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Original article

Efficacy of prolonged elemental diet therapy after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: A pilot prospective randomized trial (UMIN000004108)

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SUMMARY

Backgrounds and aims: This randomized clinical trial examined efficacy of prolonged elemental diet (ED) therapy after pancreatoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC), which often causes postoperative malnutrition leading to worsened short- and long-term outcomes.

Methods: Thirty-nine patients with PDAC receiving PD was randomly assigned to prolonged ED group (PEDG) and control group (CG). Fat-free ED (Elental®, EA Pharma CO., Ltd., Tokyo, Japan) via tube jejunostomy was initiated on postoperative day 1 and increased to maintain with 600 kcal/day in addition to oral intake. ED was discontinued if sufficient oral intake was achieved in CG but continued during 3 postoperative months in PEDG. Primary outcome was complication necessitating readmission. Secondary outcomes were nutritional parameters, relative dose intensity (RDI) in cases of adjuvant chemotherapy, and survival outcomes.

Results: Twenty patients were assigned to CG and 19 to PEDG. Cumulative post-discharge readmission rate was significantly lower in PEDG than in CG (PEDG vs CG; 12.6% vs 43.7% at 12-post-discharge-month; $p = 0.018$). Total calorie and ED-derived protein intakes were significantly larger in PEDG than in CG up to 3-postoperative-month but thereafter similar among groups. Lymphocyte counts were significantly increased and neutrophil-to-lymphocyte-ratio (NLR) was significantly reduced in PEDG than in CG at 2-, 3-, and 6-postoperative-month. However, other outcome measures did not differ among groups.

Conclusion: This trial failed to show survival benefit of prolonged ED therapy but demonstrated its favorable effect on increased lymphocyte counts, reduced NLR, and prevention of complications necessitating readmission, those which may lead to survival benefit with some modifications.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) has been still known as one of the most notorious malignancies with extremely dismal prognosis despite recent advancements in medical technology enabling various treatment options [1,2]. First of all, most patients with PDAC have been judged to have unresectable disease at presentation even currently [1,2]. Furthermore, PDAC devastates pancreas not only morphologically but also both exocrine- and endocrine-functionally, leading to impaired nutritional status [3–6]. In addition, complete surgical removal, which is still a sole therapeutic modality that can provide a chance of cure, requires highly invasive procedures [1–6]. Especially, pancreatoduodenectomy (PD) has been known as one of the most burdensome surgical procedures, which can still cause early postoperative mortality in a few percentages of patients [1–6]. Patients with PDAC receiving PD often suffer from long-term malnutrition due to functional devastation of pancreas due to PDAC itself as well as procedural nature of PD [1–7]. As such, although prognostic dismalness of PDAC is multifactorial, negative impact of PDAC itself, short- and long-term troublesomeness of post-PD status on nutritional status has consistently attracted attention [1–7].

On the other hand, most clinicians have realized effectiveness of enteral feeding in daily clinical practice and recent proposal

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announced from the International Study Group on Pancreatic Surgery addressed oral intake and/or enteral nutrition as a recommended nutritional therapy in the perioperative period of PD [6] although several randomized trials failed to show obvious superiority of elemental diet (ED) over parenteral nutrition [8,9]. In our institution, we initiated the program of pancreatic surgery in early 1990's. Since initiating this program, we have utilized ED via tube jejunostomy as per unit "routine practice", which was initiated immediately after pancreatic resection and usually extended during several months after hospital discharge even if oral food intake of the patient was reached at sufficient level [10]. Considering potential devastation of pancreatic exocrine function caused by PDAC itself and procedural nature of PD, we have been using fat-free completely digested formula ED (Elental®, EA Pharma Co., Ltd., Tokyo, Japan) although several recent studies reported the efficacy of perioperative administration of ED containing some fatty components, such as omega-3 fatty acid [11,12]. This single institution randomized clinical trial examined efficacy of prolonged fat-free ED therapy after PD for PDAC.

2. Patients and methods

2.1. Enrollment of the patients

This single institution prospective randomized clinical trial was performed at the Department of Gastroenterological Surgery, Yokohama City University Hospital between January 2011 and December 2015, approved by the ethical committee of Yokohama City University, and was a declaration of Helsinki compliant. The study was registered at the University Hospital Medical Information Network (UMIN), registration number UMIN000004108.

Adult (aged 18 years or more) patients with histologically-proven PDAC receiving PD were eligible for enrollment. The exclusion criteria were as follows: failure to obtain consent; previous history of gastrectomy, severe hepatic dysfunction (Child-Pugh classification B or C), severe renal dysfunction (hemodialysis), severe psychiatric disorder, R2 resection status, unavailability of tube jejunostomy, participation in another trial, histological diagnosis of intraductal papillary mucinous neoplasm (IPMN)-derived carcinoma, and when the investigator was unavailable. Written informed consent was obtained from all patients before enrollment and randomization.

