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Original article

The utility of nutritional supportive care with an eicosapentaenoic acid (EPA)-enriched nutrition agent during pre-operative chemoradiotherapy for pancreatic cancer: Prospective randomized control study

Hirofumi Akita [a, e, *], Hidenori Takahashi [a], Kei Asukai [a], Akira Tomokuni [a], Hiroshi Wada [a], Satoko Marukawa [b], Tomoyuki Yamasaki [b], Yoshitomo Yanagimoto [a], Yusuke Takahashi [a], Keijiro Sugimura [a], Kazuyoshi Yamamoto [a], Junichi Nishimura [a], Masayoshi Yasui [a], Takeshi Omori [a], Hiroshi Miyata [a], Ayami Ochi [c], Ayano Kagawa [c], Yuko Soh [d], Yuko Taniguchi [d], Masayuki Ohue [a], Masahiko Yano [a], Masato Sakon [a]

[a] *Department of Surgery, Osaka International Cancer Institute, Japan*
[b] *Department of Endocrinology and Metabolism, Osaka International Cancer Institute, Japan*
[c] *Department of Nursing, Osaka International Cancer Institute, Japan*
[d] *Department of Nutrition, Osaka International Cancer Institute, Japan*
[e] *Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Japan*

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SUMMARY

Background & aims: Neoadjuvant chemoradiotherapy (NACRT) for pancreatic cancer (PC) is potentially associated with various toxicities, which can lead to impaired nutritional status. Eicosapentaenoic acid (EPA) can reduce proinflammatory cytokines and positively influence cancer cachexia syndrome. The aim of this study is to clarify the utility of EPA enriched nutrition support during NACRT for PC.
Methods: We randomly assigned 62 patients with PC that received NACRT to either a nutrition intervention (NI) or a normal diet (ND). Patients in the NI group received 2 bottles/day (550 kcal/day) of an EPA-enriched nutrition supplement during NACRT. The primary endpoints were the before-to-after NACRT ratios (post/pre ratios) of skeletal muscle mass and psoas major muscle area (PMA). The secondary endpoints were the post/pre ratios of other nutritional parameters and treatment-related toxicities.
Results: Only 14 patients (45.2%) in the NI group consumed more than 50% of the EPA-enriched supplement provided. The post/pre ratio of skeletal muscle mass in the NI group (0.99 ± 0.060) was not significantly different from that of the ND group (0.96 ± 0.079, $p = 0.102$). However, patients that consumed ≥50% of the EPA-enriched supplement (the good intake group) had significantly higher skeletal muscle mass ratios than patients in the ND group ($p = 0.042$). The PMA ratio was significantly higher in the NI group (0.96 ± 0.081) than in the ND group (0.89 ± 0.072, $p = 0.001$). The NI and ND groups were not significantly different in other nutritional parameters or in NACRT-related toxicity.
Conclusions: We found that EPA-enriched intake could potentially improve the nutritional status of patients with PC that received NACRT, but it was difficult for many patients to drink, due to its disagreeable taste.
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* Corresponding author. Department of Surgery, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka City, Osaka, 541-8567, Japan. Fax: +81 6 6945 1900.
E-mail address: hirofumiakita@hotmail.com (H. Akita).

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of tumor-related mortality, with a 5-year survival rate of <10% [1]. Surgical resection for localized disease is the only treatment option for a complete cure, but the prognosis after complete resection alone is poor. Indeed, ≥50% of patients develop tumor recurrence at distant or locoregional sites, and their estimated 5-year survival is only 20% [2]. Because surgical resection alone appears to afford minimal survival benefit, a variety of multimodal approaches have been applied in treatments for PDAC [3,4]. Preoperative neoadjuvant chemoradiation therapy (NACRT) with subsequent surgery is a promising treatment for PDAC [5,6]. Additionally, we previously reported that NACRT showed prognostic benefit for locally advanced resectable and borderline resectable PDAC [7,8].

On the other hand, chemoradiotherapy is associated with various acute and delayed toxicities, such as gastritis, nausea, and an altered sense of taste [9,10]. Moreover, the toxicities were previously reported to lead to impaired nutritional status, increased treatment-related morbidity and mortality, and an impaired quality of life, among patients with lung cancer [11].

