



## Randomized Control Trials

## Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: A randomized controlled trial



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## SUMMARY

**Background & aims:** Evidence of the advantages of enhanced recovery after surgery (ERAS) protocols following pancreaticoduodenectomy (PD) is limited. The aim of this study was to examine the efficiency of ERAS protocols in patients following PD.

**Methods:** Between June 2014 and October 2016, patients undergoing PD were randomly assigned to receive ERAS protocols or standard care. The primary endpoint was the postoperative length of stay. Secondary endpoints included postoperative complications, postoperative quality-of-life (QoR-40J), readmission, and medical cost.

**Results:** Of 80 eligible patients, 74 were analyzed in intention-to-treat principles: 37 in the control group and 37 in the ERAS group. The mean length of stay in the ERAS group was significantly shorter than that in the control group ( $20.1 \pm 5.4$  vs  $26.9 \pm 13.5$  days,  $P < 0.001$ ). The ERAS group had a significantly lower percentage of postoperative complications (32.4% vs 56.8%,  $P = 0.034$ ) and readmissions (0% vs 8.1%,  $P = 0.038$ ). Quality-of-life was also significantly better in the ERAS group ( $184 \pm 12.4$  vs  $177 \pm 14.5$ ,  $P = 0.022$ ). The total medical cost was lower in the ERAS group, but not significantly ( $\$25,445 \pm 5065$  vs  $\$28,384 \pm 9999$ ,  $P = 0.085$ ).

**Conclusions:** The optimization of ERAS protocols in patients undergoing PD is safe and accelerates perioperative recovery and quality-of-life, thereby reducing the length of stay. Morbidity was significantly decreased in the ERAS group without compromising surgical outcome.

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## 1. Introduction

Despite recent advances in surgical techniques, instruments, and perioperative care, the mortality and morbidity following pancreaticoduodenectomy (PD) remains high, even at high-volume centers in Japan, with a postoperative mortality and overall morbidity rate of 2.8–3.5% and 40%, respectively [1,2]. Furthermore, the length of stay (LOS) after PD is more than 30 days in Japan [1]. There is still a great need for further developments in perioperative care to improve postoperative outcomes, leading to shorter LOS.

Enhanced recovery after surgery (ERAS) programs are multimodal strategies aimed to accelerate postoperative recovery and

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shorten LOS. Several randomized trials for ERAS protocols were performed in patients undergoing colorectal surgery [3–6], and ERAS protocols have provided high-level evidence on improving postoperative outcomes [7]. The results have shown that ERAS protocols are safe and effective in reducing LOS without increasing morbidity. In addition, there has been a consensus agreement established that ERAS should be a standard practice in colorectal surgery [8].

The ERAS society has also recommended guidelines for perioperative items in PD [9,10]. Furthermore, previous meta-analyses have revealed that ERAS pathways for PD might be safe and help to shorten LOS compared with conventional care [11,12]; however, evidence of the efficiency of ERAS pathways for PD remains limited because a randomized controlled trial (RCT) has not yet been performed. Further research is urgently required to investigate the effect of ERAS protocols on perioperative outcomes in patients undergoing PD.

Therefore, this RCT aimed to examine the effect of ERAS protocols in patients following PD. We hypothesized that implementation of ERAS protocols in PD could accelerate postoperative recovery and reduce LOS without increasing morbidity.

## 2. Materials and methods

### 2.1. Trial design

This study was a single center, prospective, randomized trial with two parallel treatment groups receiving either ERAS protocols (ERAS group) or standard care (control group). The Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital approved this study, and the study was registered at the University Hospital Medical Information Network (UMIN), registration number UMIN000014068.

All 20-to-80-year-old patients undergoing PD at the Okayama University Hospital in Japan were eligible for enrollment. The exclusion criteria were as follows: failure to obtain consent; severe respiratory dysfunction (arterial PaO<sub>2</sub> <70 mmHg), severe cardiac dysfunction (New York Heart Association  $\geq$ 3), severe hepatic dysfunction (Child Pugh classification C), severe renal dysfunction (hemodialysis), pregnancy, preoperative chemotherapy and/or radiation therapy, acute bacterial infection, severe psychiatric disorder, advanced malignancy, palliative surgery, emergency surgery, and when the investigator was unavailable. Written informed consent was obtained from all patients before enrollment and randomization. The details of the surgical techniques were as described elsewhere [13,14]. Abdominal drains were inserted in all patients and removed according to the drain amylase level if no relevant pancreatic fistula (PF) was detected [15].

