Preoperative Biliary Stenting and Major Morbidity After Pancreatoduodenectomy: Does Elapsed Time Matter?

The FRAGERITA Study Group

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Objective: To analyze possible associations between the duration of stent placement before surgery and the occurrence and severity of postoperative complications after pancreatoduodenectomy (PD).

Background: The effect of preoperative stent duration on postoperative outcomes after PD has not been investigated.

Methods: From 2013 to 2016, patients who underwent PD for any reasons after biliary stent placement at 5 European academic centers were analyzed from prospectively maintained databases. The primary aim was to investigate the association between the duration of preoperative biliary stenting and postoperative morbidity. Patients were stratified by stent duration into 3 groups: short (<4 weeks), intermediate (4–8 weeks), and long (≥8 weeks).

Results: In all, 312 patients were analyzed. The median time from stent placement to surgery was 37 days (2–559 days), and most operations were performed for pancreatic cancer (67.6%). Morbidity and mortality rates were 56.0% and 2.6%, respectively. Patients in the short group (n = 106) experienced a higher rate of major morbidity (43.4% vs 20.0% vs 24.2%; $P < 0.001$), biliary fistulae (13.2% vs 4.3% vs 5.5%; $P = 0.031$), and length of hospital stay [16 (10–52) days vs 12 (8–35) days vs 12 (8–43) days; $P = 0.025$]. A multivariate adjusted model identified the short stent duration as an independent risk factor for major complications (odds ratio 2.64, 95% confidence interval 1.23–5.67, $P = 0.013$).

Conclusions: When jaundice treatment cannot be avoided, delaying surgery up to 1 month after biliary stenting may reduce major morbidity, procedure-related complications, and length of hospital stay.

Keywords: biliary stent, complications, pancreaticoduodenectomy, preoperative biliary drainage, surgical outcomes, timing

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Preoperative biliary stenting (PBS) in jaundice patients with periampullary malignancy is debated. PBS can reverse detrimental effects of persistent cholestasis, such as hepatic inflammation, liver cell damage, imbalanced T-cell homeostasis, and altered neutrophil phagocytosis.[1–3] Hepatic impairment, with consequent coagulopathy and immune dysfunction, has been associated with increased postoperative infections, anastomotic leakages, poor wound healing, and decreased resilience after surgery[4,5]. Consequently, preoperative biliary drainage to lower bilirubin levels before pancreatoduodenectomy (PD) has been routinely used to limit the risk of postoperative morbidity. However, recent data report high rates of postoperative morbidity in biliary stent-bearing patients. The underlying mechanisms could be as follows: endoscopic drain placement accounts for 5% to 7% of procedure-related severe complications, such as pancreatitis, bleeding, perforation, and cholangitis, which can impair preoperative homeostasis or delay the surgical procedure[6,7]; stent placement creates a communication between the biliary system and the duodenum, facilitating the upstream bacterial migration from the alimentary tract. Bacterial contamination of the bile has been independently associated with higher rates of infectious complications, severe morbidity, and postoperative mortality.[8–10] Other retrospective studies and randomized controlled trials failed to demonstrate the superiority of PBS over upfront resection in cases of jaundice for malignancy of the periampullary region.[11–15]

Based on these data, current guidelines recommend to avoid routine biliary stenting, and to limit the procedure to symptomatic jaundice before referral to pancreatic centers, cholangitis, or planned neoadjuvant treatment.[16]

Disagreement may be partially explained by the great heterogeneity of analyzed populations, including different indications for PD and different risk factors for postoperative complications. Additionally, the elapsed time between stenting and surgery could represent a confounder. Despite delaying surgery by 4 to 6 weeks having been suggested,[17] the time needed for recovery after biliary drainage is undefined, and no gold standard tests have been recognized to quantify the recovery of liver functions.

The aim of this study was to evaluate the potential association between the duration of PBS and the occurrence and severity of postoperative morbidity in patients undergoing PD.

