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Efficacy of perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy

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ABSTRACT

Objective: Malnutrition is common in patients with esophageal cancer, resulting in increased postoperative complications and mortality. Although preoperative immunonutrition can significantly reduce the incidence of postoperative infectious complications, its effect in patietns with esophageal cancer undergoing esophagectomy remains unclear. The aim of this study was to investigate the effects of perioperative immunonutritional support on the postoperative course and long-term survival of this group of patients.
Methods: This prospective, randomized study enrolled 40 patients with thoracic esophageal carcinoma undergoing esophagectomy. The patients were divided into two groups and received either immunomodulating enteral nutrition (IMPACT group; IG) or standard enteral nutrition (Ensure group; EG) continuously for 7 d before and 7 d after surgery. Nutritional status, such as rapid turnover protein, postoperative intensive care unit (ICU) length of stay (LOS), postoperative hospital LOS, morbidity, and mortality were investigated prospectively.
Results: There were no significant differences in patient demographic characteristics between the two groups. Levels of retinol-binding protein, as a rapid-turnover protein, were significantly higher on postoperative day (POD) −1, 7, and 14 in the IG compared with the EG group ($P = 0.009$, $P = 0.004$, and $P = 0.024$, respectively). The incidence of postoperative infectious complications and changes to therapeutic antibiotics were significantly lower in the IG group than in the EG group ($P = 0.048$ and $P = 0.012$, respectively). There was no significant difference in postoperative ICU or postoperative hospital LOS between the two groups. The 5-y progression-free survival rates in the IG and EG groups were 75% and 64%, respectively ($P = 0.188$), and the overall survival rates were 68% and 55%, respectively ($P = 0.187$).
Conclusions: Perioperative immunonutrition may improve early postoperative nutritional status and reduce postoperative infectious complications in patients with esophageal cancer undergoing esophagectomy.

Introduction

The incidence of esophageal cancer has been increasing in Japan, with 23 119 new cases diagnosed in 2011, and 11 543 patients dying of this disease in 2013, accounting for 3.2% of all cancer-related deaths [1]. Despite improvements in surgical techniques, management of surgical infections, and the development of successive generations of more powerful antibiotics, postoperative infectious and septic complications continue to be major factors contributing to unfavorable clinical outcomes in patients with esophageal cancer undergoing esophagectomy [2–4].

It is known that poor nutritional status is associated with an increased incidence of postsurgical complications including infections, impaired wound healing [5,6], and decreased function and

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quality of life [7,8]. Artificial enteral diets enriched with arginine, glutamine, ω-3 fatty acids, and other nutritional substrates (namely, immunonutrition) has been used to reduce postoperative morbidity [9]. IMPACT formula (Nestlé Health Science, Vevey, Switzerland), which contains a consistent combination of RNA (dietary nucleotides), arginine, and the ω-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid and docosahexaenoic acid from fish oil, is an immune-enhancing formula that has been evaluated by meta-analyses in several cancers, including gastric and colorectal cancers [10–12]. However, to our knowledge, there are only a few reports of the effects of perioperative nutritional support in patients undergoing surgery for esophageal cancer and little information is available on the long-term outcomes. Thus, there is insufficient evidence to recommend the routine use of immunonutrition in these patients [13–15].

We conducted a prospective study to investigate the effects of perioperative immunonutritional support on the postoperative course and long-term survival of patients undergoing esophageal cancer surgery.

Materials and methods

Study design

This was a single-center, prospective, randomized study to evaluate the efficacy of perioperative immunonutrition in patients undergoing esophagectomy for esophageal cancer, conducted at the Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine (Yamaguchi, Japan). The primary endpoint was numbers of infective complications (including changes to therapeutic antibiotics). Secondary endpoints were nutritional status, postoperative intensive care unit (ICU) length of stay (LOS), postoperative hospital LOS, other clinical outcomes, and long-term outcome.