### 2.2. Interventions

ERAS protocols were designed according to reviews of previously published ERAS guidelines (Table 1) [9,10]. The details of the ERAS protocols are also described in [Supplementary material 1](#). We introduced counseling, mobilization, immunonutrition, and no bowel preparation as preoperative factors. Carbohydrate loading was provided to all patients undergoing surgery. Mobilization was assessed and instructed by the rehabilitation team. Oral supplementation (IMPACT; Nestle Health Science, Japan) for 5 days (750 kcal/day) was used as immunonutrition.

Regarding intraoperative factors, fluid restriction was performed according to the goal-directed-therapy (GDT) protocol (Fig. 1). The protocol consisted of standardized crystalloid administration (3 mL/kg/hr) with additional colloid boluses based on

hemodynamic monitoring (FloTrac, Edwards Lifesciences, Irvine, CA, USA) [16]. The decompressive nasogastric tube was removed at the end of surgery.

Regarding postoperative factors, we introduced the following factors: no nasogastric tube, early oral intake, enteral tube feeding, synbiotics, early removal of urinary catheter and drains, fluid restriction, strict glycemic control, standardized multimodal analgesia, anti-thrombotic prophylaxis, and a telephone call on the day after discharge. Oral intake of liquids started on postoperative day (POD) 1–2 and solids on POD 3–4. Concerning enteral tube feeding, oligomeric formula (PEPTINO; Terumo Corporation, Japan) started on POD 1. The rate was adjusted based on oral intake. Prebiotics (GFO; Otsuka Pharmaceutical Co., Ltd, Japan) and probiotics (MIYABM; Miyarisan Pharmaceutical Co., Ltd, Japan) were used as synbiotics. The urinary catheter was removed on POD 2–3. Glycemic control was controlled by diabetologists. Fractionated low-molecular-weight heparin (CLEXANE; Kaken Pharmaceutical Co., Ltd, Japan) was used for one week. Physiotherapy was performed by the rehabilitation team from POD 1 until discharge. A telephone call to confirm the patient's status was made on the day after discharge.

### 2.3. Standard care

Patients received conventional perioperative care in our unit. We performed some of the ERAS items that had already been introduced before starting the trial. Patients preoperatively received counseling from the attending surgeon and bowel preparation, but no immunonutrition. Treatment with carbohydrates was given to all patients before surgery.

Concerning anesthesia, standardized crystalloid administration was maintained at 10 mL/kg/hr and additional colloid boluses were given based on conventional management. Other intraoperative factors were the same as in the ERAS protocol (Fig. 1).

Postoperative care was performed according to the surgeon's preference. The decompressive nasogastric tube was removed on POD 1 when the output was less than 300 mL/day. Patients did not routinely receive ERAS items. Patients with poor glycemic control (HbA1c  $\geq$ 8%) received perioperative strict glycemic control by diabetologists. Postoperative mobilization was performed by the ward nursing staff.

### 2.4. Primary endpoint and sample size

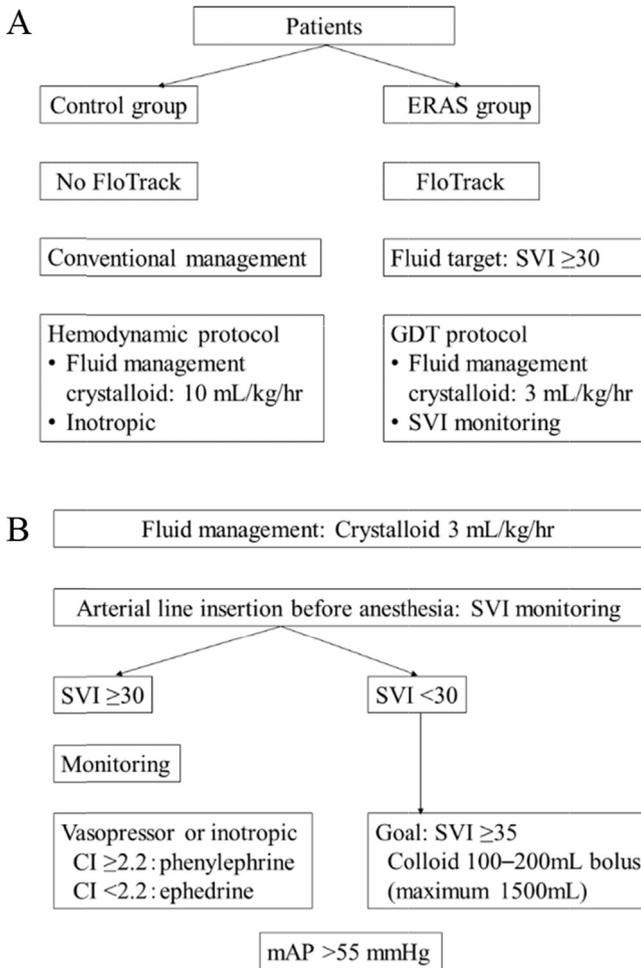
The primary outcome was postoperative LOS. The sample size was calculated based on the primary outcome, mean LOS. Based on our previous data [14], we conservatively speculated that patients treated according to the ERAS protocol would be discharged seven days sooner than those who were managed with standard care. Thus, 74 patients are required to demonstrate a difference between the two arms with 80% power at an alpha error of 5% (nQuery + nTerim 2.0, Statistical Solutions, Boston, MA, USA). With estimated exclusion after registration or loss to follow-up of six patients, 80 patients were required (40 patients in each arm).

