Modified reconstruction approach after pancreaticoduodenectomy optimizes postoperative outcomes: Results from a multivariate cohort analysis

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Abstract. Despite technical advances in recent decades and a decrease in hospital mortality (<5%), pancreaticoduodenectomy (PD) is still associated with major postoperative complications, even in high-volume centers. The present study aimed to assess the effect of a modified reconstruction technique on postoperative morbidity and mortality. A cohort study of all patients (n=218) undergoing PD between January 2010 and December 2019 was performed at Attikon University Hospital (Athens, Greece). Several variables were studied, including demographic data, past medical history, perioperative parameters, tumor markers and pathology, duration of hospitalization, postoperative complications, 30-day-survival, postoperative mortality and overall survival using multivariate logistic regression and survival analysis techniques. In this cohort, 123 patients [modified PD (mPD) group] underwent a modified reconstruction after a pylorus-preserving pancreaticoduodenectomy, which consisted of gastrojejunostomy and pancreaticojejunostomy on the same loop and an isolated hepaticojejunostomy on another loop. In the standard PD (StPD) group, 95 patients underwent standard reconstruction. The median age was 67 years, ranging from 25 to 89 years. Compared with in the StPD group, the mPD group had significantly lower rates of grade B and C pancreatic fistula (4.9% vs. 28.4%), delayed gastric emptying (7.3% vs. 42.1%), postoperative hemorrhage (3.3% vs. 20%), intensive care unit admission (8.1% vs. 18.9%), overall morbidity (Clavien-Dindo grade III-V: 14.7% vs. 42.0%), perioperative mortality (4.1% vs. 14.7%), and shorter hospitalization stay (11 days vs. 20 days). However, no difference was noted regarding median survival (35 months vs. 30 months). In this single-center series, a modified reconstruction after PD appears to be associated with improved postoperative outcomes. However, further evaluation in larger multi-center trials is required.

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Abbreviations: PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; AA, ampullary adenocarcinoma; DCC, distal cholangiocarcinoma; DA, duodenal adenocarcinoma; DGE, delayed gastric emptying; mPD, modified PD; StPD, standard PD; POPF, postoperative pancreatic fistula

Key words: mPD, postoperative morbidity, mortality, overall survival

Introduction

Periampullary carcinomas include neoplasms that originate from the epithelium of the pancreas, the ampulla of Vater, the distal bile duct and the duodenum, which results in the following four types of adenocarcinomas: Pancreatic ductal adenocarcinoma (PDAC), which is the most common, followed by ampullary adenocarcinoma (AA), distal cholangiocarcinoma (DCC) and duodenal adenocarcinoma (DA) (1). PDAC represents 17% of all new cancer cases in the digestive tract, with 60,430 estimated new cases in 2021 in the USA (2,3). In the United States, median overall survival (OS) differs among these adenocarcinomas, with DA having the most favorable prognosis (54-86 months), followed by AA (38-49 months) and DCC (18-33 months), whereas PDAC has the worst prognosis, given that its OS is only 11-18 months (4). Besides periampullary carcinoma, another lesion that can be considered benign but is a precursor of pancreatic adenocarcinoma is intraductal papillary mucinous neoplasm (IPMN). IPMNs are mucous-producing, cystic tumors originating from the pancreatic epithelium of the main pancreatic duct or its side branches (5).

Regardless of tumor histology, the surgical treatment of periampullary neoplasms includes pancreaticoduodenectomy

(PD) or Whipple's procedure, lymph node resection, as well as vascular reconstruction if necessary (6). PD is associated with increased rates of morbidity and major postoperative complications, such as delayed gastric emptying (DGE), which is the most common complication, pancreatic leak or fistula, postoperative hemorrhage requiring reoperation, embolism or blood transfusion, bile leak and intra-abdominal abscess (7). Over the last few years, the technique has significantly improved and it is now considered a safer procedure with a hospital mortality rate of <5% in high-volume centers (8). The aim of the present cohort study was to compare modified PD (mPD) with standard PD (StPD), in terms of postoperative complications, especially pancreatic fistula, which is the most severe adverse event. Furthermore, several perioperative factors for both groups of patients were assessed, concerning morbidity, mortality and OS.

Materials and methods

Study design. A retrospective cohort study was conducted at the Surgical Departments of the Attikon University Hospital (Athens, Greece) between January 2010 and December 2019. The present study received ethics approval by the Hospital's Scientific and Bioethics Committee (approval no. 47929/16-12-16).

Eligibility criteria. All consecutive patients undergoing PD for resectable pancreatic cancer or periampullary neoplasms at the Attikon University Hospital within the duration of the study period were recorded. Pancreatic cancer was defined as resectable in the case of absence of distant metastases, and absence of local tumor extension to the celiac axis, the hepatic artery and the superior mesenteric vasculature. Patients who were deemed as borderline-resectable received neoadjuvant cytotoxic chemotherapy, and were then restaged and reevaluated for resection.

The patients were assigned into two groups, according to the type of PD that they underwent. The type of modification after PD was selected by the lead surgeon based on their experience and the characteristics of the patient. In the first cohort, the patients underwent a mPD, while the patients in the second cohort underwent the StPD. The collected variables included patient demographics, presentation of jaundice, past medical history, tumor markers, intraoperative and anesthesiologic parameters, hospitalization days, postoperative complications, pathology, indication and cause of reoperation, 30-day-survival, postoperative mortality and OS. Pathological staging of malignant tumors was performed according to the Eighth Edition of the Cancer Staging Manual edited by the American Joint Committee on Cancer (9).

Pre-operative work-up. Pre-operative work-up for all patients included a routine computed tomography scan to assess the characteristics and size of the lesion. Abdominal magnetic resonance imaging, endo-ultrasonography and magnetic resonance cholangiopancreatography were also performed for selected patients. Biliary drainage before surgery was achieved with endoscopic retrograde cholangiopancreatography if the serum bilirubin was >15 mg/dl or if the patient presented with acute cholangitis (10).

Intraoperative parameters. Mannitol was used by some anesthesiologists to prevent postoperative renal dysfunction in patients with obstructive jaundice, based on a previous study (11).

