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ORIGINAL ARTICLE

Predicting Survival Outcomes at Five Years Following Administration of Omega-3 Long-Chain Fatty Acids in People Living with Squamous Cell Carcinoma of the Head and Neck

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Abstract

There is a paucity of research on longer-term outcomes following oral nutrition supplementation (ONS) in patients with cancer. An observational analysis on mortality and survival rates were conducted in patients with head and neck squamous cell carcinoma (HNSCC) that received cancer treatment ONS plus 2 g of eicosapentaenoic-acid (EPA) versus standard treatment (EN). Twenty-six participants were available (81.3% of the original cohort [n=32]) in the ONS-EPA 2 g and 24 (75% of original cohort [n=32]) in the ONS-standard groups. Mortality at five years was 50% in the ONS-EPA 2 g and 58.3% in the ONS-standard group but with longer survival time in the ONS-EPA 2 g than the ONS-standard group (35 versus 18 months, respectively). A trend toward a longer survival time five years was observed in participants who received ONS with a high EPA content compared to those who received standard-formula ONS. Results may represent a possible long-term benefit of using high EPA supplementation during active cancer treatment to address malnutrition and positively influence clinical outcomes.

Keywords: Nutritional supplementation; Eicosapentaenoic acid; Head and neck squamous cell carcinoma; 5year mortality

Introduction

Specific cancer diagnoses, including the gastrointestinal tract, head and neck, liver, and lung, are associated with a higher risk for malnutrition[(1)]. The prevalence of malnutrition in people with head and neck cancer varies considerably depending on tumor location, treatment intensity, and different definitions used to describe the condition.

Prevalence notwithstanding, it is widely recognized that malnutrition causes a wide range of physiological and clinically relevant side effects. An early nutrition intervention should be implemented to improve nutritional status, lessen metabolic derangements, maintain lean body mass and physical strength, reduce risks of treatment discontinuations/interruptions, and improve general quality of life (QoL) in people living with head and neck squamous cell carcinoma (HNSCC).[1–3]

Supplementation with oral nutrition supplements (ONS) containing 2 g per day or more of eicosapentaenoic acid (EPA), an amount higher than the recommended daily intake for the healthy population, which is 250-500 mg EPA + DHA/day, has been shown to provide a benefit over standard care nutrition supplements in the cancer setting in terms of improving several clinical, biochemical and QoL parameters[4]. Intake of ONS containing high amounts of EPA is, for example, associated with weight stabilization and decreases in muscle mass loss, decreases in inflammatory parameters, and possibly positive influences on QoL indicators.[5–7]

Few studies have addressed longitudinal effects of nutritional interventions on nutritional status in people living with cancer. Whether the use of ONS with omega-3 long-chain polyunsaturated fatty acids improves long-term clinical outcomes such as tumor response and/or overall survival remains a debated issue.[8] In this previous study, we found that compared to participants in the control group, participants receiving 2 g of long chain omega-3 fatty acids seemed to preserve their lean body mass and decreased their plasma proinflammatory cytokine levels (a-TNF, IL-1b, IL-6, and g-INF), while maintaining anti-inflammatory IL-10 levels. This study also showed an increase in emotional and physical function, as well as a decrease in fatigue in participants receiving 2g of EPA[9]. The purpose of this follow-up cohort analysis is to find determinants that can separate participants with HNSCC who have survived and those who have not survived after 5-years after a nutritional intervention with ONS-EPA 2 g versus a standard EN formula during cancer treatment.

Methods

Study design and participants

This study is a 5-year follow-up to the original single-blinded, placebo-controlled clinical trial in 64 malnourished participants with HNSCC who received high-energy, high-protein ONS enriched with 2 g per day of EPA (Supportan® DRINK) or a standard isocaloric, isoproteic EN formula without EPA/DHA (Fresubin® Protein Energy DRINK) over a period of six weeks during antineoplastic treatment (both formulas supplied by Fresenius Kabi Mexico S.A. de C.V., Mexico). The original study was published by Solis-Martinez et al[9] and approved by the Ethics and Research Committee of the Hospital General de México "Dr. Eduardo Liceaga" with the registration ID: 13/111/04/019. Participants involved in the original study provided full written consent.