### 2.5. Secondary endpoint

#### 2.5.1. Postoperative complications

Mortality and morbidity, including PF, delayed gastric emptying (DGE), bile leakage, hemorrhage, and thrombosis were evaluated. Each postoperative event was evaluated according to the Clavien-Dindo classification [17]. PF and DGE were classified into three categories (grades A, B, and C) according to the International Study Group of Pancreatic Surgery guidelines [18,19]. The infectious complications examined were as follows: incisional surgical site





**Fig. 1.** Anesthesia protocol (A) and goal-directed-therapy (GDT) protocol (B). Concerning GDT protocol, the hemodynamic monitoring was based on the stroke volume index (SVI); additional colloid bolus was given when SVI was less than 30 or monitoring when SVI was more than 30. The mean arterial pressure (mAP) was kept more than 55 mmHg at least using inotropic agents guided by cardiac index (CI). ERAS, enhanced recovery after surgery.

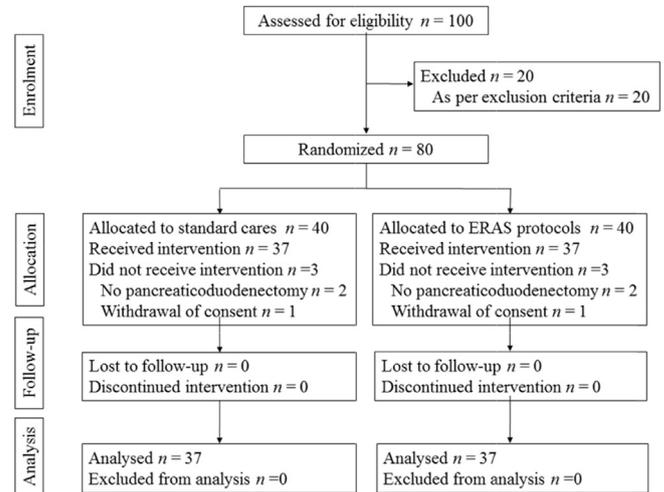
Mann–Whitney *U*-test for continuous variables and  $\chi^2$ -test for categorical variables. A *P* value of <0.05 was considered significant. Statistical analysis was performed with JMP 11.2.0 software (SAS Institute, Cary, NC, USA).

### 3. Results

#### 3.1. Study population

A total of 100 patients were screened and 80 patients randomized from June 1, 2014, to October 11, 2016 (Fig. 2). Of the 80 patients, six were excluded (four for not undergoing PD and two for withdrawal of consent). Data analysis was performed on 37 patients in the ERAS group and 37 patients in the control group.

The demographic characteristics of the 74 patients are shown in Table 2. The demographic and clinicopathological factors were not significantly different between the two groups. The mean operative time was 407 min (247–570 min), and the mean blood loss was 205 mL (10–800 mL). As to pancreatic texture, 48 (64.9%) had a soft pancreas, and 40 (54.0%) had a normal main pancreatic duct. No significant differences were observed between the groups with regard to operative factors.



**Fig. 2.** CONSORT flow diagram for the trial.

#### 3.2. Primary endpoint analysis

The mean LOS was  $20.1 \pm 5.4$  days in the ERAS group and  $26.8 \pm 13.5$  days in the control group ( $P < 0.001$ , Table 3). The median LOS was 19 days (interquartile range, 15.5–25.0 days) in the ERAS group and 23 days (interquartile range, 21.0–29.5 days) in the control group.

