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Delaying surgery after preoperative biliary drainage does not increase surgical morbidity after pancreaticoduodenectomy

Feng Yang, MD, PhD[a], Chen Jin, MD, PhD[a], Caifeng Zou, BSc[a], Yang Di, MD, PhD[a], Sijie Hao, MD, PhD[a], Haihui Huang, MD[b], Andrew L. Warshaw, MD, FACS, FRCSEd (Hon)[c], Deliang Fu, MD, PhD[a,*]

[a] Department of Pancreatic Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, China
[b] Institute of Antibiotics, Huashan Hospital, Shanghai Medical College, Fudan University, China
[c] Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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ABSTRACT

Background: The effects of the time interval from preoperative biliary drainage to pancreaticoduodenectomy on morbidity and mortality have not been established, but a recent multicenter study found that an interval greater than 4 weeks resulted in fewer major complications. We investigated whether delaying pancreaticoduodenectomy after preoperative biliary drainage led to improved postoperative morbidity and mortality.

Methods: Patients who underwent elective open pancreaticoduodenectomy between January 2009 and December 2016 were retrospectively analyzed. They were divided into a short duration group (time interval to surgery <4 weeks) and a delaying surgery group (time interval to surgery ≥4 weeks). An unstented control group (no stent group) was added. Perioperative characteristics and surgical outcomes were compared.

Results: Of 603 patients who underwent pancreaticoduodenectomy, 183 (30.3%) had preoperative biliary drainage, 110 patients (18.2%) in the short duration group and 73 (12.1%) in the delaying surgery group. The median interval between preoperative biliary drainage and pancreaticoduodenectomy was 3 weeks (interquartile range, 2–3) for the former group and 6 weeks (interquartile range, 5–7) for the latter. With the exception of wound infection, which was significantly higher in the short duration group than in the controls (8.2% vs 1.7%, $P = .002$) but not significantly increased compared with the delaying surgery group (8.2% vs 4.1%, $P = .368$), other complications were comparable among the 3 groups. Subgroup analyses in the intermediate- and high-risk cohort based on either original or alternative Fistula Risk Score showed similar outcomes. Univariate and multivariate analyses showed that short stent duration and female sex were independent factors associated with wound infection.

Conclusion: A time interval between preoperative biliary drainage and resection greater than 4 weeks does not have a negative impact on short-term surgical outcomes. This finding indicates the relative safety of postponing surgery, if necessary, for preoperative treatment, optimization, or preparation.

Introduction

The incidence of pancreatic cancer in China is increasing as in the United States.[1,2] Accordingly, more and more patients are undergoing pancreaticoduodenectomy (PD).[3] Some studies have shown that preoperative biliary drainage (PBD) for biliary obstruction caused by periampullary malignancies increases surgical morbidity after PD and have recommended against routine biliary drainage. Nevertheless, a study using the Surveillance, Epidemiology, and End Results and linked Medicare claims data showed that the use of PBD had progressively increased in the United States,[4] and the biliary stent was often placed before referral for an evaluation by a surgeon.[5] Centralization of pancreatic surgery and neoadjuvant therapy may improve outcomes of pancreatic cancer[6,7] but increase the time before the operation and the justification for PBD in patients with obstructive jaundice.[5] Although

* Reprint requests: Professor Deliang Fu, MD, PhD, Fudan University, Department of Pancreatic Surgery, Huashan Hospital, Shanghai Medical College, Shanghai 200040, China.
E-mail address: surgeonfu@163.com (D. Fu).

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PBD improves liver, coagulation, and immune functions that affect perioperative recovery in jaundiced patients,[8] its benefit remains controversial. Studies examining the effect of PBD on surgical morbidity after PD have reported conflicting results.[9–11] Additionally, most do not consider an optimal time interval between PBD and surgery.

