 5.66	0.29 ± 2.22	**0.040**
	T1	17.98 ± 5.34		17.98 ± 4.56		
	P-value‡	**0.034**		0.626		
Average skeletal muscle attenuation (HU)	T0	36.48 ± 6.76	−4.09 ± 3.32	34.21 ± 4.49	−2.47 ± 3.34	0.229
	T1	32.64 ± 3.93		31.74 ± 3.97		
	P-value‡	**0.004**		**0.016**		
FMI (kg/m^2)	T0	9.65 ± 2.66	−0.08 ± 0.82	10.31 ± 2.60	−0.05 ± 0.49	0.906
	T1	9.61 ± 2.85		10.26 ± 2.57		
	P-value‡	0.851		0.723		
FFMI (kg/m^2)	T0	16.12 ± 2.54	−1.02 ± 0.65	16.08 ± 1.61	−0.83 ± 0.66	0.445
	T1	15.16 ± 2.18		15.25 ± 1.65		
	P-value‡	**0.000**		**0.000**		

BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index; HRSMI, high-radiodensity skeletal muscle index; LRSMI, low-radiodensity skeletal muscle index; PG-SGA, Patient-Generated Subjective Global Assessment; SMI, skeletal muscle index.
P-values in bold indicate statistically significant values.
*Difference between T1 and T0.
†Two independent sample *t* tests between the different groups.
‡Dependent *t* test between the same group.