#### 3.3. Secondary endpoint analysis

Table 3 also presents the summary results of the secondary outcomes.

##### 3.3.1. Postoperative complication

There were no mortalities in the present study. The overall morbidity was significantly decreased in the ERAS group ( $P = 0.038$ ). The complications defined as Clavien grade  $\geq 2$  were significantly lower in the ERAS group than the control group (32.4% vs 56.8%, respectively,  $P = 0.034$ ). Although the incidence of PF and DGE were not significantly different, the ERAS group had a significantly lower percentage of infectious complications than the control group (18.9% vs 40.5%, respectively,  $P = 0.04$ ).

##### 3.3.2. Compliance with components of the ERAS protocol

The results of protocol compliance with the 13 items of the ERAS protocol are shown in Table 4. In the ERAS group, 31 patients (84%) were compliant to all preoperative and intraoperative pathways, and 11 patients (30%) were compliant to all postoperative pathways.

##### 3.3.3. Quality-of-life and readmission

Completed QoR-40J questionnaires were returned by all patients. The total scores were significantly higher in the ERAS group than in the control group ( $184 \pm 12.4$  vs  $177 \pm 14.5$ ,  $P = 0.022$ ) (Fig. 3). The 30-day readmission rate was 0% in the ERAS group and 8.1% in the control group ( $P = 0.038$ ).

##### 3.3.4. Medical cost

Although not significant, the total medical cost in the ERAS group was lower than that in the control group ( $\$25,445 \pm 5065$  vs  $\$28,384 \pm 9999$ ,  $P = 0.085$ ). However, the cost other than surgical and anesthetic expense was significantly lower in the ERAS group ( $\$12,339 \pm 3946$  vs  $\$15,363 \pm 7766$ ,  $P = 0.017$ ).

**Table 2**  
Demographic and clinicopathological factors between ERAS and standard care groups.

	ERAS group (n = 37)	Control group (n = 37)	P value
<b>Demographic variable</b>			
Sex (males, %)	20 (54)	20 (54)	1.00
Age (years)	67.8 (9.7)	66.8 (9.3)	0.42
BMI (kg/m <sup>2</sup> )	22.1 (3.0)	21.7 (2.8)	0.61
<b>ASA physical status</b>			
Grades 1/2/3	3/23/11	6/26/5	0.17
<b>Comorbidity</b>			
Hypertension	18 (49)	14 (38)	0.35
Diabetes	14 (38)	15 (41)	0.81
<b>Etiology of disease</b>			
Pancreatic adenocarcinoma	13 (35)	11 (30)	0.84
Bile duct carcinoma	5 (14)	7 (19)	
Ampullary adenocarcinoma	5 (14)	7 (19)	
Duodenal adenocarcinoma	3 (8)	1 (3)	
IPMN	6 (16)	5 (14)	
Other disease	5 (14)	6 (16)	
Preoperative biliary drainage	10 (27)	14 (38)	0.32
<b>Operative factors</b>			
PPPD/SSPPD/PD	6/28/3	8/27/2	0.78
Vascular reconstruction	11 (30)	7 (19)	0.28
Operative time (min)	407 (82)	407 (75)	0.91
Blood loss (mL)	194 (180)	216 (158)	0.38
Transfusion	2 (5.4)	2 (5.4)	1.00
<b>Pancreatic texture</b>			
Soft/Hard	22/15	26/11	0.33
<b>MPD diameter</b>			
Normal (≤3 mm)/Dilated (>3 mm)	19/18	21/16	0.64

Data are presented as numbers (percentages) or means (standard deviation). ASA, American Society of Anesthesiologists; BMI, body mass index; ERAS, Enhanced Recovery After Surgery; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

### 3.3.5. Anesthesia

The ERAS group had significantly lower total fluid volume and urine volume ( $P < 0.001$ ). The ERAS group received significantly lower crystalloid volume, but the colloid volume between groups was not different.

### 3.3.6. Postoperative course

The ERAS group had significantly earlier gastrointestinal function and mobilization. The results of chronologic changes in body weight, fluid volume, urine volume, and the drain amylase level are shown in [Supplementary Fig. 1](#). The median duration of postoperative fluid management was 9 days (interquartile range, 6.5–11 days) in the ERAS group and 12 days (interquartile range, 9–17 days) in the control group ( $P = 0.01$ ).