Patients

Forty patients with esophageal carcinoma who underwent radical esophagectomy were enrolled in this prospective, randomized clinical study. All patients had advanced-stage esophageal carcinoma without dysphagia. Subjective Global Assessment was performed on all patients, cases in which weight loss was ≥5% within 1 mo, cases in which oral intake decreased by >20%, or a combination of the three factors were excluded from this study. All patients underwent esophagectomy and reconstruction with a gastric tube. A jejunostomy tube was placed during surgery for postoperative enteral feeding. Patients who underwent thoracoscopic or laparoscopic procedures, or both were excluded from the study. The extent of lymph node dissection was D1 or D2, and there was no significant difference in the extent of lymph node dissection between the two groups. As prophylactic antibiotics, 1 g of cefazolin was given 30 min before surgery, followed by 1 g every 3 h during surgery, and every 12 h postoperatively for 3 d.

This study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of Yamaguchi University Hospital and the Ethical Review Committee for Gene Analysis Research of Yamaguchi University School of Medicine and University Hospital. All patients were enrolled after receiving detailed explanation of the study protocol and after written informed consent was obtained from them or from their family members.

Study protocol

This was a prospective, randomized clinical trial performed at Yamaguchi University Hospital. The patients were assigned randomly to receive immunomodulating enteral nutrition (EN) with either IMPACT (IG, n = 20), a liquid diet (1 kcal/mL with 5.6 g/100 mL protein) supplemented with arginine (12.8 g/L), ω-3 fatty acids (4.1 g/L), and RNA (1.29 g/L) or standard EN with Ensure (EG, n = 20), an enteral feed (1.5 kcal/mL with 6.25 g/100 mL protein) without immunonutrients. The patients received EN associated with their regular meals consecutively for 7 d before surgery, and postoperative EN through a jejunostomy tube placed during surgery for 7 d after surgery. The total daily calorie intake of the EN was set at 750 kcal/d. All the patients received 35 kcal/kg of energy and 1.3 g/kg of protein as the daily amount of each enteral diet and conventional diet. The amount of consumed enteral diet and oral intake was preoperatively monitored by a study nurse for the enrolled patients. Randomization was performed using blinded envelopes as follows: Equal numbers of envelopes containing IG or EG protocols were prepared in a blinded fashion and allocated sequentially as the patients were enrolled in the study. Randomization was carried out in the evening 7 d before surgery to rule out any effect of intraoperative findings on the selection.

All patients enrolled in the study were advised to drink 750 kcal/d of enteral diet as an oral supplement, in addition to consuming their regular diet, for 7 d before surgery. Postoperative EN also was administered 6 h after surgery via a jejunostomy catheter. EN was started at 10 kcal/h and increased progressively each day in a stepwise manner. Postoperative EN via jejunostomy was continued after oral intake was resumed, until ~7 d after surgery (Fig. 1). Blood samples were obtained from a peripheral cutaneous vein at 1 and 8 d before surgery (prevalue), and 1, 3, 7, and 14 d after surgery.

Clinical parameters

Clinical variables examined included age, sex, body mass index (BMI), respiratory function tests, albumin, indocyanine green test, 24-h creatinine clearance, and tumor staging. Tumor staging was based on the seventh edition of the International Union for Cancer Control (UICC) TNM staging system for esophageal carcinoma [16].

Surgical parameters included operation time, bleeding, lymphadenectomy fields, extubation, and postoperative hospital LOS.

The analysis was based on infectious complications including pneumonia and surgical site infection (SSI), anastomotic leakage, changes from prophylactic antibiotics of cefazolin to therapeutic antibiotics of broad-spectrum antibiotics such as carbapenem antibiotics or vancomycin, and progression-free and overall survival (PFS and OS) rates.

Laboratory data including plasma levels of C-reactive protein (CRP) and rapid-turnover proteins (retinol-binding protein [RBP], prealbumin, transferrin), and lymphocyte counts at 1 and 8 d before surgery, and 7 and 14 d after surgery were analyzed.

Postoperative complications

Pneumonia was diagnosed based on rhonchus, lung radiographic findings, deterioration of neutrophil count, CRP, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2), positive active surveillance culture, sputum on bronchoscopic findings, or all of the factors combined. SSI included any superficial incisional, deep incisional, or organ/space site infection according to the Centers for Disease Control and Prevention definition [17]. Anastomotic leakage was diagnosed by saliva leakage through the neck wound or upper gastrointestinal series. In every case of anastomotic leakage, a diagnosis of SSI was made. We regarded postoperative hoarseness as indicative of recurrent laryngeal nerve paralysis. Gastric conduit necrosis was diagnosed by esophagogastroduodenoscopy. Any associated arrhythmia was diagnosed by a cardiologist. Chylothorax was diagnosed by milky drainage. All postoperative complications were evaluated according to Clavien–Dindo classification [18] and grade II or more was defined as positive.