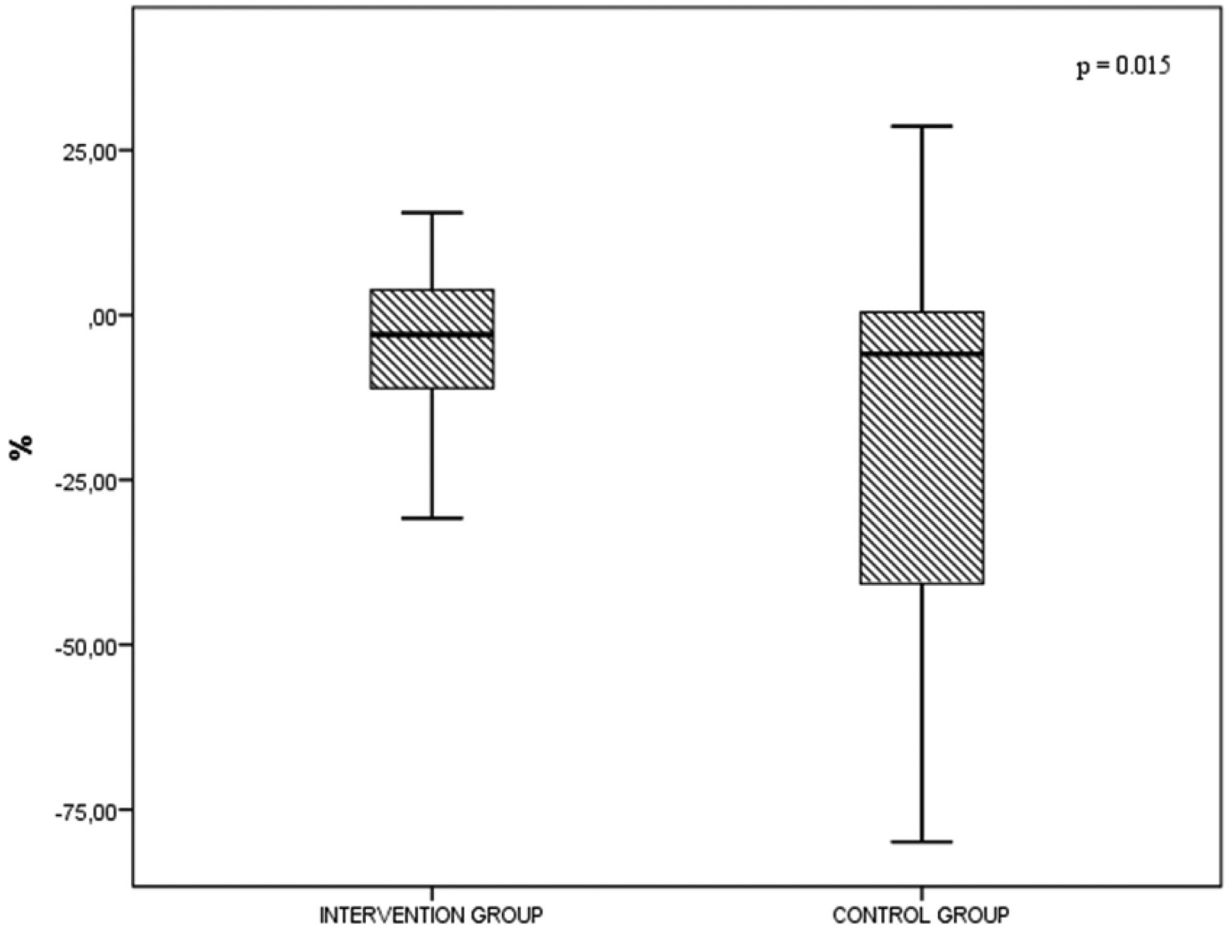

Fig. 2. Quartiles distribution of the percentage of low-radiodensity skeletal muscle index - after treatment between the control and intervention groups.

treatment in Brazil, which treats ~80% of the cases of gynecologic cancers in the state of Rio de Janeiro.

The most recent recommendations suggest that supplementation with ω-3, or EPA alone, in patients with cachexia may contribute to increased appetite, and to the maintenance of body weight and SM [18,19,38]. The main mechanisms involved in attenuating the treatment side effects are related to inflammatory modulation, and inhibition of the proteolysis-inducing factor synthesis, which in turn reduces SM proteolysis [19,39].

We found an increase in plasma EPA and DHA concentrations after oral supplementation with ω-3. There also was a significant reduction in the PG-SGA score and maintenance of body weight in patients in the IG, which did not occur in the CG. A lower score reflects decreased gastrointestinal symptoms, improved food intake, and functional capacity. Although the PG-SGA is considered a reference method for the NS assessment in patients with cancer, there are no studies in the literature that have used this tool in ω-3 intervention studies to date. Clinical trials evaluating the effect of ω-3 on the body weight of patients with lung or gastrointestinal cancers undergoing chemotherapy have found results similar to ours, with reduced weight loss in the supplemented group [40–42].

However, although the mentioned clinical trials were randomized, the type of supplement offered to groups may be considered an important limitation. In these trials, although the CG received a normocaloric and normoprotein supplement, the supplements offered to the IG presented high-calorie and high-protein characteristics, enriched with ω-3 and other antioxidant nutrients, which may have interfered with the results obtained. To eliminate this limitation in the interpretation of our results, the same nutritional powder supplement was prescribed for both groups, in addition to the ω-3 or olive oil in its isolated forms, without other nutrients.

In our study, the evaluation of body composition was performed by CT, which has been widely applied in oncology because it allows for evaluation of both the quantity and quality of SM, which indirectly reflects the degree of muscle fat infiltration [16,43]. To our knowledge, only one study to date has used CT to evaluate the effects of ω-3 on SM, in which a maintenance of SMI and muscle radiodensity was reported in the group supplemented with EPA [20]. These results differ from those obtained in the present study, which found a significant reduction in the SMI and average muscle radiodensity in both groups.

The significant reduction in the SMI in the two groups can be explained in part by the low socioeconomic level of the studied population, which was probably a determining factor for inadequacy of food intake. It should be noted that ~50% the population ingested sufficient quantities of energy and protein before the start of treatment, with no statistical difference between groups. Unfortunately, it was not possible to evaluate dietary intake after the intervention due to the patients' low understanding of and adherence to the instrument.

