Surgical Endoscopy
https://doi.org/10.1007/s00464-019-06942-4

The Yonsei experience of 104 laparoscopic pancreaticoduodenectomies: a propensity score-matched analysis with open pancreaticoduodenectomy

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Received: 20 September 2018 / Accepted: 26 June 2019

Abstract

Background With continued technical advances in surgical instruments and growing expertise, several surgeons have performed laparoscopic pylorus preserving pancreaticoduodenectomy (L-PPPD) safely with good results, and the laparoscopic approach is being performed more frequently. We performed over 100 cases of L-PPPD and compared their outcomes to those of open PPPD (O-PPPD) using the large sample size. The aim of the present study was to evaluate the safety and feasibility of L-PPPD compared with O-PPPD.

Methods From September 2012 to June 2017, PPPD was performed for 217 patients at Yonsei University Severance Hospital by a single surgeon. Patients were divided into two groups: those who underwent O-PPPD ($n=113$) and those who underwent L-PPPD ($n=104$). We performed a 1:1 propensity score-matched (PSM) analysis and retrospectively analyzed the demographic and surgical outcomes. We also reviewed all previous studies of more than 100 cases.

Results The L-PPPD group had lesser intraoperative blood loss than the O-PPPD group (548.1 ml vs. 244.7 ml; $p<0.001$). Both groups showed similar rates of negative resection margins (99.1% vs. 96.2%; $p=0.196$). Overall complication rates did not differ significantly between O-PPPD and L-PPPD (39.8% vs. 35.6%; $p=0.519$). The clinically relevant postoperative pancreatic fistula (POPF) rates in the O-PPPD and L-PPPD groups were 18.8% and 13.5%, respectively ($p=0.311$). There was no difference in 30- and 90-day mortality rates between the two groups ($p=0.479$). Similar results were obtained after PSM analysis.

Conclusions L-PPPD can be a good alternative option for well-selected patients with periampullary lesions requiring PPPD.

Keywords Pancreaticoduodenectomy · Pancreaticojejunostomy · Laparoscopy

Pylorus preserving pancreaticoduodenectomy (PPPD) remains the only curative treatment for several malignant and benign pancreatic and periampullary diseases [1]. Open PPPD (O-PPPD) is currently considered the standard surgical approach for resection of periampullary tumors [2]. Laparoscopic surgery has been applied to complex pancreatic surgical procedures [3]. With continued technical advances in surgical instruments and growing expertise, several surgeons have performed laparoscopic PPPD (L-PPPD) safely with good results, and it is being increasingly adopted [4]. As a result, reports of L-PPPD have been increasing. However, most of the previous comparative studies between O-PPPD and L-PPPD included only a small number of patients [5–7]. We have performed over 100 L-PPPDs, which has enabled us to compare the outcomes of L-PPPD to those of O-PPPD in a large patient population. The aim of the present study was to evaluate the safety and feasibility of L-PPPD compared with O-PPPD.

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Published online: 08 July 2019

Methods

Study design

From September 2012 to June 2017, PPPD was performed in 243 patients at Yonsei University Severance Hospital by a single surgeon. Patients undergoing robotic surgery, hybrid procedures, or total pancreatectomy were excluded. Consequently, 217 patients were retrospectively analyzed. Patients were divided into two groups: those who underwent L-PPPD and those who underwent O-PPPD. Selection criteria for L-PPPD consisted of patients who have good general condition capable for enduring long-time pneumoperitoneum and no severe obesity, no expecting combined vascular resection, benign or low-grade malignant tumor, periampullary cancer, and resectable pancreatic cancer with clear fat line between tumor and vascular interfaces. The institutional review board of the Yonsei University College of Medicine approved this study (4-2017-1183).

Clinicopathological parameters

Patient demographics included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, comorbidity, preoperative symptoms and preoperative nutritional statuses such as serum albumin and cholesterol level. Intraoperative variables, including operative time, amount of blood loss, pancreas texture, and pancreas duct size, were evaluated. Pathological characteristics such as pathologic diagnosis, size of the tumor, and margin status, were analyzed. R0 resection was defined as a specimen with clear resection margins and no gross tumor mass remaining at the resection site. Postoperative complications including postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and postpancreatectomy hemorrhage (PPH) were also evaluated. POPF was defined according to the International Study Group on Pancreatic Fistula's definition [8]. Only clinically relevant (CR) POPF (either grade B or C) were considered in this study. DGE and PPH were defined by the International Study Group on Pancreatic Surgery criteria [9, 10]. Postoperative complications were classified using the Clavien-Dindo classification [11]. Major complications were defined as Clavien-Dindo grade III or higher. Length of hospital stay was calculated from the date of operation to the date of discharge. Postoperative outcomes were tracked for 90 days after surgery using the patients' medical records. Re-operation was defined as any unplanned operation within 90 days of surgery. Re-admission was defined as rehospitalization within 30 days of discharge. In addition, using a PubMed search, all case series reporting more than 100 cases of L-PD were retrieved and reviewed. The number of patients and the perioperative outcomes were summarized.

