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Nutritional impact of eicosapentaenoic acid supplementation (EPA) in patients with locally advanced head and neck cancer: a double-blind placebo-controlled randomized trial

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Abstract

Background Evidence on the benefits of eicosapentaenoic acid (EPA) supplementation in cancer patients remains inconsistent, likely due to heterogeneity in tumor types, stages, treatment modalities, and nutritional strategies. This study aimed to assess the impact of EPA as a standalone supplement on body weight, body mass index (BMI), and muscle mass preservation in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) undergoing curative-intent treatment.

Methods We conducted a double-blind, placebo-controlled randomized trial between December 2015 and September 2018, enrolling 54 patients with advanced SCCHN. Participants received either 2.7 g/day of oral EPA or placebo, alongside standard nutritional support according to European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines. Assessments were performed at baseline (T0), post-induction chemotherapy (T1), and post-treatment (T2), including body composition, nutritional status, functionality, and inflammatory biomarkers. Plasma EPA (% of total fatty acids) was used as a biochemical marker of compliance.

Results Both groups were balanced at baseline (median age 58.9 years; 46.3% malnourished). Neither the intention-to-treat nor per-protocol analyses showed statistically significant differences between groups in weight loss, BMI, or body composition ($p > 0.05$). In the per-protocol analysis, estimated mean weight loss was −3.81 kg (95% CI: −5.70 to −1.91) in the EPA group, compared to −7.72 kg (95% CI: −12.8 to −6.40) in the placebo group. No differences were observed in nutritional status, energy or protein intake, physical function, or treatment-related toxicity. Complete response rates after oncological treatment were comparable (77.8% EPA vs. 66.7% placebo). Only half of the patients in the EPA group reached an increase in plasma EPA levels consistent with supplementation, and 31.5% discontinued the intervention due to intolerance.

Conclusions Our study did not demonstrate a clear benefit of EPA supplementation on weight, BMI, or muscle preservation in patients with locally advanced SCCHN receiving curative-intent treatment. While EPA was safe and

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feasible, the findings do not provide sufficient evidence to support a clinically significant effect. Further research with larger sample sizes and more robust designs is warranted to better understand the potential role of EPA in this population.

Trial registration ClinicalTrials.gov identifier: NCT02715596 (registered on March 22, 2016 at ClinicalTrials.gov).

Keywords Eicosapentaenoic acid, EPA, Head and neck cancer, Muscle mass, Weight loss, Nutritional intervention

Introduction

Reduced skeletal muscle mass is a known negative prognostic factor in cancer patients [1]. Weight loss has also been associated with decreased cancer survival [2]. In patients with squamous cell carcinoma of the head and neck (SCCHN), both weight loss and low muscle mass have been associated with chemotherapy dose-limiting toxicity [3, 4], late toxicity after radiotherapy [5] and reduced overall and progression-free survival [6]. Nutrition impact symptoms (i. e. symptoms that impair oral intake, such as odyno-dysphagia or anorexia) and severe treatment-related toxicity significantly affect nutritional status in this population [7, 8]. In patients with locally advanced SCCHN, induction chemotherapy may help alleviate initial nutritional impact symptoms and prevent further deterioration [8, 9]. However, during chemoradiation a significant decline of the nutritional status, particularly in muscle and adipose tissue, has been consistently reported, even with nutritional support [10–12]. Malnutrition affects approximately 42% of head and neck patients at diagnosis and increases to up to 77% during treatment [13, 14].

Several translational studies have demonstrated the role of inflammation in cancer-associated weight loss and muscle wasting. Omega-3 fatty acids have been suggested to reduce inflammation in cancer patients [15, 16] potentially contributing to improved body weight and muscle prevention. Eicosapentaenoic acid (EPA), a polyunsaturated fatty acid of the omega-3 class, can be rapidly incorporated into the cell membranes, contributing to metabolic regulation. Various small studies and randomized trials have assessed the effects of EPA or omega-3 supplementation across different cancer types and treatment settings. However, findings remain inconsistent regarding effects on weight loss, body composition and inflammatory biomarkers. A recent systematic review reported a positive effect in body weight in favour of omega-3 supplementation, but no effect on circulating inflammatory markers [17]. Another review concluded that EPA and/or docosahexaenoic acid (DHA) supplementation could help maintain or increase body weight, improve progression-free and overall survival, enhance quality of life, modulate immune parameters, and reduce serious adverse events [18]. Both reviews agreed that further studies are needed to clarify the role of EPA and omega-3 fatty acids during cancer treatment.

In HNC patients, most clinical trials have evaluated omega-3 fatty acids as components of commercial polymeric nutritional supplements [15, 16, 19–22]. A recent study [23] found that fish oils capsules were better tolerated than nutritional drinks with equivalent omega-3 content. To date, no study has evaluated the effect of EPA as a single-agent supplement, combined with an intensive nutritional intervention throughout the entire course of oncological treatment.

Thus, the aim of this study was to investigate whether EPA supplementation could have a positive effect on body weight, BMI and body composition in patients with locally advanced SCCHN undergoing a standardized curative-intent treatment protocol.

Methods

Study design and objectives

This randomized, double-blind placebo-controlled clinical trial (NCT02715596) assigned patients to receive either an EPA supplement or a placebo, using a block randomization method. All patients provided written informed consent prior to enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was approved by the Ethics Committee for Clinical Research at Hospital Universitari de Bellvitge (PR261/14). The primary objective was to evaluate the potential beneficial effect of EPA supplementation on body weight, BMI and body composition. Secondary outcomes included EPA compliance, changes in nutritional status, functionality, treatment-related toxicity and inflammatory biomarkers including C-reactive protein (CRP), serum albumin, interleukin- 6 (IL-6) and neutrophil-to-lymphocyte ratio (NLR).

