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Prognostic Significance of Sarcopenia and Eicosapentaenoic Acid (EPA) Levels in Patients With Unresectable Pancreatic or Biliary Tract Cancer

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Abstract. *Background/Aim: This study aimed to investigate the relationship between prechemotherapy blood eicosapentaenoic acid (EPA) levels, sarcopenia, and overall survival in patients with pancreatic and biliary tract cancer undergoing chemotherapy. Patients and Methods: Forty-five patients with recurrent, non-resected pancreatic or biliary tract cancer undergoing chemotherapy were retrospectively analyzed. The skeletal muscle mass was measured at the third lumbar vertebra. Sarcopenia cut-off values were based on the Japanese Society of Hepatology sarcopenia assessment criteria. Two months after starting chemotherapy, the patients received enteral nutrition containing omega-3 fatty acids. Results: Patients with pancreatic and biliary tract cancers with low pre-treatment blood EPA levels had significantly more intense sarcopenia than those with high EPA levels (p=0.023). Patients with sarcopenia before chemotherapy had significantly lower overall survival than those without sarcopenia. Multivariate analysis revealed blood EPA concentration as an independent prognostic factor (p<0.01). Lumbar muscle volume, a marker of sarcopenia, showed a clear positive correlation with prechemotherapy EPA concentration (p=0.008). In patients administered with enteral nutrition containing omega-3 fatty acids, both EPA concentration and lumbar muscle volume were significantly higher than those prior to intervention, indicating sarcopenia improvement due to the intervention. Conclusion: In patients with recurrent non-resected pancreatic and biliary tract cancer, low blood EPA levels before chemotherapy are associated with sarcopenia and poor prognosis.*

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Key Words: Recurrent, non-resected pancreatic or biliary tract cancer, sarcopenia, eicosapentaenoic acid, chemotherapy, lumbar muscle volume.

Sarcopenia, defined as the loss of skeletal muscle mass and strength, is associated with physical disability, decreased quality of life (QOL), and risk of adverse outcomes, including death (1). In general, patients undergoing treatment for cancer tend to lose weight as treatment causes a decrease in skeletal muscle mass (2, 3). Sarcopenia is reportedly a poor prognostic factor in the treatment of digestive cancer, including pancreatic and liver cancer (4-8). Patients who lose weight are more likely to discontinue treatment than those who do not (2, 3, 9-11). Weight loss in patients with cancer cannot be addressed by simply increasing food intake because the patient's body is chronically inflamed, which increases energy usage, resulting in the loss of skeletal muscle mass and weight loss (12, 13).

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids used in nutritional management of patients with cancer. EPA and DHA reportedly have anti-inflammatory effects (14). Several studies on EPA and DHA as adjuncts to chemotherapy have shown positive effects on tumor response to treatment, protection against treatment-related toxicity, and maintenance of QOL (7, 15-17).

Preoperative sarcopenia can predict long-term outcomes in patients with hepatocellular carcinoma (HCC) (18, 19). Low preoperative blood EPA and DHA levels are common in patients with sarcopenia and indicate poor prognoses.

In this study, we conducted a retrospective analysis to investigate the relationship between prechemotherapy blood

EPA levels, sarcopenia, and overall survival (OS) in patients undergoing chemotherapy for unresectable and postoperative recurrent pancreatic and biliary tract cancer. We assessed whether prechemotherapy EPA levels could predict sarcopenia and prognosis.

Patients and Methods

Patients. Patients with unresectable pancreatic and bile duct cancer who underwent chemotherapy between November 2014 and December 2020 were enrolled as participants. In Japan, the resectability of pancreatic cancer is classified according to the degree of local extension and presence of distant metastases (20).

Treatment and patient management. Chemotherapy regimens for pancreatic cancer included leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX), gemcitabine/cisplatin (GC), and gemcitabine/TS1 (GS), and that for biliary tract cancer included GC and GS. Two months after the start of chemotherapy, the patients were prescribed omega-3 enteral nutrition. Each patient was administered two packs (200 kcal/300 mg omega-3 fatty acid per pack) of an omega-3 fatty acid enteral nutrient (Racol®; Otsuka Pharmaceutical Factory, Tokyo, Japan) daily. A comparative analysis of blood EPA concentration and lumbar muscle volume was performed before and after eight weeks of omega-3 fatty acid administration.

