Original Article

Clinical outcomes of pancreaticoduodenectomy for pancreatic ductal adenocarcinoma depending on preservation or resection of pylorus

Yeon Jin Kim, Sang Hyun Shin, In Woong Han, Youngju Ryu,
Naru Kim, Dong Wook Choi, and Jin Seok Heo

*Division of Hepatobiliary-Pancreatic Surgery, Department of Surgery, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Seoul, Korea*

Backgrounds/Aims: The comparative effectiveness of pylorus-resecting pancreaticoduodenectomy (PRPD) and pylorus-preserving pancreaticoduodenectomy (PPPD) in pancreatic head cancer is still disputed. The aim of this study was to analyze the data obtained from a large, single center with PPPD compared with PRPD in terms of postoperative outcomes, including blood glucose levels and survival in patients with pancreatic head cancer. **Methods:** Between January 2007 and December 2016, a total of 556 patients with pancreatic head cancer underwent either PPPD or PRPD. We analyzed the clinicopathologic data to assess short- and long-term outcomes retrospectively. **Results:** For underlying disease, patients with DM in PPPD were fewer than in PRPD (33.0% vs. 46.2%, p=0.002). The median value of CA19-9 was significantly higher in PRPD than in PPPD (129.36 vs. 86.47, p=0.037). The incidence of Clavien-Dindo grade III to V major complications in PPPD was significantly higher than in PRPD (20.4% vs. 13.4%, p=0.032). Resection of pylorus was shown to reduce complications in univariate and multivariate analyses (p=0.032 and = 0.021, respectively). The 5-year survival rates were 27.6% in the PPPD group and 22.4% in the PRPD group (p=0.015). **Conclusions:** The results of PPPD and PRPD showed no significant differences from those reported conventionally in previous studies. Although further well-designed studies are needed, it is more important to select the range of surgical resection for the patient's disease regardless of resection of pylorus. **(Ann Hepatobiliary Pancreat Surg 2020;24:269-276)**

Key Words: Pancreaticoduodenectomy; Pylorus-preserving pancreaticoduodenectomy; Pylorus-resecting pancreaticoduodenectomy; Pancreatic cancer

INTRODUCTION

Pancreaticoduodenectomy (PD) is the standard treatment recommended for patients with cancer of the head of the pancreas. Historically, Godivilla, an Italian surgeon, and Kausch, a German surgeon, are credited with the introduction of partial pancreaticoduodenectomy in 1898 and 1909, respectively. This procedure was improved by Whipple et al. in 1935. PD entails removal of the head of the pancreas, duodenum, common bile duct, gall bladder, and the distal portion of the stomach together with the adjacent lymph nodes.[1] PD includes both pylorus-resecting pancreaticoduodenectomy (PRPD) and pylorus-

preserving pancreaticoduodenectomy (PPPD). PRPD entails resection of pylorus, regardless of the extent of gastric resection. The side effects of PRPD are well known: partial gastric resection is associated with early and late dumping and weight loss after surgery.

PPPD is similar except that the functional pylorus is left at the gastric outlet.[2] It was first reported by Watson[3] in 1944. In the late 1970s, Traverso and Longmire reintroduced PPPD for chronic pancreatitis.[3] PPPD was expected to shorten the operating time but also improve the gastrointestinal function, because the intact gastric mechanism provides better nutrition over a long period of time and an intact pyloric sphincter reduces the incidence of

jejunal ulceration and dumping.[1] However, postoperative gastric function is affected adversely after PPPD via delayed gastric emptying (DGE). Gastric emptying mainly depends on intact vagal innervation to the antrum, mainly the nerves of Latarjet and vagus nerve branches.

Several studies suggest that the advantages and disadvantages of PRPD and PPPD depend on postoperative changes after procedure, and not simply on decisions to resect pylorus. The relative effectiveness of the procedures is still disputed. Therefore, the current study was intended to analyze the large clinical data involving PPPD compared with PRPD based on postoperative outcomes, including blood glucose levels, and survival of patients with pancreatic head cancer.

