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# Prospective Randomized Trial of Early Postoperative Enteral and Total Parenteral Nutrition for Treating Esophageal Cancer

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**Abstract.** *Background/Aim: Surgical stress significantly decreases serum diamine oxidase (DAO), a marker of intestinal mucosal maturation and integrity. This study aimed to determine the effects of postoperative enteral and total parenteral nutrition (EN and TPN, respectively) in patients with esophageal cancer. Patients and Methods: This prospective randomized trial compared serum DAO activities, nutritional states, trace elements and complications between patients who underwent esophagectomy and received EN or TPN for seven days thereafter. Results: Fifty-one patients were randomized to receive EN or TPN. The rates of change in serum DAO activity from the day before surgery were 0.79, 0.89 and 0.91 on postoperative days (POD) 1, 3 and 7, respectively, in the EN group, and 0.64, 0.76 and 1.06, respectively, in the TPN group, with no significant differences. Furthermore, the rates of changes in indicators of nutritional status, namely total protein, albumin, total cholesterol, trace element concentrations and infectious and non-infectious complications did not significantly differ between the groups. Conclusion: EN and/or TPN can be administered for early nutritional management until resumption of oral intake after esophagectomy according to the postoperative status of individual patients with esophageal cancer.*

Esophageal cancer is the ninth most common cancer and the sixth most common cause of cancer-related death globally (1). Surgery is the best option for curative treatment of esophageal cancer, and it has recently become more standardized and centralized (1). However, esophageal surgery is still highly invasive compared with other types of gastroenterological surgery (2, 3) and patients undergoing esophagectomy are unable to take oral nutrition for several days after surgery. Therefore, enteral nutrition (EN) and/or parenteral nutrition (PN) have become routine nutritional management after surgery for patients with esophageal cancer (4). The starting date at which patients without postoperative complications after esophagectomy can tolerate oral nutrition is around postoperative day (POD) 7 (5). Therefore, postoperative nutritional management before resuming oral intake is particularly important for patients with esophageal cancer.

Stating EN soon after esophagectomy reduces the length of hospital stay (6-8), postoperative weight loss (9), postoperative morbidity (7-10) and rates of life-threatening complications (11). Therefore, early EN as perioperative care enhances the recovery of patients after surgery (ERAS) for esophageal cancer according to guidelines (3, 12). However, early EN does not confer any clinical benefit upon outcomes of esophagectomy such as the length of the hospital stay, morbidity, or mortality according to some studies (13-15). Others have not found a superior clinical benefit of postoperative early EN after esophagectomy over total parenteral nutrition (TPN) (16, 17), but have indicated that perioperative nutritional support with EN or TPN should be safe (16).

Diamine oxidase (DAO) histaminase contains copper and although it is found in various tissues, it is particularly active in the intestinal mucosa (18). It functions in the oxidative deamination of polyamines, which are essential for cell proliferation. Diamine oxidase thus plays a regulatory role in rapidly proliferating tissues such as bone marrow and intestinal mucosa (18-20). It is normally found at extremely low levels in the circulation and its basal serum level positively correlates with the maturity and integrity of the small intestinal mucosa (19-21). To the best of our knowledge, a randomized study has never evaluated whether serum DAO activity differs between nutritional management by EN and TPN after esophagectomy.

Therefore, this prospective randomized trial aimed to determine whether serum DAO activities, nutritional status, trace elements and postoperative complications differ

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*Key Words:* Complication, diamine oxidase, esophagus, intestine, nutrition, surgery.