However, when we evaluated SM using the methodology proposed by our group [44], which allows for identification of magnitude of the SM area infiltrated or not by fat from the characterization of areas with low or high radiodensity, respectively the data present important differences. These subranges

Table 6
Incidence of toxicity to the chemoradiotherapy treatment between the control and intervention groups

Adverse events*	Middle of treatment (third cycle)			End of treatment (T1)		
	Control group (n = 20)	Intervention group (n = 20)	*P*-value	Control group (n = 20)	Intervention group (n = 20)	*P*-value†
Pain and skeletal muscle						
Pain			0.256			0.677
<2	16 (80)	17 (85)		17 (85)	16 (80)	
≥2	4 (20)	3 (15)		3 (15)	4 (20)	
Arthralgia/Myalgia			0.151			0.667
<2	16 (80)	19 (95)		16 (80)	17 (85)	
≥2	4 (20)	1 (05)		4 (20)	3 (15)	
Asthenia			0.677			0.465
<2	17 (85)	16 (80)		14 (70)	16 (80)	
≥2	3 (15)	4 (20)		6 (30)	4 (20)	
Gastrointestinal symptoms						
Anorexia						**0.049**
<2	11 (55)	14 (70)	0.327	12 (60)	16 (80)	
≥2	9 (45)	6 (30)		8 (40)	4 (20)	
Nausea			0.091			**0.047**
<2	12 (60)	15 (75)		10 (50)	16 (80)	
≥2	8 (40)	5 (25)		10 (50)	4 (20)	
Vomiting						0.465
<2	16 (80)	19 (95)	0.151	14 (70)	16 (80)	
≥2	4 (20)	1 (05)		6 (30)	4 (20)	
Constipation						
<2	15 (75)	12 (60)	0.212	19 (95)	19 (95)	1.000
≥2	5 (25)	8 (40)		1 (05)	1 (05)	
Diarrhea			0.723			0.311
<2	16 (80)	15 (75)		12 (60)	15 (75)	
≥2	4 (20)	5 (25)		8 (40)	5 (25)	
Dry mouth			0.098			**0.005**
<2	17 (85)	19 (95)		15 (75)	19 (95)	
≥2	3 (15)	1 (05)		5 (25)	1 (05)	
Dysgeusia			0.723			**0.028**
<2	16 (80)	15 (75)		12 (60)	18 (90)	
≥2	4 (20)	5 (25)		8 (40)	2 (10)	

P-values in bold indicate statistically significant values.
*Adverse events to the chemoradiotherapy treatment were graded according to the Common Toxicity Criteria for Adverse Events, version 4.0 and subdivided into two grades: <2 and ≥2.
†Statistical analysis between control and intervention groups, χ^2 test.

have determined a stronger association with worse outcomes in women with gynecologic cancer [35,45], but to our knowledge, this was the first time that the methodology was used to evaluate a nutritional intervention.

Using the subranges approach, the present data presented important differences. Interestingly, LRSMI maintenance was observed in patients in the IG, whereas in the CG there was a significant increase in this index, reflecting greater intramuscular fat infiltration after chemoradiotherapy treatment in the CG and preservation of SM quality in the IG. Furthermore, when comparing only those patients with optimal adherence to supplementation, this result was even more important as both the maintenance of high-radiodensity SM and preservation of intramuscular infiltration in the IG were found. Thus, the results