Eicosapentaenoic acid (EPA) is a polyunsaturated fatty acid with a double bond (C=C) at the third carbon atom from the end (n-3). It is derived from fish oil and EPA can reduce the impaired nutritional status caused by several reasons such as inflammation and chemotherapy related toxicities [12]. van der Meij et al. reported that oral nutritional supplements containing EPA affected nutritional status by maintaining body weight and fat free mass in patients with stage III non-small cell lung cancer, during a multimodal treatment [13]. Recently, other reports have shown that EPA-enriched supplements given in nutritional interventions could reduce the incidence of chemotherapy-related toxicities during preoperative chemotherapy in esophageal cancer [14,15]. Fietkau et al. also showed that enteral nutrition enriched with EPA and DHA improved nutritional status by maintaining body weight, body cell mass, and fat-free mass in patients with head and neck cancer during chemoradiotherapy [16]. However, few studies have investigated nutritional interventions for patients with pancreatic cancer that receive NACRT. We hypothesized that EPA-enriched nutritional interventions might prevent impairments in nutritional status and reduce the incidence of toxicities in patients with pancreatic cancer that receive NACRT. The present prospective randomized controlled trial aimed to assess whether a nutritional intervention with an EPA-enriched supplement might affect the nutritional status of patients that received NACRT for pancreatic cancer.

2. Patients and methods

2.1. Patients

Patients were enrolled in the study when they met the following eligibility criteria: (*1*) diagnosed with untreated, histopathologically-confirmed, resectable pancreatic cancer (clinical stage IIA or IIB, according to TNM classification, 7th edition [17]) and scheduled to receive neoadjuvant chemoradiotherapy (NACRT); (*2*) age ≥20 and ≤80 years; (*3*) an Eastern Cooperative Oncology Group performance status of 0–1; (*4*) adequate hepatic, renal, and bone-marrow reserves (AST and ALT levels below twice the normal levels; total serum bilirubin <3.0 mg/dl; creatinine level <1.3 mg/dl; leukocyte count >2000/mm^3; hemoglobin >10 g/dl; platelet count >100,000/mm^3); (*5*) capable of oral intake, and (*6*) written informed consent provided before randomization. The study protocol was approved by the Human Ethics Review Committee of Osaka International Cancer Institute (OICI) and registered in the University Hospital Medical Information Network (http://www.umin.ac.jp; registration number ID 000033589). Signed consent was obtained from each participant.

2.2. Study design and treatment

From June 2014 to March 2016, 64 patients who received NACRT were assigned for eligibility. Two patients declined to participate and 62 patients were enrolled in this study. Patients were randomly assigned to either a nutrition intervention (NI) group (n = 31) or a normal diet (ND) group (n = 31; Fig. 1). Groups were balanced in terms of the severity of diabetes mellitus and the inflammatory status, based on the Glasgow Prognostic Score (GPS) [18]. In both groups, all patients received gemcitabine-based NACRT, as previously described [7,19]. Patients assigned to the NI group received 2 bottles (440 ml) per day (560 kcal/day) of EPA-enriched nutritional supplement (Prosure®; Abbott Japan, Tokyo, Japan) during the irradiation component of treatment (about 5 weeks). In all patients, nutrition parameters, including skeletal muscle mass and body fat mass, were measured with a body composition analyzer based on the bioelectrical impedance analysis (InBody720; Inbody Japan, Tokyo, Japan) immediately before (pre) and immediately after (post) the completion of radiotherapy. In addition, the sum of the cross-sectional areas of bilateral psoas major muscles area (PMA, cm^2) at the level of the L3 vertebrae was evaluated from computed tomography scans acquired before (pre) and after (post) radiotherapy. PMA was reported to be useful for the assessment of nutrition status in urothelial carcinoma of the bladder, liver transplantation and pancreatic cancer [20–22].

All patients also received nutritional guidance three times: immediately before, at 3 weeks, and immediately after radiotherapy. In these nutrition guidance, managerial dietician recorded both the content of meals and total caloric intake and consulted patients in NI group how much supplements they took.

The primary endpoints of this study were the pre–to-post ratios (post/pre) of skeletal muscle mass and PMA. The secondary endpoints were the post/pre ratios of other nutritional parameters, such as serum pre-albumin, serum albumin, BMI, and lymphocyte count, and the severity of treatment-related toxicity, according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0. In this study, it was unclear whether enrolled patients could complete designated amount of nutritional supplement, so the relationship between the amount of intake ratio and nutritional parameters were also examined. The amount of intake ratio was calculated as follows; actual amount of nutritional supplement intake/designated amount of nutritional supplement intake. We also examined the progression rate of diabetes mellitus during NACRT, because Prosure® included some sugar to buffer the taste of fish oil; consequently, it could potentially increase the severity of preoperative diabetes mellitus. A power analysis indicated that 29 patients were necessary for each group to provide a two-sided alpha error of 0.05, statistical power of 80%, and an effect size (Cohen's d value) of 0.75, which was expected from our preliminary data.