MATERIALS AND METHODS

Patient database

This study was retrospectively performed at the Samsung Medical Center to compare PPPD and PRPD in 556 patients with pancreatic head cancer between January 2007 and December 2016. Patients who did not undergo resection after exploration as well as patients who underwent palliative procedures such as gastroenteric bypass surgery were excluded. In this retrospective study, both PPPD and PRPD were not conducted randomly. Pylorus resection is only performed if the patient manifests pylorus invasion or aggressive disease. This study was approved by the institutional review board (Approval number: 2018-05-079) of the Samsung Medical Center. We reviewed the electronic medical records of 556 patients to retrieve clinical, pathological and surgical data. We included patient demographics such as age, body mass index (BMI), underlying diseases such as diabetes, history of cardiovascular disease (coronary heart disease, myocardial infarction, severe carotid stenosis or peripheral arterial occlusive disease), pulmonary disease (e.g., chronic obstructive pulmonary disease, interstitial lung disease), liver disease (e.g., liver cirrhosis, chronic hepatitis B or C), chronic kidney disease, and history of cerebrovascular disease (e.g., stroke, haemorrhage), and American Society of Anaesthesiology (ASA) score.[4] Starting from 2010, we included the criteria associated with revised microscopic resection margin: rR1 (revised grossly negative but microscopically positive resection margin) tumor present within

less than 1 mm from surgical margin.[5-7] Tumor differentiation was graded according to the nomenclature defined by the World Health Organization, and tumor, node, and metastasis (TNM) staging was classified according to the American Joint Committee of Cancer (AJCC) manual, 8th ed.[8] All patients were evaluated preoperatively using computed tomography (CT) with pancreatic protocol and magnetic resonance cholangiography (MRCP). In principle, patients diagnosed with pancreatic head cancer meeting resectable criteria were candidates for preoperative resection. When the patient was diagnosed with borderline resection of pancreatic head cancer, either surgery or neoadjuvant therapy was selectively administered.

Postoperative outcomes included length of hospital stay, major complications defined as Clavien-Dindo grades III to V,[9] and postoperative morbidity and mortality (within 90 days). Pancreatic fistula was defined according to the International Study Group for Pancreatic Fistula (ISGPF) 2016 classification,[10] and DGE according to the ISGPS 2007 definition.[11] In this study, DGE incidence was included from grade A.

All patients received proton pump inhibitor (PPI) prophylaxis against stress ulceration, and octreotide treatment was continued for 7 days. To determine whether the blood glucose level was adjusted after surgery, it was monitored every 6 hours after surgery and followed up until postoperative day 3. After PD, all patients underwent CT scan to evaluate surgical complications, including postoperative pancreatic fistula (POPF), on day 6 or 7 post-surgery. Survival data were obtained from the electronic medical records, and the follow-up period was measured from the time of initial treatment until death or the last follow-up examination. Patient follow-up was completed up to October 2018.

Statistical analysis

Categorical variables were presented by number and percentage, and continuous variables were reported as mean, median, and range whenever appropriate. The categorical variables were compared using χ^2 or linear-by-linear association test, and continuous variables were compared using the Student's t-test. Overall survival and comparison of univariable analyses were performed using the Kaplan−Meier method with the log-rank test. $p < .05$ was considered statistically significant. Multivariable analysis

of significant factors yielded results similar to univariable analysis conducted using the Cox proportional hazard model, which was used to calculate the hazard ratio with a 95% confidence interval (CI). All statistical analyses were carried out using IBM SPSS v 25.0 (SPSS, Inc, Chicago, IL).

