Pylorus Resection Does Not Reduce Delayed Gastric Emptying After Partial Pancreatoduodenectomy

A Blinded Randomized Controlled Trial (PROPP Study, DRKS00004191)

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Objectives: The aim of this study was to investigate the effect of pylorus resection on postoperative delayed gastric emptying (DGE) after partial pancreatoduodenectomy (PD).

Background: PD is the standard treatment for tumors of the pancreatic head. Preservation of the pylorus has been widely accepted as standard procedure. DGE is a common complication causing impaired oral intake, prolonged hospital stay, and postponed further treatment. Recently, pylorus resection has been shown to reduce DGE.

Methods: Patients undergoing PD for any indication at the University of Heidelberg were randomized to either PD with pylorus preservation (PP) or PD with pylorus resection and complete stomach preservation (PR). The primary endpoint was DGE within 30 days according to the International Study Group of Pancreatic Surgery definition.

Results: Ninety-five patients were randomized to PP and 93 patients to PR. There were no baseline imbalances between the groups. Overall, 53 of 188 patients (28.2%) developed a DGE (grade: A 15.5%; B 8.8%; C 3.3%). In the PP group 24 of 95 patients (25.3%) and in the PR group 29 of 93 patients (31.2%) developed DGE (odds ratio 1.534, 95% confidence interval 0.788 to 2.987; $P = 0.208$). Higher BMI, indigestion, and intraabdominal major complications were significant risk factors for DGE.

Conclusions: In this randomized controlled trial, pylorus resection during PD did not reduce the incidence or severity of DGE. The development of DGE seems to be multifactorial rather than attributable to pyloric dysfunction alone. Pylorus preservation should therefore remain the standard of care in PD.

Trial Registration: German Clinical Trials Register DRKS00004191

Keywords: delayed gastric emptying, partial pancreatoduodenectomy, postoperative complications, pylorus resection

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Partial pancreatoduodenectomy (PD) is the standard treatment for benign and malignant tumors of the pancreatic head and chronic pancreatitis in this region.[1,2] The historical standard procedure, classic PD with resection of the distal stomach, was modified in the 1970 s by Traverso and Longmire,[3] who introduced preservation of the pylorus. This modification has been shown in numerous studies to be equivalent to classic PD with regard to tumor recurrence and long-term survival.[4] Pancreatic surgery has several specific complications and recent developments in postoperative patient management have led to continuous improvement in outcomes.[5,6] One common complication after either method of PD is delayed gastric emptying (DGE).[7,8] DGE inhibits postoperative return to a normal solid diet, impairs patients' quality of life (QoL), and causes delays in hospital discharge and in further adjuvant treatment.[9] DGE is believed to be a functional impairment of the physiological propulsive action of the stomach and especially the pylorus. Therefore, some patients react well to propulsive medication such as erythromycin.[10] In 2007, the International Study Group of Pancreatic Surgery (ISGPS) proposed a standardized definition of DGE with 3 grades of severity, A to C.[11] In an earlier retrospective analysis of patients at the university of Heidelberg, the overall frequency of DGE was 45%, comprising 28% DGE grade A, 8% grade B, and 9% grade C.[12]

Several studies, including 2 randomized controlled trials, did not demonstrate conclusive evidence for or against pylorus resection.[13–16] Therefore, the aim of this trial was to investigate the effect of pylorus resection on postoperative DGE in PD.

METHODS

The PROPP study was a single-center, randomized, controlled, patient- and observer-blinded trial (RCT) with 2 parallel groups and a statistical superiority hypothesis (pylorus resection is associated with less DGE than pylorus preservation). The study protocol was approved by the Ethics Committee of the University of Heidelberg, Germany, on May 17, 2012 (reference number S-121/2012). The trial was registered with the World Health Organization (WHO) network (German Clinical Trials Register DRKS00004191) on June 29, 2012, and the final protocol was published with open access.[17] The trial was conducted at the Clinical Trial Center of the Department of General, Visceral and Transplantation Surgery at the University Hospital of Heidelberg. Data management and statistical analysis was performed at the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg. Monitoring was

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Disclosure: The authors declare no conflicts of interests.

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carried out in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 (Good Clinical Practice). The introduction and the methods section are based on the published protocol,[13] which was published under a Creative Commons license (http://creativecommons.org/licenses/by/4.0).

