ORIGINAL ARTICLE

Early Versus Late Oral Refeeding After Pancreaticoduodenectomy for Malignancy: a Comparative Belgian-French Study in Two Tertiary Centers

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Abstract

Background In the era of fast-track surgery, because pancreaticoduodenectomy (PD) carries a significant morbidity, surgeons hesitate to begin early oral feeding and achieve early discharge. We compared the outcome of two different approaches to the postoperative management of PD in two tertiary centers.

Methods Of patients having undergone PD for malignancy from 2008 to 2017, 100 patients who received early postoperative oral feeding (group A) were compared to 100 patients from another center who received early enteral feeding and a delayed oral diet (group B). Surgical indication and approach and type of pancreatic anastomosis were similar between both groups. Postoperative outcomes were retrospectively reviewed.

Results Patient characteristics were similar between both groups, except significantly more neoadjuvant treatment in group A (A = 20% vs. B = 9%, $p < 0.01$). Mortality rates were 3% and 4% in groups A and B, respectively ($p = 0.71$). The rate of severe postoperative morbidity was significantly lower in group A (13% vs. 26%, $p = 0.02$), resulting in a lower reoperation rate ($p < 0.01$). Delayed gastric emptying and clinically relevant pancreatic fistula were similar between both groups but chyle leaks were more frequent in group A (10% vs. 3%, $p = 0.04$). The median hospital stay was shorter in group A (16 vs. 20 days, $p < 0.01$).

Conclusion In the present study, early postoperative oral feeding after PD was associated with a shorter hospital stay and did not increase severe postoperative morbidity or the rate of pancreatic fistula. However, it resulted in more chyle leaks and did not prevent delayed gastric emptying.

Keywords Pancreaticoduodenectomy · Early oral feeding · Pancreatic fistula · Delayed gastric emptying · Chyle leaks

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Introduction

In the past decade, the use of fast track has increased in gastrointestinal surgery, especially in colorectal and bariatric surgery. This multidisciplinary approach focuses on many aspects of perioperative care, such as minimally invasive techniques, optimized pain control, rapid mobilization, and early oral nutrition.[1] In addition to shortening the hospital stay and reducing hospital costs, fast-track surgery has been shown to decrease postoperative morbidity and to accelerate recovery.[2] Although fast-track programs are widely employed, data remains limited for more complex procedures.

Pancreaticoduodenectomy (PD) is a complex procedure that is the only potentially curative treatment for periampullary and pancreatic cancers. PD is associated with high morbidity and mortality. Although recent advances in endoscopic, radiological, and surgical techniques have

resulted in a 90-day mortality rate less than 5%, morbidity is still around 30–40% even in high-volume centers.[3, 4] The two most common complications following PD are postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE). Thus, despite the limited data on fast-track protocols in pancreatic surgery, most surgeons hesitate to implement early oral feeding and discharge after PD, because of the potential risk of stimulating pancreatic secretions and promoting POPF or DGE.[5, 6]

The purpose of the present study was to compare postoperative outcomes after PD for malignant tumors between two tertiary centers with two different policies of postoperative oral feeding.

Methods

This observational, non-interventional, retrospective study of patients undergoing PD for malignancy in 2 tertiary centers was approved by the Institutional Review Board (IRB 12-055) of Hôpital Beaujon and was performed in accordance with the Declaration of Helsinki. Inclusion criteria included patients having undergone open PD with antrectomy and reconstruction with pancreaticojejunostomy. Exclusion criteria included patients suffering from benign pancreatic diseases (non-invasive ampullary, intraductal and papillary mucinous neoplasms, insulinoma, benign cysts, chronic pancreatitis, or solid pseudopapillary tumors), patients who underwent laparoscopic or pylorus-preserving PD, PD associated with adjacent organ resection, PD with pancreaticogastrostomy, or total pancreatectomy. The last 100 patients who met the inclusion criteria were included from each center, from 2012 to 2017 at Hôpital Beaujon (Clichy, France) (group A) and from 2009 to 2017 at Cliniques Universitaires Saint-Luc (Brussels, Belgium) (group B). During the same study periods, the number of PD performed in both groups were 795 (center A) and 173 (center B), respectively. Data were obtained from a prospective database in group A and from a retrospective database in group B. The differences in perioperative management are described between both groups in Table 1.

