Original Article

Surgical Outcome of Patients Undergoing Pancreaticoduodenectomy: Analysis of a 17-Year Experience at a Single Center

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The operative mortality and morbidity of pancreaticoduodenectomy (PD) remain high. We analyzed PD patients' clinical characteristics and surgical outcomes and discuss how PD clinical outcomes could be improved. We retrospectively reviewed the cases of 400 patients who underwent a PD between January 1998 and April 2014 at Okayama University Hospital, a very-high-volume center. We identified and compared the clinical outcomes between two time periods (period 1: 1998-2006 vs. period 2: 2007-2014). The total postoperative mortality and major complication rates were 0.75% and 15.8%, respectively, and the median postoperative length of stay (LOS) was 32 days. Subsequently, patients who underwent a PD during period 2 had a significantly shorter LOS than those who underwent a PD during period 1 (29 days vs. 38.5 days, $p < 0.001$). The incidence of mortality and major complications did not differ between the two periods. In our multivariate analysis, period 1 was an independent factor associated with a long LOS ($p < 0.001$). The improvement of the surgical procedure and perioperative care might be related to the shorter LOS in period 2 and to the consistently maintained low mortality rate after PD. The development of multimodal strategies to accelerate postoperative recovery may further improve PD's clinical outcomes.

Key words: pancreaticoduodenectomy, surgical outcome, mortality, major complication, length of stay

Pancreaticoduodenectomy (PD) is one of the most complex abdominal operations involving the pancreas, duodenum, and other organs. A PD is performed to treat tumors on the head of the pancreas, malignant tumors involving the common bile duct and duodenal papilla, or other diseases. The operative technique, surgical instruments, and perioperative care have evolved considerably over the years; however, the operative mortality and morbidity due to PD remain high, even at high-volume centers. The postoperative mortality after PD has been reported to be 2.8-3.5% in a Japanese nationwide survey [1]. Nationwide surveys in Western countries suggested higher mortality rates of 6.4-8.4% [2-4]. Moreover, the overall morbidity rate after PD was 40.0% in another Japanese nationwide survey [5].

Here we retrospective reviewed the clinical charac-

teristics and surgical outcomes of patients who underwent a PD at a single center, and we discuss how the clinical outcomes of PD could be improved.

Materials and Methods

Patients. This study was approved by the Ethics Committee of Okayama University School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (approval no. 2035), and conducted in accordance with the Declaration of Helsinki. The need for informed consent was waived. We retrospectively reviewed the medical records of 400 consecutive patients who underwent PD at Okayama University Hospital (Okayama, Japan) in the 17-year period from January 1998 to April 2014.

Clinical data. From our database, the following demographic and clinical data were collected as preoperative factors: age, sex, height, weight, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, laboratory values (total lymphocyte count, albumin, and cholesterol level), comorbidities, and disease etiology. The ASA physical status was preoperatively evaluated by anesthesiologists. Data regarding the surgical procedure, the type of PD, operative time, and amount of blood loss were recorded as operative factors. The postoperative factors were as follows: postoperative mortality, morbidity, and length of stay (LOS). The postoperative morbidity was assessed by using the Clavien-Dindo classification, according to major complications defined as Clavien grade ≥ 3 [6]. Pancreatic fistula (PF) and delayed gastric emptying (DGE) were evaluated according to the International Study Group of Pancreatic Surgery guidelines, and classified into three categories (grades A, B, and C) [7, 8].

We identified the clinical outcomes and compared them between two time periods (period 1: 1998-2006 vs. period 2: 2007-2014). We assessed the impact of prognostic factors associated with a long LOS by performing a multivariate analysis.

Surgical procedures. The details of the surgical techniques were as described [9]. In patients with malignant disease, a classic PD or subtotal stomach-preserving PD (SSPPD) with D2 lymph node dissection was performed. Lymph nodes from the following areas were removed: hepatoduodenal ligament, circumferentially around the common hepatic artery, and the right-half circumference of the superior mesenteric artery. Vascular reconstruction, including portal vein reconstruction, was performed in cases of advanced malignancy.

