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Role of Preoperative Biliary Drainage in Resectable Hilar Cholangiocarcinoma

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Abstract

Background: To review the literature to investigate indications, advantages and complications of the different procedures for biliary drainage (percutaneous or endoscopic techniques) for resectable hilar cholangiocarcinoma.

Methods: Pubmed and Medline databases were interrogated for articles published between January 1970 and November 2014. After screening for relevance, 56 articles were selected for the review.

Results: Hilar cholangiocarcinoma is the most common primitive adenocarcinoma of the bile ducts, involving the proximal extra hepatic biliary system. Prognosis has been strongly related to tumour's resectability and extended combined hepatic and biliary resections are often required in order to achieve radical margin and survival benefit. Obstructive jaundice is the most common clinical presentation; preoperative hyperbilirubinemia is an independent risk factor for increased operative morbidity and mortality.

Conclusion: PBD was shown to be helpful only in those patients having a bilirubin level greater than 3-10 mg/dl; we might conclude that PBD is probably useless with bilirubin level below 3 mg/dl, advisable between 3-10 mg/dl and mandatory above 10 mg/dl especially in patients undergoing an extended hepatic resection.

In the initial management of HC, ENBD should be preferred as it is characterized by a less invasive approach and less complications (lower morbidity) . In case of suboptimal jaundice regression or in presence of complications PTBD might be combined, leaving EBD as last option. Drain should be limited to FLR. The optimal drain duration is debated: the drain should be left in place the time needed to reduce bilirubin level, meanly 2-6 weeks.

Keywords: Klatskin tumor; Hilar cholangiocarcinoma; Preoperative biliary drainage

Abbreviations: Hc : Hilar Cholangiocarcinoma; Ebd : Endoscopic Biliary Drainage; Ptbd : Percutaneous Transhepatic Biliary Drainage; Enbd : Endoscopic Naso-Biliary Drainage; Flr : Future Liver Remnant

Introduction

Hilar cholangiocarcinoma (HC), also known as 'Klatskin tumor', is a primitive adenocarcinoma of the proximal extra hepatic bile duct. It may involve either the common bile duct, the left or right main branches or the biliary confluence [1] and it is commonly classified on anatomical basis according to the modified Bismuth-Corlette classification [2]. It represents the most common type of cholangiocarcinoma with a prevalence of 46-97% [3]. The prognosis has been strongly related to tumour resectability. Combined hepatic and biliary resection of the affected duct is an independent favourable survival prognostic factor [4]. Extended hepatic surgery is often required in order to achieve radical resection and survival benefit [5].

The most frequent clinical presentation is obstructive jaundice (80-90%), alone or in association with itching, abdominal pain, cholangitis, malaise, malnutrition and renal failure. Elevated serum bilirubin at surgery is an independent risk factor for increased postoperative morbidity and mortality [6]; biliary drainage procedures aim to reduce bilirubin serum levels in obstructive jaundice. Although these techniques are affected by specific morbidity, it has been speculated that morbidity and mortality after major hepatectomy may be reduced if biliary drainage is performed preoperatively. The actual effectiveness of preoperative biliary drainage (PBD) has been widely debated in literature and a definitive consensus has to be reached yet.

The aim of this review is to identify some principles that are currently recommended and commonly adopted in clinical practice.

Materials and Methods

We performed a systematic electronic review of English language published articles between January 1970 and November 2014 using PubMed and Medline databases Search terms were: "Hilar Cholangiocarcinoma", "Klatskin tumor", "PBD" or "Preoperative biliary drainage". All studies concerning hepatic resections in patients affected by HC were included in the study. Studies using PBD as simple palliation were excluded from the research. We mainly focused on articles which investigated how the presence or absence of preoperative biliary drainage (PBD) affects the surgical results.

1484 studies were retrieved. 76 studies on hepatic resections for HC focusing on biliary drainage met the inclusion criteria; studies in which PBD was performed as palliative treatment were excluded. After screening for relevance, 56 articles were selected for the review.

Drainage techniques

An accurate analysis of the literature shows that the most frequently used techniques of BD are: endoscopic biliary drainage (EBD), percutaneous trans-hepatic biliary drainage (PTBD), and endoscopic nasobiliary

drainage (ENBD). To date, there are no prospective randomized controlled studies which compared the efficacy of those techniques as PBD of HC.

Endoscopic biliary drainage: EBD consists in an endoscopic drainage of bile duct by introducing a plastic or metallic stent. It is usually combined with sphincterotomy of the papilla of Vater. This technique has several advantages: it is more physiologic, it improves patient's nutritional status, it reduces blood endotoxins, normalizes dyslipidemia and it improves immune response [7].