Patients

All patients scheduled for PD for any indication were eligible. Further inclusion criteria were age equal to or older than 18 years and written informed consent. The exclusion criteria were participation in another interventional trial resulting in interference with the intervention and/or outcome of this study, anticipated lack of compliance, and language problems. Patients were informed about the trial and the trial interventions and asked to participate. Patients screened but not included in the trial were recorded in the screening log with the reasons for nonenrollment.

Randomization and Blinding

All patients were randomized intraoperatively to 1 of the 2 groups after the surgeon had confirmed that PD was feasible and preservation of the pylorus technically and oncologically possible. Validated online randomization software (randomizer.at: provided online by the Institute for Medical Informatics, Statistics and Documentation, University of Graz, Austria) was used for unstratified randomization with fixed confidential block sizes in a 1:1 allocation ratio.

Patients were blinded to the intervention until discharge or final assessment of the primary and secondary endpoints. Blinding of the operating surgeon was not possible; however, the operating surgeons were not involved in the assessment of outcomes. The staff collecting data and assessing the endpoint were blinded to the intervention during the whole trial. The data manager and statistician were not blinded; however, they acted and evaluated data according to a predefined analysis plan.

Interventions

In both groups, open partial PD was carried out and reconstructed with an omega loop. A double-layer end-to-side pancreaticojejunostomy and a monolayer end-to-side hepaticojejunostomy were performed, all with 5/0 monofilament atraumatic single sutures.

In the control group, with preservation of the pylorus (PP), the duodenum was divided 2 cm distal to the pylorus with a linear stapling device, preserving the gastric vessels along the lesser and the greater curvature. An antecolic end-to-side duodenojejunostomy using 2-layer 4/0 monofilament atraumatic running sutures was performed, approximately 50 cm distal to the hepaticojejunostomy. No pyloric dilatation or pyloromyotomy was performed.

In the intervention group, with pylorus resection (PR), the stomach was resected using a linear stapling device within 1 cm proximal to the pyloric ring with complete preservation of the gastric vessels along both curvatures to maintain perfusion of the distal stomach via the gastroepiploic vessels and the left gastric artery, respectively. An antecolic end-to-side gastrojejunostomy using 2-layer 4/0 monofilament atraumatic running sutures was performed, approximately 50 cm distal to the hepaticojejunostomy (Fig. 1).

All interventions were performed by attendings of the Department of General, Visceral, and Transplantation Surgery at the University Hospital of Heidelberg in a standardized fashion. Adherence was controlled by monitoring of the official operation report.

In both groups, the nasogastric tube (NGT) was removed as soon as mechanical ventilation was stopped, usually at the end of the operation. All patients were part of a fast-track concept and received standardized oral nutrition and were supported with parenteral or enteral nutrition if oral uptake was not enough. Follow-up examinations were scheduled on postoperative days (POD) 7, 14 (or on the day of discharge, if earlier), and 30. The 30-day follow-up visit was done by a telephone interview if the patient had already been discharged.

Objectives and Outcomes

The objective of the PROPP study was to investigate whether there is a difference in the rate of DGE between PP and PR within 30 days after operation. In a confirmatory analysis, the alternative hypothesis of higher rates of DGE occurrence within 30 days after PP than after PR was assessed.

The primary endpoint was DGE, as defined by the ISGPS, within 30 days after the index operation. DGE was assessed as present if the NGT had to be reinserted after the operation and was still in place on or after POD 4. In accordance with the ISGPS definition, DGE was assessed as grade A if the NGT was inserted during the first postoperative week but the patient returned to a solid oral diet before POD 14. For DGE grade B, the NGT was in place (still inserted or reinserted) during postoperative week 2 but return to solid diet was achieved before POD 21. Patients assessed as suffering from DGE grade C needed a NGT during the third week after operation. Solid oral intake was defined as the first solid food in the course of standard care after pancreatic surgery, for example, bread, rice, or fruit (not soup or rice porridge). Gastric distension, vomiting, NGT insertion and removal dates, start of solid food intake, medication with metoclopramide, erythromycin, and strong oral laxatives, and diagnostic and interventional measures because of DGE were assessed.