### 3.3.7. Glycemic control

No differences were observed in preoperative HbA1c, blood sugar level, and 1,5-anhydroglucitol level.

### 3.3.8. Skeletal muscle mass

The SMI was not significantly decreased on POD 21 in the ERAS group ( $P = 0.94$ ) but significantly decreased in the control group ([Fig. 4](#)).

### 3.3.9. Immune response

No differences in the level of interleukin-6, Th 1/2 and natural killer cell activity, and TGF-β1 were observed between the groups; however, albumin levels on POD 3 and POD 31 were significantly higher in the ERAS group ( $P < 0.05$ ) (see [Supplementary Fig. 2](#)).

**Table 3**  
Primary and secondary outcomes.

	ERAS group (n = 37)	Control group (n = 37)	P value
Length of stay (days)	20.1 (5.4)	26.9 (13.5)	<0.001
<b>Complication</b>			
Mortality	0 (0)	0 (0)	–
Overall morbidity <sup>a</sup> (Grades 0/I/II/III/IV)	14/11/6/6/0	5/11/15/6/0	0.038
PF (0/A/B/C)	21/9/6/1	11/16/9/1	0.12
DGE (0/A/B/C)	32/1/4/0	30/4/3/0	0.34
Bile leakage	1 (3)	3 (8)	0.29
Hemorrhage	1 (3)	1 (3)	1.00
Thrombosis	1 (3)	2 (5)	0.55
Any infections	7 (19)	15 (41)	0.04
Incisional SSI	5 (14)	9 (24)	0.23
Organ/space SSI	1 (3)	4 (11)	0.15
Cholangitis	1 (3)	1 (3)	1.00
Pneumonia	1 (3)	0 (0)	0.24
Enteritis	0 (0)	0 (0)	–
Bacteremia	1 (3)	4 (11)	0.15
Others	0 (0)	0 (0)	–
Quality-of-life (QoR-40J)	184 (12.4)	177 (14.5)	0.022
Readmission	0 (0)	3 (8)	0.038
<b>Total cost (\$)</b>			
Surgery/Anesthesia (\$)	25,445 (5065)	28,384 (9999)	0.085
Others <sup>b</sup> (\$)	13,107 (2199)	13,021 (2940)	0.66
<b>Anesthesia</b>			
Total fluid volume (mL)	2139 (872)	4569 (995)	<0.001
Crystalloid volume (mL)	1657 (765)	4186 (983)	<0.001
Colloid volume (mL)	482 (342)	364 (421)	0.054
Urine volume (mL)	421 (341)	841 (387)	<0.001
Temperature (Max, degrees)	36.2 (0.5)	35.9 (0.6)	0.012
Temperature (Min, degrees)	37.2 (0.5)	36.9 (0.5)	0.008
Shivering	7 (19)	16 (43)	0.022
<b>Postoperative course</b>			
<b>Gastrointestinal function</b>			
First liquid (days)	2.0 (1.5)	3.9 (2.0)	<0.001
First solid (days)	4.1 (2.1)	5.8 (2.7)	<0.001
First bowel gas (days)	1.6 (0.7)	3.1 (1.5)	<0.001
First stool (days)	2.5 (1.2)	5.1 (2.3)	<0.001
<b>Mobilization</b>			
Standing position (days)	1.4 (0.6)	2.1 (0.7)	<0.001
Walking (days)	1.9 (0.7)	2.6 (1.1)	0.005
Urinary catheter removal (days)	2.9 (0.4)	6.2 (2.1)	<0.001
Drain removal (days)	12.4 (8.4)	18.1 (15.3)	0.057
<b>Glycemic control</b>			
Preoperative HbA1c (%)	6.1 (0.9)	6.5 (1.4)	0.33
Blood sugar level (POD 1–7, mg/dL)	156 (27.9)	145 (27.8)	0.11
1,5-anhydroglucitol (POD 21, μg/mL)	11.0 (5.6)	9.3 (5.6)	0.16

Data are presented as numbers (percentages) or means (standard deviation). DGE, delayed gastric emptying; ERAS, Enhanced Recovery After Surgery; PF, pancreatic fistula; POD, postoperative day; SSI, surgical site infection.

<sup>a</sup> Stratified according Clavien-Dindo classification.

<sup>b</sup> Calculated medical costs for wards and beds, laboratory and radiologic examinations, medications, and other minor expenses.

