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

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Highlights

- First randomized controlled trial with omega-3 supplementation in cervical câncer;
- We used an innovative methodology for skeletal muscle quality assessment;
- The results suggest a protective role of omega-3 in skeletal muscle quality;
- Omega-3 supplementation significantly reduced the chemorradiotherapy toxicity.

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TITLE PAGE

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

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Abstract

Background & Aims: Omega-3 supplementation has shown to favor the preservation of body weight and skeletal muscle (SM). The aim was to evaluate the efficacy of omega-3 supplementation on nutritional status (NS), SM quantity and quality; and toxicity for treatment of women with cervical cancer. **Methods:** 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 (IG) received 4 capsules with omega-3 (2.5g/day) and the control group (CG) received the same number of capsules, identical, with olive oil, for 45 days. NS was measured by anthropometry and Patient-Generated Subjective Global Assessment (PG-SGA). Body composition was assessed by computed tomography. The skeletal muscle index (SMI) was calculated using the range -29 to +150 Hounsfield Units (HU). For SM quality, the area comprised between -29 to +29HU was denominated low-radiodensity skeletal muscle index (LRSMI) and the range between +30 to +150HU high-radiodensity skeletal muscle index (HRSMI), representing the SM area with high or low intramuscular fat infiltration,

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respectively. **Results:** The study population comprised 40 patients, with an average age 44.53 ± 8.73. IG maintained body weight and showed an improvement in PG-SGA score. A significant reduction in SMI was observed in both groups. However, in regard to SM quality, IG patients preserved LRSMI and HRSMI, while GC gained LRSMI and significantly reduced HRSMI, reflecting high intramuscular fat infiltration only in the CG. The incidence of chemotherapy toxicity was significantly lower in IG. **Conclusions:** The results suggest that omega-3 supplementation is effective in maintaining NS, SM quality and reduced symptoms of chemoradiotherapy among women with cervical cancer.

Keyword: Cervical cancer; Computed tomography; Body composition; Nutritional status; Omega-3; Skeletal muscle

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 roughly 85% of the cases [1], most of them 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 are often 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 chemoradiotherapy treatment [8,9]. Loss of weight, as well as skeletal muscle (SM), is associated with unfavorable oncologic outcomes, such as the higher risk of toxicity and shorter survival [10–12].

The quality of SM has also been associated with worse outcomes in cancer patients [13,14]. This can be evaluated by different methods, but computed tomography (CT) has

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been gaining prominence in the last decade because it is a commonly performed exam in this population [15], and is also able to assess the quality of SM by a radiological measurement of muscle density [16].

Intervention strategies are essential to avoid worsening nutritional state (NS) during oncological treatment, such as omega-3 supplementation which has shown to be promising, favoring the preservation of body weight and SM [17–20]. Furthermore, it has been suggested that omega-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 omega-3 supplementation, few clinical trials have been developed in humans. Studies report the potential benefit of omega-3 supplementation in cancer patients 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 skeletal muscle [17]. An improvement in short-term survival was also described in lung cancer patients [20].

However, the studies available to date have some methodological limitations, such as: 1. use of electrical bioimpedance to determine body composition, which has low accuracy and reproducibility in cancer patients [26]; 2. lack of sample size calculation, blinding and randomization; and 3. use of hypercaloric and high-protein industrialized oral supplements, enriched with other antioxidant nutrients other than omega-3.

We hypothesized that omega-3 supplementation could reduce muscle loss and prevent fat infiltration in muscles among cervical cancer patients submitted to chemoradiotherapy treatment. Based on this, the objective of the present study was to

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evaluate the efficacy of omega-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 undergone chemoradiotherapy.

Materials and Methods

Data collection

This is a triple-blind, placebo-controlled, randomized controlled trial (RCT), in which women enrolled at the National Cancer Institute of Brazil, aged 19-59, with cervical cancer, never-treated and who undergone curative chemoradiotherapy during the period of March 2016 and July 2017. Patients with human immunodeficiency virus and those with renal disease under dialysis were excluded from the study, in addition to those without oral feeding conditions and with malabsorption disorders. Elderly were excluded to discard the age-related decline in skeletal muscle 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. The selection of this tool considered its high sensibility and specificity in detecting nutritional risk in oncologic patients [27].