In cases of suspected disease involvement of adjacent portal and/or major arterial systems (National Comprehensive Cancer Network category BR-PV, BR-A, BR-PV/A, or UR-LA) [13], preoperative chemoradiation therapy was performed. Regimens and protocols were described elsewhere [14–16]. The standard method for PD in our institution was subtotal stomach preserving PD [17]. Reconstruction was done by the modified Child method. Duct-to-mucosa end-to-side anastomosis in pancreaticojejunostomy was performed with polyethylene internal stent tube. Pancreatic parenchyma and jejunal serosa were bound by the modified Kakita's method [18]. Construction of the tube jejunostomy was performed as the final step of the operation. A polyvinyl chloride 8 Fr ED tube was inserted into jejunum at 20 cm distal from the Braun anastomosis with approximately 30 cm extended into the jejunal lumen. Tube insertion site was covered with Witzel seromuscular inversion and fixed with abdominal wall. This tube jejunostomy procedure was performed as per unit "routine practice" since early 1990's [10,19]. Abdominal drains were placed in all patients and removed according to the drain amylase level, drain culture status, and patient's condition if no relevant pancreatic fistula was developed.

2.2. Elemental diet therapy and randomization

Elental® was dissolved in tap water so as to make solution 1 kcal/ml, which was initiated with 10 ml/h via tube jejunostomy on the day after surgery and increased to 600–900 kcal/day in a few days. As to oral intake, liquid intake was recommenced on postoperative day (POD) 1 and food intake was initiated on POD 2. Enrolled patients were randomly assigned to prolonged ED group (PEDG) and control group (CG). Randomization was conducted by the minimization method using age, gender, main pancreatic duct diameter, preoperative chemoradiation therapy, and diabetes before surgery. In the CG, ED therapy was discontinued if sufficient oral intake {≧20 kcal/(kg body weight)/day} was achieved. In PEDG, ED therapy with 600 kcal/day was continued until 3 months after surgery even if their oral intake was reached at sufficient level and/or they were discharged from hospital. This recommended dose of ED was determined based on the fact that a pack of Elental® includes 300 kcal and thus multiple of 300 kcal was considered convenient. As a result, 2 packs, i.e. 600 kcal, of Elental R appeared able to be reasonably administered at home and thus was determined as the recommended dose regardless of patients' body size. Occasional increase in dose of home ED was allowed in PEDG if patients and/or caregivers considered oral intake was insufficient. In both study groups, any restriction was not lorded regarding oral intake. If moderate to severe diarrhea (exceeding 5–10 times of defecation a day) was developed due to ED administration and/or acceleration, dose and/or administration rate of Elental® was moderated so as to relieve symptoms. Antidiarrheal was indicated if diarrhea was prolonged or exacerbated without infection.

Before hospital discharge, our institutional nutritionist team gave patients and/or caregivers a nutritional instruction regarding a proper dietary therapy after discharge. Ideal oral calorie and protein intakes were set at 35 kcal/kg/day and 1 g/kg/day, respectively. Patients and/or their family recorded their daily dietary intake using a simple dietary survey sheet, in which they filled out daily food menu, rough amount of each menu, and what proportion of each menu was eaten, throughout 6 months after surgery. In PEDG, patients and/or caregivers were trained in the correct use of home ED and instructed to record administered dose of ED during the study period. After hospital discharge, patients in both groups received bi-weekly follow-up outpatient visit and submitted the dietary survey sheets until 6 months after surgery.

2.3. Primary and secondary outcomes

Primary outcomes were complications necessitating readmission after discharge. Secondary outcomes were nutritional status, relative dose intensity of adjuvant chemotherapy (RDI) in cases receiving adjuvant chemotherapy, and survival outcomes. Primary outcome measures were readmission rate at 90-postoperative-day, 6 and 12 postoperative months. Readmission rate was calculated as the following: (number of patients who necessitated admission after hospital discharge in each group until each time point)/(Number of patients in each group) (%). In patients with PDAC, markedly early disease recurrence is sometimes observed and patients with such early recurrence often suffer from severe symptoms requiring readmission. Thus, readmission for symptoms obviously caused by recurrent disease was excluded from the readmission. Furthermore, in Japan, average postoperative length of hospital stay has been reportedly approximately 30 days in patients receiving PD [20,21]. Therefore, in patients who require prolonged hospitalization after surgery, readmission rate calculated based on postoperative days cannot precisely reflect the situation of complications necessitating

readmission. Thus, we used post-discharge cumulative readmission rate (Cum-RR) as one of primary outcome measures. Post-discharge readmission-free duration was defined as a period from the day of hospital discharge to the day of readmission, or most recent follow-up visit in patients without readmission. Regarding cases where complications necessitating readmission were not observed but developed recurrent disease which caused symptoms requiring readmission, these cases were regarded as censored cases at the time of readmission for symptoms caused by recurrent disease. Cum-RR was calculated by Kaplan–Meier method using this duration of each patient.

