Effects of perioperative eicosapentaenoic acid-enriched oral nutritional supplement on the long-term oncological outcomes after total gastrectomy for gastric cancer

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Abstract. Basic and clinical reports have suggested that eicosapentaenoic acid (EPA) exhibits anti-tumor activity. The present study evaluated whether perioperative EPA could improve the survival of patients with localized gastric cancer as a key secondary endpoint of a randomized clinical study. The present study was designed as multicenter, open-label, superiority, randomized trial to confirm the preventive effect of EPA on body weight loss after total gastrectomy for gastric cancer. Eligible patients were randomized to either the standard-diet group (EPA-off group) or EPA-on group by a centralized dynamic method. An EPA-enriched supplement (ProSure®) was given to the EPA-on group in addition to their standard diet. This supplement included 600 kcal with 2.2 g/day of EPA. Among the 126 patients who were randomized, 123 patients (EPA-off group, n=60; EPA-on group, n=63) were examined in the survival analyses. All background factors were well balanced between the two groups. The 3-year and 5-year overall survival rates were 74.6 and 67.8%, respectively, in the EPA-off group, and 77.8 and 76.2% in the EPA-on group. There was no significant difference between the EPA-off and EPA-on groups (hazard ratio, 0.77; P=0.424). In the subgroup analysis, the hazard ratio was 0.39 in patients who received neoadjuvant chemotherapy and 0.57 in patients with nodal metastasis. In conclusion, a clear survival benefit of perioperative EPA was not observed in localized gastric cancer. The value of EPA should be further tested in a future study in patients with unfavorable advanced gastric cancer. Clinical trial number: UMIN000006380; date of registration, September 21, 2011.

Introduction

Gastric cancer is the third most-common cancer and the second leading cause of cancer-related death in the world (1,2). D2 gastrectomy combined with chemotherapy is a standard treatment for gastric cancer; however, almost half of the patients had recurrence, even after modern multidisciplinary treatment (3-5). To further improve the patient's survival, approaches than conventional chemotherapy should be considered.

The administration of eicosapentaenoic acid (EPA), a long-chain polyunsaturated fatty acid of the omega-3 (n-3) family, may be an attractive approach (6,7). Many previous studies have clarified that EPA could be selectively cytotoxic to various tumor cells *in vitro* and *in vivo* (8-10). Moreover, EPA was reported to suppress pro-inflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factors (TNF), which is released by surgical stress (11,12). Recent studies clarified that pro-inflammatory cytokines play a critical roles in tumors (e.g., survival, proliferation, metastasis, and resistance to chemotherapy) (13,14). Thus, the perioperative administration of EPA could improve the prognosis of gastric cancer patients.

However, there is little evidence to support that EPA is associated with a clear survival benefit in cancer patients (15-17).

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Cockbain *et al* examined the efficacy of EPA in a small randomized study targeting colorectal cancer patients with liver metastasis who had undergone liver surgery (15). In their study, the EPA group showed better survival than a placebo group; however, the difference was not statistically significant. In the multivariate analysis, they only showed that EPA supplementation was an independent prognostic factor for overall survival (P=0.05). Thus, an apparent clinical benefit of EPA was not demonstrated. Moreover, the efficacy of EPA on long-term outcomes in other human malignancies has not been examined.

Previously, we conducted a prospective multicenter randomized trial to evaluate whether perioperative EPA-enriched nutritional supplementation can improve the short-term and long-term outcomes of patients with localized gastric cancer who require total gastrectomy as curative treatment (18,19). In the primary analysis, we evaluated whether body weight loss caused by surgical stress and gastrectomy was prevented by EPA supplementation. Although perioperative EPA can be safely administered, postoperative weight loss was not prevented. We herein report the long-term oncological outcomes, which reflect antitumor activity, a key secondary endpoint, in this randomized study.