There are currently no guidelines on the optimal timing of PD after PBD.[12] The commonly accepted practice is to perform surgery when metabolic disorders have reversed, commonly requiring 4 to 6 weeks.[13] This elapsed time has been accepted as appropriate in a randomized controlled trial,[14] which resulted in a paradigm shift in the management of pancreatic head cancer by showing a limited benefit of PBD followed by PD 4 to 6 weeks later. Notably, 46% of enrolled patients in the biliary-drainage group from this trial had complications related to PBD. A short duration of drainage may not be sufficient to achieve the goal of reducing jaundice, but a prolonged duration increases the risk of PBD-related complications, such as cholangitis, and may result in further delaying surgery. In clinical practice, PD is sometimes postponed even beyond this timeframe owing to the patient's poor condition or for neoadjuvant therapy, which is increasingly considered for both borderline or locally advanced and resectable pancreatic ductal adenocarcinoma. Although postponing surgery after PBD has not been shown to influence oncological outcome,[15] biliary stenting facilitates bacterial migration upstream from the alimentary tract and increases the chances of postoperative infectious complications.

Whether extending the time interval from PBD to surgery has an effect on postoperative morbidity and mortality after PD is not clear. A prospective multicenter study investigating the association between the duration of PBD and surgical outcomes after PD showed that major complications were greater when the interval to operation was <4 weeks after PBD.[16] It is the only investigation addressing the elapsed time from PBD to surgery, but it may have selection bias as more patients in the short duration group had a higher body mass index and soft pancreas, both of which are risk factors for postoperative pancreatic fistula (POPF).[17] In addition, the study lacks a comparison with a group without a biliary stent. Given the paucity of existing data, we sought to determine whether delaying PD after PBD resulted in increased surgical morbidity.

Methods

All patients with benign or malignant disease of the pancreatic head, duodenum, ampulla of Vater, and distal common bile duct who underwent surgery in our department between January 2009 and December 2016 were identified from a review of the hospital physician workstation.[17,18] Only patients receiving an elective open PD were enrolled in this study. Those who lacked information about main pancreatic duct diameter and gland texture ($n = 87$) were excluded. The study was approved by the ethics committee of Huashan Hospital affiliated to Fudan University.

PBD and perioperative care

PBD by means of endoscopic retrograde cholangiopancreaticography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) was performed in patients with total bilirubin levels equal to or higher than 10 mg/dL (170 mmol/L), cholangitis at presentation, and expected delay in surgery (planned neoadjuvant therapy, preoperative clinical assessment, and correction of comobidities). Patients who underwent initial diagnosis and PBD at other hospitals before referral for surgery were included in this study. The majority of our patients (89%) underwent biliary decompression by ERCP. Plastic stents placed at ERCP were commonly used for resectable cancer, but an uncovered, self-expanding metal stent was used in candidates for neoadjuvant therapy. Endoscopic deployment of a metal stent or PTBD was used in the event of primary stent occlusion.

The surgical techniques and perioperative management have been reported previously.[17] The operations were mainly performed by 2 experienced surgeons during the study time period. Although the case numbers they performed were significantly different, no relation between pylorus preservation and individual surgeon preference was noted. Bile specimens were collected intraoperatively after division of the bile duct and cultured for aerobic or anaerobic microorganisms. Antibiotic prophylaxis was administered with intravenous cephalosporins (cefazolin, cefotiam, cefoxitin, or cefuroxime) pre-incision and redosed after 4 hours during the procedure. A course of ceftriaxone or cefoperazone and sulbactam was given for about 5 days if there was evidence of cholangitis before the operation. Antibiotics were adjusted according to the susceptibility of the bacteria in bile cultures. The antibiotic regimens for postoperative infectious complications have been described in our previous study.[17]

Study group and data collection

Patients who underwent PBD were divided into 2 groups, based on the time to surgery after PBD. One group comprised patients whose time interval was <4 weeks (short duration group); the other group had a time interval of ≥4 weeks (delaying surgery group). A no stent group was added as a control. Patient demographics, medical history, clinicopathologic features, date and route (endoscopic or percutaneous) of stent placement, and perioperative data were collected and compared for surgical outcomes.