Nutritional status was assessed by body weight (BW), serum albumin, prealbumin, triglyceride, total cholesterol, lymphocyte count, plasma free amino acid (PFAA) level [22], and the following inflammatory indices: neutrophil-to-lymphocyte-ratio (NLR) [23] and C-reactive-protein-to-albumin-ratio [24]. These measures were evaluated at just before surgery, 1, 2, 3, and 6 postoperative months using standard laboratory methods in daily clinical practice except for PFAA level, which was determined by high performance liquid chromatography at one-night fasting condition. Regarding PFAA, 9 essential amino acids, 11 non-essential amino acids, and several other functional amino acids were evaluated [22]. Postoperative changes in BW was assessed by body weight ratio (BWR) calculated as the following: {BW at each time point (kg)}/{preoperative BW(kg)} (%). Furthermore, chronological changes in oral calorie intake, ED-derived calorie intake, total enteral calorie intake (i.e. sum of oral intake and ED), and ED-derived protein intake were compared between groups. These values were calculated from the medical records before hospital discharge. After hospital discharge, the above-stated dietary survey sheets were used to calculate these values. Daily food menu and its ingredients markedly varied according to each home. Therefore, although oral calorie intake was roughly calculatable using the dietary survey sheets, calculation of oral protein intake at home was considered impractical. Thus, with regard to the difference of protein intake between groups, we focused on ED-derived protein intake, which was calculated based on 4.4 g of protein per 100 kcal included in Elental®. Mean values of daily calorie intake and ED-derived protein intake per every postoperative week were calculated until 6 months after surgery. Daily calorie and protein intakes were expressed as kcal/kg/day and g/kg/day, respectively. Preoperative body weight was used for calculation. Compliance to the planned treatment after hospital discharge in PEDG was assessed using the proportion (%) of days when more than 600 kcal/day of Elental® was administered to the total days in which Elental® was planned to be administered.

Indications and regimens of adjuvant chemotherapy were described elsewhere [15]. RDI was calculated as follows. Total amount of actual administered dose of each chemotherapeutic agent was divided by dose determined in regimen and protocol. Survival outcomes were assessed by disease-free and overall survival.

2.4. Sample size

Readmission rate at more than 90 days after PD has been reportedly approximately 30% [25–27]. We expected two third reduction of this rate obtained by prolonged ED therapy, i.e. 10% readmission rate at 6 months. Based on these rates, alpha-value at 0.05, and beta-value at 0.2, yielding 80% power, sample size of each arm was calculated to be 48.

2.5. Statistical analysis

Numerical variables were expressed as median with range and categorical variables as numbers and percentages. Difference of variables between groups was assessed by Man-Whitney U test for numerical variables and Fischer' exact probability test for categorical variables. Disease-free survival (DFS) duration was defined as duration from the day of surgery to the day of diagnosing relapsed disease or most recent follow-up visit in patients without recurrent disease. Overall survival (OS) duration was defined as duration from the day of surgery to patient's death or most recent follow-up visit of surviving patients. Cumulative survival rates were calculated using Kaplan–Meier method. Difference of cumulative rates were assessed by Breslow-Gehan-Wilcoxon test. All statistical analyses were performed using IBM® SPSS® Statistics 24.0 (IBM, Armonk, NY, USA) .

3. Results

3.1. Patient's characteristics

Between January 2011 and December 2015, we performed PD for 134 patients with preoperative diagnosis of PDAC, of which 88 patients were ineligible for enrollment mainly due to participating in other trials. Among the remaining 46 patients, 7 patients were excluded because their original disease was judged as distal bile duct cancer from the histological findings of resected specimen in 4 patients, IPMN-derived carcinoma in 2 patients, and no evidence of PDAC observed in the resected specimen despite preoperative diagnosis of PDAC in 1. Thus, the remaining 39 patients were eligible for this study: 19 patients assigned to PEDG and the other 20 to CG. At the end of study period, planned sample size was not accumulated. Thus, we decided to adopt this study as a pilot study to gain information on the size of effect and recruitment rate for planning an adequately powered future study.

In all 39 patients eligible for this study, ED therapy could be initiated on the day after surgery. Patient demographics and perioperative clinicopathological variables are summarized in Table 1. There were no significant differences among groups in these variables except for duration of ED therapy {PEDG vs CG, 91 days (87–93) vs 10 days (8–45), $p < 0.001$}. Furthermore, duration of ED therapy after hospital discharge ranged 36–80 days with a median of 75 days in PEDG. Discontinuation of ED was not necessitated in any patients although some moderation of ED dose and/or administration rate was required after discharge in 3 of 19 patients in PEDG. In 19 patients in PEDG, number of total days after hospital discharge when ED was planned to be administered was 1315. In these 1315 days, more than 600 kcal/day ED administration was achieved in 1002 days. Thus, compliance to the planned ED administration at home was judged to be 76.2% (1002/1315) of days when ED was planned to be given.

3.2. Primary and secondary outcome measures

3.2.1. Complications requiring readmission and readmission rate

Complications requiring readmission within 12 postoperative months were cholangitis in 2 patients in PEDG, and were dehydration in 4 patients, symptomatic hypoalbuminemia causing edema and/or ascites in 3 patients, cholangitis in 2, peptic ulcer in gastrojejunostomy in 2, and intestinal obstruction in 1 in CG (some are overlapped). As such, readmission rate at 90-postoperative-day, 6 and 12 postoperative months were 0 and 25.0%, 5.3% and 35.0%, and 10.5% and 40.0%, in PEDG and CG, respectively. These rates were higher in CG than in PEDG, significantly both at 90-postoperative-day ($p = 0.047$) and 6 postoperative months ($p = 0.044$) but marginally at 12 postoperative months ($p = 0.065$) (Table 2). Furthermore, Cum-RRs at 3-, 6-, 12-, and 24-post-discharge months were 0 and 24.7%, 5.3% and 31.7%, 12.6% and 43.7%, and 25.1% and 43.7% in PEDG and CG, respectively. Difference between groups was statistically significant ($p = 0.018$) (Fig. 1).