In patients with benign disease, a pylorus-preserving PD (PPPD) was performed. The basic reconstruction of the digestive system was performed according to a modification of the method described by Child [10]. The pancreatojejunostomy was performed by means of a duct-to-mucosa, end-to-side pancreatojejunostomy. An external drainage catheter was used as a stent for PD, if necessary. An end-to-side hepatojejunostomy was performed through a one-layer anastomosis 10 cm distal to the pancreatojejunostomy. A duodenojejunostomy or gastrojejunostomy was performed by means of a two-layer anastomosis 50 cm distal to the hepatojejunostomy. A Braun anastomosis was also added.

To prevent postoperative pseudoaneurysms after PD, an omental flap placement over splanchnic vessels was performed from 2003 onward [9]. From 1998 to 2006, an open drainage system was employed by using 12-mm silicone Penrose drains (Kaneka, Osaka, Japan). From 2007 to the present, a closed drainage system was used with 19- or 24-Fr BLAKE silicone drains (Johnson & Johnson, Somerville, NJ, USA).

Concerning the type of operations, a classic PD was usually performed for pancreatic cancer; however, from 2007, the Hospital's standard surgical procedure for malignant diseases was changed to SSPPD. In addition, the reconstruction of the duodenojejunostomy or gastrojejunostomy was made through a postcolic route between 1998 and 2006, but was changed to an antecolic route from 2007 [11].

Statistical analyses. JMP version 10 software (SAS Institute, Cary, NC) was used for the statistical analyses. Data are presented as mean, median, and standard deviation (SD) for continuous variables. Categorical data are presented as proportions. Differences between groups were assessed by using the Mann-Whitney U-test for continuous variables, and Fisher's exact test or χ^2-test for categorical variables. To investigate the impact of prognostic factors associated with a long LOS, we used a logistic regression model for univariate and multivariate analyses, and we calculated odds ratios (ORs) and 95% confidence intervals (95% Cis). A *p*-value of < 0.05 was considered significant.

Results

The annual volume of PD cases between 1998 and 2013 at Okayama University Hospital is shown in Fig. 1. The volume of PD cases rapidly increased after 2006. During period 1 (1998–2006), 120 PDs were performed (mean, 13.3 cases per year). During period 2 (2007–2014), 280 PDs were performed (mean, 38.7 cases per year).

The demographic and clinicopathological factors of the patients who underwent a PD are listed in Table 1. The study population consisted of 242 men (60.5%) and 158 women (39.5%) with a mean age of 65.2 ± 14.4 years. Most of the patients (90.5%) had an ASA physical status of 1 or 2. The laboratory values, comorbidities, and disease etiologies are also shown in Table 1. The most common pathological indication for PD was pancreatic adenocarcinoma (40.8%). The age, sex distribution, body composition, and ASA status of patients were not significantly different between the two periods.

Concerning comorbidities, the proportion of patients with hypertension was significantly increased in period 2. The etiology of diseases was also significantly different between the two periods ($p = 0.009$). In period 1, there were no patients with duodenal adenocarcinoma or pancreatic neuroendocrine tumor, and the proportion of patients with either of those

diseases was increased in period 2.

Concerning operative procedures, the following data were revealed for the entire patient population: PPPD (25.5%), SSPPD (62.5%), and PD (12.0%). The rate of vascular reconstruction was 27.0%. The mean operative time was 450 ± 94.2 min, and the mean blood loss was 699 ± 725 ml. Significant differences between the two periods were observed in the type of PD ($p < 0.001$), rate of vascular reconstruction ($p = 0.002$), operative time ($p = 0.002$), and blood loss ($p < 0.001$). The operative time and blood loss were significantly decreased in period 2.

