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REVIEW ARTICLE

Effectiveness and risk of biliary drainage prior to pancreatoduodenectomy: review of current status

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Abstract Preoperative biliary drainage (PBD) prior to pancreatoduodenectomy (PD) has gained popularity as bridge management to resolve jaundice, but its role is being challenged as it is thought to increase morbidity. To clarify the current recommendations for PBD prior to PD, we reviewed the literature, including all relevant articles published in English up until December, 2015. There is increasing evidence that PBD causes bile infection, which is related to the morbidity of infectious complications. Results of transhepatic drainage are poorer than those of endoscopic stenting, especially in an oncologic setting, although it is still unclear whether metallic stents are superior to nasobiliary drainage. PBD should be avoided whenever possible and performed only in selected cases, such as the emergency setting, an inevitable long delay (>4 weeks) before PD, and jaundice-related anorexia. Seemingly, transhepatic drainage should be reserved for refractory cases if endoscopic drainage is not possible. Further studies comparing endoscopic drainage techniques, such as metallic stents and nasobiliary drainage, are required to assess the most effective technique of PBD. Bile infection should be prevented by adequate antibiotic prophylaxis and treated even in the absence of symptoms, and bile status should be assessed systematically.

Keywords Jaundice · Preoperative biliary drainage · Pancreatoduodenectomy · Bile infection · Outcomes

Abbreviations

PD	Pancreatoduodenectomy
PBD	Preoperative biliary drainage
RCT	Randomized controlled trial
EBD	Endoscopic biliary drainage
PTBD	Percutaneous transhepatic biliary drainage
EBS	Endoscopic biliary stenting
SEMS	Self-expanding metallic stent
ENBD	Endoscopic nasobiliary drainage
ERCP	Endoscopic retrograde cholangio pancreatography

Introduction

The head of the pancreas is a complex anatomical area involving the digestive system and biliary tract, portal vein, celiac trunk, and superior mesenteric vessels. Resection of the head of pancreas usually requires a major surgical procedure, pancreatoduodenectomy (PD), which, beyond the pancreatic resection, involves the duodenum, the distal part of the stomach, the first jejunal loop, the distal common bile duct, and three demanding anastomoses. Despite morbidity and mortality reaching 41 and 5% in reference centres [1, 2], it remains the only treatment with curative intent for periampullary lesions.

The intrapancreatic portion of the common bile duct makes obstructive jaundice a common presentation of periampullary lesions. Traditionally considered a risk factor

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for poor outcome after PD [3–5], obstructive jaundice was conventionally treated before surgical resection for decades [6–8]. Historically managed by open hepaticojejunostomy [6], minimally invasive approaches have revolutionized the management of jaundice prior to PD in the last 30 years [9–13].

Recently, systematic preoperative biliary drainage (PBD) has been criticized because of several reports on increased morbidity [14–26], mortality [14–16, 27], and prolonged hospital stay [11, 25] after PD. Some authors have also reported PBD to be associated with wound infection [22, 25, 26, 28], perioperative cholangitis [22, 25, 26], delayed gastric emptying [22, 25], pancreatic anastomositic fistula [24, 27], and other perioperative infectious complications [12, 16, 27].

With new evidence of potential adverse effects, the role of PBD prior to PD is now being reassessed. To clarify the recommendations, we performed a systematic review of current scientific literature, aiming to answer the three key questions concerning jaundiced patients requiring PD:

1. Should jaundiced patients undergo PBD before PD?
2. Are there any associations among PBD, bile infection, and PD outcomes?
3. What types of PBD should be preferred?

Materials and methods

To answer these questions, we searched the literature in accordance with the PRISMA recommendations, as shown in Fig. 1. This research was performed by two independent researchers (AZLB, RC), enabling a double check. Discrepancies were discussed until an agreement was reached.