Definitions of postoperative complications

Definitions of postoperative complications have been previously described.[17,19,20] In brief, we used the consensus statements on POPF, delayed gastric emptying, postpancreatectomy hemorrhage, and chyle leak by the International Study Group of Pancreatic Surgery.[21–24] The severity of surgical morbidity was classified according to the Clavien-Dindo system, and complications of grade ≥III were considered as major.[25,26] Mortality was defined as death during the hospital stay or within 90 days after surgery. Readmission was defined as unplanned hospital admission within 90 days after initial surgery.[17,19,20]

Statistical analysis

Data were described as frequencies (percentages of population) and mean ± standard deviation or median (interquartile range [IQR]), depending on data distribution and type. Comparisons of variables among multiple independent groups were performed by means of the χ^2 or Fisher exact test, as appropriate for nominal variables, and the one-way ANOVA or Kruskal-Wallis test for continuous variables. Bonferroni correction was applied for pairwise comparisons when significant differences were detected ($\alpha = 0.05/3$). Univariate and multivariate logistic regression analyses were performed to assess the associations between clinicopathologic variables and morbidity. Statistical analyses were conducted using the Statistical Package for Social Sciences version 24.0 (SPSS Inc, Chicago, IL).

Results

During the study period, 603 patients who underwent PD were enrolled. The majority were men ($n = 354$, 58.7%), and the median age was 64 years. There were 561 (93%) patients who underwent a

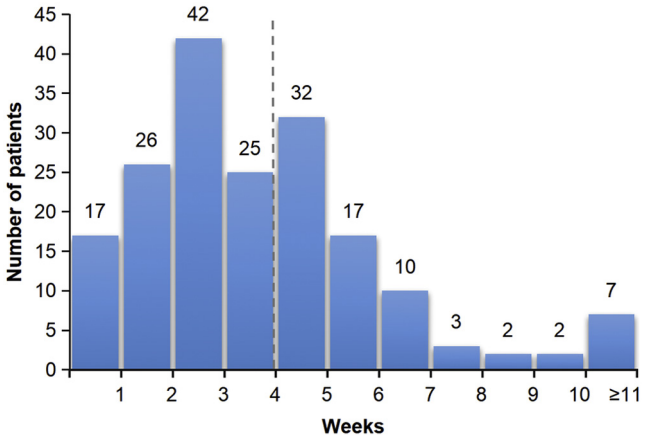

Fig 1. Distribution of time interval between PBD and surgery (weeks).

classical Whipple procedure, and 42 (7%) patients who underwent pylorus preserving PD. One hundred and eighty-three (30.3%) were stented, 162 (88.5%) by endoscopic and 21 (11.5%) by percutaneous drainage. The distribution of time intervals between stent placement and surgery is shown in Fig 1. The distribution of time intervals was consistent over the course of this study (first half vs second half: 4.6 ± 2.3 weeks vs 4.5 ± 5.8 weeks, $P = .953$). One hundred and ten (18.2%) patients were in the short duration group and 73 (12.1%) in the delaying surgery group. The median interval between PBD and PD was 3 weeks (IQR, 2–3) for the former group, and 6 weeks (IQR, 5–7) for the latter. The proportion of patients delaying ≥4 weeks was similar between the first and second half of the PBD cohort (44.6% vs 35.2%, $P = .194$). Fourteen patients had delayed operation for more than 7 weeks, with reasons including recurrent cholangitis ($n = 7$), neoadjuvant therapy ($n = 4$), delayed referral ($n = 2$), and slow regression of jaundice ($n = 1$). The median time to surgery from diagnosis in the control group was 1 week (IQR, 1–2).

Patient demographics and clinicopathologic characteristics are summarized in Table I. The groups did not significantly differ in sex, body mass index, comorbidity, neoadjuvant therapy, lesion size, and American Society of Anesthesiologists classification. There were no differences among patients whose stent was endoscopic versus percutaneous. Patients in the delaying surgery group were older by nearly 4 years than those in the control group ($P = .023$). The levels of total bilirubin (TB), whether ≥2 or ≥5 mg/dL, progressively improved in the interval from PBD to surgery. Serum albumin level was within the normal range for all groups; however, its median value was significantly higher in non-stented patients than in either stented group (both $P < .001$). The majority of patients (96.2%) in this study had malignant disease, whereas 3.6% of the short duration and 4.1% of the delaying surgery groups had benign disease. Overall, 300 (49.8%) patients had pancreatic cancer. Details of patient characteristics and pathologic diagnoses are shown in Table I.

