Enteral Diet Enriched with ω-3 Fatty Acid Improves Oxygenation After Thoracic Esophagectomy for Cancer: A Randomized Controlled Trial

Yasunori Matsuda, Daiki Habu, Sigeru Lee, Satoru Kishida, Harushi Osugi

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Yasunori Matsuda,[1] Daiki Habu,[2] Sigeru Lee,[1] Satoru Kishida,[1] and Harushi Osugi[1]

[1]Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka City University, Osaka, Japan

[2]Faculty of Human Life Science, Graduate School of Human Life Science, Osaka City University, Osaka, Japan

Correspondence and reprint requests to:

Yasunori Matsuda, MD, PhD

Department of Gastroenterological Surgery

Graduate School of Medicine, Osaka City University

1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

Tel: +81 6 6645 3841

Fax +81 6 6646 6057

E-mail: m1293311@msic.med.osaka-cu.ac.jp

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Abstract

Background Although the anti-inflammatory effects of immunomodulating diets (IMDs) have recently attracted attention, the efficacy of enteral feeding of such diets after radical surgery remains controversial. Thus, we conducted a new prospective, randomized controlled study to elucidate any beneficial effect of an IMD containing eicosapentaenoic acid (EPA) and γ-linolenic acid (GLA) in patients undergoing radical esophagectomy for thoracic esophageal cancer.

Methods From November 2009 to July 2011, 87 consecutive patients were randomized to receive either an IMD enriched with EPA, GLA, and antioxidants (n = 42) or a standard isocaloric, isonitrogenous diet (Control group, n = 45) after esophagectomy with radical lymphadenectomy. The primary outcome measure was changes in the oxygenation status (PaO_2/FIO_2 ratio), and the secondary outcome measures were body composition, inflammation-related factors, coagulation markers, cholesterol concentrations, and major clinical outcomes.

Results Oxygenation was significantly better on postoperative days (PODs) 4, 6, and 8 in the IMD than Control group (366.5 ± 63.3 vs. 317.3 ± 58.8, $P = 0.001$; 361.5 ± 52.6 vs.

314.0 ± 53.2, $P < 0.001$; 365.4 ± 71.2 vs. 315.2 ± 56.9, $P = 0.001$, respectively). Changes in the ratio of body weight on PODs 14 and 21 and lean body weight on POD 21 were significantly greater in the IMD than Control group. No significant differences were observed in other measures.

Conclusions An enteral IMD enriched with EPA and GLA improved oxygenation and maintained the body composition of patients undergoing radical esophagectomy, indicating the potential efficacy of such a diet after esophagectomy. (249 words)

Introduction

Esophageal resection for cancer with restoration of gastrointestinal continuity remains a technically challenging procedure. This procedure is characterized by initiation of a systemic inflammatory response [1, 2] that is possibly associated with an increase in pulmonary microvascular permeability [3]. Additionally, it is associated with marked perioperative major morbidity and hospital mortality, with reported rates of up to 24.0% and 2.7%, respectively [4]. Moreover, like other cardiothoracic surgeries, it carries a risk of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [3]. Early enteral feeding is widely considered a promising means of minimizing life-threatening complications after esophagectomy [5]. A variety of enteral feeding formulations were recently developed for patients with specific critical illnesses. However, no particular formulation has consistently demonstrated a beneficial effect on clinical outcomes after radical esophagectomy.

Eicosanoids derived from ω-3 polyunsaturated fatty acids (PUFA) less potently induce cellular responses than do those derived from arachidonic acid and are therefore usually

associated with less marked inflammatory responses [6]. Eicosanoids also alter cytokine production and intracellular signaling [7]. Enteral nutrition supplemented with PUFA, such as eicosapentaenoic acid (EPA), docosahexaenoic acid, and γ-linolenic acid (GLA), is referred to as an immunomodulating diet (IMD). Several recent animal [8-10] and clinical [11] studies have shown that nutritional support with diets containing EPA and GLA provide a means of decreasing the amounts of arachidonic acid in immune cells, thereby possibly reducing production of inflammatory mediators and improving clinical outcomes in patients with ARDS, ALI, and critical illness [11-15].

However, there is conflicting evidence concerning the benefits of enteral nutrition enriched with such PUFA [16-18]. Various studies are still under scrutiny, and there is little high-quality evidence on the benefit of any enteral nutrients for any surgical patients, let alone those undergoing esophagectomy [19-22]. In the current study, we aimed to elucidate whether enteral nutrition enriched with particular PUFA improves the postoperative course of patients who have undergone radical esophagectomy for cancer. With this aim, we conducted a prospective randomized study to compare an IMD containing EPA, GLA, and

antioxidants with a standard isocaloric and isonitrogenous diet in such patients. The primary outcome was the improvement in oxygenation that was considered appropriate for the therapeutic goal in such patients at risk of ARDS or ALI.

Materials and methods

This was an open, randomized comparative trial on an enteral IMD enriched with EPA, GLA, and antioxidants versus a standard isocaloric, isonitrogenous diet for thoracic esophagectomy. This study proposal was finalized and approved by the Ethics Committee of Osaka City University Hospital and was registered with UMIN Clinical Trials Registry (UMIN000002659). The trial was conducted in accordance with the Helsinki Declaration of 2008 and performed from November 2009 to July 2011. Written informed consent was obtained from all participants.