Table 1
Comparison of patient demographics and clinicopathological variables between prolonged elemental diet and control groups.

	Prolonged ED[a] group (n = 19)	Control group (n = 20)	p-value
Patient demographics			
Age at surgery (years)	66 (41–83)	64 (41–83)	0.425
Gender (M/F)	11/8	12/8	1.000
Body mass index (kg/m^2)	20.4 (15.0–26.2)	20.2 (17.7–29.9)	0.708
Diabetes (yes/no)	8 (42.1%)	6 (30.0%)	0.514
Biliary drainage (yes)	14 (73.7%)	11 (55.0%)	0.320
Serum albumin (g/dl)	3.9 (2.5–5.0)	3.8 (2.8–4.6)	0.728
Lymphocyte count (/ul)	1184 (588–2002)	991 (323–2713)	0.258
Prognostic nutritional index	46.7 (29.0–52.5)	42.6 (35.0–71)	0.728
Preoperative variables			
NCCN[b] resectablity category			
R/BR-PV/BR-A/UR-LA	8/7/3/1	8/7/4/1	0.795
Preoperative treatment (yes/no)	16/3	15/5	0.695
Intraoperative variables			
Operation time (min)	664 (553–874)	647 (347–785)	0.513
Blood loss (ml)	936 (346–4714)	872 (250–2153)	0.627
Soft pancreatic texture	1 (5.3%)	2 (10.0%)	0.487
Pancreatic duct diameter (mm)	6.0 (4.0–15.0)	6.0 (3.0–10.0)	0.749
Combined vascular			
resection and reconstruction	15 (78.9%)	16 (80.0%)	0.716
Blood transfusion	9 (47.3%)	7 (35.0%)	0.748
Pathological variables			
AJCC[c] staging (I/II/III/IV)	1/7/10/1	5/8/7/0	0.262
R status (R0/R1/R2)	17/2/0	18/2/0	1.000
Postoperative variables			
Dindo-Clavien grade≧2	14 (73.7%)	11 (55.0%)	0.234
Dindo-Clavien grade≧3	3 (15.8%)	3 (15.0%)	0.558
Grade B/C POPF[d]	0	1 (5.0%)	1.000
Grade B/C DGE[e]	1 (5.3%)	1 (5.0%)	1.000
Re-celiotomy	**0**	**0**	
30- or 90-day Mortality	0	0	
Postoperative hospital stay (days)	16 (10–54)	15 (10–53)	0.708
Length of ED therapy (days)	**91 (87–93)**	**10 (8–45)**	**<0.001**

The findings that were considered should be emphasized were shown in bold letters.
[a] Elemental diet.
[b] According to the 2016 version of the National Comprehensive Cancer Network classification.
[c] American Joint Committee on Cancer;
[d] Postoperative pancreatic fistula.
[e] Delayed gastric emptying.

3.2.2. Nutritional status

Perioperative changes in nutritional status are summarized in Table 2. BWR at 2-postoperative-month was significantly larger in PEDG than in CG (94.8% vs 88.6%, p = 0.038) whereas it was similar among groups at other measured time points (Table 2). Lymphocyte count did not differ among groups up to 1-postoperatve-month. Thereafter, however, it was significantly higher in PEDG than in CG at 2- (1058 [502–2239] vs 568 [184–1702], p = 0.001), 3- (935 [405–2153] vs 626 [166–1404], p = 0.009), and at 6-postoperative-month (847 [566–1984] vs 608 [177–1859], p = 0.038). In relation with higher lymphocyte count in PEDG, NLR was significantly lower in PEDG than in CG at 2- (1.95 [0.63–4.17] vs 3.30 [1.09–39.2], p = 0.016), 3- (1.86 [0.53–5.04] vs 5.03 [1.24–8.17], p = 0.001), and at 6-postoperaive-month (1.84 [0.20–4.92] vs 3.83 [0.77–17.35], p = 0.006) (Table 2). Regarding PFAA, significant differences were sporadically observed in several substances (Table 2). However, differences between groups and/or chronological changes that were considered relevant to affect other parameters were not observed. Similarly, there were no difference regarding serum albumin, prealbumin, total cholesterol, or triglyceride among groups (data not shown).

3.2.3. Chronological changes in enteral calorie intake and additional protein intake brought on by elemental diet

Chronological changes in total enteral calorie intake, oral calorie intake, and ED-derived calorie intake were shown in Fig. 2. Oral calorie intake was significantly smaller in PEDG than in CG between postoperative-week-3 and postoperative-week-13 whereas total enteral calorie intake was significantly larger in PEDG than in CG during the same period. This significant increase in total enteral calorie intake in PEDG during the period was obviously attributed to the prolonged administration of ED (Fig. 2). Table 3 shows results of comparison of total enteral calorie intake and ED-derived protein intake between groups during the period between postoperative-week-1 and -12. During this period, total enteral calorie intake between postoperative-week-3 and -12 and ED-derived protein intake between postoperative-week-2 and -12 were significantly greater in PEDG than in CG, respectively. Furthermore, total enteral calorie intake during this period transited around 30 kcal/kg/day in PEDG and around 25 kcal/kg/day in CG, respectively. These values were smaller than 35 kcal/kg/day, which was set at ideal daily oral intake. In addition, since the postoperative-week-14, i.e. after prolonged ED therapy ended, total enteral calorie intake in PEDG reduced to around 25 kcal/kg/day, which was similar to that of CG (Fig. 2). Median ED-derived protein intake in PEDG ranged 0.38–0.52 g/kg/day until postoperative-week-12, which was roughly equivalent to the half of ideal daily protein intake (Table 3).