Patients and methods

Patients. The present study was designed as a multicenter, open-label, superiority, randomized trial comparing perioperative care with or without EPA-enriched oral nutritional supplementation for patients diagnosed with gastric cancer who required total gastrectomy as a curative treatment (clinical trial number: UMIN000006380, 21/September/2011). This study was approved by Kanagawa Cancer Center Institutional Review Board committee (IRB approval no. rinsyokenkyu:34) and we obtained written informed consent from the patients. The primary endpoint was body weight loss at 1 and 3 months after surgery. Key secondary endpoints were overall survival (OS). The details of this trial were described in a previous report. Briefly, key eligibility criteria included histologically proven adenocarcinoma of the stomach, clinical T1-T4a and M0, planned R0 resection by total gastrectomy. Eligible patients were randomized to either the EPA-off group or EPA-on group.

Perioperative care. In addition to the standard diet, an EPA-enriched supplement (ProSure®, Abbott Japan, Tokyo, Japan) was given to the EPA-on group but not to the EPA-off group. This supplement included 600 kcal with 2.2 g/day of EPA. The supplement was given from 1-7 days before surgery and 2-21 days after surgery.

Surgery. Based on the Japanese gastric cancer treatment guidelines published in 2010 (ver. 3), total gastrectomy with lymph node dissection to the D1+ or D2 level was planned (20). Principally, D1+ lymphadenectomy was selected for patients with cT1N0 tumors other than those for whom endoscopic mucosal resection or endoscopic submucosal dissection were recommend. D2 lymphadenectomy was indicated for patients with potentially curable T2-T4 tumors, as well as for those with cT1N+ tumors.

Perioperative chemotherapy. When patients had unfavorable advanced gastric cancer (e.g., cT3) in the case of junctional cancer/scirrhous type/giant type 3, cT4, para-aortic nodal metastasis, and/or bulky nodal metastasis around the major branched artery, neoadjuvant chemotherapy with S-1/CDDP or docetaxel/CDDP/S-1 (2 or 4 courses) would have been planned as a clinical trial (21,22).

After surgery, S-1 chemotherapy for 1 year would be planned for patients diagnosed with pathological stage II or III (23).

Follow-up. The patients were followed at outpatient clinics. The follow-up program of postoperative surveillance principally consisted of a physical examination and blood chemistry assessments (including carcinoma tumor markers) every 3 months for the first year and every 6 months thereafter; and computed tomography of the neck, chest, and abdomen every 6 months.

Evaluations and statistical analyses. OS was defined as the period between random assignment and death. The data of patients who had not experienced an event were censored at the date of the final observation. OS curves were calculated using the Kaplan-Meier method and were compared by the log-rank test. The SAS software program (version 9.4; SAS Institut) was used to perform all of the statistical analyses.

Results

Patient background characteristics. A total of 127 patients from eight hospitals were enrolled in the present trial between October 2011 and July 2014. Fig. 1 shows the CONSORT diagram. Among 127 patients who were entered, 123 patients (EPA-off group; n=60 and EPA-on group; n=63) were finally eligible for inclusion in the present study. Table I shows the patient background characteristics and operative details. The baseline characteristics and surgical procedures were well balanced between the two groups. Median relative performance of supplement in EPA-ON group was 100% before surgery and 54% after surgery. There were no adverse events due to EPA-enriched supplement. Postoperative surgical complications were observed in 8 patients in the EPA-off group and 9 patients in the EPA-on group, and did not differ to a statistically significant extent (Table II). In the EPA-on group, the median relative performance of supplementation was 100% before surgery and 54% after gastrectomy. The median dose of the EPA was 15.4 g before surgery and 23.1 g after surgery. In total, the median cumulative dose of EPA was 38.5 g.

Survival analysis. Fig. 2 shows the OS curves. The 3-year and 5-year OS rates were 74.6 and 67.8%, respectively in the EPA-off group, and 77.8 and 76.2% in the EPA-on group, which did not amount to a statistically significant difference [hazard ratio, 0.77; 95% confidence interval (CI), 0.40-1.47; P=0.424].

Subgroup analysis of overall survival and recurrence free survival. Fig. 3 shows the subgroup analyses by neoadjuvant chemotherapy, and pathological T and N factors for OS.