Patients

Patients with thoracic esophageal cancer presenting for elective surgical treatment were eligible for randomization to the trial. All patients were examined and staged by endoscopy and biopsies, CT and FDG-PET scans from the neck to the pelvis, and endoscopic ultrasonography before surgery. Disease stages were classified according to the seventh edition of the TNM classification of the UICC. The inclusion criteria for the study

were as follows: (i) curative esophagectomy with simultaneous two- or three-field lymphadenectomy and reconstruction and (ii) assessed by attending physician as able to tolerate enteral feeding by postoperative day (POD) 2. The exclusion criteria were as follows: (i) palliative or emergency esophagectomy; (ii) cervical esophageal cancer needing pharyngolaryngectomy; (iii) severe immunosuppression; (iv) severe cardiac, liver, or renal failure; (v) congenital disorders of amino acid metabolism; (vi) known allergy to milk protein or lactose intolerance; and (vii) assessed by attending physician as unsuitable for postoperative enteral feeding.

Interviews to ascertain current smoking habits and whether there had been more than 5% weight loss prior to surgery were conducted with all participants. Respiratory function was measured by spirometry (CHESTAC-8800 or -55V; CHEST M.I., Tokyo, Japan). Whether the patients had any comorbidities, including diabetes (HbA1c > 6.5%), chronic kidney disease (eGFR < 60 mL/min/1.73 m^2), liver cirrhosis, or continuous arrhythmia, was also ascertained.

Surgical Procedures

This series of patients underwent standard open esophagectomy through a conventional right posterolateral incision in the bed of the resected fifth rib or video-assisted thoracoscopic esophagectomy (VATS). Details of the surgical techniques for VATS have been published elsewhere [23]. All patients underwent two-field (thoracic and abdominal) or three-field (neck, thoracic, and abdominal) radical lymphadenectomy. Reconstruction was performed using a gastric conduit or a jejunal graft through the posterior mediastinum. All operations were performed or supervised by a specialist surgeon (H.O.) with experience in more than 300 cases managed with both approaches. A jejunostomy tube (Phycon® NCJ kit; Fuji Systems, Tokyo, Japan) was inserted for postoperative enteral feeding.

All operations were performed with the patients under general anesthesia. During the intrathoracic operation, one-lung ventilation was performed using a double-lumen

endotracheal tube. We also routinely provided pressure-controlled ventilation with a tidal volume of 4 to 6 mL/kg and end-expiratory pressure of 4 to 6 cm H_2O while limiting peak pressures to <35 cm H_2O. Anesthesia was maintained with inhaled sevoflurane, sustained intravenous administration of remifentanil and rocuronium, and thoracic epidural analgesia with ropivacaine. Limiting the intraoperative intravenous fluid volume to <5000 mL was recommended for patients undergoing 6- to 8-h procedures and those who received intravenous antibiotics (cefazolin sodium, 1.0 g every 3 hours). The radial artery was cannulated for invasive blood pressure monitoring and frequent blood sampling.

Neoadjuvant Therapy

Patients suspected to have lymph node metastasis or T4 tumors were treated with neoadjuvant chemotherapy or chemoradiotherapy. Neoadjuvant chemotherapy comprised 5-fluorouracil (800 mg/m^2) on days 1–5 plus cisplatin (80 mg/m^2) on day 1. Three to four weeks later, the same regimen was repeated once more provided the patient's condition was stable. Neoadjuvant chemoradiotherapy comprised 5-fluorouracil (300 mg/m^2) plus

cisplatin (10 mg/m^2) on days 1–5, 8–12, 15–19, and 22–26 and concurrent irradiation (41.4 Gy in 23 fractions) on days 1–5, 8–12, 15–19, 22–26, and 29–31. The surgery described above was performed 4–8 weeks after completion of neoadjuvant treatment.

Enteral Feeding Protocol

Patients who had undergone surgery and met the inclusion criteria were randomized immediately following the operation into one of two groups using a concealed envelope method. The IMD group received an experimental diet enriched with EPA, GLA, and antioxidants (Oxepa®; Abbott Japan, Tokyo, Japan), and the Control group received a standard isocaloric, isonitrogenous diet (Pulmocare®; Abbott Japan); the main components of the two enteral diets can be found in the Supplementary Table. All participants were started on continuous enteral feeding through a jejunostomy tube within 48 h of surgery. The initial administration rate in both groups was 10 mL/h; this was increased by 10 mL/h every 2 days to 30 mL/h. If feasible, oral intake was introduced on POD 7 and enteral feeding was reduced to 400 mL/day. Enteral feeding of the study diets was continued for 2

weeks (to POD 21) through a jejunostomy tube. If the patient required enteral nutritional support after POD 21, enteral diets different from the study diets (Oxepa® and Pulmocare®) individualized for each patient by the attending physician were administered. Daily caloric and protein intake was consistently assessed by the attending physician and prevented from dropping below the basal energy expenditure (determined using the Harris–Benedict equation) × 1.3 kcal and kg of ideal body weight × 1.2 g by oral intake or parenteral or enteral nutrition during the follow-up period.

Outcome Measurements

The primary outcome, namely the change in the oxygenation status (PaO_2/FIO_2 ratio), was assessed at baseline and on PODs 1 to 4, 6, and 8.

