Stent placement as a bridge to surgery in malignant biliary obstruction (pancreatic cancer, distal bile duct cancer, and hilar tumors)

Mario Rodarte-Shade, Michel Kahaleh

Abstract

Preoperative biliary drainage (PBD) has been a matter of controversy for years. It was initially aimed to improve the clinical status of patients with malignant obstructive jaundice prior to surgery. However, its efficacy and safety have not been proven by randomized controlled trials. Most drawbacks of PBD are related to the increase in procedure-related adverse events and inappropriate biliary decompression. Current trends in PBD show that using self-expanding metallic stents (SEMSs) may reduce the high incidence of stent-related complications with improved outcomes. The aim of this study was to review the existing literature concerning the use of PBD in patients with resectable distal pancreaticobiliary malignancies. Preoperative biliary drainage in hilar tumor is also discussed separately.

Keywords: distal bile duct cancer, hilar tumor, malignant biliary obstruction, pancreatic cancer, preoperative biliary drainage

Introduction

Malignant biliary obstruction encompasses a group of neoplasms that compromise bile duct flow and clinically presents with obstructive jaundice. Obstruction can be anatomically classified as “distal” or “proximal.” Proximal bile duct obstruction refers to hilar bile duct cholangiocarcinomas (i.e., Klatskin tumors), whereas distal bile duct obstruction refers to periampullary tumors. Periampullary tumors are defined as neoplasms arising from the head of the pancreas, the distal bile duct, the ampulla of Vater, or the second portion of the duodenum. Because of the broad range of tumors, pancreatic cancer by far remains the most common malignancy in Western countries. During 2014 in the United States, 46,420 patients were expected to be diagnosed with pancreatic cancer. It is also the fourth most common cause of cancer-related death among men (after lung cancer, prostate cancer, and colorectal cancer) and among women (after lung cancer, breast cancer, and colorectal cancer). At the time of diagnosis, approximately only 20% of patients can receive curative surgery. Hence, most patients will require palliative decompression.

Preoperative biliary drainage (PBD) is an old concept that was first described in 1935 by Allen O. Whipple. Preoperative biliary drainage emerged as a treatment to counteract the deleterious effects of biliary obstruction. Literature suggests that performing surgical resection (i.e., pancreatoduodenectomy) in the setting of hyperbilirubinemia is associated with higher perioperative mortality. However, conflicting data has been published regarding the efficacy and safety of routine PBD. The aim of this article was to review the existing literature concerning the use of PBD in patients with resectable distal pancreaticobiliary malignancies. Preoperative biliary drainage in hilar tumor is also discussed separately.

Pathophysiology of biliary obstruction

Biliary obstruction and cholestasis has several deleterious effects on patient homeostasis. Most evidence comes from experimental studies in animals that received bile duct ligation. Gut functions are severely impaired in different ways. Jaundiced rats indicate that intestinal barrier function is compromised. Such impairment has been related to a decreased number and function of gut mucosal T lymphocytes, decreased Kupffer cell function, increased intestinal permeability, impaired cell-mediated immunity, impaired reticuloendothelial function, and altered mucosal immunity. In addition, these gut barrier dysfunctions have been associated with significant bacterial translocation that may be related to endotoxinemia that adversely affects patients with biliary obstruction. Other experimental studies in animals and clinical observations in jaundiced patients have demonstrated a high concentration of tumor necrosis factor (TNF) and interleukin-6, which may also contribute to the high morbidity rate of jaundiced patients. In addition to these experimental observations, obstructive jaundice has been associated with deleterious effects on the cardiovascular system and on renal function. Other detrimental consequences of cholestasis include direct hepatic injury with altered hepatic protein synthesis that, in conjunction with deficient vitamin K absorption, produce coagulation...
patients. Some studies also report that PBD is associated with lower operative morbidity in treated patients than in jaundiced normalization of hepatic function and theoretically resulted in a described as a safe and potentially helpful procedure that allowed case series with methodological assets and contradictory results.

These studies were mostly represented by retrospective and small case series with methodological flaws and contradictory results. Percutaneous transhepatic biliary decompression was initially described as a safe and potentially helpful procedure that allowed normalization of hepatic function and theoretically resulted in a lower operative morbidity in treated patients than in jaundiced patients. Some studies also report that PBD is associated with reduced mortality, less morbidity, and shorter hospital stays. By contrast, further early trials showed that routine PBD by percutaneous methods did not offer any advantage in comparison to surgery without drainage. Furthermore, some publications report that patients who undergo preoperative percutaneous transhepatic biliary drainage have an increased rate of complications resulting from the procedure and do not benefit from preoperative drainage. The preoperative percutaneous biliary drainage was also associated with increased hospital cost related to the procedure and without any clear benefit in operative risk.