Table I. Background characteristics between the EPA-on and EPA-off groups.

Characteristic	EPA-on group (n=63)	EPA-off group (n=60)
Median age, years (range)	65.1 (31-79)	65.6 (30-80)
Sex, male/female	46/17	43/17
Preoperative mean body weight, kg	47.1±9.8	47.8±8.6
Mean height, cm	160.6±8.4	163.7±8.0
Preoperative mean lean body mass, kg	45.7±9.3	47.0±7.5
Mean preoperative serum albumin, mg/dl	4.1±0.5	4.2±0.4
Mean preoperative C-reactive protein, mg/dl	0.3±0.5	0.2±0.5
Location of primary tumor, upper third/middle third/lower third	42/17/4	35/24/0
Clinical T factor, T1/T2/T3/T4	12/13/12/26	16/10/11/23
Clinical N factor, negative/positive	40/23	39/21
Surgical approach, conventional/laparoscopic	52/11	47/13
Extent of lymph node dissection, D0/D1/D2/D3	0/10/53/0	1/15/43/1
Mean operation time, min (range)	296 (145-510)	295 (83-523)
Mean blood loss, ml (range)	340 (0-3,560)	320 (0-2,080)

EPA, eicosapentaenoic acid.

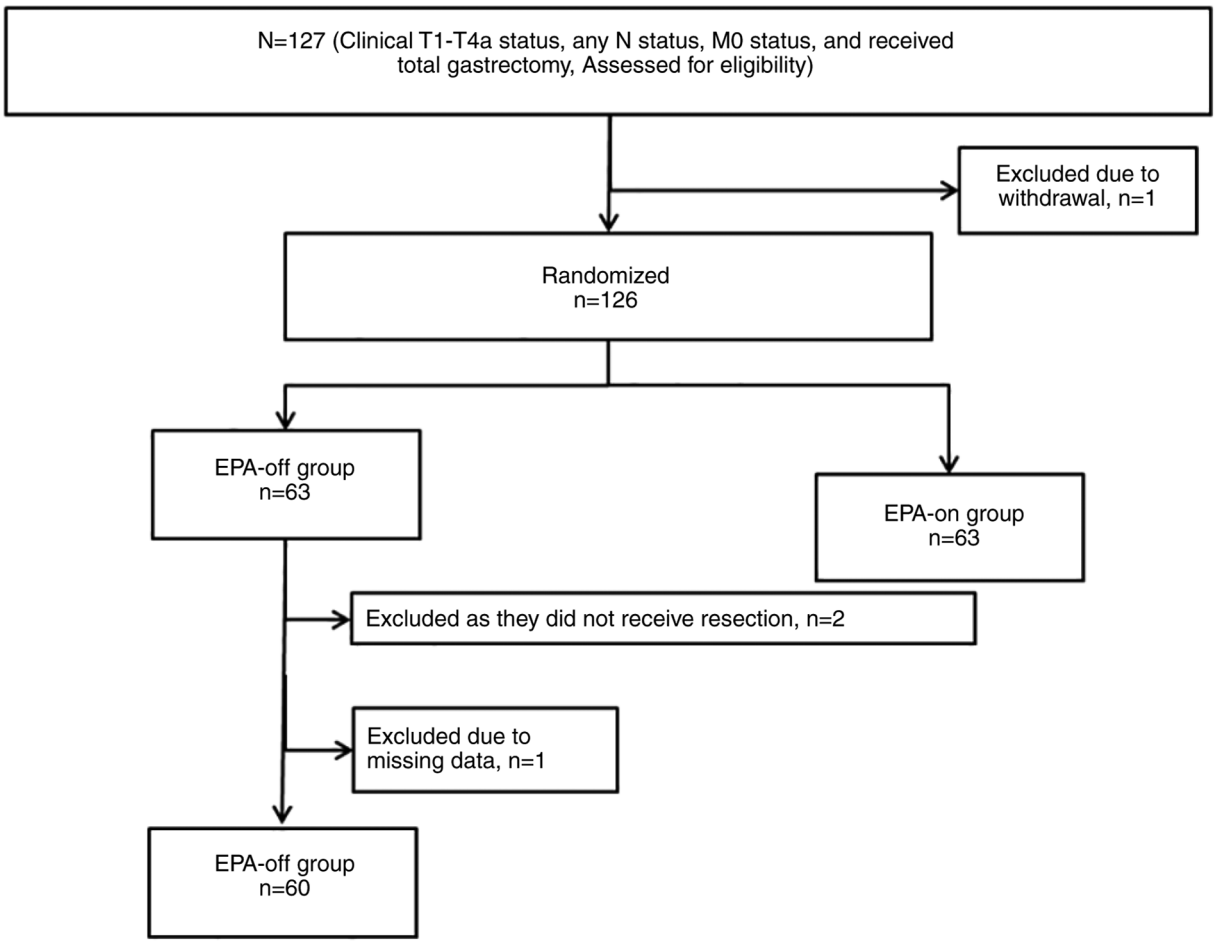

Figure 1. Flow diagram of the 127 patients. EPA, eicosapentaenoic acid.

Among the various sub-group factors, the patients in the EPA-on group who received neoadjuvant chemotherapy (NAC) and who had lymph node metastasis showed slightly better survival. In the patients who received NAC, the 5-year OS rate was 43.8% (95% CI, 19.4-68.1%) in the EPA-off group and 71.4% (95% CI, 47.8-95.1%) in the EPA-on group

