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Effects of Preoperative Use of an Immune-Enhancing Diet on Postoperative Complications and Long-Term Outcome: A Randomized Clinical Trial in Colorectal Cancer Surgery in Japanese Patients

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Abstract

Background: Despite recent advances in surgical techniques and perioperative management, postoperative infectious complications remain a problem in surgical patients. We performed a prospective randomized clinical trial to examine the effects of preoperative Immune Enhancing Diets (IEDs) on postoperative complications in Japanese patients who underwent curative colorectal cancer surgery. This study was also designed to evaluate the optimal dose of preoperative IEDs for the patients without malnutrition. Finally, we analyzed recurrence free survival (RFS) and disease-specific survival (DSS) after surgery in patients who did and did not receive IEDs preoperatively.

Material and Methods: This was a prospective, randomized clinical trial conducted at the Department of Surgery, National Defense Medical College, from October 2002 to October 2005. The 88 patients undergoing colorectal surgery were enrolled and were randomly divided into 3 groups. The high- (High, *N*=26) and low- (Low, *N*=31) dose groups received normal food and, respectively, 750ml/day or 250ml/ day of IEDs for 5 days before the operation. The primary endpoint was the rates of surgical site infection (SSI) and non- infectious complications. We also evaluated the RFS and DSS rate, respectively.

Results: The patients were followed for 77±10 months (9-133 months) after surgery. Incisional SSI rates in the IEDs (High and Low) groups were significantly lower than in the Control group. (0%*, 0%* and 17%) (*$P<0.01$ vs. Control) The incidences of the infections not involving the surgical site (non-SSI) and the lengths of hospital stay were similar among the three groups. No significant differences were observed in RFS or DSS.

Conclusion: In Japanese patients undergoing colorectal cancer surgery, preoperative IEDs significantly reduced the rate of incisional SSI as compared with the control group. Very interestingly, in Japanese patients, preoperative 250ml/day IED intake may be adequate for colorectal cancer patients without malnutrition. However, with regard to the long term outcome, beneficial effects of preoperative IEDs are not evident.

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INTRODUCTION

Despite recent advances in surgical techniques and perioperative management, postoperative infectious complications remain a problem in surgical patients. Once this infectious complication has occurred, it increases medical costs, worsens quality of life for patients and prolongs hospitalization in the short term. Postoperative infectious complications may delay the initiation of adjuvant therapy or modify the systemic inflammatory response and provide favorable conditions for tumor growth, resulting in poor long term outcomes.[1-3] Among infectious complications, with colorectal surgery especially, surgical site infection (SSI) is a frequent cause of morbidity with an incidence of up to 30% in previous studies.[4-6] Decreasing postoperative infectious complications are thus an important issue.

With the advent of novel nutritional formulas containing agents that modulate the immune system, such

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as glutamine, arginine, n-3 fatty acids and RNA, a new era of nutritional therapy began almost two decades ago. The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines[7], published in 2006, recommend an immunomodulating formula (enriched with arginine, omega-3 fatty acids, and nucleotides), especially for patients with an obviously severe nutritional risk and those who underwent major surgery. To date, randomized clinical studies have shown preoperative Immune Enhancing Diets (IEDs) containing arginine and ω-3 fatty acids to be useful for improving the **immunological** response and for decreasing infection rates after resection of colorectal and other gastrointestinal cancers.[8-9] However, nearly all of these studies were conducted in western countries.

In Japan, since an enteral diet was introduced for immunonutrition in 2002, many reports have examined the preventive effects of enteral diets on infectious complications in patients undergoing gastrointestinal surgery. However, there are only a few Japanese reports focusing on colorectal surgery.[10] Moreover, to the best of our knowledge, the effects of preoperative intake of IEDs on long-term outcomes of cancer surgery have not yet been reported.

We performed a prospective randomized clinical trial to examine the effects of preoperative IEDs on postoperative complications in Japanese patients who underwent curative colorectal cancer surgery. This study was also designed to evaluate the optimal dose of preoperative IEDs for patients without malnutrition undergoing elective colorectal resection. Finally, we analyzed recurrence free survival (RFS) and disease-specific survival (DSS) after surgery in patients who did and did not receive IEDs preoperatively.