Surgical Procedure

All procedures were performed by laparotomy and involved standard PD with antrectomy. Standard lymphadenectomy was routinely performed in group A, including the anterior and posterior pancreaticoduodenal lymph nodes, nodes along the right lateral border of the superior mesenteric artery and vein, and nodes in the lower hepatoduodenal ligament. Extended lymphadenectomy was performed in group B, including standard lymphadenectomy coupled to retroperitoneal lymph node dissection extending from the right renal hilum to the left border of the aorta.[7] All pancreaticojejunal

reconstructions were hand-sewn anastomoses with non-absorbable sutures. An end-to-side hand-sewn gastrojejunostomy was constructed, in antecolic position in group A and in retrocolic position in group B. The abdominal cavity was routinely drained in both groups with an open multichannel silicone drain close to the pancreatic anastomosis. A nasogastric tube (NGT) was left in place and planned to be removed at postoperative day (POD) 1 in group A, while a transanastomotic nasojejunal feeding tube and a NGT were placed at the end of the procedure in group B. In both groups, somatostatin analogues were administered and started intraoperatively only to patients with a soft pancreas. Patients were also routinely transferred to an intensive care unit for at least 12 h of surveillance.

Postoperative Management (Table 1)

In group A, antimicrobial prophylaxis was administered depending on the risk of biliary contamination and according to a previously reported protocol.[8] After early removal of the NGT, water was given on POD 1 or 2, a semi-liquid diet on POD 2, and solid food was started on POD 3. Postoperative analgesia included systemic opioid-based analgesia.

In group B, patients received antimicrobial prophylaxis by cefuroxime intraoperatively. The NGT was kept in place until POD 5 to 7. Enteral nutrition was delivered through the nasojejunal tube when intestinal motility returned on auscultation. Solid food was given on POD 10 in the absence of clinically significant POPF, and in case of POPF with decreasing output. Postoperative analgesia was administrated through the epidural route during 3 to 5 days unless contraindicated. In the latter case, it was replaced by a "patient-controlled analgesia" pump with systemic opioids and painkillers.

Both groups received thromboembolic prophylaxis with low-molecular-weight heparin and wore compression stockings. Amylase was measured in the drain fluid at least twice on days 3 and 5. The drain was removed in the absence of complications or in case of negative measure of amylase in the drain fluid from POD 6.

Outcome Measurements

Postoperative morbidity was defined as any complications until discharge and readmission within 90 days after surgery, and was graded according to the Clavien-Dindo classification.[9] Clavien-Dindo grade ≥ 3 events were considered to be severe complications. Postoperative mortality was defined as any death occurring before POD 90. POPF was defined according to the International Study Group of Pancreatic Surgery (ISGPS).[10] Due to the design of this comparative study, only DGE graded B and C according to the ISGPS were considered.[11] Chyle leaks were defined as milky-

Table 1 Differences in intraoperative and postoperative management in groups A and B

	Group A	Group B
Antimicrobial prophylaxis	No biliary stent: cefoxitin	Cefuroxim
	Biliary stent: piperacillin/tazobactam	
Lymphadenectomy	Standard	Extended
Gastrojejunostomy position	Antecolic	Retrocolic
Peroral tubes	Nasogastric tube	Nasogastric and nasojejunal tubes
Postoperative analgesia	Systemic opioid-based	Epidural
Nasogastric tube removal	POD 1 or 2	POD 5 to 7
Oral feeding		
- Semi-liquid diet	From POD 2	–
- Solid diet	From POD 3	From POD 10

POD, postoperative day

colored fluid from the abdominal drainage after refeeding, with a triglyceride level of ≥ 1.2 mmol/L (≥ 110 mg/dL).[12]

Statistical Analysis

Values are expressed as medians (interquartile range, IQR), means (standard deviations, SD), or the number of patients and percentages, as appropriate. The chi-square test was used to compare more than two categorical variables (with Cook's correction for dichotomous categorical variables), the Kolmogorov-Smirnov test for ordinal variables, and the Student's t test for continuous variables, after normalization by Yeo and Johnson transformation, if needed. Multivariate analysis was performed by using binomial logistic regression and included all factors associated with a p value ≤ 0.05 in univariate analysis. Two-sided $p \leq 0.05$ was considered to be statistically significant.