The intraoperative features of the 3 groups are listed in Table II. There was no difference among the groups in terms of surgical approach, except that there was more pylorus preservation in the control group. Most intraoperative outcomes, including operation time and estimated blood loss, were comparable among the groups, but the control group had a lower rate of intraoperative blood transfusion and higher proportion of soft pancreas. Although a small main pancreatic duct (<3 mm) was observed more often in non-stented versus stented patients, the difference was not significant. Among the 126 stented patients with bile culture results, 86.5% had bacterobilia (84.4% in the short duration group vs 89.8% in the delaying surgery group, $P = .389$), compared with only 18.1% of non-stented patients ($P < .001$).

The postoperative outcomes of the 3 groups are summarized in Table III. The overall morbidity and mortality rates were 40.8% and 0.3%, respectively. No significant differences were observed in the rates of POPF, delayed gastric emptying, postpancreatectomy hemorrhage, pulmonary complications, and major complications. Similarly, the occurrence of gastrointestinal, biliary, and chyle leaks had no significant difference among the 3 groups, with the exception of wound infection, which was significantly higher in the short duration group. The other infectious complications, including intra-abdominal abscess and sepsis, were similar. Wound infection occurred in 7 (1.7%), 9 (8.2%), and 3 (4.1%) patients in the control, short duration, and delaying surgery groups, respectively (control versus short duration group, $P = .002$; short duration versus delaying surgery group, $P = .368$). The incidence of Clostridium difficile colitis did not differ among the 3 groups ($P = .820$). There were no differences in the rates of other clinical outcomes (reoperation, median postsurgical hospital stay, 90-day mortality, and readmission). Subgroup analyses in the intermediate- and high-risk cohort based on either Fistula Risk Score[27] or alternative Fistula Risk Score[28] showed no differences (Table IV & Supplementary Table I). Likewise, the same results were found in the cohort with malignant disease (Supplementary Table II). No significant difference in outcomes was detected between patients with and without preoperative cholangitis (Supplementary Table III), but patients who presented with higher bilirubin levels (TB ≥5 mg/dL) developed more wound infections versus those with TB <5 mg/dL (Supplementary Table IV). There was no significant difference in complications with ERCP placed stents versus PTBD (Supplementary Table V).

Univariate logistic regression analysis showed that delaying surgery did not affect wound infection, but short stent duration was significantly associated with a higher rate of wound infection. This finding was confirmed in multivariate analysis. In addition to PBD, gender (female sex) was an independent factor significantly associated with the likelihood of wound infection in both univariate and multivariate analyses. Bacterobilia attained statistical significance in univariate analysis, but its impact was lost in multivariate analysis. These analyses are summarized in Table V.

Discussion

In recent decades, PD has become safer. Although the postoperative morbidity we report here is consistent with a large series from the Massachusetts General Hospital,[9] other studies have indicated that PBD significantly increased the occurrence of morbidity.[10,11] The conflicting outcomes published in the literature could be due to selection bias, including variations in hospital volume, drainage route, stent type (plastic or metal), duration of PBD, severity of jaundice, disease spectrum, age, and metabolic derangement. Although our patients were older and had lower serum albumin levels, the incidence of overall morbidity and major complications, including POPF,[27,29] was similar whether or not they had PBD.

Although some studies[14,30] have advocated waiting 4 to 6 weeks after stent placement, an optimal time interval between PBD and PD is not clear. Arkadopoulos et al reported that surgery as little as 2 to 4 weeks after PBD increased postoperative infectious complications.[31] A recent meta-analysis revealed that stenting resulted in a greater overall morbidity compared with no stenting, while delaying surgery had no such effect.[32] A more recent study comparing different durations of PBD followed by PD found that a short duration of stenting was associated with higher biliary fistula rates, increased major complications, and a longer hospital stay.[16]