3.2.4. Relative dose intensity of adjuvant chemotherapy and survival outcomes

Among the 39 enrolled patients, 33 patients (85.0%) received postoperative adjuvant chemotherapy after surgery: 16 patients in PEDG and 17 in CG. Agents used for adjuvant chemotherapy were S-1 and/or gemcitabine (S-1 alone, gemcitabine alone, or both) [15].

Table 2
Comparison of primary and secondary outcome measures between prolonged elemental diet group and control group.

	Prolonged ED[a] group (n = 19)	Control group (n = 20)	p-value
Primary outcome measures			
Readmission rate			
at 90-postoperative-day	**0**	**5 (25.0%)**	**0.047**
at 6-POM[b]	**1 (5.3%)**	**7 (35.0%)**	**0.044**
at 12-POM	2 (10.5%)	8 (40.0%)	0.065
Secondary outcome measures			
Body-weight ratio (%)			
at 1-POM	92.5 (81.0–109)	93.0 (81.1–108)	0.628
2-POM	**94.8 (75.8–109)**	**88.6 (75.5–105)**	**0.038**
3-POM	93.1 (73.4–106)	87.9 (79.2–102)	0.425
6-POM	88.9 (72.5–110)	87.2 (73.5–110)	0.388
Lymphocyte count (/ul)			
Preoperative	888 (31–1819)	844 (105–2119)	0.876
At 1-POM	900 (158–2002)	885 (151–1983)	0.764
2-POM	**1058 (502–2239)**	**568 (184–1702)**	**0.001**
3-POM	**935 (405–2153)**	**626 (166–1404)**	**0.009**
6-POM	**847 (566–1984)**	**608 (177–1859)**	**0.038**
Plasma free amino acid level			
Histidine at 2-POM	**75.0 (64.5–77.3)**	**66.7 (58.7–74.1)**	**0.020**
Tyrosine at 3-POM	**51.4 (22.6–92.1)**	**62.6 (33.5–79.9)**	**0.034**
Ornithine at 3-POM	**56.2 (22.3–104)**	**69.7 (33.7–167.7)**	**0.034**
Inflammatory indices			
Preoperative NLR[c]	2.29 (1.44–66.9)	2.96 (1.06–27.09)	0.876
NLR at 1-POM	2.69 (0.82–11.79)	3.80 (1.67–17.86)	0.628
2-POM	**1.95 (0.63–4.17)**	**3.30 (1.09–39.20)**	**0.016**
3-POM	**1.86 (0.53–5.04)**	**5.03 (1.24–18.17)**	**0.001**
6-POM	**1.84 (0.20–4.92)**	**3.83 (0.77–17.35)**	**0.006**

The findings that were considered should be emphasized were shown in bold letters.
[a] Elemental diet.
[b] Postoperative month.
[c] Neutrophil-to-lymphocyte ratio.

Regimens and RDI of each agent did not differ among groups (Table 4). Furthermore, frequency, magnitude, and types of adverse effects caused by adjuvant chemotherapy were also similar among groups (Table 4).

Three- and 5-year DFS rates were 32.7% and 32.7% in the CG, and 40.6% and 24.4% in PEDG, respectively ($p = 0.399$). Furthermore, 3- and 5-year OS rates were 47.8% and 47.8% in CG, and 45.2% and 38.8% in PEDG, respectively ($p = 0.492$). These rates were similar among groups.

4. Discussion

This single institution randomized trial demonstrated that prolonged ED therapy after PD for PDAC is markedly useful for preventing complications necessitating readmission although obvious nutritional and survival benefit could not be proven. PDAC is still the major representative of extremely dismal malignancies. With the recent advancements in adjuvant therapy, surgical outcomes of patients with PDAC have markedly improved but cannot be said to have reached at satisfactory level [1,2]. Furthermore, surgical invasiveness of PD has long been recognized since the establishment of this procedure [3–7]. With the technical and technological refinements and accumulated surgeon's experiences, short-term outcomes have been dramatically improved with markedly decreased mortality, reduced hospital stay, and reduced medical costs [1–8]. However, many issues remain to be overcome for further improvement of outcomes of PD for PDAC. Among the issues to be overcome, postoperative malnutrition after PD for PDAC has been considered one of the biggest problems, frequently causing short- and long-term morbidity [3–7]. We have been aware of importance of nutritional support after PD and thus long been utilizing prolonged ED therapy since early 1990's as per unit daily routine clinical practice without confirming its effectiveness. Thus, we conducted the present study. We expected that prolonged ED therapy via tube jejunostomy brings the following beneficial effects. First of all, it works as an effective nutritional supply compensatory for oral intake insufficiency and/or absorptive dysfunction caused by status after PD for PDAC. Second, sufficient nutritional supply improves nutritional status. Third, improved nutritional status prevents early and mid-term postoperative complications, leading to earlier initiation of adjuvant chemotherapy as well as improved completion rate and increased RDI of adjuvant chemotherapy. Fourth, favorable effect on performing adjuvant chemotherapy improves survival outcomes. As shown in Fig. 2 and Table 3, during the period of prolonged ED therapy, total calorie intake and ED-derived protein intake were certainly increased. However, after the end of prolonged ED therapy, enteral nutritional intake of PEDG was reduced to the same level as that of