Results

Both study groups were similar for age, sex ratio, body mass index, comorbidities, as well as clinical data at diagnosis and preoperative biological parameters (Table 2). The most frequent indications were ductal pancreatic adenocarcinoma and ampullary carcinoma, followed by cholangiocarcinoma and duodenal cancer, with no difference between both groups. Stage of disease was not different between groups regarding upfront resectable, borderline, and locally advanced tumors. However, patients in group A more frequently received neoadjuvant treatment, mostly chemoradiotherapy (20% vs. 9%, respectively, $p < 0.01$). Preoperative biliary stenting was not significantly different between both groups, as well as the rate of preoperative cholangitis. The texture of the pancreas (soft or hard), the main pancreatic duct size, and the number of venous reconstructions during PD were not different between groups. The rate of venous reconstruction was 22% in both groups. Red blood cell transfusion was more frequently performed in group B ($p = 0.04$).

Mortality rate was not significantly different between groups (3% and 4%, $p = 0.71$, respectively). Causes of death included pancreatic fistula complicated by massive arterial hemorrhage ($n = 2$, at POD 19 and 20) and early metastatic recurrence following multiple septic and arterial complications ($n = 1$, at POD 78) in group A. In group B, 3 patients died from peritonitis and septic shock due to biliary fistula (at POD 14, 34, and 39), and one patient developed massive mesenteric ischemia from intramural dissection of the superior mesenteric artery at POD 14. The rate of severe postoperative morbidity was significantly lower in group A (16% vs. 30%, respectively, $p = 0.02$) with a lower reoperation rate ($p < 0.01$). The median intensive care unit (ICU) stay and the ICU readmission rates were similar in both groups. No difference was observed in the rates of septic, cardiac, respiratory, hemorrhagic, or gastrointestinal complications (Fig. 1).

In the immediate postoperative period, the median duration of NGT decompression was 2 and 7 days in groups A and B, respectively ($p < 0.01$) (Table 2). Postoperative nasogastric decompression was prolonged more than 14 days due to daily output > 1000 mL in 2 patients in group A and 4 patients in group B ($p = 0.41$). After receiving oral drinks and a semi-liquid diet, solid oral feeding was started after a median 5 days and 13 days in groups A and B, respectively ($p < 0.01$).

The occurrence of grade B+C DGE did not differ between the groups, with a rate of 17% and 12% in groups A and B, respectively ($p = 0.39$). All 17 patients with grade B+C DGE in group A were treated by erythromycin including 8 who required NGT reinsertion. Seven of the 12 patients in group B with grade B+C DGE required NGT reinsertion (including 3 who later underwent endoscopic dilation of the gastrojejunal anastomosis and one treated with erythromycin), 4 had a prolonged NGT decompression, and one received erythromycin alone.

There was a trend towards a lower rate of clinically relevant (grade B+C) POPF (CR-POPF) in group A (21% vs. 31%,

Table 2 Patient characteristics and perioperative data

	Group A (n = 100)	Group B (n = 100)	p value
Age (years), median (range)	65.5 (24–83)	65.0 (27–83)	0.666
Sex ratio: male/female (n)	50/50	55/45	0.479
Body mass index (kg/m^2), median (range)	24.8 (15.4–46.1)	24.4 (14.8–38.1)	0.860
Stage of disease, n			
- Resectable	80	84	0.577
- Borderline	17	15	
- Locally advanced	3	1	
Main pancreatic duct diameter (mm), median (range)	4 (2–25)	3.7 (2–25)	0.312
Neoadjuvant treatment, n			
- No	80	91	0.007
- Chemotherapy	4	6	
- Chemoradiotherapy	16	3	
Pancreas texture, n			
- Soft	47	55	0.258
- Hard	53	45	
RBC transfusion			
- Number of patients (n)	10	21	0.021
- Units/patient (n), mean (± SD)	2.30 (± 1.77)	2.05 (± 1.50)	0.592
Analgesia, n			
- Epidural pump	0	85	< 0.001
- Morphine pump or others	100	15	
Early use of somatostatin analogs, n	57	64	0.311
Nasogastric tube duration (d), median (range)	2 (0–7)	7 (1–32)	< 0.001
Solid oral feeding (d), median (range)	5 (2–16)	13 (4–81)	< 0.001
ICU stay (d), median (range)	1 (0–16)	1 (1–26)	0.817
ICU readmission, n	13	10	0.633
Nasogastric tube reinsertion, n	8	7	0.788
Reoperation, n	4	15	0.008
Hospital stay (d), median (range)	16 (8–61)	20 (7–86)	0.010
Adjuvant chemotherapy, n	64	60	0.560

