# Surgical outcomes after early unplanned reoperation after pancreaticoduodenectomy: a retrospective cohort study

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**Background**
Pancreaticoduodenectomy (PD) is associated with high morbidity rate. About 15% of its complications need reoperation. The current study was conducted to evaluate the indications and outcomes of early reoperations after PD.
**Patients and methods**
A retrospective review of consecutive 948 cases that underwent PD for malignant lesions between 2000 and 2018 was done. Our primary outcome was hospital morbidity and mortality for early unplanned reoperation following PD, whereas secondary outcomes included prevalence, risk factors, indications, and long-term outcomes of reoperation.
**Results**
Early postoperative complications occurred in 328 (34.6%) patients. However, 76 (8%) patients underwent early reoperation. Post-pancreatectomy hemorrhage was the most common cause of exploration (48 cases) and anastomotic leakage (26 cases). On univariate analysis, BMI more than 25 kg/m$^2$, liver cirrhosis, mass size more than 2 cm, soft pancreas, and pancreatic duct less than 3 mm were risk factors for reoperation, and all these items remained significant on multivariate analysis except for BMI. In addition, bile leakage was a strong predictor of reoperation on the same multivariate analysis. Cases that underwent reoperations showed significant delay in oral intake, prolonged hospitalization, higher morbidity, and mortality rates. Although survival was comparable between both groups for 5-year-follow up, reoperation was associated with a significant increase in recurrence after 2 years.
**Conclusion**
Unplanned reoperation increases morbidity, mortality, and 2-year recurrence after PD. Liver cirrhosis, large mass size, soft pancreatic texture, small pancreatic duct, and bile leakage are strong predictors for dreadful complications.

**Keywords:**
outcomes, pancreaticoduodenectomy, reoperation

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## Introduction

Periampullary tumors are currently the seventh leading cause of cancer-related deaths worldwide and is expected to be the third in the future [1]. Pancreaticoduodenectomy (PD) is the mainstay in the surgical treatment of periampullary tumors. It is a complex procedure that entails technically challenging resection and reconstruction by multiple anastomoses [2]. Recently, the procedure complexity has increased by the addition of neoadjuvant chemotherapy and increasing the candidate pool to include older, obese, and patients requiring vascular reconstruction [3–5].

The rate of postoperative morbidities reaches up to 30–60% of patients despite technical refinement, improved perioperative care, advances in biochemical markers of inflammation, and regionalization to high volume center [6]. Given the reduced reserve of the patients and the complexity of the surgery, minimally invasive radiological or endoscopic intervention is preferred for the management of complications after PD [7]. Nevertheless, the need for surgical reintervention for the management of complications after PD is still reported to be 2.5–15% [2,7–9].

Data on reoperation after PD are reported as part of the general experience of centers with little emphasis on the indications and outcome of reoperations. Few reports have exclusively studied the indications and outcome of unplanned reoperation after PD [2,5,9–12]. Moreover, available studies are limited by the small sample size, and only one study reported the impact on oncological outcomes [5]. The aim of the present study

is to evaluate the indications and outcomes of early reoperations after PD.

## Patients and methods

This is a retrospective cohort study of all patients who underwent PD for malignant periampullary lesions in the duration between January 2000 and September 2018. PD performed for benign tumors, recurrent malignant tumors, chronic pancreatitis, or inflammatory strictures were excluded from the study. Patient data were retrieved from a prospectively maintained computerized database for pancreatic surgery employed since January 2000. The study was approved by the Institutional Review Board (IRB No: R.20.04.819), and it was registered on clinical trials (Clinicaltrials ID: NCT04387903).

### Statement of ethics

Written consent was obtained from every patient before every intervention. This study complies with the guidelines for human studies. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical Committee approval from Mansoura University was obtained.

## Methods

The primary outcome in the study was hospital morbidity and mortality for early unplanned reoperation after PD. Secondary outcome included prevalence, risk factors, indications, and long-term outcomes of reoperation after PD. Postoperative pancreatic fistula (POPF) was defined as the presence of drainage fluid of any amount containing amylase more than three times compared with the serum level. It was graded according to the management plan into grade A which needed no change in the management plan, grade B which needed additional drainage or patient discharge with drains, and grade C which needed surgical intervention, ICU admission, or led to patient mortality [13]. Biliary leakage was defined as presence of bile in the drainage fluid that persists to postoperative day (POD) 4 [14].