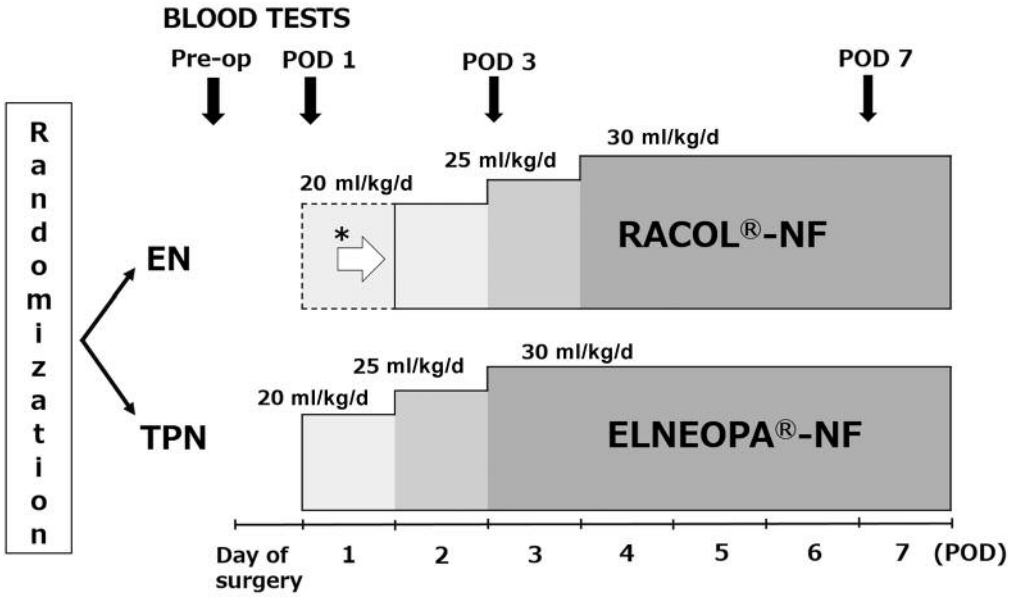



Figure 1. *Study design. Eligible patients who agreed to participate in this study were randomly assigned in a 1:1 ratio to EN and TPN groups. RACOL®-NF was administered to the EN group from POD 1, and amounts were gradually increased to POD 7 [protocol for RACOL®-NF doses was changed (May 2013) to start from POD 2]. In the TPN group, ELNEOPA®-NF was administered from POD 1, and amounts were gradually increased to POD 7. Blood was collected before surgery, and on POD 1, 3 and 7. EN, Enteral nutrition; POD, postoperative day(s); TPN, total parenteral nutrition.*

between patients who receive EN and TPN from the early postoperative period after esophagectomy.

## Patients and Methods

*Eligibility and exclusion criteria*. Patients were considered eligible to participate in the study if they met the following inclusion criteria: age of 20-80 years; histologically proven malignant neoplasm of the esophagus; scheduled for esophagectomy *via* thoracotomy or a thoracoscopic approach and gastric tube reconstruction; adequate bone marrow function (leucocytes 3,000-12,000/mm$^3$; neutrophils ≥1,500/mm$^3$; hemoglobin ≥9.5 g/dl, platelets ≥100,000/mm$^3$); adequate renal function (creatinine ≤1.5 mg/dl); adequate liver function [bilirubin ≤1.5 mg/dl, aspartate transaminase (AST) and alanine transaminase (ALT) ≤60 IU/l, alkaline phosphatase ≤600 IU/l] and albumin ≥2.8 g/dl. All patients included in the study provided written informed consent to participate.

Patients were considered ineligible to participate if they had a history of gastrectomy, active double cancer, comorbidities including liver, cardiac, mental, and autoimmune diseases, diabetes mellitus, contraindications to TPN and EN products, were pregnant or breast-feeding, or were deemed ineligible for this study by an investigator.

*Study design*. This prospective randomized study included 51 patients with esophageal cancer who were treated by esophagectomy followed by gastric tube reconstruction between November 2011 and January 2014. Figure 1 shows the study design. Eligible patients who agreed to participate were randomly assigned to EN ($n$=26) and TPN ($n$=25) groups. Caloric intake was similarly adjusted in both groups.

The EN group was started on 20 ml/kg/day of RACOL®-NF (Otsuka Pharmaceuticals Co., Ltd., Tokyo, Japan) on POD 1 and 2, increased to 25 ml/kg on POD 3, then to 30 ml/kg/day on POD 4-7. The amount of water was adjusted by injecting hot water into the feeding jejunostomy tube. We changed the protocol from May 2013 by administering RACOL®-NF during POD 2-7 (POD 2, 3 and 4-7: 20, 25, and 30 ml/kg/day), because slight chylothorax and chylous ascites developed when RACOL®-NF was started on POD 1.

We administered the TPN group with 20 ml/kg of ELNEOPA®-NF (Ohtsuka Pharmaceuticals Co. Ltd.) from POD 1 *via* a central venous catheter and increased the amount on POD 2 to 25 ml/kg, and on POD 3-7 to 30 ml/kg/day. The amount of water was adjusted by injecting normal saline into a central intravenous catheter.

We measured the concentrations of albumin, total protein, total cholesterol and trace elements as well as DAO activity in serum separated from blood collected before surgery and on POD 1, 3 and 7. The Institutional Review Board at Hiroshima University approved this study (approval number: RIN–254 and Clinical trial registration number: UMIN000004777).

*Endpoints*. The primary endpoint was differences in rates of changes in serum DAO activities between the EN and TPN groups based on the day before surgery through POD 1, 3 and 7, respectively. The integrity of the intestinal mucosa was evaluated by evaluating DAO.

Secondary endpoints were differences in change rates of nutritive value indexes including albumin, total protein, total cholesterol, and the trace elements iron (Fe), copper (Cu) and zinc (Zn)