Statistical analysis

The primary endpoint of the study was non-occurrence of infective complications including pneumonia or SSI after esophagectomy. The expected non-occurrence rate of infective complications was estimated at 85%, and its threshold was estimated at 65%. With a statistical power of 80% and a one-sided type I error of 5%, the number of eligible patients required for this study was calculated to be 33, using Simon's two-stage design [19]. The projected sample size was 40 patients, with the expectation that 10% would be deemed ineligible.

Non-parametric continuous variables were reported as median and interquartile range and compared using Mann-Whitney U-tests. Categorical variables were compared using Pearson's χ^2 or Fisher's exact tests. PFS and OS were determined

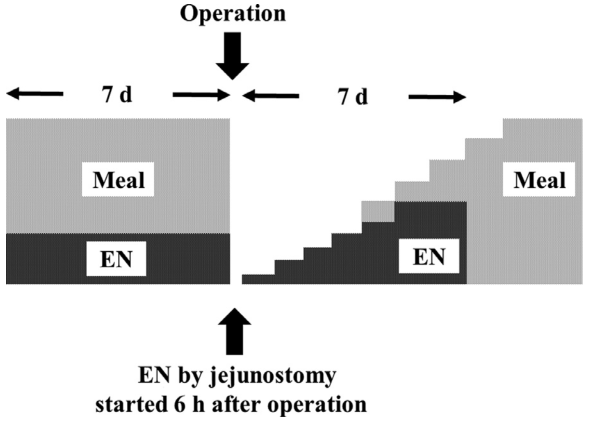

Fig. 1. Treatment schema. EN, enteral nutrition.

Table 1
Patient demographic characteristics

Variables	IMPACT group (n = 20)	Ensure group (n = 20)	*P*-values
Age, median (y [IQR])	65 [60–70]	62 [60–72]	0.588*
Sex			>0.95†
Male	16	16	
Female	4	4	
Amount of oral intake (% [IQR])	85 [80–90]	90 [81.3–95]	0.242*
Subjective Global Assessment			>0.95†
Well nourished	15	15	
Mild-moderately malnourished	5	5	
Severely malnourished	0	0	
BMI, median [IQR]	21.9 [19.3–25.3]	21.5 [19.4–23.0]	0.499*
%VC, median (% [IQR])	117.1 [107.5–123.3]	116.6 [107.4–125]	0.672*
FEV1%, median (% [IQR])	75.9 [72.3–77.9]	73.2 [65.5–79.1]	0.312*
Albumin, median (mg/dL [IQR])	3.9 [3.8–4.2]	4.3 [4–4.4]	0.056*
ICG15 R, median (% [IQR])	11.5 [8.4–14.1]	9.5 [7.4–11]	0.176*
24 hCcr, median (mL/min [IQR])	115.9 [93.8–132.1]	105.6 [84.3–114.2]	0.066*
P-Stage (UICC 7)			>0.95†
0, I	7	7	
II, III, IV	13	13	

BMI, body mass index; FEV_1%, % forced expiratory volume in 1 second; ICG15 R, indocyanin green retention rate after 15 min; IQR, interquartile range; %VC, % vital capacity; 24-h ClCr, 24-h creatinine clearance
*Wilcoxon rank sum test.
†Fisher's exact test.

by Kaplan–Meier actuarial analysis and differences between survival curves were analyzed using log-rank tests. All statistical analyses were performed using JMP 11.0.0 (SAS Institute Inc., Cary, NC, USA) software. $P < 0.05$ was considered statistically significant.