Surgical technique. Two different surgical techniques were performed with an open approach. All of the patients in the first cohort underwent a mPD procedure with an isolated pancreaticojejunostomy and pylorus preservation, whereas all of the patients in the second cohort underwent the StPD procedure without pylorus preservation. The mPD used a Roux-en-Y configuration, draining the pancreatic duct and the stomach via the short limb and the bile duct separately via a long jejunal limb. The pylorus was preserved and mechanically dilated with two fingers prior to the construction of the gastrojejunostomy (12), retaining propulsion, while its dilatation removes an obstacle from gastric emptying. For StPD, the configuration was performed with all three anastomoses in a single jejunal loop. In all cases of mPD and StPD, the pancreatojejunostomy was performed duct to mucosa with interrupted, absorbable polydioxanone sutures, reinforced with a second continuous prolene layer incorporating seromuscular jejunum, pancreatic parenchyma and serosa. In both techniques, a stent was used in the pancreatojejunostomy.

Postoperative outcomes. The primary outcome assessed in the present study was perioperative mortality, defined as death within 30 days after operation or within index admission, irrespective of cause.

As secondary outcomes, overall morbidity, hospitalization time, recurrence and OS were recorded. Complications were categorized according to the Clavien-Dindo classification (13). Causes of morbidity were postoperative pancreatic fistula (POPF) or anastomotic leak from the pancreaticojejunostomy, DGE, postoperative hemorrhage necessitating blood transfusion, embolization or relaparotomy, intra-abdominal abscess, and postoperative hepaticojejunostomy leak. POPF, in particular, was defined as 'drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula'. A grading system was also used for POPF, in which a grade A POPF was now redefined and called a 'biochemical leak', because it has no clinical importance and no longer refers to a true pancreatic fistula, a grade B POPF referred to patients requiring medical or minimally invasive treatment, and a grade C POPF was a leakage in need of surgical intervention (12,14). Patients were assessed as to whether or not they received neoadjuvant or adjuvant chemotherapy. OS was determined from the date of operation until the date of death from any cause or the final date of follow-up, which was at the end of December 2021.

Statistical analysis. Sample characteristics were summarized as absolute (n) and relative (%) frequencies (categorical variables), or as the median and interquartile range (continuous variables). P-values were determined using the Fisher's exact test for categorical variables, and non-parametric tests (Mann-Whitney U-test) for continuous variables.

Analysis of overall mortality was based on survival methods. Univariate tests of association with potential

predictors were performed using the log-rank test for categorical variables and univariate Cox models for continuous variables (data not shown). Multivariate models were based on proportional-hazards Cox regression. Hazard ratios >1 indicated higher probabilities of death, whereas hazard ratios <1 indicated lower probabilities of death. Survival probabilities over time were graphically presented using the Kaplan-Meier method and were analyzed using the log-rank test.

Analysis of time to hospital discharge and time to recurrence were also based on time-to-event analyses; however, in these two cases, methods for competing risks were used considering that death can in both cases occur before the main event of interest (i.e. hospital discharge or recurrence). Univariate tests were based on respective Fine and Gray models of the cumulative incidence function (data not shown). The same models were used for multivariate analysis. Subdistribution hazard ratios >1 indicated higher probabilities of a positive outcome (i.e. hospital discharge or recurrence), whereas subdistribution hazard ratios <1 indicated lower probabilities of a positive outcome.

In all multivariate models, the type of operation, sex and age variables were kept in the models irrespectively of their statistical significance due to interest in them or their potential confounding effects.

For binary outcomes, associations of the outcomes with potential prognostic factors were assessed using multivariate logistic regression. In all cases, odds ratios >1 indicated higher probabilities of a positive outcome (i.e. presence of the outcome), whereas odds ratios <1 indicated lower probabilities of a positive outcome. P<0.05 was considered to indicate a statistically significant difference. All analyses were performed using Stata version 15.1 (StataCorp, LLC).

Results

Patient characteristics. Between January 2010 and December 2019, PD was performed in 218 patients. Among them, 123 patients underwent a mPD procedure, while 95 underwent the StPD procedure. The median age was 67 years, ranging from 25 to 89 years. A total of 117 patients were male and 101 patients were female. The patients' demographics and comorbidities are presented in Table I. There were no differences between the two groups in terms of sex (male 54.5% vs. 52.6%; P=0.891), smoking status (P=0.338), body mass index (BMI) status (25.10 vs. 25.87 kg/m^2; P=0.349) or American Society of Anesthesiology (ASA) scores (P=0.204) (15). Moreover, there were no major differences in the incidence of comorbidities or past surgical history.

Preoperative factors. The incidence rate of jaundice was higher among patients who underwent StPD compared with that in patients who underwent mPD (64.2% vs. 78.9%; P=0.024). However, no differences were noted in terms of blood biomarkers, such as neutrophil-to-lymphocyte ratio (NLR; 2.57 vs. 2.83; P=0.554), CEA (3.20 ng/ml vs. 2.70 ng/ml; P=0.118) and CA19-9 (58.40 U/ml vs. 50.95 U/ml; P=0.365) (Table I).

Pathology. The vast majority of neoplasms were adenocarcinomas of the pancreas in both groups (62.6% vs. 60%) followed by adenocarcinoma of Vater (12.2% vs. 12.6%), bile duct adenocarcinoma (7.3 vs. 13.7%) and IPMN (5.7% vs. 6.3%). In total, benign neoplasm or premalignant entities represented 9.8% of the tumors in the first group and 9.5% of neoplasms in the second group. There were no significant differences between the two groups regarding the tumor size (3.0 cm vs. 2.8 cm; P=0.369) (Table I).

Intraoperative parameters. Table I also shows intraoperative outcomes and anesthesiologic data for the two study groups. No differences were noted in the type of analgesia that was used during the operation, except for the use of PCA morphine and tramadol, which was higher in the first group (9.6 vs. 1.1%; P=0.006). The operative time was significantly lower in the first group (190 min vs. 320 min; P<0.001) as were the units of blood transfused [red blood cell (RBC) units (P=0.002) and fresh frozen plasma (FFP) units (P<0.001)].

Postoperative outcomes

Primary outcome. Table II shows that the perioperative mortality rates (4.1% vs. 14.7%; P=0.007) were significantly higher in the second group compared with those in the first group. Multivariate analysis for the probability of perioperative mortality revealed that StPD (P=0.040), history of coronary disease (P=0.037), intraoperative use of mannitol (P=0.009) and increased transfusion with RBCs (P=0.032) were independent significant risk factors associated with an increased rate of perioperative mortality (Table III).