METHODS

Patient Selection

Prospectively maintained databases from 5 European academic medical centers [Hôpital Nord (A), Marseille, Hôpital Michalon (B), Grenoble; University Medical Center Schleswig-Holstein (C), Luebeck; San Gerardo Hospital (D), Monza,

Humanitas Research Hospital (E), Rozzano] were searched for patients who had undergone a PD from January 2013 to December 2016. Centers C and E are classified as very high-volume, tertiary centers, whereas centers A, B, and D as high-volume centers.[18]

All patients who underwent PBS before PD were included. Biliary drain was performed according to international guidelines[16] when bilirubin level was equal or greater than 15 mg/dL (250 mmol/L), in case of cholangitis or when neoadjuvant treatment was planned. The elapsed time from stent to surgery was related to several factors, such as benign versus malignant disease, indication for neoadjuvant treatment and degrees of response to the latter, recovery of liver function, and occurrence of poststent complications. Demographic and perioperative characteristics, data on postoperative complications, and indication for surgery were collected. Information on the date of stent placement, route of stent placement (endoscopic or percutaneous), stent type (plastic or metal), and postprocedure complications were retrospectively retrieved from the medical records.

Patients were divided into 3 groups, based on the interval time between biliary stenting and surgery based on prior results[9]: short, when the operation was scheduled within 4 weeks after the stent placement; intermediate, between 4 and 8 weeks; and long, after more than 8 weeks.

Liver Function

To estimate liver function, we calculated the preoperative albumin-bilirubin (ALBI) score. The ALBI formula combines the plasma levels of albumin and bilirubin. It restitutes a score, which provides high accuracy in estimating long-term survival after surgical resection for primary liver disease.[19]

Surgical Technique and Postoperative Management

Pylorus-preserving PDs or classic Whipple procedures were performed by experienced hepatobiliary and pancreatic surgeons. Antibiotic prophylaxis was carried out with intravenous cefazolin 2 g (centers A, B, D, and E), or cefoxitin 2 g plus metronidazole 500 mg (center C), and repeated after 4 hours during operation. Drain amylase levels were checked on postoperative days 1, 3, and 5. The postoperative management of the patients was carried out according to international guidelines at all institutions.[16]

Intraoperative Bile Culture

In 269 patients, intraoperative cultures of the bile were available. The results of cultures and antimicrobial susceptibility tests performed at each center were reviewed by 1 investigator to avoid bias. The pattern of antibiotic resistance was defined according to the classification of Magiorakos et al,[20] and used to stratify into multidrug-sensitive (MDS), multidrug-resistant (MDR), extensive drug-resistant (XDR), and pandrug-resistant (PDR) infection.

Postoperative Complications

Complications were considered as any 30-day deviation from the patient recovery, prolonging the length of hospitalization, requiring supplementary care or readmission. Major complications were defined as any complications equal or more than grade 3 according to the Clavien-Dindo classification.[21] Pancreatic fistula, delayed gastric emptying, and postpancreatectomy hemorrhage were diagnosed and classified per the International Study Group of Pancreatic Surgery classification.[22–24] Biliary fistula was defined as any bilious fluid from the abdominal drains, or bile collection requiring drainage. Infectious morbidity was considered as a composite outcome, including wound, organ space and urinary tract infection, pneumonia, sepsis, infected POPF, or cholangitis.[25] Postoperative mortality was intended as any deaths occurring within 90 days after surgery.

Statistical Analysis

Continuous variables were assessed for normal distribution by the Shapiro-Wilk test, and are expressed as mean values and standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as absolute numbers and percentages.

Nonrandom association was tested using the Fisher exact chi-square test for categorical variables and Bonferroni comparison for multiple groups, whereas the Student t test or the Mann-Whitney U test and Bonferroni correction were used to compare continuous data. The likelihood of postoperative major complications was calculated as odds ratio (OR) and adjusted for confounders on a logistic regression model. For each test, a 2-sided P value of 0.05 was considered significant. Statistical analysis was performed using IBM SPSS, version 24 (IBM Corp., Armonk, NY).