Patient prognostic factors were evaluated by measuring various parameters, including EPA and lumbar muscle mass by Computed Tomography (CT) (*i.e.*, sarcopenia), and the number of times the patient skipped therapy in the first two months after initial chemotherapy.

This study was approved by the Jikei University School of Medicine Ethics Committee (review number: 27-177(8062)). All procedures were performed in accordance with the ethical standards of the committee responsible for human experimentation and the Declaration of Helsinki. Prior informed consent was obtained from all participants.

Measurements. The skeletal muscle index (SMI) at the L3 body lower endplate obtained by CT was used to assess the presence and severity of muscle weakness. L3 SMI was obtained by dividing the total skeletal muscle mass at the L3 level by the square of the height. The cutoff for the diagnosis of low muscle mass was L3-SMI <42 cm^2/m^2 for men and L3-SMI <38 cm^2/m^2 for women, according to the guidelines of the Japan Society of Hepatology (21). Skeletal muscle mass was measured based on bioelectrical impedance analysis using a body composition meter DF860K® (Yamato Scale CO., LTD., Hyogo, Japan). The chemotherapy continuation rate was assessed by the number of times chemotherapy was skipped due to neutropenia two months before and after the start of the study.

Statistical analysis. Continuous variables are presented as medians and compared using the Mann–Whitney *U*-test. Data are expressed as mean±standard error. Statistical significance was set at p-value <0.05. The cumulative OS rate was calculated using the Kaplan–Meier method, and differences between the curves were evaluated using the log-rank test. These analyses were conducted using IBM SPSS (version 20.0; IBM Japan, Tokyo, Japan).

Table I. *Patient characteristics*.

	Total (n=45)
Sex, male (%)	28 (62%)
Age, years, median (range)	68 (37-83)
Pancreatic cancer : Biliary tract cancer	30 (67%):15 (33%)
Recurrent : Unresectable	21 (47%):24 (53%)
BMI, median (IQR)	20.1 (16.0-28.2)
SMI (cm^2/m^2), median (IQR)	39.5 (32.2-47.9)
SM (kg), median (IQR)	14.8 (12.2-16.9)
Sarcopenia, yes	24 (53%)
Prealbumin (mg/dl), median (IQR)	18.6 (14.7-23.0)
RBP (mg/dl), median (IQR)	2.4 (1.7-2.8)
EPA (mg/ml), median (IQR)	38.6 (32.5-63.2)
DHA (mg/ml), median (IQR)	118.8 (99.8-140.5)
CEA (ng/ml), median (IQR)	5.6 (3.0-9.4)
Chemotherapy regimens	
Pancreatic cancer	30
FOLFIRINOX	6 (20%)
GEM+nab-PTX	9 (30%)
GEM+TS1	9 (30%)
Others	6 (20%)
Biliary tract cancer	15
GEM+Cisplatin	12 (80%)
Others	3 (20%)
Number of chemotherapies skipped, median (range)	1.0 (1.0-7.0)

SMI: Skeletal muscle index: SM: skeletal muscle: EPA: eicosapentaenoic acid: DHA: docosahexaenoic acid: CEA: carcinoembryonic antigen: RBP: retinol-binding protein.

Results

Effect of sarcopenia and prechemotherapy EPA levels on OS in patients with advanced recurrent pancreatic and biliary tract cancer. Patient backgrounds before chemotherapy treatment are shown in Table I. We determined whether the presence or absence of prechemotherapy sarcopenia affected survival. The results showed that patients with sarcopenia before chemotherapy had significantly lower OS than those without sarcopenia (p=0.023) (Figure 1A). Comparing OS between the high and low EPA groups before chemotherapy, the low EPA group had a significantly poorer prognosis than that of the high EPA group (p=0.002) (Figure 1B).

To identify prognostic factors in patients with pancreatic and biliary tract cancer undergoing chemotherapy, a univariate analysis followed by multivariate analysis was conducted using sex, age at the start of treatment, blood and biochemical indices, and the number of skipped chemotherapy sessions two months after treatment started as independent variables and OS as the dependent variable. The multivariate analysis showed that the number of chemotherapy skips (p=0.02), carcinoembryonic antigen (CEA) levels (p<0.01), and blood EPA levels (p<0.01) were prognostic factors (Table II). Sarcopenia was not detected as an independent poor prognostic factor (p=0.48) (Table II).