The secondary outcomes were: (i) change in the body composition, (ii) inflammation-related factors, (iii) coagulation markers, (iv) cholesterol concentrations, and (v) major clinical outcomes. Measures of body composition, namely body weight (BW), lean BW (LBW), and skeletal muscle mass, were measured using a bioelectrical impedance

measurement device (InBody430; Biospace, Cheonan, Korea) and assessed at baseline and on PODs 7, 14, 21, and 28. Body composition was assessed by independent managerial dieticians who were blinded to the enteral diets administered. Inflammation-related factors (including maximum body temperature, white blood cell count, and C-reactive protein concentration), coagulation markers (including platelet count, fibrinogen concentration, and fibrin/fibrinogen degradation products), and cholesterol concentrations (including total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) were examined in our institutional laboratory and assessed at baseline and on PODs 1 to 8. The major clinical outcomes assessed were the incidence of postoperative complications, including pneumonia, anastomotic leakage, and surgical site infection; in-hospital mortality; and the duration of the postoperative hospital stay. Anastomotic leakage was diagnosed according to the definition by the Common Terminology Criteria for Adverse Events, version 4.0. Specifically, discontinuity of the esophagogastric or esophagojejunal anastomosis as detected by endoscopy, esophagography, or CT was defined as anastomotic leakage. The clinical significance of the leakage was not considered in this study.

Sample Size Calculation and Statistical Analyses

In our previous pilot study of 27 patients undergoing esophagectomy, the mean PaO_2/FIO_2 ratio and its standard deviation were 350.4 ± 63.34 at baseline and on PODs 1 to 4, 6, and 8. Previous clinical studies have reported that an IMD increases the mean PaO_2/FIO_2 ratio by 40–100; thus, improvement of >35 in the mean PaO_2/FIO_2 ratio was considered clinically significant. To detect a difference of this magnitude, a sample size of 35 patients was required in each group (two-tailed alpha value = 0.05, 1-beta value = 0.9). Allowing for a 15% attrition rate, 42 patients per group were required for the study.

Differences in continuous normally distributed variables were analyzed by Student's *t*-test (when variances were equal) and Welch's *t*-test (when variances were unequal). Abnormally distributed variables were analyzed by the Mann–Whitney U test. Pearson's test, χ^2 analysis, or Fisher's exact test was used for comparison of categorical variables. All analyses were performed using IBM SPSS statistics version 21 (IBM Japan, Tokyo, Japan), and the results were considered significant when *P* values of <0.05 were obtained by a

two-sided test.

Results

As shown in Figure 1, 92 patients were enrolled, 87 of whom were randomized to either the Control (n = 45) or IMD (n = 42) group postoperatively. Five patients were excluded from the study because curative surgery and radical lymph node dissection were not performed. Fifteen patients could not continue enteral feeding because of chylothorax (n = 11), paralytic ileus (n = 1), liver dysfunction (n = 1), intractable ascites (n = 1), and pulmonary embolism (n = 1) (interrupted at attending physician's discretion). Seventy-two patients (Control, n = 37; IMD, n = 35) completed the study protocol, and their data were analyzed in detail.

Clinical and Pathological Characteristics of Patients

Clinical and pathological characteristics of patients in both study groups are shown in Table 1. There were no significant differences between the two groups regarding age, sex, American Society of Anesthesiologists score, preoperative respiratory function, BW, or body mass index. Twenty-one patients each in the Control (56.8%) and IMD (60.0%)

groups received neoadjuvant chemotherapy or chemoradiotherapy. Twelve patients in the Control group (32.4%) and 14 in the IMD group (40.0%) had one or more comorbidities, and 21 patients in the Control group (32.4%) and 14 in the IMD group (42.9%) were current smokers. Nine patients in the Control group (24.3%) and 16 in the IMD group (45.8%) had lost >5% of their BW in the 6 months before surgery. There were no significant differences between the two groups in operative procedure, operative time, or bleeding volume. Additionally, the pathological characteristics did not differ significantly between the two groups.

Feasibility of Enteral Feeding Regimen

Twenty-eight (80.0%) patients in the IMD group and 30 (81.1%) in the Control group could introduce oral intake and reduce the enteral feeding according to the protocol. Routine enteral feeding was finished in 2 weeks in 17 (48.6%) patients in the IMD group and 19 (51.3%) in the Control group. In all patients, the calorie and protein intake per day did not drop below the lower limit (basal energy expenditure × 1.3 kcal and kg of ideal

body weight × 1.2 g, respectively) by enteral and parenteral nutrition support during the study period. Mild diarrhea was reported in one patient of each group.

Oxygenation

There were no statistically significant differences between the two groups in the PaO_2/FIO_2 ratio from baseline to POD 3. However, oxygenation improved significantly on PODs 4, 6, and 8 in the IMD group compared with that in the Control group (366.5 ± 63.3 vs. 317.3 ± 58.8, $P = 0.001$; 361.5 ± 52.6 vs. 314.0 ± 53.2, $P < 0.001$; 365.4 ± 71.2 vs. 315.2 ± 56.9, $P = 0.001$, respectively) (Fig. 2).

Body Composition Assessment

Changes in the ratio of BW on PODs 14 and 21 and LBW on POD 21 were significantly greater in the IMD group than in the Control group (0.991 ± 0.024 vs. 0.968 ± 0.032, $P = 0.003$; 0.968 ± 0.030 vs. 0.947 ± 0.034, $P = 0.013$; 0.991 ± 0.048 vs. 0.968 ± 0.040, $P = 0.043$, respectively) (Fig. 3). There were no significant differences between the

two groups in skeletal muscle mass. Body composition tended to be maintained better during follow-up in the IMD group than in the Control group.

Inflammation-Related Factors

The maximum body temperature, white blood cell count, and C-reactive protein concentration peaked on PODs 1 or 2 in both groups. There were no significant differences between the two groups in these variables on any POD (Fig. 4).