The mortality and major complication rates for all 400 patients in this study were 0.75% and 15.8%, respectively. The rate of PF and DGE (grade B or C) were 34.3% and 19.5%, respectively. The median LOS was 32 days (interquartile range, 25–42 days). The incidence of mortality and major complications did not differ significantly between the two periods. The rate of PF was essentially the same for both periods, whereas the rate of DGE was significantly decreased in period 2 (28.3% in period 1 vs. 15.7% in period 2, $p = 0.004$). The patients who underwent a PD during period 2 had a significantly shorter LOS than those who underwent a PD during period 1 (38.5 days in period 1 vs. 29 days in period 2, $p < 0.001$).

Table 2 shows the results of the univariate and multivariate analyses performed to identify prognostic factors associated with a long LOS (> 30 days) after PD. In the univariate analysis, seven variables were independent predictors. In the multivariate analysis, six variables were significant prognostic factors: period 1 ($p < 0.001$), hypertension ($p = 0.015$), operative time ($p = 0.043$), presence of major complications ($p < 0.001$), presence of PF ($p < 0.001$), and presence of DGE ($p < 0.001$). Preoperative factors other than hypertension and operative factors other than operative time were not significant in this study.

Discussion

This retrospective study shows the clinical characteristics and surgical outcomes after PD in a single-institution series of 400 patients over a 17–year period. The results demonstrated that the annual volume of PD cases increased over the past decade, and that the mortality rate was extremely low even when compared with a Japanese nationwide survey
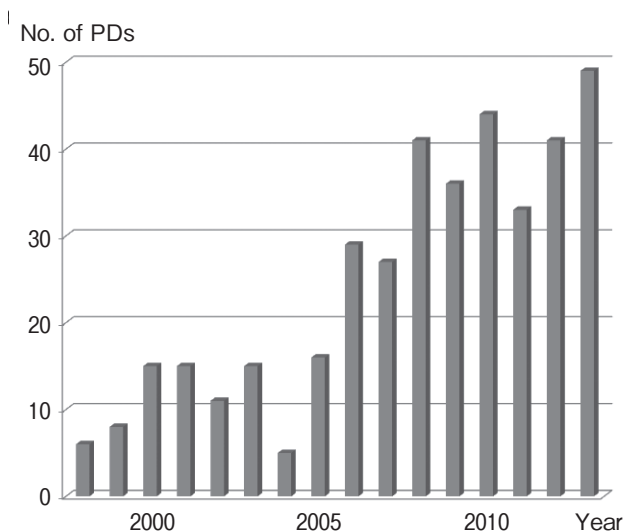

Fig. 1   Annual volume of pancreaticoduodenectomy (PD) cases between 1998 and 2013 at Okayama University Hospital.

Table 1 Demographic and clinicopathological factors of the 400 patients who underwent a pancreaticoduodenectomy at during the 17-year period from Jan. 1998 to April 2014 at Okayama University Hospital