Secondary outcomes. Significant differences were also reported in terms of hospitalization stay, postoperative complications and morbidity. Patients in the first group had a shorter hospitalization stay compared with that in patients in the second group (11 days vs. 20 days; P<0.001). Moreover, the rates of POPF (4.9% vs. 28.4%; P<0.001) and the grades of POPF (Grade B: 1.6% vs. 16.8%; Grade C: 3.3% vs. 11.6%; P<0.001), DGE (7.3% vs. 42.1%; P<0.001) and postoperative hemorrhage (3.3% vs. 20%; P<0.001), as well as reoperation (6.5% vs. 15.8%; P=0.043), intensive care unit (ICU) admission (8.1% vs. 18.9%; P=0.024) and overall morbidity (Clavien-Dindo grades III-V: 14.7% vs. 42%; P<0.001), were lower in the mPD group than in the StPD group. However, no differences were noted regarding the rates of postoperative abscess (3.3% vs. 9.5%; P=0.081), the overall recurrence (41.5% vs. 38.9%; P=0.385) and the death rate (51.2% vs. 53.7%; P=0.678) or the median survival (35 months vs. 30 months; P=0.247) between the groups. The median follow-up was 25 months for the mPD group and 16.5 months for the StPD group (P=0.082) (Table II).

Hospitalization days. Multivariate analysis showed that StPD (P<0.001), history of coronary disease (P<0.001), increased BMI (P=0.002), biochemical leak (P<0.001), grade C POPF (P=0.001), DGE (P<0.001) and reoperation (P=0.001) were independent significant risk factors associated with longer hospital stay. On the other hand, the use of patient-controlled analgesia morphine and tramadol as analgesia (P<0.001) seemed to act as a protective factor for shorter hospitalization stay (Table IV). Fig. 1 depicts the cumulative probabilities of discharge by time since operation with death as competing risk.

Table I. Patients' perioperative data.

Characteristic	Operation type		Total	P-value
	mPD	StPD		
Total, n (%)	123 (100.0)	95 (100.0)	218 (100.0)	
Patient demographics				
Male sex, n (%)	67 (54.5)	50 (52.6)	117 (53.7)	0.891
Smoking status, n (%)				0.338
Smoker	49 (39.8)	38 (40.0)	87 (39.9)	
Non-smoker	48 (39.0)	44 (46.3)	92 (42.2)	
Ex-smoker	24 (19.5)	12 (12.6)	36 (16.5)	
N/A	2 (1.6)	1 (1.1)	3 (1.4)	
Coronary disease, n (%)				>0.999
No	101 (82.1)	78 (82.1)	179 (82.1)	
Yes	20 (16.3)	16 (16.8)	36 (16.5)	
N/A	2 (1.6)	1 (1.1)	3 (1.4)	
Previous abdominal surgery, n (%)				0.682
No	61 (49.6)	45 (47.4)	106 (48.6)	
Yes	59 (48.0)	49 (51.6)	108 (49.5)	
N/A	3 (2.4)	1 (1.1)	4 (1.8)	
ASA score, n (%)				0.204
I	10 (8.1)	10 (10.5)	20 (9.2)	
II	62 (50.4)	54 (56.8)	116 (53.2)	
III	46 (37.4)	27 (28.4)	73 (33.5)	
IV	0 (0.0)	2 (2.1)	2 (0.9)	
N/A	5 (4.1)	2 (2.1)	7 (3.2)	
Median age, years (IQR)	67 (59, 74)	68 (60, 76)	67 (60, 75)	0.510
Median BMI, kg/m^2 (IQR)	25.10 (23.25, 27.78)	25.87 (23.02, 29.22)	25.34 (23.23, 28.58)	0.349
Preoperative characteristics				
Jaundice, n (%)				0.024
No	44 (35.8)	20 (21.1)	64 (29.4)	
Yes	79 (64.2)	75 (78.9)	154 (70.6)	
Median NLR (IQR)	2.57 (1.94, 3.44)	2.83 (1.85, 3.49)	2.59 (1.92, 3.48)	0.554
Median CEA, ng/ml (IQR)	3.20 (1.90, 6.10)	2.70 (1.70, 4.20)	2.90 (1.70, 5.20)	0.118
Median CA19-9, U/ml (IQR)	58.40 (15.90, 275.60)	50.95 (15.23, 213.65)	51.50 (15.30, 256.10)	0.365
Pathology				
Histological type, n (%)				0.844
AdenoCa Pancreas	77 (62.6)	57 (60.0)	134 (61.5)	
AdenoCa Vater	15 (12.2)	12 (12.6)	27 (12.4)	
AdenoCa BD	9 (7.3)	13 (13.7)	22 (10.1)	
AdenoCa Duodenum	4 (3.3)	1 (1.1)	5 (2.3)	
AdenoCa Gallbladder	1 (0.8)	0 (0.0)	1 (0.5)	
IPMN	7 (5.7)	6 (6.3)	13 (6.0)	
Miscellaneous	10 (8.1)	6 (6.3)	16 (7.3)	
Benign	12 (9.8)	9 (9.5)	21 (9.6)	
Median tumor size, cm (IQR)	3 (2.10, 3.60)	2.80 (2, 3.50)	2.85 (2, 3.60)	0.369
Intraoperative parameters				
Analgesia type, n (%)				0.006
PCEA	71 (57.7)	69 (72.6)	140 (64.2)	
PCA morphine	33 (26.8)	19 (20.0)	52 (23.9)	
PCA morphine and tramadol	12 (9.8)	1 (1.1)	13 (6.0)	
N/A	7 (5.7)	6 (6.3)	13 (6.0)	
Median operation duration, min (IQR)	190 (175, 216)	320 (275, 405)	230 (185, 330)	<0.001

Table I. Continued.

Characteristic	Operation type		Total	P-value
	mPD	StPD		
Median PRBC, units (IQR)	0 (0, 1)	1 (0, 2)	1 (0, 2)	0.002
Median FFP, units (IQR)	0 (0, 0)	0 (0, 2)	0 (0, 1)	<0.001

mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; IQR, interquartile range; ASA, American Society of Anesthesiology; BMI, body mass index; AdenoCa, adenocarcinoma; BD, bile duct; IPMN, intraductal papillary mucinous neoplasm; PCEA, patient-controlled epidural analgesia; PCA, patient-controlled analgesia; PRBC, packed red blood cells; FFP, fresh frozen plasma.

Table II. Postoperative outcomes.

