The Effect of Pylorus Removal on Delayed Gastric Emptying after Pancreaticoduodenectomy: A Meta-Analysis of 2,599 Patients

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Abstract

Background: Delayed gastric emptying is a serious complication of pancreaticoduodenectomy. The effect of pylorus removal on delayed gastric emptying has not been well evaluated.

Study Design: We searched five databases (PubMed, EMBASE and the Cochrane Central Register of Controlled Trials, Scopus and Web of Science) up to July 2014. The meta-regression analysis was performed to evaluate any factors accountable for the heterogeneity. Publication bias was assessed by Egger’s test, and corrected by Duval’s trim and fill method. Subgroup analyses were conducted for different surgical techniques of pyloric removal. Other intraoperative and postoperative parameters were compared between two groups.

Methods: We included 27 studies involving 2,599 patients, with a moderate-high heterogeneity for primary outcome ($I^2 = 63\%$). Meta-regression analysis showed that four variables primarily contributed to the heterogeneity, namely nasogastric tube intubation time, solid food start time, preoperative diabetes percentage and the number of patients in pylorus-preserving group. After excluding four studies, the remaining twenty-three studies showed reduced heterogeneity ($I^2 = 51\%$). Then we used Duval’s trim and fill method to correct publication bias. The corrected MH odds ratio was 0.78 (95% CI: 0.52–1.17). A subgroup analysis showed that pylorus removal tends to reduce delayed gastric emptying incidence for subtotal stomach-preserving pancreaticoduodenectomy or pylorus-rectecting pancreaticoduodenectomy, compared with pylorus-preserving group. However, standard Whipple procedure failed to show any significant reduction of DGE compared with pylorus-removal group. No significant differences were observed in terms of length of hospital stay, infection and pancreatic fistula; however, pylorus removal resulted in longer operation time, more blood loss and higher mortality.

Conclusion: The pylorus removal does not significantly reduce the overall incidence of delayed gastric emptying. Subtotal stomach-preserving pancreaticoduodenectomy or pylorus-rectecting pancreaticoduodenectomy tends to reduce delayed gastric emptying incidence, but needs further validation.

Introduction

Pancreaticoduodenectomy is an important surgical intervention for periampullary diseases. According to resection extent of pyloric region, pancreaticoduodenectomy uses either pylorus-preserving or pylorus-removing procedures. Specifically, pylorus-preserving pancreaticoduodenectomy (PPPD) preserves all of the stomach and part of the proximal duodenum [1,2]. On the contrary, pylorus-removing pancreaticoduodenectomy (PRPD) includes different surgical techniques, namely the standard Whipple procedure (SWP), subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) and pylorus-rectecting pancreaticoduodenectomy (PrPD). SWP usually resects the pylorus along with 30–40% of the distal stomach [3]. SSPPD and PrPD involve the resection of the pyloric ring together with 2–3 cm of the distal stomach and preserve the majority of the stomach [3,4].

Delayed gastric emptying (DGE) is a serious postoperative morbidity of pancreaticoduodenectomy. DGE may prolong hospital stay, compromise the quality of life, and impair long-term nutrition status. The International Study Group of Pancreatic Surgery (ISGPS) has proposed a grading system to categorize different level of severity of DGE. ISGPS grade B/C DGE usually has more clinical impacts since it might change the postoperative clinical management. In additional, ISGPS grade C DGE are more frequently seen with other postoperative complications [5,6].

It is believed that postoperative pyloric dysfunction will predispose a patient to DGE. Pancreaticoduodenectomy may
cause pyloric dysfunction due to the devascularization and denervation of the pyloric region. Inadequate blood supply that leads to ischemic gastroparesis is one of the mechanisms that may cause DGE [7]. Pyloric denervation, such as vagal nerve injury, may cause pylorospasm and DGE [8]. The preservation of blood supply and innervation of the pyloric region or the dilatation of the pylorus may reduce the incidence of DGE [9,10].

Previously meta-analyses [11–13] have compared the PPPD with SWP, and one recent meta-analysis analyzed the intraoperative and postoperative outcomes of several randomized controlled trials (RCTs) [14]. As for DGE, all of the meta-analyses indicated a high heterogeneity among studies. In fact, many preoperative and postoperative factors might influence incidence of DGE, including preoperative diabetes, pancreatic fistula, postoperative complications, preoperative biliary drainage, and method of reconstruction. These variables may account for the observed heterogeneity across individual studies [15]. In addition, the variations in the surgical techniques, specifically the proportion of the stomach that is resected during PRPD, may be a confounding variable; therefore, further subgroup analyses are needed.

In this study, we systematically evaluated the following questions: 1) Whether pyloric ring removal reduces the overall incidence of DGE; 2) The factors that contribute to the overall heterogeneity among studies; and 3) Whether the variations in the surgical techniques (PrPD/SSPPD versus SWP) lead to different results with regard to the incidence of DGE.