## 4. Discussion

To our best knowledge, this study is the first RCT to investigate the effect of ERAS protocols in patients following PD. The present study suggests that the implementation of ERAS protocols in PD is as safe as conventional care, with significantly improved postoperative recovery and quality-of-life and shortened LOS. Furthermore, ERAS significantly decreased postoperative morbidity and 30-day readmission. Multimodal optimization was associated with earlier gastrointestinal function and mobilization, which facilitated earlier patient recovery.

Previous meta-analyses have shown the effect of ERAS pathways for PD [11,12]; however, these studies were based on a limited

**Table 4**  
Protocol compliance.

	ERAS group (n = 37)	Control group (n = 37)	P value
<b>Preoperative compliance</b>			
Counseling	37 (100)	0 (0)	<0.001
Mobilization	37 (100)	0 (0)	<0.001
No bowel preparation	36 (97)	0 (0)	<0.001
Oral carbohydrate loading	37 (100)	37 (100)	–
<b>Intraoperative compliance</b>			
No premedication	37 (100)	37 (100)	–
Goal-directed-therapy	36 (97)	0 (0)	<0.001
Avoiding hypothermia	37 (100)	37 (100)	–
Epidural analgesia	33 (89)	34 (92)	0.69
<b>Postoperative compliance</b>			
No nasogastric tube	37 (100)	12 (32)	<0.001
Early oral intake <sup>a</sup>	16 (43)	2 (5)	<0.001
Early removal of urinary catheter <sup>b</sup>	36 (97)	1 (3)	<0.001
Early removal of drains <sup>c</sup>	19 (51)	7 (19)	0.003
Early scheduled mobilization	37 (100)	1 (3)	<0.001

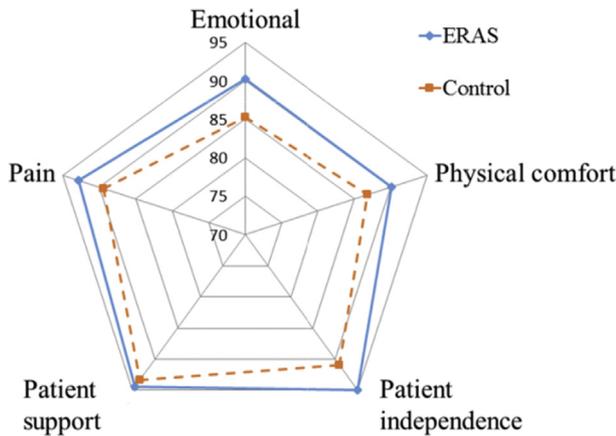
Data are presented as numbers (percentages).

ERAS, Enhanced Recovery After Surgery.

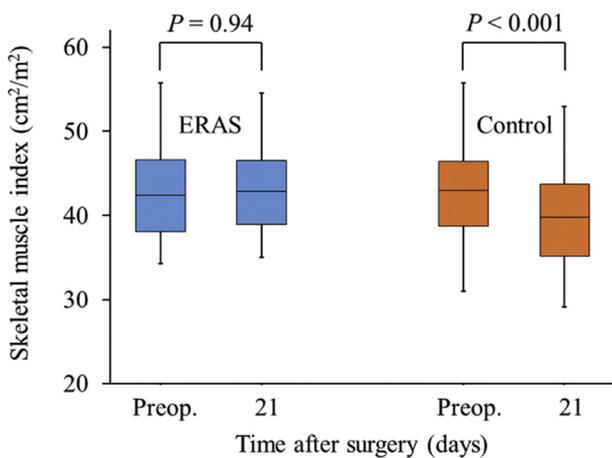
<sup>a</sup> Starting oral intake of solids within the first 3 postoperative days.

<sup>b</sup> Within postoperative day 3.

<sup>c</sup> Within postoperative day 7.



**Fig. 3.** Quality-of-life before discharge in the two groups, assessed using the Japanese version of the QoR-40 (QoR-40J) (100 is the best outcome).



**Fig. 4.** Skeletal muscle index (cm<sup>2</sup>/m<sup>2</sup>) in the two groups during the first 21 days after PD. Boxes show median with interquartile range; whiskers give the range.

number of studies and did not include any RCTs. Performing RCTs to investigate multimodal interventions like ERAS protocols is considered difficult, but RCTs are required to provide further evidence on ERAS for PD [23]. As hypothesized, the present study

demonstrated the safety and efficiency of implementing ERAS in PD and supported previous findings.