Characteristic	Operation type		Total	P-value
	mPD	StPD		
Total, n (%)	123 (100.0)	95 (100.0)	218 (100.0)	
PF grading, n (%)				<0.001
No fistula	106 (86.2)	58 (61.1)	164 (75.2)	
Biochemical leak (A)	11 (8.9)	10 (10.5)	21 (9.6)	
B	2 (1.6)	16 (16.8)	18 (8.3)	
C	4 (3.3)	11 (11.6)	15 (6.9)	
PF clinical significance, n (%)				<0.001
Non-significant: (None or Grade A)	117 (95.1)	68 (71.6)	185 (84.9)	
Significant: (Grades B and C)	6 (4.9)	27 (28.4)	33 (15.1)	
Hemorrhage, n (%)				<0.001
No	119 (96.7)	76 (80.0)	195 (89.4)	
Yes	4 (3.3)	19 (20.0)	23 (10.6)	
Delayed gastric emptying, n (%)				<0.001
No	114 (92.7)	55 (57.9)	169 (77.5)	
Yes	9 (7.3)	40 (42.1)	49 (22.5)	
Abscess, n (%)				0.081
No	119 (96.7)	86 (90.5)	205 (94.0)	
Yes	4 (3.3)	9 (9.5)	13 (6.0)	
Reoperation, n (%)				0.043
No	115 (93.5)	80 (84.2)	195 (89.4)	
Yes	8 (6.5)	15 (15.8)	23 (10.6)	
ICU, n (%)				0.024
No	113 (91.9)	77 (81.1)	190 (87.2)	
Yes	10 (8.1)	18 (18.9)	28 (12.8)	
Clavien-Dindo classification, n (%)				<0.001
No complications	72 (58.5)	21 (22.1)	93 (42.7)	
Grade I	21 (17.1)	9 (9.5)	30 (13.8)	
Grade II	12 (9.8)	25 (26.3)	37 (17.0)	
Grade III	6 (4.9)	18 (18.9)	24 (11.0)	
Grade IV	7 (5.7)	8 (8.4)	15 (6.9)	
Grade V	5 (4.1)	14 (14.7)	19 (8.7)	
30-days mortality, n (%)				0.019
No	120 (97.6)	85 (89.5)	205 (94.0)	
Yes	3 (2.4)	10 (10.5)	13 (6.0)	
Perioperative mortality, n (%)				0.007
No	118 (95.9)	81 (85.3)	199 (91.3)	
Yes	5 (4.1)	14 (14.7)	19 (8.7)	

Table II. Continued.

Characteristic	Operation type		Total	P-value
	mPD	StPD		
Adjuvant therapy, n (%)				0.186
No	46 (37.4)	29 (30.5)	75 (34.4)	
Yes	63 (51.2)	61 (64.2)	124 (56.9)	
N/A	14 (11.4)	5 (5.3)	19 (8.7)	
Recurrence, n (%)				0.385
No	53 (43.1)	50 (52.6)	103 (47.2)	
Yes	51 (41.5)	37 (38.9)	88 (40.4)	
N/A	19 (15.4)	8 (8.4)	27 (12.4)	
Death, n (%)				0.678
No	59 (48.0)	41 (43.2)	100 (45.9)	
Yes	63 (51.2)	51 (53.7)	114 (52.3)	
N/A	1 (0.8)	3 (3.2)	4 (1.8)	
Median survival, months (IQR)	35 (25, 45)	30 (17, 49)	33 (26, 42)	0.247
Median hospitalization time, days (IQR)	11 (9, 15)	20 (15, 30)	14 (10, 22)	<0.001
Median follow-up, months (IQR)	25 (10, 42)	16.5 (4.75, 40)	20 (7, 42)	0.082

mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; IQR, interquartile range; PF, pancreatic fistula; ICU, Intensive Care Unit.

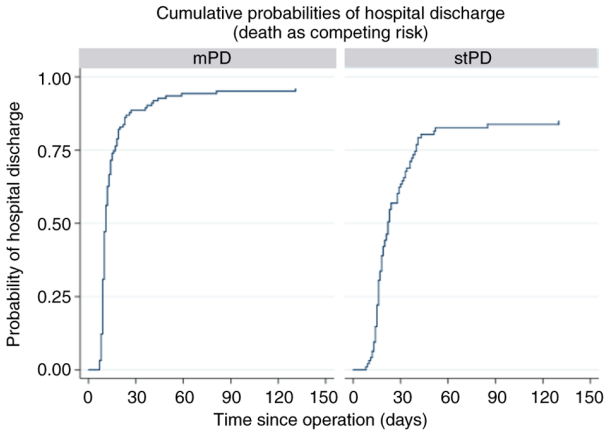

Figure 1. Cumulative probabilities of discharge by operation type (P<0.001, multivariate Fine & Gray model). mPD, modified PD; stPD, standard PD; PD, pancreaticoduodenectomy.

POPF. Multivariate analysis for the probability of clinically significant POPF revealed that StPD (P<0.001), increased NLR (P=0.012), history of previous abdominal surgery (P=0.049) and AA histological type (P=0.014) were independent significant risk factors associated with an increased rate of clinically significant POPF (Grade B and C) (Table V).

DGE. Multivariate analysis for the probability of postoperative DGE showed that StPD (P<0.001), clinically significant POPF (P=0.001) and reoperation (P=0.004) were independent significant risk factors associated with an increased rate of DGE in the patients (Table V).

Hemorrhage. Multivariate analysis for the probability of postoperative hemorrhage necessitating blood transfusion, embolization or relaparotomy showed that only clinically significant POPF (P=0.001) and increased intraoperative transfusion of FFP (P=0.019) were independent significant risk factors associated with an increased rate of postoperative hemorrhage (Table V).

Reoperation. The multivariate logistic regression model for the probability of reoperation revealed that presentation of jaundice (P=0.045), clinically significant POPF (P=0.001) and postoperative hemorrhage (P<0.001) were independent significant risk factors associated with an increased rate of reoperation, whereas history of past abdominal surgery may act as a protective factor regarding the need for reoperation (P=0.009) (Table VI).

ICU admission. Multivariate analysis for the probability of ICU admission showed that history of coronary disease (P=0.013), presentation of jaundice (P=0.026), DGE (P=0.012) and reoperation (P<0.001) were independent significant risk factors associated with an increased rate of ICU admission (Table VI).