### Materials and Methods

**Review Strategy and Quality Assessment**

The review process was adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [16]. The literature search strategy and eligibility criteria for inclusion and exclusion of studies and study outcomes were specified in advance to avoid bias. We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus and Web of Science for studies published up until July 2014, without restrictions placed on the language or publication date. The search strategy was as follows:

**PubMed**: ‘pancreaticoduodenectomy’ AND (‘pyloric’ OR ‘pylorus’) [in Title/Abstract]

**EMBASE**: ‘pancreaticoduodenectomy’ AND (‘pyloric’ OR ‘pylorus’) [in Keywords with ‘Map Term to Subject Heading’]

**CENTRAL** and **Scopus**: ‘pancreaticoduodenectomy’ AND (‘pyloric’ OR ‘pylorus’) [in Title, Abstract, Keywords]

**Web of Science**: ‘pancreaticoduodenectomy’ AND (‘pyloric’ OR ‘pylorus’) [in Topic]

All abstracts were retrieved and reviewed independently by two authors according to the eligibility criteria (listed below). A third author supervised the review process and settled disagreements on the study inclusion. To determine the inconsistency between reviewers, an inter-reviewer reliability analysis was conducted using a kappa statistic. If a study was included, the full-text of the article was retrieved and the relevant data were extracted. If additional data were considered to be necessary, the reviewers would contact the authors of the original articles. We evaluated the quality and the risk of bias of nonrandomized studies using the Newcastle-Ottawa quality assessment tool [17].

### Eligibility Criteria

Inclusion and exclusion criteria were pre-defined to avoid bias.

**Inclusion criteria.** (1) Studies had to feature a comparison between PRPD and PPPD; and (2) the sample size in each surgical procedure should be greater than 10 patients.

**Exclusion criteria.** (1) Only data from a single group of patients (either PRPD or PPPD) were reported; (2) the incidence of DGE was not reported; or (3) the article was published in the form of a case report, review article, letter to the editor, editorial or conference abstract.

### Outcomes

**Primary outcomes.** (1) Incidence of DGE

Definition: An International Study Group of Pancreatic Surgery (ISGPS) grade of DGE B/C was calculated for studies that followed the scoring system of the ISGPS [6]. For those studies that did not use the ISGPS scoring system, the overall incidence of DGE was considered.

**Secondary outcomes.** (1) Blood loss, (2) operation time, (3) length of hospital stay, (4) mortality, (5) pancreatic fistula, and (6) infection.

### Statistical Analysis

For the baseline characteristics, we applied the **Chi-squared test** for categorical variables and Student’s *t*-test for continuous variables. The mean and standard deviation (S.D.) of the continuous variables were estimated using the median, range and the number of patients [18]. *P*-values less than 0.05 were considered statistically significant. With respect to the outcomes, data from the original articles were extracted and analyzed using the Review Manager 5.1 software (Cochrane Collaboration). The $I^2$ index was used as an indicator of the between-study heterogeneity.

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**Figure 1. Flowchart of the literature search and studies inclusion.** Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials. doi:10.1371/journal.pone.0108380.g001
Table 1. Clinical characteristics of the included studies.