The project was approved by the National Cancer Institute José de Alencar Gomes da Silva Research Ethics Committee, under protocol nº1.150.108 and participation of the patients required signing of the informed consent form. The study was conducted according to recommendations of the CONSORT (Consolidated Standards of Reporting Trials) and the flowchart of patients eligible for the study is described in Figure 1. The study is also recorded in the Clinical Trials database (www.clinicaltrials.gov) under the number NCT02779868.

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The primary outcomes were the mean changes in the SM quantity and quality before and after omega-3 supplementation. The secondary outcomes were the incidence of adverse events during chemotherapy, as well as the mean differences in polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) serum concentration 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 omega-3 intervention in the study conducted by Murphy et al. (2011) [20]. Considering a two-tailed test at a significance level of 5% and a power of 80%, 28 participants were required, 14 in each group.

The patient´s allocation in the control group (CG) or 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 about 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: the IG was instructed to take four capsules per day, totaling 2.5g of omega-3, of which 2g is EPA and 450mg is DHA; and the CG was advised to take the same number of capsules, which were identical to those of the IG but contained only olive oil. The supplements used are registered with the Ministry of Health under the numbers 6.6981.0038.001-1 (Supra Ômega

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50 EPA/10 DHA Global Suplementos) and 6.6981.005.001-1 (Azeite de Oliva Extravirgem 1000MG 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 calories and 16 grams of protein per day. The supplementation occurred for 45 days, 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 by means of a digital platform scale (Filizola®) and for height, a stadiometer coupled to the same scale was used.

The validated Portuguese version of the PG-SGA was used [30], which classifies the 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 nutritional status [31].

The classification of cancer cachexia followed the recommendations of the international consensus proposed by Fearon et al. (2011) [32]: 1) pre-cachexia, when there was weight loss of up to 5% in six months and presence of anorexia; and 2) cachexia, when weight loss was greater than 5% in 6 months, or a combination of weight loss >2% with a BMI of less than 20 kg/m^2.

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Body composition by computed tomography

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 up to 20 days 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 parameters followed the same parameters, in order 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 by Mitsiopoulos et al. (1998) [33]. The cross-sectional area representative of SM (-29 to +150 Hounsfield Unit - HU) was normalized by the height squared and denominated skeletal muscle index (SMI, cm^2/m^2). SMI $\leq$ 38.9 cm^2/m^2 was used to classify sarcopenia, as per the cut-off point established for women [34]. In order to estimate the total body content of fat-free mass and fat mass, the regression equations developed by Mourtzakis et al. (2008), expressed in kg and later normalized by the height squared, were used to generate the variables fat-free mass index (FFMI, kg/m^2) and fat mass index (FMI, kg/m^2), respectively [34].

The SM quality was determined using the method proposed by Paula et al. (2018) [35]. This method divides the total density range of SM into two sub-ranges. 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

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radiodensity skeletal muscle index (HRSMI, cm^2/m^2). To evaluate the SM quality, the average skeletal muscle 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-day 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 to those recommended for cancer patients, which is, according to the European Society of Parenteral and Enteral Nutrition (ESPEN) 25 kcal/kg and 1.2 g/kg/day, respectively [18].

The capsules intake of the placebo/omega-3 was evaluated weekly until completion of the 45 days of supplementation. At the end of the chemoradiotherapy, in the T1 appointment, 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 to 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 $40mg/m^2$, for five or six consecutive weeks, 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 in two moments: in the middle of cancer treatment (third chemotherapy cycle) and at the end of

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supplementation (T1). Dose-limiting toxicity (DLT) was defined as any serious adverse event which resulted in discontinuation, delayed treatment or the need for a chemotherapy dose reduction [12].