Table II. Surgical morbidity between EPA-on group and EPA-off group.

Morbidity[a]	EPA-on group (n=63)	EPA-off group (n=60)
Overall	9	9
Pancreatic fistula	2	2
Abdominal abscess	2	1
Anatomic leakage	0	1
Bleeding	1	0
Others	4	4

[a]Defined as grade III or more by Clavien-Dindo classification (29). EPA, eicosapentaenoic acid.

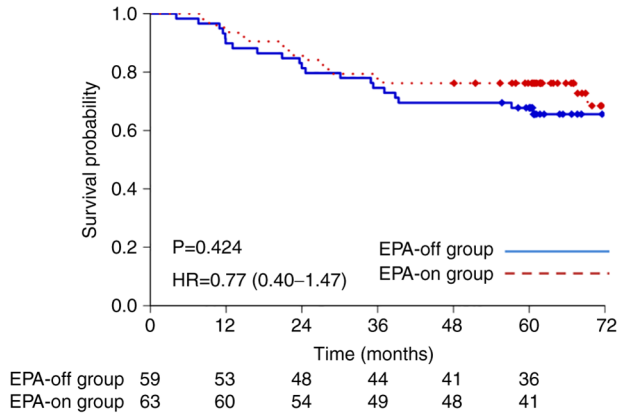

Figure 2. Comparison of overall survival in the patients in the EPA-on and EPA-off groups. EPA, eicosapentaenoic acid.

(hazard ratio, 0.39; 95% CI, 0.12-1.28; P=0.108) (Fig. 4). In patients who had lymph node metastasis, the 5-year OS rate was 52.0% (95% CI, 32.4-71.6%) in the EPA-off group and 71.8% (95% CI, 57.7-86.0%) in the EPA-on group (hazard ratio, 0.57; 95% CI, 0.12-1.28; P=0.148). On the other hand, in the patients who did not receive NAC, the 5-year OS rate was 76.7% (95% CI, 64.0-89.3%) in the EPA-off group and 77.6% (95% CI, 65.9-89.2%) in the EPA-on group (hazard ratio, 1.06; 95% CI, 0.47-2.37; P=0.887) (Fig. 5). In lymph node metastasis-negative patients, the 5-year OS rate was 81.8% (95% CI, 68.7-95.0%) in the EPA-off group and 83.3% (95% CI, 68.4-98.2%) in the EPA-on group (hazard ratio, 0.94; 95% CI, 0.27-3.33; P=0.923).