RESULTS

Among 556 patients with pancreatic head cancer, 318 underwent PPPD and 238 underwent PRPD. Patient demographics are presented in Table 1. The proportion of men to women ranged from 54.7% to 45.3% and 67.2% to

32.8% in the PPPD and PRPD groups, respectively. The proportion of sex varied significantly between the two groups (*p*=0.003). There was no significant difference between the two groups for underlying disease except diabetes mellitus (DM). Patients with DM in PPPD were fewer than in PRPD (33.0% vs. 46.2%, *p*=0.002). Among tumor markers, the median value of CA19-9 was significantly higher in PRPD than in PPPD (129.36 vs. 86.47, *p*=0.037). Most intraoperative parameters were not significantly different but intraoperative transfusion in PPPD was less than in PRPD (9.4% vs. 15.5%, *p*=0.028). The number of patients who received neoadjuvant therapy in PPRD was higher than in PPPD (6.3% vs. 2.5%, *p*=0.027).

Table 1. Clinical characteristicsof patients undergoing pancreaticoduodenectomy

Variables	Total (n=556)	Pylorus-preserving surgery (n=318)	Pylorus-resecting surgery (n=238)	*p*
Age (years), mean (range)	62.56 (31-88)	62.11 (35-88)	63.17 (31-88)	0.177
Sex				0.003*
Male, n (%)	334 (60.1)	174 (54.7)	160 (67.2)	
Female, n (%)	222 (39.9)	144 (45.3)	78 (32.8)	
BMI (kg/m^2), mean (range)	22.72 (14.43-39.70)	22.80 (14.43-37.57)	22.61 (15.42-39.70)	0.385
Underlying disease				
Cardiology, n (%)	238 (42.8)	127 (39.9)	111 (46.6)	0.114
DM, n (%)	215 (38.7)	105 (33.0)	110 (46.2)	0.002*
Pulmonary, n (%)	53 (9.5)	33 (10.4)	20 (8.4)	0.433
Liver, n (%)	21 (3.8)	13 (4.1)	8 (3.4)	0.657
Brain, n (%)	24 (4.3)	10 (3.1)	14 (5.9)	0.116
CKD, n (%)	6 (1.1)	2 (0.6)	4 (1.7)	0.410
CEA (ng/ml), median (range)	2.87 (0.20-45.16)	1.91 (0.45-18.99)	3.17 (0.20-45.16)	0.351
CA19-9 (U/ml), median (range)	107.95 (1.00-117557.63)	86.47 (1.00-117557.63)	129.36 (1.00-22999.47)	0.037*
ASA score, n (%)				0.306
1	102 (18.3)	59 (18.6)	43 (18.1)	
2	396 (71.2)	232 (73.0)	164 (68.9)	
3	57 (10.3)	26 (8.2)	31 (13.0)	
4	1 (0.2)	1 (0.3)	0 (0)	
Intraop transfusion, n (%)	67 (12.1)	30 (9.4)	37 (15.5)	0.028*
EBL (ml), mean (range)	527.03 (50-5000)	483.11 (100-2650)	585.71 (50-5000)	0.104
Op duration (min), mean (range)	357.32 (138-748)	353.13 (138-620)	362.93 (145-748)	0.219
PV resection, n (%)	146 (26.3)	74 (23.3)	72 (30.3)	0.064
Soft pancreas, n (%)	110 (19.8)	82 (25.8)	28 (11.8)	<0.001*
P-duct size, n (%)	4.2 (0.5-25.0)	4.2 (1.0-25.0)	4.2 (0.5-19.0)	0.590
Postop initial BST (mg/dL), mean (range)	193.9 (49-370)	189.3 (49-370)	200 (51-365)	0.004*
Postop mean BST (mg/dL), mean (range)	182.22 (111.17-271.70)	180.12 (111.17-271.70)	185.15 (128.27-266.58)	0.043*
Neoadjuvant Tx, n (%)	23 (4.1)	8 (2.5)	15 (6.3)	0.027*
Adjuvant Tx, n (%)	339 (62.9)	197 (64.0)	142 (61.5)	0.554

BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; ASA, American Society of Anesthesiologists; Intraop, intraoperative; EBL, estimated blood loss; Op, operative; PV, portal vein; P-duct, pancreatic duct; Postop, postoperative; BST, blood sugar test; Tx, treatment
*indicates statistically significant values

Pathological findings are presented in Table 2. The status of resection margin was significantly different between the two groups: R1 including rR1 in PRPD group was higher than in PPPD (37.8% vs. 29.2%, *p*=0.033).