RESULTS

During the study period, 712 PDs were performed. In all, 312 patients (43.8%) underwent PD after preoperative biliary stenting, representing the study population. Perioperative patient features are described in Table 1 and Supplementary Table 1 (http://links.lww.com/SLA/B434). The median time from stent placement to surgery was 37 days (2–559; mean 60.9 ± 75.8 SD): among the 17 patients (5.4%) who had the operation after more than 6 months after stent placement, 12 had pancreatic ductal adenocarcinoma (PDAC) (7 underwent neoadjuvant therapy), 1 pancreatic neuroendocrine tumor, 1 intraductal papillary mucinous neoplasm, and 3 chronic pancreatitis. Figure 1 depicts the distribution of patients according to the elapsed time from stent to surgery. One hundred and six (34.0%) patients were in the short group, 115 (36.9%) in the intermediate, and 91 (29.1%) in the long group. We observed no differences in terms of type of stent used (plastic vs bare metal stent). Patients in the long group experienced the highest rate (31.9%) of stent-related complications versus 20.0% in the intermediate and 17.9% in the short group ($P = 0.041$). Moreover, the short group had the shortest operative time and the highest proportion of soft pancreatic parenchyma ($P = 0.012$).

We observed a statistical difference in the plasma levels of preoperative albumin ($P = 0.001$) and hemoglobin ($P = 0.031$), which were progressively increased consistent with the elapsed time from PBS to surgery. However, both albumin and bilirubin levels were within the normal range for all groups. Conversely, no significant differences were observed for preoperative levels of international normalized ratio (INR), or bilirubin. The ALBI score was calculated for each patient, and the score was dichotomized into ALBI 1, 2, or 3 (18). The mean values of the ALBI score progressively improved over time (from -1.45 ± 0.86 units in the short groups to -2.29 ± 0.69 units in the long one), consistent with the rate of patients with ALBI score 1 (18.1% in the short vs 35.4% in the long group).

Intraoperative bile cultures were available for 269 patients (86.2%). The lowest likelihood of bacteriobilia was observed in the short group (35.8% of negative biliary cultures, vs 10.1% and 12.0% in the intermediate and long groups, respectively). Similarly, the short group showed the lowest rate of MDR and XDR bacteria ($P < 0.001$).

Postoperative outcomes are shown in Table 2. Patients in the short group experienced significantly higher rate of major morbidity (43.4% vs 20.0% and 24.2% in the intermediate and long groups, respectively; $P < 0.001$). Similarly, the occurrence of surgical morbidity and biliary fistula was significantly higher for patients in the short group than for those in the other 2 groups. When the

TABLE 1. Perioperative Patient Characteristics

	Overall (N = 312)	Short (n = 106)	Intermediate (n = 115)	Long (n = 91)	*P*
Age, yrs	68 ± 11	67 ± 12	68 ± 10	68 ± 10	0.919
Sex, M/F	175/137 (56.1/43.9)	58/48 (54.7/45.3)	66/49 (57.4/42.6)	51/40 (56.0/44.0)	0.923
ASA ≥3	87 (26.6)	34 (32.1)	25 (21.7)	26 (28.6)	0.637
BMI, kg/m^2	24.4 ± 4.0	25.0 ± 4.1	23.7 ± 4.1	24.4 ± 3.5	0.038†
Diabetes	73 (23.4)	28 (26.4)	26 (22.6)	19 (20.9)	0.637
Albumin, g/dL	3.8 ± 0.5	3.7 ± 0.6	3.8 ± 0.4	3.9 ± 0.4	0.001‡
Bilirubin, mg/dL	6.6 ± 16.6	8.0 ± 12.4	7.1 ± 23.4	2.7 ± 4.6	0.064
Type of stent					0.314
Plastic	228 (73.1)	83 (78.3)	80 (69.6)	65 (71.4)	
Metal	84 (26.9)	23 (21.7)	35 (30.4)	26 (28.6)	
Stent-to-surgery complication	71 (22.8)	19 (17.9)	23 (20.0)	29 (31.9)	0.041
Neoadjuvant treatment*	13 (6.2)	—	—	13 (14.3)	—
Soft pancreas	108 (34.6)	48 (45.3)	32 (27.8)	28 (30.8)	0.012
Small MPD	132 (42.3)	45 (42.5)	54 (47.0)	33 (36.3)	0.399
Pathology					0.247
PDAC	211 (67.6)	76 (71.7)	79 (68.7)	59 (64.8)	
Biliary cancer	40 (12.8)	19 (17.7)	11 (9.6)	10 (11.0)	
IPMN	8 (2.5)	1 (0.9)	3 (2.6)	4 (4.4)	
pNET	8 (2.6)	1 (0.9)	3 (2.6)	4 (4.4)	
Duodenal cancer	3 (1.0)	1 (0.9)	2 (1.7)	0 (0.0)	
Chronic pancreatitis	39 (12.5)	8 (7.5)	17 (14.8)	14 (15.4)	