Coagulation Markers and Cholesterol Concentrations

No significant differences were observed between the two groups in coagulation markers (platelet count, fibrinogen, and fibrinogen degradation products) and cholesterol concentrations (total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) on any POD (Fig. 5).

Evaluation of Postoperative Complications and Hospital Stay

There were no significant differences in postoperative complications, including pneumonia, anastomotic leakage, and surgical site infection, or in the length of postoperative hospital stay between the two groups (Table 2). No patients died during hospitalization.

Discussion

In this open, prospective, randomized, controlled, single-center study, we demonstrated that an enteral IMD enriched with EPA, GLA, and antioxidants improved oxygenation and maintained the body composition of patients who had undergone thoracic esophagectomy for cancer. These findings are consistent with those of previously published studies that reported beneficial effects of IMDs in the realm of critical care [11-15] and confirmed the findings of the study by Ryan et al. [19].

The improvement in oxygenation is thought to be attributable to the anti-inflammatory effect of an IMD. In animal models, enteral feeding with an IMD containing plentiful EPA and GLA reportedly rapidly modulates the fatty acid composition of alveolar macrophage phospholipids and promotes a shift toward the formation of less inflammatory eicosanoids by stimulated macrophages [10]. Enteral diets that modulate eicosanoid metabolism also attenuate lung microvascular protein permeability, reduce pulmonary neutrophil accumulation [9], and improve gas exchange and oxygen delivery [8]. In specific clinical settings, such as ARDS or ALI, a primary therapeutic goal is to increase oxygenation by

decreasing pulmonary inflammation and permeability. One clinical study has shown that administering enteral nutrition containing EPA and GLA to patients with ARDS reduces the concentrations of proinflammatory mediators, such as interleukin (IL)-8 and leukotriene B4, which recruit and activate neutrophils in bronchoalveolar lavage fluid [12]. These results suggest that IMDs ameliorate ventilatory insufficiency and increase oxygenation by decreasing pulmonary inflammation and permeability in patients at risk of developing postoperative ARDS or ALI.

Ryan et al. [19] provided proof for the postulate that IMDs enriched with EPA and GLA are associated with better preservation of LBW post-esophagectomy than is standard enteral nutrition. The present study showed that IMDs have sustained effects on metabolism; however, the mechanisms remain unclear. Protein catabolism stimulated by major surgical injury results in marked weight loss and muscle wasting. The stress of surgery not only creates a hypermetabolic state, increasing protein and energy requirements, but induces a systemic inflammatory response with release of cytokines, including tumor necrosis factor-α, IL-6, and IL-1β [24]. Similar observations have been made in cachectic

patients with several types of cancers [25, 26], and high concentrations of cytokines are associated with a lower serum albumin concentration, total protein concentration, and body mass index and a poor performance status. Additionally, in experimental animals, systemic injection of proinflammatory cytokines such as tumor necrosis factor-α, IL-6, IL-1β, and others elicits anorexia, lipolysis, and muscle breakdown [27, 28]. *In vitro* studies have shown that EPA can attenuate the stimulation of adenylate cyclase activity and lipolysis produced by tumor-derived lipid-mobilizing factor [29]. It may also suppress IL-6 production and retard weight loss in patients with pancreatic cachexia [30]. Metabolic changes following major surgery may be mediated by EPA via a similar pathway.

In this study, there were no significant differences between the two groups in the inflammation-related factors on any POD. Our study design was likely underpowered for changing systemic inflammatory reactions and major clinical outcomes related to nutritional immunomodulation. Although we did not analyze the serum cytokines, several studies have reported that IMD reduced serum IL-8 levels after esophagectomy [19] and the concentrations of IL-8, leukotriene B4, and neutrophils in bronchoalveolar lavage fluid in

patients with ARDS [12]. It is possible that IMD might selectively affect the pulmonary parenchyma through the modulation of cytokines without changing the systemic inflammatory reactions.

During inflammation in which endothelial cells interact with leukocytes, a particular series of resolvins, which are novel anti-inflammatory mediators, are generated from EPA [31]. Administration of resolvin E1 to mice strongly reduces inflammatory pain behaviors and has anti-inflammatory activity as evidenced by reduced neutrophil infiltration, paw edema, and proinflammatory cytokine expression [32]. Resolvin E1 also prevents the development of severe experimental colitis induced by 2,4,6-trinitrobenzene sulfonic acid, reduces leukocyte infiltration, and sustains BW [33]. These recent studies may shed light on new therapeutic prospects for EPA in patients with uncontrolled inflammatory responses.

In patients with ARDS, ALI, and critical illness, the clinical benefit of enteral supplementation of ω-3 PUFA remains inconsistent. Previous studies have produced positive findings [11, 13, 14], while others that reported opposite outcomes [16-18] were analyzed in several systematic reviews and meta-analyses [34-36]. According to these

analyses, enteral supplementation of ω-3 PUFA basically could not demonstrate an overall effect on mortality, ventilator-free days, or ICU-free days in patients with ARDS. However, Li et al. [34] performed a subgroup analysis and showed that such supplementation could benefit patients with high mortality. Interestingly, the studies that produced positive findings used a continuous high-fat diet in both the treatment and control groups [11, 13, 14], while the studies that reported opposite outcomes used a low-fat diet in the control group [16-18]. Additionally, it was striking that two [16, 17] of the latter studies used a bolus injection of ω-3 PUFA in the treatment group. This finding may indicate that a high-fat diet not containing ω-3 PUFA and a bolus injection of concentrated fat might be harmful for patients with ARDS. Although their backgrounds differ, the same can be said for patients who have undergone esophagectomy. Our study used a continuous high-fat diet in both the IMD and Control groups; thus, future comparisons with other low-fat formulas are still required to clarify the effectiveness of enteral supplementation of ω-3 PUFA in esophagectomy.