More recent publications include a greater number of patients who underwent internal drainage by endoscopic retrograde cholangiopancreatography (ERCP), and report that patients who underwent PBD did not have any difference in outcomes in comparison to patients who went directly to surgery. A retrospective analysis of 257 patients who underwent pancreatoduodenectomy showed that a subgroup of 99 patients who had PBD did not have any difference in morbidity, infectious complications, reoperation rate, mortality, or long-term survival. Another retrospective cohort reported the outcomes of 311 patients who were submitted to pancreatoduodenectomy. Of these, 232 patients received preoperative internal biliary drainage. They were compared to the patients who underwent immediate surgery \( (n = 58) \). The authors found that PBD did not influence the incidence of postoperative complications. A retrospective review of 184 patients of 241 consecutive patients who underwent surgery showed no significant incidence of postoperative complications between patients who had preoperative drainage and patients who did not. Several studies have not associated PBD with an increased rate of complications; however, there are other authors with contradictory results that claim an increased risk of adverse events—primarily, infectious complications. Most results come from retrospective reviews of prospectively collected consecutive series at major pancreaticobiliary centers. Research has found that PBD increases the risk of positive intraoperative bile cultures, which also has been associated with postoperative infectious complications and a similar microorganism profile. Experience with 240 consecutive cases of pancreatoduodenectomy performed at the Memorial Sloan Kettering Cancer Center (New York, NY, USA) revealed that PBD (performed in 175 patients) was associated with a high rate of complications, infectious complications, intra-abdominal abscess, and postoperative death. A subsequent study from the same group, which involved 340 consecutive patients who underwent pancreatoduodenectomy, showed that PBD was associated with a stent-related complication rate of 23\% and a two-fold increase in postpancreatectomy infectious complications. A retrospective analysis of 567 patients who underwent pancreatoduodenectomy at the John Hopkins University School of Medicine (Baltimore, MD, USA) found that 408 (72\%) of patients underwent PBD. The authors of this analysis found that preoperative biliary stenting did not increase the overall complication rate or mortality rate in patients who underwent pancreatoduodenectomy; however, stenting did appear to increase the rate of pancreatic fistula, wound infection, and bile contamination. Another research group found that PBD was associated with increased operative time, intraoperative blood loss, and higher incidence of wound infection; however, it did not increase major morbidity and mortality. A group at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) evaluated perioperative morbidity and mortality in 300 consecutive patients who underwent pancreatoduodenectomy. The group found that PBD (performed in 172 patients) did increase the risk of postoperative wound infection; however, there was no increase in the risk of major postoperative complications or death.

Several recent meta-analyses have been published regarding the controversy of PBD. Major drawbacks of these meta-analyses are the inclusion of retrospective series, methodological flaws, and the inclusion of patients who underwent percutaneous PBD or endoscopic PBD. Table 2 shows the results of the most recent meta-analyses.

### Table 1 The Adverse Effects of Biliary Obstruction

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Impaired intestinal barrier function</td>
<td>Decreased number and function of gut mucosal T lymphocytes</td>
</tr>
<tr>
<td>Decreased Kupffer cell function</td>
<td>Increased intestinal permeability</td>
</tr>
<tr>
<td>Impaired cell-mediated immunity</td>
<td>Bacterial translocation</td>
</tr>
<tr>
<td>Impaired reticuloendothelial function</td>
<td>Endotoxemia (high TNF and IL-6 levels)</td>
</tr>
<tr>
<td>Altered mucosal immunity</td>
<td>Cardiovascular dysfunction</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Direct hepatic injury</td>
<td>Direct hepatic injury</td>
</tr>
<tr>
<td>Coagulation abnormalities</td>
<td>IL-6, interleukin-6; TNF, tumor necrosis factor.</td>
</tr>
</tbody>
</table>

Preoperative biliary drainage versus early surgery

Routine PBD in patients with pancreaticobiliary malignancies has been a matter of controversy for years. Early studies primarily included patients who underwent percutaneous biliary drainage. These studies were mostly represented by retrospective and small case series with methodological flaws and contradictory results. Percutaneous transhepatic biliary decompression was initially described as a safe and potentially helpful procedure that allowed normalization of hepatic function and theoretically resulted in a lower operative morbidity in treated patients than in jaundiced patients. Some studies also report that PBD is associated with reduced mortality, less morbidity, and shorter hospital stays. By contrast, further early trials showed that routine PBD by percutaneous methods did not offer any advantage in comparison to surgery without drainage. Furthermore, some publications report that patients who undergo preoperative percutaneous transhepatic biliary drainage have an increased rate of complications resulting from the procedure and do not benefit from preoperative drainage. The preoperative percutaneous biliary drainage was also associated with increased hospital cost related to the procedure and without any clear benefit in operative risk.

