Preoperative Endoscopic Biliary Stenting Before Pancreaticoduodenectomy: Does Timing Matter?

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Abstract
Background. The role of preoperative biliary stenting (PBS) before pancreaticoduodenectomy (PD) in patients with obstructive jaundice is debatable. The objective of the current study was to assess PD outcomes after upfront surgery or PBS and determine the impact of stent to surgery duration on PD outcomes. Methods. We reviewed patients who underwent PD between 2011 and 2019. Patients were grouped based on whether they underwent upfront surgery (n = 67) or PBS (n = 66). We further assessed outcomes based on stent to surgery duration. Results. There was no significant difference in 30-day mortality (3% vs. 2.9%, P = 1), 90-day mortality (7.5% vs. 4.4%, P = .4), and Grade B-C pancreatic fistula rates (7.5% vs. 4.4%, P = .4) in the PBS and upfront surgery groups, respectively. A significant increase in wound infections (22.7% vs. 7.4%, P = .01) and readmissions (10.6% vs. 0, P = .006) was seen in the PBS group. The highest rate of wound infection was seen when stent to surgery duration was 4-6 weeks (41.6%). The wound infection rates in the upfront surgery group, high-risk PBS group (4-6 weeks), and low-risk PBS group were 5/67(7.4%), 5/12(41.6%), and 7/36(19.4%), respectively (P = .008). Conclusions. PBS increases postoperative wound infections when compared with upfront surgery. Patients operated between 4 and 6 weeks after stenting have the highest rate of wound infection.

Keywords
pancreaticoduodenectomy, morbidity, mortality, endoscopic stenting

Introduction
The role of preoperative biliary stenting (PBS) in jaundiced patients with periampullary malignancy is debatable. It was introduced to reduce the risk of infections and anastomotic leaks after pancreaticoduodenectomy (PD).1,2 It is assumed that PBS corrects physiological disturbance secondary to hyperbilirubinemia in the malignant biliary obstruction. However, improvement in postoperative outcomes after PD has not been consistently demonstrated in clinical practice.3-5 In fact, a direct relationship between rate of postoperative infections and morbidity has been shown in patients with PBS.6,7 This has not only challenged the conventional approach of routine PBS but also raises questions regarding the timing of surgery after biliary drainage and the impact of delay in surgical intervention on postoperative outcomes.

Data remain limited and conflicting, with some reports demonstrating improved outcomes with a short stent to surgery interval (<2 weeks), while others showing superior outcomes with a stent to surgery duration of >4 weeks.3,9

The objective of the current study was to determine postoperative outcomes in patients who underwent upfront surgery and PBS and assess the impact of time interval between stenting and surgery.

Methods
A total of 157 PDs were performed between January 2011 and July 2019. Adult patients(age >18 years), who underwent upfront surgery or endoscopic retrograde cholangiopancreatography (ERCP) stenting before standard PD, with a minimum follow-up of 3 months after surgery were included (n = 133). At our center, experienced gastroenterologists perform PBS via ERCP. In case ERCP...
is not feasible or not successful, percutaneous transhepatic cholangiography is performed for biliary decompression. For the purpose of this study, we only included patients who underwent stenting via ERCP.

We routinely perform PBS in patients with cholangitis or total bilirubin (TB) > 10 mg/dl. However, many patients are referred from other centers for surgery after PBS. As a result, patients who undergo PD have variable TB cutoffs before PBS. For the purpose of this study, time between last PBS and PD was used to determine stent to surgery interval. We excluded patients who underwent percutaneous transhepatic cholangiography (PTC), combined ERCP/PTC, or surgical bypass before PD. All patients included in the study had good functional status (Eastern Cooperative Oncology Group 0 and 1) and underwent plastic stent placement. Details pertinent to patient selection, operative procedure, and postoperative care have been detailed elsewhere.\(^\text{10,11}\)

For this study, all patients with positive wound cultures or culture positive abdominal collections were considered to have wound infection or infected abdominal collections, respectively. Superficial surgical site infection involving skin and subcutaneous tissue and deep surgical site infection involving fascia and muscle layers were grouped as wound infection. Sepsis was defined as previously,\(^\text{12}\) and postoperative pancreatic fistula (POPF) was defined based on International Study Group for Pancreatic Fistula guidelines.\(^\text{13}\)

We looked at 90-day morbidity and mortality in PBS and upfront surgery groups. We also compared outcomes based on stent to surgery group. For a majority of outcomes, there was no significant difference between the 2 groups. There was significant increase in wound infection rate (22.7% vs. 7.4%, \(P = .01\)) and readmission rate (10.6% vs. 0, \(P = .006\)) in patients who underwent PBS. Median hospital stay in the PBS group vs. upfront surgery group was 10(7-28) and 9(6-20) days (\(P = .005\), respectively. Cause of death in the PBS group was sepsis in 2 patients, pulmonary embolism in 1, pancreaticojejunal leak in 2, and recurrence in 1 patient. Cause of death in the upfront surgery group was sepsis in 1 patient and myocardial infarction in 2 patients.