In addition, delayed gastric emptying was defined as the need for nasogastric (NG) tube for 15 days or the need for reinsertion after removal [15]. Leakage from the gastrojejunal anastomosis was identified by either detection of gastric or intestinal content through the drains, or through upper gastrointestinal gastrografin series showing contrast leakage [16]. Dindo–Clavien classification was adopted for the grading of complications after PD [17]. Early reoperation was defined as unplanned reoperation for the management of procedure-related complications mortality within 30 days or within the same admission. Hospital mortality was defined as mortality within 30 days or within the same admission after index surgery.

Preoperative assessment was performed by clinical examination and detailed laboratory investigations, including complete blood count, liver function tests, renal function tests, and tumor markers. Assessment of local extension of the tumor and metastatic workup was performed by pelvi-abdominal ultrasound (US), triphasic abdominal computed tomography (CT) with the angiographic assessment of the surrounding vessels, bone survey, and chest radiograph. Preoperative biliary drainage was performed in the case of hyperbilirubinemia (>20 mg/dl), renal insult, and the need for preoperative nutritional preparation.

Resection by classic PD or pylorus-preserving PD was performed by experienced surgeons who finished training in pancreatic surgery. Pancreatic stump reconstruction was performed by pancreaticogastrostomy (PG) or pancreaticojejunostomy either as a simple loop or a Roux-en-Y reconstruction. Gastric continuity was restored by duodenojejunostomy in pylorus-preserving PD and by manual or stapled gastrojejunostomy (GJ) in classic PD. The choice of the operative technique was based on the operating surgeon's preference. The evolution of our surgical practice in PD was detailed in previous reports [18,19].

Patients were transferred to the intensive care unit after PD for at least 1 day. Prophylactic antibiotic therapy and selective octreotide prophylaxis, in patients at risk for pancreatic fistula, were started intraoperatively and continued till the fourth POD. The daily output of abdominal drains and NG tubes were recorded. The patient started an oral fluid diet after removal of NG tube when he passed flatus or when the daily output of the NG tube was less than 500 ml/day. Drainage fluid amylase was measured on POD 1 and 5. Routine abdominal US was performed on the fourth POD and repeated on suspicion of intraabdominal collections. Patients were scheduled for regular outpatient visits at 2-week, 1-month, and 6-month intervals after discharge, followed by a visit every 6months lifelong.

Surgical reintervention was performed in case of failure or infeasibility of management by interventional radiology or endoscopy. Reoperation for anastomotic leakage or infected abdominal collection was performed when it was infeasible for US or CT-guided drainage. Reoperation for intraluminal or extraluminal bleeding

was performed if angiographic or endoscopic control fails, and also in cases of patients' hemodynamic instability, hemoglobin drop more than 5 g/dl, or blood transfusion more than five units of packed red blood cells. Other indications included management of wound dehiscence, employment of feeding tube, and intestinal complications such as obstruction or ischemia.

Patient data included demographic characteristics, associated comorbidities, symptoms, and signs on presentation, results of laboratory investigations, and findings on preoperative imaging studies. Operative variables included pancreatic consistency, liver status, tumor size, reconstruction techniques, pancreatic duct diameter, blood transfusion, and operative time. POD were recorded, including complications, hospital stay, abdominal drainage output, drainage fluid amylase, timing, and an indication of reintervention, and hospital mortality. Follow-up data, including overall survival and disease-free survival, was also reported.

### Statistical analysis

Data distribution was tested for normality using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The statistical significance level was set at less than 0.05. Categorical variables are expressed as group percentages and were compared for independent samples using the $\chi^2$ test. Continuous data are presented as medians with range or means with SD and were compared for independent samples using the *t* test or Mann–Whitney test. The strength of the association between variables was further assessed by the Spearman correlation coefficient. Variables with *P* value less than 1 were entered into a logistic regression model to determine independent risk factors of a specific outcome. The independent risk factors of the variables were expressed as odds ratios with their 95% confidence intervals. Cumulative survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Statistical analyses were performed using SPSS, version 17 (SPSS Inc., Chicago, Illinois, USA).

## Results

In all, 948 patients underwent PD for the management of periampullary tumors during the study period.