MATERIALS AND METHODS

Patients and Clinical Protocol

This was a prospective, randomized clinical trial conducted at the Department of Surgery, National Defense Medical College **in Tokorozawa Saitama Japan.** From October 2002 to October 2005, 88 patients undergoing colorectal surgery were enrolled in this clinical study. The exclusion criteria were age younger than 18 years, active preoperative infection, administration of corticosteroids or other immune-suppressive agents, gastrointestinal obstruction, respiratory dysfunction (arterial PaO_2<70mmHg), cardiac dysfunction (New York Heart Association class>3), renal failure (serum creatinine >3mg/dl or hemodialysis), hepatic dysfunction (Child-Pugh grade C), history of recent immunosuppressive or immunologic diseases, and preoperative evidence of widespread metastatic disease. The study protocol was performed following the approval of the Institutional Review Board of the National Defense Medical College and was registered in the University Hospital Medical Information Network (UMIN) database (ID 000012679). The subjects were enrolled in the current study only when wrote informed consent was obtained from the patient and/or from family members, once the study protocol had been explained in detail. After enrollment, the secretary of the surgical department opened a sealed opaque envelope and randomized the patients into the control or trial groups. The 88 patients were randomly divided into 3 groups. The high- (High, *n*=26) and low- (Low, *n*=31) dose groups received normal food and, respectively, 750 ml/day or 250 ml/ day of IEDs enriched with arginine, omega-3 fatty acids and RNA (oral IMPACT®; Ajinomoto Pharma Co., Ltd, Tokyo, Japan) for 5 days before the operation. The constituents of IMPACT® are shown elsewhere (Table 1). The control group (Control, *n*=31) was given normal food without an IED. The clinical protocol is shown in Figure 1. No patients received steroids or non-steroidal anti-inflammatory drugs postoperatively. After the operation, 3 patients were excluded because of non-curative resection.

Table 1
Composition of IMPACT®

	Amount (per100ml)
Energy (kcal)	101
Protein (g)	5.6
Fat (g)	2.8
Eicosapentaneoic acid (g)	0.20
Docosahexaenoic acid (g)	0.14
n-6:n-3 ration	4:5
Carbohydrate (g)	13.4
Arginine (g)	1.28
RNA (mg)	0.13

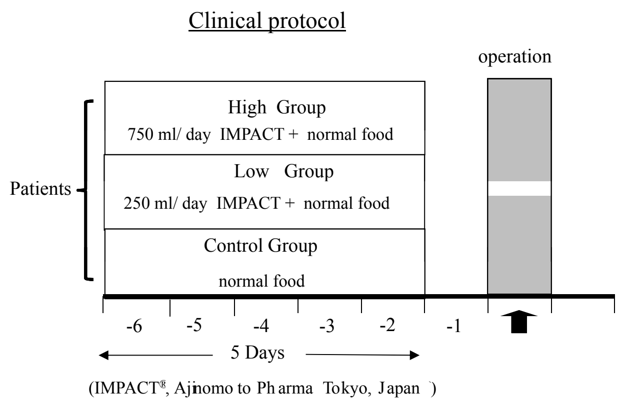

Figure 1
Flow Diagram of the Study Protocol

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Figure 2 shows the patient distribution of this analysis.