We believe that this study was well-designed; however, it does have several clinical

limitations. First, enteral nutrition was not administered preoperatively. A previous study showed that the daily intake of capsules containing only 1 g each of a concentrate of ω-3 PUFA (85% of EPA + docosahexaenoic acid ethyl esters in a ratio of 1.2:1.0) induces striking changes in the fatty acid composition of blood cell membranes within 1 week [37]. In our protocol, the patients in the IMD group received >1 g each of EPA and GLA from the beginning of enteral feeding. We started enteral nutrition postoperatively as expeditiously as was practicable at a dosage that we considered sufficient to modulate the protracted inflammation that can occur after esophagectomy induced by aspiration pneumonia, wound infection, anastomotic leakage, and other conditions. However, postoperative administration does not address operative stress itself. It is possible that preoperative administration of an enteral IMD would be beneficial to patients undergoing esophagectomy, likely significantly decreasing the frequency of postoperative complications and serum concentrations of inflammation-related factors. Second, the study subjects underwent two different types of surgical procedures. As has previously been reported, the overall frequency of complications in our institution does not differ

significantly between open surgery and VATS [38]. Thus, we believe that the outcomes of this study were minimally affected by the type of surgical procedure. Third, the study was not blinded. It was difficult to mask the types of enteral diets; IMD smelled like fish because of its EPA and GLA components and was therefore easily identified. We could only blind the type of enteral diets from independent managerial dieticians who assessed the body composition.

Conclusions

Our study indicates the potential efficacy of an enteral IMD enriched with EPA, GLA, and antioxidants in patients who have undergone thoracic esophagectomy with radical lymphadenectomy for cancer. The optimum timing, amount administered, and comparisons with other low-fat formulas warrant further investigation and discussion.

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Figure legends

Fig. 1 Trial flow chart

The immunomodulating diet (IMD) group received an experimental diet enriched with eicosapentaenoic acid, γ-linolenic acid, and antioxidants; the Control group received a standard isocaloric, isonitrogenous diet

Fig. 2 Changes in oxygenation status (PaO_2/FIO_2 ratio) at baseline and on postoperative days 1 to 4, 6, and 8. Values are shown as the mean (standard deviation). IMD, immunomodulating diet

Fig. 3 Changes in ratio of body composition including body weight (BW), lean BW (LBW), and skeletal muscle mass (SMM) at baseline and on postoperative days 7 to 14, 21, and 28. Values are shown as the mean (standard deviation)

Fig. 4 Changes in inflammation-related factors including maximum body temperature (Max-BT), white blood cell count (WBC), and C-reactive protein (CRP) concentration at baseline and on postoperative days 1 to 8. Values are shown as the mean (standard deviation)

Fig. 5 Changes in coagulation markers, including platelet count, fibrinogen concentration, fibrin/fibrinogen degradation products (FDP), and cholesterol concentrations including total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC) at baseline and on postoperative days 1 to 8. Values are shown as the mean (standard deviation)