In all, 328 (34.6%) patients had early postoperative complications, and 76 (8%) patients underwent early reoperation for management. Details of postoperative complications and indications for reoperations are summarized in Table 1. Post-pancreatectomy hemorrhage (PPH) was the most common

**Table 1 Postoperative complications after pancreaticoduodenectomy**

| | Conservative (*N*=252) | Reoperation (*N*=76) | Interval between reoperation and index surgery |
|---|---|---|---|
| Internal hemorrhage | 0 | 20 | 1 (1–2) |
| Subcutaneous hematoma | 0 | 1 | 1 |
| Bleeding PG | 5 | 11 | 1 (1–3) |
| Bleeding GJ | 10 | 10 | 1 (1–2) |
| POPF | 140 | 14 | 6 (5–15) |
| Leakage from HJ | 74 | 8 | 6 (5–12) |
| Leakage from GJ/DJ | 7 | 4 | 5 (4–10) |
| Obstructed GJ | 0 | 3 | 6 (5–12) |
| Pancreatitis | 16 | 1 | 5 |
| Burst abdomen | 0 | 3 | 11 (10–12) |
| Intestinal ischemia | 0 | 1 | 2 |

DJ, duodenojejunostomy; GJ, gastrojejunostomy; HJ, hepaticojejunostomy; PG, pancreaticogastrostomy; POPF, postoperative pancreatic fistula.

(*n*=48, 5.1%) indication for reoperation including subcutaneous (*n*=1), intraluminal (*n*=21), extraluminal (*n*=20), and secondary hemorrhage (*n*=6). Sources of extraluminal bleeding included gall bladder bed (three), mesenteric vessels (give), gastroduodenal artery (six), superior mesenteric vein (one), portal vein (two), and from the attachment of the mesopancreas (three). Intraluminal bleeding was managed through gastrotomy and underrunning of the bleeding points. A feeding jejunostomy was employed in case of bleeding PG.

Anastomotic leakage was the second most common (*n*=26, 34.2%) indication of reoperation. Most of the leakage from pancreatic (91%), biliary (90.2%), and GJ (63.6%) anastomoses were managed conservatively. POPF (*n*=14) presented with manifestations of local abdominal sepsis, and six patients presented with secondary hemorrhage. POPF was managed by lavage and drainage (eight), anastomotic dismantling and stump closure (two), repair over internal stent (two), or completion of pancreatectomy (two). Feeding jejunostomy was employed during reoperation for POPF. Leaking hepaticojejunostomy was managed by drainage only (five) or reanastomosis over stents (three). Leakage or obstruction at the GJ was managed by refashioning of the anastomosis and feeding jejunostomy. One patient had a large mesenteric hematoma and bowel ischemia, which was managed by evacuation of hematoma and heparin infusion with no need for resection on a second look.

On univariate analysis, factors significantly associated with higher risk of reoperation included BMI higher

than 25 kg/m$^2$ ($P$=0.02), liver cirrhosis ($P$=0.01), larger mass size more than 2 cm ($P$=0.016), soft pancreatic consistency ($P$=0.03%), and pancreatic duct diameter less than or equal to 3 mm ($P$=0.015). On multivariate analysis, independent risk factors for reoperation after PD were male sex, BMI more than 25 kg/m$^2$, liver cirrhosis, larger mass size, soft pancreas, pancreatic duct diameter less than 3 mm, GJ performed by a stapler, and biliary leakage. Univariate and multivariate analyses of factors associated with a higher risk of reoperation are summarized in Tables 2 and 3.

Complications after reoperations included anastomotic leakage, PPH, and pancreatitis. Nineteen patients had

**Table 2 Univariate analysis for factors predicting the need for early reoperation**

| Parameters | Early reoperation (76) [*n* (%)] | No reoperation (872) [*n* (%)] | *P* value |
|---|---|---|---|
| Age (years) | | | |
| <60 | 54 (71.1) | 615 (70.5) | 0.92 |
| >60 | 22 (28.9) | 257 (29.5) | |
| Sex | | | |
| Male | 53 (69.7) | 522 (59.9) | 0.09 |
| Female | 23 (30.3) | 350 (40.15) | |
| BMI (kg/m$^2$) | | | |
| <25 | 40 (52.6) | 574 (65.8) | 0.02 |
| >25 | 36 (47.4) | 298 (34.2) | |
| Jaundice | 70 (92.1) | 790 (90.6) | 0.66 |
| Diabetes mellitus | 13 (17.1) | 145 (16.6) | 0.91 |
| Preoperative biliary drainage | 43 (56.6) | 410 (47) | 0.11 |
| Liver cirrhosis | 20 (26.3) | 110 (12.6) | 0.01 |
| Mass size (cm) | | | |
| ≤2 | 22 (28.9) | 495 (56.8) | 0.016 |
| >2 | 54 (71.1) | 377 (43.2) | |
| Pancreatic texture | | | |
| Soft | 52 (68.4) | 486 (55.7) | 0.03 |
| Firm | 24 (31.6) | 386 (44.3) | |
| Pancreatic duct diameter (mm) | | | |
| ≤3 | 43 (56.6) | 242 (27.8) | 0.015 |
| >3 | 33 (43.4) | 630 (72.2) | |
| Type of pancreatic reconstruction | | | |
| PG | 58 (76.3) | 703 (80.6) | 0.62 |
| PJ | 15 (19.7) | 126 (14.4) | |
| Isolated PJ | 3 (3.9) | 43 (4.9) | |
| GJ by stapler | 11 (15.9) | 75 (9.7) | 0.09 |
| Operative time (h) | 5 (3–9) | 5 (3–10) | 0.89 |
| Blood loss (ml) | 500 (50–4000) | 500 (50–5000) | 0.47 |
| Approach | | | |
| Open | 72 (94.7) | 837 (95.9) | 0.67 |
| Laparoscopic | 4 (5.3) | 35 (4.01) | |
| POPF | 14 (18.4) | 140 (16.1) | 0.59 |
| Bile leak | 8 (10.5) | 74 (8.4) | 0.05 |