Surgical technique

Reconstruction in all PPPD procedures consisted of an end-to-side pancreaticojejunostomy, an end-to-side hepaticojejunostomy, and side-to- side duodenojejunostomy using the first jejunal loop, according to Child's procedure [12]. The principle of pancreaticojejunostomy is all interrupted suture, duct-to-mucosa (4–6 stitches), and short stent insertion without fixation.

After laparoscopic hepaticojejunostomy, mini-laparotomy was performed using an umbilical port to remove the specimen. The specimen was extracted and extracorporeal duodenojejunostomy was performed through the enlarged umbilical port site.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as percentages. Analysis was performed with the Student *t* test for continuous variables and the Chi-squared test for categorical variables. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY). The propensity score was generated by binary logistic regression, and patients with similar propensity scores were selected from the O-PPPD and L-PPPD groups (1:1 matching) to reduce the bias in patient distribution. Propensity score was matched using a caliper width of 0.25 standard deviation that was calculated by a logistic regression. Comparative analyses were performed in the propensity score-matched groups as well as the total population.

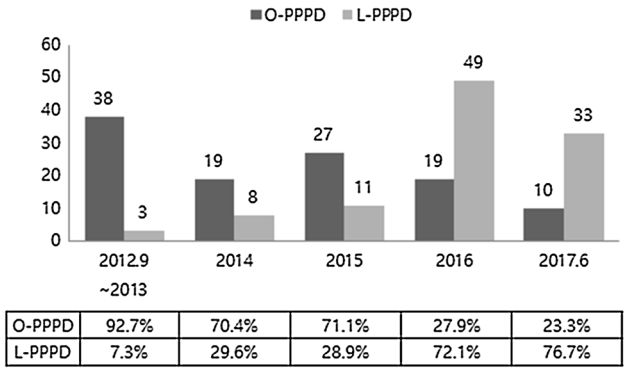
Results

Chronological changes in approach to pancreaticoduodenectomy

Figure 1 shows the surgical approach by year. The proportion of patients undergoing L-PPPD increased from 7.3% in 2012 to 76.7% in 2017. With the increasing experience, L-PPPD was performed more often than O-PPPD ($p < 0.001$).

Clinicopathological characteristics

We identified 113 patients who underwent O-PPPD and 104 who underwent L-PPPD. Patient characteristics are shown in Table 1. There were no differences in gender, BMI, ASA class, comorbidity, preoperative symptoms, serum albumin level and serum cholesterol level. The L-PPPD group was younger (64.5 years vs. 61.5 years; $p = 0.037$) and had a



O-PPPD	92.7%	70.4%	71.1%	27.9%	23.3%
L-PPPD	7.3%	29.6%	28.9%	72.1%	76.7%

Fig. 1 Chronological changes in approach to pancreaticoduodenectomy. *PPPD* pylorus preserving pancreaticoduodenectomy, *O-PPPD* open PPPD, *L-PPPD* laparoscopic PPPD

higher proportion of patients with soft pancreatic texture (54.9% vs. 70.2%; $p=0.020$) than the O-PPPD group. Both groups differed in pathologic diagnosis ($p<0.001$). In the L-PPPD group, pancreatic ductal adenocarcinoma was the most common (45.1%), while common bile duct cancer was the most common in the O-PPPD group (26.0%). The median operative times in the O-PPPD and L-PPPD groups were 451.3 min and 472.8 min, respectively ($p=0.081$). Patients in the L-PPPD group had lesser intraoperative blood loss than those in the O-PPPD group (548.1 ml vs. 244.7 ml; $p<0.001$). Tumor size was not significantly different between the O-PPPD and L-PPPD groups (2.79 cm vs. 2.55 cm; $p=0.177$). Both groups showed similar rates of negative resection margins (99.1% vs. 96.2%; $p=0.196$).