Recurrence. Fig. 2 depicts the cumulative probabilities of recurrence by time since operation, with death as a competing risk. There was no significant difference regarding the recurrence rates between the two groups (P=0.353). Multivariate analysis for the probability of recurrence showed that higher pathological stage of malignant tumors (stage II/IIA: P=0.073, stage IIB: P=0.026, stage III: P=0.016) were independent significant risk factors associated with increased rate of recurrence (Table VII).

OS. The 1-, 2- and 5-year survival rates were 79.4, 61.5 and 37.9% for the patients operated with mPD, and 67.3, 56.2 and 37.8% for the patients operated with StPD (Fig. 3). Fig. 4 depicts the OS rates according to the histological type of the

Table III. Multivariate logistic regression (without any post-operative factor) model for the probability of perioperative mortality and death.

A, Perioperative mortality

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	3.70	(1.06, 12.91)	0.040
Coronary disease			
No[a]	1		
Yes	3.74	(1.08, 12.89)	0.037
Mannitol			
No[a]	1		
Yes	5.53	(1.54, 19.89)	0.009
PRBC, units			
Per unit	1.57	(1.04, 2.37)	0.032

B, Death

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	1.60	(1.04, 2.45)	0.032
Histological type (grouped)			
AdenoCa Pancreas[a]	1		
AdenoCa Vater	0.54	(0.26, 1.10)	0.090
AdenoCa BD	0.69	(0.37, 1.29)	0.247
IPMN	0.06	(0.01, 0.46)	0.007
Other	0.31	(0.13, 0.74)	0.009
ASA score			
I[a]	1		
II	3.43	(1.05, 11.18)	0.041
III	7.83	(2.31, 26.55)	0.001
IV	2.53	(0.25, 25.27)	0.428
Jaundice			
No[a]	1		
Yes	1.78	(1.04, 3.03)	0.034

[a]Reference category. mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; PRBC, packed red blood cells; AdenoCa, adenocarcinoma; BD, bile duct; IPMN, intraductal papillary mucinous neoplasm; ASA, American Society of Anesthesiology.

neoplasms, with a 5-year survival rate of 22.8% for the PDAC, 56.7% for AA and 27.4% for DCC. Multivariate analysis for the probability of death revealed that StPD (P=0.032), II and III ASA score (P=0.041 and P=0.001, respectively), and jaundice presentation (P=0.034) were independent significant risk factors associated with increased rate of death (Table III).

Table IV. Multivariate model (Fine and Gray) for the probability of hospital discharge.

Factor	SHR	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	0.51	(0.38, 0.67)	<0.001
Coronary disease			
No[a]	1		
Yes	0.34	(0.19, 0.62)	<0.001
BMI, kg/m^2			
Per unit	0.94	(0.90, 0.98)	0.002
Fistula grading			
No fistula[a]	1		
Biochemical leak	0.37	(0.22, 0.64)	<0.001
B	0.64	(0.37, 1.10)	0.104
C	0.11	(0.03, 0.40)	0.001
Delayed gastric emptying			
No[a]	1		
Yes	0.43	(0.29, 0.63)	<0.001
Reoperation			
No[a]	1		
Yes	0.27	(0.12, 0.58)	0.001
Analgesia type			
PCEA[a]	1		
PCA morphine	0.70	(0.46, 1.08)	0.107
PCA morphine and tramadol	2.24	(1.42, 3.52)	<0.001

[a]Reference category. Death before hospital discharge acts as a competing risk. SHR, sub-distribution hazard ratio; mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; BMI, body mass index; PCEA, patient-controlled epidural analgesia; PCA, patient-controlled analgesia; PRBC, packed red blood cells.

Discussion

In 1945, Allen O. Whipple reported for the first time a one-stage procedure for the removal of periampullary neoplasms with a postoperative mortality rate of 31% (12). Since then, >70 years of experience in the PD procedure have resulted in a decrease in hospital mortality to <5% in high-volume centers (8).

Notably, an increased rate of intraoperative mortality when using mannitol was determined in the present study, resulting in omission of the diuretic from the anesthesiologists' practice. The reason for this association has yet to be determined and may be assessed in future studies.

The global morbidity rates of PD remain high, ranging between 32 and 52%, and the majority of complications result from POPF, with an incidence rate of 10-28.5%, and DGE, with an incidence rate of 20-40% (8,14-20). One of the most useful tools to depict morbidity is the Clavien-Dindo classification. In the present study, severe postoperative complications (Clavien-Dindo grades III-V) were detected in only 14.7% of

Table V. Multivariate logistic regression model for the probability of clinically significant postoperative pancreatic fistula, delayed gastric emptying and hemorrhage.

A, Probability of clinically significant POPF

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	8.77	(3.18, 24.14)	<0.001
NLR			
Per unit	1.14	(1.03, 1.26)	0.012
Previous abdominal surgery			
No[a]	1		
Yes	2.56	(1, 6.55)	0.049
Histological type (grouped)			
AdenoCa Pancreas[a]	1		
AdenoCa Vater	4.66	(1.37, 15.82)	0.014
AdenoCa BD	3.08	(0.83, 11.50)	0.094
IPMN	3.07	(0.60, 15.59)	0.177
Other	3.22	(0.80, 12.97)	0.099

B, Probability of delayed gastric emptying

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	6.87	(2.82, 16.72)	<0.001
Clinically significant POPF			
Non-significant (No or Grade A)[a]	1		
Significant (Grades B and C)	5.14	(1.97, 13.44)	0.001
Reoperation			
No[a]	1		
Yes	5.42	(1.72, 17.08)	0.004

C, Probability of hemorrhage

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	3.86	(0.96, 15.51)	0.057
FFP (units)			
Per unit	1.60	(1.08, 2.38)	0.019
Clinically significant POPF			
Non-significant (No or Grade A)[a]	1		
Significant (Grades B and C)	6.86	(2.24, 20.95)	0.001

[a]Reference category. mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; POPF, postoperative pancreatic fistula; NLR, neutrophil-lymphocyte ratio; AdenoCa, adenocarcinoma; BD, bile duct; IPMN, intraductal papillary mucinous neoplasm; FFP, fresh frozen plasma.

patients in the mPD group, whereas in the StPD group, overall morbidity remained relevantly high at 42.0%.

Pancreatic fistulas remain an important complication of the Whipple procedure and significantly contribute to overall

Table VI. Multivariate logistic regression model for the probability of reoperation and ICU admission.