With respect to primary outcome, we selected LOS, which would be the best indicator to evaluate the effect of multimodal ERAS [3–6,11,12]. The present study demonstrated a significant reduction in LOS. This may be clinically important because improving patient recovery results in lower overall morbidities, thus reducing LOS. Indeed, high morbidity was related to additional treatment and extending LOS. However, multiple factors contribute to the timing of discharge including patient recovery and the healthcare system. In Japan, LOS was longer than in other countries [24]. The reasons were that most hospitals usually provide not only postoperative care, but also subsequent rehabilitation in a single hospitalization, which reflects a longer LOS [1]. In this study, the mean LOS of 74 patients was 23.5 days, shorter than that seen in Japanese high-volume hospitals (>30 days) but much longer than that seen in the US (16.7 days) [25]. However, the 30-day readmission rate in this study was 4.1%, which is much lower than that seen in the West (>15%) [26,27].

This study also demonstrated the efficiency of ERAS protocols for decreasing postoperative morbidity including infectious complications. A previous RCT on colorectal surgery showed that implementation of ERAS reduced infections [28]. In contrast, no significant reduction was found in PF and DGE. ERAS could have a protective effect only on nonsurgical morbidities [29]. The main surgical morbidities in PD were related to PF and were unlikely to be influenced by ERAS [23]. Moreover, we could not find a significant reduction of DGE, unlike a previous meta-analysis [12]. This result may be influenced by the low sample size of this study.

In this study, the protocol compliance was 84% for preoperative and intraoperative pathways and 30% for postoperative pathways in the ERAS group. Among ERAS protocols, the compliance with early oral intake and early drain removal was lower. Concerning oral feeding, in our protocol, oral solids were started on POD 3–4; therefore, our results on postoperative oral feeding that began on POD 4 might be late. However, we decided that patients should be given a normal diet after surgery without restrictions. Concerning drain removal, ERAS after PD was adopted only in low-risk patients according to drain amylase in a previous study [30]; however, in this study, it was implemented in all patients including 59% of patients with soft pancreas. Higher rates of soft pancreas may have led to lower compliance with drain removal. Although high-risk patients are more prone to morbidity related to PF, this study suggests that ERAS protocols are acceptable in all patients undergoing PD. Indeed, the level of postoperative drain amylase did not differ between the groups. This might suggest that early oral intake or enteral tube feeding did not increase the risk of PF.

Analysis of quality-of-life revealed that the ERAS group had significantly better scores. Few studies have dealt with postoperative recovery measured by patient-reported questionnaires. The advantage of patient-reported outcomes was that they allowed a comprehensive assessment of patient condition across several domains in the recovery process [23]. A previous study showed that ERAS after PD did not influence the quality-of-life [31], while this study showed significant differences in QoR-40J score. Multi-disciplinary support by specialized teams could contribute to improving patient quality-of-life compared with the conventional approach.

ERAS pathways have been reported to reduce healthcare costs during PD [12]. In this study, the cost, other than surgical and anesthetic costs, was significantly lower in the ERAS group; however, total medical cost was not different. The reasons may be that approximately half of the total costs were surgical and anesthetic cost, and the number of subjects was small. However, the calculated difference of \$2939 per patient represented the overall cost-

effectiveness of ERAS. Shorter LOS and lower overall morbidity may contribute to lower medical costs.

Another topic of concern in anesthesia is the fact that identifying the optimal fluid amount is still controversial despite recommendations of near-zero fluid balance to avoid fluid overload. Recently GDT has been recognized as an important element of ERAS [32]. Furthermore, previous meta-analyses have shown that GDT strategies improved postoperative outcomes [33,34]. However, only a few studies have focused on GDT in patients undergoing PD [35]. In this study, the ERAS group received significantly less intraoperative fluids according to the GDT protocol. Although our GDT protocol consisted of a lower fluid allowance than the previous fluid restriction policy (between 5 and 10 mL/kg/hr) [35,36], we could perform GDT without adding more fluids than allowed by the protocol. Less blood loss and a lower transfusion rate contributed to the safety of the protocol. In particular, 31 (83.8%) patients in the ERAS group received additional colloid boluses compared with 19 (51.4%) in the control group; the colloid volume between groups did not differ. We believe that our GDT protocol is safe and effective, but further studies will be needed to identify more optimal fluid balance.