Table 1 Clinicopathological characteristics of patients who underwent PPPD ($n=217$)

	O-PPPD ($n=113$)	L-PPPD ($n=104$)	p Value
Age (year)	64.5 ± 9.2	61.5 ± 12.0	*0.037
Gender (male:female)	70 (61.9%): 43	53 (51.0%) : 51	0.103
BMI (kg/m^2)	23.22 ± 3.09	23.57 ± 2.72	0.385
ASA class (minimal/moderate/severe)	5/55/53	9/57/38	0.194
Comorbidity			
Hypertension	49 (43.4%)	37 (35.6%)	0.241
Diabetes mellitus	42 (37.2%)	33 (31.7%)	0.216
Pulmonary disease	4 (3.5%)	2 (1.9%)	0.468
Cardiovascular disease	6 (5.3%)	4 (3.8%)	0.371
Renal failure	4 (3.5%)	2 (1.9%)	0.468
Symptom			0.120
Abdominal pain	22 (19.5%)	24 (23.1%)	
Jaundice	52 (46.0%)	33 (31.7%)	
General weakness	5 (4.4%)	6 (5.8%)	
Dysphagia	8 (7.1%)	4 (3.8%)	
Diagnosis			*<0.001
PDAC	51 (45.1%)	18 (17.3%)	
NET	1 (0.9%)	7 (6.7%)	
IPMN	2 (1.8%)	13 (12.5%)	
AOV cancer	11 (9.7%)	25 (24.0%)	
CBD cancer	39 (34.5%)	27 (26.0%)	
Others**	9 (8.0%)	14 (13.5%)	
Albumin	3.7 ± 0.5	3.8 ± 0.5	0.156
Cholesterol	167 ± 53	175 ± 59	0.194
Operating time, min	451.3 ± 105.5	472.8 ± 70.8	0.081
Blood loss (ml)	548.1 ± 419.3	244.7 ± 189.3	*<0.001
Pancreas texture (soft:hard)	62 (54.9%): 51	73 (70.2%): 31	*0.020
Pancreas duct size (mm)	4.00 ± 2.49	3.99 ± 2.52	0.987
Tumor size (cm)	2.79 ± 1.29	2.55 ± 1.37	0.177
Margin status (R0: R1)	112 (99.1%): 1	100 (96.2%): 4	0.196

*$p<0.05$ as statistically significant

**Metastatic cancer, duodenal cancer, AOV adenoma, solid pseudopapillary tumor

PPPD pylorus preserving pancreaticoduodenectomy, *O-PPPD* open PPPD, *L-PPPD* laparoscopic PPPD, *ASA* American society of anesthesiologists, *PDAC* pancreatic ductal adenocarcinoma, *NET* neuroendocrine tumor, *IPMN* intraductal papillary mucinous neoplasm, *AOV* ampulla of Vater, *CBD* common bile duct

Postoperative outcomes

The postoperative outcomes are summarized in Table 2. Overall complication rates did not differ significantly between the O-PPPD and L- PPPD groups (39.8% vs. 35.6%; $p=0.519$). The CR-POPF rates in the O-PPPD and L-PPPD groups were 18.8% and 13.5%, respectively ($p=0.311$). In both groups, most CR-POPF were grade B (O-PPPD : 17.7%, L-PPPD : 11.5%). The medians of postoperative hospital day in the O-PPPD and L-PPPD groups were 17.9 days and 18.3 days, respectively ($p=0.827$). Reoperation was required in 7 patients, 2 in the O-PPPD group, and 5 in the L- PPPD group. The reasons for reoperation were intestinal obstruction ($n=5$), secondary suturing of the wound ($n=2$), and postoperative bleeding ($n=1$). Reoperation (1.8% vs. 4.8%; $p=0.264$) and readmission rates (8.0% vs. 5.8%; $p=0.524$) were similar in the O-PPPD and L- PPPD groups, respectively. There was no difference in the 30- and 90-day mortality rates between the two groups ($p=0.479$). There was one in-hospital death (1.0%) within 30 days in the L-PPPD group. The patient was an elderly man who developed POPF and pneumonia.

Propensity score analysis

As mentioned earlier, the L-PPPD group was younger and had a higher proportion of patients with soft pancreatic texture than the O-PPPD group. To reduce the impact of selection bias, matching between the O-PPPD and L-PPPD groups was performed by estimating a propensity score for each patient (Table 3). Age and pancreatic texture were the matching criteria. Eighty-seven patients who underwent L-PPPD were matched to those who underwent O-PPPD ($n=87$) in a 1:1 ratio. After matching, there were no significant differences between the two groups in most perioperative outcomes, similar to the unmatched results. Similarly, the amount of blood loss was lesser in the L-PPPD group than that in the O-PPPD group (585.8 ± 452.0 ml vs. 246.7 ± 187.8 ml; $p<0.001$).