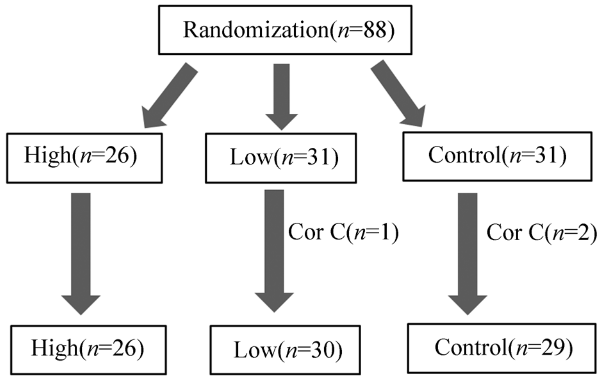

Figure 2
Patient Distribution

Surgical Procedure

The anesthesia, surgical procedure, and postoperative care following colorectal cancer surgery are standardized in the National Defense Medical College.[11-12] All patients underwent elective resection of the colon and rectum via laparotomy. Mechanical bowel preparation was performed in all the patients. **No patients in any of the groups received preoperative oral antibiotics.** Single-shot antibiotics (1g cefmetazole IV) were routinely used for infection prophylaxis and were given during induction of anesthesia and repeated every 4 hours during surgery. Administraion of antibiotics was continued twice a day for 3 days after surgery. Before closing the abdomen, the abdominal cavity was washed with 3,000 ml of warm saline. The pathological classification of the primary tumor, the degree of lymph node involvement, and the presence of organ metastasis were characterized according to the TNM/UICC classification.

Measurement of Nutritional Variables and Blood Biochemical Examinations

The WBC and serum C-reactive protein (CRP) levels were measured preoperatively and at 1, 4, and 7 days after surgery. Before and after administration of the IEDs, the following parameters were determined in all patients: The total protein (TP), albumin (Alb), total cholesterol (TCHO), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood urinary nitrogen (BUN), creatinine (CRE) and cholinesterase (ChE) concentrations in serum and total lymphocyte count (P-LYMPH).

Definitions of Infectious and Other Complications

We analyzed the data for age, sex, height, weight, body mass index (BMI), cancer site and stage, operative procedures on the rectum, and operative time and blood loss. Postoperative complications were defined in the following manner. SSI was diagnosed according to CDC definitions of nosocomial SSI.[13] SSI are divided into incisional SSI and organ/space SSI. Organ/space SSI included intra-abdominal or pelvic abscess and anastomotic leakage. Follow-up for SSI was performed during office visits for 30 days after hospital discharge. **Non-SSI was defined as an infection in an organ remote from the surgical site, e.g., urinary tract infection, pneumonia, and so on.** The length of stay (LOS) was defined as the number of days from the day of the operation until the date of discharge. Systemic inflammatory response syndrome (SIRS) was diagnosed by the presence of two or more of the following: body temperature >38℃ or <36℃; heart rate > 90 beats/min; respiratory rate > 20 beats/min or $PaCO_2$ < 32 torr; and white blood cell (WBC) count > 12,000 or < 4,000 cells/mm^3 or > 10% immature band forms at 1, 4, and 7 days after surgery.[14] We evaluated the rates of RFS and DSS after surgery. The RFS was defined as the interval between the date of surgery and the date of recurrence. **Date of recurrence was established by radiographic studies, laboratory studies, physical examination, and/or histopathology.** The DSS was calculated from the date of surgery to the time of last visit or cancer specific death. Follow-up was updated in October 2013 for the current study.

Statistical Analysis

The primary endpoint was the incidence of SSI. Secondary objectives were rates of **non-SSI, perioperative morbidity**, LOS and highest CRP value or WBC count on day 1, 4 or 7 after surgery. All data except LOS are expressed as the mean ± standard error of the mean for each group. LOS was defined as the median value in days. Statistical significance was determined using analysis of variance (ANOVA) followed by the post hoc test of Fisher's protected least significant difference. The Chi-square test was used for comparison of the incidence of postoperative complications. A minimum sample size required 30 patients in each arm to insure 80% power at the 5% significance level for detecting a 20% improvement in the incidence of postoperative complications from 5% to 25%. Each variable affecting the survival rate was estimated using the Kaplan–Meier method. The significance of differences in RFS and DSS between subgroups was calculated using the log-rank test. $P < .05$ considered statistically significant.

RESULTS

The clinical background factors of all patients are summarized in **Table 2**. No significant differences were observed in age, gender, height, body weight or BMI.