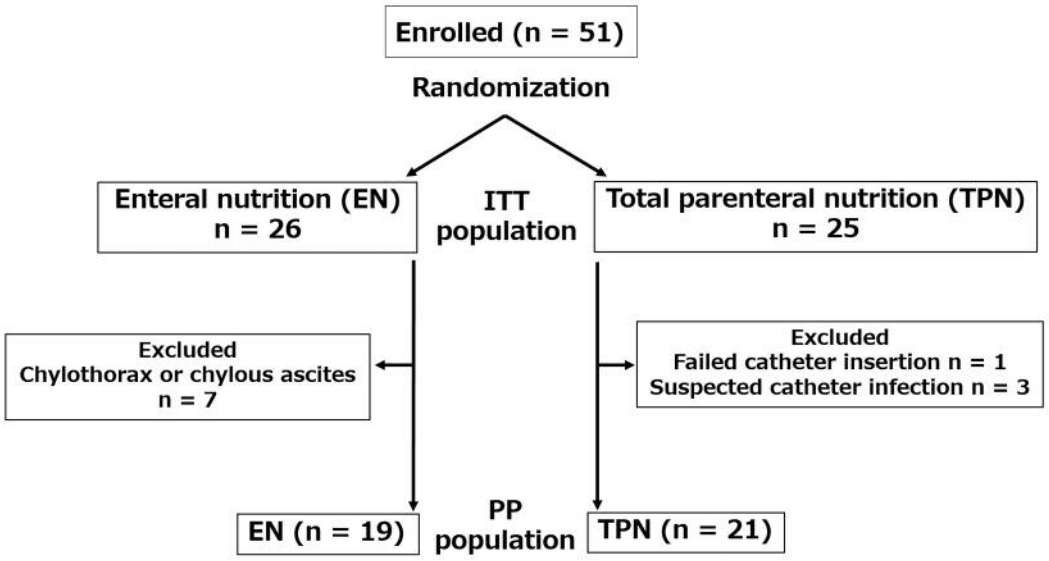



Figure 2. *CONSORT diagram. Fifty-one patients were randomized to EN or TPN group (n=26 and 25, respectively). Seven patients of the EN group were excluded during the early postoperative period, because of very slight chylothorax or chylous ascites due to early EN administration on POD 1. One patient in TPN group was excluded, because the central venous catheter could not be inserted after induction of anesthesia. Three others were excluded within the early postoperative period due to an infected central venous catheter that was removed as it might have been associated with persistent fever. Forty patients who could tolerate TPN or EN until POD 7 were analyzed per-protocol (PP), and postoperative complications in all enrolled patients were analyzed per intention-to-treat (ITT).*

concentrations between the EN and TPN groups, based on levels on the day before surgery and on POD 1, 3 and 7. Differences in postoperative infectious and non-infectious complications between the EN and TPN groups were also evaluated. We defined postoperative infectious complications as anastomotic leakage, pneumonia, pyothorax, catheter infection and wound infection.

*Neoadjuvant therapy and surgery*. Patients with stage I tumors were surgically treated. Those with tumors of a higher stage received neoadjuvant therapy followed by surgery. The surgical procedure for all patients was transthoracic or thoracoscopic esophagectomy with at least two-field LN dissection (thoracic and abdominal fields). Esophageal cancer in the upper and middle thirds of the thoracic esophagus or LN metastasis in the superior mediastinum were treated by cervical lymphadenectomy (three-field LN dissection: cervical, thoracic and abdominal fields). The gastric tube was subsequently lifted *via* the posterior mediastinal, retrosternal or subcutaneous route for cervical anastomosis with the esophagus. Anesthesia was induced, then a central intravenous catheter was inserted into the subclavian veins of all patients for TPN. A feeding jejunostomy tube for EN was placed during surgery.

*Measurement of serum diamine oxidase levels*. Blood samples were collected early in the morning of the day before surgery and on POD 1, 3 and 7; they were placed in tubes containing heparin and were then separated by centrifugation (1,000 rpm for 15 min) for serum sampling. The activities of DAO were assessed in serum samples stored at –80˚C using enzyme-linked immunosorbent assay (ELISA) kits (Immundiagnostik AG, Bensheim, Germany).

*Statistical analysis*. Categorical and continuous variables were analyzed using $\chi^2$ and unpaired *t*-tests, respectively. Values with $p<0.05$ were considered statistically significant. All data were statistically analyzed using SPSS software version 27 (IBM Corporation, Armonk, NY, USA).

## Results

*Patient characteristics*. The CONSORT diagram details the flow chart (Figure 2). Fifty-one patients were randomized to receive EN ($n$=26) or TPN ($n$=25). We excluded 7 patients from the EN group during the early postoperative period, because they developed very slight chylothorax or chylous ascites from POD 1, and RACOL®-NF was immediately discontinued. Therefore, we changed the RACOL®-NF protocol to start from POD 2 in May 2013.

One patient in the TPN group was excluded, because a central venous catheter could not be inserted after the induction of anesthesia. Three patients were excluded during the early postoperative period because of infected central venous catheters possibly associated with persistent fever, and these were removed.

Postoperative complications were evaluated in all patients in an intention-to-treat analysis. Forty patients who tolerated TPN or EN until POD 7 were analyzed per-protocol. Table I shows that the clinical characteristics of the patients did not

Table I. *Characteristics of the patients*.