RBC, red blood cell; ICU, intensive care unit

$p = 0.107$). Only 2 patients in group A treated preoperatively with chemoradiotherapy developed CR-POPF, and none in group B. CR-POPF were treated with artificial nutrition (enteral or parenteral) in both groups, somatostatin analogues in grade B fistula, and resuscitation and surgical or radiological procedures in grade C fistula. More chyle leaks were observed in group A (10% vs. 3%, $p = 0.04$). All chyle leaks were treated with a fat-free diet except for medium chain triglycerides.

In multivariate analysis, age superior to 70 years old, pancreatic duct diameter less than 5 mm and soft pancreatic texture but not early oral feeding were significant risk factors of CR-POPF (Table 3). No predictive factors of grade B+C were identified by univariate analysis (supplementary table 1). Severe complications (Clavien-Dindo ≥ 3) were more frequent after delayed oral feeding, in patients ≥ 70 years, in patients ASA > 2, after extended lymphadenectomy or RBC

transfusion, but none of these factors were significant in multivariate analysis (supplementary table 2).

The median hospital stay was significantly shorter in group A (16 days vs. 20 days, $p < 0.01$). There was no difference between groups for the hospital readmission rate within 3 months (7% versus 11%, $p = 0.36$) or regarding the number of patients who received adjuvant chemotherapy.

Discussion

The present study suggests that early postoperative oral feeding after PD seems to be safe since it was not associated with an increased rate of severe complications, CR-POPF, or grade B+C DGE, compared to delayed oral feeding. Furthermore, hospital stay was shorter after early food intake. Although these encouraging results should be considered carefully

Fig. 1 Number of postoperative complications in groups A and B
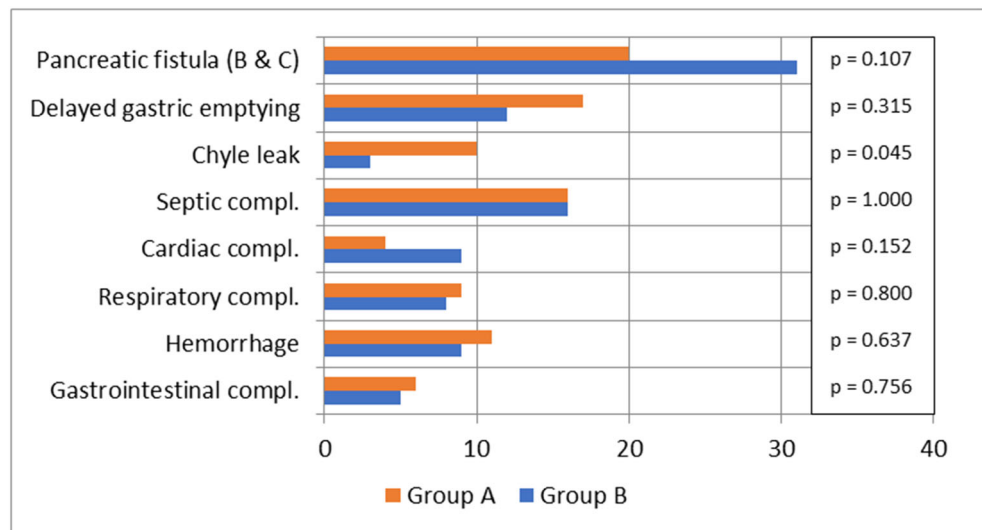
given the retrospective design of this study and the differences in perioperative management between both groups, they support the simpler and quicker return to oral feeding following PD.

After abdominal surgery, nasogastric decompression has been a standard of care for many decades to treat postoperative ileus and to reduce the flow of digestive secretions in contact with recently fashioned anastomoses. Nevertheless, it can be very uncomfortable for the patient and is related to several complications, including pulmonary infection.[13] At present, there is an increasing tendency to avoid NGT or for its early removal. However, this approach is debated following PD due to the high risk of POPF and DGE, which may require postoperative NGT reinsertion. Recent comparative retrospective studies have suggested that routine nasogastric decompression can be safely avoided in most patients after PD with an incidence of NGT reinsertion of less than 10% and no increase in overall postoperative morbidity.[14, 15] However, regarding elective hepatic resection, one randomized controlled trial demonstrated that NGT reinsertion was more frequent in women and non-smokers,[13] suggesting that NGT placement following PD could be indicated selectively in patients at high risk of postoperative DGE or vomiting.