Data are means ± standard deviation or number (%).
P values refer to the Student *t* or Fisher exact tests.
*Related to 211 PDAC patients.
†*P* value refers to short versus intermediate.
‡*P* value refers to short versus intermediate.
ASA indicates American Society of Anesthesiologists; BMI, body mass index; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumor.

infectious composite outcome was considered, patients in the short group had the highest likelihood of complications ($P = 0.025$). A detailed report of infections is provided with Supplementary Table 2 (http://links.lww.com/SLA/B434), and details on postoperative morbidity per center volume are provided with Supplementary Table 3 (http://links.lww.com/SLA/B434).

By a logistic regression model adjusted for the center surgical volume, less than 4 weeks from PBS to the operation and soft texture of the pancreas were independently associated with the likelihood of major complications, with adjusted ORs of 2.64 and 2.48 for short group and soft parenchyma, respectively (Table 3).

The occurrence of complications across the 3 study groups according to the features of the pancreatic parenchyma – hard or soft – are provided with Supplementary Fig. 1 (http://links.lww.com/SLA/B434).

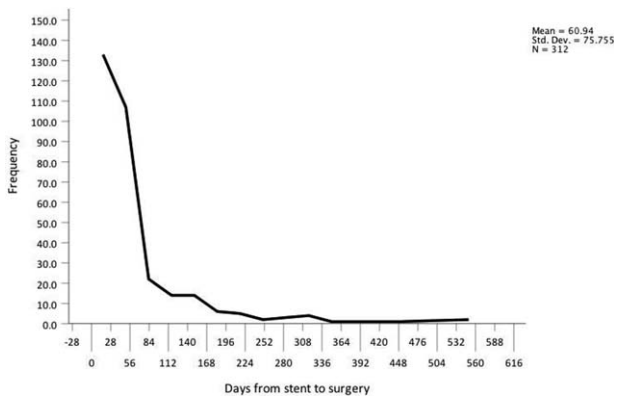

FIGURE 1. Distribution of patients according to the elapsed time from stent to surgery.

DISCUSSION

Placement of biliary drains before PD remains a topic of extensive debate. The intended justification of treating jaundice is to reverse the detrimental effects of cholestasis on liver and immune functions. Obstructive jaundice may impair the function of T lymphocytes[26] and produce a reversible phagocytic dysfunction of neutrophils and monocytes.[27] These effects potentially explain the increased risk of postoperative complications observed in jaundice patients,[28] whereas the reversibility of immune impairment could justify the treatment of jaundice via biliary drainage.

However, PBS has been extensively associated with increased risk of postoperative morbidity.[8] Thus, even with the limitation of heterogeneous analyzed cohorts and few opposing results,[11,12] the accepted recommendation is not to drain the biliary duct with the exception of patients exhibiting symptomatic jaundice, cholangitis, or planned neoadjuvant treatment. These exceptions, however, account for more than a half of all PD candidates,[9] and this number is likely to increase given the promising results on resectability and survival observed after neoadjuvant treatment in pancreatic cancer patients.[29] Several mechanisms may account for the high postoperative complication rate in stent-bearing patients: the occurrence of postprocedural morbidity, the migration of bacterial microorganisms from the duodenum to the biliary system and subsequent selection of resistant species, or the local inflammation directly related to the stent itself.[6–10] Whether waiting – and how long – after the stent placement may affect surgical outcomes remains unclear.