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## Drainage vs Operation (DROP-trial)

A recent multicenter controlled trial randomized patients with resectable cancer of the pancreatic head to undergo PBD for 4–6 weeks, followed by surgery, or to undergo surgery alone within 1 week after diagnosis. This Dutch study enrolled 202 patients. It was conceived to compare the outcome of both strategies. The primary outcome studied in the trial was the rate of serious complications. The rate of overall serious complications were significantly higher in patients who underwent PBD (74\% vs. 39\%, \( P < 0.001 \)). However, there was not a significantly increased rate of surgery-related complications (47\% vs. 37\%, \( P = 0.14 \)). In addition, the mortality and length of stay did not differ between the two groups. Based on these results, the authors concluded that routine PBD in patients undergoing surgery for pancreatic cancer increases the rate of serious complications.

Despite the adequate methodology used in this study, there are some major drawbacks that need to be considered and have been previously noted. The DROP-trial, which included low-volume ERCP centers, reports a high number of serious complications in the PBD group that were mostly related to the drainage procedure. Endoscopic retrograde cholangiopancreatography is a technically demanding and potentially high-risk procedure that needs to be performed in tertiary centers by experienced therapeutic endoscopists. In the best scenario, there is a consistently expected failure rate of up to 10\%. However, the DROP-trial shows a failure rate of 25\% in patients who subsequently required a second drainage.
Table 2 Meta-analysis Comparing Preoperative Biliary Drainage and no Preoperative Biliary Drainage

<table>
<thead>
<tr>
<th>Year, Author</th>
<th>Studies included</th>
<th>Patients (n)</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002, Sewnath et al</td>
<td>18 comparative cohort studies</td>
<td>2832</td>
<td>No difference in the death rate</td>
<td>Preoperative biliary drainage does not offer any benefits</td>
</tr>
<tr>
<td>2002, Saha et al</td>
<td>2 RCT, 18 retrospective studies</td>
<td>749</td>
<td>No difference in postoperative complications and mortality between the two groups.</td>
<td>No difference in mortality, pancreaticobiliary leak, abdominal abscesses.</td>
</tr>
<tr>
<td>2010, Gao et al</td>
<td>36 studies (which include 6 RCTs and 3 meta-analysis studies)</td>
<td>1728 (radical and palliative surgery)</td>
<td>Preoperative biliary drainage increased the wound and bile infection rates</td>
<td>Positive bile culture negatively impacted mortality and morbidity after surgery.</td>
</tr>
<tr>
<td>2011, Qin et al</td>
<td>14 retrospective cohort studies</td>
<td>504</td>
<td>No difference in postoperative complications and mortality between the two groups.</td>
<td>No difference in mortality, pancreaticobiliary leak, abdominal abscesses.</td>
</tr>
<tr>
<td>2012, 2013, Fang et al</td>
<td>520</td>
<td>No difference in the length of the hospital stay</td>
<td>No difference in postoperative complications and mortality between the two groups.</td>
<td>No difference in mortality, pancreaticobiliary leak, abdominal abscesses.</td>
</tr>
</tbody>
</table>

PBD, preoperative biliary drainage; RCT, randomized controlled trial.

Indications for PBD

Routine PBD has been a matter of controversy, although there are some clinical scenarios in which patients with resectable distal pancreaticobiliary tumors need to undergo biliary drainage. Routine preoperative biliary drainage (controversial) permits prompt biliary decompression and subsequent stent placement. Indications for PBD are shown in Table 3 and are discussed later.