| Parameters | Intention-to-treat | | | Per-protocol | | |
|---|---|---|---|---|---|---|
| | EN n=26 | TPN n=25 | *p*-Value | EN n=19 | TPN n=21 | *p*-Value |
| Mean age±SD (y) | 63.3±7.7 | 63.4±9.4 | 0.96 | 63.6±6.6 | 64.2±9.7 | 0.82 |
| Gender | | | | | | |
| Male | 18 (69.2) | 22 (88.0) | 0.10 | 12 (63.2) | 18 (85.7) | 0.10 |
| Female | 8 (30.8) | 3 (12.0) | | 7 (36.8) | 3 (14.3) | |
| BMI | 22.8±2.7 | 22.9±4.5 | 0.94 | 21.7±4.6 | 22.2±2.6 | 0.70 |
| Primary tumor location | | | | | | |
| Upper third | 7 (26.9) | 8 (32.0) | 0.92 | 5 (26.3) | 7 (33.3) | 0.89 |
| Middle third | 10 (38.5) | 9 (36.0) | | 7 (36.8) | 7 (33.3) | |
| Lower third and esophagogastric junction | 9 (34.6) | 8 (32.0) | | 7 (36.8) | 7 (33.3) | |
| Histological type | | | | | | |
| Squamous cell carcinoma | 22 (84.6) | 22 (88.0) | 0.61 | 15 (78.9) | 18 (85.7) | 0.56 |
| Adenocarcinoma | 3 (11.5) | 3 (12.0) | | 3 (15.8) | 3 (14.3) | |
| Small cell carcinoma | 1 (3.8) | 0 | | 1 (5.3) | 0 | |
| cT[a] | | | | | | |
| 1 | 12 (46.2) | 8 (32.0) | 0.57 | 9 (47.4) | 7 (33.3) | 0.51 |
| 2 | 2 (7.7) | 3 (12.0) | | 1 (5.3) | 3 (14.3) | |
| 3 | 12 (46.2) | 14 (56.0) | | 9 (47.4) | 11 (52.4) | |
| cN[a] | | | | | | |
| 0 | 12 (46.2) | 9 (36.0) | 0.06 | 10 (52.6) | 8 (38.1) | 0.25 |
| 1 | 13 (50.0) | 9 (36.0) | | 8 (42.1) | 8 (38.1) | |
| 2 | 1 (3.8) | 7 (28.0) | | 1 (5.3) | 5 (23.8) | |
| cM[a] (Supraclavicular LN metastasis) | | | | | | |
| 0 | 24 (92.3) | 22 (88.0) | 0.60 | 18 (94.7) | 19 (90.5) | 0.61 |
| 1 | 2 (7.7) | 3 (12.0) | | 1 (5.3) | 2 (9.5) | |
| cStage[a] | | | | | | |
| I | 8 (30.8) | 6 (24.0) | 0.63 | 7 (36.8) | 5 (23.8) | 0.78 |
| II | 7 (26.9) | 4 (16.0) | | 4 (21.1) | 4 (19.0) | |
| III | 9 (34.6) | 12 (48.0) | | 7 (36.8) | 10 (47.6) | |
| IV | 2 (7.7) | 3 (12.0) | | 1 (5.3) | 2 (9.5) | |
| Neoadjuvant therapy | | | | | | |
| None | 7 (26.9) | 7 (28.0) | 0.70 | 6 (31.6) | 6 (28.6) | 0.75 |
| Chemotherapy | 10 (38.5) | 7 (28.0) | | 7 (36.8) | 6 (28.6) | |
| Chemoradiotherapy | 9 (34.6) | 11 (44.0) | | 6 (31.6) | 9 (42.9) | |
| Thoracic procedure | | | | | | |
| Open | 16 (61.5) | 16 (64.0) | 0.86 | 11 (57.9) | 14 (66.7) | 0.57 |
| Thoracoscopy | 10 (38.5) | 9 (36.0) | | 8 (42.1) | 7 (33.3) | |

Values are shown as n (%) or as mean±SD. [a]Pretherapeutic staging according to TNM Classification, 7th edition. BMI, Body mass index; EN, enteral nutrition; SD, standard deviation; TPN, total parenteral nutrition.

significantly differ between the EN and TPN groups due to the random allocation.

*Serum DAO activity*. Rates of change in serum DAO activity compared with levels on the day before surgery were 0.79±0.36, 0.89±0.54 and 0.91±0.44 on POD 1, 3 and 7, respectively, in the EN group; 0.64±0.33, 0.76±0.37 and 1.06±0.48, respectively, in the TPN group. These values did not significantly differ on POD 1, 3, 7 between the EN and TPN groups. Although the DAO activities decreased to POD 1 in both groups, they returned almost to preoperative levels by POD 7 (Figure 3A).

Rates of change in serum DAO activities on POD 1, 3, 7 did not significantly differ between patients with and without neoadjuvant therapy, although DAO activities on POD 1 and 3 were lower in the patients with, than without neoadjuvant therapy (Figure 3B), and did not differ between those who underwent open thoracotomy and thoracoscopy (Figure 3C).

*Changes in nutritive indexes*. The rates of change in total protein were 0.68±0.07, 0.74±0.06 and 0.85±0.07 on POD 1, 3 and 7, respectively, in the EN group, and 0.67±0.05, 0.74±0.07 and 0.81±0.08 respectively, in the TPN group (Figure 4A). The rates of change in albumin were