Table I
Demographic and clinicopathological characteristics

Variables	No stent ($n = 420$)	Short duration ($n = 110$)	Delaying surgery ($n = 73$)	P value
Age in years, mean ± SD	58.6 ± 11.6	60.7 ± 9.9	62.5 ± 11.4	.014*
Sex M/F, n (%)	235/185 (56/44)	72/38 (65.5/34.5)	47/26 (64.4/35.6)	.114
BMI, kg/m^2, mean ± SD	22.48 ± 2.85	22.25 ± 2.67	21.68 ± 2.71	.076
Comorbidity, n (%)				
Smoking	96 (22.9)	32 (29.1)	20 (27.4)	.334
Diabetes	105 (25)	33 (30)	19 (26)	.568
Hypertension	129 (30.7)	26 (23.6)	18 (24.7)	.247
History of abdominal surgery	110 (26.2)	23 (20.9)	18 (24.7)	.522
Stent placement route n (%)				.858
Endoscopic		97 (88.2)	65 (89)	
Percutaneous		13 (11.8)	8 (11)	
Stent to surgery in days, median (IQR)		18 (10–21)	37 (31–47.5)	< .001
Neoadjuvant therapy,† n (%)	17 (4)	4 (3.6)	6 (8.2)	.259
Total bilirubin ≥2 mg/dL, n (%)	68 (16.2)	62 (56.4)	26 (35.6)	< .001‡
Total bilirubin ≥5 mg/dL, n (%)	30 (7.1)	17 (15.5)	1 (1.4)	.001§
Serum albumin, g/L, mean ± SD	40.5 ± 3.9	37.7 ± 3.6	38.4 ± 4.0	< .001‖
ASA II–III, n (%)	272 (64.8)	78 (70.9)	49 (67.1)	.471
Lesion size, cm, median (IQR)	3 (2-4)	3 (2-4)	3 (2-3.9)	.019¶
Histology, malignant/benign, n (%)	296/124 (70.5/29.5)	106/4 (96.4/3.6)	70/3 (95.9/4.1)	< .001‖
Pathology, n (%)				< .001‖
Pancreatic cancer	184 (43.8)	73 (66.4)	43 (58.9)	
Pancreatic cystic tumor	86 (20.5)	1 (0.9)	0 (0)	
PNET	12 (2.9)	0 (0)	0 (0)	
Ampullary cancer	53 (12.6)	26 (23.6)	22 (30.1)	
Duodenal cancer	43 (10.2)	6 (5.5)	3 (4.1)	
Biliary cancer	7 (1.7)	0 (0)	2 (2.7)	
Chronic pancreatitis	22 (5.2)	2 (1.8)	1 (1.4)	
Others	13 (3.1)	2 (1.8)	2 (2.7)	

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *F*, female; *M*, male; *PNET*, pancreatic neuroendocrine tumor; *SD*, standard deviation.

* $P = .023$ no stent versus delaying surgery.

† Neoadjuvant therapy regimens included gemcitabine-based combination chemotherapy ($n = 20$), gemcitabine alone ($n = 2$), S-1 alone ($n = 2$), radiation therapy ($n = 2$), and chemoradiation therapy with gemcitabine plus S-1 ($n = 1$).

‡ $P < .001$ no stent versus short duration, $P < .001$ no stent versus delaying surgery, $P = .006$ short duration vs delaying surgery.

§ $P = .006$ no stent versus short duration, $P = .002$ short duration versus delaying surgery.

‖ $P < .001$ no stent versus short duration, $P < .001$ no stent versus delaying surgery.

¶ Adjusted $P = .058$ no stent versus short duration.

Table II
Intraoperative data

Variables	No stent ($n = 420$)	Short duration ($n = 110$)	Delaying surgery ($n = 73$)	P value
PPPD, n (%)	41 (9.8)	1 (0.9)	0 (0)	< .001*
Vessel resection, n (%)	64 (15.2)	23 (20.9)	11 (15.1)	.342
Combined colectomy, n (%)	18 (4.3)	5 (4.5)	4 (5.5)	.865
Operation time in hours, mean ± SD	6.3 ± 1.2	6.6 ± 1.2	6.4 ± 1.1	.128
Estimated blood loss in mL, mean ± SD	441.1 ± 335.9	468.2 ± 268.7	434.2 ± 230.9	.687
Intraoperative RBC transfusion, n (%)	163 (38.8)	61 (55.5)	43 (58.9)	< .001†
Soft pancreas, n (%)	277 (66)	54 (49.1)	34 (46.6)	< .001‡
MPD <3 mm, n (%)	145 (34.5)	31 (28.2)	18 (24.7)	.153
Bacterobilia, n (%)	43 (18.1)††	65 (84.4)‡‡	44 (89.8)***	< .001**