Results

The clinical backgrounds of the patients enrolled in this study are shown in Table 1. There were no significant differences in median age, sex, amount of oral intake, Subjective Global Assessment, body mass index (BMI), % vital capacity (%VC), % forced expiratory volume in 1 second (FEV_1%), albumin, indocyanin green retention rate after 15 min (ICG15 R), 24-h creatinine clearance (24-h CrCl), or pathologic stage (UICC seventh) between the two groups.

The surgical findings are shown in Table 2. There were no significant differences in operation time, operative blood loss, lymphadenectomy fields, extubation, or postoperative hospital LOS between the two groups.

Changes in rapid-turnover proteins during the perioperative period are shown in Figure 2. Retinol-binding protein levels were significantly higher in the IG group on postoperative day (POD) −1, 7, and 14 compared with the EG group ($P = 0.009$, $P = 0.004$, and $P = 0.024$, respectively). Prealbumin levels also tended to be higher in the IG group than in the EG group on POD −1 and 7 ($P = 0.054$ and $P = 0.054$, respectively). There was no significant difference in transferrin levels between the two groups.

There were no significant differences in changes in total lymphocyte counts and CRP during the perioperative period between the two groups (Fig. 3).

Morbidity and mortality

Morbidities are shown in Table 3. Of 20 patients in the IG group, 4 (20%) developed infectious complications, including pneumonia or SSI, as did 11 of 20 patients (55%) in the EG group. The number of patients with infectious complications who were administered therapeutic antibiotics was significantly lower in the IG group than in the EG group ($P = 0.048$ and $P = 0.012$, respectively). Duration of antibiotic use after surgery was significantly shorter in the IG group than in the EG group ($P = 0.021$). Recurrent laryngeal nerve paralysis occurred in two and four patients in the IG and EG groups, respectively ($P = 0.661$). Anastomotic leakage occurred in none and one patient in the IG and EG groups, respectively ($P > 0.95$). Arrythmia occurred in three patients in each group ($P > 0.95$). Chylothorax occurred in one patient in each group ($P > 0.95$). There were no hospital deaths in this study.

Survival

The 5-y PFS and OS rates in the IG and EG groups were 75% versus 64%, and 74% versus 55%, respectively. There were no

Table 2
Surgical findings

Variables	IMPACT group (n = 20)	Ensure group (n = 20)	*P*-value
Operation time, median (min [IQR])	435 [390–469]	419 [376–435]	0.180*
Operative blood loss, median (mL [IQR])	535 [425–728]	460 [320–648]	0.199*
Lymphadenectomy fields†			0.127‡
2	13	18	
3	7	2	
Extubation (POD [IQR])	2 [1–2]	2 [1–2]	0.418*
Postoperative hospital LOS (d [IQR])	28 [24–30]	28 [24–39]	0.463*

IQR, interquartile range; LOS, length of stay; POD, postoperative day
*Wilcoxon rank sum test.
†2 fields, mediastinal and perigastric lymphadenectomy; 3 fields, 2 fields + cervical lymphadenectomy.
‡Fisher's exact test.