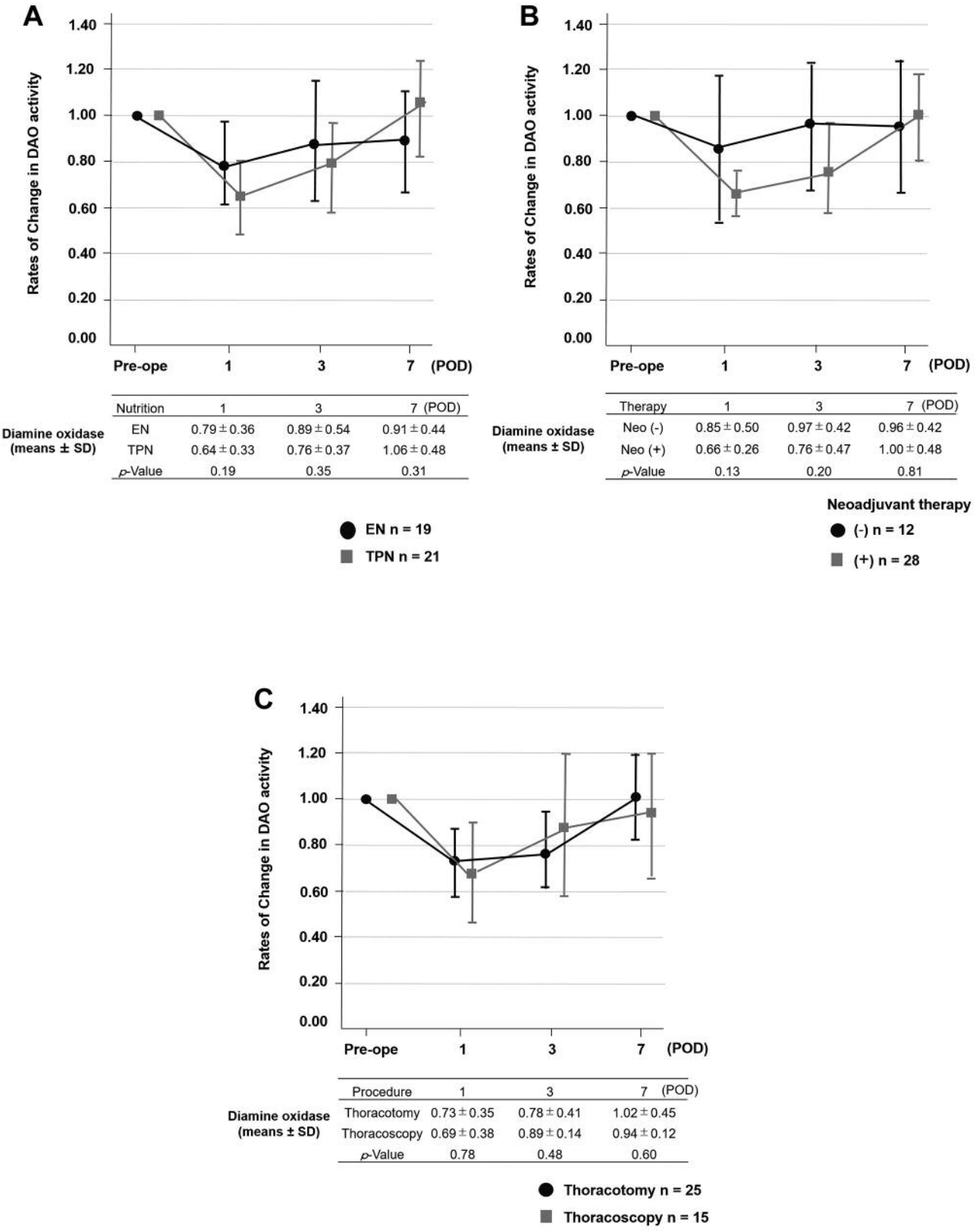
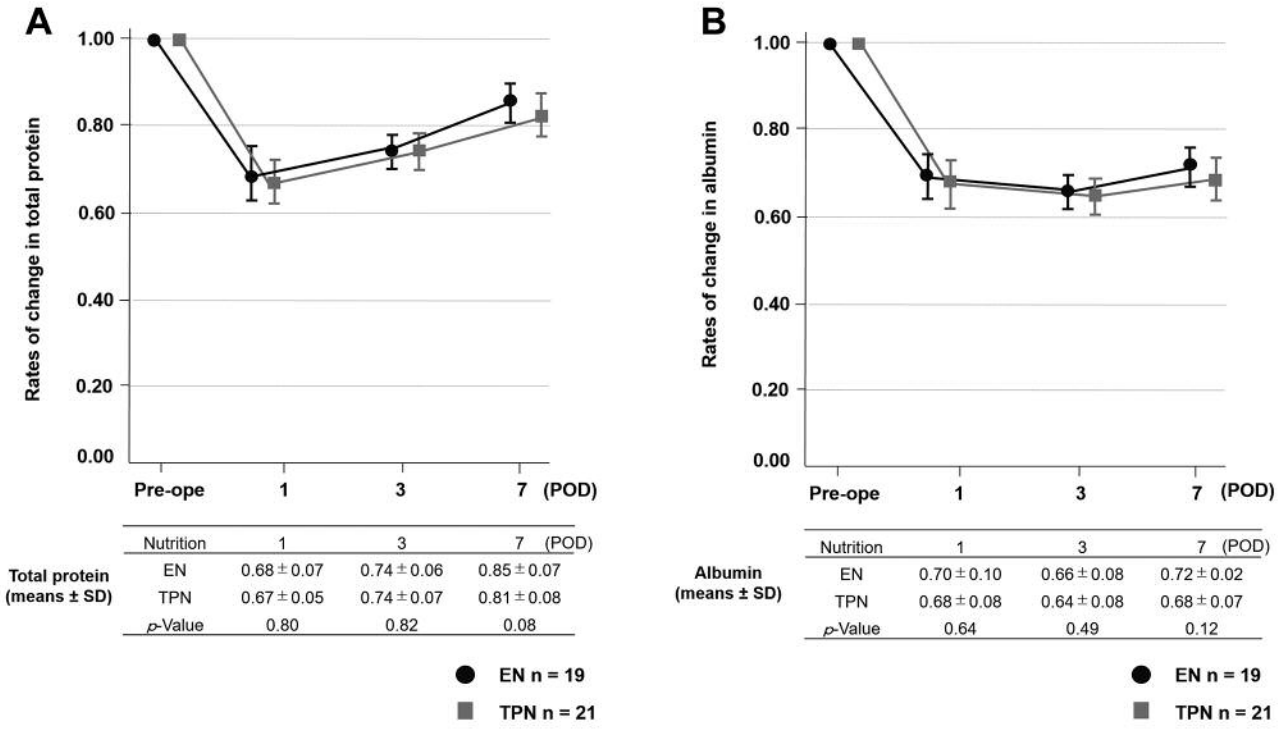