| First author | Publication year | Study design | Surgical techniques of PRPD group | DGE definition | Gender (M: F) | Age (Mean ± S.D.) |
|--------------|------------------|--------------|-----------------------------------|----------------|--------------|------------------|
| Akizuki [4]  | 2008             | PNR          | SSPPD                             | NGT ≥ POD 10 or Solid food ≥ POD 14 | 18, 12       | 65±10            | 66±13            | 0.56            |
| Di Carlo [21]| 1999             | PNR          | SWP                               | NGT ≥ POD 10 or Vomiting ≥ POD 10 | 24, 15       | 61.1±8.8        | 62.0±8.3         | 0.59            |
| Duffy [22]   | 2003             | Retro        | SWP                               | NGT ≥ POD 7 or Oral Intake ≥ POD 7 | 14, 9        | 67.3±9.3        | 67.3±14.0        | 1.00            |
| Fujii [23]   | 2012             | Retro        | SSPPD SWP                         | ISGPS Grade B/C | 74, 51       | 63.7±7.3        | 63.8±12.0        | 0.95            |
| Gao [24]     | 2007             | Retro        | SWP                               | NGT ≥ POD 10 or Solid food ≥ POD 14 | 64, 40       | 58.2±11.9       | 58.4±14.5        | 0.93            |
| Hackert [25] | 2013             | PNR          | PPDP                              | ISGPS Grade B/C | 22, 18       | 65.0±10.0       | 65.0±10.0        | 1.00            |
| Hayashibe [26]| 2007            | Retro        | SSPPD                             | NGT ≥ POD 10 or Oral Intake ≥ POD 14 | 8, 13        | 64.3±9.5        | 60.9±8.5         | 0.40            |
| Hoem [27]    | 2012             | PNR          | SWP                               | NGT ≥ POD 7 or Regular diet ≥ POD 14 | 22, 16       | 69.5±9.8        | 66.0±12.3        | 0.17            |
| Horstmann [28]| 2004            | PNR          | SWP                               | NGT ≥ POD 7 or Regular diet ≥ POD 14 | 62, 59       |                 |                 |                |
| Jimenez [29] | 2000             | Retro        | SWP                               | Oral intake ≥ POD 14 | 16, 17       | 50.0±15.5       | 45.0±15.8        | 0.18            |
| Kawai [3]    | 2011             | RCT          | PPDP                              | ISGPS Grade B/C | 38, 28       | 67±9            | 68±9             | 0.58            |
| Kurahara [30]| 2010             | Retro        | SSPPD                             | ISGPS Grade B/C | 38, 26       | 66.8            | 66.4             | 0.24            |
| Lin [31]     | 2005             | RCT          | SWP                               | NGT ≥ POD 10   | 13, 6        | 66.7±9.5        | 64.5±8.5         | 0.50            |
| Makhija [32] | 2002             | PNR          | SWP                               | NGT ≥ POD 7    | 22, 18       | 66.0±10.0       | 66.0±8.5         | 1.00            |
| Matsumoto [19]| 2014            | RCT          | SSPPD                             | ISGPS Grade B/C | 35, 15       | 67±9            | 66±10            | 0.81            |
| Mosca [33]   | 1997             | Retro        | SWP                               | NGT ≥ POD 14   | 15, 12       | 66.6±12         | 68±8             | 0.56            |
| Nanashima [34]| 2013            | Retro        | SSPPD                             | ISGPS Grade B/C | 15, 12       | 66.5±12         | 68.8±13          | 0.30            |
| Paquet [35]  | 1998             | RCT          | SWP                               | NGT > POD 7    | 15, 12       | 66.0±12         | 68±8             | 0.56            |
| Patel [36]   | 1995             | Retro        | SWP                               | Oral fluids ≥ 7 POD | 28, 24       | 63.0±15.0       | 61.3±13.6        | 0.70            |
| Pirro [37]   | 2002             | Retro        | SWP                               | NGT > POD 7    | 28, 24       | 63.0±15.0       | 61.3±13.6        | 0.70            |
| Roder [38]   | 1992             | PNR          | SWP                               | NGT > POD 5    | 32, 30       | 60.0±12.5       | 64.0±9.5         | 0.07            |
| Sellier [39] | 2005             | RCT          | SWP                               | NGT > POD 5    | 33, 33       | 65.0±13.2       | 64.8±14.3        | 0.30            |
| Srinarmwong [40]| 2008         | RCT          | SWP                               | NGT ≥ POD 10 or Regular diet ≥ POD 90 | 8, 5         | 62.5±5.8        | 62.2±6.6         | 0.93            |
| Takahashi [41]| 1999            | Retro        | SWP                               | NGT ≥ POD 10 or Regular diet ≥ POD 14 | 11, 6        | 65.0±12.6       | 69.3±8.8         | 0.15            |
| Tani [42]    | 2009             | Retro        | SWP                               | NGT ≥ POD 10 or Regular diet ≥ POD 14 | 11, 6        | 65.0±12.6       | 69.3±8.8         | 0.15            |
heterogeneity. We used meta-regression to identify potential variables causing the heterogeneity. The meta-regression analysis and Duval's trim and fill correction were conducted by Comprehensive Meta Analysis Version 2.2 (Biostat, Englewood, NJ, USA). For meta-regression analyses, the factors were predefined. All of the following factors were previously reported to influence the incidence of DGE and were thus used as variables: preoperative diabetes, pancreatic fistula, postoperative complications, preoperative biliary drainage, method of reconstruction, percentage of malignancies, DGE evaluation method, nasogastric tube (NGT) intubation and solid food start time for the conventional method, and the use of prokinetic medicine [15,19,20]. Other common variables that were also routinely included were publication year, study design, total patient number, patient number in PRPD group, patient number in PPPD group, blood loss, operation time and infection. Subgroup analyses were conducted to assess the different surgical techniques of PRPD.

Results

Literature Search

Our search strategy yielded 4,076 abstracts from the aforementioned five databases. After the exclusion of duplications, two reviewers independently reviewed 2,055 abstracts. In this step, case reports, review articles, letters to the editor, editorials and conference abstracts were excluded. Abstracts that did not compare PRPD with PPPD or that did not report the incidence of DGE were also excluded. Thus, twenty-seven original articles were included, and the full-text of the manuscripts were read and evaluated [3,4,19,21–44]. Finally, we included all twenty-seven studies for this systematic review and meta-analysis with an inter-reviewer reliability of kappa = 0.978 (P <0.001) (Figure 1).