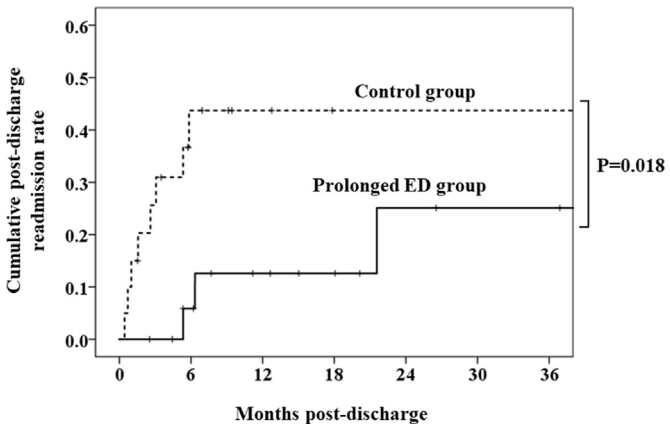

Fig. 1. Comparison of cumulative post-discharge readmission rate. Cumulative post-discharge readmission rate was 12.6% and 43.7% at 12 post-discharge months, and 25.1% and 43.7% at 24 post-discharge months in the prolonged elemental diet and control groups, respectively. Difference between groups was statistically significant ($p = 0.018$). ED, elemental diet.

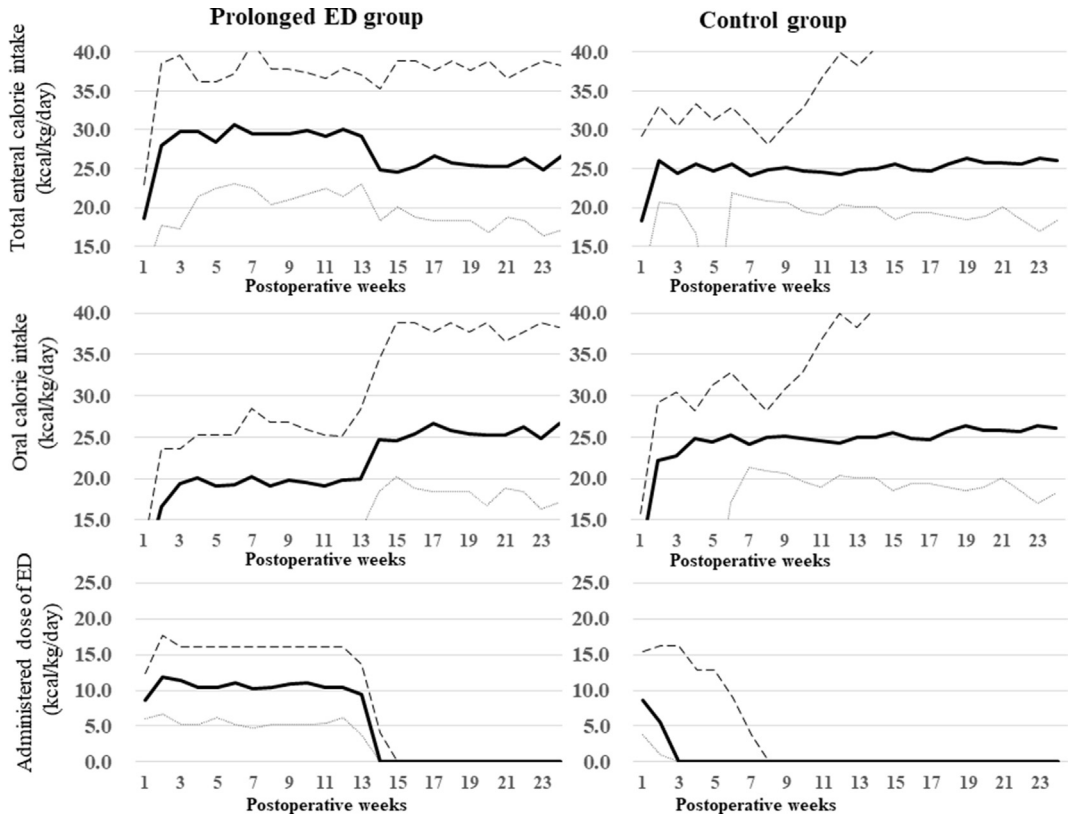

Fig. 2. Chronological changes of total enteral calorie intake, oral calorie intake, and elemental-derived calorie intake in each group. Oral calorie intake between postoperative-week-3 and -13 was significantly smaller in prolonged elemental diet group (PEDG) than in control group (CG) (Middle row). However, since postoperative-week-14, oral calorie intake was similar among groups. Furthermore, total enteral calorie intake between post-operative-3 and -13 was significantly larger in PEDG than in CG (Upper row). This significant increase in total calorie intake during the period in PEDG was obviously attributed to the effect of prolonged elemental diet (ED) therapy (Lower row). However, since postoperative-week-14, total calorie intake was not different between groups because of the end of prolonged ED therapy. (Black thick lines indicate median values, black dotted lines upper ranges, and gray thin lines lower ranges.) ED, elemental diet.