GJ, gastrojejunostomy; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; POPF, postoperative pancreatic fistula.

**Table 3 Multivariate analysis for factors predicting the need for early reoperation**

| Variables | *B* | SE | Wald | Significance | Exp(*B*) | 95% CI for Exp(*B*) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Male sex | –0.442 | 0.286 | 2.388 | 0.122 | 0.643 | 0.367 | 1.126 |
| BMI >25 | 0.377 | 0.273 | 1.907 | 0.167 | 1.458 | 0.854 | 2.492 |
| Liver cirrhosis | 0.818 | 0.272 | 9.043 | 0.003 | 2.267 | 1.330 | 3.864 |
| Size of the mass >2 cm | –0.706 | 0.291 | 5.879 | 0.015 | 0.494 | 0.279 | 0.873 |
| Soft pancreas | –0.721 | 0.283 | 6.490 | 0.011 | 0.486 | 0.279 | 0.847 |
| Pancreatic duct <3 mm | –0.590 | 0.274 | 4.627 | 0.031 | 0.554 | 0.324 | 0.949 |
| GJ by stapler | 0.547 | 0.289 | 3.567 | 0.059 | 1.728 | 0.980 | 3.047 |
| Bile leakage | 0.901 | 0.339 | 7.046 | 0.008 | 2.461 | 1.266 | 4.786 |

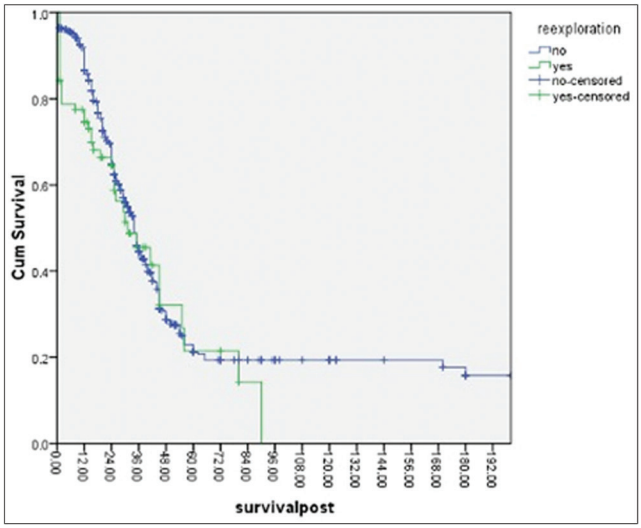
GJ, gastrojejunostomy.

**Table 4 Comparison of postoperative course in terms of individual complications**

| Parameters | Early reoperation | No reoperation | *P* value |
|---|---|---|---|
| Time to oral intake (days) | 7 (5–51) | 5 (3–56) | 0.0001 |
| Hospital stay (days) | 15 (8–70) | 8 (5–71) | 0.0001 |
| DGE [*n* (%)] | 23 (30.3) | 151 (17.3) | 0.005 |
| Wound infection [*n* (%)] | 6 (7.9) | 48 (5.5) | 0.39 |
| Abdominal collection [*n* (%)] | 11 (14.5) | 55 (6.3) | 0.007 |
| Pulmonary complication [*n* (%)] | 8 (10.5) | 34 (3.9) | 0.007 |
| Hospital mortality [*n* (%)] | 10 (13.2) | 32 (3.7) | 0.0001 |
| Recurrence rate after 1-year [*n* (%)] | 10 (13.2) | 72 (8.3) | 0.15 |
| Recurrence rate after 2-year [*n* (%)] | 18 (23.75) | 102 (11.7) | 0.003 |
| Median survival (months) | 31 | 34.1 | 0.23 |
| 1-year survival | 77% | 92% | |
| 3-year survival | 46% | 67% | |
| 5-year survival | 22% | 24% | |