Figure 3. *Rates of change in serum DAO activity. Rates of change in serum DAO activity in patients (A) managed by EN or TPN, (B) with or without neoadjuvant therapy, and (C), after surgery via open thoracotomy or thoracoscopy. Each value was analyzed using unpaired t-test.*



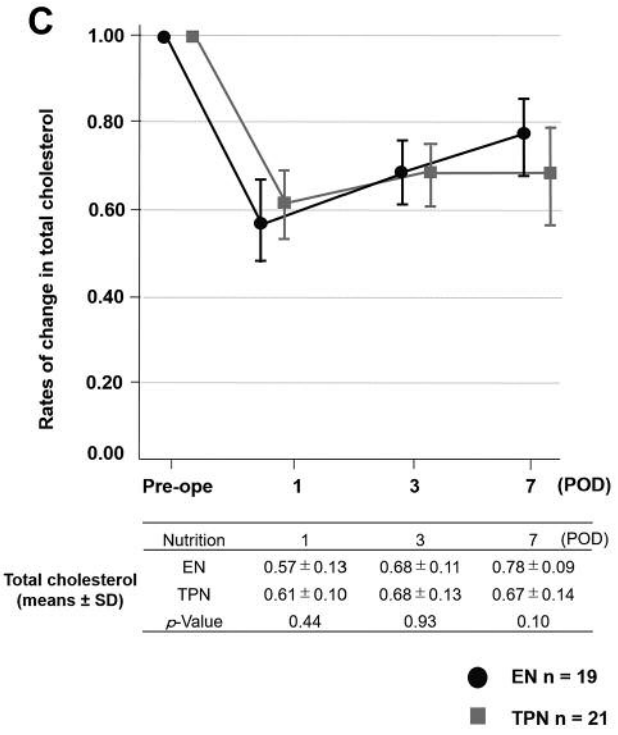




Figure 4. *Rates of change in nutritive value indexes. Rates of change in (A) total protein, (B) albumin, and (C) total cholesterol in patients managed by EN or TPN. Each value was analyzed using unpaired t-test.*