Patients and oncological treatment

Since cancer stage, treatment toxicity and response are closely related to progressive muscle and fat loss over time [24], we focused on a homogeneous treatment plan for patients with locally advanced SCCHN, who typically present with nutritional impact symptoms. To ensure cohort consistency, we excluded other treatment approaches as surgery and early-stage disease. Eligible patients were ≥ 18 years old and diagnosed with stage III–IVa,b SCCHN (7th TNM edition). All were scheduled to receive curative-intent treatment consisting of induction chemotherapy followed by chemoradiotherapy (CRT) or radiotherapy (RT) plus

cetuximab, according to local clinical guidelines [25]. Additional inclusion criteria required pathologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx, with no prior history of recurrent disease.

The induction chemotherapy regimen (Fig. 1) was based on the TPF scheme: Taxanes, Platinum and 5-Fluorouracil [26]. For the subsequent radiotherapy phase, patients received either cisplatin (100 mg/m^2 every 21 days) [27] or cetuximab (250 mg/m^2 weekly, with a 400 mg/m^2 loading dose) [28], administered concurrently with intensity-modulated radiotherapy (IMRT) at a total dose of 69.96 Gy (2.12 Gy per session). Assignment to CRT or RT plus cetuximab was determined by the multidisciplinary head and neck tumor board, based on individual treatment response and/or toxicity during induction chemotherapy [29].

Study products and compliance

Patients were instructed to take one stick pack daily from the first day of chemotherapy and continuing throughout the entire treatment period (i.e. induction chemotherapy followed by CRT or RT plus cetuximab). Those in the intervention group received 2.7 g/day of EPA in liquid stick-pack format, while the placebo group received 2.7 g/day of mineral oil, matched in colour and odor to the EPA product. Given the poor compliance reported in previous studies [30, 31], a liquid formulation was chosen to enhance adherence, particularly in HNC patients who often experience swallowing difficulties. Both EPA and placebo supplements were manufactured, blinded, and supplied by Ferrer SA (Spain). The manufacturer had no access to the study results and did not influence the study's design or conclusions. The EPA formulation did not contain DHA.

Compliance was assessed at each chemotherapy cycle by tracking the number of stick packs distributed, returned and the corresponding dates. In addition, plasma EPA levels were used as a biochemical marker of compliance. Total lipids were extracted from plasma samples, and fatty acid methyl esters (FAMEs) were analyzed by gas chromatography (GC). Results were expressed as the proportion of EPA relative to total identified plasma fatty acids (relative percent).

Assessments

Body weight, BMI and body composition were assessed before starting the oncological treatment (T0), after the induction chemotherapy (T1) and two months following completion of RT (T2). BMI was also calculated as [(weight (kg)/height (m^2)] and categorized according to WHO standards.

All patients underwent an abdominal computed tomography (CT) scan prior to treatment and again approximately two months completing RT (i.e. an overall span of 7–8 months), as part of routine clinical practice. The third lumbar vertebra (L3) on axial cross-section images was used as the reference point for analysis, following established methodology [32–34]. Skeletal muscle and adipose tissue areas were determined using SliceOmatic© software (v5.0 Rev 8, Tomovision, Magog, Canada), applying standard Hounsfield Unit (HU) ranges: −29 to + 150 HU for skeletal muscle, −150 to −50 HU for visceral adipose tissue (VAT), −190 to −30 HU for subcutaneous adipose tissue (SAT). Cross-sectional areas were normalized for height and reported as skeletal muscle index (SMI, cm^2/m^2) and total adipose tissue index (TATI, cm^2/m^2, including SAT and VAT) [34–36]. Analyses were performed by a single observer blinded to clinical data, with precision of ± 0.92 cm^2 for skeletal muscle area and ± 1.37 cm^2 for total adipose tissue area.

Nutritional data included baseline height, percentage of weight loss in the 3 months prior to induction chemotherapy, current weight, nutritional status

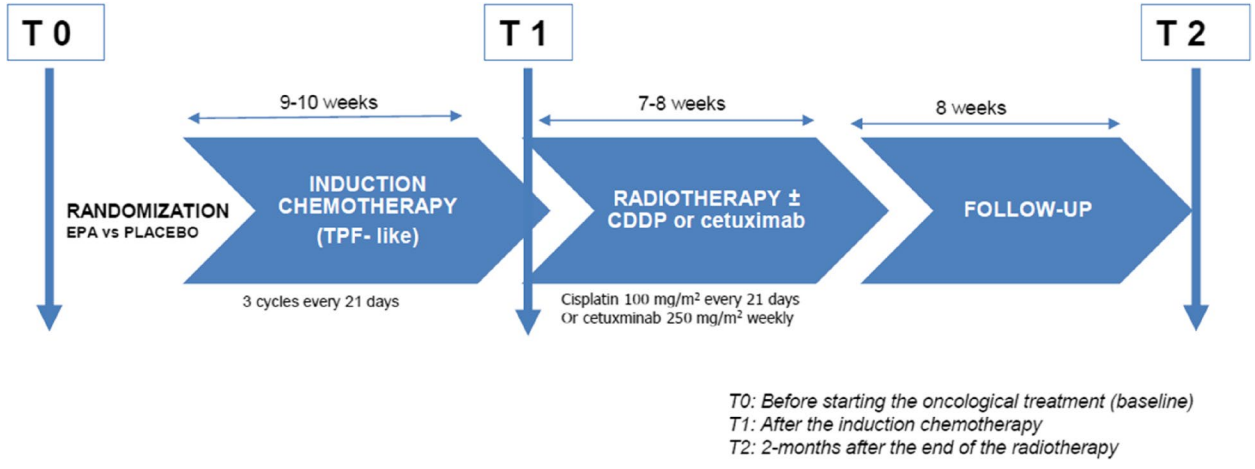

Fig. 1 Oncological treatment plan

(Patient-Generated Subjective Global Assessment, PG-SGA) [37, 38], and the type of nutritional support at each time point. Energy and protein intake were estimated via 24-h dietary recall using Dietsource© software (v3.0, InterCath, Spain), and expressed in kcal/day and g/day.

Inflammatory markers were assessed through routine laboratory testing. Albumin and CRP were used to calculate the Glasgow Prognostic Score (GPS) [39]; the NLR was derived from complete blood counts [40]. Interleukin-6 (IL-6) was measured using a human cytokine-specific ELISA kit (Biosource Europe, Belgium), following the manufacturer's instructions.