We analyzed a convenience sample taken during 2013-2016 from the original study cohort of 64 participants, to evaluate differences in survival at 5 years post-intervention between the two study groups. All participants in the original study were contacted through telephone calls to determine mortality and survival time. Data such as sex, clinical stage, type of medical intervention, percentage of weight changes during the intervention, fat-free mass, and fat mass were gathered for the follow-up analysis. Methods for obtaining each indicator are detailed in[8] the date of death was registered in months. The cut-off date for survival was 66 months after the conclusion of the nutritional intervention of the first patient in the original study.

Statistical assessment

Participant characteristics were described using percentages (%) for categorical variables and medians and interquartile ranges (IQR) for quantitative variables. Baseline differences between experimental and control groups in quantitative variables were computed by the Mann-Whitney test, while differences in proportions in categorical variables were computed with Fisher's exact tests. Changes in weight, fat free mass, fat mass, phase angle, energy intake, protein intake, long-chain omega-3 polyunsaturated (LC-PUFA) intake, serum albumin, and hemoglobin were normalized against baseline values and expressed as percentages. Correlations between quantitative variables were assessed with Spearman rank correlation coefficients and significance was adjusted for multiple comparisons using the Bonferroni correction. Correlation analysis was stratified for control vs. experimental group belonging in previous RCT. A linear discriminant analysis (LDA) was performed to find a linear model that is able to classify participants who survived and those who did not survive after 5 years. Variables included as predictive dimensions were the normalized changes in weight, fat free mass, fat mass, phase angle, protein intake, omega-3 LC-PUFA intake, serum albumin, serum hemoglobin, age, and clinical stage. All analyses were carried out in STATA 14.

Results

According to the original study with Sixty-four participants with HNSCC included, fourteen could not be reached because the telephone number had been changed or it was no longer functional. This study included fifty participants for the survival analysis, 52% (n=26) who had received ONS with 2 g EPA and 48% (n=24) who had received ONS-standard. Characteristics of the study population used in the follow-up analysis are presented in Table 1. At baseline, both groups were not different from each other.

Table 1. Characteristics of the Study Groups at Enrolment

Characteristics	ONS-EPA 2 g (n=26)	ONS-standard (n=24)	All (N=50)	p-value
Age (years), median (IQR)	60 (28.2)	59.5 (24.2)	60 (25)	0.496
Sex, Male, n (%)	14 (26)	11 (24)	25 (50)	0.778
Clinical stage I, n (%)	2 (7.7)	1 (4.2)	3 (6)	0.746
II, n (%)	4 (15.4)	5 (20.8)	9 (18)	
III, n (%)	12 (46.2)	8 (33.3)	20 (40)	
IV, n (%)	8 (30.8)	10 (41.7)	18 (36)	
Surgery, n (%)	8 (30.8)	10 (41.7)	18 (36)	0.556
Radiotherapy, n (%)	15 (56.7)	11 (45.8)	26 (52)	0.572
Chemotherapy, n (%)	14 (53.9)	12 (50.0)	26 (52)	1.000
Combined treatment, n (%)	11 (42.3)	9 (37.5)	20 (40)	0.779
Weight (kg), median (IQR)	62.5 (25.9)	59.8 (18)	60.5 (21.3)	0.985
BMI (kg/m^2) median (IQR)	23.6 (7.8)	24.4 (6.8)	24.1 (7.6)	0.341
Lean body mass (kg), median (IQR)	39.2 (15.8)	38.3 (13.3)	38.8 (13.3)	0.786
Fat mass (kg), median (IQR)	18.6 (12.3)	18.1 (10.0)	18.2 (10.6)	0.892
Tube feeding, n (%)	2 (7.7)	1 (4.2)	3 (6.0)	0.531

Follow-up median survival time was 26 months after the completion of supplementation (IQR = 39.5 months). Median survival time in the ONS-Standard group was of 18 months (IQR = 45 months), while the median survival time in the ONS-EPA 2g group was 35 months (IQR = 32 months); however, survival time distributions did not differ between groups (p=0.2891). During the 5-year follow-up, 54% of all participants in the study died (n=27). There were no statistical differences in mortality at 5 years between the two groups: 50% (n=13) in the ONS-EPA 2 g group and 58.3% (n=14) in the ONS-standard group (RR=0.86, CI 95% 0.41 – 1.43).