2.3. Statistical analysis

All data are expressed as the mean ± standard deviation (SD). Differences in continuous values were evaluated with the paired t-test or the Student's *t*-test (Tables 1 and 2, Fig. 2, Supplementary Figs. 1, Supplementary Table 1). Categorical data were compared with the Fisher's exact probability test (Table 3) and Pearson's chi-square test (Table 1). All analyses were performed with IBM SPSS

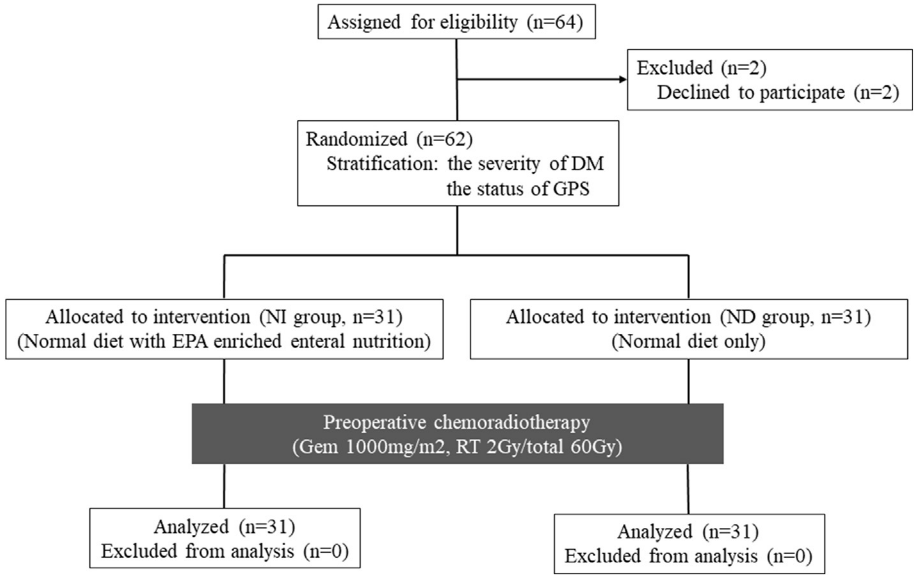

Fig. 1. Consort diagram for the trial. Groups were balanced in terms of the severity of diabetes mellitus and the inflammatory status, based on the Glasgow Prognostic Score (GPS).

statistics version 21.0 (IBM Japan Business Logistics, Tokyo, Japan). A p-value <0.05 was considered significant.

3. Results

3.1. Patient characteristics in each group

The two groups had similar pretreatment parameters, including age, gender, BMI, HbA1c, serum levels of albumin, pre-albumin, and CRP, and the average total caloric intake (Table 1). Before initiating CRT, the average skeletal muscle mass and body fat mass were similar in the NI group (23.1 ± 5.36 and 15.2 ± 4.93 kg, respectively) and the ND group (21.8 ± 5.74 and 14.0 ± 4.59 kg, respectively; p = 0.350 and 0.329, respectively). The average PMA values were also similar in the NI (17.6 ± 5.58 cm^2) and ND (16.7 ± 6.33 cm^2, p = 0.548) groups. In the NI group, only four patients consumed the total amount of EPA-enriched supplement provided. Many patients did not drink it, because they did not like the taste. As a result, 17 patients consumed less than 50% of the provided supplement, including 8 patients that did not drink it at all. Nevertheless, the average total caloric intakes during NACRT were similar in the NI group (1370 ± 630 kcal) and the ND group (1340 ± 400 kcal, p = 0.830; Supplementary Fig. 1).

Table 1
Patients characteristics.