Analysis of plasma long-chain polyunsaturated fatty acids (LCPUFA)

Blood was collected in heparinized tubes, centrifuged and immediately stored at -80°C until analysis. The LCPUFA contents of the samples were analyzed by gas chromatography using an Agilent Technologies 7890A CG System equipped with a flame ionization detector coupled to the program EZChrom Elite CDS (Agilent Technologies, Inc., C.A., U.S.A.). The methyl esters of FA were obtained by the direct alkaline methylation method AOCS 2b-11 (adapted) and then separated in a SP-2560 fused silica capillary column of bis-cyanopropyl polysiloxane (Supelco Inc., PA, USA). The injector and detector temperatures were 250ºC. 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., methyl esters mixture 463). FAs were then expressed in amount (μg/mL) and percentage of total fatty acids.

Data analysis

Statistical analysis was performed with the aid of the statistical program Statistical Package for Social Sciences, version 22.0, SPSS (IBM, Chicago-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 and standard deviation, and proportions

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for the categorical variables. Associations between the categorical variables were analyzed using the chi-square test ($\chi 2$) 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 the 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) x 100. The percent change in LRSMI was later classified in distribution quartiles to categorize the percent loss or gain.

The macronutrients 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, the 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 roughly 60% of the women had cachexia and 25% sarcopenia. No significant difference was observed between groups prior to chemoradiotherapy treatment for any sociodemographic, clinical and nutritional status variables (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 intervention, 70% of women met this criterion, being 13 and 15 patients in the CG and IG, respectively.

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Significantly higher intakes of energy, protein, and lipids (calories/day) were observed in the control group. 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 statistical difference between the groups (Chi-square test, $p = 0.449$ and $p = 0.704$). In relation to plasma concentrations of the long chain polyunsaturated fatty acids EPA and DHA, there was a statistically significant increase of both fatty acids 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, while the IG did not present significant variation in these parameters. In addition, a significant improvement in PG-SGA scores was observed only in the group receiving omega-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 IG and CG. 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 omega-3 supplementation. On the other hand, in the CG there was a significant reduction of HRSMI and increase in LRSMI after treatment. In the intergroup analysis, a significant difference was observed only for LRSMI, with a trend towards significance for the HRSMI (Table 5).

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The percentage of LRSMI alteration after cancer treatment was classified in distribution quartiles to assess the magnitude of intramuscular fat infiltration (Figure 2). LRSMI values below the 1st 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 3rd 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 of 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), the IG presented a significantly lower incidence of anorexia, nausea, dry mouth and dysgeusia symptoms (Table 6). Among patients with high compliance o supplementation, the results were similar and are described in a Supplementary Table 1.

A significant association was found for the presence of moderate to severe toxicity and DLT between the intervention and control groups (Figures 3), patients supplemented with omega-3 had significantly lower DLT. It should be noted that 80% of patients with DLT belonged to 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-blind study

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design is considered the gold standard method for evaluation of nutritional interventions. However, as the majority of the RCTs testing the efficacy of the omega-3 intervention in cancer patients are conducted in high-income countries, we emphasize that is extremely important to obtain data in other populations. 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 treatment in Brazil, which treats roughly 80% of the cases of gynecological cancers in the state of Rio de Janeiro.

The most recent recommendations suggest that supplementation with omega-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 (PIF) synthesis, which in turn reduces skeletal muscle proteolysis [19,39].

We found an increase in plasma EPA and DHA concentrations after oral supplementation with omega-3. There was also a significant reduction of the *PG-SGA* score and maintenance of body weight 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 cancer patients, there are no studies in the literature that have used this tool in omega-3 intervention studies to date. Clinical trials evaluating the effect of omega-3 on the body weight of lung and gastrointestinal cancer patients 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,

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while the CG received a normocaloric and normoprotein supplement, the supplements offered to the IG presented high-calorie and high-protein characteristics, enriched with omega-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 omega-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 the quality of SM, which indirectly reflects the degree of muscle fat infiltration [16,43]. To date, only one study has used CT to evaluate the effects of omega-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 our study, which found a significant reduction of the SMI and average muscle radiodensity in both groups.

The significant reduction of the SMI in both groups can be explained in part by the low socioeconomic level of the studied population, which was probably a determining factor for the inadequacy of food intake. It should be noted that approximately only half 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 intervention due to the patients' low understanding and adherence to the instrument.