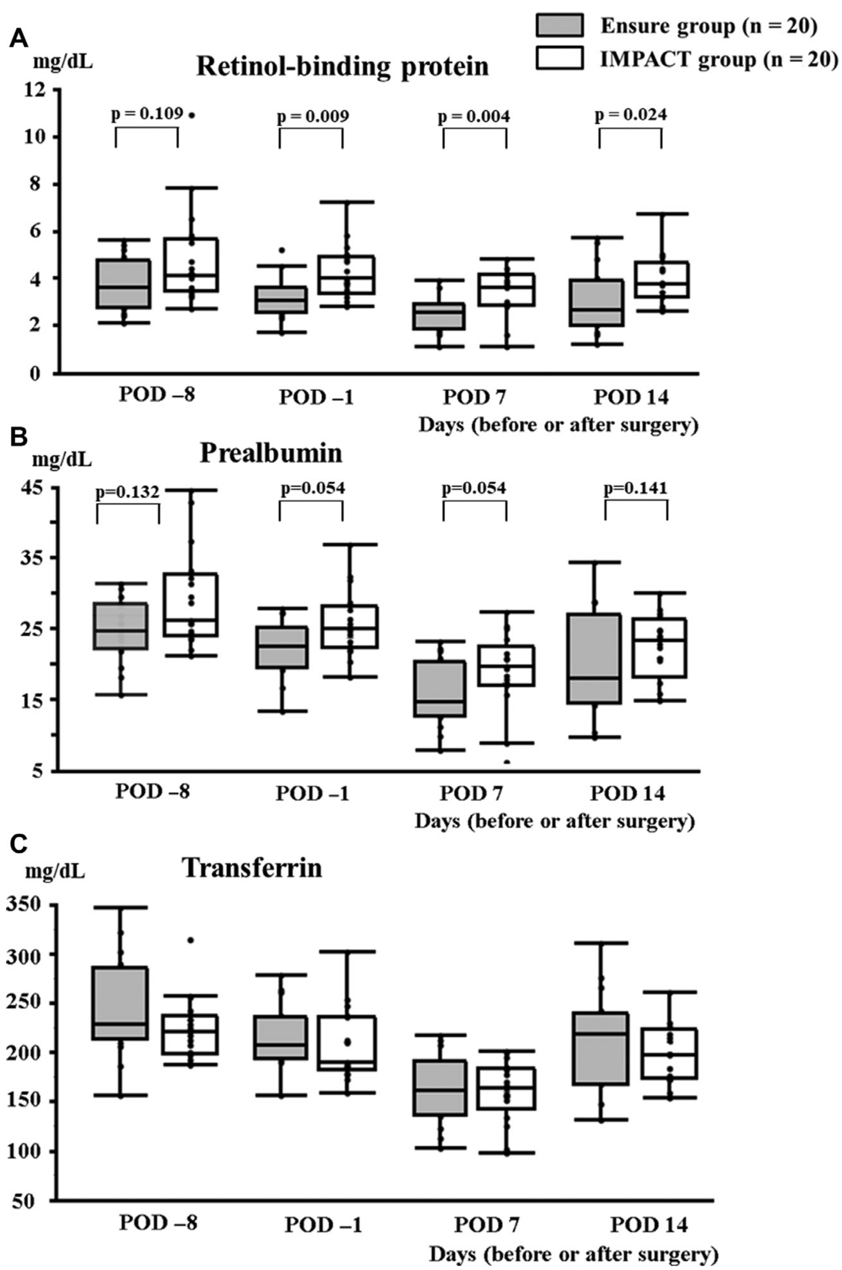

Fig. 2. Perioperative changes in rapid-turnover proteins in the IMPACT and Ensure groups. POD, postoperative day.

significant differences in survival curves between the two groups ($P = 0.1878$ and $P = 0.1283$, respectively; Fig. 4).

Discussion

Most patients with esophageal cancer are at severe nutritional risk, as defined by the European Society for Clinical Nutrition and Metabolism working party [20]. Various approaches, including nutritional intervention, have been used to overcome this problem. Preoperative immunonutrition (specifically using IMPACT) significantly improved short-term outcomes, including postoperative morbidity and hospital LOS among patients undergoing esophagectomy [21]. However, there is insufficient clinical evidence for the use of immunonutrition in these patients. Therefore, we investigated the efficacy of perioperative nutritional support on the postoperative course and the long-term survival of patients with esophageal cancer undergoing esophagectomy. The current results showed that the incidence of postoperative infectious complications and changes to therapeutic antibiotics was significantly lower in patients receiving immunonutrition compared with those receiving standard EN.

Immunonutrition has been reported to have pharmacologic effects on the immune system and may potentially improve the patient's immune response [22]. In addition, perioperative immunonutrition was shown to improve inflammatory, metabolic, and immune responses after esophagectomy [23,24]. However, although previous studies reported that short-term outcomes such as anastomotic leakage, pulmonary complications, and postoperative hospital LOS were improved by immunonutrition [23,24], information on the effects on long-term outcomes is lacking. The effects of immunonutrition may be explained by the effects of arginine and ω-3 PUFAs. Arginine administration has been shown to