Postoperative outcomes were shown in Table 3. The incidence of major complications defined as Clavien-Dindo grades III to V in PPPD was significantly higher than in PRPD (20.4% vs. 13.4%, *p*=0.032).The major complications are listed in Table 4.

As shown in Table 5, univariate and multivariate analyses were used to identify risk factors affecting major complications (grade III or higher). Univariate analysis revealed 23 parameters as potential risk factors. Two factors were identified as possible severe complications after pancreaticoduodenectomy: liver disease (*p*=0.005) and ASA score greater than 3 (*p*=0.001). Multivariate logistic regression analysis revealed that two factors were also statistically significant. Resection of pylorus was shown to reduce complications in both univariate and multivariate analyses.

Fig. 1 shows the overall survival of PPPD and PRPD. The 5-year survival rates were 27.6% in the PPPD group

Table 2. Pathological characteristics

Variables	Total (n=556)	Pylorus-preserving surgery (n=318)	Pylrus-resecting surgery (n=238)	*p*
T Stage, n (%)				0.316
1	105 (18.9)	67 (21.1)	38 (16.0)	
2	386 (69.4)	219 (68.9)	167 (70.2)	
3	55 (9.9)	27 (8.5)	28 (11.8)	
4	9 (1.6)	4 (1.3)	5 (2.1)	
N stage, n (%)				0.366
0	169 (30.5)	104 (32.8)	65 (27.3)	
1	246 (44.3)	137 (43.2)	109 (45.8)	
2	140 (25.2)	76 (24.0)	64 (26.9)	
Poorly differentiated, n (%)	149 (26.8)	79 (24.8)	70 (29.4)	0.229
Harvest LN, n (%)	23.7 (3-113)	23.5 (3-113)	24.1 (4-71)	0.206
Positive LN, n (%)	2.6 (0-31)	2.4 (0-24)	3.0 (0-31)	0.212
Perineural invasion, n (%)	486 (94.6)	278 (93.6)	208 (95.9)	0.267
Lymphovascular invasion, n (%)	278 (79.7)	152 (80.0)	126 (79.2)	0.862
R status, n (%)				0.033
R0	373 (67.1)	225 (70.8)	148 (62.2)	
R1 (including rR1*)	183 (32.9)	93 (29.2)	90 (37.8)	
PV invasion, n (%)	113 (20.6)	63 (20.0)	50 (21.4)	0.695

LN, lymph node; rR1, revised R1; PV, portal vein
*Revised R1 was defined as a distance of the tumor from the resection margin of ≤1 mm

Table 3. Postoperative outcomes

Variables	Total (n=556)	Pylorus preserving surgery (n=318)	Pylrus-resecting surgery (n=238)	*p*
Hospital stay (days), mean (range)	13.71 (7-80)	14.22 (7-80)	13.04 (8-42)	0.692
Major complications[†], n (%)	97 (17.4)	65 (20.4)	32 (13.4)	0.032
Clinically relevant POPF[‡], n (%)	41 (7.4)	24 (7.5)	17 (7.1)	0.857
DGE, n (%)	40 (7.2)	21 (6.6)	19 (8.0)	0.533
Re-admission*, n (%)	63 (11.3)	30 (9.4)	33 (13.9)	0.103
Re-operation*, n (%)	17 (3.1)	8 (2.5)	9 (3.8)	0.391
Mortality*, n (%)	41 (7.4)	24 (7.5)	17 (7.1)	0.857
Recurrence, n (%)	379 (70.7)	225 (73.8)	154 (66.7)	0.074

POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying
*within 90 days
[†]Major complications were defined as Clavien-Dindo Grade III or higher
[‡]Clinically relevant POPF was defined as ≥Grade B of international study group for pancreatic fistula definition

and 22.4% in the PRPD group (*p*=0.015). There was no significant difference in disease-free survival of recurrence in both groups (Fig. 2).