	All patients (n = 400)	Period 1 (1998–2006, n = 120)	Period 2 (2007–2014, n = 280)	p-value
Demographic variables				
Mean age (yrs)*	65.2 ± 11.4	64.7 ± 10.1	65.5 ± 11.9	0.20
Sex ratio (men/women)†	242/158	67/53	175/105	0.21
Height (m)*	1.60 ± 0.09	1.59 ± 0.09	1.60 ± 0.09	0.40
Weight (kg)*	56.1 ± 10.6	54.8 ± 9.9	56.5 ± 10.8	0.38
BMI (kg/m²)*	21.8 ± 3.2	21.6 ± 3.0	21.9 ± 3.3	0.50
ASA physical status†				
Grades 1–2/3–4	362/38	110/10	252/28	0.60
Laboratory values*				
TLC (/mm³)‡	1,628 ± 589	1,575 ± 623	1,650 ± 574	0.09
Alb (g/dl)§	4.0 ± 0.48	3.9 ± 0.48	4.0 ± 0.48	0.006
T-cho (mg/dl)¶	191 ± 51.8	184 ± 50.1	194 ± 52.3	0.03
Comorbidity†				
Hypertension	143	30	113	0.003
Diabetes	107	33	74	0.82
Hyperlipidemia	93	21	72	0.08
Etiology of disease†				
Pancreatic adenocarcinoma	163 (40.8)	50	113	0.009
Bile duct carcinoma	48 (12.0)	19	29	
Ampullary adenocarcinoma	50 (12.5)	16	34	
Duodenal adenocarcinoma	14 (3.5)	0	14	
IPMN	66 (16.5)	24	42	
PNET	17 (4.2)	0	17	
Others	42 (10.5)	11	31	
Operative factors				
PPPD/SSPPD/PD†	102/250/102	24/63/33	78/187/15	<0.001
Vascular reconstruction (%)†	108 (27.0)	45 (37.5)	63 (22.5)	0.002
Operative time (min)*	450 ± 94.2	475 ± 94.4	440 ± 92.4	0.002
Blood loss (ml)*	699 ± 725	990 ± 841	574 ± 631	<0.001
Postoperative factors				
Mortality (%)†	3 (0.75)	0	3 (1.07)	0.26
Major complications (%)†	63 (15.8)	21 (17.5)	42 (15.0)	0.53
PF (grades B–C, %)†	137 (34.3)	39 (32.5)	98 (35.0)	0.63
DGE (grades B–C, %)†	78 (19.5)	34 (28.3)	44 (15.7)	0.004
Median length of stay*	32 (25–42)	38.5 (29–48)	29 (23–38)	<0.001

*Mann-Whitney U-test. †Fisher's exact test or χ²-test. ‡Data of three patients were missing. §Data of two patients were missing. ¶Data of 11 patients were missing.

Values are mean±SD, n (%), or median (interquartile range), unless otherwise indicated. BMI, body mass index; ASA, American Society of Anesthesiologists; TLC, total lymphocyte count; Alb, albumin; T-cho, total cholesterol; IPMN, intraductal papillary mucinous neoplasm; PNET, pancreatic neuroendocrine tumor; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; PF, pancreatic fistula; DGE, delayed gastric emptying.

[1]. In addition, the postoperative LOS became significantly shorter. This finding is supported by those of previous reports, in which a higher hospital case volume was related to lower in-hospital mortality and a shorter LOS [1, 12, 13].

At the single very-high-volume center examined, the annual volume of PD cases increased from 1998 to 2013 (Fig. 1). The mean number of PD cases during period 2 was 2.9 times higher than that during period 1. This is because in Japan the surgical indications for PD have been expanded to benign tumors such as intraductal papillary mucinous neoplasms [14–16] or pancreatic neuroendocrine tumors [17, 18], and the procedure has been centralized.

Table 2   Univariate and multivariate analysis of prognostic factors associated with a long postoperative length of stay (> 30 days)

Variable	No. patients (n = 400)	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-value*	OR	95% CI	p-value*
Period 1 (vs. period 2)	120	3.46	2.18–5.59	<0.001	4.80	2.75–8.60	<0.001
Sex (men)	242	1.38	0.93–2.07	0.11			
Age (≥ 70 yrs)	157	1.39	0.93–2.09	0.11			
BMI (≥ 25 kg/m^2)	58	1.02	0.58–1.79	0.94			
ASA (≥ grade 3)	38	0.69	0.35–1.36	0.28			
Hypertension	143	1.64	1.09–2.49	0.02	1.87	1.13–3.12	0.015
Diabetes	107	0.79	0.50–1.22	0.29			
Etiology of disease (malignancy)	280	1.19	0.77–1.82	0.43			
PPPD (vs. SSPPD/PD)	102	1.11	0.71–1.74	0.66			
Vascular reconstruction	108	0.94	0.60–1.46	0.78			
Operative time (≥ 420 min)	142	2.02	1.33–3.09	0.001	1.74	1.02–3.01	0.043
Blood loss (≥ 1,000 ml)	86	2.02	1.23–3.35	0.005	1.10	0.56–2.14	0.78
Major complications	63	7.88	3.85–18.4	<0.001	6.20	2.77–15.5	<0.001
PF (grades B–C)	137	5.06	3.20–8.20	<0.001	5.93	3.52–10.2	<0.001
DGE (grades B–C)	78	3.43	1.99–6.15	<0.001	2.40	1.26–4.71	<0.001

*Logistic regression model. BMI, body mass index; ASA, American Society of Anesthesiologists; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; PF, pancreatic fistula; DGE, delayed gastric emptying; OR, odds ratio; CI, confidence interval.