2,599 patients were included (1,289 who underwent PRPD and 1,310 who underwent PPPD). The publication year ranged from 1992 to 2014. Seven studies were RCTs, eight studies were prospective nonrandomized studies, and another twelve studies were retrospective ones. Nineteen studies featured SWP as a procedure for the pyloric removal group; five studies used SSPPD, and two studies used PrPD. One study [23] featured both SSPPD and SWP as PRPD. The definition of DGE varied across the studies; therefore, we listed the detailed information for each in Table 1. The gender and age of patients in the two groups were not significantly different.

For nonrandomized studies, a modified table that included the key components of the Newcastle-Ottawa quality assessment tool was employed to assess the quality and the risk of publication bias [17,45]. The modified table focused on the representativeness, comparability, ascertainment of exposure and follow-up. The overall bias was also estimated at the end of the table (Table S1).

Primary Outcomes

The overall DGE incidence of PRPD to PPPD was not significantly different. First, we analyzed the effect of pyloric removal for all included studies. The $I^2$ index was 63%, which indicated that heterogeneity was moderate to high. We used meta-regression to explore the potential variables that might account for the heterogeneity. We used method of movement as the calculation method and considered a variable to be significant if the $P$ value in ‘Model’ section was less than 0.05 (Table 2). Four variables showed statistical significance for the meta-regression, which were patient number in PPPD group, presence of...
preoperative diabetes, NGT intubation time and solid food start time. For each variable, we aimed to identify studies that might contribute to the heterogeneity. Two studies [26,34] featured a longer NGT intubation period and solid food start time. In detail, the NGT intubation time was over POD 11 and the solid food start time was over POD 15 for these two studies. One of them [34] also had a higher rate of preoperative diabetes, with 67.3% of total patients diagnosed of diabetes. We also sequentially removed studies with the smallest number of participants in PPPD group. Three studies [26,31,40] was removed, with PPPD patient number of 12, 14 and 14, respectively. Therefore, four studies [26,31,34,40] were removed from further analysis with a reduced of 12, 14 and 14, respectively. Therefore, four studies [26,31,34,40] were removed from further analysis with a reduced heterogeneity ($I^2 = 51\%$).

The remaining 23 studies were included in the meta-analysis using a random-effect model. The MH odds ratio was 0.61 (95% CI: 0.41–0.88; $P<0.01$) (Figure 2A). However, publication bias was detected by Egger’s test ($P = 0.05$). Then, Duval’s trim and fill method was used to correct the result (Figure 2B). Six potential missing studies were replaced to the right of the mean odds ratio, which were illustrated as black dots. The MH odds ratio was 0.78 (95% CI: 0.52–1.17) after correction. Therefore, we concluded that the removal of the pylorus did not reduce the overall incidence of DGE.

Next, we wanted to evaluate whether different surgical techniques within the PRPD group would have different impacts on DGE. The PRPD group contained three different surgical techniques, namely SSPPD, PrPD and SWP. Two of them, SSPPD and PrPD, were similar, because both preserve the majority of the stomach. In contrast, SWP usually resects 20–40% of the stomach volume. Therefore, we conducted subgroup analyses of SWP, SSPPD, PrPD and SSPPD/PrPD, respectively.

### Table 2. Meta-regression for variables that influence the incidence of DGE.

| Variables                          | Model (Qmodel) | P value | Residual (Qresid) | P value |
|------------------------------------|----------------|---------|------------------|---------|
| Study Design (Randomized Versus Nonrandomized) | 0.011           | 0.912   | 28.964           | 0.266   |
| Surgery Type (SWP Versus SSPPD/PrPD) | 3.320           | 0.068   | 30.248           | 0.215   |
| Method of Reconstruction (Antecolic versus Retrocolic) | 1.100           | 0.294   | 9.571            | 0.386   |
| DGE Evaluation Method (Whether using ISGPS Grading System) | 3.583           | 0.058   | 29.820           | 0.231   |
| Prokinetic Medicine Usage (Whether routinely used)* | NA             | NA      | NA               | NA      |
| Total Patients Number              | 2.674           | 0.102   | 27.974           | 0.309   |
| Patients Number in PRPD group      | 0.176           | 0.675   | 28.359           | 0.292   |
| Patients Number in PPPD group      | 5.534           | 0.019   | 28.956           | 0.266   |
| Publication Year                    | 0.655           | 0.419   | 29.573           | 0.241   |
| Operation Time                     | 2.353           | 0.125   | 18.219           | 0.197   |
| Blood Loss                         | 0.126           | 0.722   | 17.224           | 0.244   |
| Percentage of Malignancies         | 0.068           | 0.793   | 27.095           | 0.300   |
| Pancreatic Fistula                  | 2.018           | 0.155   | 28.096           | 0.256   |
| Infection                          | 0.013           | 0.908   | 25.957           | 0.302   |
| Postoperative Complications        | 0.084           | 0.771   | 26.731           | 0.268   |
| Preoperative Diabetes              | 10.271          | 0.001   | 4.861            | 0.431   |
| Preoperative Biliary Drainage      | 0.087           | 0.767   | 3.364            | 0.339   |
| NGT Intubation Period              | 4.104           | 0.043   | 7.442            | 0.490   |
| Solid Food Start Time for Conventional Methods† | 3.864           | 0.049   | 8.302            | 0.504   |