Secondary endpoints were operation time (time from incision to skin closure in minutes), blood loss (estimated blood loss within the suction system and on the surgical cloth measured in milliliters), 30-day mortality (death from any cause) and morbidity—that is, postoperative pancreatic fistula (POPF),[18] intraabdominal fluid collection, chyle leak,[19] postoperative hemorrhage, and pulmonary aspiration and pneumonia and other complications as defined by Dindo et al.[20] In addition, reoperations and reinterventions were captured because of complications [including computer tomography (CT)-guided drainage], postoperative hospital stay in days (from day of surgery to day of discharge), interventions because of DGE (gastrography or endoscopy), medications because of nausea, vomiting or DGE (metoclopramide, erythromycin, strong oral laxatives), parenteral nutrition, and QoL on the day of the screening visit and 30 days after the operation (EORTC QLQ C30 and PAN26).

Sample Size

Based on existing evidence,[12–16] the DGE rate was predicted to be 32% in the PP group and 12% in the PR group. This meant that 89 patients had to be analyzed in each group to assure power of 90% with the χ^2 test applied at a 2-sided level of significance of 5% in a superiority setting. Ten more patients per group were added to counteract the anticipated dropout. Therefore, enrollment stopped after randomization of 198 patients.

Statistical Analysis

The analysis of the primary endpoint was based on the full analysis set and followed the intention-to-treat (ITT) principle. However, patients without follow up of the primary endpoint for at least 21 days were excluded. The confirmatory analysis of the primary endpoint was performed with a logistic regression model including the covariables intervention, age, and BMI. In the published protocol,[17] surgeon experience was also considered as a factor in the analysis of the primary endpoint; however, no interventions were carried out by a nonboard-certified surgeon so this factor was omitted. As a sensitivity analysis, the primary endpoint was also evaluated on the basis of the per protocol population. Any major

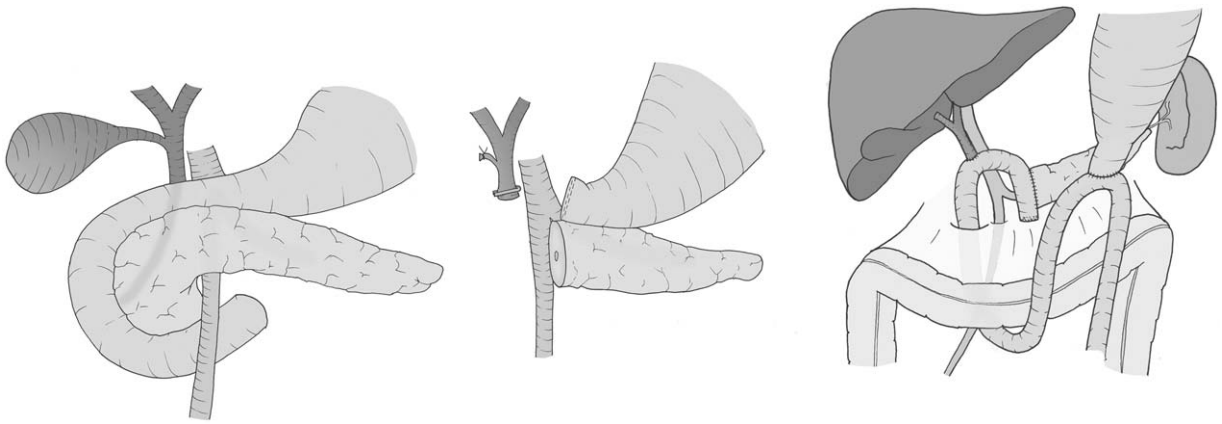

FIGURE 1. Standard reconstruction technique with a single loop and either pylorus preservation (duodeno-jejunostomy) or pylorus resection (gastro-jejunostomy).

deviation from the protocol led to exclusion of the patient from the per protocol analysis set. For missing data, imputation was performed by means of the ICA-r method described by Higgins et al.[21] All analyses were performed using SAS version 9.4.

All secondary endpoints were analyzed descriptively based on the ITT population. Exploratory data analysis was performed, with calculation of appropriate summary measures for the empirical distribution and of descriptive 2-sided *P*-values. In addition, we conducted a univariable analysis of a potential association of DGE with baseline characteristics (age, BMI, sex, weight loss, diabetes mellitus, exocrine insufficiency, chronic renal insufficiency, COPD, ASA $\geq$ III, and indigestion) and early postoperative events (intraabdominal fluid collection, chyle leak, POPF, and major complications arising from an intraabdominal focus, ie, POPF, SSI, and so on together). All variables with $P< 0.15$ were evaluated in a multivariable model to identify independent prognostic factors for DGE.

RESULTS

A total of 198 patients were randomized into the 2 interventional groups between February 20, 2013 and June 10, 2016. With 10 patients excluded from analysis (Fig. 1), the ITT population consisted of 188 patients (95 PP and 93 PR). Seventeen patients had major protocol deviations, resulting in a per-protocol set of 171 patients. The CONSORT flow diagram is shown in Figure 2.