After the intervention, those participants receiving 2 g of omega-3 LC-PUFA had a more positive median % weight change (1.17% vs. -4.23% respectively, p=0.0214) and median % BMI change than those in the control group. Similar but non-statistically significant effects are seen in the median % change in fat mass, fat free mass, energy intake, omega-3 LC-PUFA intake, and hemoglobin, where the group receiving 2 g of omega-3 LC-PUFA had more positive changes. (Table 2). Median % change in protein intake, phase angle and albumin were higher but not statistically significant in the control group. These trends are replicated in both the control and the group receiving 2 g of omega-3 LC-PUFA in survivors and non-survivors; however, survivors seemed to have higher, but not statistically significant median % changes in energy, and omega-3 LC-PUFA intakes, haemoglobin, fat mass and fat free mass, and more negative median % changes in phase angle (Table 2).

Correlation analysis showed that for the general sample, changes in weight were positively associated with changes in fat free mass (ρ=0.65, p<0.0001) and with changes in fat mass (ρ=0.46, p=0.0386). Furthermore, changes in omega-3 LC-PUFA intake were positively correlated with changes in protein intake in the general sample (ρ=0.70, p<0.0001). For the surviving participants, changes in weight were positively with changes in fat free mass (ρ=0.77, p=0.0009), while changes in omega-3 LC-PUFA intake showed a positive correlation with changes in protein intake (ρ=0.93, p<0.0001). No significant correlations were found between variables in the non-surviving participants Figure 1.

Linear discriminant analysis (LDA) was performed to separate participants in survivors and non-survivors. Only 32 participants had complete data for this analysis. LDA showed that age, clinical stage at the beginning of the study, as well as % change in weight, fat mass, fat free mass, phase angle, protein intake, omega-3 LC-PUFA intake, albumin, and hemoglobin could be used to classify participants into groups of survivorship. The canonical correlation coefficient for this analysis was 0.737 (LR=0.4568, p=0.0371), with a canonical discriminant function shown in Table 3. This function maps z-scores for each of the aforementioned variables into a survival score (SS) contained in the set of the real numbers. Logistic Regression analysis shows that for every one-unit increase in SS for participants in this sample, there was a 91.2% reduction in the risk of dying (OR = 0.0822, CI 95% 0.0146 – 0.4625). SS distribution of survivors and non-survivors is shown in Figure 2. The generated SS is such