Functional status was assessed via handgrip strength, using a hydraulic dynamometer (SI Instruments Pty Ltd, Adelaide, Australia). The test was performed on the dominant hand, with the patient seated, shoulder in adduction and neutral rotation, and elbow flexed at 90º, always using the same hand [41].

Additional data were collected on nutrition impact symptoms and treatment-related toxicity, classified according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [42].

Sample size calculation

To determine the sample size, we considered the objective of the study to evaluate the effect of EPA supplementation, comparing two groups: one supplemented and one control. The expected mean relative weight loss from baseline (T0) in the control group was −10% and −3% in the supplemented group. Assuming a standard deviation (SD) of 9, with a significance level of 5% and a power of 80%, 54 patients were needed (27 per group) to find statistically significant differences between the two groups.

Statistical analyses

Descriptive statistics of baseline characteristics in the EPA and placebo participants were reported. The coprimary end points were the percentage change in weight and body composition from T0 and the absolute weight and body composition change from T0. Intention-to-treat (ITT) analyses as well as per-protocol (PP) analyses were conducted for outcomes of weight and body composition. Based on the ITT principle, all participants who were randomized were included in the analysis, regardless of protocol compliance. Per-protocol analysis compared intervention groups that included only those patients who completed the intervention.

The percentage of change from baseline in weight and body composition outcomes were assessed using an analysis of covariance model (ANCOVA) adjusted for age, sex, malnutrition. Each ANCOVA model further comprised the baseline variable of the respective outcome at T0. The dynamics estimations in weight and body composition outcomes at each time point were obtained from linear mixed models (LMM) including intervention group and time as fixed factors, a group x time interaction term and a random intercept for subject. LMM were adjusted for age, sex and malnutrition, and each model further comprised the baseline variable of the respective outcome at T0. In the LMM models, p-values for the T2 vs T0 comparisons within groups were obtained using Tukey's method for multiple post-hoc comparisons between time and group. All results will be reported as mean and 95% confidence interval (CI), adjusted for the previously mentioned covariates.

In the ITT analysis, missing data due to noncompliance or dropout were imputed using the Reference-based multiple imputation method with the *jump to reference* (J2R) approach [43], with $n = 100$ imputations. The R package RefBasedMI [44], was used to build separate imputation models to each end point outcome and to generate imputed data considering multiple imputation under the assumption that, after dropout, participants in the EPA group no longer receive intervention and behave like those in the placebo group following their last observed time point. For the ANCOVA models, the transformation into percentage change in weight and body composition was performed later. The estimated marginal means (EMMs) were obtained using the R package emmeans [45].

The validity of PP effect estimates required correct adjustment for confounding due to incomplete adherence to the assigned interventions [46]. The Inverse Probability Weighting (IPW) enabled us to appropriately adjust for postrandomization biases due to protocol compliance. The probability of adherence in each group of treatment was estimated using logistic regression models considering age, sex, BMI and malnutrition as common regressors for the adherence status and the outcomes. Stabilized weights were computed from the estimated probabilities and further used in the ANCOVA and linear mixed models to reduce imbalance between groups of interventions in measured confounders [47].

Statistical analyses were performed using R version 4.4.2 with the RStudio 2024.04.0.

Results

Study population

Between December 2015 and September 2018, 54 patients with locally advanced SCCHN were enrolled and randomly assigned to receive EPA ($n = 27$) or placebo ($n = 27$). Figure 2 presents the participant flow diagram, including reasons for exclusion. Differences in sample size for the PP analysis were due to protocol deviations, as detailed in the Statistical Analyses section.