The foremost finding of our study is that the lowest complication rate occurred when surgery was delayed up to 4 weeks after biliary drainage. This observation cannot be fully explained by a

TABLE 2. Postoperative Outcomes

	Total (312)	Short (106) (34.0)	Intermediate (115) (36.8)	Long (91) (29.2)	*P*
Overall complications	176 (56.4)	70 (66.0)	59 (51.3)	47 (51.6)	0.075
Surgical	125 (40.1)	55 (51.9)	39 (33.9)	31 (34.1)	0.009*
Medical	90 (28.8)	39 (36.8)	30 (26.1)	21 (23.1)	0.076
Infectious	86 (27.6)	39 (36.8)	24 (20.90)	23 (25.3)	0.025†
Major complications	91 (29.2)	46 (43.4)	23 (20.0)	22 (24.2)	<0.001‡
CR-POPF	62 (19.9)	26 (24.5)	20 (17.4)	16 (17.6)	0.335
PPH					0.324
Early	19 (6.1)	4 (3.8)	10 (8.7)	5 (5.5)	0.299
Delayed	18 (5.8)	10 (9.4)	4 (5.5)	4 (4.4)	0.132
DGE	56 (18.0)	24 (22.6)	17 (14.8)	15 (16.5)	0.286
Biliary fistula	24 (7.7)	14 (13.2)	5 (4.3)	5 (5.5)	0.031
Enteral perforation	5 (1.6)	3 (2.8)	1 (0.9)	1 (1.1)	0.460
Respiratory failure	14 (4.5)	8 (7.5)	2 (1.7)	4 (4.4)	0.114
Cardiac complications	16 (5.1)	6 (5.7)	5 (4.3)	5 (5.5)	0.891
90-day mortality	8 (2.6)	3 (2.8)	4 (3.5)	1 (1.1)	0.550
LOS	13 (9–20)	16 (10–52)	12 (8–35)	12 (8–43)	0.025§

Data are median (IQR) or number (%).
P values refer to the Kruskal-Wallis or Fisher exact test.
*$P = 0.021$ short versus intermediate, and $P = 0.036$ short versus long.
†$P = 0.026$ short versus intermediate.
‡$P = 0.001$ short versus intermediate, and $P = 0.014$ short versus long.
§$P = 0.027$ short versus Intermediate, and $P = 0.084$ short versus long (all post hoc test by Bonferroni correction).
CR-POPF indicates clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying; LOS, length of hospital stay; PPH, postpancreatectomy hemorrhage.

complete recovery from jaundice. In fact, bilirubin levels dropped after more than 8 weeks, and both albumin levels and INR were in the normal range across all the 3 groups. Moreover, a growing body of evidence shows that patients who undergo neoadjuvant treatment – generally for longer than 1 month – despite stent placement, do not experience higher rates of postoperative morbidity than those who receive upfront resections.[30–33] Particularly, we observed a significantly higher rate of biliary fistulas in the short group, when compared with the others. A possible underlying reason is the increased fibrotic tissue deposition due to a long-standing biliary prosthesis.

Our data may be explained by previous results in experimental models of obstructive jaundice, demonstrating rapid recovery of liver function tests and glycogen metabolism, but slower (up to 6 weeks) recovery of beta-oxidation and other mitochondrial functions after reversal of the biliary obstruction.[34–36] Other human studies showed how restoration of vitamin K-dependent synthesis and consequent coagulability occur after 4 to 6 weeks of biliary drainage, despite normal INR levels before stenting.[37] Additionally, inflammation, hepatic reticuloendothelial function, and inhibited cell-mediated immunity can take longer than 2 weeks to regenerate.[38,39]

It can be argued that recovery of the immune function occurring when the elapsed time from stent to surgery exceeded 4 weeks could be a key factor in improving patient resilience and decreasing the rate of severe postoperative morbidity. The role of immunity impairment in increasing the complication rate in major surgery is unequivocal, and interventions aimed at restoring the capability of the immune system have shown potential improvement in surgical outcomes.[40]

Our second notable finding is the characteristic of bacterial bile contamination across all 3 groups. The number of positive intraoperative biliary cultures and the likelihood of retrieving germs with higher patterns of antibacterial resistance increased with elapsed time from stenting to surgery. Bacterial contamination of the bile is a