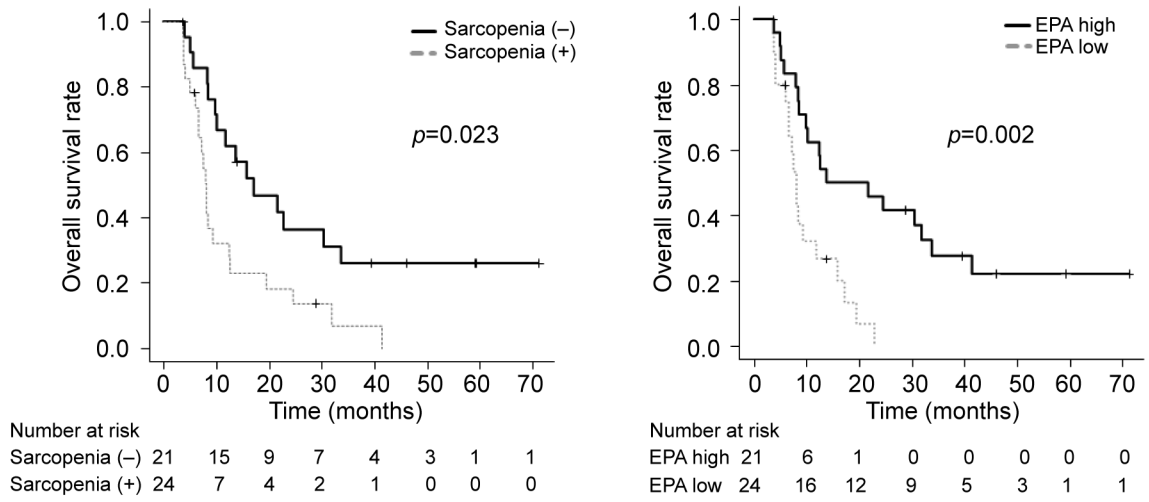

Figure 1. *Kaplan–Meier plots. A) The relationship between the presence or absence of sarcopenia before chemotherapy and overall survival rate. B) The relationship between high and low EPA levels before chemotherapy and overall survival rate.*

Table II. *Univariate and multivariate analyses for overall survival.*

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Sex, male	1.22 (0.61-2.43)	0.57		
Age, >69 years	1.08 (0.56-2.13)	0.79		
Diagnosis, pancreatic cancer	1.37 (0.91-2.00)	0.10		
Unresectable, yes	0.92 (0.66-1.28)	0.63		
Sarcopenia, yes	1.56 (1.11-2.17)	0.01	1.15 (0.78-1.72)	0.48
EPA, <39 mg/ml	3.13 (1.47-6.67)	<0.01	2.08 (1.40-3.09)	<0.01
DHA, <112 mg/ml	1.61 (1.14-2.29)	<0.01	1.21 (0.80-1.81)	0.37
CEA, >4 ng/ml	1.28 (1.02-2.00)	0.04	1.72 (1.19-2.44)	<0.01
Number of chemotherapies skipped, <3.5	1.35 (0.95-1.92)	<0.01	1.54 (1.19-2.22)	0.02

CEA: Carcinoembryonic antigen: EPA: eicosapentaenoic acid: DHA: docosahexaenoic acid.

Effect of blood EPA on lumbar muscle volume in patients with advanced recurrent pancreatic and biliary tract cancer. Correlation analysis of lumbar muscle volume with EPA and DHA levels before chemotherapy revealed a clear positive correlation (p=0.008 and 0.015, respectively) (Figure 2).

When patients were administered enteral nutrition containing omega-3 fatty acids two months after initial chemotherapy, both EPA concentration (Figure 3A) and lumbar muscle volume (Figure 3B) increased significantly compared to those before the intervention, suggesting that omega-3 fatty acid administration improved sarcopenia.