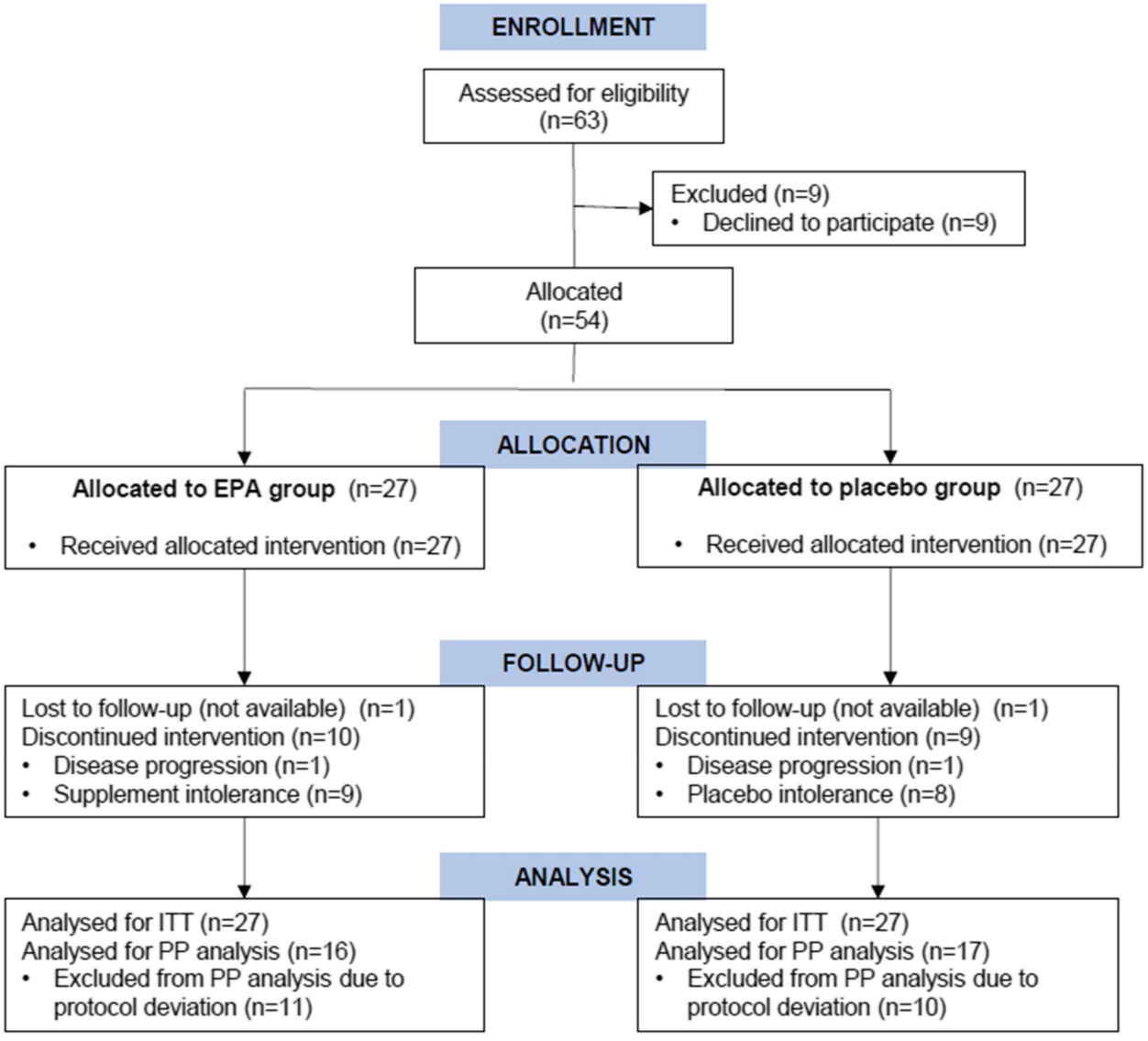

Fig. 2 Consort diagram

Baseline characteristics are shown in Table 1. The median age was 58.9 years (SD 6.8) and 78% of participants were male. The most common tumor site was larynx (37.0%). Following induction chemotherapy, 49.1% received RT and cetuximab. The median duration from diagnosis (T0) to completion of oncological treatment (T2) was 6.2 months (SD 2.1). Most patients had good baseline clinical status (ECOG performance status 0–1). At diagnosis, 54% were classified as well-nourished according to the PG-SGA, and 39% were overweight or obese. Sarcopenia, as defined by Martin et al. [2] was present in 22% of cases, with a mean skeletal muscle index (SMI) of 50.9 cm^2/m^2 (SD 11.4).

After completion of treatment, complete response rates were similar between groups: 78% (18/27) in the EPA group vs. 67% (21/27) in the placebo group.

Coprimary end points: weight and body composition

ITT analysis

In the ITT analysis, the mean percentage of weight loss from baseline (T0) to the end of treatment (T2) was −7.88% (95% CI: −13.4% to −2.40%) in the EPA group and −5.15% (95% CI: −11.4% to 1.11%) in the placebo group (Fig. 3A), with no statistically significant difference between groups (−2.73, 95% CI: −10.6; 5.17; $p = 0.474$) (Table 2).

Modelling the dynamics of weight over time (T0, T1, T2), both groups showed significant weight loss. The estimated mean change was −4.25 kg (95% CI: −7.04 to −1.45; p = 0.0373) in the EPA group and −5.05 kg (95% CI: −8.20 to −1.90; p = 0.0256) in the placebo group. A similar pattern was observed for BMI (Fig. 4), with mean reductions of −1.55 kg/m^2 (95% CI: −2.54 to −0.56; p = 0.0286)

Table 1 Characteristics of the participants at baseline (T0)

	Total (*n = 54*)	**Placebo (*n = 27*)**	**EPA (*n = 27*)**
Age, year	58.9 (6.8)	59.7 (6.0)	58.1 (7.6)
Sex, male, n (%)	42 (77.8%)	19 (70.4%)	23 (85.2%)
Primary tumour site, n (%)			
Oral cavity	9 (16.7%)	5 (18.5%)	4 (14.8%)
Oropharynx	10 (18.5%)	5 (18.5%)	5 (18.5%)
Larynx	20 (37.0%)	12 (44.4%)	8 (29.6%)
Hypopharynx	10 (18.5%)	3 (11.1%)	7 (25.9%)
Nasopharynx	5 (9.3%)	2 (7.4%)	3 (11.1%)
HPV[a] positive	3 (33.3%)	1 (25.0%)	2 (40.0%)
Pathological Stage (TNM), n (%)			
III	12 (22.2%)	5 (18.5%)	7 (25.9%)
IVa	31 (57.4%)	18 (66.7%)	13 (48.1%)
IVb	11 (20.4%)	4 (14.8%)	7 (25.9%)
Performance status, n (%)			
0	8 (14.8%)	3 (11.1%)	5 (18.5%)
1	43 (79.6%)	23 (85.2%)	20 (74.1%)
2	3 (5.6%)	1 (3.7%)	2 (7.4%)
Type of concomitant treatment, n (%)			
CDDP[b]	20 (37.7%)	9 (34.6%)	11 (40.7%)
Cetuximab	26 (49.1%)	14 (53.8%)	12 (44.4%)
Radiotherapy alone	4 (7.5%)	1 (3.8%)	3 (11.1%)
Others [c]	3 (5.7%)	2 (7.7%)	1 (3.7%)
Active smoker	17 (31.5%)	10 (37.0%)	7 (25.9%)
Active drinker	9 (16.7%)	4 (14.8%)	5 (18.5%)
PG-SGA[d]			
A—well nourished	29 (53.7%)	18 (66.7%)	11 (40.7%)
B—moderate malnutrition	16 (29.6%)	5 (18.5%)	11 (40.7%)
C—severe malnutrition	9 (16.7%)	4 (14.8%)	5 (18.5%)
Weight, kg	67.6 (15.0)	71.0 (16.2)	64.2 (13.0)
BMI[e,] kg/m^2, n (%)	24.4 (5.1)	25.7 (5.4)	23.1 (4.4)
Underweight (< 18.5 kg/m^2)	4 (7.4%)	2 (7.4%)	2 (7.4%)
Normal weight (18.5–24.9 kg/m^2)	29 (53.7%)	13 (48.1%)	16 (59.3%)
Overweight (25–29.9 kg/m^2)	13 (24.1%)	6 (22.2%)	7 (25.9%)
Obesity (≥ 30 kg/m^2)	8 (14.8%)	6 (22.2%)	2 (7.4%)
Albumin, g/L	44.8 (4.4)	45.5 (3.5)	44.1 (5.0)
CRP[f], mg/L	22.0 (23.9)	21.4 (21.3)	22.7 (26.8)
IL-6 [g], pg/mL	11.0 (10.9)	10.6 (10.8)	11.3 (11.2)
SMI[h,] cm^2/m^2	50.9 (11.4)	50.7 (12.5)	51.0 (10.4)
TATI[i], cm^2/m^2	112.5 (50.8)	123.5 (54.2)	101.2 (45.4))
Energy intake, kcal/d	2120.1 (849.0)	2207.2 (975.0)	2233.0 (709.2)
Protein intake, g/d	80.2 (28.4)	78.9 (29.4)	81.6 (27.8)
Hand grip strength, kg	30.0 (10.5)	31.3 (12.4)	28.7 (8.4)