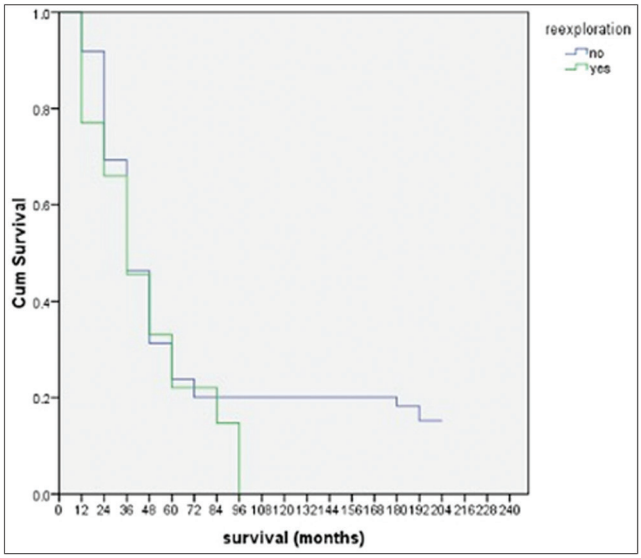
DGE, delayed gastric emptying.

**Figure 1**




Actuarial survival (Kaplan–Meier analysis) after PD according to reexploration. PD, pancreaticoduodenectomy.

**Figure 2**




Life table after PD according to reexploration. PD, pancreaticoduodenectomy.

anastomotic leakage from the pancreas (12, 26.3%), hepaticojejunostomy (five, 6.6%), and GJ (one, 1.3%). Extraluminal bleeding occurred in five (6.6%) patients, who were managed by a second reoperation. Intraluminal bleeding from PG occurred in one (1.3%) patient and from GJ in four (5.3%) patients. Pancreatitis occurred in two (2.6%) patients.

The postoperative course after reoperation compared with patients who did not undergo reoperation is summarized in Table 4. The main cause of hospital mortality in the reoperation group was due to uncontrollable bleeding (five) followed by persistent leakage and sepsis (three), severe chest infection (one), and pulmonary embolism (one). Causes of hospital mortality in the nonreoperation group were persistent leakage and sepsis (15), multiorgan failure (10), pulmonary embolism (six), and severe pancreatitis (one). Two-year recurrence was significantly higher in the reoperation group, while the two groups showed comparable findings regarding 1-, 3-, and 5-year survival rates (Figs 1 and 2). Despite that, the nonoperation group had better survival compared with the reoperated cases.

## Discussion

PD is a technically demanding procedure. The reported rate of postoperative morbidities is high ranging from 10 to 60% [10]. A substantial percentage of complications require reoperation despite advances in postoperative care. Unplanned reoperation is considered a more objective quality indicator in comparison to hospital readmissions [7]. Besides pressure on health systems, reoperation after PD is also associated with high morbidity and mortality rate [8]. Nevertheless, few studies have exclusively reported outcomes and risk factors for reoperation after PD. Also, the long-

term impact of reoperation on survival and oncological outcome was not reported.

POPF is known to be the Achilles' heel of pancreatic surgery, but it seems that PPH is a dark horse in the context of reoperation after PD. Despite the low prevalence (6–15%) [20], PPH is the most frequent indication (25–70%) of unplanned reoperation after PD with a hospital mortality rate up to 55% [2,5,8]. Also, a substantial percentage of reoperation for POPF is due to secondary PPH [21]. In a retrospective study by Wolk *et al.* [21] comparing management of PPH in the time periods between 1994–2009 and 2010–2014, there was no significant difference in the rate of surgical intervention (48.6 vs. 42.1%, $P$=0.47), while there was a significant increase in management by IR (24.6 vs. 4.3%, $P$<0.001) on the expense of a significant reduction in endoscopic management (7.0 vs. 30%, $P$<0.001). Wellner *et al.* [22] reported reoperation in 51% of patients with extraluminal bleeding as the first line of treatment. Also, surgical reintervention was the second line of treatment in 22% of patients with PPH with a success rate of 100%.