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Table 2
Clinical Characteristics of the Three Groups

	High	Low	Control
N	26	30	29
Age (yrs)	64.7±2.3	64.8±2.3	63.8±2.0
Male	15	19	18
Female	11	11	11
Height (cm)	159±1.8	159±2.1	160±1.8
Weight (kg)	57.3±2.3	56.8±2.3	57.1±2.2
BMI	22.6±0.8	22.0±0.7	22.2±0.6

Change in Nutritional Parameters After 5 days of IEDs intake (Table 3)

Table 3
Nutritional Parameters and Biochemical Examination of Blood

	High	Low	Control
Pre BW(kg)	57.3±2.3	56.8±2.3	57.1±2.2
Post BW(kg)	57.3±2.2	56.6±2.2	56.9±2.1
Pre P-LYMPH(/mm^3)	1340±110	1400±90	1610±150
Post P-LYMPH(/mm^3)	1470±140	1440±90	1740±160
Pre Alb(g/dl)	4.1±0.1	4.1±0.1	4.2±0.1
Post Alb(g/dl)	4.1±0.1	4.2±0.1	4.2±0.1
Pre ChE (IU/l)	1600±70	1540±50	1570±60
Post ChE (IU/l)	1610±70	1560±50	1590±60
Pre GOT(IU/l)	22.2±1.6	20.0±1.2	24.0±1.7
Post GOT(IU/l)	22.7±1.6	19.7±1.0	23.7±1.6
Pre GPT(IU/l)	19.6±2.4	19.4±2.1	23.5±2.5
Post GPT(IU/l)	24.9±2.8	19.5±2.4	22.9±2.5
Pre BUN(mg/dl)	14.6±0.9*	12.3±0.6	14.9±0.5*
Post BUN(mg/dl)	16.7±1.0	13.0±0.8#	13.1±0.7#
Pre CRE(mg/dl)	0.78±0.03	0.75±0.03	0.76±0.03
Post CRE(mg/dl)	0.76±0.03	0.73±0.03	0.77±0.03
Pre TP(g/dl)	6.8±0.1	6.7±0.1	6.9±0.1
Post TP(g/dl)	6.9±0.1	6.6±0.1	6.9±0.1
Pre TCHO(mg/dl)	195.0±7.4	196.5±5.5	207.2±9.9
Post TCHO(mg/dl)	193.8±8.3	199.0±5.1	202.3±10.0

Note. BW; Body weight, P-LYMPH; peripheral lymphocytes, Alb; albumin, ChE; cholinesterase, GOT; glutamic oxaloacetic transaminase, GPT; glutamic pyruvic transaminase, BUN;blood urinary nitrogen, CRE; creatinine, TP; Total protein, TCHO; Total cholesterol; Values are mean±S.E * P<.01 vs Low #P<.01 vs High

Compliance with the administration of IEDs in the High and Low groups was excellent, because all patients allocated to the IEDs groups could drink the full amounts of IEDs prescribed. During the preoperative period, none of the patients in either group developed adverse gastrointestinal effects associated with the immunonutrition. P-Lymph, Alb, ChE, BUN, CRE, TP and TCHO before and after 5-days IEDs intake are shown in Table 3. Before IEDs intake, BUN was lower in the Low than in the other two groups. After administration, BUN was higher in the High than in the other two groups. No parameters except BUN showed any significant difference before versus after IEDs intake in the three groups.

The three groups were comparable in terms of pathological stage, tumor location, operative method for rectal cancer, intraoperative blood loss and operative time. The numbers of patients given preoperative chemotherapy and/or radiotherapy were similar among the three groups.

Table 4
Surgical Baseline Characteristics of the Three Groups

	High	Low	Control
Stage **0**/ Ⅰ/ Ⅱ/Ⅲ**a**/Ⅲ**b**	0/9/9/6/2	0/10/11/6/3	2/7/15/4/1
Location Colon/Rectum	10/16	14/16	17/12
Rectum LAR/sLAR/APR	5/9/2	9/7/0	4/5/3
Operative time (min)	246±22	222±18	223±16
Operative blood loss (ml)	540±174	350±70	297±63
Pre chemotherapy and/ or radiation	9	7	7

Note. Values are mean±S.E, LAR: low anterior resection, sLAR: super low anterior resection, APR: abdominoperineal resection

Effects of IEDs on Postoperative WBC Counts and Serum CRP Levels

WBC counts and CRP levels in the postoperative period are shown in Figures 3 and 4. At day 7, the WBC count was lower in the Low than in the Control group. There were no differences among the groups in CRP levels at any time point.