Table 3
Comparison of total enteral calorie intake and elemental-diet-derived protein intake between prolonged elemental diet group and control group until 12-postoperative-week.

	Prolonged ED[a] group (n = 19)	Control group (n = 20)	p-value
Total enteral calorie intake (kcal/kg/day)			
ED[a]-derived protein intake (g/kg/day)			
Postoperative-week-1	18.7 (11.0–22.9)	18.4 (10.0–29.2)	0.569
	0.38 (0.27–0.54)	0.38 (0.16–0.68)	0.901
−2	28.0 (17.8–38.5)	26.1 (20.7–33.0)	0.461
	0.52 (0.29–0.78)	0.24 (0.04–0.72)	0.009
−3	29.8 (17.6–39.6)	24.5 (20.4–30.5)	0.001
	0.50 (0.23–0.70)	0.00 (0.00–0.72)	<0.001
−4	29.8 (21.4–36.2)	25.6 (16.7–33.3)	0.002
	0.46 (0.23–0.70)	0.00 (0.00–0.57)	<0.001
−5	28.5 (22.4–36.2)	24.8 (1.7–31.3)	0.001
	0.46 (0.27–0.70)	0.00 (0.00–0.57)	<0.001
−6	30.7 (23.1–37.1)	25.6 (22.0–32.8)	0.001
	0.49 (0.23–0.70)	0.00 (0.00–0.39)	<0.001
−7	29.4 (22.4–41.2)	24.1 (21.3–30.5)	0.001
	0.45 (0.21–0.70)	0.00 (0.00–0.17)	<0.001
−8	29.4 (20.4–37.8)	24.9 (20.9–28.2)	0.008
	0.45 (0.23–0.70)	0.00 (0.00–0.00)	<0.001
−9	29.5 (21.1–37.8)	25.2 (20.6–30.8)	0.001
	0.48 (0.23–0.70)	0.00 (0.00–0.00)	<0.001
−10	29.9 (21.8–37.4)	24.7 (19.6–32.8)	<0.001
	0.49 (0.23–0.70)	0.00 (0.00–0.00)	<0.001
−11	29.1 (22.4–36.6)	24.6 (19.0–36.8)	0.002
	0.46 (0.24–0.70)	0.00 (0.00–0.00)	<0.001
−12	30.1 (21.4–37.0)	24.2 (20.4–39.9)	<0.001
	0.49 (0.27–0.70)	0.00 (0.00–0.00)	<0.001

[a] Elemental diet.

Table 4
Comparison of secondary outcome measures regarding adjuvant chemotherapy between prolonged elemental diet group and control group.

	Prolonged ED[a] group (n = 19)	Control group (n = 20)	p-value
Application of adjuvant chemotherapy	16 (84.2%)	17 (85.0%)	1.000
Days from surgery to initiation of adjuvant chemotherapy (days)	64 (43–117)	67 (43–139)	0.589
Regimens of adjuvant chemotherapy			0.712
S-1 alone	7 (43.7%)	8 (47.1%)	
Gemcitabine alone	1 (6.3%)	3 (17.6%)	
Both S-1 and gemcitabine	8 (50.0%)	6 (35.3%)	
Relative dose intensity			
S-1	64.7% (26–100)	75.0% (27–100)	0.347
Gemcitabine	100% (13–100)	100% (13–100)	1.000
Adverse events Overall ≧ grade 3 occurrence	9 (56.3%)	9 (52.9%)	1.000
Hematological ≧ grade 3	7[b] (43.8%)	8[b] (47.1%)	1.000
Neutropenia	7	8	
Thrombocytopenia	2	2	
Anemia	1	1	
Non-hematological ≧ grade 3	2[b] (12.5%)	1[b] (5.9%)	0.589
Cholangitis	2	0	
Nausea	1	1	
Diarrhea	1	0	
Malaise	0	1	

[a] Elemental diet.
[b] Some are overlapped.