MPD, main pancreatic duct; *PPPD*, pylorus preserving pancreaticoduodennctomy; *RBC*, red blood cell; *SD*, standard deviation.

* $P = .002$ no stent versus short duration, $P = .005$ no stent versus delaying surgery.

† $P = .002$ no stent versus short duration, $P < .001$ no stent versus delaying surgery.

‡ $P = .001$ no stent versus short duration, $P = .002$ no stent versus delaying surgery.

** $P < .001$ no stent versus short duration, $P < .001$ no stent versus delaying surgery.

†† 237 patients had intraoperative bile culture results.

‡‡ 77 patients had intraoperative bile culture results.

*** 49 patients had intraoperative bile culture results.

Based on these reports, it seems that 4 to 6 weeks between stenting and surgery is acceptable.

In the present study, delaying surgery did not translate into greater morbidity or major complications. Patients in this group had fewer wound infections than those in the short stent group, although not significantly. Normalization of serum bilirubin levels, which was accomplished in nearly two thirds of the delaying surgery group, was associated with lower rates of wound infection. This explanation is supported by Sandini et al, who showed that patients with short stent duration had the highest bilirubin levels and were most likely to develop surgical site infections.[16] Although the lack of significant difference between short and long intervals in our study might be a type II error owing to inadequate sample size, the results remained the same when we included data from the 87 patients who had been excluded (Supplementary Table VI).

The low rate of wound infection in our patients was congruent with a recent study from Japan,[33] partly attributed to the relatively lower body mass index of the Asian population. Female sex was also revealed as a risk factor for wound infection in our study. It may be related to the effect of sex hormone levels on immune function,[34]

Table III
Postoperative outcomes in the total cohort ($N = 603$)

Variables	No stent ($n = 420$)	Short duration ($n = 110$)	Delaying surgery ($n = 73$)	*P* value
Overall complications	171 (40.7)	46 (41.8)	29 (39.7)	.959
Clavien-Dindo classification				.754
I	42 (24.6)	11 (23.9)	7 (24.1)	
II	78 (45.6)	25 (54.3)	17 (58.6)	
IIIa	23 (13.5)	6 (13)	3 (10.3)	
IIIb	19 (11.1)	1 (2.2)	1 (3.4)	
IVa	7 (4.1)	2 (4.3)	1 (3.4)	
IVb	1 (0.6)	1 (2.2)	0 (0)	
V	1 (0.6)	0 (0)	0 (0)	
Major complications	51 (12.1)	10 (9.1)	5 (6.8)	.323
CR-POPF	70 (16.7)	15 (13.6)	12 (16.4)	.741
Grade B	60 (85.7)	13 (86.7)	12 (100)	
Grade C	10 (14.3)	2 (13.3)	0 (0)	
Delayed gastric emptying	32 (7.6)	9 (8.2)	3 (4.1)	.525
Grade A	11 (34.4)	3 (33.3)	0 (0)	
Grade B	9 (28.1)	2 (22.2)	1 (33.3)	
Grade C	12 (37.5)	4 (44.4)	2 (66.7)	
PPH	21 (5)	4 (3.6)	1 (1.4)	.421
Pulmonary complications	47 (11.2)	12 (10.9)	7 (9.6)	.921
Chyle leak	27 (6.4)	3 (2.7)	8 (11)	.079
GI and/or bile leaks	2 (0.5)	1 (0.9)	0 (0)	.663
Intra-abdominal fluid collection	8 (1.9)	4 (3.6)	0 (0)	.262
Intra-abdominal abscess	14 (3.3)	2 (1.8)	3 (4.1)	.619
Sepsis	6 (1.4)	2 (1.8)	1 (1.4)	.872
Wound infection	7 (1.7)	9 (8.2)	3 (4.1)	.003*
Positive drainage culture	126 (30)	33 (30)	28 (38.4)	.351
Reoperation	19 (4.5)	1 (0.9)	1 (1.4)	.124
90-day mortality	1 (0.2)	1 (0.9)	0 (0)	.515
90-day readmission	42 (10)	11 (10)	6 (8.2)	.891
Postsurgical hospital stay (d)	12 (9–16)	11.5 (9–17.3)	12 (9.5–17.5)	.844