	NI (n = 31)	ND (n = 31)	P value
Age (years)	67.8 ± 10.7	66.4 ± 9.8	0.596
Sex (male/female)	11/20	16/15	0.44
BMI	22.3 ± 2.39	22.0 ± 3.06	0.735
Total intake (kcal)	1750 ± 544	1670 ± 401	0.523
HbA1c (%)	6.54 ± 1.20	6.66 ± 1.32	0.694
Alb (g/dl)	3.95 ± 0.49	3.88 ± 0.41	0.598
pre-Alb (mg/dl)	24.0 ± 6.81	23.2 ± 5.84	0.635
Lymphocyte (/ul)	1230 ± 580	1270 ± 511	0.767
T-Chol (mg/dl)	180.7 ± 43.9	175.2 ± 30.0	0.574
Triglyceride (mg/dl)	106.4 ± 34.2	97.0 ± 40.7	0.311
CRP (mg/dl)	0.45 ± 0.78	0.46 ± 1.27	0.975
Skeletal muscle mass	23.1 ± 5.36	21.8 ± 5.74	0.35
Amount of body fat	14.9 ± 5.41	14.0 ± 4.66	0.481
Psoas major muscle area (cm^2)	17.6 ± 5.58	16.7 ± 6.33	0.548

3.2. Nutritional status changes between pre and post CRT

Table 2 shows the changes in nutritional status between pre- and post-NACRT in each group. In the NI group, the average skeletal muscle mass did not change significantly from pre-NACRT (23.1 ± 5.36 kg) to post-NACRT (22.9 ± 5.33 kg; p = 0.339, paired t-test). In the ND group, the average skeletal muscle mass post-NACRT (21.8 ± 5.74 kg) was significantly lower than that pre-NACRT (21.0 ± 6.03 kg, p = 0.014). In contrast, the average PMA was significantly lower post-NACRT than pre-NACRT, in both the NI (p = 0.002) and ND groups (p < 0.001). Similarly, other nutritional indicators, such as BMI, albumin, pre-albumin, lymphocytes, and total cholesterol, were significantly lower post-NACRT than pre-NACRT in both groups. However, triglyceride, C-reactive protein, and HbA1c levels were not significantly different between pre-NACRT and post-NACRT in both groups.

3.3. Comparison of nutritional status between the NI and ND groups

Figure 2A shows that the post/pre NACRT ratios of skeletal muscle mass were not significantly different between the NI and ND groups, but the ratio was marginally higher in the NI group (0.99 ± 0.060) compared to the ND group (0.96 ± 0.079, p = 0.102). The PMA after NACRT in the NI group (16.8 ± 5.2 cm^2) was not significantly different from that of the ND group (14.9 ± 5.9 cm^2, p = 0.189, data not shown). However, the post/pre ratio of PMA in the NI group (0.96 ± 0.81) was significantly higher than that of the ND group (0.89 ± 0.72, p = 0.001; Fig. 2B).

As the time of study planning, it was not known the capacity to comply to the intervention, so we examined the relationship between the proportion of EPA-enriched supplement consumed (%) and the post/pre ratio of skeletal muscle mass in the NI group. The diagram of the relationship between the proportion of EPA-enriched supplement consumed (%) and the post/pre ratio of skeletal muscle mass in the NI group revealed that the post/pre skeletal muscle mass ratio significantly increased with increases in supplement intake (p = 0.021; Fig. 2C). Next, we performed a sub-analysis of the NI group, to compare skeletal muscle mass changes between subgroups with good (≥50%) or poor (<50%) supplement

Table 2
The comparison between pre and post nutrition indicators.

	Nutrition intervention (NI) group			Normal diet (ND) group		
	pre	post	P value[a]	pre	post	P value[a]
Skeletal muscle mass	23.1 ± 5.36	22.9 ± 5.33	0.339	21.8 ± 5.74	21.0 ± 6.03	0.014
Psoas major muscle area (cm^2)	17.6 ± 5.58	16.8 ± 5.24	0.002	16.7 ± 6.33	14.9 ± 5.91	<0.001
BMI	22.3 ± 2.39	21.9 ± 2.52	0.011	22.0 ± 3.06	21.4 ± 2.93	0.001
Albumin (g/dl)	3.95 ± 0.49	3.75 ± 0.37	0.001	3.88 ± 0.41	3.72 ± 0.37	0.008
Pre albumin (mg/dl)	24.0 ± 6.81	20.5 ± 6.72	0.001	23.2 ± 5.84	19.8 ± 5.95	0.001
Lymphocyte (/ul)	1230 ± 580	358 ± 191	<0.001	1270 ± 511	354 ± 162	<0.001
Total cholesterol (mg/dl)	180.7 ± 43.9	163.5 ± 38.3	0.015	175.2 ± 30.0	161.3 ± 34.2	0.011
Triglyceride (mg/dl)	106.4 ± 34.2	103.6 ± 35.9	0.571	97.0 ± 40.7	110.3 ± 48.0	0.108
CRP (mg/dl)	0.45 ± 0.78	0.84 ± 2.13	0.338	0.46 ± 1.27	0.31 ± 0.46	0.539
HbA1c (%)	6.54 ± 1.20	6.69 ± 0.99	0.16	6.66 ± 1.32	6.69 ± 1.08	0.843

[a] Paired t-test.