Concerning postoperative clinical course, the present study showed that implementation of ERAS could contribute to earlier gastrointestinal function and mobilization without compromising patient safety. To keep a near-zero fluid balance, postoperative fluid allowance was kept significantly lower in the ERAS group without increasing adverse events. Furthermore, ERAS prevented postoperative weight reduction. Although postoperative enteral tube feeding may increase blood sugar level, the blood sugar level in the ERAS group was controlled at the same value as the control group with strict glycemic control.

Recent researchers have advocated body composition measurements, such as skeletal muscle mass, to assess sarcopenia. However, there are no studies investigating perioperative changes of muscle mass and the impact of ERAS on muscle mass. The present results indicate that implementation of ERAS could have an effect on preventing skeletal muscle depletion during the perioperative course.

There were even fewer studies assessing the association between ERAS and physiological outcomes including immune response markers. Contrary to our expectation, no difference was found in the inflammatory cytokine level. It is likely that PD itself introduces a large amount of physiologic stress, and that the impact of ERAS would not affect the overall stress level. Conversely, ERAS contributed to improved postoperative albumin levels. These results suggest that ERAS could improve a malnourished status quickly. More relevant physiological markers should be investigated.

Despite our important findings, several limitations should be acknowledged. First, this was a small-sized, single-center study conducted at a high-volume institution in Japan. The findings may be different for studies conducted in other hospitals or in other countries. Moreover, there has been no multi-center study to investigate ERAS protocols in PD. A multi-center study should be conducted in the future. Second, the study design did not include blinding, which has been used in many ERAS trials [29]. Clearly, blinded implementation of the ERAS was impossible. Therefore, all endpoints and objective criteria were strictly standardized before starting the trial to decrease bias. Only patients meeting the discharge criteria were eligible for discharge in both groups. Furthermore, two surgeons primarily performed perioperative management in the ERAS group and other surgeons primarily performed perioperative management in the control group. We had neutral expectations for both groups before starting the RCT; therefore, the possibility of bias was relatively limited. Third, some

ERAS items recommended by the guideline were not included in the control group because they were not included in our previous conventional management. Other ERAS items were modified in the ERAS group. To compare the differences between conventional management and ERAS management, we continued our conventional management in the control group and introduced ERAS items in ERAS group. Concerning anti-thrombotic prophylaxis, the incidence of pulmonary embolism after PD has been reported to be only 0.2% in Japan [2]; therefore, anti-thrombotic prophylaxis was not routinely included in conventional care at our unit. Although administration for 4 weeks is recommended [9,10], we stopped anti-thrombotic prophylaxis one week after surgery in the ERAS group after confirming there were no signs of thrombosis on postoperative CT images and the patient had independent mobility. Fourth, we excluded 20 patients because of severe organ dysfunction or preoperative chemotherapy. However, a greater proportion of patients with pancreatic cancer may receive preoperative systemic treatment with chemotherapy [37]. Future studies should clarify the effect of ERAS in these high-risk patients. Fifth, it is unclear which factors were most associated with a reduction in LOS. However, it was revealed that the ERAS program itself was the only factor independently associated with shorter LOS [38]. Finally, the long-term outcomes of ERAS remain unclear. Long-term results should be investigated in future studies.

In conclusion, this RCT demonstrated that optimization of ERAS protocols in patients undergoing PD can be safe and effective. Implementation of ERAS in PD contributed to earlier recovery and a shorter hospital stay without compromising surgical outcomes. ERAS protocols could also improve quality-of-life and save on medical costs.

#### Statement of authorship

KT and RY were involved in the development of overall study design, conducted overall study managements and data collection, contributed to writing the manuscript, and were responsible for enrollment and informed consent for general population participants. TY, YU, DN, TK, and TF were involved in the study design, conducted the study, and contributed to writing the manuscript in the field of gastroenterological surgery. SH was involved in the study design, calculated the sample size, and contributed to data analysis and writing the manuscript as a statistician. TM and HM were involved in the study design, conducted the study and data collection and contributed to writing the manuscript in the field of anesthesiology. JE and JW were involved in the study design, conducted the study and data collection and contributed to writing the manuscript in the field of glycemic management. MS was involved in the study design, conducted the study and data collection, and contributed to writing the manuscript in the field of rehabilitation. All authors read and approved the final version of the article.

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#### Clinical trial registration

The Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital approved this study, and the trial was registered at the University Hospital Medical Information Network (UMIN), registration number UMIN000014068.

## Conflict of interest

The authors declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnu.2018.01.002>.

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