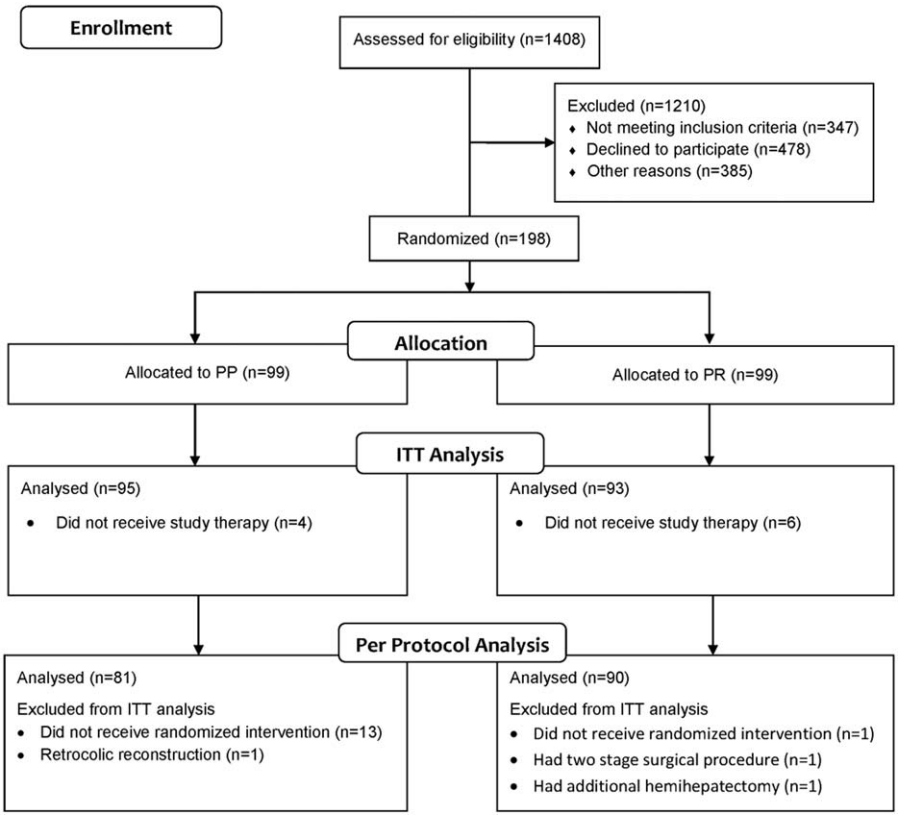

FIGURE 2. CONSORT flow diagram.

TABLE 1. Baseline Data

N (%) or mean (SD)	PP (n = 95)	PR (n = 93)	P*
Sex			
Male	55 (57.9%)	49 (52.7%)	0.473
Female	40 (42.1%)	44 (47.3%)	
Age, yrs	62.9 (11.1)	63.8 (11.5)	0.568
BMI, kg/m^2	26.2 (4.5)	24.8 (3.7)	0.051
Indigestion	18 (19.1%)	22 (23.7%)	0.452
Weight loss, kg	7.4 (5.0)	7.8 (5.6)	0.926
Diabetes mellitus	22 (23.2%)	15 (16.1%)	0.226
Exocrine insufficiency	7 (7.4%)	15 (16.1%)	0.062
Chronic renal insufficiency	3 (3.2%)	1 (1.1%)	0.322
COPD	4 (4.2%)	6 (6.5%)	0.494
ASA ≥ III	40 (42.6%)	41 (44.1%)	0.559
Portal vein/superior mesenteric vein involvement	22 (23.4%)	28 (31.1%)	0.240
Neoadjuvant chemotherapy	3 (3.2%)	8 (8.6%)	0.228
Histology			
Pancreatic ductal adenocarcinoma	35 (36.8%)	45 (48.4%)	0.109
Intraductal papillary mucinous neoplasia	22 (23.2%)	14 (15.0%)	0.158
Chronic pancreatitis	17 (17.9%)	20 (21.5%)	0.534
Other	21 (22.1%)	14 (15.1%)	0.169

ASA indicates American Society of Anesthesiologists; BMI, body mass index; PP, preservation of the pylorus; PR, pylorus resection.
*Categorical variables: χ^2 test; continuous variables: Wilcoxon test.