First, we identified publications in the MEDLINE, EMBASE, and Cochrane Central databases (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Cochrane Methodology Register) from January, 1966 to December, 2015, using the keywords and MeSH terms: "preoperative biliary drainage", "obstructive jaundice", "bile infection", and "pancreaticoduodenectomy". Reference lists of identified studies were scrutinized to reveal additional sources. We then screened included publications, to remove duplicates and irrelevant publications using abstracts. Eligibility and inclusion were defined using full-text articles. Articles including patients who underwent palliative drainage or drainage because of hilar stricture or hilar

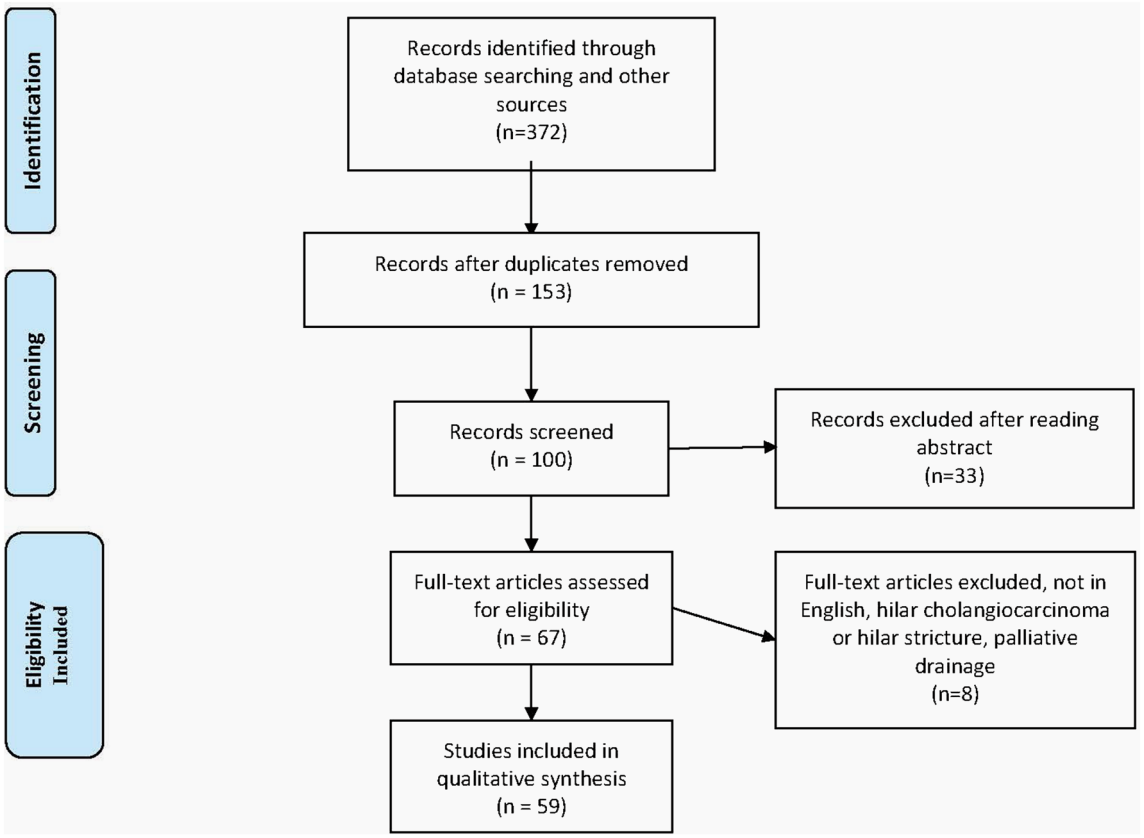

Fig. 1 Systematic review flowchart

cholangiocarcinoma were not included. Only articles published in English were included.

Finally, we performed qualitative synthesis of the selected publications to answer the three specific questions:

1. Should jaundiced patients undergo PBD before PD?
2. Are there any associations among PBD, bile infection, and PD outcomes?
3. What types of PBD should be preferred?

Results

"To drain or not to drain?" (Should jaundiced patients undergo biliary drainage prior to PD?)

In 2002, the first meta-analysis leading to reassess systematic PBD [11] was released. Five randomized controlled trials (RCTs) and 18 retrospective studies over 35 years (1966–2001) failed to reveal any change in PD mortality, but showed increased overall morbidity (when the analysis included both level 1 and level 2 studies) and length of postoperative hospital stay. It was concluded that PBD should not be performed systematically in jaundiced patients prior to PD. Interestingly, when PBD was uneventful, the postoperative complication rate was in favour of drainage based on level 1 studies and showed no difference based on level 2 studies.