TABLE 3. Univariate and Multivariate Analysis for Severe Complications

	Univariate		Multivariate Model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.03 (0.99–1.05)	0.080	—	
Body mass index	1.09 (1.03–1.16)	0.006	1.04 (0.96–1.13)	0.317
Albumin	0.59 (0.34–1.01)	0.054	—	
Hemoglobin	0.99 (0.87–1.12)	0.855	—	
INR	1.41 (0.13–15.73)	0.780	—	
Bilirubin	1.02 (0.99–1.03)	0.085	—	
ALBI score	1.54 (1.11–2.13)	0.010	1.48 (0.95–2.31)	0.149
Elapsed time from stent to surgery				
<4 vs 4–8 wks	3.07 (1.69–5.57)	<0.001	2.64 (1.23–5.67)	0.013
>8 vs 4–8 wks	1.28 (0.66–2.47)	0.472	1.22 (0.53–2.81)	0.647
Intraoperative bile culture-pattern of drug resistance*	0.87 (0.64–1.18)	0.359	—	
Soft pancreas	2.48 (1.49–4.11)	<0.001	2.48 (1.32–4.68)	0.005
Small MPD	1.58 (0.96–2.59)	0.070	—	
Center volume	1.82 (1.06–3.13)	0.031	1.61 (0.62–4.18)	0.332

MPD indicates main pancreatic duct.

common event after drainage of the biliary duct, as both the procedure and the presence of the stent itself disrupt the mechanical barrier of Oddi sphincter and allow colonization.[41] Therefore, severe and infectious postoperative complications seemed to increase in stent-bearing patients after PD compared with upfront resections. Moreover, the severity of morbidity has been associated with the presence of drug-resistant bacteria in bile cultures.[8,10]

However, our results contrast these previous findings, as patients in the short group had the lowest rate of biliary contamination, and, yet, the highest rate of severe complications. Nevertheless, we did not compare the high-grade complication and infection rates with a group without the stent. This could also explain why we observed a higher rate of severe and infectious morbidity than reported in large published series.[42,43] Another explanation is that improvement of the host conditions and immune response, as a consequence of the delay between the biliary drainage and surgery, can modulate the biliary microbiome and reduce the pathogenic activity of high-resistant pattern microorganisms. Bacteria can express highly variable phenotypes and microbial burden depending on the local environment modification of their genotype. Thus, the potential threat of microbes cannot be completely understood by bacterial isolation and antibiotic sensitivities.[44]

Clinical tools to assess the recovery of liver function and immune activity are lacking. While we observed a significant improvement in protein synthesis over time, the significance of the observed increase in albumin levels is limited. Similarly, the INR values were in-range across all groups. Whereas the patient outcomes significantly improved after 4 weeks, the bilirubin levels were misleading, as a biochemical recovery of jaundice was observed 8 weeks after biliary drainage.

Recently, Johnson et al developed an objective score to assess liver function in patients with different degree of chronic liver dysfunction either of viral or nonviral origin. This score is based on the plasma levels of ALBI score, and stratifies the patients into 3 categories according to the risk of death after liver resection.[18] Consistent with their findings, patients who experienced severe morbidity after PD were more likely to be ALBI 3. We observed a significant improvement in the ALBI score over time after stenting, suggesting a progressive recovery of the liver function. Our data suggest that the ALBI score can possibly represent a promising biomarker to monitor the improvement of liver function after biliary drainage.

Despite the limitation of retrospective design, this is the only study addressing the matter of elapsed time from biliary drainage to surgery. In a multicenter setting, we found the 4-week cut-off and soft pancreatic texture to be independent factors associated with the occurrence of major morbidity after PD in stent-bearing patients. Even though the stratification time was partially arbitrary, several published data suggest that, after treatment of jaundice, recovery of the liver and immune functions occur within 4 to 8 weeks.[4,37–39] Therefore, the present results may serve as solid background for future prospective or randomized trials.

Better understanding of interactions between hepatic synthesis, immune-modulation, and microbiome interactions after biliary drainage, and also the potential utility of biomarkers such as the ALBI score, should be addressed in future studies. Until then, when drainage of the biliary tract cannot be avoided, deferral of the surgical procedure up to 1 month after stent placement may be the best option to lessen the risk of severe complications and infections after PD.