TABLE 2. Primary and Secondary Endpoints

N % or mean (SD)	PP (n = 95)	PR (n = 93)	P*
Primary endpoint			
DGE	24 (25.3%)	29 (31.2%)	0.367
Secondary endpoints			
DGE grade A	13 (14.3%)	15 (16.7%)	0.489
DGE grade B	6 (6.6%)	10 (11.1%)	
DGE grade C	2 (2.2%)	4 (4.4%)	
Diagnostics procedures because of DGE	14 (14.9%)	15 (16.1%)	0.815
Gastrography	8 (9.3%)	8 (9.4%)	0.980
Endoscopy	4 (4.7%)	7 (8.2%)	0.350
Other diagnostic procedures	5 (5.9%)	6 (7.1%)	0.755
Prokinetic medication	60 (63.2%)	58 (62.4%)	0.911
Metoclopramide	56 (58.9%)	52 (55.9%)	0.674
Erythromycin	11 (11.6%)	14 (15.1%)	0.483
Strong oral laxatives	15 (15.8%)	21 (22.6%)	0.237
Parenteral nutrition	30 (31.6%)	28 (30.1%)	0.827
Operation time, minutes	315.1 (71.5)	313.6 (73)	0.736
Intraoperative blood loss, mL	778.4 (662.1)	734.0 (533.3)	0.828
NGT removed immediately after OP	85 (89.5%)	87 (93.5%)	0.317
Total time NGT was inserted, days	2.6 (5.5)	2.5 (4.7)	0.529
Invasive interventions because of complications	24 (24.2%)	18 (19.4%)	0.524
CT drainage	10 (10.5%)	8 (8.6%)	0.654
Reoperation	14 (14.7%)	10 (10.8%)	0.413
Postoperative hospital stay, days	15.4 (8.2)	14.1 (7.5)	0.112
Postoperative weight change, kg/day†	0.2 (0.1)	0.1 (0.2)	0.556

CT indicates computer tomography; DGE, delayed gastric emptying; NGT, nasogastric tube; PP, preservation of the pylorus; PR, pylorus resection.
*Categorical variables: χ^2 test; continuous variables: Wilcoxon test.
†Until postoperative day 30.

There was no significant difference in baseline parameters between the PP group and the PR group. Baseline data are shown in Table 1.

Primary Endpoint

The DGE rate was 31.2% in the PR group (29 of 93 patients) and 25.3% in the PP group (24 of 95 patients) ($P = 0.367$). In the confirmatory analysis correcting for BMI and age, no significant difference of DGE rate was found between the 2 groups (odds ratio, OR, 1.534, 95% confidence interval, CI, 0.788–2.987; $P = 0.208$). Similarly, the sensitivity analysis in the per-protocol set showed no significant difference (OR 1.591, 95% CI 0.793–3.193; $P = 0.191$). Most patients with DGE had grade A (28 of 188 patients; 15.5%), followed by grade B (16 of 188 patients; 8.8%), and grade C (6 of 188 patients; 3.3%). The distribution of the DGE grades did not differ significantly between PP and PR. Moreover, the total time in days an NGT was inserted in both groups did not differ (PP: 2.6 +/− 5.5 vs PR: 2.5 +/−4.7; $P = 0.529$). Independently of the intervention group, higher grades of DGE were associated with higher BMI (mean BMI: no DGE, 25.1 kg/m^2; DGE A, 26.5 kg/m^2; DGE B, 26.8 kg/m^2; DGE C, 27.0 kg/m^2; $P = 0.039$). These outcomes are shown in Table 2.

Secondary Endpoints

Operating time did not differ between the 2 groups (PP: 315.1 min vs PR: 313.6 min; $P = 0.736$). Blood loss was also not different (PP: 778.4 mL vs PR: 734.0 mL; $P = 0.828$). The 30-day mortality was 2.7% (PP: 3 of 95 patients, 3.2% vs PR: 2 of 93 patients, 2.2%; $P = 0.668$). Regarding postoperative complications, POPF occurred in 27 of 188 patients (14.4%). The 2 groups showed no significant difference in POPF (PP: 18 of 95 patients, 18.9% vs PR: 9 of 93 patients, 9.7%; $P = 0.109$). Intraabdominal fluid collections were detected in 53 of 188 (28.2%) patients (PP: 29 of 95 patients, 30.5% vs PR: 24 of 93, 25.8%; $P = 0.472$) and chyle leak in 23 of 188 (12.3%) patients (PP: 11 of 95 patients, 11.6% vs PR: 12 of 93 patients, 13.0%; $P = 0.760$). Postoperative hemorrhage was seen in 18 of 188 (9.6%) patients (PP: 9 of 95 patients, 9.5% vs PR: 9 of 93 patients, 9.7%; $P = 0.962$). An overview of all postoperative complications is shown in Table 3. Overall, 40 of 188 (21.3%) patients needed at least one reintervention (reoperation or CT-guided drainage); however, the rate of reintervention did not differ significantly between the groups (PP: 22 of 95 patients, 23.2% vs PR: 18 of 93 patients, 19.4%; $P = 0.524$). No difference was seen in patients' length of hospital stay (PP: 15.4 days vs PR: 14.1 days; $P = 0.112$).