CG. In other words, although effectiveness of prolonged ED as a simple compensatory nutritional measure was confirmed by significant reduction in readmission rate, obvious nutritional and survival benefit could not be proven in the present study. As to nutritional status, nutritional advantage of prolonged ED therapy was suggested by increased lymphocyte counts, reduced NLR, and prevention of short-term weight reduction. As shown in Table 3, approximately 0.5 g/kg/day of protein intake was provided by ED alone in PEDG. This value was considered sufficient as the supplemental nutrition. In CG, 3 of the 20 patients suffered from symptomatic hypoalbuminemia causing abnormal fluid retention such as edema and/or ascites whereas no patients in PEDG suffered such hypoalbuminemia although serum albumin level did not differ among groups. As such, preventive effect for symptomatic malnutrition may be brought on by the above-stated additional ED-derived calorie and protein intake. However, representative nutritional parameters, such as serum albumin, prealbumin, total cholesterol, or triglyceride, were similar among groups. Moreover, only trivial differences were observed even in PFAA levels. Most notably, these nutritional parameters did not recover to preoperative levels in most patients regardless of groups. Fat deficiency in Elental® is considered advantageous to exocrine pancreatic insufficiency (EPI) after PD for PDAC but unbeneficial in terms of deficiency in essential nutrients. Several reports suggested that patients undergoing PD suffer from prolonged hypercatabolic state [3–8]. In such situation, dietary fatty acids such as omega-3 are reportedly essential for efficient absorption of amino acid through intestinal mucosa, protein synthesis, and sufficient energy supply [28]. Furthermore, this beneficial effect of fatty acids is reported to be expectable through parenteral administration [29]. In addition, we did not use pancrelipase in this study [30]. Patients with PDAC easily suffer from EPI, which can be further deteriorated by receiving PD [3–7]. Pancrelipase has been reportedly effective for treating EPI related with PD for PDAC as well as improving long-term outcomes [30,31]. Hence, we should have provided pancrelipase as well as enteral or parenteral additional fatty-acids to the present study cohort.

With regard to the beneficial impact of ED on long-term oncological outcomes, any advantageous effect of prolonged ED was not confirmed in this study. As stated-above, we expected that long-term oncological outcomes are improved by the favorable effect of prolonged ED therapy on adjuvant chemotherapy. However, days from surgery to initiation of adjuvant chemotherapy ranged 43–139 days with a median of 66 in the present study. Namely, adjuvant chemotherapy could not be initiated until 1.5–3.5 months after surgery. Completion of adjuvant chemotherapy usually requires at least 6 months [15,31]. Generally, adverse effects of chemotherapy are likely to develop as cycles of therapy increase. In other words, ED therapy might have been discontinued before the period when ED was most desirable. Furthermore, ED was not administered in most of the adjuvant chemotherapy period in the present study. In addition, a recent study reported that PD for PDAC is more likely to cause late death due to malnutrition than PD for other disease entities [32]. Hence, ED therapy during 3 months after surgery in the present study setting may be too short to derive long-term oncological benefit. Furthermore, even during the period of prolonged ED therapy in PEDG, median total enteral calorie intake in PEDG did not reach 35 kcal/kg/day, which was set at ideal daily calorie intake in the present study. Moreover, in CG, median daily total enteral calorie intake transited around only 25 kcal/kg/day, which was also much smaller than ideal calorie intake, until 6 postoperative months. After the end of prolonged ED therapy period, total enteral calorie intake was reduced to around 25 kcal/kg/day in PEDG. These values of daily calorie intake may be too small to bring the advantageous nutritional effects to patients receiving PD for PDAC. In the present study, recommended dose of ED was determined conveniently based on included calorie of a pack of Elental® without considering patients' age and body size. This indiscreet determination of recommended dose might have led to insufficient calorie intake even during the period of prolonged ED therapy in PEDG and thus prolonged ED therapy might have not shown any obvious advantages in nutritional parameters or survival outcomes. In addition, deficiency of fat in Elental R and/or disuse of pancrelipase may have a negative nutritional as well as prognostic impact.

In addition to the above-stated limitations, most critical drawback of this study was incompleteness due to insufficient sample size. Thus, this study resulted to be a pilot study. However, difference of readmission rate between CG and PEDG in the present study was 25.0%, 29.7%, and 29.5% at 90-postopearive-day, 6-, and 12-postoperative-month, respectively. Required sample size for confirming these differences in a prospective randomized trial fashion was calculated to be 21, 22, and 26 in each arm for a difference level at 90-postopearive-day, 6-, and 12-postoperative-

month, respectively. These required sample sizes were not considerably different from the size of the present study. Furthermore, increased absolute lymphocyte counts and reduced NLR were proven in PEDG up to at least 6-postoperative-month. Several studies reported that inflammatory indices such as NLR, CAR, or Glasgow prognostic score have been reportedly independently correlated with treatment outcomes of PDAC [33–35]. In the present study, significant changes in elements of these indices were obtained only in lymphocyte counts and thus favorable effect could be proven only on NLR, which might be too weak to bring oncological benefit. Conversely, establishment of nutritional therapy which brings significant improvement of nutritional parameters may improve long-term oncological outcomes. Thus, in order to transcend the above-stated limitations, we are currently planning future studies in terms of more prolonged ED therapy, addition of fatty acids, and use of pancrelipase.

In conclusion, prolonged ED therapy during 3 months after PD for PDAC failed to show obvious nutritional or oncological benefit but demonstrated its efficacy for increasing absolute lymphocyte counts, reducing NLR, and preventing complications necessitating readmission. More prolongation and some additional substances may lead to favorable effect on the improvement of nutritional status and oncological outcomes.

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Statement of authorship

RM, RM, KT, EI: study conception and design; KG, KM, SH, YH, YO: laboratory and clinical data; RM, RM, YH, YO, TK, DM, IE: analysis and interpretation of the data; RM, DM, EI: draft of the article; all authors: critical revision and final approval.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.07.017.

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