Although this meta-analysis [11] has the selection bias of the inclusion of a non-negligible proportion of patients with cholangiocarcinoma, these results and conclusions were strengthened by other meta-analyses from 2011 to 2015 [19–22, 29], showing the following:

1. No decreased postoperative mortality after PBD (14 retrospective studies from 1995 to 2009) [29];
2. No change in mortality, but an increased morbidity after PBD in six trials including two and four evaluating endoscopic biliary drainage (EBD) and percutaneous transhepatic biliary drainage (PTBD), respectively [19, 20];
   - No significant impact of PBD on PD morbidity/mortality, at least when metal stents are used for >4 weeks in 14 studies from 2000 to 2014 [21];
   - A significant increase in postoperative infections after PBD, wound infections and delayed gastric emptying in 8 RCTs, 13 prospective studies, 20 retrospective studies, and 3 local retrospective studies [22]. The most recent article concluded that PBD probably should not be performed routinely prior to PD.

According to these reports, PBD should not be performed systematically prior to PD, since it does not reduce mortality, but it may increase morbidity after PD. Although there are no consistent data on the long-term results of PBD for cancer, some recent articles have addressed this issue [8, 30–33]. The first two studies did not find any difference in long-term survival [8, 32], although the only RCT [33] reported a lower rate of tumor resections (58 vs. 67%) and R0 resections (62 vs. 73%) after stenting, without reaching statistical significance. Interestingly, the incidence of pancreatic adenocarcinoma among resectable tumors after stenting and early surgery was 57 and 78%, respectively [32]. In the most recent papers [30, 31], univariate analysis revealed PBD associated with poor prognosis and decreased survival, whereas multivariate analysis revealed some discrepancy in confirming this [30, 31]. RCTs are needed to clarify long-term outcomes after PBD and PD as these conclusions are based on small retrospective series.

Since the mid-2000s [15, 33, 34], several studies have attempted to identify appropriate indications for PBD prior to PD. Although addressed far less in the current literature, some heterogeneous papers, including meta-analyses, observational studies, and multicentric retrospective series, have focussed on this issue [21, 24, 35–37] and identified the following clear indications for preoperative drainage:

1. In an emergency setting, such as for acute cholangitis, obstruction with bilirubin levels exceeding 250 μmol/L, or severe pruritus;
2. When jaundice is associated with renal failure or comorbidities needing preoperative work up or management;
3. When a patient's nutritional status compels relief of anorexia, so they can tolerate nourishment before PD;
4. When PD is delayed for ≥4 weeks, including for neoadjuvant chemotherapy for borderline resectable pancreatic cancer.

Are there any relationships among PBD, bile infection, and outcome?

Before considering the relationships among PBD, bile infection, and surgical outcomes, the morbidity linked to PBD and endoscopic procedures should be established. Complications of ERCP include acute pancreatitis, perforation, hemorrhage, and mortality, which occur in 1.6–3.8, 0.4–1, 0.9–1, and 1% of patients, respectively [38–40]. These complications may jeopardize the treatment and thus the prognosis.

Stent-associated bile infection seems to increase morbidity after PD. The current literature on the subject is mostly heterogeneous, comparing PD results in stented

vs. non-stented patients [11, 12, 17, 18, 29, 36, 41]. Yet, an association between PBD and bile infection seems to exist, as biliary infection has been shown in 47–100% of endoscopically stented patients [14, 15, 27, 30], with a doubled rate of infected bile in stented vs. non-stented patients (63–78 vs. 31–36%) [42, 43]. Interestingly, polymicrobial infection is found in 61–66% of stented patients [27, 43]. Consequently, stent placement seems to favour ascending common bile duct bacterial colonization from the duodenum [14, 42]. In a recent paper, immunodeficiency was raised as a hypothesis for bile infection and polymicrobial infection [27].

When bile infection is related to stent placement, associated morbidity has been suggested by the frequent concordance of isolated bacteria, reaching 89% [41, 42] in the bile and infectious complication site. Some investigators [44] compared the early outcomes of patients undergoing PD with bile infection vs. those with sterile bile, demonstrating that all patients with endoprothesis had bile infection and that this was associated with increased infectious complications and morbidity [44].

On analyzing the impact of bile infection on severe morbidity/mortality, several studies show a significant association between bile infection and mortality [14–16]. Yet, when those authors could not find any correlation between bile infection and pancreatic fistula, in relation to severe morbidity/mortality, bile infection was demonstrated to be associated with intra-abdominal collections/abscesses [14, 16] and the modern pancreatic fistula definition and classification [45] were not used. Thus, the pancreatic leak rate and its association with severe morbidity/mortality may be underestimated. This hypothesis is seemingly confirmed by a recent report [27] that a grade C fistula was found in all deceased patients after PD with documented stent-associated infected bile at intraoperative sampling. Those findings were confirmed by a recent meta-analysis, showing that PBD significantly increases wound and bile infection rates but has no adverse effect on mortality and morbidity, although positive bile culture for bacteria impairs both mortality and morbidity after surgery [46].