Delayed surgery

The process by which a patient with malignant biliary obstruction goes can be long and complex because of logistics, health care services, waiting lists, referrals, and an extensive diagnostic protocol. Patients are usually seen at primary or secondary health care services where the initial evaluation with general laboratory and imaging are performed. The patient eventually is sent to a tertiary referral center with a clinical question of or diagnosis of pancreaticobiliary malignancy. The treatment of patients at high-volume referral centers is of major importance because expert advanced care at these institutions can achieve better outcomes when treating patients with pancreaticobiliary malignancies. Further workup may include other time-consuming imaging studies such as computed tomography (CT; for staging or pancreatic imaging protocol), magnetic resonance imagining (MRI), and endoscopic ultrasound. A pathologic diagnosis is not absolutely required before surgery; however, patients can undergo different biopsy protocols that may include CT-guided fine-needle aspiration biopsy, endoscopic ultrasound-guided fine-needle aspiration, ERCP-guided biopsy, ductal brushings, cholangioscopy-guided biopsy, or laparoscopic biopsy. Patients will eventually be seen by a multidisciplinary team that specializes in cancer management, and will subsequently undergo different consultations (e.g., medical

Table 3 Indications for Preoperative Biliary Drainage

| Distal pancreaticobiliary malignancies |
| Cholangitis |
| Neoadjuvant treatment |
| Severe pruritus |
| Delayed surgery |
| Routine preoperative biliary drainage (controversial) |

| Hilar tumors |
| Cholangitis |
| NeoAdjuvant treatment |
| Severe pruritus |
| Delayed surgery |
| Right hepatectomy |
| Portal vein embolization |
| Routine preoperative biliary drainage (controversial) |
oncologist, pancreaticobiliary surgeon, radiotherapy, and preoperative assessment). Depending on the clinical conditions, patients will also need to undergo an extensive preoperative assessment (e.g., cardiovascular/pulmonary clearance). Most patients will need to improve their clinical condition prior to surgery (e.g., nutritional status, coagulopathy, and treatment of comorbidities). Waiting lists and other administrative issues may preclude prompt surgery. All of these factors should be considered when deciding to perform PBD. An expected delay in definitive treatment with surgery should be an indication to perform PBD.

**Neoadjuvant therapy**

Most pancreaticobiliary malignancies are not resectable at the moment of diagnosis. However, there is increasing evidence that neoadjuvant chemoradiation may be useful in patients with borderline or unresectable pancreatic adenocarcinoma (i.e., locally advanced disease). Several meta-analyses show that up to one-third of unresectable locally advanced tumors can be ultimately resected after neoadjuvant treatment with comparable outcomes as patients with initially resectable tumors.54,55 Surgery can be delayed for several months when receiving preoperative chemoradiation. Inside in most instances, the administration of chemotherap**

An expected delay in definitive treatment with surgery should be an indication to perform PBD.

**Stent selection: Plastic versus metal**

Plastic stents have traditionally been used for temporary drainage in patients with potentially resectable pancreaticobiliary malignancy. Plastic stents are inexpensive and can be easily placed endoscopically without sphincterotomy. The use of the SEMS in surgical candidates was initially avoided because of the concern that a metallic foreign body may preclude or have an impact on surgical resection. However, there is increasing evidence that short uncovered or fully covered SEMS can be safely placed in patients who will undergo surgery.50-52

Self-expanding metallic stents represent a safe option in patients undergoing neoadjuvant chemoradiotherapy for pancreatic cancer.53 The median time from stent placement to surgery was 150 days (range, 71–227 days). The authors found that up to 55% of the patients required a repeat ERCP for stent dysfunction and exchange.54 Another prospective study assessed the efficacy and safety of SEMS in 55 patients with resectable or borderline resectable pancreatic cancer receiving neoadjuvant therapy.55 This study found that the mean time for neoadjuvant therapy before surgery was 104 days (range, 70–260 days) and that 88% of the SEMS remained patent at the end of the therapy. In the end, 49% of the patients underwent surgery and the presence of the SEMS did not interfere with surgical resection. These results show that biliary drainage in patients undergoing neoadjuvant treatment should be durable to avoid repeat endoscopic procedures. It also suggests that the best stent for pancreaticobiliary malignancies is the SEMS because of its high patency rate and low reintervention rate.56-58

Preoperative biliary drainage for hilar tumors

Tumors of the biliary confluence are also known as Klatskin tumors. As with distal pancreaticobiliary malignancies, obstructive jaundice is the presenting symptom; the only potential chance of long-term survival is by surgical resection. Hilar tumors deserve a separate discussion because to achieve complete surgical resection most often requires bile duct and major liver resection (i.e., right or left hepatectomy). Performing liver resections in patients with obstructive jaundice can carry increased morbidity and mortality; thus, most major hepatobiliary centers usually offer patients PBD to improve their clinical condition and outcomes.59 The value of PBD has been acknowledged as part of “preoperative liver optimization” in conjunction with portal vein embolization. These actions prevent postoperative acute liver failure and improve postoperative outcomes in patients with hilar tumors.60-62