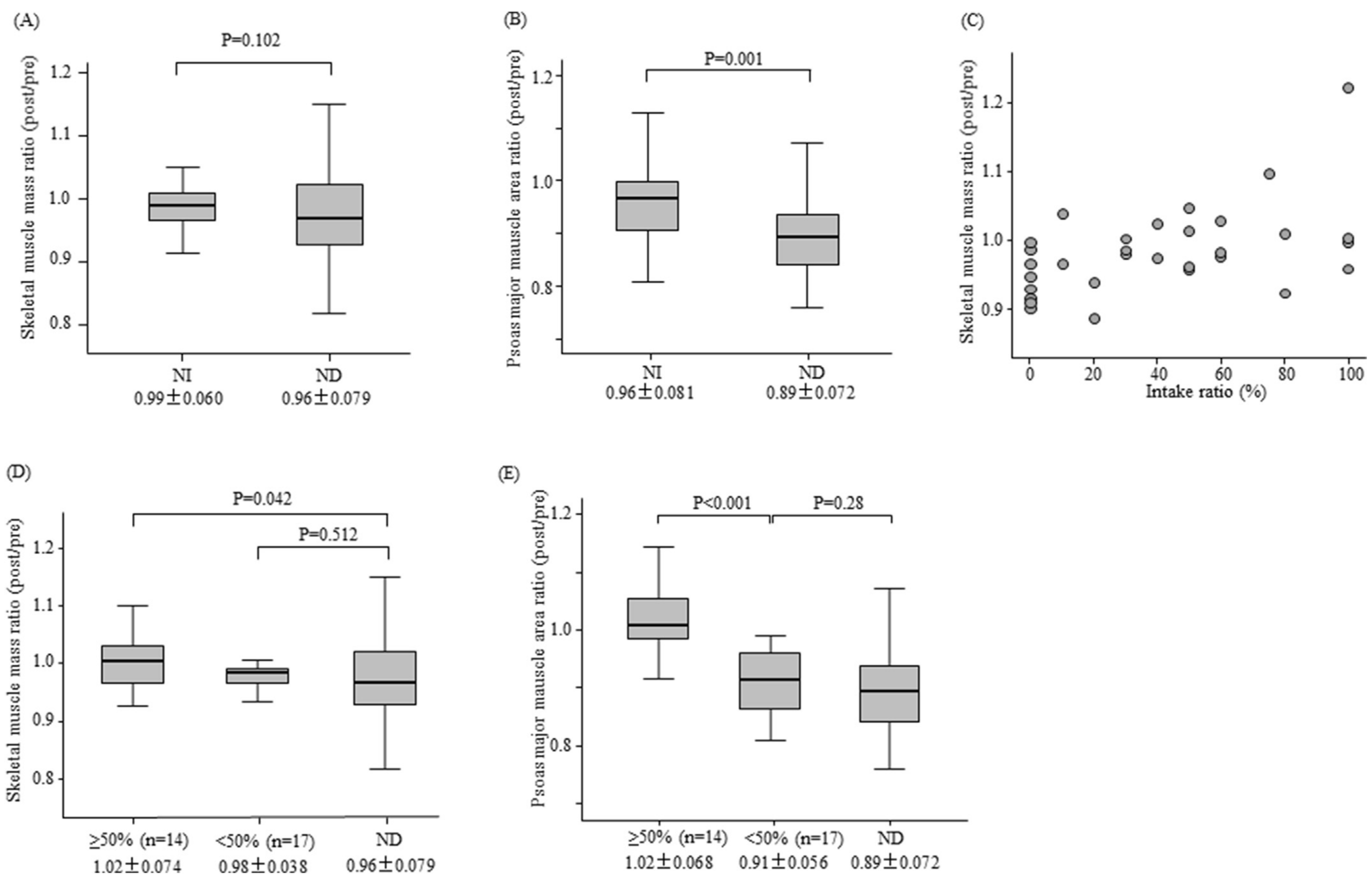

Fig. 2. The post/pre NACRT ratios of skeletal muscle mass were not significantly different between the NI and ND group (A). The post/pre ratio of PMA in the NI group was significantly higher than that of the ND group (2B). The diagram of the relationship between the proportion of EPA-enriched supplement consumed (%) and the post/pre ratio of skeletal muscle mass in the NI group revealed that the post/pre skeletal muscle mass ratio significantly increased with increases in supplement intake ($p = 0.021$) (1C). The post/pre ratio of skeletal muscle mass in the good (>50%) supplement intake subgroup was significantly better than that of the ND group, while the poor (<50%) supplement intake subgroup and the ND group had similar post/pre skeletal muscle mass ratios (2D). The post/pre ratio of PMA in the good (>50%) supplement intake subgroup was significantly better than that of the poor (<50%) supplement intake group and ND group (2E).

intakes. The post/pre ratio of skeletal muscle mass in the good supplement intake subgroup (1.02 ± 0.074), was significantly better than that of the ND group ($p = 0.042$); however, the poor supplement intake subgroup and the ND group had similar post/pre skeletal muscle mass ratios ($p = 0.512$; Fig. 2D). In addition, the post/pre ratio of PMA in the good supplement intake subgroup (1.02 ± 0.068) was significantly better than that of the poor supplement intake group (0.91 ± 0.056, $p < 0.001$; Fig. 2E).

The other nutritional parameters, including post/pre ratios of pre-albumin, albumin, and lymphocytes, were not significantly different between the NI and ND groups (Supplementary Table 1).

Table 3
Adverse events.

	Group	Gr0	Gr1	Gr2	Gr3	Gr4	P value
Leukopenia	NI	9	5	10	7	0	0.845
	ND	11	3	9	8	0	
Neutropenia	NI	8	3	8	9	3	0.985
	ND	9	3	9	7	3	
Thrombocytopenia	NI	15	7	6	2	1	0.813
	ND	14	9	5	3	0	
Increased AST	NI	27	4	0	0	0	0.99
	ND	28	3	0	0	0	
Increased ALT	NI	28	3	0	0	0	0.99
	ND	28	3	0	0	0	
Increased creatinine	NI	31	0	0	0	0	0.99
	ND	30	1	0	0	0	
Fibrile neutropenia	NI	30	1	0	0	0	0.99