A, Probability of reoperation

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	0.33	(0.07, 1.49)	0.150
Previous abdominal surgery			
No[a]	1		
Yes	0.09	(0.01, 0.55)	0.009
Jaundice			
No[a]	1		
Yes	5.95	(1.04, 33.98)	0.045
Clinically significant POPF			
Non-significant (No or Grade A)[a]	1		
Significant (Grades B and C)	20.63	(3.72, 114.42)	0.001
Hemorrhage			
No[a]	1		
Yes	38.06	(8.16, 177.46)	<0.001

B, Probability of ICU admission

Factor	Odds ratio	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	0.65	(0.13, 3.33)	0.606
Coronary disease			
No[a]	1		
Yes	8.92	(1.60, 49.77)	0.013
Jaundice			
No[a]	1		
Yes	9.92	(1.32, 74.43)	0.026
PRBC (units)			
Per unit	2.14	(1.23, 3.72)	0.007
Type of anesthesia			
General and epidural anesthesia[a]	1		
General anesthesia	5.73	(1.26, 26.10)	0.024
Delayed gastric emptying			
No[a]	1		
Yes	7.48	(1.54, 36.19)	0.012
Reoperation			
No[a]	1		
Yes	166.51	(18.92, 1465.02)	<0.001

[a]Reference category. SHR, sub-distribution hazard ratio; mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; POPF, postoperative pancreatic fistula; ICU, Intensive Care Unit; PRBC, packed red blood cells.

morbidity after a PD. The risk factors for POPF include soft texture of the parenchyma, a small pancreatic duct, the presence of activated digestive fluids, decreased regional blood supply, the surgeon's experience and the underlying disease pathology. Several surgeons have assessed different approaches to eliminate POPF and its serious complications. Nonetheless, currently, there is no specific technique that can substantially eradicate the development of POPF (21). The aim

Table VII. Multivariate logistic regression model for the probability of recurrence.

Factor	SHR	95% CI	P-value
Operation type			
mPD[a]	1		
StPD	0.81	(0.52, 1.26)	0.353
Stage (grouped)			
I/IA[a]	1		
IB	3.00	(0.65, 13.90)	0.160
II/IIA	4.55	(0.87, 23.90)	0.073
IIB	5.67	(1.23, 26.22)	0.026
III/IIIA/IIIB	6.94	(1.42, 33.78)	0.016
Benign tumor	0.00	(0 , 0)	<0.001

[a]Reference category. Death before hospital discharge acts as a competing risk. SHR, sub-distribution hazard ratio; mPD, modified pancreatoduodenectomy; StPD, standard pancreatoduodenectomy; POPF, postoperative pancreatic fistula; ICU, Intensive Care Unit; PRBC, packed red blood cells.

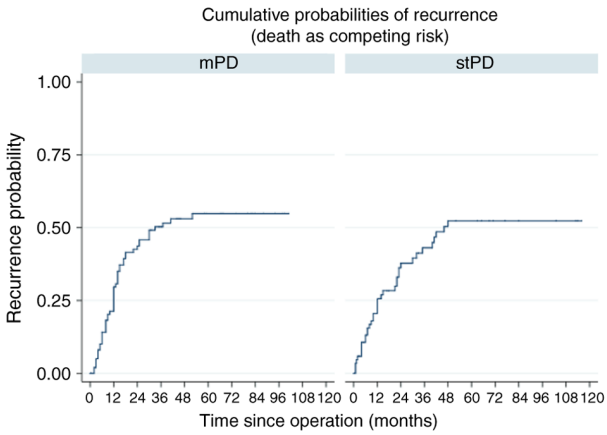

Figure 2. Cumulative probabilities of recurrence by operation type (P=0.353, multivariate Fine & Gray model). mPD, modified PD; stPD, standard PD; PD, pancreaticoduodenectomy.

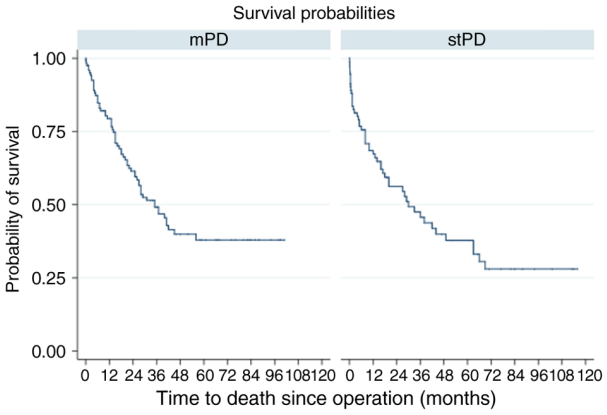

Figure 3. Survival probabilities by operation type (P=0.032, multivariate Cox model). mPD, modified PD; stPD, standard PD; PD, pancreaticoduodenectomy.

of the current study was to assess a number of preoperative and intraoperative factors, and to determine how they alter the postoperative course after a PD. Among these perioperative factors, the type of the procedure performed was revealed to be associated with significantly lower morbidity (14.7% vs. 42.0%; P<0.001) and perioperative mortality rates (4.1% vs. 14.7%; P=0.007). Besides the StPD, the present study introduced a new technique regarding the restoration of gastrointestinal continuity, which involves a Roux-en-Y configuration, with the pancreaticojejunostomy and gastrojejunostomy in the short limb and the hepaticojejunostomy separately in the long jejunal limb. Pancreatic leak is the main risk of StPD, whereas optimization of the type of anastomosis could reduce the risk of the leaks. The theory behind this approach is that the activation of pancreatic enzymes (lipase, protease, amylase) by bile salt and alkalized pH could possibly be avoided when the pancreatic anastomosis is placed far from the biliary tree and closer to the low pH of the gastric fluid. This may be due to the fact that the activity of pancreatic amylase and lipase is dependent on the pH, and thus is decreased when placed away from the hepaticojejunostomy (12). The present results showed that, overall, clinically significant POPF complicated 15.1% of the cases. Nonetheless, the rates were different between the two groups. Only 4.9% of patients operated with the mPD procedure were complicated with POPF, whereas in the StPD group the POPF rate was 28.4%. In addition, in the multivariate analysis, the type of PD performed was indicated as an independent risk factor for the probability of POPF.