Although percutaneous drainage is currently the mainstay in the treatment of POPF, a substantial proportion of cases are still treated by surgical reintervention [23]. In this series, 9.1% of patients with clinically relevant POPF were treated by reoperation, while the majority (90.9%) was treated by tube drainage, nutritional support, and observation. A recent multicenter study, including nine Dutch centers, stated that about 25% of cases of POPF were treated by relaparotomy in the period between 2005 and 2013 [10]. Moreover, POPF can be complicated or associated with secondary PPH, infected abdominal collection, biliary leakage, and life-threatening sequelae such as multiorgan failure [24]. These sequelae may be a stand-alone indication for reoperation even with well-drained POPF.

Given the technical complexity of the procedure and the high risk for reoperation, approaching the reoperation after PD as a stand-alone procedure with regard to risk factors, surgical techniques, and postoperative care would help standardization of the process for better short-term and long-term outcome. Currently, the main concern of the literature on PD is the determination of risk factors for POPF or other individual complications. Extension of analysis to reoperation after PD in general yields information not extractable from the analysis of individual post-pancreatectomy complications. This series reported risk factors for reoperations related to gastric and biliary reconstruction and to complications as PPH and biliary leakage, which are not reported with analysis of risk factors for POPF and biliary leakage separately, such as male sex, larger mass (>2 cm), liver cirrhosis, GJ performed by a stapler, and biliary leakage [25].

Determination of risk factors for reoperations after PD, collectively, has many clinical implications. First, selective implementation of an enhanced recovery program for patients at lower risk for reoperation allows the rational direction of medical resources [26,27]. Second, the determination of patients at high risk allows for informative patient counseling leading to knowledge-based consent. Also, institutional measures for prophylaxis against POPF, PPH, and biliary leakage should be implemented in high-risk patients [28]. Prophylactic measures include regionalization of the risky patients to experienced pancreatic surgeons, prophylactic somatostatin-analog therapy, omental flaps on anastomosis and major vessels, serosal covering of major vessels, application of local tissue adhesive, individualized pancreaticoenteric anastomosis, anastomotic stenting, and tailored management of surgical drains [29,30].

It goes without debate that reoperation after PD should be limited to the hands of experienced pancreatic surgeons in tertiary centers with facilities of IR and endoscopy. The current literature is lacking standardization of the surgical technique for reoperation after PD. This is a step behind other disciplines and techniques as reoperations after bariatric surgery and complicated cholecystectomy. More effort toward standardization of the surgical management of PD complications would define a step-wise procedure, avoid unnecessary steps, and provide a targeted reoperative field. Another aspect of procedural standardization is the proper timing of intervention. Currently, there is a significantly higher mortality rate in complicated PD managed by surgery compared with IR and endoscopy [8]. However, this is biased by that candidates for reoperations are patients who are vitally unstable or in whom other nonsurgical interventions failed. Improvement of the reoperative outcome can be achieved through a dynamic and realistic definition of candidates for surgical intervention leading to an earlier intervention.

Lessing *et al.* [5] found no significant impact of reoperation on the oncologic outcome and overall survival (907 ± 130 vs. 1029 ± 202 days, $P$=0.416). On the other hand, in this series, reoperations after PD had a negative impact on patient 1- and 3-year survival ($P$=0.001). The recurrence rate was also significantly higher after 2 years ($P$=0.003). This latter finding advocates a different follow-up protocol for the reoperation group. A suggested follow-up protocol entails more frequent evaluation visits, optimized adjuvant chemotherapy, and low threshold for suspicion of recurrence.

The limitations of this study are its retrospective nature. This is also a single-center experience, and extrapolation of results requires a larger scale multicenter study. Reoperations were performed by multiple surgeons, and despite sharing high expertise, this may be a source of performance bias.

## Conclusion

On the basis of previous findings, unplanned reoperation increases morbidity, mortality, and 2-year recurrence after PD. Liver cirrhosis, large mass size, soft pancreatic texture, small pancreatic duct, and bile leakage are strong predictors for this dreadful complication.

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Author contributions: This study was carried out in collaboration between all authors. Ayman El Nakeeb designed the study; Hosam Hamed and Mohamed Abdelgawad wrote the protocol and managed the literature research. Youssif Elmahdy and Mohamed Attia performed the statistical analysis. All surgical procedures were carried out by the same surgical team including the six authors. All authors read and approved the final manuscript.

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### Conflicts of interest

There are no conflicts of interest.

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