*Only one study reported the routine use of prokinetic medicine, and thus the meta-regression for this variable could not be conducted.
†Solid food start days were obtained from the original publications or from the authors. If this parameter was not available, the mean days solid food in the PPPD (the conventional method) group was used.

Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PrPD, pylorus-resecting pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; SWP, Standard Whipple procedure; NGT, Nasogastric tube.

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The DGE incidence of SWP to PPPD was not significantly different. With respect to SWP, eighteen studies were included. The MH odds ratio was 0.64 (95% CI: 0.40–1.00; $P = 0.05$, random-effect model) with moderate heterogeneity ($I^2 = 57\%$) (Figure 3A). Although publication bias was not significant by Egger’s test ($P = 0.069$), Duval’s trim and fill method could replace four missing studies to the right of the mean odds ratio (Figure 3B). After correction, the MH odds ratio was 0.85 (95% CI: 0.53–1.38).

The DGE incidence of SSPPD to PPPD was significantly different. With respect to SSPPD, four studies were included. The MH odds ratio was 0.46 (95% CI: 0.25–0.83; $P = 0.01$, fixed-effect model) with little heterogeneity ($I^2 = 24\%$) (Figure 3C). No significant publication bias was detected by Egger’s test ($P = 0.56$). The removal of the pylorus did reduce the incidence of DGE after SSPPD compared with PPPD.

The DGE incidence of PrPD to PPPD was significantly different. With respect to PrPD, only two studies were included. The MH odds ratio was 0.31 (95% CI: 0.11–0.91; $P = 0.03$, fixed-effect model) with little heterogeneity ($I^2 = 0\%$) (Figure 3D). Egger’s test was not conducted due to the low number of included studies. The removal of the pylorus did reduce the incidence of DGE after PrPD compared with PPPD.

The DGE incidence of SSPPD/PrPD to PPPD was significantly different. With respect to SSPPD/PrPD, six
studies were included. The MH odds ratio was 0.41 (95% CI: 0.25–0.70; \(P\) < 0.01, fixed-effect model) with little heterogeneity \(I^2 = 0\)% (Figure 3E). No significant publication bias was detected by Egger’s test \(P = 0.77\). The removal of the pylorus did reduce the incidence of DGE after SSPPD/PrPD compared with PPPD.

### Secondary Outcomes

PRPD significantly increased blood loss (Figures S1), operation time (Figures S2) and mortality (Figures S4). Other parameters, including length of hospital stay (Figures S3), pancreatic fistula (Figures S5) and infection (Figures S6), were not significantly different between the PRPD and PPPD groups. Detailed information was summarized in Table 3.
Discussion

DGE prolongs the hospitalization and the quality of life of patients. The removal of the pylorus is believed to influence the incidence of DGE, because postoperative pyloric dysfunction could occur secondary to devascularization and denervation [7,8,46]. Whether the removal of additional area of the pylorus during PPPD reduces the incidence of DGE has been investigated by several studies and is a matter of debate. It is necessary to realize that DGE is affected by various confounding factors, such as the route of reconstruction, prokinetic drug usage and the postoperative recovery program [3,47,48]. Different studies may not be consistent with respect to these factors, which would increase heterogeneity across studies. In contrast, a single study may suffer from an inadequate number of patients needed to reach adequate statistical power. Therefore, it is critical to identify the major confounding factors that would explain the heterogeneity. The subsequent analysis would be possible and meaningful after the exclusion of studies most accountable for the heterogeneity.

We first tested the heterogeneity concerning the incidence of DGE, which was moderate-high. To explore the potential variables, we conducted meta-regression analyses for the list of nineteen variables. Four of them showed statistical significance for the meta-regression. A longer solid food start time or NGT intubation time was associated with a greater reduction of DGE in the RPPD, compared with the PPPD group. In fact, the solid food start time was an important indicator of postoperative management. Balzano et al reported that the incidence of DGE would reduce for fast-track recovery program compared with the conventional method after pancreaticoduodenectomy [48]. Therefore, whether an additional resection of the pylorus could reduce the incidence of DGE should be evaluated within studies with a similar solid food start time and NGT intubation time. Another confounding factor, preoperative diabetes, has also been reported as a risk factor for DGE by a recent meta-analysis [13]. As for the number of patients in PPPD group, we sequentially excluded studies with the smallest patient number. When we excluded the studies with fewer than 15 patients, the patient number was no longer significantly contributed to the overall heterogeneity of DGE. In summary, four studies were excluded after meta-regression analysis, and a 12% reduction of $I^2$ index was achieved by the exclusion. A meta-analysis of the remaining 23 studies showed no significantly difference whether or not the pylorus was removed.