Review of studies reporting more than 100 cases of laparoscopic PD

Three studies included more than 100 cases of laparoscopic PD (Table 4). Among them, Senthilnathan et al. [13], and Kim et al. [14] did not compare laparoscopic PD with open PD. Croome et al. [15] compared 214 cases of open PD and 108 of laparoscopic PD. Similar to our results, there were no differences in operative time ($p=0.45$), overall complications ($p=0.17$), and mortality ($p=0.50$) between the two groups. In addition, intraoperative blood loss was less in the laparoscopic group ($p<0.001$). In the last study, however, unlike our study, the postoperative hospital stay was shorter after laparoscopic PD than that after open PD ($p<0.001$).

Discussion

L-PPPD is a technically challenging operation currently performed at a few selected centers [15]. Gagner et al. [16] described the first laparoscopic PD in 1994 and demonstrated its feasibility. However, L-PPPD is still controversial. Some studies have reported that L-PPPD is associated with higher morbidity, mainly due to more severe POPF [17]. By contrast, other studies have indicated that L-PPPD is safer and more feasible than O-PPPD [18, 19]. In our study, L-PPPD was superior or comparable to O-PPPD in terms of perioperative outcomes. POPF remains one of the most threatening complications after PD [20]. In spite of higher proportion of soft remnant pancreas in L-PPPD group, it is interesting to find that laparoscopic approach did not lead to a higher increase in the POPF rate than open surgery despite the higher prevalence of a soft pancreas in the L-PPPD group, which is a recognized risk factor for POPF [21]. This observation appears quite opposite to what

Table 2 Postoperative outcomes of patients who underwent PPPD ($n=217$)

	O-PPPD ($n=113$)	L-PPPD ($n=104$)	p Value
All complications	45 (39.8%)	37 (35.6%)	0.519
*Pancreatic fistula	21 (18.8%)	13 (13.5%)	0.311
Delayed gastric emptying	19 (16.8%)	16 (15.4%)	0.775
Postpancreatctomy hemorrhage	2 (1.8%)	2 (1.9%)	1.000
Re-operation	2 (1.8%)	5 (4.8%)	0.264
Re-admission	9 (8.0%)	6 (5.8%)	0.524
30 days mortality	0 (0.0%)	1 (1.0%)	0.479
90 days mortality	0 (0.0%)	1 (1.0%)	0.479
Postoperative hospital stay (day)	17.9 ± 7.7	18.3 ± 13.9	0.827

*Including Grade B and C

PPPD: pylorus preserving pancreaticoduodenectomy; O-PPPD: open PPPD; L-PPPD: laparoscopic PPPD

Table 3 Clinicopathological and postoperative characteristics of patients who underwent PPPD after propensity score matching ($n=174$)

	O-PPPD ($n=87$)	L-PPPD ($n=87$)	p value
Age (year)	63.6 ± 9.5	65.1 ± 8.8	0.279
Gender (male:female)	53 (60.9%) : 34	49 (56.3%) : 38	0.538
BMI (kg/m$^{2)}$	23.32 ± 3.08	23.52 ± 2.74	0.650
ASA class (minimal/moderate/severe)	5/39/43	5/47/35	0.457
Operating time (min)	448.4 ± 107.1	470.4 ± 73.6	0.116
Blood loss (ml)	585.8 ± 452.0	246.7 ± 187.8	* < 0.001
Pancreas texture (soft:hard)	51 (58.6%) : 36	57 (65.5%) : 30	0.349
Pancreas duct size (mm)	4.07 ± 2.35	3.93 ± 2.41	0.698
Tumor size (cm)	2.80 ± 1.32	2.62 ± 1.42	0.385
Margin status (R0: R1)	86 (98.9%): 1	83 (95.4%): 4	0.368
All complications	33 (37.9%)	30 (34.5%)	0.636
**Pancreatic fistula	17 (19.8%)	11 (13.9%)	0.318
Delayed gastric emptying	13 (14.9%)	12 (13.8%)	0.829
Postpancreatctomy hemorrhage	2 (2.3%)	1 (1.1%)	1.000
Re-operation	2 (2.3%)	3 (3.4%)	1.000
Re-admission	5 (5.7%)	4 (4.6%)	1.000
30 Days mortality	0 (0.0%)	1 (1.1%)	1.000
90 Days mortality	0 (0.0%)	1 (1.1%)	1.000
Postoperative hospital stay, day	17.1 ± 6.9	18.6 ± 14.1	0.394

*$p < 0.05$ as statistically significant

**Including Grade B and C

PPPD pylorus preserving pancreaticoduodenectomy, *O-PPPD* open PPPD, *L-PPPD* laparoscopic PPPD, *ASA* American society of anesthesiologists