Discussion

Patients with pancreatic and biliary tract cancer with low prechemotherapy blood EPA levels had significantly worse sarcopenia and poorer prognosis than those with high EPA levels. Multivariate analysis of OS also revealed that a low prechemotherapy EPA concentration was an independent poor prognostic factor. Patients with sarcopenia had significantly lower 2-year OS than those without, however sarcopenia was not detected as a poor prognostic factor in multivariate analysis. Multivariate results may indicate confounding factors because sarcopenia is a complex syndrome. Therefore, it may be advised to use prechemotherapy EPA concentrations as a prognostic factor in patients with advanced pancreatic and biliary tract cancer.

Prechemotherapy EPA was strongly correlated with lumbar muscle volume in patients with unresectable pancreatic and biliary tract cancer. Currently, CT is used to measure lumbar muscle to diagnose sarcopenia; however, this process is time-consuming, and measurements vary depending on the method

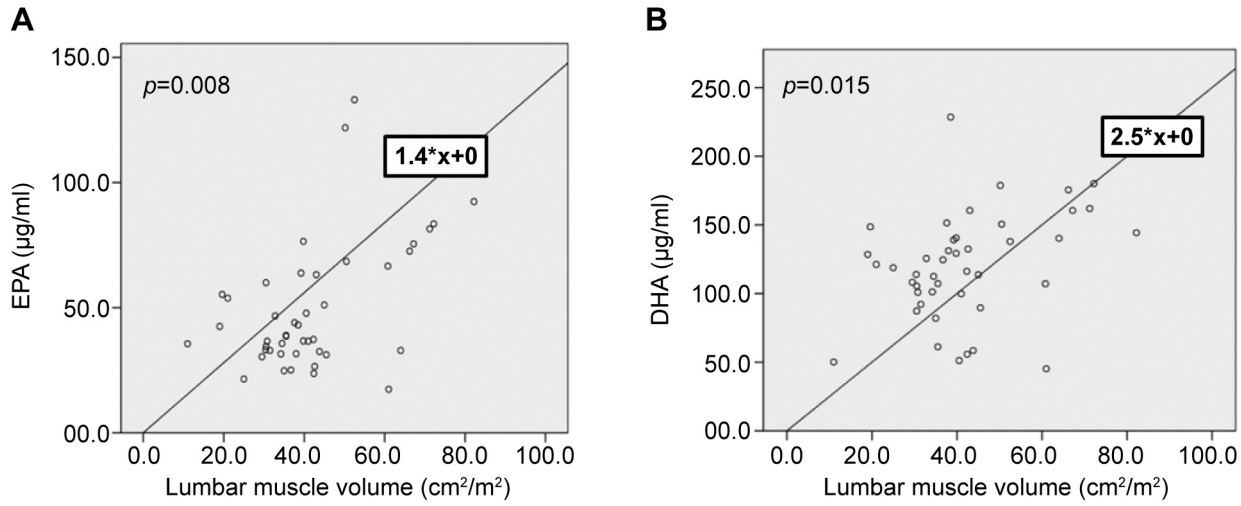

Figure 2. *Relationship between lumbar muscle volume and blood EPA (A) and DHA (B) levels before chemotherapy.*