Discussion

The aim of the present analysis was to explore whether perioperative eicosapentaenoic acid (EPA) supplementation could improve the survival of patients with localized gastric cancer that required curative total gastrectomy. This is the first randomized study to demonstrate a prognostic effect of EPA in patients with gastric cancer. The major finding of this study was that a clear survival benefit of perioperative EPA was not observed in gastric cancer patients.

Previously, Cockbain *et al* showed that EPA therapy had a marginal survival in patients with liver metastasis of colorectal cancer (15). There were some differences between the present study and the study by Cockbain *et al*. The first difference was the median cumulative dose of EPA, which was 38.5 g in this study but 60 g (calculated from their results) in their study. Thus, the cumulative EPA dose of their study was higher than that of the present study. Second, the tumor stage was different. In the present study, patients with localized tumors were targeted, while their study targeted patients with metastatic tumors. In addition to the marginal survival benefit in their study, they also demonstrated that EPA had anti-angiogenesis effects using biopsy specimens. Angiogenesis plays an important role in metastatic tumors but would not play an important role in micro-metastatic tumor cells. Several pivotal phase III studies demonstrated that the patient survival was significantly improved by bevacizumab and ramucirumab (vascular endothelial growth factor inhibitors) in metastatic colorectal cancer and by ramucirumab in metastatic gastric cancer (24-26). On the other hand, the efficacy of bevacizumab was not confirmed in the phase III trials, not only for resectable gastric cancer but also for colorectal cancer (27,28). Whether the target is micrometastatic or metastatic disease might affect the efficacy of EPA.

Although the OS rates were similar between the two groups, the hazard ratio was slightly lower than 1.0 for OS, which suggests some clinical efficacy of EPA in gastric cancer. In the subgroup analyses for OS, the hazard ratio was 0.39 for OS in patients who received NAC and 0.57 in patients who had nodal metastasis. In the present cohort, patients who received NAC were limited to patients with cT3 in the case of junctional cancer, scirrhous type, or giant type 3, cT4, para-aortic nodal metastasis, and/or bulky nodal metastasis around the major branched artery. Thus, patients showing a low hazard ratio were considered to have a relatively poor prognosis. It would be interesting to investigate whether EPA is effective for such unfavorable advanced gastric cancer in a future study. On the other hand, the hazard ratio was almost 1.0 in patients who did not receive the NAC and in patients who had no nodal metastasis. EPA would not be effective for these patients.

The present study was associated with some limitations. First, the primary endpoint of the present randomized study was not survival. The sample size was relatively small and was not set to investigate differences in survival. Thus, the results were not confirmatory. Second, EPA could be included in the dietary supplements. The clinical trial using the dietary supplements had bias that the patients buy the corresponding dietary supplements outside of the clinical trial without letting their physicians know. Thus, the negative results may be the result of a bias that the placebo group took the dietary supplement without permission and thereby falsified the end results. We con not exclude that their negative outcome is the result of such a bias. Third, we used oral nutritional supplementation including EPA in this study. The differences between the two groups were not limited to EPA, there were also differences in other nutrients. Thus, we cannot deny the effects of other nutrients.

In conclusion, the present study could not demonstrate a clear survival benefit of EPA supplementation in patients who received curative gastrectomy for gastric cancer. The value of EPA should be further tested in a future study by selecting patients with unfavorable advanced gastric cancer.