Bile infection is often polymicrobial and seems to be population-dependent. In a recent multicentric study [47] showing preoperative bile stenting as the strongest predictor of postoperative wound infection, the prevalence of different bacteria varied widely among centres, with *E. coli*, *Staphylococcus aureus*, and *Enterococcus faecalis*/*Enterobacter cloacae* being the most common bacteria. Although bacteria isolated in bile vary considerably, Gram-positive cocci are found constantly, especially Enterococcus, which is identified in the bile of 20–74% of patients [15, 27, 42, 43, 48]. Augenstein et al. [42] isolated as many as 19 micro-organisms, but Enterococcus, Klebsiella, or Staphylococcus were present in 50%, Limongelli et al. [15] found Enterococcus species or Lactose-fermenting Coliform in 75% of patients, and Sudo et al. [43] found Enterococcus or Klebsiella in about 30%. Gavazzi et al. [48] found an unusually high rate of Enterococcus (74%) followed by *E. coli* (37%) and Klebsiella (35%). Similar rates were reported by Beaujon et al. (Enterococcus 51%, *E. coli* 37%, and Klebsiella 14%) and Verona et al., who found Enterococcus in 41% and *E. coli* in 28%, the latter being associated with grade C pancreatic fistula and mortality [27]. These results are summarized in Table 1.

Regardless of targeted antibiotic therapy, antibiotic prophylaxis before PD in stented patients is seemingly mandatory. The recent report of increased severe morbidity/mortality in patients with bile infection caused by enterobacteria (specifically, *E. coli*) [14, 27] after ciprofloxin [14] or amoxicillin/sulbactam [27] should probably widen antibiotic prophylaxis, with agents like cefuroxime/metronidazole (and ciprofloxacin for instrumentation) [15] or tazobactam/piperacillin with ciprofloxacin [44], especially for high-risk patients, until antibiogram results are available.

Which type of drainage should be preferred prior to PD?

There are two main techniques used for PBD prior to PD: PTBD and EBD (Fig. 2).

In the mid-80s, PTBD was considered a non-optimal treatment for jaundice before PD, because it was associated with increased morbidity [28], mortality, and hospital stay/cost [49] versus surgery without PBD. This has been recently criticized [25] as the minimally invasive management shifted from PTBD to EBD during the 80s–90s. EBD was increasingly perceived as the least invasive procedure with several advantages over PTBD in the preoperative work up of surgery for periampullary tumor: it may achieve histologic diagnosis (by tumor biopsy) and staging of neoplastic disease (with ERCP and endoscopic ultrasound) during the same procedure/anaesthesia, despite specific concerns about migrating drains and dehydration. However, some authors [50] recommended PTBD for patients with obstructive jaundice awaiting PD, because it could achieve rapid biliary decompression with fewer catheter-related complications. These recommendations should be

Table 1 Polymicrobial bile infection: main bacteria isolated from stented patients

Bacteria	Rate (%)
Enterococcus	20–74
E. coli	37–75
Klebsiella	14–66
Staphylococcus	44–50

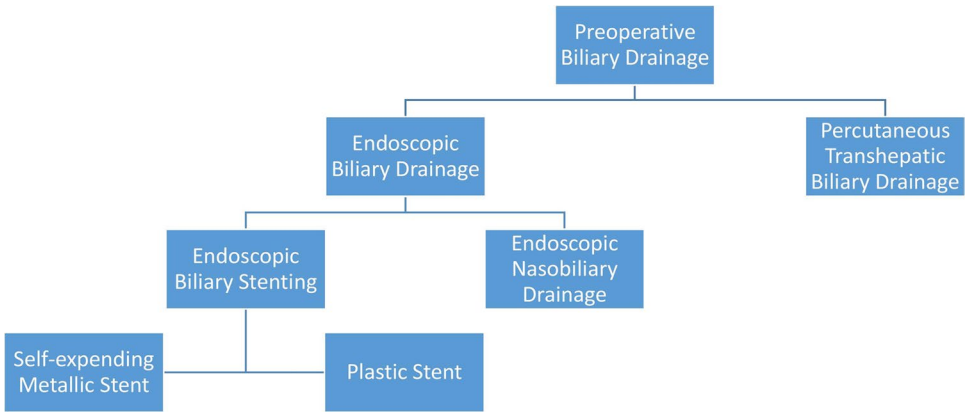

Fig. 2 Different techniques of preoperative biliary drainage before pancreatoduodenectomy

tempered for patients with pancreatic adenocarcinoma [31, 51, 52] as carcinomatosis has been linked to PTBD [31].