Next, we were interested in the different surgical techniques within the PRPD group. The major difference lay in the resected proportion of the stomach. The SSPPD and PrPD procedures only involve the resection of a relatively small portion of the pyloric stomach compared with SWP. SSPPD and PrPD are intended to preserve the pooling ability of the stomach [4]. Because DGE is closely related to stomach function, different surgical techniques in the PRPD group should be analyzed separately. A subgroup analysis showed that SSPPD, PrPD and SSPPD/PrPD, but not SWP, reduced the incidence of DGE. We interpreted the results in the following ways: 1) Preservation of the majority of stomach during the resection of the pylorus may help reduce the incidence of DGE; and 2) Because the SSPPD group only had four studies, PrPD group only contained only two studies, these results should be interpreted with cautions. More studies are needed to validate the results.

As for secondary outcomes, PRPD tended to involve a longer operation time, more blood loss and a higher mortality rate. However, the length of hospital stay was not significantly different. Similarly, the incidence of pancreatic fistula and infection was not significantly different between the two groups.

We acknowledged that our meta-analysis has several limitations. First, only four and two studies in SSPPD and PrPD group, respectively; therefore, the conclusion that removal of additional portions of the pylorus would significantly reduce the incidence of DGE after SSPPD or PrPD needs to be validated by more well-designed, prospective randomized studies with adequate patient sample sizes. Second, studies included in this meta-analysis were more non-RCTs than RCTs; therefore, cautions should be taken when interpreting the results from the analysis. We expect better designed studies to address whether or not SSPPD or PrPD will truly reduce DGE incidence.

In conclusion, this meta-analysis shows that pylorus removal doesn’t reduce the overall incidence of DGE, compared with pylorus-preservation procedure. Subgroup analysis shows that pylorus removal may reduce the incidence of DGE when patients undergo SSPPD or PrPD. However, pylorus removal doesn’t

### Table 3. Outcomes of blood loss, operation time, and length of hospital stay, mortality, pancreatic fistula and infection after PRPD versus PPPD.

| Outcomes                  | No. Patients | No. Studies | Risk Difference/ Mean Difference (95% CI) | P value | $I^2$ index |
|---------------------------|--------------|-------------|------------------------------------------|---------|-------------|
| Blood Loss                | 1417         | 16          | 273 (129, 418)                           | <0.01   | 67%         |
| Operation Time            | 1408         | 16          | 35.6 (17.3, 53.9)                        | <0.01   | 75%         |
| Length of Hospital Stay   | 1262         | 13          | 0.05 (−1.74, 1.85)                       | 0.95    | 43%         |
| Mortality                 | 2487         | 26          | 0.02 (0.00, 0.03)                        | 0.02    | 0%          |
| Pancreatic Fistula        | 2467         | 26          | 0.00 (−0.03, 0.03)                       | 0.96    | 41%         |
| Infection                 | 2229         | 24          | 0.01 (−0.01, 0.04)                       | 0.29    | 0%          |

Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy.

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significantly reduce the incidence of DGE when patients undergo SWP.

**Supporting Information**

**Figure S1** Forest plot of blood loss for included studies. Blood loss is significant more in PRPD than PPPD. Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy. (TIF)

**Figure S2** Forest plot of operation time for included studies. Operation time is significant longer in PRPD than PPPD. Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy. (TIF)

**Figure S3** Forest plot of length of hospital stay for included studies. There is no significant difference between PRPD and PPPD. Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy. (TIF)

**Figure S4** Forest plot of mortality for included studies. Mortality incidence is significant higher in PRPD than PPPD. Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy. (TIF)

**Figure S5** Forest plot of pancreatic fistula for included studies. There is no significant difference between PRPD and PPPD. Abbreviations: PRPD, pylorus-removing pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy. (TIF)