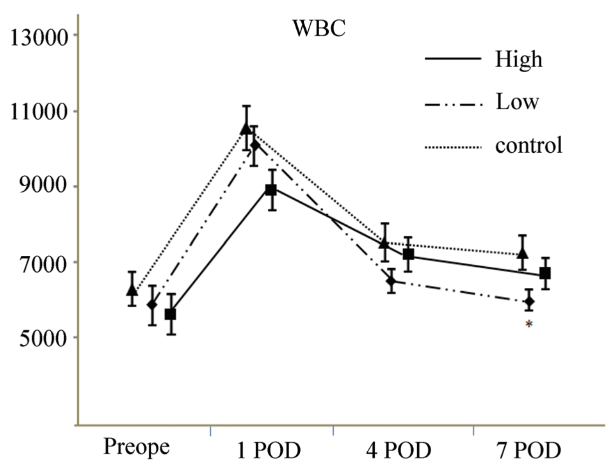

Figure 3
WBC Counts in the Postoperative Period

Note. Values are means±SE , *P<.05 vs. Control at day 7 ANOVA

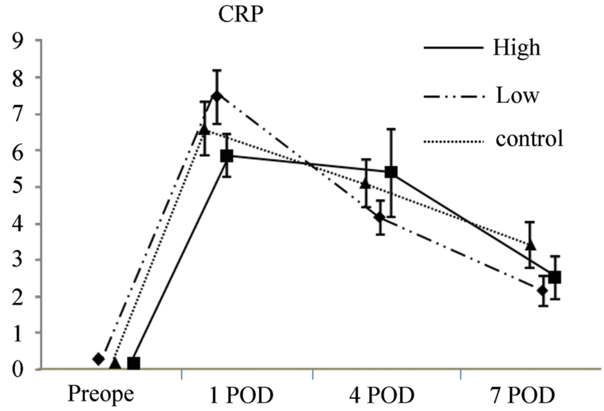

Figure 4
CRP levels in the Postoperative Period

Surgical Outcomes

Postoperative complications, the duration of SIRS and LOS are summarized in Table 5. Incisional SSI rates were 0%*, 0%* and 17% (5/29) (**P*<.01 vs. Control) in the High, Low and Control groups. The rates of organ/space SSI were 12% (3/26), 0% and 11% (3/29). The incidences of non-SSI and LOS were similar among the three groups. In the IEDs group, the duration of SIRS tended to be shorter than in the Control group, but the difference did not reach statistical significance (*P*=.08). No patient died while in the hospital in any of the three groups.

Table 5
Surgical Outcome

	High	Low	Control
Number	26	30	29
Infectious complication	5	2	8
Incisional SSI	0 *	0 *	5 (17%) Wound infection 5
Organ/space SSI	3 (12%) Anastomotic leakage 2 Intra-abdominal abscess1	0	3 (11%) Anastomotic leakage 3
Non-SSI	2 (8%) Urinary tract 2	2 (7%) Urinary tract 2	2 (7%) Urinary tract 2
Noninfectious complication	4 (15%) Ileus 2 Stoma necrosis 1 Urinary disturbance 1	5 (17%) Ileus 2 Thrombosis 1 Lymphocele 1 Urinary disturbance 1	1 (3%) Ileus 1
SIRS (day)	0.28±0.1	0.20±0.1	0.50±0.1
LOS (day)	16	16.5	16

Note. Values are mean±S.E, * *P*<.01 vs control

Impact of preoperative IEDs on RFS and DSS (Figure 5)

The patients were followed for **77±10 months (9-133 months)**after surgery. The 5-year RFS rates were 85, 73 and 86%, in the High, Low and Control groups, respectively. The 5-year DSS rates were 89, 93 and 93%, respectively. No significant differences were observed in RFS or DSS.