The safety and oncological outcomes of EBD versus PTBD have been recently reported: three retrospective studies suggested poorer survival of patients who underwent PTBD versus EBD [31, 51, 52]. Murakami et al. [31] and Uemura et al. [51] demonstrated PTBD as an independent risk factor of worse overall survival compared with EBD or no PBD. They hypothesized metastatic tumor seeding along the PTBD sinus tract to explain the higher rate of peritoneal recurrence, with a significant difference in both analyses, but positioning of the PTBD (transtumoral or not) was not described. Indeed, such a conclusion has already been drawn for hilar cholangiocarcinoma [53] and may be related to the transtumoral positioning of the PTBD. Strom et al. [52] came to the same conclusion, reporting 5-year survival after PTBD, EBD, and no PBD, to be 3, 24, and 32%, respectively, although PTBD tended to be performed in patients with more severe lesions, probably after failure of ERCP. Therefore, the current literature suggests that EBD should be preferred to PTBD, but without an RCT, no definitive conclusion can be drawn. Moreover, considering oncological outcomes, transtumoral PTBD should be investigated.

As both early and oncological outcomes of EBD seem to be superior to those of PTBD, different endoscopic techniques have been proposed and evaluated, including endoscopic biliary stenting (EBS), using a plastic or self-expanding metallic stent (SEMS) and endoscopic nasobiliary drainage (ENBD). EBS is used more frequently, but the results of ENBD are seemingly comparable. Currently, EBS seems to be a better option than ENBD for moderate acute cholangitis related to gallstones [54], but when ENBD is used, a larger catheter (7 Fr) is more effective [55]. Considering PBD prior PD, the first retrospective analysis to evaluate safety and efficacy in a series of 76 patients was reported in 2013 and did not show any difference between the techniques [56]. More recently, ENBD was compared with EBS in patients with pancreatic cancer [24] and was demonstrated to be a better option in terms of postoperative complications after PD. This result was confirmed by a prospective study showing an increased complication rate related to EBS, and no effect related to ENBD [25]. Better results of ENBD may be attributed to less bile contamination by ascending bacterial colonization, as ENBD implies external bile drainage. RCTs are required, but ENBD seems to be a promising alternative.

Considering EBS, plastic and SEMS have been compared in retrospective series [57–59]. One study showed SEMS as superior for pancreatic cancer patients [57], but two others did not demonstrate any clinical difference [58, 59]. In 2015, Tol et al. reported the first RCT comparing plastic stents and fully covered SEMS in pancreatic cancer patients [60]. When no difference was demonstrated in the PD surgical outcome, SEMS was associated with a lower complication rate, with mainly stent-related complications such as mobilization or obstruction. Short fully covered SEMS resulted in fewer days of delay in the initiation of neoadjuvant treatment and a longer time to stent occlusion [61]. These results suggest that fully covered SEMS may be the preferred option for patients requiring PBD, including those with borderline pancreatic cancer requiring neoadjuvant chemoradiation prior to PD [51, 52]. Ultimately, no RCT has shown the best technique for PBD.

Discussion

Several questions have been raised about biliary drainage prior to PD, leading to many studies, as seen in this review. To assess the recommendations, we attempted to give clear, evidence-based answers to three simple questions: (1) should jaundiced patients undergo PBD before PD? (2) Are there any associations among PBD, bile infection, and PD outcomes? (3) What types of PBD should be preferred?