High Risk Group for Wound Infection in the PBS Group

On ROC analysis, no significant stent to surgery duration cutoff was identified for wound infections in the PBS group (Area under curve = .49, \(P = .9\)). We further assessed wound infection rates at 2 weekly intervals in the PBS group. The highest rate of wound infection was seen in patients with stent to surgery interval of 4-6 weeks (41.6%) as shown in Figure 1. The wound infection rate in the upfront surgery group was 5/67(7.4%), high-risk group (stent to surgery = 4-6 weeks) was 5/12(41.6%),

### Results

#### Patient characteristics

Mean age was 57.3 ± 12.9 years. Median follow-up was 11.1(2.79) months. Median TB before intervention in the PBS and upfront surgery group was 5.2(49) mg/dl. Median TB at the time of surgery was 1.7(31.2) mg/dl and 5.1(24.8) mg/dl (\(P = .1\)) in the PBS and upfront surgery groups, respectively, as shown in Table 1. Six patients did not show improvement in jaundice after PBS and underwent PD despite high TB levels. Reasons included failure to retrieve occluded stent (n = 3) and upper gastrointestinal bleed (n = 3). Similarly, 6 patients underwent upfront surgery despite high bilirubin levels due to gastric outlet obstruction.

### Upfront surgery vs. PBS

Table 2 demonstrates comparison of outcomes in patients with PBS and upfront surgery. For a majority of outcomes, there was no significant difference between the 2 groups. There was significant increase in wound infection rate (22.7% vs. 7.4%, \(P = .01\)) and readmission rate (10.6% vs. 0, \(P = .006\)) in patients who underwent PBS. Median hospital stay in the PBS group vs. upfront surgery group was 10(7-28) and 9(6-20) days (\(P = .005\), respectively. Cause of death in the PBS group was sepsis in 2 patients, pulmonary embolism in 1, pancreaticojejunal leak in 1, and recurrence in 1 patient. Cause of death in the upfront surgery group was sepsis in 1 patient and myocardial infarction in 2 patients.

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### Table 1. Preoperative Characteristics in Upfront Surgery and Preoperative Biliary Stenting Groups.

|                      | Preoperative Biliary Stenting (n = 66) | Upfront Surgery (n = 67) | \(P\) Value |
|----------------------|---------------------------------------|--------------------------|------------|
| Age (mean ± SD)      | 57.9 ± 13.9                           | 56.6 ± 11.8              | .5         |
| Gender (male)        | 44(66)                                | 43(64)                   | .7         |
| Preoperative total bilirubin (median/range) | 1.7(2–31.2)                          | 5.1(2–24.8)              | .1         |
| Benign etiology      | 10(15.1)                              | 5(7.4)                   | .2         |
| Charlson comorbidity index (median/range) | 3(2–6)                               | 3(2–6)                   | 1          |
Discussion
The current study demonstrates improved outcomes with upfront PD vs. PBS in patients with obstructive jaundice. When PBS is performed, patients with stent to surgery interval of 4-6 weeks appear to have significantly high rates of wound infections. A number of studies have shown increased morbidity in patients with PBS with no impact on mortality.6,15 Although a judicious approach to PBS is warranted, there

| Table 2. Comparison of Postoperative Outcomes in Upfront Surgery vs. Preoperative Biliary Stenting Group. |
|---------------------------------------------------------------|
| Preoperative Biliary Stenting (n = 66) | Upfront Surgery (n = 67) | P Value |
|----------------------------------------|---------------------------|---------|
| 30-day mortality                       | 2                         | 3       | 2.9    | 1 |
| 90-day morbidity                      | 39                        | 59      | 37     | 55.3  | .6 |
| 90-day mortality                      | 5                         | 7.5     | 3      | 4.4   | .4 |
| Grade B/C POPF                        | 5                         | 7.5     | 3      | 4.4   | .4 |
| Grade 3A                              | 4                         | 6       | 2      | 2.9   |     |
| Grade 3B                              | 1                         | 1.5     | 1      | 1.5   |     |
| Wound infection                       | 15                        | 22.7    | 5      | 7.4   | .01 |
| Grade 1                               | 10                        | 15.1    | 4      | 5.9   |     |
| Grade 2                               | 5                         | 7.6     | 1      | 1.5   |     |
| Sepsis                                | 12                        | 18.1    | 7      | 10.4  | .2 |
| Grade 4                               | 10                        | 15.1    | 6      | 8.9   |     |
| Grade 5                               | 2                         | 3       | 1      | 1.5   |     |
| Infected intra-abdominal collections   | 4                         | 6       | 9      | 13.4  | .2 |
| Grade 3A                              | 6                         | 9       | 6      | 8.9   | .9 |
| Sterile intra-abdominal collections    | 6                         | 9       | 6      | 8.9   |     |
| Grade 3A                              | 21                        | 31.8    | 15     | 22.3  | .2 |
| Overall infectious complications       | 21                        | 31.8    | 15     | 22.3  | .2 |
| Re-exploration                        | 1                         | 1.5     | 2      | 2.9   | 1 |
| Readmission rate                      | 7                         | 10.6    | 0      |        | .006 |
| Length of stay (days)                 | 10(7–28)                  | 9(6–20) |        |        | .005 |
| ICU stay                              | 2(1–18)                   | 2(1–7)  |        |        | .5 |
| Surgery duration (minutes)            | 475(240–670)              | 460(270–720) |    |        | .7 |
| Blood loss (milliliters)              | 600(150–2500)             | 500(200–5000) |    |        | .4 |