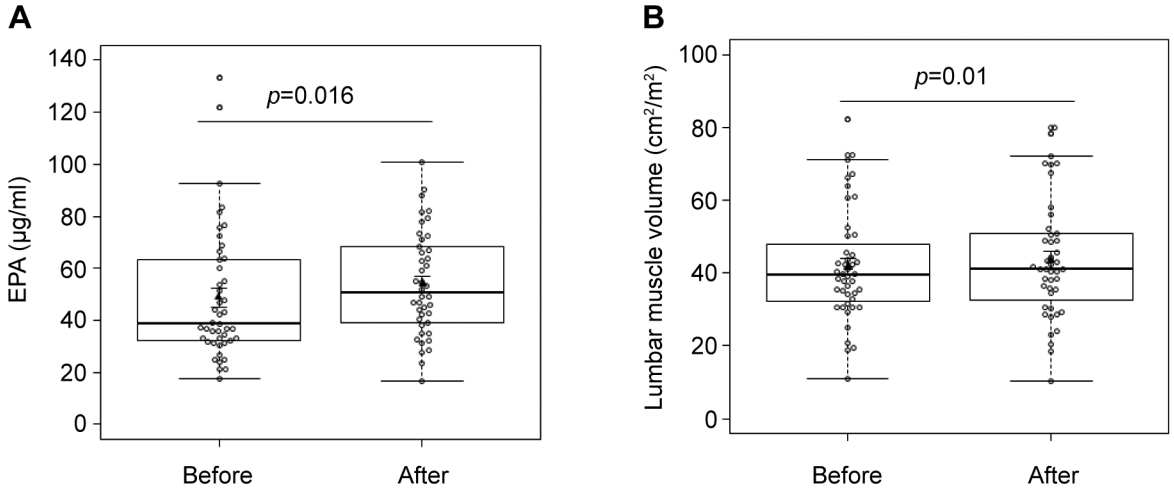

Figure 3. *Changes in EPA levels and skeletal muscle mass after omega-3 fatty acid intervention. A) EPA value. Data are expressed as mean±standard error of the mean (SEM). Wilcoxon rank-sum test was used to compare pairs of results. B) Lumbar muscle volume. Data are presented as mean±SEM (▲: mean). Paired t-test was used to compare pairs of results.*

used. Prechemotherapy blood EPA concentration is effective in evaluating sarcopenia. Blood EPA concentration is easy to measure, has a fixed value, and has no risk of error introduced by the person performing measurements. Measuring EPA levels before chemotherapy and predicting prognosis can lead to effective treatment strategies.

Itoh *et al*. found that preoperative sarcopenia was significantly correlated with adverse survival in patients with HCC after liver resection, and low levels of EPA and DHA were associated with preoperative sarcopenia (18). However, whether nutritional support with omega-3 fatty acids could prevent or manage skeletal muscle mass loss remains unelucidated. In this study, when patients received enteral nutrition containing omega-3 fatty acids two months after the start of chemotherapy, both EPA levels and lumbar muscle volume increased significantly at eight weeks post-intervention compared with that at pre-intervention, suggesting an improvement in sarcopenia.

When the amount of EPA increases in cell membrane phospholipids, arachidonic acid and EPA become competitive substrates for the same enzymes. As a result, the relative increase in the less bioactive leukotriene-5 and prostaglandin-3 produced by EPA reduces the activity of inflammation-inducing substances (14). Furthermore, lysorbin, a metabolite of EPA, suppresses NF-κB activation *via* Toll-like receptors

and is a potent regulator of inflammatory cytokine production (22). In patients with recurrent, non-resected pancreatic or biliary tract cancer, high blood EPA levels reduce inflammation, and consequently, sarcopenia progression. This effect can be replicated by intervention with omega-3 fatty acids during chemotherapy.

The limitations of this study are as follows: first, the number of cases analyzed was small. Second, because this is a retrospective study, the temporal order of observations is the opposite of the causal order, which may introduce recall bias when collecting past information (23). Third, while the enteric nutrients used in this study have the highest omega-3 fatty acid content among those currently used in Japan, they also include other nutrients, such as carbohydrates, proteins, and vitamins.

Based on evidence from various systematic reviews (15, 24-26), the ESPEN guidelines on nutrition in cancer patients recommend using supplementation with long-chain omega-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass, and weight in patients with advanced cancer receiving chemotherapy who are at risk for weight loss or malnutrition; however, evidence is lacking (27). The reasons include the small number of evidence-based studies, variations in supplement dosages and methods, and differences in primary endpoints (16). Improving this requires randomized, blinded trials with justified sample sizes, appropriate dosing, monitored compliance, and measuring clinically important endpoints.

In conclusion, low prechemotherapy blood EPA levels were associated with poor prognosis in patients with recurrent non-resected pancreatic and biliary tract cancers. Pre-treatment EPA intervention may contribute to improved prognosis.

Conclusion

Low EPA levels in the blood prior to chemotherapy are linked to sarcopenia and a poor prognosis in patients with recurrent non-resected pancreatic and biliary tract cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Study conception and design: Kyohei Abe, Kenei Furukawa. Acquisition of data: Yoshihiro Shirai, Shinji Onda, Miyabi Tsunematsu, Koichiro Haruki, Munetoshi Akaoka. Analysis and interpretation of data: All Authors. Drafting of manuscript: Kyohei Abe.

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