Table 4. Major complications

Variables	Total (n=97)	Pylorus-preserving surgery (n=65)	Pylorus-resecting surgery (n=32)
Surgical wound problem, n	32	21	11
Intra-abdominal fluid collection, n	27	19	8
Arterial pseudoaneurysm, n	17	9	8
Postoperative bleeding, n	3	3	0
Postoperative sepsis, n	4	4	0
SMV/PV stenosis or thromboembolism, n	2	2	0
Gastric jejunal ulceration, n	4	3	1
Intestinal obstruction or stenosis, n	6	4	2
Bowel perforation, n	2	0	2

SMV/PV, superior mesenteric vein/portal vein

DISCUSSION

Several studies compared morbidity and mortality of PPPD and PRPD. No significant differences were found in pancreatic fistulas, wound infections, post-operative bleeding, or biliary leakage between PPPD and PRPD.[12] Further, the results of several randomized controlled trials (RCTs) or meta-analyses comparing PPPD and PRPD found that the two procedures were identical with respect to morbidity and mortality associated with the treatment of pancreatic head tumors.[13-18]

However, a lower rate of DGE was found with PRPD compared with PPPD.[12] According to previous study, several factors play a role in the pathophysiology of DGE. Gastric dysrhythmias, abnormal gastroduodenal nerve connections, ischemia of the pyloric sphincter, and ligation of the right gastric artery are associated with DGE. Resection of the duodenum, the primary production site

Table 5. Univariate and multivariate analysis of risk factors for major complications

Variables	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	0.423	0.987-1.031	0.423			
Male	1.285	0.814-2.030	0.280			
BMI	1.051	0.982-1.126	0.151			
Cardiology	1.458	0.940-2.263	0.091*	1.283	0.802-2.052	0.299
DM	0.974	0.620-1.528	0.907			
Pulmonary disease	1.112	0.538-2.298	0.774			
Liver disease	3.810	1.558-9.314	0.005*	3.628	1.451-9.071	0.006*
Brain disease	0.418	0.097-1.809	0.406			
CKD	4.851	0.964-24.406	0.069*	3.285	0.601-17.949	0.170
Neoadjuvant Tx	0.701	0.204-2.406	0.781			
PV resection	1.102	0.675-1.800	0.698			
ASA≥3	2.623	1.441-4.776	0.001*	2.749	1.477-5.114	0.001*
Intraop transfusion	1.292	0.685-2.437	0.428			
Total IV input	1.000	1.000-1.000	0.278			
EBL	1.000	1.000-1.001	0.146			
Op duration	1.003	1.000-1.005	0.407			
Soft pancreas	0.985	0.568-1.710	0.957			
P-duct size	1.020	0.943-1.103	0.622			
R1 resection	1.062	0.668-1.688	0.798			
Pylorus resection	0.605	0.381-0.959	0.032*	0.564	0.351-0.906	0.018*
Postop initial BST	1.000	0.996-1.005	0.952			
Postop mean BST	0.999	0.991-1.006	0.723			
Poor BST control[†]	1.038	0.670-1.611	0.864			

OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; ASA, American Society of Anesthesiologists; Intraop, intraoperative; IV, intravenous; EBL, estimated blood loss; Op, operative; P-duct, pancreatic duct; Postop, postoperative; BST, blood sugar test
*indicates statistically significant values
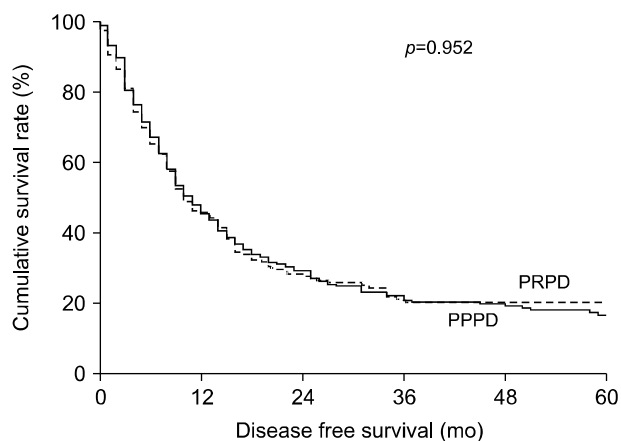[†]Poor BST control was defined as mean BST >180 mg/dL