However, when we evaluated the 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. These sub-ranges have determined a stronger association with worse outcomes in women with

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gynecological cancer [35,45], but this was the first time that the methodology was used to evaluate a nutritional intervention.

Using the sub-ranges approach, our data presented important differences. Interestingly, LRSMI maintenance was observed 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 patients with optimal adherence to supplementation this result was even more important since both the maintenance of high radiodensity SM and preservation of intramuscular infiltration in the IG were found. Thus, the results suggest a protective role of omega-3 with regards to SM quality during cancer treatment.

The mechanisms by which omega-3 alters the quality of SM remain unclear, but the ability of this nutrient to suppress lipogenesis, reduce the deposition of free fatty acids 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 omega-3 significantly reduced the fat content in SM after the 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 equal to or greater than grade 2 was observed in both groups, however, the IG presented a significantly lower incidence when compared to the CG. Similar results were found in 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

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high-radiodensity muscle preservation in the omega-3 supplemented group may justify the positive results observed in this population.

This study has 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 cancer patients [40]. The low socioeconomic level of our 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 omega-3 supplementation in more diverse populations are needed. Although the comparison with the other studies carried out in populations with high purchasing power and high educational level should be done with caution, our results, especially the maintenance of HRSMI, indicate the potential benefits of omega-3 supplementation in cancer patients.

The strengths of the study include those related to the methodology developed: randomized, triple-blind 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 since it was possible to more clearly identify how the loss and/or gain of SM between the IG and CG occurred.

In conclusion, omega-3 supplementation resulted in maintenance of body weight and improvement of symptoms with impact 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 omega-3 on the SM quality during cancer treatment. In addition, supplementation with

2.5g/day of omega-3 for 45 days, 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.

Conflict of Interest Statement

The authors declare that they have no conflict of interest to be stated.

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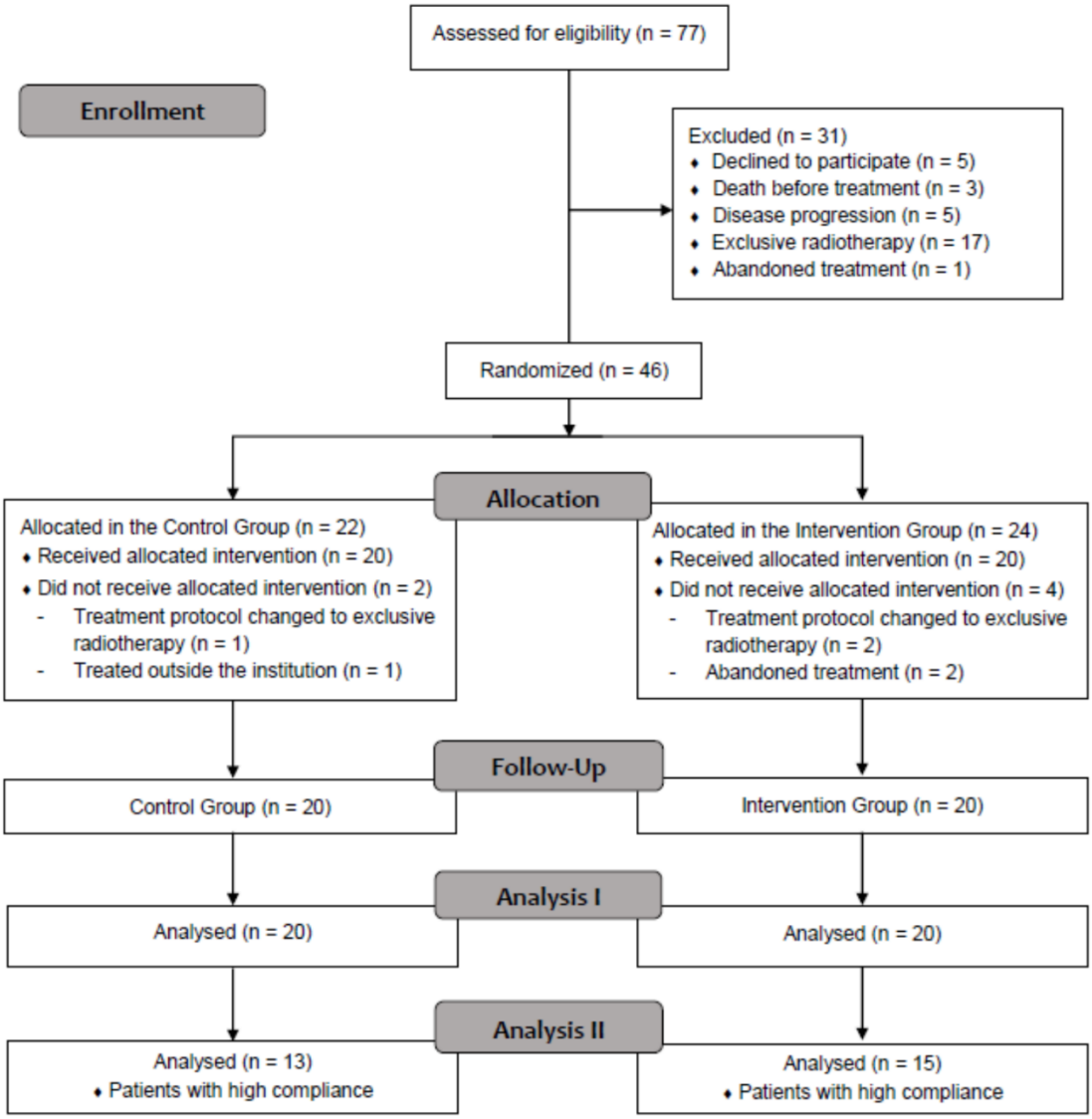