Diagnostic procedures because of DGE were performed in 29 of 188 (15.5%) patients, including gastrography (16 of 188 patients, 9.4%), endoscopy (11 of 188 patients, 6.5%), and other procedures such as plain abdominal radiography or CT (11 of 188, 6.5%). There were no differences in diagnostic procedures between the PP and PR groups. Prokinetic medication was given in 60 of 95 (63.2%) patients in the PP group and 58 of 93 (62.4%) patients in the PR

TABLE 3. Postoperative Complications

N % or mean (SD)	PP (n = 95)	PR (n = 93)	P*
30-Day mortality	3 (3.2%)	2 (2.2%)	0.668
POPF			
Biochemical leak	13 (13.7%)	11 (11.8%)	0.871
Grade B	9 (9.5%)	5 (5.4%)	0.428
Grade C	9 (9.5%)	4 (4.3%)	0.267
Intraabdominal fluid collection	29 (30.5%)	24 (25.8%)	0.472
Chyle leak	11 (11.6%)	12 (13.0%)	0.760
Postoperative hemorrhage	9 (9.5%)	9 (9.7%)	0.962
Pulmonary aspiration and pneumonia	6 (6.3%)	11 (11.8%)	0.188
Pulmonary embolism	2 (2.1%)	1 (1.1%)	0.573
Surgical site infection	6 (6.3%)	4 (4.3%)	0.538
Wound dehiscence	3 (3.2%)	2 (2.2%)	0.668

*Categorical variables: χ^2 test; continuous variables: Wilcoxon test.
POPF indicates postoperative pancreatic fistula; PP, preservation of the pylorus; PR, pylorus resection.

TABLE 4. Prognostic Factors for DGE

Variable	DGE (n = 53; 28.2%)	No DGE (n = 135; 71.8%)	Univariable P^*	Multivariable OR (95% CI)	P^*
Age (mean ± SD, yrs)	65.3 (10.3)	62.5 (11.5)	0.127	1.03 (0.99–1.07)	0.105
BMI (mean ± SD, kg/m^2)	26.7 (4.8)	25.1 (3.8)	0.024	1.09 (1.01–1.19)	0.043
Female (n = 84)	27 (50.9%)	57 (42.2%)	0.358	–	
Weight loss (n = 102)	33 (62.3%)	69 (51.1%)	0.106	2.07 (0.98–4.40)	0.057
PDAC (n = 80)	22 (41.5%)	58 (43.0%)	0.828	–	
Diabetes mellitus (n = 37)	12 (22.6%)	25 (18.5%)	0.612	–	
Exocrine insufficiency (n = 22)	3 (5.7%)	19 (14.1%)	0.138	0.34 (0.08–1.39)	0.134
Chronic renal insufficiency (n = 4)	2 (3.8%)	2 (1.5%)	0.321	–	
COPD (n = 10)	5 (9.4%)	5 (3.7%)	0.160	–	
ASA ≥ III (n = 81)	27 (50.9%)	54 (40.0%)	0.246	–	
Indigestion (n = 40)	15 (28.3%)	25 (18.5%)	0.087	2.63 (1.07–6.46)	0.036
Intraabdominal fluid collection (n = 16)	8 (15.1%)	8 (5.9%)	0.045	1.86 (0.51–6.75)	0.348
Chyle leak (n = 18)	2 (3.8%)	16 (11.9%)	0.084	0.34 (0.07–1.71)	0.190
POPF (n = 7)	5 (9.4%)	2 (1.5%)	0.010	3.30 (0.47–23.25)	0.231
Major abdominal complications	16 (30.2%)	14 (10.4%)	0.001	3.16 (1.32–7.54)	0.010

ASA indicates American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DGE, delayed gastric emptying; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula.