Among the 400 PD cases reviewed herein, there were three cases (0.75%) of in-hospital mortality. This mortality rate is lower than that in other very-high-volume centers (> 28 PDs per year) in Japan (1.4%) [1]. The causes of death were pseudoaneurysm rupture (n = 1) and acute respiratory distress syndrome (n = 2). From 2011 to the present, a PD-related mortality rate of 0% has been maintained. The incidence of postoperative major complications was 15.8%, which is equal to that in a previous report [19].

The median LOS was 32 days, and the mean LOS from 2011 to 2013 was 31.7 ± 11.5 days, which is much longer than that in Western countries (7–21 days) [8]. Even in very-high-volume hospitals in Japan, the mean LOS after a PD was 32.8 ± 19.2 days [1]; thus, the LOS at our institution was similar to that in other very-high-volume centers in the country.

With regard to comparisons between the two periods, the rates of DGE and LOS were both significantly decreased in period 2; however, the rates of major complications and PF remained the same from period 1 to period 2. Major complications occurred at a constant rate after PD, which is one of the most complex and highly invasive operations; however, in the last 3 years of the study period, the rate of major

complications was 10.1% and had gradually decreased. Concerning PF, its presence can now be more accurately evaluated after standard diagnostic criteria were established in 2005 [7], and this might be related to the absence of a decrease in PF in period 2. We have been making efforts aimed at further improving the outcomes as mentioned below.

Our multivariate analysis revealed that period 1 was an independent factor related to a long LOS (> 30 days) after PD (Table 2). The incidences of major complications, the presence of PF and DGE, hypertension, and operative time were significantly associated with a long LOS. These results suggest that decreased postoperative complications and operative time contributed to shortening of the LOS.

To improve clinical outcomes, several changes in surgical procedure have been applied at our institution on the basis of the available evidence. The placement of an omental flap over splanchnic vessels could be an efficient surgical procedure to prevent postoperative pseudoaneurysms after PD [9]. Changes in the drain system, the disconnection line of the stomach, and the route of duodenojejunostomy or gastrojejunostomy were applied in 2007, and these might have contributed to the improvement of clinical outcomes. In fact, the development of stylized surgical procedures and

techniques resulted in the shortening of the operative time and the reduction of blood loss in period 2.

Strategies for perioperative care such as nutritional treatment and exercise therapy may improve the postoperative outcomes after PD. The Enhanced Recovery After Surgery (ERAS) program and the Fast-Track recovery program have been widely used, especially in colorectal surgery; these are multimodal perioperative management programs designed to achieve early recovery for patients undergoing major surgery [20–23]. Similarly, guidelines for perioperative care for PD are provided by the ERAS Society [24]. In these guidelines, the available evidence is summarized and recommendations are given regarding 27 perioperative care items. The ERAS program may be effective in the perioperative management for PD.

Despite our important findings, there are a few limitations to the present study. It was a retrospective, single-center analysis, and there thus may be a potential selection bias concerning the patients indicated for PD. Second, the number of patients was small. The clinical outcomes may also have been influenced by the hospital volume, surgeon volume, hospital training status, hospital compliance, surgical instruments, and surgical procedures [5]. How these variables affected the mortality, morbidity, and LOS should be investigated in a future study.

In conclusion, the improvement of surgical procedures and perioperative care might be related to a shorter LOS and maintaining a low mortality rate after PD. With the aim to further improve clinical outcomes, we are now performing a randomized controlled trial to investigate the efficiency of an ERAS protocol after PD (UMIN 000014068).

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