While gastrointestinal motility is expected to recover within 48–72 h after surgery, all patients undergoing abdominal surgery develop a transient episode of intestinal dysmotility, and even postoperative ileus when bowel inactivity persists after 3 days.[16] Fast-track management protocols including early ambulation and oral feeding, opioid-free analgesia, and limited intravenous fluids administration have been shown to reduce the risk of gastrointestinal dysfunction. In studies focusing only

on postoperative feeding after surgery, it has been shown that early oral feeding accelerates the return of gastrointestinal function and shortens the length of stay without increasing postoperative morbidity, as demonstrated in infra-mesocolic surgery.[17, 18] Gerritsen et al. showed the benefits of early oral feeding after PD compared to early enteral feeding through a nasojejunal tube in a small group of patients having undergone PD including pylorus-preserving PD and total pancreatectomy, for both benign and malignant indications.[19] In the present study, we focused on two homogeneous groups of patients with malignancy, open approach for PD with antrectomy and pancreaticojejunostomy to perform a more relevant comparison.

The delayed oral diet used in group B in the present study was associated with enteral feeding through a transanastomotic nasojejunal tube, which was begun at the return of intestinal motility. Certain studies have suggested that this management was effective after PD to improve clinical outcomes and avoid malnutrition.[20] However, a recent randomized controlled trial has shown that enteral nutrition via a nasojejunal tube was associated with more postoperative complications than total parenteral nutrition following PD.[21] Particularly, rate and severity of POPF significantly increased with enteral nutrition, which should be no longer recommended. Although parenteral nutrition is often associated with a high risk of infectious complications, enteral nutrition has not been shown to have any benefits after PD regarding the risk of postoperative infection.[22]

Postoperative DGE is frequent after PD, being reported in up to 10–50% of patients.[23] The 2007 ISGPS consensus definition of DGE includes a clinical grading in which the need for a postoperative NGT for more

Table 3 Univariate and multivariate analysis of risk factors for developing clinically relevant postoperative pancreatic fistula

	No CR-POPF	CR-POPF	Univariate	Multivariate	
	$N = 148$	$N = 52$	p	OR	p
Oral feeding (early vs. delayed)	79/69	21/31	0.107		
Age (≥ 70 vs. < 70 years)	38/110	23/29	0.012	2.438 (1.073, 5.537)	0.033
Gender (M vs. F)	76/72	29/23	0.583		
ASA score (> 2 vs. ≤ 2)	33/115	14/38	0.499		
Preop. biliary stenting (yes vs. no)	85/63	31/21	0.784		
Preop. cholangitis (yes vs. no)	8/140	6/46	0.136		
Disease's stage (resectable vs. BL-LA)	115/33	50/2	0.003	0.397 (0.062, 2.552)	0.330
Main pancreatic duct (≥ 5 vs. < 5 mm)	79/69	4/48	< 0.001	0.159 (0.049, 0.515)	0.002
Neoadjuvant chemoradiotherapy (yes vs. no)	17/131	2/50	0.106		
Pancreas texture (soft vs. hard)	56/92	46/6	< 0.001	4.377 (1.530, 12.525)	0.006
Extended lymphadenectomy (yes vs. no)	63/85	26/26	0.354		
Venous reconstruction (yes vs. no)	41/107	3/49	0.001	0.380 (0.081, 1.783)	0.220
RBC transfusion (yes vs. no)	27/118	4/46	0.077		
Analgesia (epidural vs. others)	89/59	26/26	0.203		
Prophylactic use of SMS analogs (yes vs. no)	80/68	41/11	0.002	1.259 (0.505, 3.136)	0.621
Solid oral feeding (≥ 5 days) (yes vs. no)	107/41	46/6	0.018	0.494 (0.161, 1.519)	0.218
ICU stay (≥ 3 vs. < 3 days)	36/112	20/32	0.051	1.642 (0.707, 3.810)	0.249