Table 2. Participant Anthropometric, Dietetic and Biochemical Indicators

median, (IQR)	TOTAL				Survivors				Non-Survivors				Survivors vs. Non-Survivors		
	Total	ONS-Control	ONS-EPA2g	p-value	Total	ONS-Control	ONS-EPA2g	p-value	Total	ONS-Control	ONS-EPA2g	p-value	p-total	p-control	p-EPA
% ΔWeight	-2.36 (8.85)	-4.23 (8.34)	1.17 (11.26)	0.0214	-2.43 (9.66)	-3.30 (7.44)	1.11 (11.42)	0.1137	-2.27 (7.72)	-5.28 (7.78)	1.24 (10.91)	0.0989	0.7480	0.8604	0.8175
% ΔBMI	-2.25 (8.85)	-4.23 (8.34)	1.17 (11.26)	0.0236	-2.34 (9.66)	-3.30 (7.44)	1.11 (11.42)	0.1137	-2.22 (7.72)	-5.28 (7.78)	1.24 (11.05)	0.1204	0.7628	0.9064	0.9067
% ΔFM	-2.54 (20.24)	-3.96 (15.82)	-0.41 (25.46)	0.3126	-2.22 (22.57)	-2.19 (21.22)	-2.86 (31.54)	0.7098	-3.00 (15.69)	-5.23 (12.52)	2.55 (20.08)	0.3082	0.5333	0.9766	0.9766
% ΔFFM	-1.27 (12.46)	-2.71 (12.27)	0.86 (13.83)	0.3413	-0.28 (15.48)	-2.38 (13.55)	3.03 (20.80)	0.4201	-2.93 (9.18)	-3.71 (11.65)	0.00 (10.93)	0.6447	0.8380	0.9300	0.9300
% ΔEnergy Intake	-16.64 (47.79)	-21.47 (55.49)	-10.17 (56.74)	0.4141	-1.32 (68.02)	-24.26 (65.45)	0.00 (68.71)	0.2913	-21.29 (54.52)	-21.47 (55.00)	-18.13 (50.77)	0.9806	0.4075	0.8140	0.1997
% ΔProtein Intake	-0.23 (2.07)	0.00 (1.92)	-0.33 (2.11)	0.8004	-0.19 (2.04)	-0.81 (2.17)	-0.19 (2.98)	0.3848	-0.28 (1.95)	0.00 (2.11)	-0.93 (1.96)	0.5118	0.8838	0.4445	0.3050
% ΔLCPUFA Intake	-30.17 (89.33)	-66.67 (97.5)	0.00 (121.46)	0.2168	-21.15 (153.23)	-42.31 (126.63)	0.00 (297.46)	0.7895	-30.17 (94.39)	-87.75 (100.00)	-14.38 (74.18)	0.1928	0.3414	0.2501	0.8038
% ΔPhase Angle	-3.44 (26.42)	-0.98 (18.66)	-7.50 (32.14)	0.2642	-6.67 (24.69)	-2.57 (22.86)	-9.84 (29.24)	0.6642	-2.86 (26.80)	1.39 (16.85)	-3.77 (48.98)	0.3824	0.4419	0.3640	0.8175
% ΔSerum Albumin	-0.97 (12.01)	0.23 (18.49)	-1.41 (10.03)	0.6010	-2.15 (8.95)	-1.27 (34.53)	-2.15 (6.97)	0.8170	-0.26 (14.03)	2.07 (18.48)	-0.61 (10.93)	0.6220	0.7345	0.8688	0.8431
% ΔSerum Hemoglobin	-2.72 (12.67)	-5.74 (15.02)	-0.69 (12.23)	0.1774	-5.33 (13.39)	-6.17 (13.15)	-0.69 (13.61)	0.7728	-2.61 (14.36)	-5.17 (17.36)	-0.08 (12.76)	0.1661	0.3216	0.9385	0.1914