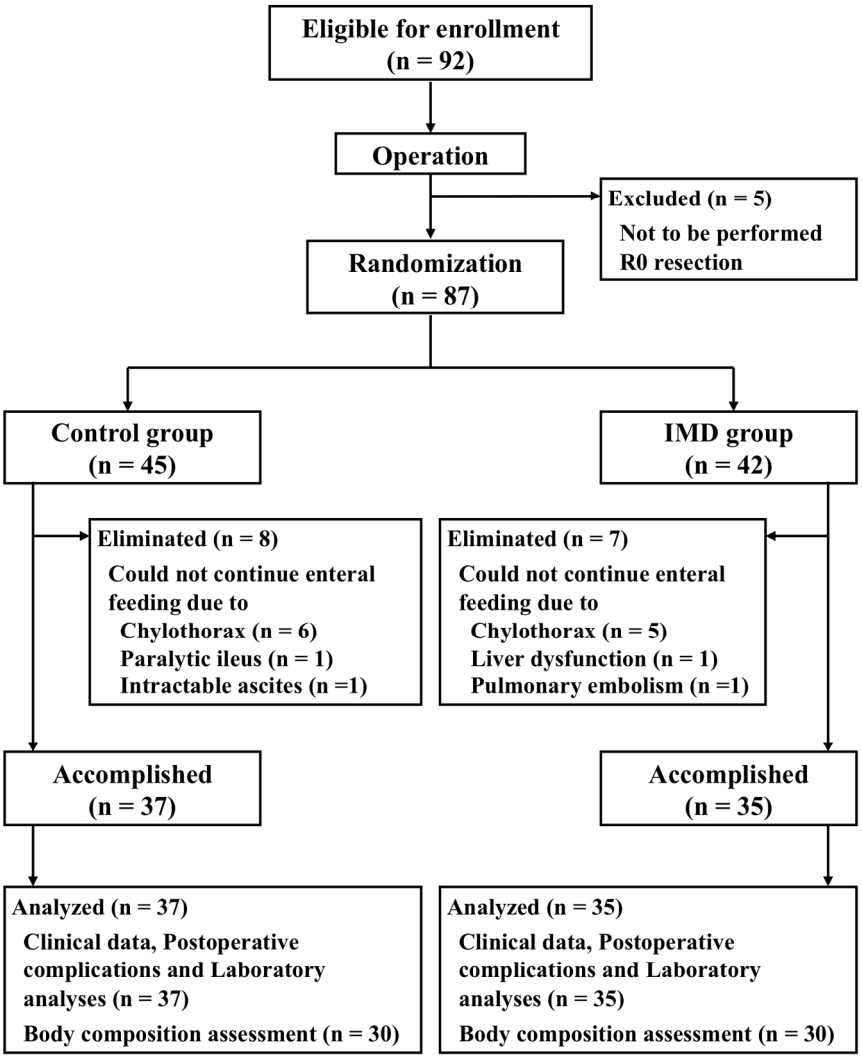

Figure 1

Trial flow chart
The immunomodulating diet (IMD) group received an experimental diet enriched with eicosapentaenoic acid, γ-linolenic acid, and antioxidants; the Control group received a standard isocaloric, isonitrogenous diet.

Fig. 1
595x793mm (72 x 72 DPI)

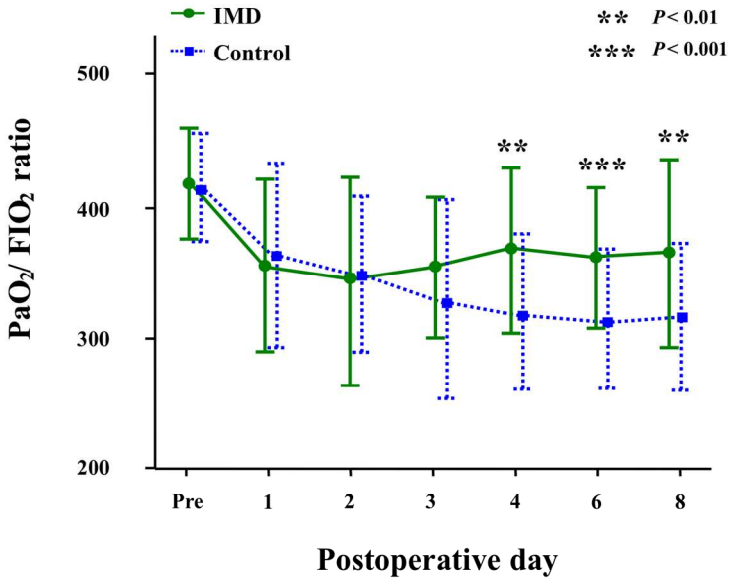

Figure 2

Changes in oxygenation status (PaO2/FIO2 ratio) at baseline and on postoperative days 1 to 4, 6, and 8. Values are shown as the mean (standard deviation). IMD, immunomodulating diet

Fig. 2

595x793mm (72 x 72 DPI)

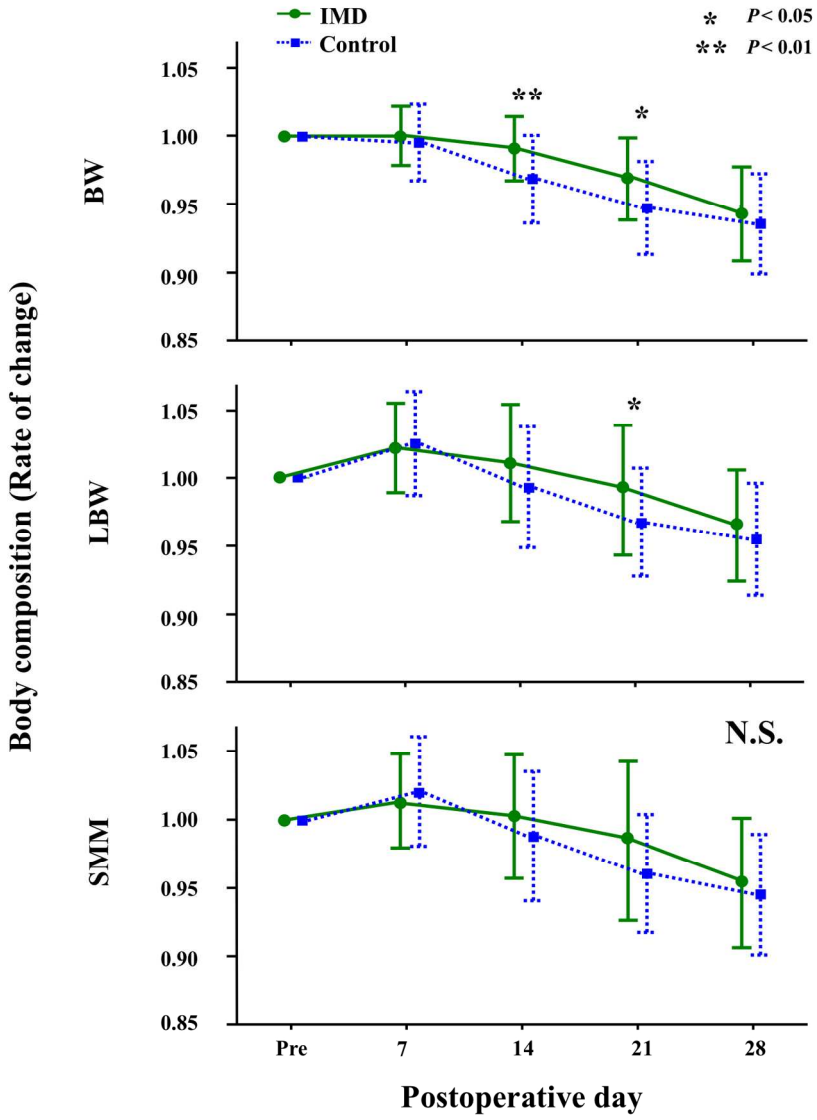

Figure 3

Changes in ratio of body composition including body weight (BW), lean body weight (LBW), and skeletal muscle mass (SMM) at baseline and on postoperative days 7 to 14, 21, and 28. Values are shown as the mean (standard deviation).