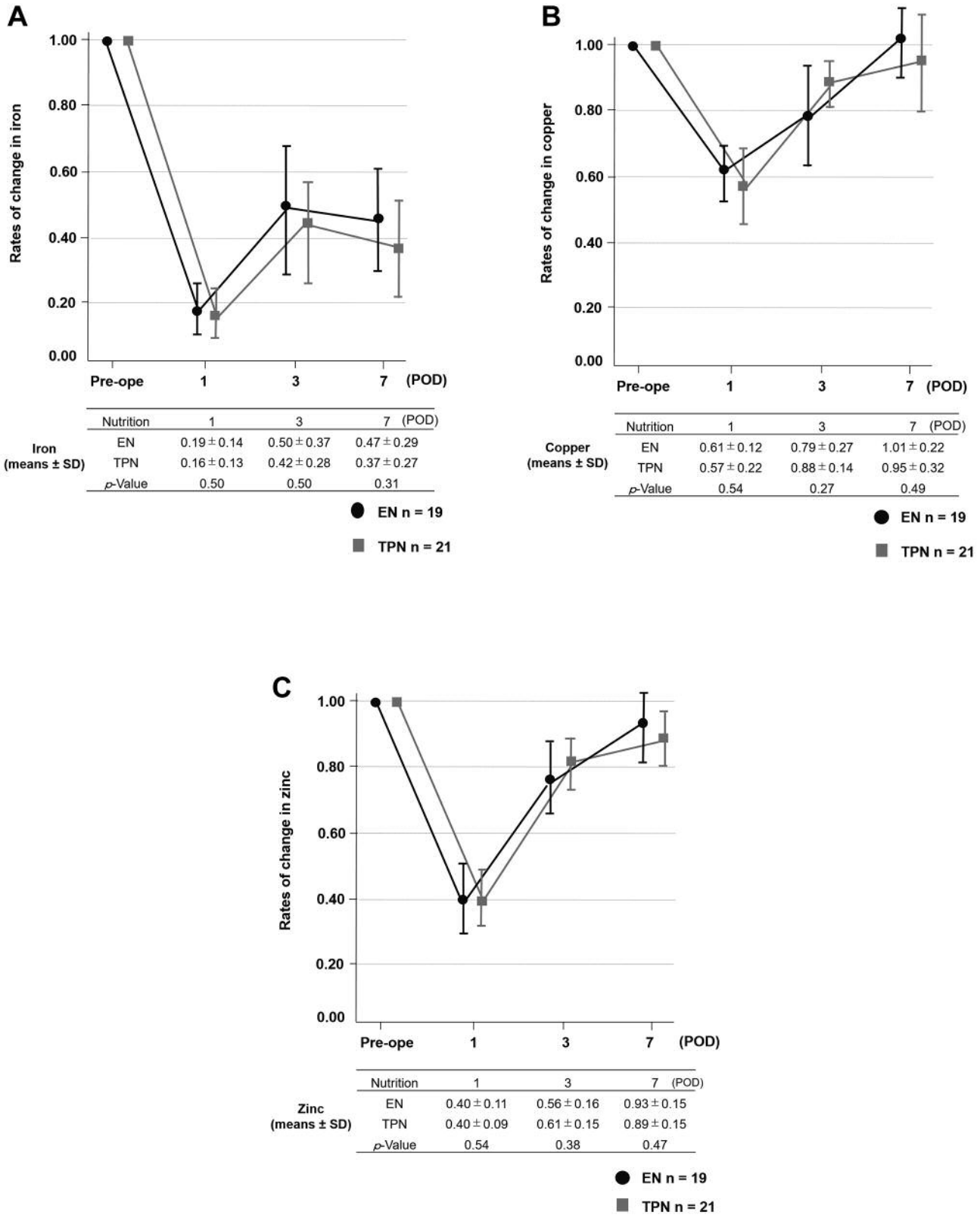



Figure 5. *Rates of change in trace elements. Rates of change in (A) Fe, (B) Cu, and (C) Zn in patients managed by EN or TPN. Each value was analyzed using unpaired t-test. Cu, Copper; Fe, iron; Zn, zinc.*

0.70±0.10, 0.66±0.08 and 0.72±0.02 on POD 1, 3 and 7, respectively, in the EN group, and 0.68±0.08, 0.64±0.08 and 0.68±0.07, respectively, in the TPN group (Figure 4B). The rates of changes in total cholesterol were 0.57±0.13, 0.68±0.11 and 0.78±0.09 on POD 1, 3 and 7, respectively, in the EN group, and 0.61±0.10, 0.68±0.13 and 0.67±0.14 on POD 1, 3 and 7, respectively, in the TPN group (Figure 4C). Rates of changes in the nutritive indexes of total protein, albumin, and total cholesterol did not significantly differ between the EN and TPN groups on POD 1, 3, 7 (Figure 4A-C).

*Changes in trace elements*. The rates at which Fe changed were 0.19±0.14, 0.50±0.37 and 0.47±0.29 on POD 1, 3 and 7, respectively, in the EN group, and 0.16±0.13, 0.42±0.28 and 0.37±0.27 on POD 1, 3 and 7, respectively, in the TPN group (Figure 5A). The rates of change in Cu, were 0.61±0.12, 0.79±0.27 and 1.01±0.22 on POD 1, 3 and 7, respectively in the EN group, and 0.57±0.22, 0.88±0.14 and 0.95±0.32, respectively, in the TPN group (Figure 5B). The rates of changes in total cholesterol were 0.40±0.11, 0.56±0.16 and 0.93±0.15 on POD 1, 3 and 7, respectively, in the EN group, and 0.40±0.09, 0.61±0.15 and 0.89±0.15 on POD 1, 3 and 7, respectively, in the TPN group (Figure 5C). The rates at which concentrations of Fe, Cu and Zn concentrations changed did not significantly differ between the EN and TPN groups on POD 1, 3, 7 (Figure 5A-C).

*Postoperative complications*. The differences of postoperative infectious and non-infectious complications between EN and TPN groups were evaluated in all enrolled all patients ($n$=51) as intent-to-treat analysis (Table II). Infectious complications developed in 10 (38.5%) and 14 (56.0%) patients in the EN and TPN groups, respectively ($p$=0.21). Non-infectious complications developed in 11 (44.0%) and 11 (42.3%) patients in the EN and TPN groups, respectively ($p$=0.90). These complications did not significantly differ between the two groups, although slightly more infectious complications developed in patients given TPN than EN.

Table II. *Postoperative complications*.

| | EN n=26 | TPN n=25 | $p$-Value |
|---|---|---|---|
| Infectious complications[a] | 10 (38.5%) | 14 (56.0%) | 0.21 |
| Non-infectious complications | 11 (42.3%) | 11 (44.0%) | 0.90 |

[a]Postoperative complications were defined as anastomotic leakage, pneumonia, pyothorax, catheter and wound infections. EN, Enteral nutrition; TPN, total parenteral nutrition.