	ND	31	0	0	0	0	
Nausea	NI	25	6	0	0	0	0.193
	ND	19	11	1	0	0	
Vomitting	NI	29	2	0	0	0	0.99
	ND	30	1	0	0	0	
Gastritis	NI	22	8	1	0	0	0.274
	ND	18	13	0	0	0	
Appetite loss	NI	19	9	3	0	0	0.399
	ND	17	13	1	0	0	

3.4. Incidence ratio of adverse events and progression of diabetes mellitus

Table 3 shows the summary of adverse events in each group during NACRT. Grade 3/4 neutropenia occurred in 12 patients in the NI group and 10 patients in the ND group ($p = 0.985$). The occurrences of other hematologic adverse events, including increases in transaminase levels and impaired renal function, were not significantly different between the NI and ND groups. Similarly, the occurrences of non-hematologic side effects, such as nausea, vomiting, and appetite loss, were not significantly different between the NI and ND groups.

The average HbA1c after NACRT was similar in the NI group (6.69 ± 0.99%) and the ND group (6.66 ± 1.07%, $p = 0.894$; Supplementary Fig. 2). The post/pre HbA1c ratio was also similar between the NI and ND groups (1.00 ± 0.21 vs. 1.01 ± 0.97, $p = 0.773$). Three patients in the NI group and two patients in the ND group received additional treatment for the progression of diabetes mellitus. The rates of diabetes mellitus progression were similar between the NI and ND groups (Supplementary Fig. 2).

4. Discussion

In the present study, we found that an EPA-enriched supplement showed promise in providing nutritional benefit to patients with pancreatic cancer that received preoperative NACRT. In general, chemotherapy causes various toxicities, including myelosuppression, stomatitis, nausea, and diarrhea, which result in reduced oral intake. In addition, it is well known that radiation therapy triggers the immune response, which results in a systemic inflammatory reaction [23,24]. Due to these adverse effects, the patient's preoperative nutrition status worsens, which can lead to several postoperative complications [25,26]. In this study, our results also showed that most nutrition indicators significantly decreased after preoperative NACRT.