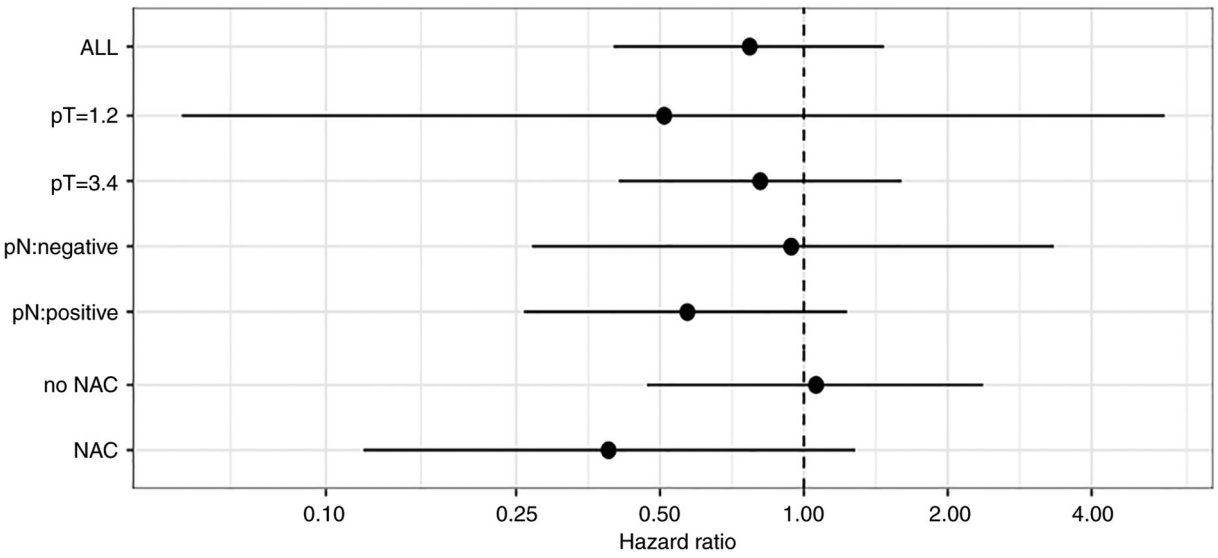

Figure 3. Overall survival in the subgroups. NAC, neoadjuvant chemotherapy.

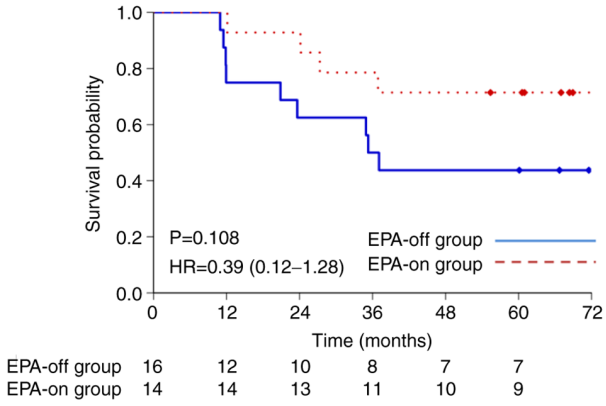

Figure 4. Comparison of overall survival in the patients who received neoadjuvant chemotherapy in the EPA-on and EPA-off groups. EPA, eicosapentaenoic acid.

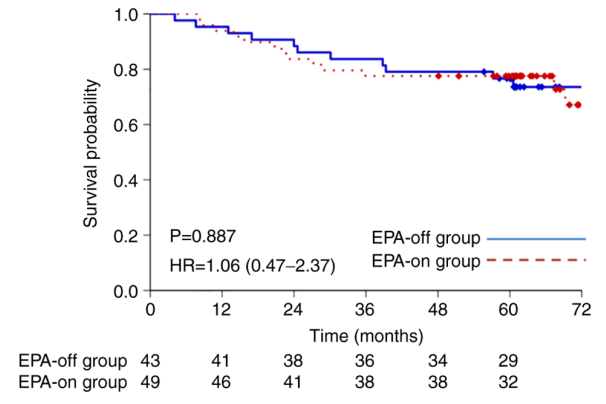

Figure 5. Comparison of overall survival in the patients who did not receive neoadjuvant chemotherapy in the EPA-on and EPA-off groups. EPA, eicosapentaenoic acid.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TA and TY made substantial contributions to the conception and design. TA and TY confirm the authenticity of all the raw data. SI, HC, KS, YI, KF, NT, YK, KN, SN and NH made substantial contributions to the acquisition of data, or the analysis and interpretation of data. TA and TY were involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study data and informed consent were obtained in accordance with the Declaration of Helsinki and were approved by Kanagawa Cancer Center Institutional Review Board committee (IRB approval no. rinsyokenkyu:34). Written informed consent or a substitute for it was obtained from all patients for inclusion in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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