## Discussion

Patients with surgically-treated esophageal cancer cannot intake oral nutrition for several postoperative days. Therefore, EN and/or PN are essentially needed for routine nutritional management after surgery. The introduction of early EN for perioperative care is beneficial in patients undergoing surgery for esophageal cancer according to ERAS guidelines (3, 12), but differences in serum DAO activities between nutritional managements by EN and TPN after esophagectomy have never been evaluated in a randomized study. Therefore, the present, prospective randomized trial compared DAO activities, nutritional indicators, trace elements and postoperative complications between patients with esophageal cancer who received EN and TPN during the early postoperative period until oral intake was resumed. This study found no significant differences in the above factors between the EN and TPN groups.

Diamine oxidase is normally abundant in the intestinal mucosa, kidneys, and placenta of humans and other mammals, and the intestinal mucosa is the prime source of serum DAO (19-22). Serum levels of this enzyme activity closely reflect the maturity and integrity of the intestinal mucosa; serum enzyme activity increases as the rat intestinal mucosa differentiates and contains increasing amounts of enzyme and decreases as the adult rat mucosa is progressively damaged (19). The small intestinal mucosa contains the most DAO activity in humans. Serum DAO activity might be a good marker of intestinal mucosal maturation and integrity (19-22). Human DAO can be reliably and accurately quantified in various biological fluids using ELISAs (18).

Surgical stress influences intestinal integrity after esophagectomy for esophageal cancer, and serum DAO activity was obviously decreased in such patients (23). A comparison of DAO activity between patients with gastric cancer who received postoperative nutrition with EN and TPN found decreased DAO activity in both groups after total gastrectomy and recovery within 1 week in the EN, but not in the TPN group (24). Furthermore, in another study, elderly patients with esophageal or cardiac cancers were divided into EN or PN groups based on nutrition support modes. The early postoperative EN could more effectively improve nutritional status and postoperative intestinal permeability assessed as serum DAO activity and protect the intestinal mucosal barrier (25). The present study did not find significant differences in serum DAO activities between the EN and TPN groups. Although the DAO activities decreased to POD 1 levels in both groups, they returned almost to preoperative levels. Although surgical stress temporarily influences postoperative intestinal integrity and permeability, the subsequent amount of change of DAO activity might also be influenced depending on the status of each patient and types of gastrointestinal tract diseases, operative procedures, as well as enteral and parenteral nutrients.

We evaluated whether rates at which the nutritive indexes, namely albumin, total protein, total cholesterol, and trace element concentrations changed between the EN and TPN groups and found no significant differences in any of them. RACOL®-NF and ELNEOPA®-NF both include enough calories, trace elements and multivitamins that postoperative patients need. Although all nutritive indexes were decreased to POD 1, they increased to about 80% of preoperative levels in both groups.

Although Cu and Zn decreased on POD 1, they recovered almost to preoperative levels on POD 7 in both groups. On the other hand, Fe increased to only ~40% of preoperative levels by POD 7 in both groups. A previous study of sequential perioperative changes in the nutritional and immune status of patients after esophageal cancer surgery also found that the deterioration in serum iron was most severe by POD 3 (26). Other than iron-related parameters, all measured nutritional parameters returned to preoperative levels within 2-3 weeks after surgery. However, serum levels of iron returned to normal after more than 1 month. Therefore, postoperative iron and protein supplementation might be needed for 1-3 months to prevent an iron deficiency.

Early EN initiated after esophagectomy reduced the length of the hospital stay (6-8), postoperative weight loss (9), postoperative morbidity (8-10), and the rate of life-threatening complications (11). On the other hand, early EN did not generate any evidence or confer any clinical benefits upon the length of hospital stays, morbidity, and mortality after esophagectomy (13-15). Although postoperative complications also did not significantly differ between the groups, infectious complications, especially catheter infection, developed slightly more often in the TPN group. Therefore, catheter infection should be carefully monitored in patients who are administered with TPN *via* a central venous catheter. Furthermore, the very slight chylothorax and chylous ascites that developed when EN was administered from POD 1 indicated that EN administered from POD 1 might confer the risk of developing these states. Therefore, EN containing fat might be appropriate to administer from day 2 after esophagectomy.

Although we compared patients who received EN and TPN until POD 7, estimation over a longer period should be applied for postoperative nutritional management in patients with esophageal cancer. Enteral nutrition is needed for patients who are forced to fast over the long term due to postoperative anastomotic leakage (27), and to improve nutritional status during long postoperative periods even after discharge (28). Therefore, EN is essential for postoperative management of esophageal cancer. On the other hand, TPN might be also needed to conservatively manage patients who develop postoperative chylothorax (29). Thus, TPN and EN should be appropriately administered for short- and long-term postoperative nutritional management according to the status of individual patients with esophageal cancer because each might confer specific advantages.

In conclusion, the change of serum DAO activity, nutritional state, trace elements and postoperative complications were similar in the EN and TPN groups within 7 days after esophagectomy. Thus, either TPN and/or EN can be administered for the early postoperative nutritional management of individual patients with esophageal cancer according to their status.

## Conflicts of Interest

The Authors have no commercial support or conflicts of interest to disclose in relation to this study.

## Authors' Contributions

YH drafted the article. ME, YI, TK, TY, RH, MO and NK contributed to patient care. YH performed the literature search. JH and MO participated in the critical revision of the article. All Authors read and approved the final article.

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