As with distal pancreaticobiliary malignancies, routine PBD for hilar tumors is controversial. A recent systematic review of the literature included 10 studies with 442 patients who underwent routine PBD and 233 patients who did not have PBD. This meta-analysis could not provide evidence of a clinical benefit of using routine PBD in obstructive jaundice secondary to hilar tumors.63 However, there are some clinical scenarios in which PBD may be an acceptable approach. First, cholangitis is an absolute indication for PBD. Another indication for PBD includes patients who undergo right hepatectomy (for Bismuth type IIIa or IV hilar cholangiocarcinoma). A recent European multicenter retrospective analysis reviewed the outcomes of 386 patients with hilar cholangiocarcinoma in whom 180 PBD procedures were performed.64,65 The authors of this analysis found that PBD did not affect the overall mortality in patients with hilar cholangiocarcinoma; however, PBD...
was associated with a decreased mortality rate after right hepatectomy and an increased mortality rate after left hepatectomy. The data show that patients with PBD and hilar cholangiocarcinoma who underwent left hepatectomy had a higher rate of septic complications. By contrast, patients who underwent right hepatectomy had a lower rate of liver failure. These observations may be related to the fact that the residual right liver in patients with left hepatectomy is larger than the smaller residual left liver after right hepatectomy.\(^2,3\) In addition, after right hepatectomy, a high level of serum bilirubin was also associated with increased mortality.\(^2\)

This finding reflects the importance of PBD in selected cases of patients with hilar tumors.\(^4,5\) Other indications for PBD include patients who will undergo neoadjuvant chemoradiation, patients who will receive portal vein embolization (i.e., “preoperative liver optimization”), and patients with severe intractable pruritus.\(^7\) Table 3 shows the indications of PBD in patients with hilar tumors.

Techniques for PBD in patients with hilar tumors can also be divided into percutaneous or endoscopic approaches. Current techniques are percutaneous transhepatic biliary drainage, endoscopic nasobiliary drainage, and endoscopic biliary drainage. The choice of any given approach depends on center experience, patient condition, and the ability to cannulate and gain access to the hilar tumor. However, a recent retrospective study reviewed 141 patients with hilar tumor that underwent percutaneous PBD or endoscopic PBD.\(^6\) The authors of this study found an oncological benefit and improved prognosis with the endoscopic approach. Patients who underwent the percutaneous approach had a higher rate of peritoneal tumor seeding and poor survival, compared to the endoscopic approaches. Increasing evidence has been published regarding tumor seeding when using the percutaneous transhepatic approach (up to 5–20%).\(^4,7\)

Therefore, endoscopic biliary drainage (e.g., nasobiliary drainage or transpapillary drainage) represents the best approach when performing PBD in patients with hilar tumors.\(^7\)

Endoscopic drainage can be accomplished by endoscopic nasobiliary drainage (ENBD) or by endoscopic retrograde biliary drainage (ERBD). Both techniques seem to effectively achieve adequate biliary drainage. However, there are some aspects to be considered. Endoscopic retrograde biliary drainage represents a more physiological drainage procedure; however, it seems to be associated with a higher rate of complications and duodenobiliary reflux that may be related to a higher degree of inflammatory action in the bile ducts. By contrast, the major drawbacks of ENBD are patient discomfort and tube dislodgement.\(^1\) To date, there is no consensus regarding which is the optimal endoscopic technique.

**Conclusion**

Biliary obstruction in patients with pancreaticobiliary malignancies results in several deleterious effects on patient physiology. Routine PBD has been proposed to counteract these adverse effects; however, its efficacy has not been completely proven because of the high rate of procedure-related adverse events. However, the use of SEMSs may reduce the incidence of adverse events related to PBD and eventually improve postoperative outcomes. The current absolute indications for PBD in patients with distal pancreaticobiliary malignancies are cholangitis, an expected delay in surgery, and patients with a borderline or unresectable pancreaticobiliary malignancy who are receiving neoadjuvant therapy. Furthermore, indications for preoperative drainage in patients with hilar tumors include cholangitis, patients who have undergone right hepatectomy, and patients receiving neoadjuvant chemoradiation and/or portal vein embolization. Further well-designed randomized controlled trials are required to assess the efficacy and safety of PBD in patients with distal pancreaticobiliary malignancies and hilar tumors.

**Conflicts of interest**

All authors declare no conflicts of interest.

**References**