Figure 1. Flow diagram of the randomized controlled trial.

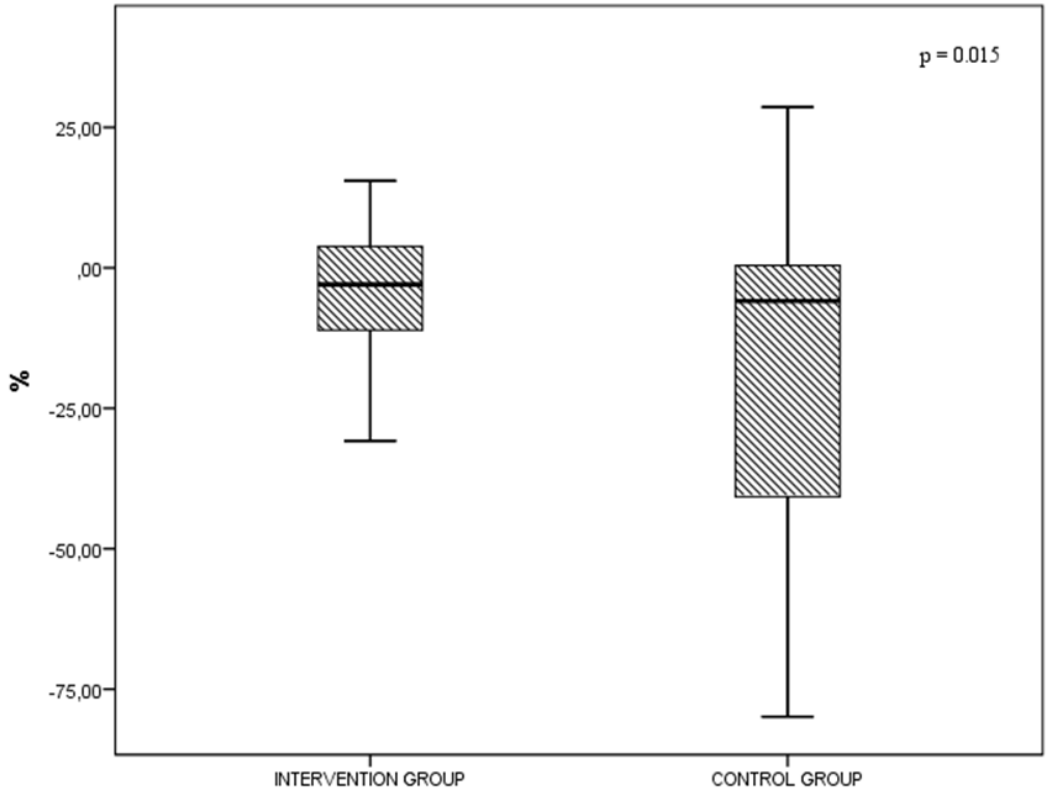

Figure 2 – Quartiles distribution of the percentage of low radiodensity skeletal muscle index (LRSMI) after treatment between the control and intervention groups.