Regarding PBD indications, the bridge management of jaundiced patients requiring PD became minimally invasive during the mid-80s, leading to the uncontrolled

implementation of PBD. Consequently, during the 90s, PBD became the systematic approach to obstructive jaundice related to periampullary malignancy [28]. On one hand, as obstructive jaundice was thought to alter homeostasis (including hemostasis), kidney and liver functions, and to worsen PD outcomes, common bile duct clearance was encouraged before the surgical procedure [3–5]. On the other hand, as new less invasive techniques replaced surgery for jaundice management, the PBD indications widened and became systematic in most environments without any real assessment of potential drawbacks. Consequently, many patients underwent PBD without appropriate indication. From 1992 to 2007, 52.6% patients with pancreatic cancer had preoperative biliary stenting done (with an increasing incidence during the 2000s) and 77.6% of these patients underwent stenting even before being referred to a surgeon [13]. Recent trends towards a centralization of pancreatic surgery [7, 62] may have played a role in the increasing popularity of PBD as it may have been considered the ideal waiting management for patients with worsening jaundice who were referred to high volume centres. Indeed, considering the importance of nutrition [63] and preoperative chemotherapy [64] prior to PD, the growing popularity of PBD is relevant. It is now clearly established that PBD should not be performed systematically prior to PD, since it does not reduce mortality and may increase morbidity after PD. Increased morbidity, including mild-to-moderate complications, may also have a significant impact on patient early-to-long-term outcomes by postponing mobilization, feeding, and eventually adjuvant chemotherapy, with potentially worse survival.

There is increasing evidence of the association between stenting and bile infection and of the impact of bile infection on PD outcomes, with a frequent concordance of isolated bacteria in bile and an infectious complication site. Such an association may be underestimated in the current literature for several reasons: morbidity and mortality have been compared in patients depending on stent placement [11, 12, 18, 29, 36, 41] and not on bile infection. "Postoperative infection", as defined in some articles, is a vague concept as it includes heterogeneous complications such as wound infections, intra-abdominal abscess, and pulmonary complications. Moreover, the few studies [14–16] investigating this relationship had the flaws of being retrospective and analyzing this only as a secondary focus on the impact of bile infection on outcome.

To decrease this morbidity, various management strategies have been proposed. First, intraoperative bile sampling [15, 18, 19, 27, 42, 43] is thought to enable early identification of infectious agents for targeted antibiotic therapy, especially in patients at high risk of complications [27]. The potential clinical relevance of intraoperative bile sampling is limited as bacterial development and antibiogram may take several days, when it could be too late to prevent complications. Unlike percutaneous stenting, which allows for easy sampling of bile preoperatively to target "secondary" antibiotic prophylaxis, preoperative bile assessment in endoscopically stented patients requires a second invasive procedure. Yet, the colonization seems to occur during the procedure. Sudo et al. [43] suggested specific antibiotic prophylaxis based on preoperative bile culture as a higher rate of antibiotic resistant bacteria is found in drainage fluid, mainly from PTBD. Augenstein et al. [42] described a protocol involving the gram stain of a bile sample during PD, to help decide on the appropriate antibiotic treatment intraoperatively before receiving bile culture results. Both those studies [42, 43] concluded that prompt and targeted antibiotic use leads to morbidity and infection rates similar to those in patients without stents. Finally, antibiotic prophylaxis before PD in stented patients is required prior to identification of bacteria in bile.

Finally, various techniques of PBD have been proposed; however, EBD should be chosen over PTBD in the oncological setting. As no technique of EBD has been demonstrated as superior, a trial comparing EBS using SEMS and ENBD should be performed.

Conclusion

There is increasing evidence that PBD is related to bile infection, and that bile infection is related to morbidity by increased infectious complications. Therefore, PBD should be performed in specific conditions and, as bile infection in PD is a major issue, intraoperative prophylaxis (and empirical) and then postoperative prophylaxis with wide-spectrum antibiotic therapy are recommended, even in the absence of symptoms. Finally, while PTBD should not be done in the oncological setting, EBD is preferred as the first intention.

There is currently no consensus or strong evidence regarding the preferred PBD technique among PTBD (in the non-oncological setting), ENBD, EBS, or the best kind of stent, the optimal timing in relation to the surgical procedure, and the best management of bile infection, involving bile sampling with identification of bacteria, and the choice of antibiotics for prophylaxis. The recent trend towards an indiscriminate diffusion of PBD before PD should prompt a consensus statement concerning indications, antibiotic prophylaxis, and techniques. As PBD is becoming a standard procedure while referring patients to high volume centres, the future health policy for periampullary cancer management should not underestimate the potential risks of this procedure. RCTs should be conducted to assess these major concerns.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

Ethical approval This article does not include any studies on animals performed by any of the authors.

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