Lee *et al* (17) suggested that pylorus preservation is an independent risk factor for DGE; their results showed that there was a significant difference in the DGE rates between patients that underwent pylorus-preserving and pylorus-resected PD (39.2% vs. 8.8%; P<0.001) (17). In the mPD procedure described in the present study, the pylorus was preserved. Nonetheless, a key step of the suggested procedure is the additional mechanical dilation of the pyloric muscle fibers prior to the construction of the anastomosis. This allows for future preservation of the propulsion of the pylorus, while removing the obstacle of a constricted muscle during the initial postoperative days. In addition, nonactivation of pancreatic proenzymes (trypsinogen, chymotrypsinogen, procarboxypeptidase) close to the pancreaticojejunal anastomoses could be associated with reduced local inflammation and gastroparesis, while placement of the hepaticojejunostomy distally from the stomach prevents bile salt reflux (11). This could explain the extremely low DGE rates that were recorded in the mPD group when compared not only to the StPD group (7.3 vs. 42.1%), but also to all common rates reported in the literature (7,13-19).

On a long-term basis, the most significant aspect of a novel surgical technique is the ability to prolong the life duration of a patient. The global mortality rate associated with PD has steadily decreased in experienced centers to 5% (8,14-20). Arjunan *et al* (15) observed that there was not a notably significant survival difference between patients with POPF and those without POPF (P=0.457). Veillette *et al* (22) demonstrated that there was a statistically significant increase in mortality in the presence of a fistula (P<0.01), with an ~8-fold increase detected (9.3% of patients with fistula and 1.2% in the group

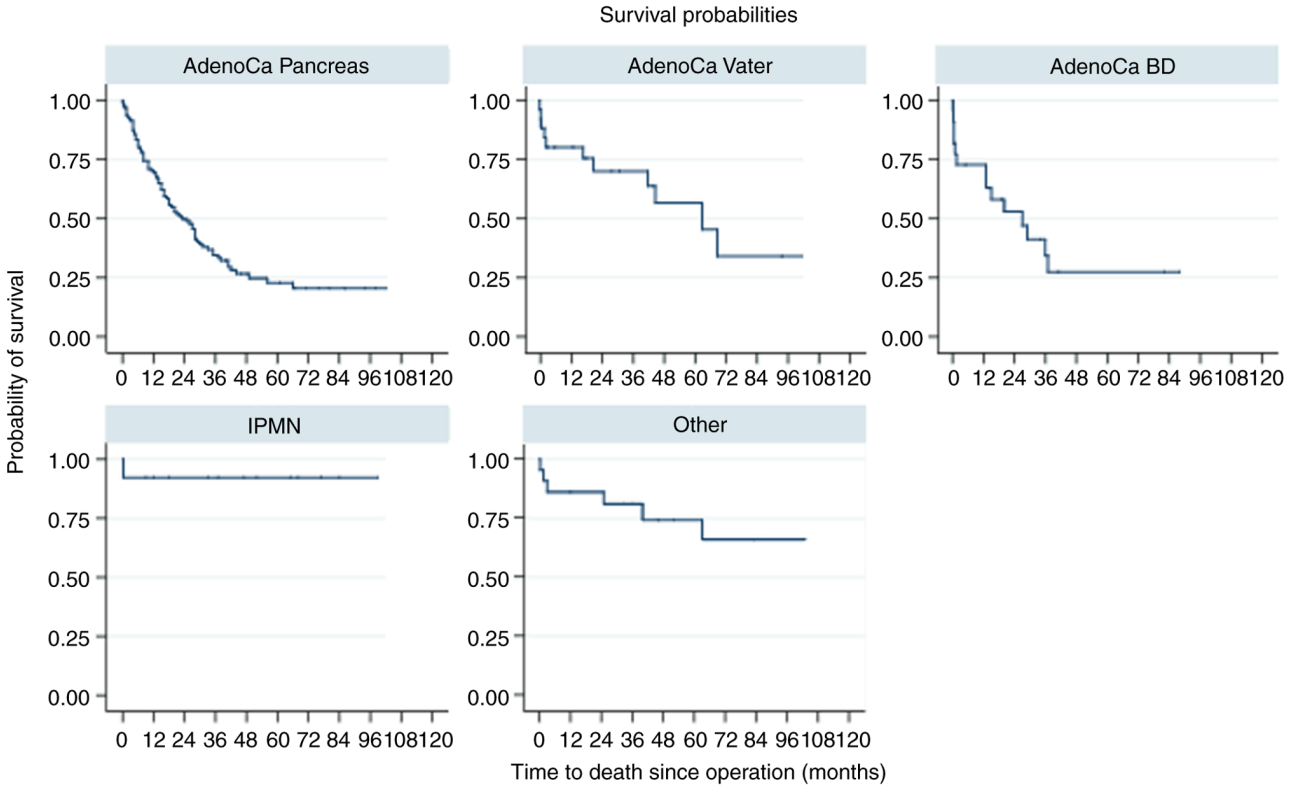

Figure 4. Survival probabilities by histological type (grouped) (P=0.005, multivariate Cox model). AdenoCa, adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; BD, bile duct.

without fistula). In a previous study, it was revealed that the major means by which a fistula can lead to death is hemorrhage (22). Thus, we can easily conclude that the presence of a POPF is a major determinant of morbidity but not mortality. As concerns the histological type, PDAC has been reported to have the worst prognosis (6). Cameron and He (8) showed that the 5-year survival rate for PDAC was 19% in the first 1,000 PDs and 24% in the second 1,000 (P=0.02). The difference between these two groups may demonstrate an increase in margin-negative resections and improved adjuvant therapy, but there was no statistically significant difference. These results were similar to the present outcomes, with a 5-year survival rate of 22.8% for PDAC. In the two study groups, there was a statistically significant difference in the perioperative mortality (4.1 vs. 14.7%; P=0.007) but not in the 5-year survival rate (51.2% vs. 53.7%; P=0.678). Therefore, even if the perioperative mortality and morbidity were radically diminished in the mPD group, the overall long-term outcome after both procedures was similar. Nonetheless, multivariate analysis for the probability of death revealed that StPD (P=0.032) was an independent significant risk factor associated with an increased rate of death. On the other hand, IPMN histopathology (P=0.007) seemed to act as a protecting factor against the incidence of death. Further studies are required to conclude if the modified technique used in the present study can increase the OS of patients.

The present study has some limitations. First, it has a moderate sample size and a retrospective study design. Although it is a single institutional study, surgical procedures were carried out by four different surgical teams, which may be a source of bias. However, they have almost an equal experience in PD. The present study emphasizes the importance of adhering to a single reproducible anastomotic technique in lowering morbidity and the survival data adds to the literature regarding cancer care.