Table 4 Review of the literature works reporting more than 100 cases of laparoscopic PD

Authors, year	Group (n)	Gender (M:F)	Op time (min)	Blood loss (ml)	Complications (%)	POPF (%)	Mortality (%)	Hospital stay (day)
Senthilnathan, 2015 [13]	Laparo ($n=130$)	50:80	310	110	29.7	8.46	1.53	8.06
Kim, 2013 [14]	Laparo ($n=100$)	46:54	475	NA	25	6	1	15
Croome, 2014 [15]	Open ($n=214$)	131:83	387.6	866.7	13.6	12	2	9
	Laparo ($n=108$)	51:57	379.4	492.4	5.6	11	1	6
Present, 2018	Open ($n=113$)	70:43	451.3	548.1	39.8	18.8	0	17.9
	Laparo ($n=104$)	53:51	472.8	244.7	35.6	13.5	1	18.3

PD pancreaticoduodenectomy, *POPF* postoperative pancreatic fistula, *NA* not available

pancreatic fistula risk score predict [22]. This may be due to the potential bias or limited number of the patients. However, this finding needs to be further investigated to reveal potential role of laparoscopic approach in minimize clinical impact of CR-POPF.

Laparoscopic surgery has demonstrated lesser pain, shorter hospital stay, and more rapid return to baseline performance status than open procedures [23]. In addition, laparoscopy can reduce gastrointestinal tract stimulation and allow for faster recovery of gastrointestinal function and postoperative oral intake [24]. Because of these advantages, laparoscopic surgery can be superior to the open approach, if demonstrated to be safe. However, the technical challenges of L-PPPD may increase perioperative mortality. One study demonstrated significantly higher mortality in patients undergoing L-PPPD than in those undergoing O-PPPD [25]. Another study concluded that mortality was equivalent between the two groups [26]. The disparate results are due to a combination of different surgical learning curves, patient selection bias, publication bias, and the higher mortality rates reported by low-volume centers [27]. In the present study, there were no significant differences in the L-PPPD and O-PPPD groups in terms of 30- and 90-days mortality.

L-PPPD is challenging due to the retroperitoneal location of the pancreas, the complex anastomoses required, and the substantial dissection needed around major vessels. Therefore, L-PPPD can result in longer operative times [28]. Recent meta-analyses and reviews showed that operative times were significantly prolonged in the L-PPPD group [29, 30]. However, our results showed no significant difference between the L-PPPD and O-PPPD groups in terms of operative times. This difference could be explained by the nature of the laparoscopic procedure itself and the operators' experience with laparoscopic and pancreatic surgeries [31].

Intraoperative blood loss is an important index to judge the safety of an operation [32]. In this study, intraoperative blood loss was significantly lesser in the L-PPPD group than that in the O-PPPD group. A distinct advantage of laparoscopic approach is the superior view and the magnification of the operative field over open surgery, which may result in less intraoperative blood loss [33].

A number of studies have reported that the length of hospital stay was shorter in the laparoscopic group [34, 35]. However, we did not observe shorter length of hospital stay than that with O-PPPD. We think that this may be explained by our country's insurance and medical policy that because the cost of hospitalization is very low, even if patients can be safely discharged, they may prefer not to.

One of the concerns associated with L-PPPD is oncologic safety. Several studies have shown no difference in R0 resection between open and laparoscopic surgeries [36, 37]. In the present study, R0 resection rates were similar in the two groups, and L-PPPD was comparable with O-PPPD in terms of oncologic success based on the resection margin status.

This study has several limitations. First, it was a retrospective analysis with significant potential for selection bias. For example, laparoscopic surgery might be preferred if surgical condition was good. Second, this study was limited due to the heterogeneity of the diseases being treated. Third, only the short-term results are presented here, and outcomes that can only be assessed over a longer period of follow-up, such as survival and long-term complications, were not examined.

In conclusion, R0 rates and mortality rates were similar after L-PPPD and O-PPPD. The overall complication rates and, in particular, POPF rates, showed no significant difference between the O-PPPD and L-PPPD groups. In addition, L-PPPD had the advantage of lesser intraoperative blood loss than O-PPPD. Therefore, L-PPPD is a safe and technically feasible procedure. L-PPPD can be a good alternative surgical approach in appropriately selected patients with periampullary pathologic conditions requiring PPPD.

Acknowledgements There were no Grants from any industry to develop and accomplish this study.

Compliance with ethical standards

Disclosures Dr. Sang Hyup Han, Chang Moo Kang, Ho Kyoung Hwang, Dong Sup Yoon, and Woo Jung Lee have no conflicts of interest or financial ties to disclose.

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