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DISCUSSANTS

Marc G. Besselink (Amsterdam, The Netherlands):

First, Dr. Sandini and co-authors gathered data on biliary drainage from 312 patients in 5 large European centers from Italy, France and Germany, and concluded that shorter drainage duration (<4 weeks) is associated with an increased risk of morbidity, when it comes to the timing of the pancreatoduodenectomy after biliary drainage and complications. Their findings are surprising, since significantly more stent-related complications were seen with longer drainage (32% in the long group, 20% in the intermediate group and 18% in the short group, $P = 0.041$). How do the authors explain the differences in the timing of drainage? Why did some patients undergo earlier surgery than others? Is there a selection bias at play; did some centers routinely operate earlier than others? If not, how did these large differences occur? Did the early drainage group have problems with the drainage itself or were there other clinical reasons for earlier surgery?

Second, the patients in the early surgery group had a soft pancreas more often. As we know, this is the most important predictor of a pancreatic fistula. How do you explain this difference? Is this also a sign of selection bias?

Third, when we look at the complications found in detail, the high rates of post-pancreatectomy hemorrhage (12%) and biliary fistula (13%) are particularly surprising. What is the proposed mechanism of why early drainage would induce these complications? Could it be a random high finding?

Finally, our group has previously shown that a metal stent is superior to a plastic stent, both in terms of complications and overall costs. Furthermore, we will move to metal stents, since most pancreatic cancer patients will receive neoadjuvant treatment, especially with the recently completed Dutch PREOPANC trial in mind. The authors do not show data on short vs intermediate drainage in the 20% subgroup that received a metal stent. Were there no differences or was the subgroup too small?

Response From Marta Sandini (Monza, Italy):

Thank you for your questions and for revising the manuscript. First, the timing from stent to surgery was affected by several variables. For instance, all patients who received neoadjuvant treatment were in the long group, which also included more patients with benign diseases. These patients could, of course, wait longer before having surgery. Finally, the diagnosis during the final pathology was not always consistent with the preoperative diagnosis, as some cancer patients had PDAC arising from IPMNs or chronic pancreatitis. This is why some patients were operated later on. Unsurprisingly, the center volume was a variable associated with the duration of preoperative biliary drainage because higher volume centers have a longer waiting list. The association between center volume and the complication rate is well set and could have represented a selection bias. Consequently, we analyzed this correlation within a univariate analysis and confirmed the advantage of being operated in high volume centers. However, when we evaluated this correlation within the multivariate analysis, the effect was no longer significant.

Second, concerning the prevalence of a soft pancreas, we also adjusted for this confounder within the multivariate analysis.

With regard to your third question, after revising the manuscript, we only considered Grade B and C post-pancreatectomy hemorrhages, removing Grade A, and the difference was no longer detectable. The biliary fistulas could possibly be due to acute versus chronic inflammation, related to either short- or long-standing stents. These can produce a different environment, with respectively higher neutrophil or fibroblast infiltration. The difference in local condition may prevent or favor the healing of the anastomosis. This is our interpretation of the observed higher rate of biliary fistulas in the short group.

Finally, I absolutely agree with you about the need for neoadjuvant treatment in pancreatic cancer patients. Actually, only 20% of the patients had a metal stent. This is related to local habits and consistency across all countries and institutions. We did not perform a subgroup analysis, according to the type of stent, because of the small sample size and consequent high risk of Type II errors.

Attila Olah (Györ, Hungary):

Thank you very much for this interesting paper. I only have a short question. Four to 6 weeks may not be very long, but it's still a considerable waiting period. If your conclusion is correct, do you think that it might be beneficial to patients to receive a short-term chemotherapy or chemo-radiation therapy during this period?

Response From Marta Sandini (Monza, Italy):

Thank you for your question. Yes, I agree with you. If we could have a protocol in place for a short-term chemomotherapy or chemo-radiation treatment before surgery, it might be a future option for these patients.