*Categorical variables: χ^2 test; continuous variables: Wilcoxon test.

group ($P = 0.911$). A total of 58 of 188 (30.9%) patients received parenteral nutrition (PP: 30 of 95 patients, 31.6% vs PR: 28 of 93 patients, 30.1%; $P = 0.827$).

Preoperatively, the patients' QoL did not differ between the groups. On POD 30, however, the QoL questionnaires showed significant differences in 5 of 21 categories. Although fatigue, pain, appetite, and diarrhea favored significantly PP, the domain ''hepatic'' was significantly better in the PR group. Thus, 4 of 5 categories significantly favored the PP group on POD 30. Appendix 1 gives an overview of QoL scores.

Regarding prognostic factors (Table 4), a multivariable analysis showed that higher BMI (OR 1.09, 95% CI 1.01–1.19, $P = 0.043$), the presence of preoperative indigestion (OR 2.63, 95% CI 1.07–6.46, $P = 0.036$), and major abdominal complications (OR 3.16, 95% CI 1.32–7.54, $P = 0.010$) were factors independently associated with the occurrence of DGE.

DISCUSSION

The PROPP study did not detect a significant difference in DGE rate within 30 days after PD between patients in whom the pylorus was resected and those in whom it was preserved. With an overall rate of 28.2%, DGE remains a frequent and meaningful complication after PD. The severity of DGE was also not influenced by the intervention, as the distribution of DGE grades A to C did not differ between the PP group and the PR group. A novel finding is the association between BMI and DGE severity: patients with a higher BMI are more likely to develop DGE, and DGE severity increases with increasing BMI. Besides BMI, preoperative indigestion is a second independent risk factor for development of DGE during the postoperative course. The perioperative complications did not differ between PP and PR, so safety is not a factor that needs to be taken into account when deciding whether to preserve or resect the pylorus. Based on our findings, there is no need to abandon the widely accepted strategy of pylorus preservation after PD. The association of DGE with POPF alone could not be confirmed. However, major intraabdominal complications were strongly associated with the occurrence of DGE.

The findings of the PROPP study are in contrast with those of most existing publications regarding the association of DGE and pylorus resection. Most nonrandomized studies[14,16,22–26] have concluded that resection of the pylorus is favorable regarding DGE. In 2 nonrandomized studies[13,27] there was no difference between the 2 techniques regarding DGE. A Japanese RCT[15] included 64 patients with PP and 66 patients with PR, with DGE between 7 days and 6 months postoperatively as endpoint. The observed frequency of DGE was 17.2% for PP and 4.5% for PR ($P = 0.02$). Another Japanese RCT[28] from 2014 found DGE rates of 20% in the PP group and 12% in the PR group among a total of 100 patients, representing a non-significant difference ($P = 0.414$).

One can argue that the retrospective studies may have been biased; however, the RCTs of Kawai et al[15] and Matsumoto et al[28] were of good quality. Therefore, there must be other reasons for the difference in findings. A general difference between the populations has to be assumed, as the overall DGE rate was 10.8% and 16% in the previous RCTs and 28.2% in our RCT. There may be relevant genetic differences between the Asian populations investigated in the earlier studies and our mostly Caucasian population. The reconstruction technique in the RCT of Matsumoto et al[28] was retrocolic gastroenteric anastomosis. However, the impact of ante- or retrocolic reconstruction on DGE is still under debate.[29,30] Differences in baseline characteristics are also possible, as the Asian populations had lower BMI than the population of the PROPP study. Unfortunately, BMI was not reported in the RCT of Kawai et al.[15] However, the preoperative weight of the Kawai cohort was reported as 55 ± 10 kg, compared with 76.5 ± 15.1 kg in the current RCT. In the RCT by Matsumoto et al,[28] where PR patients had a lower rate of DGE, the overall cohort had a mean BMI of 21.7 kg/m^2, compared with 25.5 kg/m^2 in the PROPP study. The hypothesis that BMI influences DGE is supported by the fact that the PROPP study found a significant association of higher BMI with higher grades of DGE. Consequently, PR may still be beneficial in patients with lower BMI; however, this remains to be investigated.