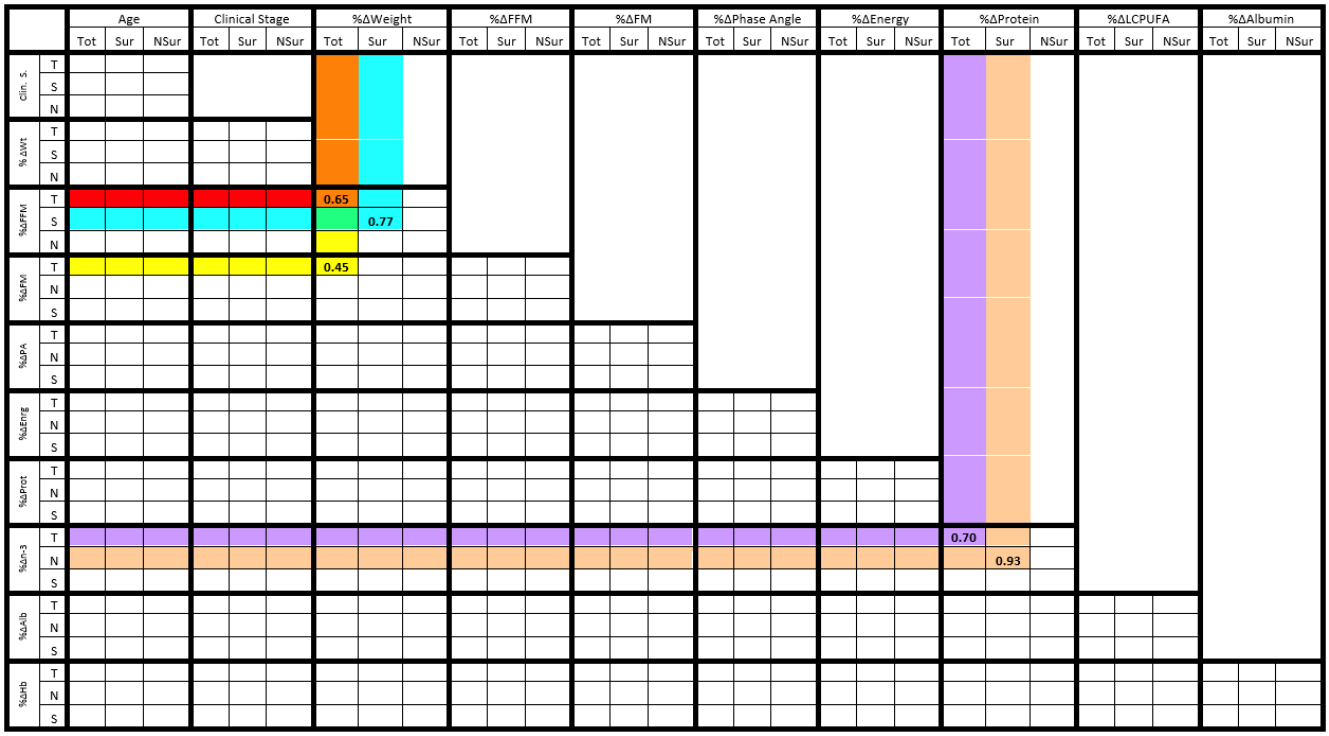

Fig 1. Spearman rank correlation coefficients (Significance adjusted for multiple comparisons using Bonferroni method). Only correlations with a p-value under 0.05 shown

that survivorship can be predicted according to the following function:

$$SURVIVORSHIP = \begin{cases} SURVIVOR\ if\ SS > 0 \\ NON-SURVIVOR\ if\ SS < 0 \end{cases}$$

Table 3. Canonical Discriminant Function for participant survivorship

Dimension	Coefficient
AGE z-SCORE	-0.849
CLINICAL STAGE z-SCORE	0.014
% Δ WEIGHT z-SCORE	6.407
% Δ FAT FREE MASS z-SCORE	-4.840
% Δ FAT MASS z-SCORE	-3.955
% Δ PHASE ANGLE z-SCORE	-1.180
% Δ PROTEIN INTAKE z-SCORE	-0.481
% Δ omega-3 LCPUFA INTAKE z-SCORE	0.891
% Δ SERUM ALBUMIN z-SCORE	1.338
% Δ SERUM HEMOGLOBIN z-SCORE	-1.679

The SS obtained with LDA was able to classify correctly 90.6% of the participants. This score had a sensitivity of 94.1%

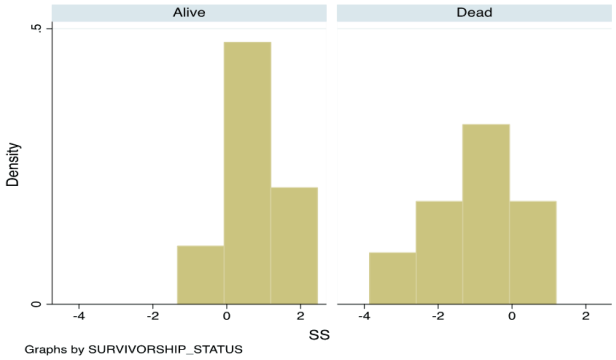

Fig 2. Survival Score (SS) distribution in Survivors and Non-Survivors

and a specificity of 86.7%. Its Positive Predictive Value was 88.9% and its Negative Predictive Value was 92.9%.