Fig. 1. Overall survival of pylorus-preserving and pylorus-resecting pancreaticoduodenectomy. The 5-year survival rates were 27.6% and 22.4% in pylorus-preserving and pylorus-resecting pancreaticoduodenectomy, respectively (*p*=0.015).
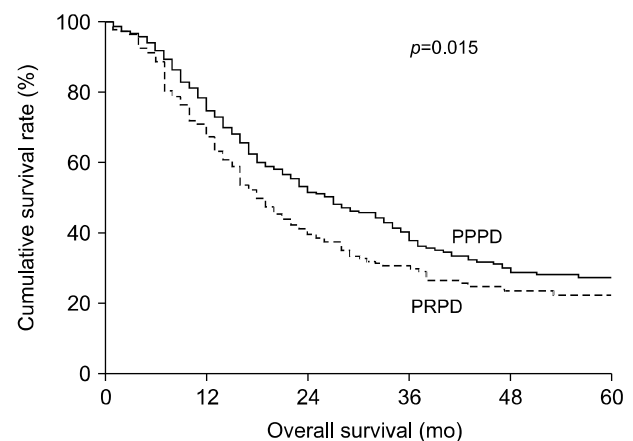

Fig. 2. Disease-free survival (DFS) of pylorus-preserving and pylorus-resecting pancreaticoduodenectomy. The 5-year DFS rates were 16.6% and 20.4% in pylorus-preserving and pylorus-resecting pancreaticoduodenectomy, respectively (*p*=0.952).

of most gastrointestinal hormones, might also play a role in the pathogenesis of this complication.[15]

Our study showed that DGE was not significantly different between PRPD and PPPD even though several studies reported that PRPD was superior to PPPD with respect to DGE.[2] This result may be attributed to the small number of DGEs in the patients reviewed in our study compared with the previous studies.

We also showed that postoperative outcomes were not significantly different between PRPD and PPPD except in Clavien-Dindo surgical complications grade ≥3. We evaluated the risk factors for major complications, and showed that systemic disorders with an ASA score more than 3 and liver disease were risk factors for Clavien-Dindo grade ≥3 complications. Similar to our results, previous studies reported that the postoperative outcomes of patients undergoing PD with systemic disorder were poor. Eeson et al.[19] suggested that an ASA score of 3 was associated with a higher 90-day and 5-year mortality rates. Age *per se* should not be considered a contraindication for pancreaticoduodenectomy, but caution is required for patients who are at least 80 years old, especially in the presence of any associated comorbidities resulting in an ASA score of 3.[19] Gouma et al.[20] claimed that serum creatinine levels were independent risk factors for complications. El Nakeeb et al.[21] reported that liver cirrhosis increased the risk of POPF. We found that the patient's ability to endure physiological stress of PD was related to the possibility of postoperative complications.[19]

Our study revealed no differences between the two groups in most of the postoperative outcomes. However, the higher incidence of major complications in PPPD should be attributed to selection bias in this study, rather than pylorus-preserving surgery.

According to PROPP trial, long-term follow-up showed no significant differences between pylorus resection compared with pylorus preservation.[22] Similarly, our study did not show differences in terms of hospitalization and rehospitalization. In addition, TNM stage and disease-free survival showed no difference between the two groups similar to previous study. However, the overall survival was significantly better in PPPD than in PRPD. In terms of clinicopathologic characteristics, the PRPD group underwent significantly higher CA19-9 and greater R1 resection, which suggested that the PRPD group in our study included patients with advanced cancer. However, the comparison based on TNM stages did not reflect significant differences. In this retrospective study, both PPPD and PRPD were not conducted randomly. Because PPPD is the basic surgical technique recommended for patients with pancreatic head cancer in our institute, pylorus resection is only performed if the patient manifests pylorus invasion or aggressive disease. Therefore, this retrospective survival analysis may not reflect differences in survival between the two procedures.