In conclusion, the present study demonstrated that the proposed configuration for PD was associated with better postoperative outcomes. It is hypothesized that this technique creates a biochemical balance. This balance, and not surgical dexterity, may diminish inflammation and enhance the healing process, leading to better outcomes. The literature lacks evidence regarding the Roux-en-Y technique of gut reconstruction in the PD procedure and its contribution to POPF-related morbidity and mortality. Given the retrospective nature of this research, a randomized prospective study from other pancreatic centers is necessary to validate the results.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NA, VS, PV, PM, PP and SP substantially contributed to the conception and design of the study. VN, SAM and SP contributed to the acquisition and interpretation of the data, as well as manuscript drafting. TS contributed to study design, and manuscript drafting and revision. NP contributed to the statistical analysis of the manuscript and interpretation of the data. NA, VS and VP revised the final manuscript. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work, so that any questions relating to research integrity or scientific accuracy in any part of the study are appropriately investigated and resolved. SP and VN confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study received ethics approval from the Scientific and Bioethics Committee of Attikon University Hospital (approval number: 47929/16-12-16; Athens, Greece). Consent to participate was deemed unnecessary due to the retrospective nature of the study.

Patient consent for publication

Written informed consent for publication was retrospectively obtained from all patients of the study. In the case of deceased patients, informed consent was obtained from close relatives.

Competing interests

The authors declare that they have no competing interests.

References

1. Wiltberger G, Krenzien F, Atanasov G, Hau HM, Schmelzle M, Bartels M and Benzing C: Pancreaticoduodenectomy for periampullary cancer: Does the tumour entity influence perioperative morbidity and long-term outcome? Acta Chir Belg 118: 341-347, 2018.
2. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA. Cancer J 70: 7-30, 2020.
3. Surveillance, Epidemiology and End Results (SEER) Program. Available at: https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed September 25, 2021.
4. Hester CA, Dogeas E, Augustine MM, Mansour JC, Polanco PM, Porembka MR, Wang SC, Zeh HJ and Yopp AC: Incidence and comparative outcomes of periampullary cancer: A population-based analysis demonstrating improved outcomes and increased use of adjuvant therapy from 2004 to 2012. J Surg Oncol 119: 303-317, 2019.
5. Peisl S, Burckhardt O and Egger B: Limitations and prospects in the management of IPMN: A retrospective, single-center observational study. BMC Surg 23: 3, 2023.
6. El Nakeeb A, El Sorogy M, Ezzat H, Said R, El Dosoky M, Abd El Gawad M, Elsabagh AM and El Hanafy E: Predictors of long-term survival after pancreaticoduodenectomy for peri-ampullary adenocarcinoma: A retrospective study of 5-year survivors. Hepatobiliary Pancreat Dis Int 17: 443-449, 2018.
7. Karim SAM, Abdulla KS, Abdulkarim QH and Rahim FH: The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): Cross sectional study. Int J Surg 52: 383-387, 2018.
8. Cameron JL and He J: Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg 220: 530-536, 2015.
9. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, *et al*: AJCC Cancer Staging Manual. 8th edition. Springer International, New York, NY, 2017.
10. Domvnguez-Muǫoz JE, Lariǫo-Noia J and Iglesias-Garcia J: Biliary drainage in pancreatic cancer: The endoscopic retrograde cholangiopancreatography perspective. Endosc Ultrasound 6 (Suppl 3): S119-S121, 2017.
11. Gubern JM, Martínez-Ródenas F and Sitges-Serra A: Use of mannitol as a measure to prevent postoperative renal failure in patients with obstructive jaundice. Am J Surg 159: 444-445, 1990.
12. Parasyris S, Ntella V, Mantanis Z, Kokoropoulos P, Vassiliu P, Smyrniotis V and Arkadopoulos N: Brief report on a novel reconstruction technique following pancreaticoduodenectomy. Ann Surg Open 2: e0552, 2021.
13. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, *et al*: The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 161: 584-591, 2017.
14. Whipple AO: Pancreaticoduodenectomy for islet carcinoma: A five-year follow-up. Ann Surg Ann Surg 121: 847-852, 1945.
15. Arjunan R, Karthik SDS, Chowdappa R, Althaf S and Srinivas C: Contemporary surgical, oncological, and survival outcomes of pancreaticoduodenectomy for periampullary tumours: A 5-Year experience from tertiary cancer center. Indian J Surg Oncol 12: 603-610, 2021.
16. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W and Buchler M; International Study Group on Pancreatic Fistula Definition: Postoperative pancreatic fistula: An international study group (ISGPF) definition. Surgery 138: 8-13, 2005.
17. Lee YH, Hur YH, Kim HJ, Kim CY and Kim JW: Is delayed gastric emptying associated with pylorus ring preservation in patients undergoing pancreaticoduodenectomy? Asian J Surg Asian J Surg 44: 137-142, 2021.
18. Romano G, Agrusa A, Galia M, Di Buono G, Chianetta D, Sorce V, Gulotta L, Brancatelli G and Gulotta G: Whipple's pancreaticoduodenectomy: Surgical technique and perioperative clinical outcomes in a single center. Int J Surg 21 (Suppl 1): S68-S71, 2015.
19. Mirrielees JA, Weber SM, Abbott DE, Greenberg CC, Minter RM and Scarborough JE: Pancreatic fistula and delayed gastric emptying are the highest-impact complications after whipple. J Surg Res 250: 80-87, 2020.
20. El Nakeeb A, Askar W, Atef E, Hanafy EE, Sultan AM, Salah T, Shehta A, Sorogy ME, Hamdy E, Hemly ME, *et al*: Trends and outcomes of pancreaticoduodenectomy for periampullary tumors: A 25-year single-center study of 1000 consecutive cases. World J Gastroenterol 23: 7025-7036, 2017.
21. Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, Yeo CJ, Fernandez-delCastillo C, Dervenis C, Halloran C, *et al*: Pancreatic anastomosis after pancreatoduodenectomy: A position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 161: 1221-1234, 2017.
22. Veillette G, Dominguez I, Ferrone C, Thayer SP, McGrath D, Warshaw AL and Fernández-del Castillo C: Implications and management of pancreatic fistulas following pancreaticoduodenectomy: The Massachusetts General Hospital experience. Arch Surg 143: 476-481, 2008.