Data are number of patients (%), or median (IQR).
CR-POPF, clinically relevant postoperative pancreatic fistula; *GI*, gastrointestinal; *PPH*, postpancreatectomy hemorrhage.
* $P = .002$ no stent versus short duration, $P = .368$ short duration versus delaying surgery.

Table IV
Postoperative outcomes in the intermediate- and high-risk cohort based on FRS ($n = 433$)

Variables	No stent ($n = 318$)	Short duration ($n = 67$)	Delaying surgery ($n = 48$)	*P* value
Overall complications	150 (47.2)	37 (55.2)	22 (45.8)	.457
Clavien-Dindo classification				.795
I	36 (24)	9 (24.3)	3 (13.6)	
II	69 (46)	21 (56.8)	14 (63.6)	
IIIa	20 (13.3)	5 (13.5)	3 (13.6)	
IIIb	18 (12)	1 (2.7)	1 (4.5)	
IVa	5 (3.3)	1 (2.7)	1 (4.5)	
IVb	1 (0.7)	0 (0)	0 (0)	
V	1 (0.7)	0 (0)	0 (0)	
Major complications	45 (14.2)	7 (10.4)	5 (10.4)	.600
CR-POPF	66 (20.8)	15 (22.4)	12 (25)	.785
Grade B	56 (84.8)	13 (86.7)	12 (100)	
Grade C	10 (15.2)	2 (13.3)	0 (0)	
Delayed gastric emptying	27 (8.5)	8 (11.9)	1 (2.1)	.164
Grade A	10 (37)	2 (25)	0 (0)	
Grade B	6 (22.2)	2 (25)	1 (100)	
Grade C	11 (40.7)	4 (50)	0 (0)	
PPH	18 (5.7)	2 (3)	1 (2.1)	.416
Pulmonary complications	42 (13.2)	8 (11.9)	6 (12.5)	.957
Chyle leak	22 (6.9)	2 (3.0)	7 (14.6)	.064
GI or bile leaks	2 (0.6)	0 (0)	0 (0)	> .999
Intra-abdominal fluid collection	8 (2.5)	3 (4.5)	0 (0)	.322
Intra-abdominal abscess	13 (4.1)	2 (3)	3 (6.3)	.683
Sepsis	6 (1.9)	1 (1.5)	0 (0)	> .999
Wound infection	7 (2.2)	8 (11.9)	1 (2.1)	.001*
Positive drainage culture	109 (34.3)	25 (37.3)	22 (45.8)	.290
Reoperation	18 (5.7)	1 (1.5)	1 (2.1)	.227
90-day mortality	1 (0.3)	1 (1.5)	0 (0)	.461
90-day readmission	33 (10.4)	9 (13.4)	3 (6.3)	.461
Postsurgical hospital stay (d)	12 (10–17.3)	12 (9–21)	12.5 (10–17.8)	.992

Data are number of patients (%), or median (IQR).
CR-POPF, clinically relevant postoperative pancreatic fistula; *GI*, gastrointestinal; *PPH*, postpancreatectomy hemorrhage.
* $P = .001$ no stent versus short duration, $P = .052$ short stent versus delaying surgery.