Discussion & Conclusion

Mortality rates and median survival times were not statistically different between the study groups, but there was a clear trend towards a longer survival time at 5-year follow-up in participants with HNSCC who had received ONS with 2 g

of omega-3 LC-PUFA during cancer treatment (35 months, IQR = 45) versus those who received a standard ONS formula (18 months, IQR = 32) (p=0.2891). Solis Martinez and cols [9] reported in the previous study there were no differences in participants in the baseline, showing that the distribution of clinical stages, cancer locations, age, weight, BMI, and body composition was similar between the groups (Table 1). This reduces the risk of bias in our results due to different types of Head and Neck Cancers and different cancer stages. Results of our original study indicated several benefits of ONS-EPA 2 g, including a slowing of weight and lean body mass loss. They lowered values of pro-inflammatory cytokines, significant reductions in fatigue, and improvement in emotional and physical functioning [9]. Moreover, median %weight change and median % BMI change were more positive in the ONS-EPA 2g group than in the ONC-Control group (p=0.0214). While the difference in changes in body composition were not statistically significant, the ONS-EPA-2g group had a trend towards a more positive increase in fat free and fat mass (Table 2).

Considering the results of our original study, perhaps the stabilized nutritional status and more positive increase in total body weight in participants who received ONS-EPA 2 g played a role in the differences in survival rates. This study replicates the results of an analysis of participants with non-small cell lung cancer who received fish oil capsules or liquids containing 2.2 g EPA/day during cancer treatment reported less weight loss in the fish oil supplemented group [6]. Although being at risk of or having malnutrition was not an inclusion criterion in their study, these authors also report a tendency to a higher 1-year survival rate in the intervention group and maintenance of muscle weight and mass and adipose tissue throughout the active therapy period in those participants who received high EPA from fish oil [6].

Furthermore, Table 2 shows that while not statistically significant; survivors had more positive % changes in total body weight, body composition, energy, protein and omega-3 LC-PUFA intakes, and serum albumin but more negative but not statistically significant %changes serum hemoglobin and phase angle. While none of these trends can be attributed to anything more than chance, another possible reason for no statistical significance is the low statistical power that results from a low sample size in effects that have very high variability between individuals (n=23 in the surviving group and n=27 in non-surviving group).

Patterns in this study (Table 2) show that individuals in the surviving may have increased their omega-3 LC-PUFA intake by a higher percentage than individuals in the non-surviving group. Variability in omega-3 LC-PUFA intake is very high, with the IQRs of the surviving and non-surviving groups being 724% and 313% of the median intake respectively. The sample size in this study was limited due to the inability to reach participants or family members coming from an already small randomized control trial justifies a large trial using high omega-3 LC-PUFAs.

Moreover, differences in variability in anthropometric measurements between participants in the EPA 2g group and the control groups are notable (Table 2). This sole fact implies that larger sample sizes may be needed to detect differences in anthropometric indicators. The requirement of large sample sizes for this study seems to be driven by the fact that there is a wide range of responses to omega-3 LC-PUFA supplementation (Table 2). Overall Spearman rank correlation coefficients showed that % changes in fat free mass and fat mass were positively correlated with % changes in total body mass, and that there was a very high correlation between % change in protein intake and % change in omega-3 LC-PUFA intake. The correlation between % change in fat free mass and % change in total body weight, as well as the correlation between % change in protein intake and % change in omega-3 LC-PUFA intake were also observed after stratifying for survivorship status. No correlations between variables were observed in the non-surviving group (Table 3). These correlation coefficients were adjusted for multiple comparisons in order to reduce the type I error rate.

It is interesting to see that correlation coefficients were higher than 0.5 and in some instances they reached over 0.8 (Table 3). Changes in fat mass and fat free mass move in the same direction as changes total body weight in the total sample. Changes in fat mass were not correlated with changes in total body weight in survivors. These patterns possibly point out to the fact that % changes in body weight, which were statistically significant between ONS EPA 2g and ONS Control (Table 2), may be driven by changes in body composition, but there was not enough statistical power to pick up such differences in these indicators through a Mann-Whitney Test. Furthermore, increases in protein intake were positively and highly correlated with increases in omega-3 LC-PUFA intake. This could be related to the fact that in the ONS EPA 2g group, the main source of omega-3 LCPUFAs was the ONS. The ONS EPA 2g group received a nutritional supplement that contained 13.3 g of protein for every gram of omega-3 LCPUFA. This high correlation did not achieve statistical significance in the group of non-survivors after adjusting for multiple comparisons with the Bonferroni correction. The Spearman correlation coefficient between these two variables in the non-surviving group was 0.5125. This could mean that the non-surviving group was not as reliant on sources that contained both protein and omega-3 LCPUFAs in sufficient amounts. Most sources of omega-3 LC-PUFA in the diet are associated to protein (fish and seafood). Fresh salmon is one of the sources with the highest content of omega-3 LCPUFA, providing nearly 9 g of protein for every gram of omega-3 LCPUFA [8]. Salmon, as well as other fish containing omega-3 LC-PUFA in large concentrations, is not widely consumed in countries