Norbert Senninger (Münster, Germany):

Thank you very much. I enjoyed your presentation enormously. We conducted animal experiments some 20 years ago. Your boss might be aware of one of our first presentations, concerning the function of the reticulendothelial system. It has to be said that we experimented on rats, mice and opossums. We observed the recovery period in these animals, and for the hepatic RES, it was about 2 to 3 weeks. Now, this was the first time that we had a clinical hint that it's not bacteria, and it may not be liver function as such, but a defensive mechanism of RES. So, if you were to extend your clinical investigation to functions of the RES, I think it could be of great interest. Thank you.

Response From Marta Sandini (Monza, Italy):

Thank you for the good hint. We will try to do this.

Pierre-Alain Clavien (Zurich, Switzerland):

I also enjoyed your presentation very much, and appreciate the message that accepting a slighter longer wait with a stent is better than rushing into surgery. My question is what happens when there is no stent at all? Most experts recommend that we omit stents, since they are associated with poorer post-operative course, particularly infectious complications. Stents are usually placed prior to proper evaluation by the surgeon or in patients planned for a neoadjuvant protocol. I understand that your study covers patients, in whom a stent was already in place. Could you please, however, comment on stenting versus not stenting?

Response From Marta Sandini (Monza, Italy):

Of course, I agree with you. No stent is the best option. There are at least 27 papers and 2 meta-analyses demonstrating that no stent is the best option. However, since we sometimes have no choice other than placing a stent, we need to determine what needs to be done once the stent is there. Our data shows that if biliary stenting cannot be avoided, then delaying surgery for up to 1 month may reduce postoperative morbidity.

Antonio D. Pinna (Bologna, Italy):

This was a very nice paper and I really enjoyed it. However, I have a couple of questions.

First, I think that the ALBI score you used is probably inappropriate in this condition. As Johnson published, the ALBI has only been validated for chronic liver disease. This is not a chronic liver disease. So, I would recommend that you eventually rank the statistics in a different way.

Second, could you please give us the exact data that shows why you put the stent? How much was the amount of bilirubin when you decided to stent these patients?

Third, I saw that the range of variation in the timing between stenting and surgery is very wide. Who were the actual patients in the long group? Did they all suffer from chronic pancreatitis? How many of the patients within the long-term group, who had a pancreatic carcinoma, actually receive neoadjuvant therapy?

Response From Marta Sandini (Monza, Italy):

With regard to your first question, according to the ALBI score, I agree with you. It has been mostly validated in patients with chronic liver disease. Indeed, jaundice patients suffer a sort of hepatic insufficiency. Moreover, it has been validated in gastric cancer, i.e. patients with normal liver function. Perhaps, the ALBI score could represent a new possibility for the assessment of liver function, also in non-cirrhotic patients, since no tools have been specifically endorsed in a pancreatic setting. Our results need to be confirmed and validated prospectively.

Second, concerning the long-standing stents, all of the patients receiving neoadjuvant treatment were in the long group. Some of these patients received a long course of neoadjuvant treatment. Other patients with chronic pancreatitis developed jaundice, and subsequently, required a stent placement.

Finally, with regard to your last question, 58 patients had a final diagnosis of PDAC in the long group, and 12 out of these patients (12%) received neoadjuvant treatment.

Olivier Farges (Clichy, France):

I have the following 3 short questions:

First, how did you choose the 4 to 8 week cut-off? Was it simply convenient or was there a clinical justification for this?

Second, you analyzed the timeframe, but did you also analyze the reasons for the delay or the indication for placing a stent?

Third, did some patients develop pancreatitis or cholangitis after stent placement, and did this influence the outcome?

Response From Marta Sandini (Monza, Italy):

With regard to your first question, the results of some reports and a meta-analysis suggest that 4 to 6 weeks is the period needed for the recovery of liver function, according to clinical parameters.

Second, we did not analyze the reason why the stent stayed longer. We considered all possible indications for surgery, and in some patients, the stent was kept in place a long time, in order to allow for full neoadjuvant treatment. The reasons for stent placement were a serum bilirubin higher than 15 mg/dL, planned neoadjuvant treatment and cholangitis at presentation.

Finally, with regard to your third question, some patients had pancreatitis. However, the most common stent-related complication was cholangitis.