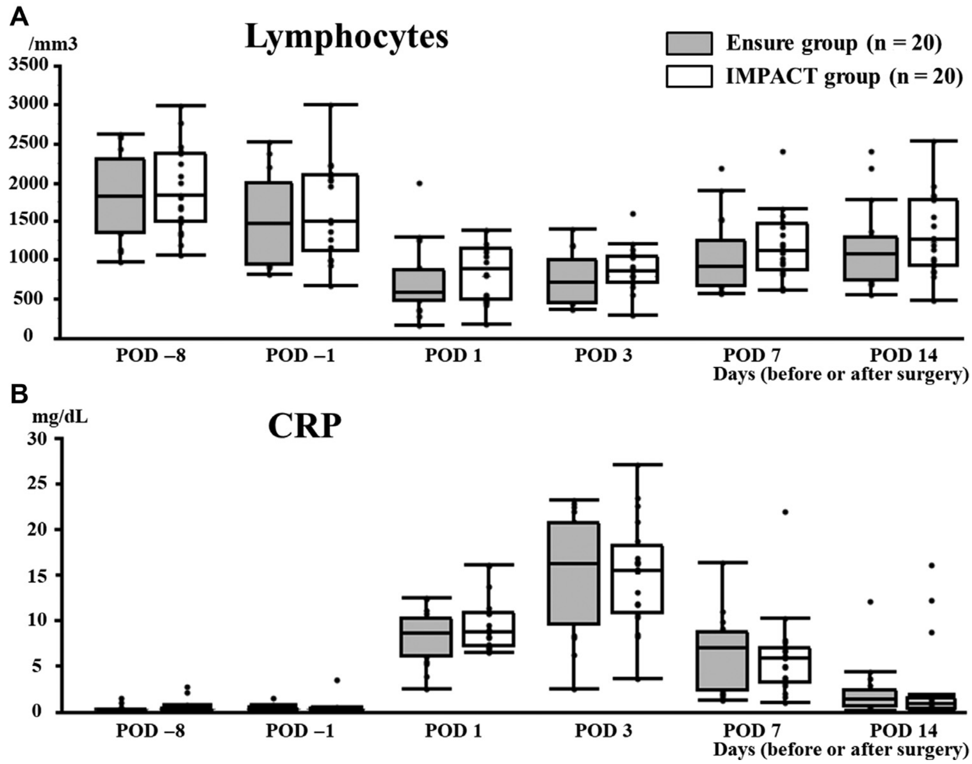

Fig. 3. Perioperative changes in total lymphocyte counts and CRP levels in the IMPACT and Ensure groups. CRP, C-reactive protein; POD, postoperative day.

Table 3
Morbidity and mortality

	IMPACT group (n = 20)	Ensure group (n = 20)	*P*-value
Pneumonia, % (n)	10 (2)	25 (5)	0.408*
SSI, % (n)	10 (2)	30 (6)	0.235*
Anastomotic leakage, % (n)	0 (0)	5 (1)	>0.95*
Recurrent laryngeal nerve paralysis, % (n)	10 (2)	20 (4)	0.661*
Arrythmia, % (n)	15 (3)	15 (3)	>0.95*
Chylothorax, % (n)	5 (1)	5 (1)	>0.95*
Infectious complications (pneumonia or SSI), % (n)	20 (4)	55 (11)	0.048*
Changes to therapeutic antibiotics, % (n)	25 (5)	65 (13)	0.012*
Duration of antibiotic use after surgery (d [IQR])	3 [3–5]	6 [3–7]	0.021†
Hospital death, % (n)	0 (0)	0 (0)	>0.95*

IQR, interquartile range; SSI, surgical-site infection
*Fisher's exact test.
†Wilcoxon rank sum test.