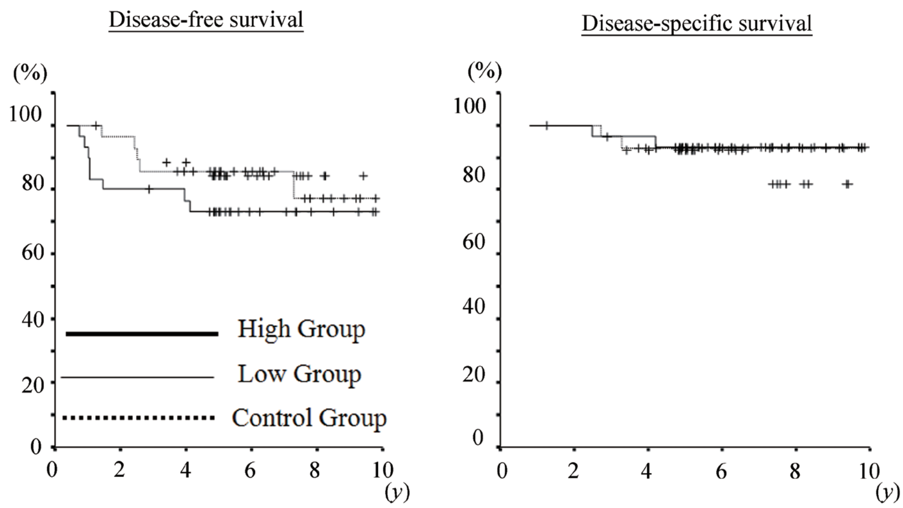

Figure 5
RFS and DSS After Surgery With Curative Intent for Colorectal Cancer

DISCUSSION

The present study demonstrated preoperative IEDs to significantly reduce the **rate** of superficial incisional SSI as compared with the control group and a trend towards shorter duration of SIRS than with conventional management was also noted. In addition, the Low dose IEDs group had no complications involving organ/specific SSI. On the other hand, preoperative

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administration of IEDs did not reduce the morbidity of non-infectious complications, nor did it affect RFS or DSS, in cancer patients.

In the present study, incisional SSI was significantly less frequent in the IEDs groups than in the Control group. Although the IEDs were provided in addition to normal foods, there were no significant differences in nutritional parameters among the groups. Therefore, the beneficial effects of IEDs on SSI were possibly due to their pharmacological actions rather than improvements in nutritional status. Several groups have reported the beneficial effects of preoperative IEDs on the prevention of incisional SSI in gastrointestinal cancer surgery. Horie et al reported favorable effects of preoperative enteral immunonutrition on SSI in patients with colorectal cancer without malnutrition[10]. **Horie et al conducted a prospective study to ascertain the effects of preoperative 5-day enteral immuno-nutrition on SSI in colorectal cancer patients without malnutrition.** They demonstrated the frequencies of superficial incisional SSI to be 0% and 11.8% in the immunonutrition and control groups, respectively. Shirakawa et al also showed effectiveness for preventing incisional wound infection in patients undergoing pancreaticoduodenectomy, with the frequency of incisional wound infection being lower in the IEDs than in the control group. (0 vs. 30.8%)[15] In the present study, the IEDs and Control groups had 0% (Low + High) and 17% (5/29) incisional SSI rates, consistent with the findings of prior studies. Because the incisional SSI rates in colon and rectal surgeries without IEDs are reportedly 9.4% and 18.0% in Japan[4], the incisional SSI rate in our control group appears to be valid. Preoperative oral IEDs, such as Impact, may be important for preventing incisional wound infection not only in Western but also in Japanese patients.