like Mexico[10], and for this reason, an ONS containing high amounts of LC-PUFA per gram of protein could be the main driver of the association. Even if the association between increase in omega-3 LC-PUFA intake and protein intake in the non-surviving group was statistically significant, the difference between correlation coefficients would be around 0.42 and statistically significant (p=0.0003). The aforementioned pattern suggests that the surviving group could have had a higher increase in consumption of omega-3 LC-PUFA mediated by the ONS, and the non-surviving group had a lower increase in omega-3 LC-PUFA intake by not being assigned to the ONS EPA 2g group or by not taking the supplement as instructed.

The classification model obtained from Linear Discriminant Analysis (LDA) was able to adequately separate surviving and non-surviving participants based on their age, clinical stage and % change in weight, body composition, phase angle, protein intake, omega-3 LC-PUFA intake, serum albumin, and serum hemoglobin. The coefficients shown in table 4 show that the z-score for % changes in total body weight, in serum albumin, and in omega-3 LC-PUFA intake have the largest positive impact in the SS. Participants with a positive SS were predicted to survive 5 years, while participants with a negative SS were predicted to not survive during this time frame. For this experiment, having % changes in total body weight, serum albumin, and omega-3 LC-PUFA intake above the mean (mean % changes were -2.58%, 0.24%, -2.57% respectively for each) had positive contributions to the SS and contributed to being assigned to the surviving group. Age, as well as % changes in fat free mass, fat mass, hemoglobin, and phase angle that were below the mean (mean age was 59.9 and mean % changes were -1.87%, -2.46%, -2.69%, and -4.43% respectively for each of the rest) contributed negatively to the SS and contributed to being assigned to the non-surviving group. The remaining dimensions in LDA (Clinical Stage, and % change in protein intake) had a mild contribution to the score.

It is interesting to see that while correlation analyses showed a positive association between % changes in total body weight and % changes in fat mass and fat free mass, the impact of each has opposite effects on the SS. This means that most patients with weight gain above the mean had positive contributions to the SS and also had positive changes in fat mass and fat free mass above the mean that contributed negatively to the SS. Conversely, most patients who lost weight below the mean and had negative contributions to SS, also had negative changes in fat mass and fat free mass below the mean that contributed positively to SS. This shows that when participants' body composition changed in the same direction as their total body weight, the total "anthropometric" contribution to the SS was very small. Around 17 participants in the survivor group (73.9%) and 21 participants in the non-survivor group (77.8%) had body composition changes and total body weight changes in the same direction with respect to the mean. In total, there were 38 participants with this pattern (76.0%). When patients gained weight with no change or decrease in fat mass or fat free mass relative to the mean, there would be a total positive contribution to the SS. There were 3 participants (13.0%) in the survivor group and 4 participants (14.8%) in the non-survivor group with this pattern, giving a total of 7 participants in total (14.0%). When patients lost weight and gained or had no change in fat mass and fat free mass with respect to the mean, there would a total negative contribution to the SS. There were 3 participants (13.0%) in the survivor group and 2 participants (7.4%) in the non-survivor group, giving a total of 5 participants in total (10.0%). Only 12 participants (24%) had body composition changes in a different direction from their total body weight relative to the mean; 7 (14.0%) where the total contribution was positive (i.e., total body weight gain larger than the mean and fat mass and fat free mass gain lower than the mean), and 5 (10.0%) with a total negative contribution (i.e., total body weight gain lower than the mean, and fat mass and fat free mass larger than the mean).