CR-POPF, clinically relevant postoperative pancreatic fistula; ASA, American Society of Anesthesiology; BL-LA, borderline-locally advanced; RBC, red blood cells; SMS, somatostatin; ICU, intensive care unit; OR, odd ratio

than 4 days and the inability to tolerate solid oral intake after 7 days are considered as grade A DGE.[11] Most published studies comparing fast-track versus conventional postoperative PD protocols used the ISGPS definition of DGE and reported a higher rate of DGE with the conventional approach.[24–29] However, like in group B patients in the present study, postoperative management in many centers included enteral feeding and delayed oral intake with routine NGT decompression for sometimes more than 4 days, with no increase in the rate of DGE.[30] This suggests that the ISGPS definition of DGE may not be suitable to compare policies of early versus delayed oral feeding, so as in the present study, only grade B+C DGE should be considered.

Several technical and pharmaceutical methods have been proposed to reduce the rate of POPF following PD, but none of them have been shown to significantly influence results.[31] Because gastrointestinal hormones released after ingesting food promote digestive secretions such as pancreatic juices that could theoretically exacerbate POPF, fasting has frequently been used in the management of patients with CR-POPF.[32] However, the randomized clinical trial by Fujii et al. did not demonstrate any difference in the healing duration and the complications of CR-POPF after fasting compared to maintained oral intake.[33] In the present

study, the rate of CR-POPF tended to increase in the enteral feeding group, but the difference was not significant. Nevertheless, maintaining oral intake has not been shown to be the most appropriate option in cases of high-volume output and persistent POPF, so artificial nutrition (enteral or parenteral) with somatostatin analogues is preferred by many pancreatic surgeons to promote POPF closure.[32]

In the present study, we observed a significantly higher rate of chyle leaks after early oral feeding. Because of lymph node dissection, the lymphatic vessels of the mesenteric root and the retroperitoneal compartment are frequently injured during PD, resulting in chyle leaks in up to 10% of patients, which should be actively treated due to the risk of malnutrition and compromised immunity.[12, 34] Several risk factors of chyle leaks following PD have been identified, including early enteral feeding and extended lymph node dissection.[12, 35] Although the extension of lymphadenectomy was different in both groups, the higher rate of chyle leaks in group A cannot be explained by the extent of lymph node dissection since the most extended lymphadenectomy was performed in group B. The present study confirms that early feeding, even oral, could favor chyle leaks, even after standard lymphadenectomy which was routinely performed in group A. However, this complication was always easily treated by a fat-free diet with no further adverse consequences.

Fast-track surgery is increasingly reported to shorten patient recovery and to reduce costs. Several studies have found this approach to be highly feasible following PD with shorter hospital stays and without increased morbidity or mortality compared to traditional management.[6, 24–29] Although there was no specific fast-track protocol for PD in the present study, our results confirm that an early oral diet can be safely administrated, thus markedly reducing unnecessary tube placement and patient discomfort, without increasing the readmission rate.

Our study has certain limitations, including its retrospective design, the absence of comparison in a concurrent fashion between two centers with two different perioperative managements. Nevertheless, it was performed in patients undergoing surgery over a relatively short period of time, thus postoperative management was unchanged in both centers. Also, postoperative analgesia was different in both groups. Systemic opioid-based analgesia, which is known to slow the return of gastrointestinal function compared to epidural analgesia, was routinely used in group A in which oral feeding was introduced earlier and better tolerated than in group B, as already reported.[36] Thirdly, the position of the gastrojejunostomy was different in both groups, but this position did not influence the incidence of DGE in a recent randomized controlled trial.[37] Fourth, patients in group A received more preoperative chemoradiation therapy, but this difference cannot explain the better tolerance of oral feeding in group A since radiation therapy is not presumed to alter early postoperative gastric emptying.[38] Lastly, lengths of stay in both centers were higher than reported in some high-volume centers but conversely rates of readmission (7% and 11%) were lower.

Conclusions

Early postoperative oral feeding after PD was associated with a shortened hospital stay and did not increase the severe complication rate compared to delayed oral feeding. It also resulted in an increased prevalence of chyle leaks, which were easily treated by only diet changes. The occurrence of delayed gastric emptying was not influenced by early oral feeding, suggesting that further comparative studies are needed to reduce its prevalence following PD.

Compliance with Ethical Standards

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