The optimal quantity of preoperative IEDs intake has also been a matter of debate. To date, many studies have adopted an IEDs volume of 500-1,000 ml/ day.[8-9,16-18] Braga et al prescribed 1,000ml/day of IEDs to patients without malnutrition, and the actual mean intake was 890 ml.[19] When compared with Western patients, body weights of Japanese patients are generally low. Thus, we chose 750 ml/ day and 250ml/ day intakes for the two IEDs groups. Indeed, Horie et al reported that compliance with 1,000 ml/day IEDs intake is very low, at <50%, in Japanese patients [10]. They concluded the preoperative 5-day administration of IMPACT Japanese version (750 ml/day) to be effective in preventing SSI. Nakamura et al also showed low compliance (60%) of patients receiving 1000ml/day of IEDs and recommended an intake of 500 ml/day as an optimal dose.[20]

Interestingly, even the 250ml /day IEDs intake could reduce the rates of incisional and organ/ specific SSI. This dose is far lower than those reported previously. One possible reason for such a small dose being effective may be the healthy dietary lifestyles of Japanese people. Because Japanese people tend to consume more fish than Western populations, with fish consumption in Japan being approximately double that in other countries [21-22], the serum level of 3 fatty acids, one of the immunonutrients in IMPACT, may have already been relatively high as compared with Western patients even before hospital admission. In addition, the food served during hospitalization may include meals rich in 3 fatty acids, while 6 fatty acids might be restricted. We plan to evaluate serum fatty acid profiles in a future study.

Interestingly, the number of organ/space SSI was decreased in the low-intake group whereas an increase was observed in the high-intake group. The organ/ space SSI in the high-intake group were due to major anastomotic leakage, suggesting that we cannot expect IEDs to prevent SSI due to serious technical problems with the surgical procedure. Although there were no statistically significant differences in the percentages of operative procedures for rectal cancer among the 3 groups, the High group included somewhat more sLAR cases than the other two groups (Cases of sLAR: High 9 , Low 7, Control 5). Thus, this may account for the higher incidence of organ/space SSIs in the High group.

Compliance with preoperative IEDs intake was excellent and there were no adverse side effects such as nausea, vomiting and diarrhea. However, serum BUN after 5-day intake was higher in the High than in the other two groups. This finding suggested that 750ml/ day IEDs intake may be an excessive renal burden in patients who simultaneously consume regular meals. Indeed, Suzuki D et al., who showed the beneficial effects of perioperative IEDs in patients receiving pancreaticoduodenectomy, reduced the amount of ordinary diets by half in their IEDs group.[17] The patients in the IEDs group consumed 1,000ml/day before surgery for 5 days. Thus, it is possible that 250 ml/day IED intake is adequate for well-nourished patients who can consume all regular meals.

We analyzed RFS and DSS after surgery in patients who did and did not receive IEDs preoperatively. It is very disappointing that preoperative IEDs had no impact on RFS or DSS after colorectal surgery in these patients. We can speculate as to possible mechanisms underlying this lack of beneficial effects. In the present study, preoperative IEDs prevented incisional SSI only, not major complications, such as anastomotic leakage which has the effect of upstaging the disease and increasing the incidence of locoregional relapse.[23] Indeed, the presence of incisional SSI did not prolong LOS, suggesting that this type of infection may not have a major impact on host tumor immunity in Japanese patients who generally have a thin layer of abdominal wall fat. Tsujimoto et al also showed anastomotic leakage to be the strongest predictor

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of a poor outcome, while wound infection was not associated with either cancer-specific survival or overall survival.[24-25]

This study has limitations. First, the number of patients recruited for this study is relatively small. Second, various staff members performed the surgeries. Therefore, differences in surgical skill among these surgeons might have affected the incidence of postoperative infectious complications. Finally, Japanese people generally consume larger amounts of -3 fatty acids from fish than Western populations. Therefore, -3 fatty acid levels in plasma may have differed markedly among the patients in this study, which could have affected clinical outcomes. However, we did not evaluate plasma fatty acid profiles during the perioperative period.

In conclusion, in Japanese patients undergoing colorectal cancer surgery, preoperative IEDs significantly reduced the rate of incisional SSI and showed a trend towards shorter duration of SIRS as compared with the control group. Very interestingly, in Japanese patients, preoperative 250ml/day IEDs intake may be adequate for colorectal cancer patients without malnutrition. However, with regard to the long term outcome, beneficial effects of preoperative IEDs are not evident.

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