This shows that for the most part, weight changes do not affect the SS by much. Only in 24% of the cases, weight changes did not follow the expected pattern, and in 5 of those, did the pattern contributed negatively to the SS. As far as we are concerned, a pattern where total body weight decreases while maintaining or increasing fat mass and fat free mass could be related to dehydration. The opposite, where there is weight gain with decreases in fat mass and fat free mass respective to the mean related to recovery in hydration status that would explain a positive contribution in the SS. This, however; does not explain the detrimental effect of fluid overload.

Regarding changes in phase angle, changes under -4.43% had positive contributions to the SS. This does not agree with current evidence. One systematic review consistently found in 48 published articles that negative phase angle values are associated with higher mortality rates[11]. Cut-off points seem to vary between studies, and some studies show that phase angle values at either too large or too low extremes predict mortality. Phase angle values are an indicator of cell membrane integrity, with low phase angles indicating cell mass destruction[12]. It is unclear why or how an increase in cell mass destruction would lead to a more positive contribution to the SS in the context of this study.

Changes in omega-3 LC-PUFA intake that are positive or even less negative than -2.57% increased the possibility of assigning a participant into the surviving group. While the effect of the change in this nutrient is not as strong as the change in weight or fat mass and fat free mass by themselves, it had a larger effect on the SS than % changes in protein intake, age and clinical stage (Table 3), and even possibly

similar to the combined effect of total body weight change, fat free mass change, and fat mass change for 76.0% of the cases. This underscores the importance of further studying the effect omega-3 LC-PUFA for survival in head and neck cancer patients while considering a wider variety of factors.

Some evidence supports the effect of omega-3 LC-PUFA intake on clinical outcomes, including mortality and survival. A study by Shirai et al.[5] reported there were no improvement in overall survival in their total cohort although survival in those participants with an increased inflammatory response at baseline and receiving ONS high in omega-3 LCPUFA-(1.6 to 3.2 g EPA + DHA/day) had a significantly greater survival than those with the same inflammatory response receiving standard nutritional care. Other study by Taha HM et al.[13] that analyzed the intakes of various fat subtypes in 476 newly diagnosed patients with HNSCC, concluded that prognosis may vary depending on the fat types consumed before cancer treatment because of population with high intakes of omega-3 and 6 were significantly associated with a reduced all-cause mortality risk. Our outcomes showed similar results in means between survivors and non-survivors but without statistical differences between groups.

Omega-3 LC-PUFA metabolism can be affected by several non-dietary factors. Nearly one quarter of the total variability in LC-PUFA blood levels can be attributed to heritability[14]. A systematic review found that minor allele carriers of the Fatty Acid Desaturase (FADS) may have lower EPA blood concentrations than those without those SNPs. This effect is replicated in 6 out of 9 studies looking at the influence of FADS variation in LC-PUFA plasma levels. The effect of elongated variations seems to be less clear, some studies finding positive effects on blood LC-PUFA concentration and others finding a negative effect. Sex, age, and body size have also been implicated in variability in LC-PUFA metabolism[14].

Additionally, the most limitation of this study is that the small sample size and the loss of patients during the follow-up impact the analysis of our results establishing a trend in clinical outcomes in the ONS-EPA 2 g group and their long-term advantages in survival. It's important consider LC-PUFA intake prior to cancer treatment and during intervention to reduce bias for future research. Considering the lack of research, this study provides preliminary evidence on the potential benefits of ONS enriched with EPA during cancer treatment.

Early assessment of patients at risk for developing malnutrition and the provision of any nutritional intervention versus no nutritional intervention can provide clinical benefits including reducing complications and facilitating the implementation of treatment and improving patients' quality of life. In this study, ONS with high EPA content administered during anticancer treatment did not show statistical differences in survival compared with participants that received standard-formula ON. However clinical trends toward in longer survival time at five years of follow-up in ONS-EPA 2 g group. Studies with large sample sizes and their relationship with body composition changes during follow-up must be considered in further research to fully uncover these associations.

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