Values are presented as mean (standard deviation) for continuous variables and as number (percentage) for categorical variables. No formal statistical comparisons were conducted, as these represent baseline characteristics

[a]HPV: Human papillomavirus

[b]CDDP: cisplatin

[c]Others: include one patient loss of follow up before stating the concomitance and two patients with progression and change the oncological treatment

[d]PG-SGA: Patient Generated Subjective Global Assessment

[e]BMI: body mass index

[f]CRP: C- Reactive Protein

[g]IL-6: Interleukin-6

[h]SMI: Skeletal muscle index

[i]TATI: Total adipose tissue index

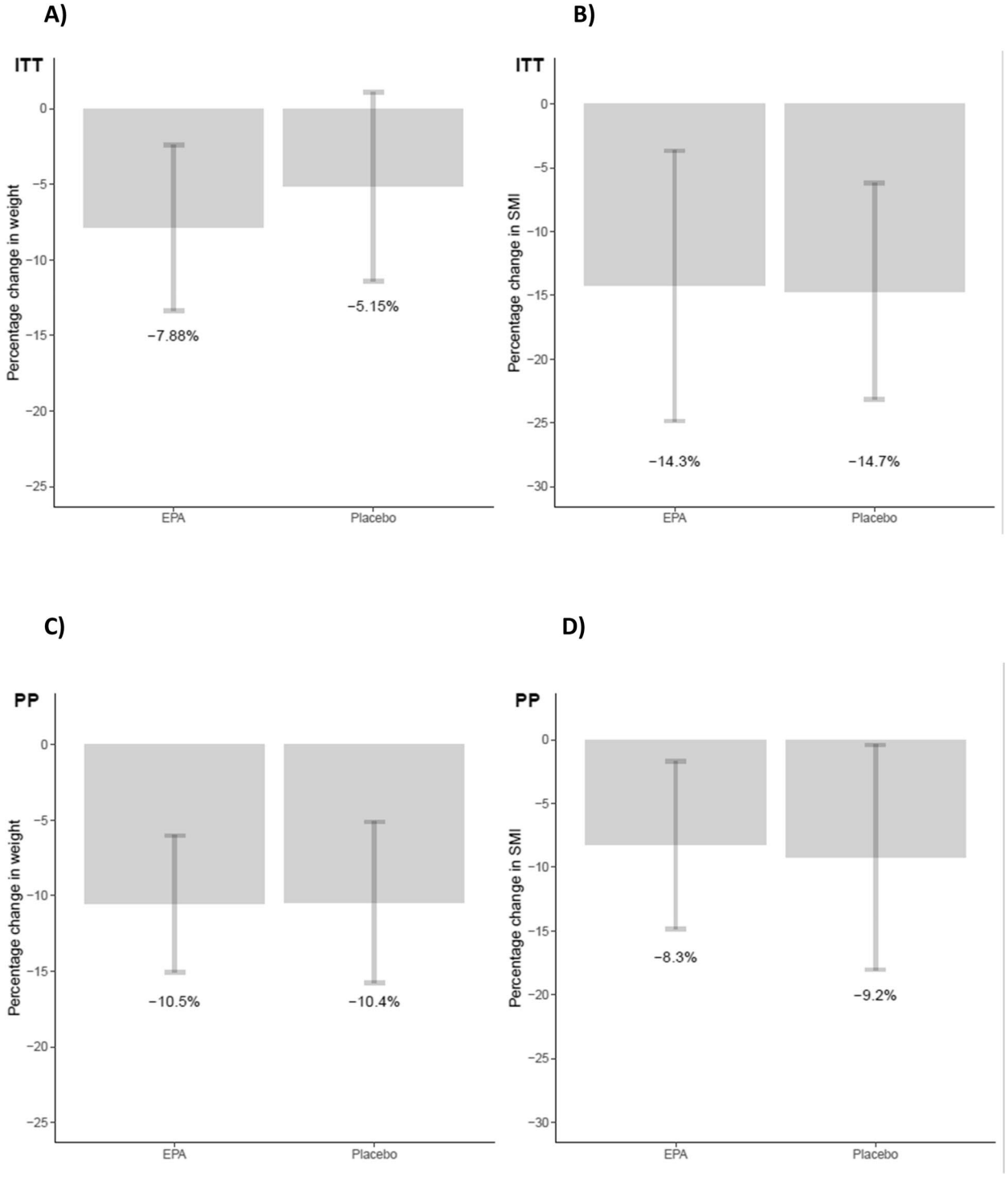

Fig. 3 Mean percentage change in body weight and skeletal muscle index (SMI) from baseline (T0) and end of treatment (T2) in the EPA and placebo groups according intention-to-treat (ITT) and per-protocol (PP) analysis. Bars represent mean percentage change from baseline (T0) to T2; error bars indicate 95% confidence intervals. Estimates are derived from an analysis of covariance model (ANCOVA) adjusted for age, sex, malnutrition, and baseline values

Table 2 Comparisons of the coprimary end points for the intention-to-treat (ITT) and the per-protocol sample (PP)