Furthermore, the common hypothesis is that DGE represents a functional impairment of gastric motility and pyloric function, which is supported by the observation that antecolic reconstruction of the duodenojejunal passage significantly lowered DGE incidence, probably because of less chemical irritation from potential subclinical leakage of the pancreatic anastomosis in the first few days after operation. The additional anatomical modification represented by removal of the pylorus would be expected to significantly enhance this effect. However, this was not confirmed in the PROPP study. As the multivariable analysis identified preoperative indigestion as an independent risk factor for DGE, lack of preoperative stimulation of

the gastrointestinal tract by regular oral food intake could be another important pathophysiological mechanism. Therefore, the development of DGE is likely to be multifactorial rather than attributable to pyloric dysfunction alone. Consequently, our pathophysiological understanding of DGE is not yet complete and additional strategies to avoid DGE must be developed. Furthermore, as suggested by the multivariable analysis, some instances of DGE may be because of toxic intraabdominal sepsis.

Given the finding of no difference between PP and PR with regard to DGE and other postoperative complications, one possible conclusion is that both procedures can be widely used. However, the potential long-term disadvantages of PR are as yet unknown. For example, unimpeded reflux could lead to gastric stump cancer. Such long-term problems may not be clinically relevant in pancreatic cancer patients; in benign indications for PD, however, they may well be. Therefore, pylorus preservation should remain the standard of care in PD unless evidence accumulates to demonstrate the long-term safety of pylorus resection.

The strengths and limitations of the PROPP study have to be addressed. Sources of bias were reduced as far as possible by multiple methodological measurements, and the risk of bias can be considered low in all common domains.[31,32]

Moreover, negative trial results in the presence of a superiority hypothesis should be interpreted cautiously. The PROPP study assumed that PR would be associated with 20% less DGE than PP. In fact, the effect in this study was opposite to the expected effect (PR tended to have a higher DGE rate than PP). This results in a theoretical post hoc power of 14% in a 2-sided superiority setting. This further implies that the conclusion that both interventions are equivalent is not permitted from a test for superiority. In other words, with a 6% difference of DGE rate as cut-off, a total of 2400 patients would have been needed to show equality. Consequently, the only valid interpretation of the data of the PROPP study is the rejection of the alternative hypothesis (PR is superior to PP). Furthermore, the study was conducted in a single-center setting, which may reduce the generalizability of the findings to high-volume pancreatic surgery centers.

CONCLUSIONS

In this RCT, pylorus resection during PD did not reduce the incidence or severity of DGE. The development of DGE seems to be multifactorial rather than attributable to pyloric dysfunction alone. Pylorus preservation should therefore remain the standard of care in PD.

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APPENDIX 1. Quality of life at POD 30

Mean (SD)	PP (n = 95)	PR (n = 93)	*P**	Direction
Role functioning	31.6 (29.6)	22.1 (24.3)	0.057	↑
Emotional functioning	59.0 (27.6)	56.3 (25.9)	0.427	↑
Cognitive functioning	74.7 (28.4)	74.8 (22.9)	0.542	↑
Social functioning	49.8 (32.6)	44.9 (31.7)	0.260	↑
Global health status	48.8 (22.6)	43.7 (19.1)	0.140	↑
Fatigue	61.1 (24.8)	69.6 (22.2)	0.032	↓
Nausea/Vomiting	17.3 (22.7)	21.7 (27.5)	0.435	↓
Pain	32.7 (30.0)	43.4 (31.9)	0.031	↓
Dyspnea	30.7 (33.2)	33.3 (29.4)	0.414	↓
Insomnia	40.8 (34.3)	41.8 (30.7)	0.720	↓
Appetite loss	51.3 (37.1)	64.3 (36.7)	0.025	↓
Constipation	19.9 (31.2)	19.5 (31.8)	0.841	↓
Diarrhea	24.7 (36.4)	37.1 (37.4)	0.022	↓
Financial problems	22.8 (29.4)	21.5 (33.3)	0.463	↓
Pancreatic pain	34.0 (23.6)	40.6 (23.8)	0.077	↓
Digestive symptoms	58.2 (32.4)	64.8 (29.0)	0.232	↓
Altered bowel habit	42.2 (30.4)	42.9 (32.3)	0.989	↓
Hepatic	18.0 (24.1)	10.2 (17.5)	0.041	↓
Body image	47.2 (33.8)	50.4 (32.7)	0.517	↓
Satisfaction with health care	78.7 (26.6)	82.7 (24.8)	0.381	↑
Sexuality	49.5 (38.6)	42.4 (41.3)	0.338	↓

*Wilcoxon-test.
↑, higher is better; ↓, lower is better.