DM is an independent risk factor associated with complications for pancreatic cancer.[23] A study reported factors contributing to impaired glucose homeostasis and devel-

opment of DM after pancreatectomy.[23] Factors include age, BMI greater than 23.5 kg/m^2, family history of DM and resection type.[24] Other studies have shown that pancreatic cancer-related DM improves after tumor resection.[25,26] The improved glycemic control after PD surgery may be attributed to reduced BMI, altered life style including dietary habits as well as physiological and anatomical changes resulting from gastrointestinal tract reconstruction.[27] The physiological and anatomical changes were attributed to the obesity bypass procedure, which removed duodenal mucosa as a surface of food absorption, and improved blood sugar levels and enhanced weight loss. According to this theory, PRPD is better for the control of blood glucose than PPPD. However, our results did not show statistically significant results.

The study limitations are also worth mentioning. First, our data were collected and analyzed retrospectively. Significant biases may affect the selection of controls. Unlike a meta-analysis, which showed no difference in survival rate,[1] the higher survival rate of patients undergoing PPPD in this study may be attributed to selection bias. Second, we did not investigate the influence of pancreatic cancer-related DM on the survival, mortality and morbidity due to unavailable data. Third, glucose levels are influenced by various factors. Long-term glucose data are needed to clearly demonstrate the effects of DM and the two procedures. However, in the absence of long-term glucose data, the effects might be underestimated. Fourth, long-term data such as dumping syndrome, nutrition status, and marginal ulcer reflecting possible complications are needed. The limitations may be due to difficulties in data collection. Fifth, because the surgical method was not randomly selected, surgical preferences and extent of cancer may have contributed to selection biases. Nevertheless, we believe that our large data provide a comparative and meaningful analysis of the overall differences underlying pylorus preservation and resection in patients with pancreatic head cancer.

In conclusion, PPPD and PRPD showed no significant differences in outcomes compared with conventional interventions reported in previous studies. Although further well-designed studies are needed, it is more important to select the surgical resection range of the patient's disease than the effect of pylorus resection on the patient's short- or long-term outcomes.

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CONFLICT OF INTEREST

ORCID

Yeon Jin Kim: https://orcid.org/0000-0002-8733-1659
Sang Hyun Shin: https://orcid.org/0000-0002-2533-4491
In Woong Han: https://orcid.org/0000-0001-7093-2469
Youngju Ryu: https://orcid.org/0000-0002-3523-0776
Naru Kim: https://orcid.org/0000-0002-8900-5582
Dong Wook Choi: https://orcid.org/0000-0002-0751-7841
Jin Seok Heo: https://orcid.org/0000-0001-6767-2790

AUTHOR CONTRIBUTIONS

Conceptualization: YJK, SHS, JSH. Data curation: YJK, SHS, YR, IWH, DWC. Formal analysis: YJK, SHS, YR, NK, JSH. Methodology: YJK, SHS, YR, NK, IWH, DWC. Project administration: SHS, JSH. Visualization: SHS. Writing - original draft: YJK, SHS, NK, JSH. Writing - review & editing: YJK, SHS, JSH.

REFERENCES

1. Iqbal N, Lovegrove RE, Tilney HS, Abraham AT, Bhattacharya S, Tekkis PP, et al. A comparison of pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy: a meta-analysis of 2822 patients. Eur J Surg Oncol 2008;34:1237-1245.
2. Yang C, Wu HS, Chen XL, Wang CY, Gou SM, Xiao J, et al. Pylorus-preserving versus pylorus-resecting pancreaticoduodenectomy for periampullary and pancreatic carcinoma: a meta-analysis. PLoS One 2014;9:e90316.
3. Watson K. Carcinoma of the ampulla of vater successful radical resection. Br J Surg 1944;31:368-373.
4. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). In: StatPearls. Treasure Island (FL): StatPearls Publishing LLC., 2020.
5. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. Br J Surg 2006;93:1232-1237.
6. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H,

et al. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008;15:1651-1660.