	Intention-to-treat (ITT)			Per- protocol (PP)	
Variable	**Contrast**	**Estimate (95% CI)**	***P*-value***	**Estimate (95% CI)**	***P*-value***
% Weight change	EPA vs Placebo	−2.73 (−10.6; 5.17)	0.4747	−0.10 (−6.79; 6.59)	0.9752
Weight (kg)	EPA: T2 vs T0	−4.25 (−7.04; −1.45)	0.0373	−3.81 (−5.70; −1.91)	0.0009
	Placebo: T0 vs T2	−5.05 (−8.20; −1.90)	0.0256	−7.72 (−12.8; −6.40)	< 0.0001
BMI (kg/m^2)	EPA: T2 vs T0	−1.55 (−2.54;—0.56)	0.0286	−1.35 (−1.96; −0.74)	0.0002
	Placebo: T2 vs T0	−1.75 (−2.92;—0.58)	0.0438	−2.61 (−3.59; −1.63)	< 0.0001
% SMI change	EPA vs Placebo	−0.42 (−13.3; 12.5)	0.9477	−0.95 (−10.4; 8.44)	0.8365
SMI (cm^2/m^2)	EPA: T2 vs T0	−7.00 (−11.3; −2.66)	0.0235	−4.99 (−7.52; −2.46)	0.0015
	Placebo: T2 vs T0	−7.67 (−11.9; −3.47)	0.0067	−5.68 (−9.73; −1.62)	0.0660

This table represents estimated changes in clinical outcomes (weight, BMI, body composition) between baseline (T0), post-induction chemotherapy (T1) and end of treatment (T2) in the EPA and placebo groups

EPA vs Placebo: estimate of the mean difference between arms of the outcome percent change. Estimates are derived from an analysis of covariance model (ANCOVA) adjusted for age, sex, malnutrition. Each ANCOVA model further comprised the baseline variable of the respective outcome at T0

EPA (or Placebo): T2 vs T0: estimate of the mean difference between time points derived from a linear mixed model adjusted for age, sex and malnutrition. Each linear mixed model further comprised the baseline variable of the respective outcome at T0

*p-values of EPA and placebo: T2 vs T0 comparisons are obtained using Tukey's method for multiple post-hoc comparisons between time and group

For the ITT analysis imputations were performed based on age, sex, malnutrition, stage, body mass index and respective outcome at T0

in the EPA group and −1.75 kg/m^2 (95% CI: −2.92 to −0.58; p = 0.0438) in the placebo group (Table 2).

Regarding SMI, the mean percentage loss was −14.3% (95% CI: −24.9% to −3.66%) in the EPA group and −14.7% (95% CI: −23.2% to −6.19%) in the placebo group (Fig. 3B), with no significant difference between groups (difference: 0.42%, 95% CI: −12.5% to 13.3%; p = 0.9477) (Table 2). Mean absolute reductions in SMI were also similar: −7.00 cm^2/m^2 (95% CI: −11.3 to −2.66) in the EPA group and −7.67 cm^2/m^2 (95% CI: −11.9 to −3.47) in the placebo group.

Other body composition compartments (VATI, SATI, TATI) showed no statistically significant differences between groups (see Supporting Information Table S1). Nevertheless, a trend toward smaller decreases in the EPA group was observed across several measures (see Supporting Information Figure S1).

PP analysis

The per-protocol analysis included 33 patients who completed the intervention at T2: 16 in the EPA group and 17 in the placebo group.

The mean percentage of weight loss was −10.5% (95% CI: −15.1% to −6.02%) in the EPA group and −10.4% (95% CI: −15.8% to 5.11%) in the placebo group (Fig. 3C), with no statistically significant difference between groups (−0.10%, 95% CI: −6.79 to 6.59; p = 0.9752) (Table 2).

When modeling weight dynamics over time, both groups showed significant weight loss. In the EPA group, the estimated mean change was −3.81 kg (95% CI: −5.70 to −1.91; p = 0.0009), compared to −7.72 kg (95% CI: −12.8 to −6.40; p < 0.001) in the placebo group. A similar trend was observed for BMI as shown in Fig. 4, with reductions of −1.35 kg/m^2 (95% CI: −1.96 to −0.74; p = 0.0002) in the EPA group and −2.61 kg/m^2 (95% CI: −3.59 to −1.63; p < 0.0001) in the placebo group (Table 2).

SMI decreased in both groups, with a mean percentage loss of −8.3% (95% CI: −14.9% to −1.67%) in the EPA group and −9.2% (95% CI: −18.0% to −0.39%) in the placebo group (Fig. 3D). The difference was not statistically significant (mean difference: 0.95%, 95% CI: −10.4% to 8.44%; p = 0.8365). Absolute changes in SMI were also similar: −4.99 cm^2/m^2 (95% CI: −7.52 to −2.46) in the EPA group vs −5.68 cm^2/m^2 (95% CI: −9.73 to −1.62) in the placebo group.

No statistically significant differences were observed in the percentage change of adipose compartments (VATI, SATI, TATI) between groups (Supporting Information Table S1). Nevertheless, a trend toward smaller decreases in the EPA group was again observed across all compartments (Supporting Information Figure S1).

EPA compliance

At baseline, plasma EPA levels (expressed as % of total fatty acids) were similar between groups: 0.7% in the EPA group vs 0.5% in the placebo group. At T1 and T2, plasma EPA levels increased in the EPA group but remained stable in the placebo group.

At T1, 10 patients (62.5%) in the EPA group showed increases in plasma EPA levels consistent with incorporation of the supplement, whereas no increased were observed in the placebo group. By the end of treatment (T2), approximately half of the patients in the EPA group maintained elevated EPA levels (Table 3).

A total of 17 participants (31.5%) discontinued the intervention due to intolerance. Reported side effects included nausea, vomiting, heartburn, gastric fullness, and reflux, and were reported in both groups: 9 in the EPA group and 8 in the placebo group.