Fig. 3

595x793mm (72 x 72 DPI)

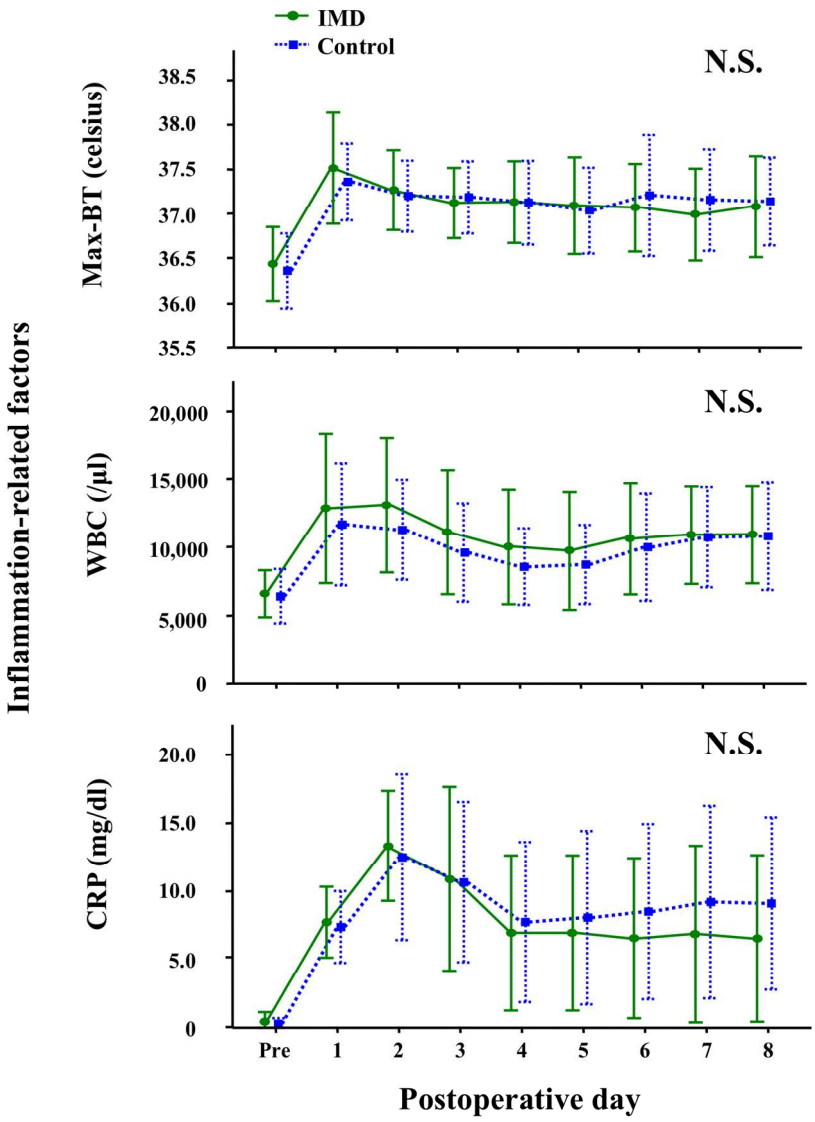

Figure 4

Changes in inflammation-related factors including maximum body temperature (Max-BT), white blood cell count (WBC), and C-reactive protein (CRP) concentration at baseline and on postoperative days 1 to 8. Values are shown as the mean (standard deviation).

Fig. 4

595x793mm (72 x 72 DPI)