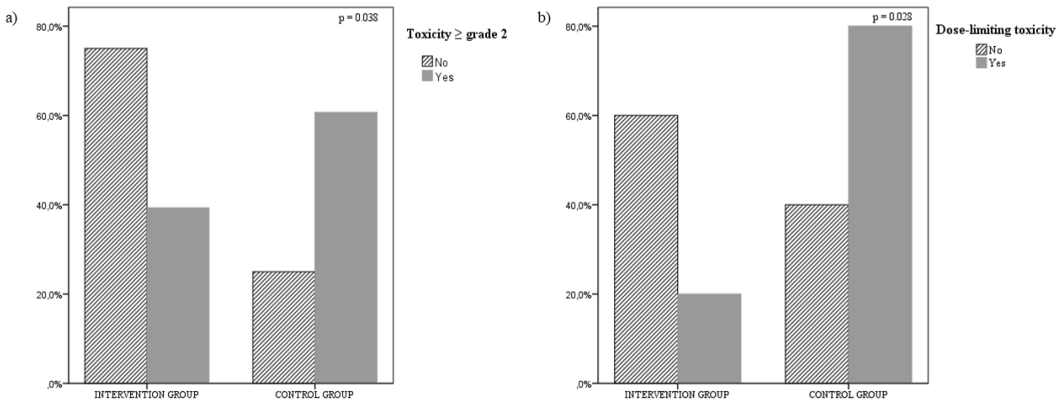

Figure 3. Incidence of chemotherapy toxicity in the control and intervention groups: **a)** toxicity ≥ grade 2 and **b)** dose-limiting toxicity.

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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 (years)[a]	44.53 ± 8.73	43.90 ± 7.88	45.14 ± 9.67	0.657
Marital Status[b]				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 [b]				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 (years)[b]				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[b]				
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 [b]				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%)	

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Stage [§,b]				0.762
II	23 (57.5%)	12 (60%)	11 (55%)	
III	17 (42.5%)	8 (40%)	9 (45%)	
Histologic type [b]				0.486
SCC	36 (90%)	17 (85%)	19 (95%)	
Adenocarcinoma	4 (10%)	3 (15%)	1 (5%)	
Weight (kg)[a]	66.49 ± 15.39	66.99 ± 16.29	65.98 ± 14.83	0.839
BMI (kg/m^2)[a]	26.54 ± 5.71	26.15 ± 6.02	26.92 ± 5.52	0.674
BMI category [b]				
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 [b]				
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 [a]	13.62 ± 7.04	15.30 ± 7.94	11.95 ± 5.64	0.134
Classification of cachexia				0.337
Pre-cachexia	17 (42.5%)	10 (50%)	7 (35%)	
Cachexia	23 (57.5%)	10 (50%)	13 (65%)	
Sarcopenia[b]				
No	30 (75%)	13 (65%)	17 (85%)	0.273
Yes	10 (25%)	7 (35%)	3 (15%)	

SCC = squamous cervical cancer; ; § = Staging according to the International Federation of Gynecology and Obstetrics – FIGO; BMI = Body Mass Index; PG-SGA = Patient-Generated Subjective Global Assessment; Sarcopenia = cut-off point established for women by Mourtzaki et al. (2008): ≤ 38.9 cm^2/m^2; a = mean and standard deviation, T Test; b = absolute number (percentage), chi-square test (χ2); *Statistical analysis between control and intervention groups.

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Table 2 - Comparison of dietary intake at baseline

Characteristics[a]	Total n = 28[b]	Control group n = 14	Intervention Group n = 14	p-value*
Energy (Kcal/dia)	1473.8 (1209.72 – 1892.21)	1.829.2 (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/dia)				
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**
Macronutrientes (g/kg/dia)[c]				
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

a = median (25^{th}-75^{th} percentile); b = total number of patients who responded to the 3-day food registry; b = total amount in grams of protein, carbohydrate and lipids normalized by the body weight of each individual, in kg, at T0; *Statistical analysis between control and intervention groups, Non-parametric Mann-Whitney test.