Abbreviation: POPF = postoperative pancreatic fistula.

Figure 1. Percentage of patients with wound infection in 2 weekly stent to surgery intervals.

and for low-risk groups (all others) was 7/36(19.4%) (P = .008) as shown in Figure 2.
remains a group that could potentially benefit from PBS, and a safe stent to surgery duration in this group remains to be determined. \(^{16,17}\) The literature on the impact of duration of PBS before PD is limited. These studies have used different statistical designs, variable time period cutoffs, and showed conflicting results. Son et al. assessed outcomes in 120 patients who underwent PD after PBS and showed improved outcomes when PD was performed within 2 weeks of PBS. \(^{8}\) On the contrary, results from a recent multicenter study found a stent to surgery interval <4 weeks to be associated with frequent postoperative complications. \(^{9}\)

In the current study, we compared outcomes between stented and nonstented patients with emphasis on stent to surgery interval. When compared with patients in the upfront surgery group, patients who underwent PD between 4 and 6 weeks after PBS had significantly increased rates of wound infections. It is been shown that the risk of polymicrobial anaerobic infections increases with indwelling time after ERCP stenting. \(^{18}\) The risk of stent colonization and obstruction is lower in patients with an indwelling catheter time <15 days. \(^{19}\) This might contribute to lower rate of infectious complications in the short stent to surgery interval group. An element of selection bias cannot be ruled out, and it is possible that patients operated <4 weeks of stenting achieve superior biliary decompression and have improved nutritional status. Patients with malignant obstructive jaundice are immunocompromised. In these patients, there is lowered expression of interleukin-6 and 1\(\beta\) which appears to be inversely correlated with TB levels. It can take >4 weeks after ERCP for TB levels to return to baseline and for immune function to recover. \(^{20}\) As a result, low risk of wound infections between 6 and 8 weeks might reflect recovery of immune function in these patients.

There is no convincing evidence as to which group of patients would clearly benefit from PBS. \(^{17,21}\) Variable bilirubin cutoffs ranging from 7.5 to 14.6 mg/dl, need for neoadjuvant chemotherapy, and unexpected delays in surgery have been considered as indication for PBS. \(^{17,22,23}\) We are also unaware of the impact of delay in surgery on oncological outcomes after PD. \(^{24,25}\) In the current study, there was no significant difference in median TB levels between stented and nonstented patients before PBS, yet outcomes in nonstented patients were better. These findings suggest that a pragmatic approach should be adopted in decision making as to when PD should be offered after PBS. Patients who achieve adequate biliary decompression early and appear fit to undergo PD should not be made to wait longer unnecessarily. On the other hand, patients with cholangitis, poor nutritional status, or unanticipated delays might be offered PD between 6 and 8 weeks of PBS.

There are certain limitations of the current study. Indications for ERCP and TB cutoffs before PBS in our patient cohort who underwent PD were variable. This was due to a mix referral pattern from within and outside the hospital. For the same reason, complications associated with PBS could not be documented. This, however, provided a unique opportunity to assess outcomes in actual clinical practice where surgeons frequently see patients after PBS has been performed elsewhere.

**Conclusion**

The current study demonstrates favorable outcomes with upfront surgery for PD. PBS should not be used routinely in patients with obstructive jaundice who are potential candidates for PD. When PBS is necessary, PD can be performed early (<4 weeks), and an individualistic
approach to patient’s overall health and disease process should be taken. These results need to be validated prospectively in a larger cohort of patients.

Author Contributions
Study concept and design: Abu Bakar Hafeez Bhatti and Roshni Z. Jafri
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Data Accessibility Statement
The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics Approval
The Institutional Review Board and Ethics Committee of Shifa International Hospital/Shifa Tameer-e-Millat university approved the study (IRB# 310-800-2019). A written consent to participate was taken from patients.

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