7. You Y, Choi DW, Heo JS, Han IW, Choi SH, Jang KT, et al. Clinical significance of revised microscopic positive resection margin status in ductal adenocarcinoma of pancreatic head. Ann Surg Treat Res 2019;96:19-26.

8. Cong L, Liu Q, Zhang R, Cui M, Zhang X, Gao X, et al. Tumor size classification of the 8th edition of TNM staging system is superior to that of the 7th edition in predicting the survival outcome of pancreatic cancer patients after radical resection and adjuvant chemotherapy. Sci Rep 2018;8:10383.

9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.

10. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017;161:584-591.

11. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761-768.

12. Chen QJ, He ZQ, Yang Y, Zhang YS, Chen XL, Yang HJ, et al. Is there comparable morbidity in pylorus-preserving and pylorus-resecting pancreaticoduodenectomy? A meta-analysis. J Huazhong Univ Sci Technolog Med Sci 2015;35:793-800.

13. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg 1999;86:603-607.

14. Seiler CA, Wagner M, Sadowski C, Kulli C, Büchler MW. Randomized prospective trial of pylorus-preserving vs. classic duodenopancreatectomy (Whipple procedure): initial clinical results. J Gastrointest Surg 2000;4:443-452.

15. Tran KT, Smeenk HG, van Eijck CH, Kazemier G, Hop WC, Greve JW, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg 2004;240:738-745.

16. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection-long term results. Br J Surg 2005;92:547-556.

17. Lin PW, Shan YS, Lin YJ, Hung CJ. Pancreaticoduodenectomy for pancreatic head cancer: PPPD versus Whipple procedure. Hepatogastroenterology 2005;52:1601-1604.

18. Diener MK, Knaebel HP, Heukaufer C, Antes G, Büchler MW, Seiler CM. A systematic review and meta-analysis of pylorus-preserving versus classical pancreaticoduodenectomy for surgical treatment of periampullary and pancreatic carcinoma. Ann Surg 2007;245:187-200.

19. Eeson G, Chang N, McGahan CE, Khurshed F, Buczkowski AK, Scudamore CH, et al. Determination of factors predictive of outcome for patients undergoing a pancreaticoduodenectomy of pancreatic head ductal adenocarcinomas. HPB (Oxford) 2012;14:310-316.

20. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786-795.

21. El Nakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). World J Surg 2013;37: 1405-1418.

22. Klaiber U, Probst P, Hüttner FJ, Bruckner T, Strobel O, Diener MK, et al. Randomized trial of pylorus-preserving vs. pylorus-resecting pancreatoduodenectomy: long-term morbidity and quality of life. J Gastrointest Surg 2020;24:341-352.

23. Khadka R, Tian W, Hao X, Koirala R. Risk factor, early diagnosis and overall survival on outcome of association between pancreatic cancer and diabetes mellitus: changes and advances, a review. Int J Surg 2018;52:342-346.

24. Kwon JH, Kim SC, Shim IK, Song KB, Lee JH, Hwang DW, et al. Factors affecting the development of diabetes mellitus after pancreatic resection. Pancreas 2015;44:1296-1303.

25. White MA, Agle SC, Fuhr HM, Mehaffey JH, Waibel BH, Zervos EE. Impact of pancreatic cancer and subsequent resection on glycemic control in diabetic and nondiabetic patients. Am Surg 2011;77:1032-1037.

26. Wang F, Gupta S, Holly EA. Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. Cancer Epidemiol Biomarkers Prev 2006;15:1458-1463.

27. Fogar P, Pasquali C, Basso D, Sperti C, Panozzo MP, Tessari G, et al. Diabetes mellitus in pancreatic cancer follow-up. Anticancer Res 1994;14:2827-2830.