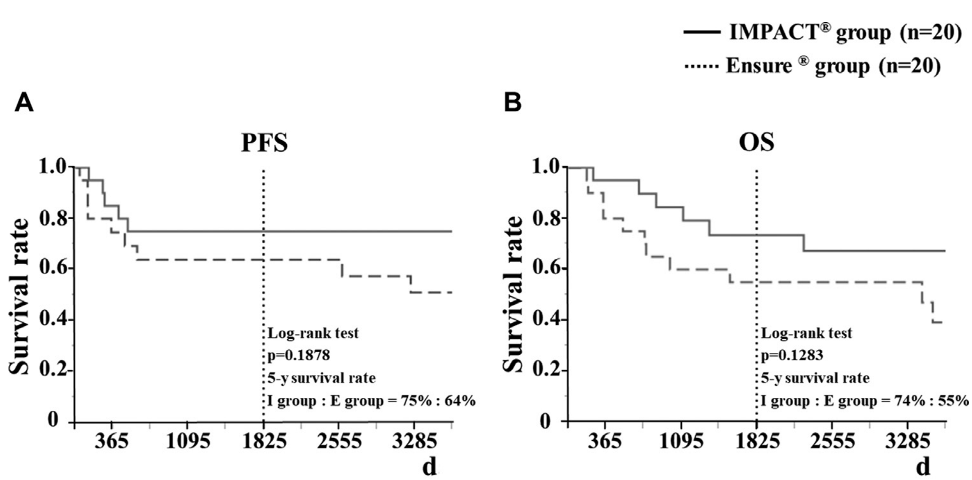

Fig. 4. Survival curves. Five-year PFS and OS curves in the IMPACT and Ensure groups. E, Ensure; I, IMPACT; OS, overall survival; PFS, progression-free survival.

improvebacterialclearance,T-cellfunction,andwoundhealing[25,26], whereas the synthesis of nitric oxide from L-arginine may increase splanchnic microperfusion and support tissue oxygen tension, delivery, and utilization [27]. ω-3 PUFAs have been shown to exert anti-inflammatory, vasodilatatory, and immunomodulatory properties through their ability to modulate the synthesis of various eicosanoids [28].

The 5-y PFS rates in the IG and EG groups were 75% and 64%, respectively, and the OS rates were 68% and 55%, respectively, in this study. Although there was no significant difference in either of these rates between the two groups, the PFS and OS for IG appeared to be better than that for EG.

Complications after radical surgery for esophageal, gastric, and colorectal cancers were associated with poor patient prognoses in a systematic review [29]. Hirai et al. [30] recognized that excessive surgical stress and postoperative complications cause a storm of perioperative cytokine release and increase tumor metastasis, resulting in a poor prognosis. Postoperative complications also are associated with a decline in performance status, and make subsequent chemotherapy difficult. A previous review at our institution found that OS was significantly better in patients without pulmonary complications than in those with pulmonary complications [31]. The occurrence of postoperative infectious complications in the present study was significantly lower in IG than in EG patients, which was in accord with previous findings. However, the this was a small-scale study and might have been underpowered; thus further studies with larger samples may demonstrate significant differences between the two groups.

Postoperative levels of RBP and prealbumin, as rapid-turnover proteins, were higher in IG than in EG patients. Arginine is known to increase hepatic protein synthesis by activating mTORC1 in collaboration with insulin and insulin-like growth factor-1 [32]. Some clinical trials suggested that perioperative immunonutrition may prevent surgery-induced alterations of the immune and inflammatory responses and influence the synthesis of short half-life proteins such as RBP [33,34]. Amino acids released from peripheral tissues act as substrates for the synthesis of acute-phase proteins and immunoglobulins during the replication of immune cells [35,36]. However, demands for specific amino acids may overtake endogenous sources, and protein deficiency impairs the acute-phase response [37]. Increasing hepatic protein synthesis supported by the amino acids supplied by immunonutrition may thus improve immune system function [38]. However, plasma protein levels including receptor-transporting protein (RTP) do not always reflect synthesis of these proteins especially in the patients with inflammation. For example, postoperative plasma albumin levels decrease significantly despite the increase in the postoperative albumin synthesis rate [39,40]. RTP may migrate into the extravascular space when inflammatory responses are underway and this escape rate seems to increase proportionally to the extent of inflammation. These phenomenon should be taken into account when interpreting the data [41,42]. Nevertheless, because preoperative RTP was increased, it was considered to have some good influence on the immune system.

Conclusion

The present study showed that immunonutrition could improve early postoperative nutritional status and reduce postoperative infectious complications in patients with esophageal cancer undergoing esophagectomy. These findings will help guide clinicians to administer EN support and thus prevent functional capacity deterioration in these patients. Further randomized controlled trials with larger samples are needed to allow the metabolic advantages of this enriched enteral diet to be translated into improved outcomes.

Acknowledgments

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