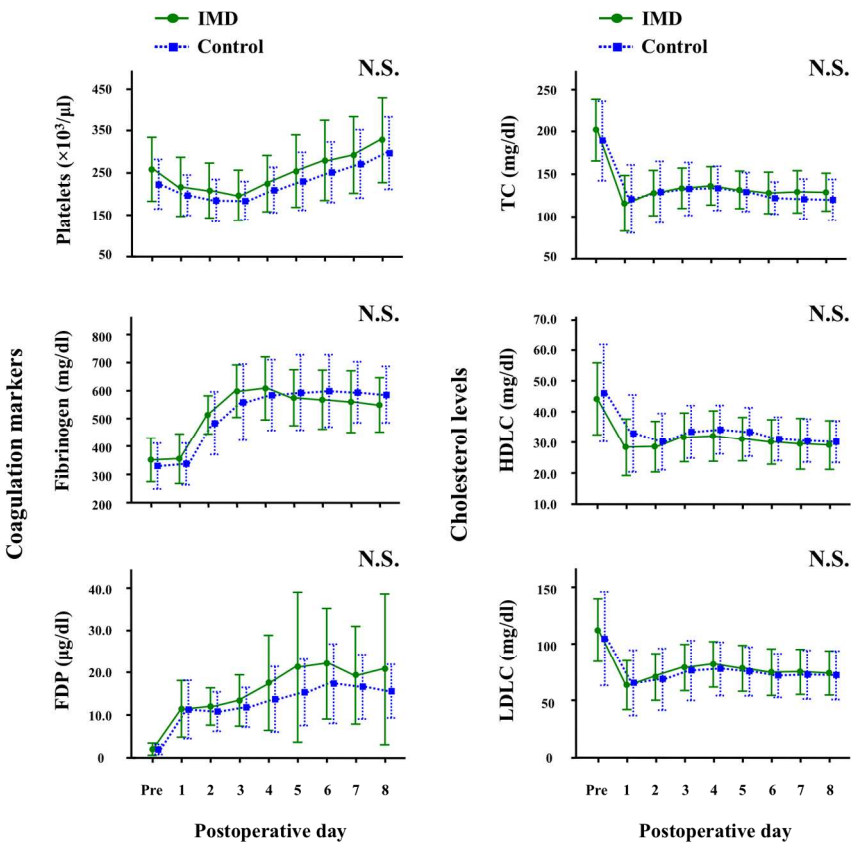

Figure 5

Changes in coagulation markers, including platelet count, fibrinogen concentration, fibrin/fibrinogen degradation products (FDP), and cholesterol concentrations including total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC) at baseline and on postoperative days 1 to 8. Values are shown as the mean (standard deviation).

Fig. 5

595x793mm (72 x 72 DPI)

Table 1 Patient Characteristics and Operative Details

	Control Group		IMD Group		*P* value
Number of patients	37		35		
Age (years)	64.6	± 6.4	64.1	± 8.3	0.747
Sex (Male / Female)	30 / 7		24 / 11		0.220
ASA score					
1	8		5		0.441
2	29		29		
3	0		1		
Neoadjuvant therapy					
None	16		14		0.904
Chemotherapy	15		16		
Chemoradiotherapy	6		5		
Comorbidity (Yes / No)	12 / 25		14 / 21		0.504
Current smoking habit (Yes / No)	12 / 25		15 / 20		0.361
Respiratory function					
%VC (%)	116.1	± 15.3	112.8	± 19.5	0.419
FEV1.0% (%)	69.6	± 7.9	72.8	± 8.4	0.102
Body weight (kg)	58.4	± 7.4	56.9	± 10.2	0.500
BMI (kg / m^2)	21.4	± 2.3	21.3	± 2.9	0.862
Weight loss (Yes / No)	9 / 28		16 / 19		0.057
Operative procedure					
VATS	26		25		0.914
Open surgery	11		10		
Operative time (min)	434.7	± 73.4	455.3	± 92.6	0.297
Operative bleeding (g)	510.7	± 249.8	544.3	± 428.9	0.688
pT					
0	1		2		0.057
1a	7		1		
1b	7		10		
2	11		6		
3	9		16		
4a	2		0		
pN					
0	21		16		0.655
1	7		11		
2	4		4		
3	5		4		

Data are given as the number or mean ± SD. IMD, immunomodulating Diet; ASA, American Society of Anesthesiologists; %VC, percent Vital Capacity; BMI, Body Mass Index; FEV1.0%, percent predicted Forced Expiratory Volume in one second; VATS, Video-Assisted Thoracoscopic Surgery; pT, pathological depth of primary tumor; pN, pathological regional lymph node metastasis

Table 2 Postoperative Outcomes for Each Group

	Control Group		IMD Group		*P* value
Postoperative complication					
Pneumonia	5 / 37	(13.5%)	3 / 35	(8.6%)	0.711
Anastomotic leakage	7 / 37	(18.9%)	6 / 35	(17.1%)	0.845
Surgical site infection	6 / 37	(16.2%)	4 / 35	(11.4%)	0.557
In-hospital mortality	0 / 37	(0%)	0 / 35	(0%)	1.000
Postoperative hospital stay (days)	28	(16 - 148)	26	(18 - 77)	0.381

Data are given as the number (%) or median (range). IMD, immunomodulating diet

Supplementary Table Main Composition of the Enteral Diet

Nutrient	Control Diet	IMD
Total calories, kcal	375	375
Protein		
Total amount, g	15.6	15.6
% of total calories	16.8	16.7
Carbohydrate		
Total amount, g	26.4	26.5
% of total calories	28.4	28.2
Lipids		
Total amount, g	23.0	23.4
% of total calories	54.8	55.1
EPA, g	0	1.3
GLA, g	0	1.1
DHA, g	0	0.55
n-6:n-3	4.6:1	1.7:1
Water, ml	197	197
Vitamins		
A, μg	396	396
β-carotene, μg	162	168
D, μg	2.6	2.7
E, mg	14.0	54.0
C, mg	80.0	210
Thiamine, mg	1.2	0.8
Riboflavin, mg	1.2	0.9
B6, mg	1.2	1.1
B12, μg	2.4	1.5
Folic acid, μg	163	105
Niacin, mg	12.0	7.3
Panthothenic acid, mg	5.3	3.3
Biotin, μg	28.0	15.0
Trace minerals		
Na, mg	325	328
K, mg	435	490
Cl, mg	375	423
Ca, mg	240	265
P, mg	240	250
Mg, mg	90.0	80.0
Fe, mg	5.3	5.0
Zn, mg	4.3	4.5
Cu, μg	525	550
Caloric density, kcal/ml	1.5	1.5
Osmolality, mOsm/l	384	384

All data are per 1 can (250 ml). IMD, immunomodulating diet; EPA, eicosapentaenoic acid; GLA, γ-linolenic

acid; DHA, docosahexaenoic acid