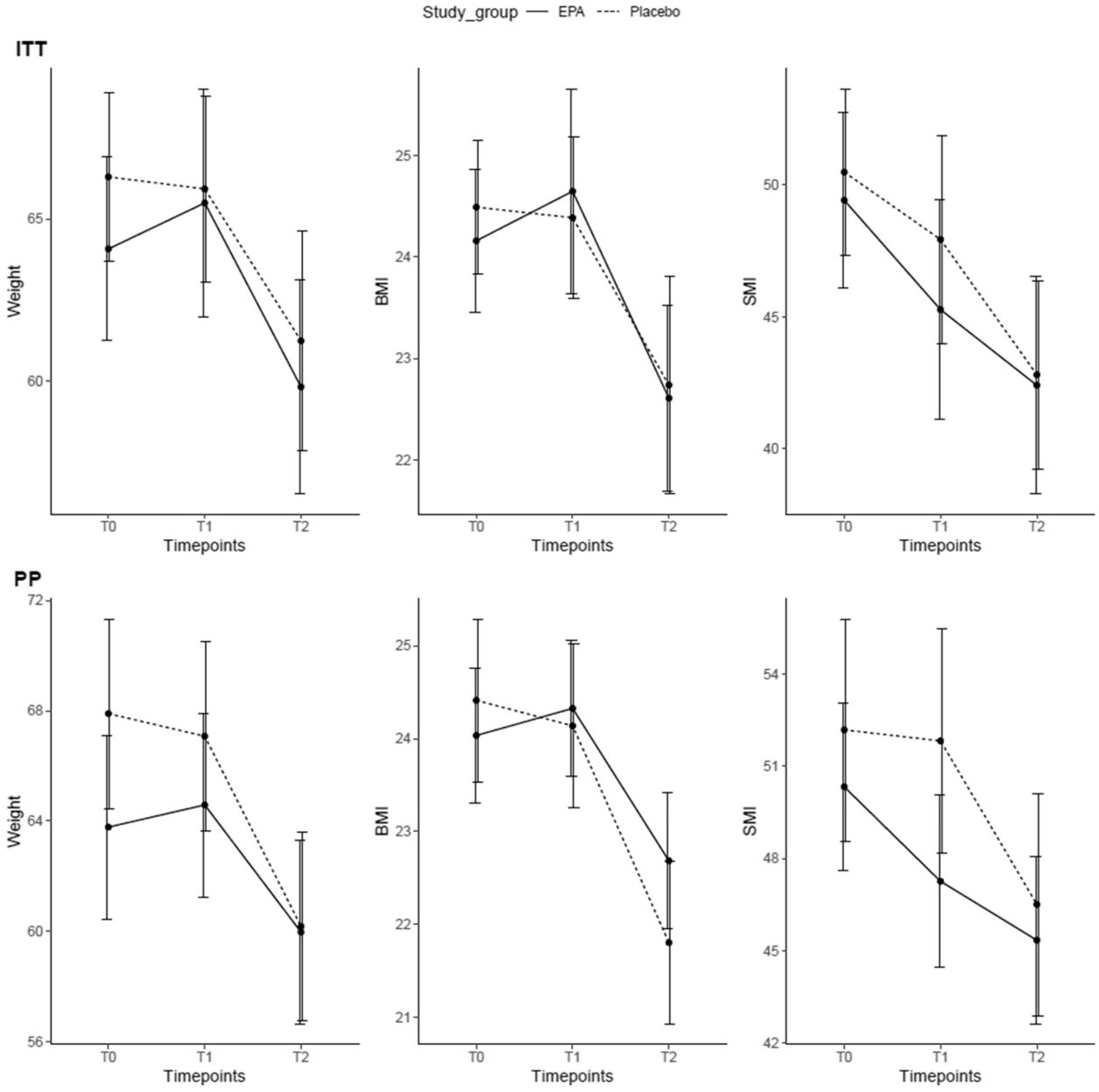

Fig. 4 Dynamic changes in body weight, body mass index (BMI) and skeletal muscle index (SMI) at baseline (T0), after induction chemotherapy (T1) and after the end of the oncological treatment (T2) according the intention-to-treat (ITT) and per-protocol (PP) analyses. Dots represent marginal means at each timepoint; error bars indicate 95% confidence intervals. Estimated are derived from a linear mixed models adjusted for age, sex, malnutrition status, and baseline values

Changes in nutritional, functional, inflammatory parameters over time

The evolution of nutritional, functional, and inflammatory parameters after induction chemotherapy (T1) and at the end of treatment (T2) is presented Table 3.

Nutritional status At baseline, 59.2% of patients in the EPA group were malnourished compared to 33.3% in the placebo group. By T1, malnutrition prevalence decreased in the EPA group and increased in the placebo group, resulting in similar rates (50.0% vs. 47.6%). This pattern remained consistent at T2. Dietary intake, including energy and protein consumption, showed no significant intra- or between-group differences at any time point.

Nutritional support All participants received nutritional support in accordance with ESPEN guidelines. No significant differences were observed between groups regarding the need for different types of nutritional support at either T1 or T2. At baseline, two patients in the EPA group and

Table 3 Nutritional, functional, inflammatory and compliance parameters at T1 and T2

	After induction chemotherapy (T1)		End of radical treatment (T2)	
	EPA (*n* = 18)	**Placebo (*n* = 21)**	**EPA (*n* = 16)**	**Placebo (*n* = 17)**
Malnutrition[a], n (%)	9 (50.0)	10 (47.6)	14 (87.5)	14 (82.4)
Energy intake, kcal/d	2401.1 (604.3)	2319.9 (494.6)	2222.8 (642.3)	2210.4 (770.6)
Protein intake, g/d	101.2 (33.1)	86.1 (31.6)	96.0 (36.6)	96.8 (37.5)
Enteral nutrition, n (%)	2 (7.4)	1 (3.7)	2 (11.8)	6 (35.3)
Hand-grip strength, kg	27.8 (8.5)	33.0 (9.6)	25.5 (8.2)	31.4 (12.2)
GPS[b], n (%)				
0	10 (58.8)	10 (50.0)	11 (68.8)	9 (56.2)
1	5 (29.4)	10 (50.0)	4 (25.0)	6 (37.5)
2	2 (11.8)	0 (0.0)	1 (6.2)	1 (6.2)
IL-6[c] pg/mL	16.7 (23.8)	10.6 (7.9)	13.8 (15.2)	19.2 (24.5)
NLR[d]	2.5 (1.6)	2.6 (2.2)	8.4 (14.6)	3.5 (1.6)
EPA (% of total plasma fatty acids)	3.1 (2.3)	0.7 (0.5)	3.5 (3.1)	0.7 (0.4)

*Values are presented as mean (standard deviation, SD) unless otherwise indicated. EPA measured in plasma and expressed as percentage of total identified fatty acids, based on gas chromatography analysis

[a]Malnutrition defined as Patients Generated Subjective Global Assessment (PG-SGA) B + C

[b]GPS: Glasgow Prognostic Score

[c]IL-6: interleukin 6

[d]NLR: neutrophil-to-lymphocyte ratio

one in the placebo group required enteral nutrition, and these same individuals remained on support at T1. By T2, six patients in the placebo group and two in the EPA group required enteral feeding.