Table V
Univariate and multivariate logistic regression analyses assessing independent predictors for wound infection

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Group		.006		.032
No stent	1.0 (reference)		1.0 (reference)	
Short duration	5.257 (1.912–14.455)	.001	9.527 (1.774–51.181)	.009
Delaying surgery	2.529 (0.639–10.011)	.186	5.119 (0.693–37.837)	.110
Age ≥63 y	1.228 (0.492–3.067)	.660		
Female	3.195 (1.197–8.524)	.020	5.941 (1.190–29.657)	.030
BMI ≥25 kg/m^2	1.132 (0.323–3.969)	.847		
Diabetes	1.015 (0.360–2.865)	.978		
Preoperative chemoradiation	1.192 (0.153–9.278)	.867		
Serum albumin <35 g/L	1.027 (0.232–4.556)	.972		
Total bilirubin ≥2 mg/dL	1.335 (0.499–3.576)	.565		
ASA (II-III)	1.447 (0.514–4.076)	.484		
Malignant disease	2.410 (0.550–10.567)	.243		
Lesion size ≥2 cm	0.997 (0.285–3.492)	.997		
Vessel resection	0.965 (0.276–3.377)	.956		
Combined colectomy	1.192 (0.153–9.278)	.867		
Intraoperative blood loss ≥600 mL	1.535 (0.573–4.116)	.394		
Operation time ≥7 h	1.462 (0.579–3.694)	.422		
Intraoperative RBC transfusion	1.414 (0.566–3.531)	.458		
Bacterobilia	5.045 (1.033–24.632)	.045	—	—

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CI*, confidence interval; *OR*, odds ratio; *RBC*, red blood cell.

and relatively thicker abdominal subcutaneous fat in Asian women.[35,36] Consistent with recent studies,[37,38] bacterobilia was associated with an increased rate of wound infection by univariate analysis in our study, but its impact was lost in multivariate analysis. Given that antibiotic treatment for bacterobilia may reduce wound infection rates after PD,[39] intraoperative bile culture is useful for prediction and prevention of wound infection.

Surprisingly, we didn't observe significant difference in the rate of other infectious complications, such as intra-abdominal abscess and sepsis. Although infected bile increased the chance of bacterial contamination in the surgical field, we failed to show significance between a positive postoperative drainage culture and surgical morbidities after PD.[17] Prophylactic antibiotics covering bacterobilia might have prevented infectious complications after PD,[40] making the differences between our study groups non-significant.

In routine practice, the time to surgery after PBD before PD is influenced by multiple factors. The common reasons for delaying surgery include slow recovery from severe jaundice, neoadjuvant therapy, recurrent cholangitis, and patient-related factors such as poor physical status, malnutrition, and comorbidities. Because PD is often referred to pancreatic surgery specialists at high-volume centers,[41] another reason for a delay is related to referral patterns (both physician-to-physician referrals and patient self-referrals[42]) and geographic or travel challenges. Some delays are caused by long waiting times for outpatient appointments or access for admissions to hospitals.

Our study has several limitations. It is retrospective and not randomized, which may lead to selection bias. The majority of patients in the control group had no jaundice. However, when we compared with those having a significant hyperbilirubinemia who got a direct operation, the outcomes remained consistent (Supplementary Table VII). Additionally, we set 4 weeks as an arbitrary cut-off point in line with previous studies.[14,16] Selection of other cut-off points may lead to different results. However, the results remained unchanged when we selected patients who were stented for more than either 6 or 7 weeks as the delaying surgery group (Supplementary Table VIII & IX). When time interval to surgery was treated as a continuous variable, only chyle leak had a significant difference ($P = .048$, Supplementary Fig 1); patients who developed a chyle leak had a longer time interval to surgery than those who did not. This result was similar to our basic analysis, which showed that delaying surgery had a higher rate of chyle leak, although not significant (Table III). Furthermore, data on specific stent type was incomplete and periprocedural antibiotics were not available for analysis. Reasons for delaying surgery were incompletely recorded. Finally, generalization of our results might be limited because they came from of a single, high-volume center study.

In conclusion, PBD increases the risk of wound infection, but neither short- nor long-term intervals until PD has a further negative impact on postoperative outcomes. This finding indicates the relative safety of postponing surgery after biliary stent placement by more than 4 weeks and allows for expanded preoperative treatment, including neoadjuvant therapy and patient optimization.

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Conflict of interest/Disclosure

We declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.07.012.

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