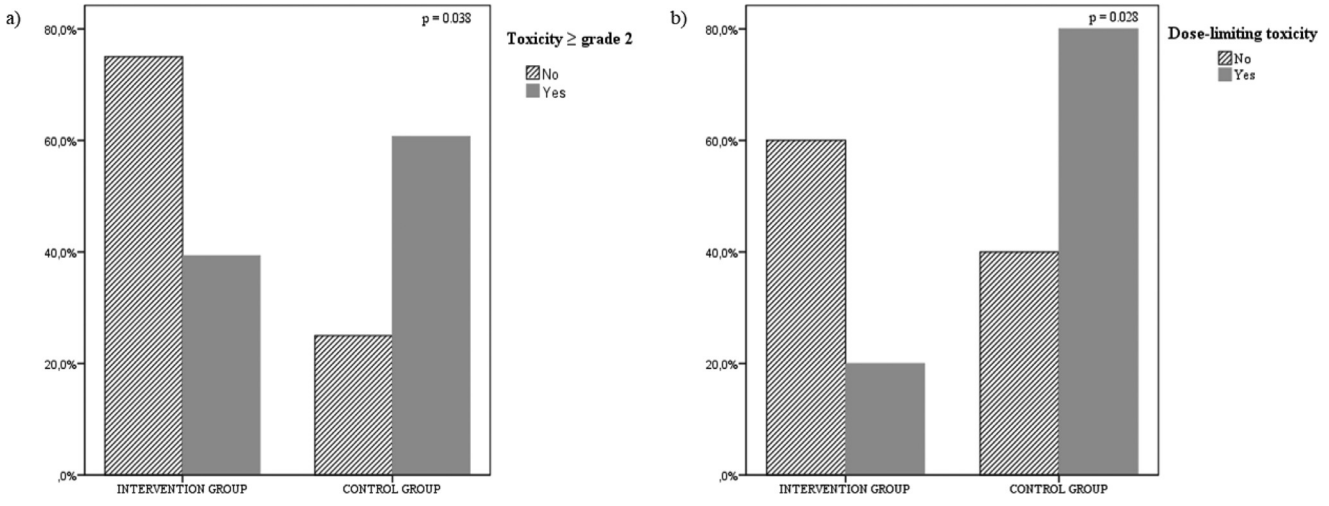

Fig. 3. Incidence of chemotherapy toxicity in the control and intervention groups: (**a**) toxicity grade ≥2 and (**b**) dose-limiting toxicity.

suggest a protective role of omega-3 with regards to SM quality during cancer treatment.

The mechanisms by which ω-3 alters the quality of SM remain unclear, but the ability of this nutrient to suppress lipogenesis, reduce the deposition of free FAs in the muscle, and stimulate its oxidation has been suggested [19,43,46]. In an experimental study simulating the chemotherapeutic treatment for colon cancer, supplementation with ω-3 significantly reduced the fat content in SM after antineoplastic treatment. The authors noted that this reduction may be associated with lower expression of transcription factors involved in adipogenesis and lipogenesis [43].

Regarding treatment toxicity, a high incidence of toxicity of grade 2 or higher was observed in both groups, however, patients in the IG presented a significantly lower incidence when compared with those in the CG. Similar results were found in the literature, where supplementation with EPA reduced symptoms associated with chemotherapy, improving tolerance to cancer treatment [47,48]. Additionally, 80% of the women who presented DLT were from the CG. Because changes in body composition, especially SM, may influence the occurrence of greater toxicity to chemotherapy [10,12], weight preservation and the high-radiodensity muscle preservation in the ω-3–supplemented group may justify the positive results observed in this population.

This study had some limitations. The first is related to adherence to supplementation, which directly influences the outcome of intervention efficacy. Low adherence to intervention protocols has been indicated as one of the main limiting factors of nutritional intervention studies in patients with cancer [40]. The low socioeconomic level of the present study population, which was previously expected as a characteristic of cervical cancer patients living in developing countries, affects directly the acquisition of foodstuffs, and may have been the main cause for the reduced SMI in both groups.

Despite this limitation, we reinforce that RCTs evaluating the efficacy of ω-3 supplementation in more diverse populations are needed. Although the comparison with other studies carried out in populations with high purchasing power and high educational levels should be done with caution, our results, especially the maintenance of HRSMI, indicate the potential benefits of ω-3 supplementation in patients with cancer.

The strengths of the study include those related to the methodology developed: randomized, triple-blinded and placebo-controlled clinical trials, as well as the use of CT as a method of determining body composition. The use of an innovative methodology for the evaluation of SM provided additional results as it was possible to more clearly identify how the loss or gain of SM between the IG and CG occurred.

Conclusion

Supplementation with ω-3 resulted in maintenance of body weight and improvement of symptoms with an effect on NS. Although there was a significant loss of SM in both groups, there was an increase in LRSMI area and loss of HRSMI among the CG patients and maintenance of these parameters in the IG, suggesting a protective role of ω-3 on SM quality during cancer treatment. Additionally, supplementation with 2.5 g/d of ω-3 for 45 d, concomitant with chemoradiotherapy treatment, significantly reduced the occurrence of toxicity in patients with cervical cancer. Finally, additional clinical trials are recommended to evaluate other important outcomes in cancer patients, such as treatment discontinuation and survival.

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