**References**

1. Traverso L, Longmire W Jr. (1978) Preservation of the pylorus in pancreaticoduodenectomy. Surgery, gynecology & obstetrics 146: 959–962.
2. Watson K. (1944) Carcinoma of ampulla of vater successful radical resection. British Journal of Surgery 31: 368–373.
3. Kawai M, Tani M, Hiroso S, Miyazawa M, Shimizu A, et al. (2011) Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreaticoduodenectomy: a prospective, randomized, controlled trial of pylorus-respecting versus pylorus-preserving pancreaticoduodenectomy. Ann Surg 253: 495–501.
4. Azizkio E, Kimura Y, Nobeuska T, Inamur M, Nishidate T, et al. (2008) Prospective nonrandomized comparison between pylorus-preserving and subtotal stomach-preserving pancreaticoduodenectomy from the perspectives of DGE occurrence and postoperative digestive functions. J Gastrointest Surg 12: 1185–1192.
5. Schaefer M, Mullhaupt B, Clavien PA. (2002) Evidence-based pancreatic head resection for pancreatic cancer and chronic pancreatitis. Ann Surg 236: 137–148.
6. Wenne MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGSP). Surgery 142: 163–169.
7. Liberski SM, Koch KL, Anup RG, Stern RM. (1990) Ischemic gastroparesis: resolution after revascularization. Gastroenterology 99: 252–257.
8. Kim DK, Hindenburgh AA, Sharmas SK, Suk CH, Gress GF, et al. (2005) Is pylorospasm a cause of delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy? Ann Surg Oncol 12: 223–227.
9. Gavrin JM, Sarmiento JM, Sari MG. (2003) Pylorus-preserving pancreaticoduodenectomy with complete preservation of the pyloroduodenal blood supply and innervation. Arch Surg 138: 1261–1263.
10. Fischer CP, Hung JC. (2006) Method of pyloric reconstruction and impact upon delayed gastric emptying and hospital stay after pylorus-preserving pancreaticoduodenectomy. J Gastrointest Surg 10: 215–219.
11. Karanicolias PJ, Davies E, Kunr Z, Briel M, Koka HP, et al. (2007) The pylorus: take it or leave it? Systematic review and meta-analysis of pylorus-preserving versus standard whipple pancreaticoduodenectomy for pancreatic or periampullary cancer. Ann Surg Oncol 14: 1825–1834.
12. Iqbal N, Lovegrove RE, Tilsley HS, Abraham AT, Bhattacharya S, et al. (2008) A comparison of pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy: a meta-analysis of 2022 patients. Eur J Surg Oncol 34: 1237–1245.
13. Dieter Markus K, Fitzmaurice C, Schwarze G, Seiler Christopher M, Antes G, et al. (2011) Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periam- putary and pancreatic carcinoma. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd.
14. Yang G, Wu H-S, Chen X-L, Wang C-Y, Gou S-M, et al. (2014) Pylorus-Preserving Versus Pylorus-Resecting Pancreaticoduodenectomy for Periampullary and Pancreatic Carcinoma: A Meta-Analysis. PLoS one 9: e90316.
15. Qu H, Sun GR, Zhou SQ, He Q. (2013) Clinical risk factors of delayed gastric emptying in patients after pancreaticoduodenectomy: a systematic review and meta-analysis. Eur J Surg Oncol 39: 213–223.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotszche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339: b2700.
17. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, et al. (2000) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm/. Accessed March 2014.
18. Hoos SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5: 13.
19. Matsumoto I, Shimazeki M, Arai S, Goto T, Shirakawa S, et al. (2014) A prospective randomized comparison between pylorus- and subtotal stomach-preserving pancreaticoduodenectomy on postoperative delayed gastric emptying occurrence and long-term nutritional status. J Surg Oncol 109: 690–696.
20. Sato G, Ishizaki Y, Yoshimoto J, Sago H, Inamur M, et al. (2014) Factors influencing clinically significant delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. World J Surg 38: 968–975.
21. Di Carlo V, Zerbi A, Balzano G, Corso V. (1999) Pylorus-preserving pancreaticoduodenectomy versus conventional whipple operation. World J Surg 23: 920–923.
22. Duff JP, Hines OJ, Lai JH, Ko CY, Cortina G, et al. (2003) Improved survival for adenocarcinoma of the ampulla of Vater: Fifty-five consecutive resections. Archives of Surgery 138: 941–950.
23. Fujii T, Kanda M, Kodera Y, Nagaï S, Sahin TT, et al. (2012) Preservation of the pyloric ring has little value in surgery for pancreatic head cancer: a comparative study comparing three surgical procedures. Ann Surg Oncol 19: 176–183.
24. Gao HQ, Yang YM, Zhuang Y, Wang WM, Wu WH, et al. (2007) Influencing factor analysis of delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. Zhonghua Wai Ke Za Zhi 45: 1048–1051.
25. Hacken T, Hinuz U, Hartwig W, Strobel O, Fritz S, et al. (2013) Pylorus resection in partial pancreaticoduodenectomy: impact on delayed gastric emptying. Am J Surg 206: 296–299.
26. Hayashi A, Kameyama M, Shinbo M, Makimoto S (2007) The surgical procedure and clinical results of subtotal stomach preserving pancreaticoduodenectomy (SSPPD) in comparison with pylorus preserving pancreaticoduodenectomy (PPPD). J Surg Oncol 95: 106–109.

27. Hoem D, Viste A (2012) Improving survival following surgery for pancreatic ductal adenocarcinoma - a ten-year experience. Eur J Surg Oncol 38: 245–251.