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Tabela 3 – Plasma phospholipid, eicosapentaenoic acid and docosahexaenoic acid in the control and intervention groups at baseline and after omega-3 supplementation[a]

	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[a]	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, %[a]	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[b]	2,15±0.85	2.35±0.81	0.305[**]	2.14±0.95	2.35±0.88	**0.012**[**]
Proportion of DHA, %[b]	1.27±0.54	1.28±0.34	0.306[**]	1.21±0.41	1.40±0.41	**0.012**[**]

[a] Results are shows as median (25^{th}-75^{th} percentile); [b] Results are shown as mean ± standard deviation; [*]Wilcoxon test; [**]paired sample T-test.

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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*	**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*	**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*	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*	**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*	**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*	**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*	**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*	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*	**0.000**		**0.000**		

BMI = Body Mass Index; PG-SGA = Patient-Generated Subjective Global Assessment; SMI = skeletal muscle index; HRSMI = high radiodensity skeletal muscle index; LRSMI = low radiodensity skeletal muscle index; FMI = fat mass index; FFMI = fat-free mass index. Δ = mean difference between T1 and T0; p value* = Dependent T-test between the same group; p-value** = Two independent samples T-test between the different groups.

Table 5 - Comparison of nutritional status and body composition parameters between the 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*	**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*	**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*	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*	**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*	**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*	**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*	**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*	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*	**0.000**		**0.000**		

BMI = Body Mass Index; PG-SGA = Patient-Generated Subjective Global Assessment; SMI = skeletal muscle index; HRSMI = high radiodensity skeletal muscle index; LRSMI = low radiodensity skeletal muscle index; FMI = fat mass index; FFMI = fat-free mass index. Δ = difference between T1 and T0; p value* = Dependent T-test between the same group; p-value** = Two independent samples t-test between the different groups.

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

Adverse events[a]	Middle of treatment (3rd 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						
< 2	16 (80)	17 (85)	0.256	17 (85)	16 (80)	0.677
≥ 2	4 (20)	3 (15)		3 (15)	4 (20)	
Arthralgia /Myalgia						
< 2	16 (80)	19 (95)	0.151	16 (80)	17 (85)	0.667
≥ 2	4 (20)	1 (05)		4 (20)	3 (15)	
Asthenia						
< 2	17 (85)	16 (80)	0.677	14 (70)	16 (80)	0.465
≥ 2	3 (15)	4 (20)		6 (30)	4 (20)	
Gastrointestinal symptoms						
Anorexia						
< 2	11 (55)	14 (70)	0.327	12 (60)	16 (80)	**0.049**
≥ 2	9 (45)	6 (30)		8 (40)	4 (20)	
Nausea						
< 2	12 (60)	15 (75)	0.091	10 (50)	16 (80)	**0.047**
≥ 2	8 (40)	5 (25)		10 (50)	4 (20)	
Vomiting						
< 2	16 (80)	19 (95)	0.151	14 (70)	16 (80)	0.465
≥ 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)	

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Diarrhea						
< 2	16 (80)	15 (75)	0.723	12 (60)	15 (75)	0.311
≥ 2	4 (20)	5 (25)		8 (40)	5 (25)	
Dry mouth						
< 2	17 (85)	19 (95)	0.098	15 (75)	19 (95)	**0.005**
≥ 2	3 (15)	1 (05)		5 (25)	1 (05)	
Dysgeusia						
< 2	16 (80)	15 (75)	0.723	12 (60)	18 (90)	**0.028**
≥ 2	4 (20)	5 (25)		8 (40)	2 (10)	

a = Adverse Events to the chemoradiotherapy treatment was performed according to the Common Toxicity Criteria for Adverse Events (CTCAE/NCI), version 4.0 and subdivided into two groups: < grade 2 and ≥ grade 2; *Statistical analysis between control and intervention groups, chi-square test ($\chi 2$);