Functionality Hand-grip strength was preserved in both groups throughout the duration of the treatment, with no significant variations observed between the groups or over the course of the treatment.

Inflammatory biomarkers There were no differences between groups regarding serum levels of proinflammatory biomarkers such as IL6, GPS and NLR.

Toxicity

No differences were observed in the incidence or severity of toxicities between the EPA and placebo groups.

At baseline, nine patients reported dysphagia to liquids (five in the EPA group, four in the placebo group), including two cases classified as grade 3. Dysphagia to solids (grade 3–4) affected 20 patients, and 19 reported odynophagia across all severity grades.

After induction chemotherapy, dysphagia persisted in two patients for liquids and in four for solids, with no cases exceeding grade 2 severity. Odynophagia remained in six patients, with one case classified as grade 3. Other nutrition impact symptoms emerged, including xerostomia (11 patients) and taste alterations (22 patients), all of mild to moderate severity (grade 1–2). Nausea and vomiting, likely related to EPA/placebo supplementation, were reported similarly in both groups.

By the end of treatment, dysphagia to liquids was reported in five patients, and dysphagia to solids in seven, prompting enteral nutrition in two patients from the EPA group and six from the placebo group. Xerostomia became the most prevalent symptom (29 patients), followed by dysgeusia (27 patients) and fatigue (26 patients). Anorexia progressively worsened throughout treatment, with the most pronounced impact observed after treatment completion.

Discussion

This study did not demonstrate a clear benefit of EPA supplementation in attenuating weight loss, BMI decline, or muscle depletion in patients with locally advanced SCCHN undergoing curative-intent treatment. Both intention-to-treat and per-protocol analyses failed to show statistically significant effects. However, among those who completed the protocol, a modest trend toward reduced weight and muscle loss in the EPA group was observed, despite most not achieving optimal biochemical compliance.

No significant differences were found in nutritional status, need for nutritional support, functionality, inflammatory biomarkers, or treatment-related toxicity. It is important to note that the study was not powered to detect differences in these secondary outcomes.

EPA has been explored for its potential role in counteracting muscle protein degradation through inhibition of proteolytic pathways such as the ubiquitin–proteasome system [48]. It was selected as the sole supplement in this trial based on previous evidence suggesting it is the main active component responsible for the muscle-preserving effects observed in fish oil formulations [49].

Previous meta-analyses have shown a positive association between omega-3 dose and body weight gain in cancer patients, but little effect on BMI or body composition [50]. In our study, EPA compliance was assessed

biochemically, and plasma EPA levels confirmed partial adherence. Although prior studies suggested that ≥ 2 g/day of oral EPA supplementation may help stabilize weight [51], we found no correlation between plasma EPA levels and clinical outcomes, even in patients with higher biochemical incorporation.

To explore whether a dose–response relationship existed in our cohort, we conducted a series of post hoc correlation analyses between plasma EPA levels and clinical outcomes. However, no significant associations were found, even among patients with higher biochemical compliance.

Our findings contrast with a previous single-blind RCT in SCCHN patients that reported benefits in weight and lean mass using an EPA-enriched high-protein supplement [15]. However, in that study, differences in the supplement formulations may have confounded the effects attributed to EPA. In contrast, both groups in our trial received standardized nutritional support, isolating the role of EPA. Consistent with other trials [22], we did not observe significant changes in inflammatory biomarkers such as CRP or IL-6.

The potential of EPA to enhance chemotherapy sensitivity remains under investigation [52, 53]. In our cohort, disease control and toxicity profiles were similar between groups. Importantly, adverse effects did not seem to impair adherence or influence clinical outcomes.

Compared to previous trials, our study offers a homogeneous cohort of locally advanced SCCHN patients, all receiving a uniform treatment protocol. We also included a longer follow-up, capturing outcomes not only during treatment but also during the recovery phase, where post-treatment inflammation is known to persist. Most prior trials assessed EPA over 4 to 12 weeks, while our study spanned 6.5 months from baseline.

Limitations include a small sample size and high dropout rate. Although we enrolled sufficient participants for baseline assessments, over one-third discontinued the intervention, largely due to intolerance. The liquid formulation, chosen to accommodate swallowing difficulties, may have hindered compliance due to taste or gastrointestinal side effects. Use of alternative formulations (e.g., capsules) might improve adherence in future studies. Moreover, lack of randomization stratification may have introduced imbalances between groups.

In conclusion, this study did not find sufficient evidence that EPA supplementation significantly attenuates weight loss, BMI decline, or muscle loss in patients with locally advanced SCCHN undergoing curative-intent therapy. However, due to the limited sample size and adherence challenges, these findings should be interpreted cautiously. Further research with larger, stratified cohorts and optimized delivery methods is warranted to better determine the clinical impact of EPA.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01203-8.

Supplementary Material 1.

Supplementary Material 2.

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Trial registration

Clinical trial registration: NCT02715596 (registered on March 22, 2016 at ClinicalTrials.gov).

Authors' contributions

LA, LH, RM contributed to the conceptualization of the study and methodology. LA, LH, ARGT and AE participated in the data curation. Formal analysis was carried out by AE. Funding acquisition was by MA and LA. LA, LH, IP, EV, AL, MT contributed to the investigation and resources. LA and AE prepared the original draft. RM and MT supervised the study. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was approved by the Ethics Committee for Clinical Research at Hospital Universitari de Bellvitge (PR261/14). All participants provided written informed consent prior to inclusion in the study.

Competing interests

The authors declare no competing interests.

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