28. Horstmann O, Markus PM, Ghadimi MB, Becker H (2004) Pylorus preservation has no impact on delayed gastric emptying after pancreatic head resection. Pancreas 28: 69–74.

29. Jimenez RE, Fernandez-del Castillo C, Rattner DW, Chang Y, Warshaw AL (2000) Outcome of pancreaticoduodenectomy with pylorus preservation or with antrectomy in the treatment of chronic pancreatitis. Ann Surg 231: 293–300.

30. Kurahara H, Takao S, Shiuchi H, Matala Y, Maemura K, et al. (2010) Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) prevents postoperative delayed gastric emptying. J Surg Oncol 102: 615–619.

31. Lin PW, Shao YS, Lin YJ, Hung CJ (2005) Pancreaticoduodenectomy for pancreatic head cancer: PPPD versus Whipple procedure. Hepatogastroenterology 52: 1601–1604.

32. Makhlai R, Tsai P, Kingswoth A (2002) Pylorus-preserving pancreaticoduodenectomy with Billroth I type reconstruction: a viable option for pancreatic head resection. J Hepatobiliary Pancreat Surg 9: 614–619.

33. Mosca F, Giulianotti PC, Balestracci T, Di Candio G, Pietrabissa A, et al. (1997) Long-term survival in pancreatic cancer: pylorus-preserving versus Whipple pancreaticoduodenectomy. Surgery 122: 553–566.

34. Nanashima A, Abe T, Sunada Y, Tobinaga S, Nomura T, et al. (2013) Comparison of results between pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy: report at a single cancer institute. Hepatogastroenterology 60: 1102–1108.

35. Paquet KJ (1998) Comparison of Whipple's pancreaticoduodenectomy with the pylorus-preserving pancreaticoduodenectomy - a prospectively controlled, randomized long-term trial. Chirurgische Gastroenterologie 14: 34–58.

36. Patel AG, Tsyama MT, Kuske AM, Alexander P, Ashley SW, et al. (1995) Pylorus-preserving Whipple resection for pancreatic cancer. Is it any better? Arch Surg 130: 838–842; discussion 842–833.

37. Pirro N, Sizenzof I, Cesari J, Consentino B, Greer R, et al. (2002) Pancreaticoduodenectomy for adenocarcinoma of the head of pancreas: does the pylorus-preserving change morbidity and prognosis? Annales De Chirurgie 127: 95–100.

38. Roder JD, Stein HJ, Hurtl W, Siewert JR (1992) Pylorus-preserving versus standard pancreatico-duodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 79: 152–153.

39. Seiler CA, Wagner M, Bachmann T, Redell CA, Schmid B, et al. (2005) Randomized clinical trial of pylorus-preserving duodenumpancreatectomy versus classical Whipple resection-long term results. Br J Surg 92: 547–556.

40. Sirnarawong C, Luechakiettisak P, Prasitvili W (2008) Standard whipple’s operation versus pylorus preserving pancreaticoduodenectomy: a randomized controlled trial study. J Med Assoc. Thai 91: 693–698.

41. Takahashi S, Iwata K, Saitou J, Hayatsu S, Hosimoto S, et al. (1999) PyIPPD and PD for advanced carcinoma of the head of the pancreas. Japanese Journal of Gastroenterological Surgery 32: 2427–2431.

42. Tani M, Kawai M, Hiroo S, Ina S, Miyazawa M, et al. (2009) Pylorus-preserving pancreaticoduodenectomy versus conventional pancreaticoduodenectomy for pancreatic adenocarcinoma. Surg Today 39: 219–224.

43. Tran KTC, Smeenk HG, van Eijck CHJ, Kazemier G, Hop WC, et al. (2004) Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure - A prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Annals of Surgery 240: 738–745.

44. van Berge Henegouwen MI, van Gulik TM, DeWit LT, Alleme JH, Raans EA, et al. (1997) Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 260 consecutive patients. J Am Coll Surg 185: 373–379.

45. Yin Z, Fan X, Ye H, Yin D, Wang J (2013) Short- and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. Ann Surg Oncol 20: 1203–1215.

46. Kurosaki I, Hatakeyama K (2005) Preservation of the left gastric vein in delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. J Gastrointest Surg 9: 846–852.

47. Ohwada S, Satoh Y, Kawate S, Yamada T, Kawamura O, et al. (2001) Low-dose erythromycin reduces delayed gastric emptying and improves gastric motility after Billroth I pylorus-preserving pancreaticoduodenectomy. Ann Surg 234: 668–674.

48. Balzano G, Zerbi A, Braga M, Rocchetti S, Benedice AA, et al. (2008) Fast-track recovery programme after pancreatico-duodenectomy reduces delayed gastric emptying. Br J Surg 95: 1387–1393.