The n-3 fatty acids, such as EPA and DHA, exhibit strong anti-inflammatory and immunomodulatory effects via direct and indirect mechanisms [27]. Pompeia et al. showed that n-3 fatty acids could inhibit immune and inflammatory functions by decreasing lymphocyte proliferation, cytokine production, natural killer cell cytotoxicity, and antibody production [28]. Moreover, van der Meij et al. showed that oral nutritional supplements containing EPA improved the mid-upper circumference measurement, which is often used as a substitute for skeletal muscle mass, in patients with stage III non-small cell lung cancer that receive chemoradiotherapy [13]. However, they also reported that the EPA intervention group had higher energy and protein intakes than the control group. Consequently, they suspected that the improvement in skeletal muscle mass observed in the EPA intervention group might have been due to the higher energy intake, rather than the inflammatory suppression.

Skeletal muscle mass, including the PMA, is one of the most important nutritional indicators. It is widely used, both for evaluating nutritional status and as a prognostic factor in various cancers [20,29,30]. We showed that PMA loss after NACRT, one of our primary endpoints, improved significantly in the NI group, despite the lack of improvement in skeletal muscle mass, our other primary endpoint. We found that the average energy intake during chemoradiotherapy was similar between the NI and ND groups. In addition, average energy intakes were similar in the good and poor supplement intake subgroups (1380 ± 610 vs. 1360 ± 670, $p = 0.929$; Supplementary Fig. 1). In our study, we didn't set the target calorie and protein, because we wanted to know the additional effect of omega-3 supplementation, so enrolled all patients received nutritional guidance about contents of the meal from managerial dietician, but they never gave guidance about meal size or target calorie unless patients asked about them. As a result, the average total caloric intakes between NI and ND group were similar although the total intake of both groups was low. These results might suggest that nutritional status have improved due to modulations in systemic inflammatory reactions. On the other hand, we did not observe EPA-related improvements in the most commonly used biochemical indicators of nutritional assessments, including albumin and pre-albumin. This lack of detection may be partially due to the relatively small sample size (31 patients/group) and the relatively short treatment period (5 weeks).

The major limitation of our study was the low intake of EPA-enriched supplement, mainly due to its taste. EPA is extracted from fish oil; thus, the fishy taste of EPA-enriched supplements generally makes them difficult to consume in large quantities. Fietkau et al. also reported that enteral nutrition with EPA improved parameters of nutritional and functional status in patients with head and neck or esophageal cancer during chemoradiotherapy; however, they provided enteral nutrition via percutaneous endoscopic gastrostomy (PEG) [16]. Other reports described the immunological benefit of enteral nutrition with n-3 fatty acid-enriched supplements in patients with esophageal cancer; however, most of those studies provided enteral nutrition via a nasal-gastric tube when the patient had difficultly drinking [14,15]. Indeed, we observed that patients that consumed more than half of the EPA-enriched supplement showed significantly better nutrition status than patients in the ND group. Conversely, patients that consumed less than half of the amount provided showed no significant differences from the ND group, in either the skeletal muscle mass ratio or the PMA ratio. These results suggested that the EPA-enriched supplement improved nutritional status during NACRT, but it was difficult to consume for some patients.

Unfortunately, in this study, we did not detect a significant difference in the incidence of NACRT-related adverse events. Miyata et al. showed that an n-3 fatty acid supplement given enterally during preoperative chemotherapy reduced the frequency of chemotherapy-induced toxicities, such as gastritis and diarrhea, in patients with esophageal cancer [31], but it did not alter the incidence of hematologic adverse events. On the other hand, in our institute, gemcitabine was typically used for NACRT. Gemcitabine rarely causes severe non-hematological toxicities, but it is often associated with severe hematologic adverse events. Indeed, we observed no Grade 3/4 non-hematologic toxicities in either the NI or ND group. This low incidence of non-hematologic toxicities may explain why we could not detect any significant difference in the overall incidence of adverse events between the NI and ND groups.

In conclusion, EPA-enriched nutrition may be useful for improving the nutritional status of patients with pancreatic cancer that receive NACRT. However, many patients could not consume sufficient EPA-enriched supplement, due to the taste; therefore, improvements in the taste of these supplements is strongly desirable.

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Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.06.003.

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