EBD in patients affected by tumors of proximal bile duct is often a difficult maneuver, affected by a high failure rate, which may require the association of more than one drainage techniques (usually PTBD). Moreover, after the procedure, evaluation of tumor length and extension may be less accurate in the presence of one or more stents and for local inflammation and fibrosis [8,9]. EBD is affected by an higher rate of post-procedural complications compared to other techniques, with an overall 25-50% morbidity and 3-5% mortality rate [9,10].

Percutaneous transhepatic biliary drainage: To date, PTBD is the most widely used technique for biliary drainage of proximal bile duct tumors. This technique consists of selectively cannulating the bile duct by a percutaneous approach, usually under ultrasound guide, and placement of one or more biliary stents in the biliary system. It has been reported that the post-procedural morbidity rate of percutaneous techniques is lower compared to the endoscopic technique [9]. PTBD is a direct approach for bile duct decompression in patient with HC and it is usually the procedure of choice in most groups due to effectiveness in decreasing serum bilirubin with low rates of cholangitis [9,10]. In particular, success rate of bile duct decompression is significantly higher by percutaneous approach than EBD in locally advanced HC [11].

Preoperative cholangiography made via PTBD may be helpful, in association with magnetic resonance cholangiopancreatography (MRCP), in determining tumor extension and preoperative staging according to Corlette-Bismuth classification. Nevertheless, PTBD is an invasive procedure which requires the insertion of one or more drainages through the hepatic parenchyma. One of the limits of this approach is the necessity of having dilated intrahepatic bile ducts prior the procedure, thus reducing the number of attempts needed to enter the bile duct. In absence of dilated bile duct, this technique may be long and laborious. The risk of vascular lesion and post-procedural haemorrhage does exist as reported by Kawakami [12], and tumor seeding of the drain tract has been histologically shown in the specimen with a rate of 5-20% [13,14]. Gerhards and co-authors suggested that preoperative radiotherapy of patients with resectable main bile duct tumor may reduce the risk of tumor seeding [14]. However, more recent studies reported a lower risk of seeding following PTBD compared to previous literature [15,16]. Further studies are needed in order to confirm these findings.

Endoscopic naso-biliary drainage: ENBD is a technique which consists in inserting a nasobiliary tube inside the dilated bile ducts via an endoscopic approach. A recent retrospective study compared the three principal techniques of biliary drainage, suggesting that naso-biliary drainage of future liver remnant (FLR) may be the technique of choice for initial management of HC [12] due to reduced rate of post-procedural complications compared to EBD and PTBD. Inflammatory response around bile ducts may be less severe with ENBD; as opposite to EBD, endoscopic sphincterotomy is frequently not required in relation to the small diameter of the nasobiliary tube compared with endoscopic stents whereas duodenal-biliary reflux is avoided with this approach [17]. Moreover, ENBD is preferred to PTBD due to the absence of tumour seeding of the drain tract associate with the percutaneous approach [12].

A Japanese retrospective study on 141 patients treated for HC in a single center from 2000 to 2008 [18] compared results of ENBD and PTBD with a mean follow up of 82 months. 121 out of 141 patients had severe obstructive jaundice (serum bilirubin >2.0 mg/dl) at presentation and were treated with PBD. Among the other 20 patients, 18 were drained with naso-biliary tube to prevent development of jaundice and PTBD was performed in the 2 remaining patients in order to obtain a preoperative cholangiography. ENBD was the initial technique of choice in most patients; one or two more drainage were inserted in the FLR in case of sub-optimal decompression or in the presence of cholangitis. PTBD was added to ENBD when the first procedure was ineffective or when a third nasobiliary tube was needed. The patients were divided in two groups for analysis: PTBD group (67 patients) and ENBD group (74). Overall survival rate was higher in the ENBD group compared to PTBD group (p 0.004). Multivariate analysis showed that preoperative PTBD was an independent predictor of poor survival compared to ENBD (HR 2.075, 95% CI 1.279–3.709, p 0.003). In the percutaneous group, tumor seeding was detected in 3 patients (4.5% - one in the hepatic parenchyma and two in the extra-hepatic tract of the drainage).

ENBD technique is not feasible in case of complete stenosis of the main bile duct; therefore its efficacy is limited in the majority of Corlette-Bismuth type IV HC [19]. Major drawbacks for ENBD are patient's discomfort and high risk of displacement of the tube. Moreover, the reduction in serum bilirubin is reportedly lower than the other procedures and a longer preoperative hospital stay may be required; also, contemporary drainage of both liver lobes is not achievable with only one tube [20]. Interestingly, Yoshida et al suggested that per-os reintroduction of drained bile may improve immune and hepatic function and overall general status, supporting the hypothesis that bile replacement may be beneficial for patients undergoing major hepatectomy [21].

Discussion

Obstructive jaundice is the most common clinical presentation of primary bile duct malignancies; hyperbilirubinemia, with reported mean values of 15 mg/dl in serum bilirubin, is directly related to the site and extension of lesions in the common bile duct and to the degree of stenosis. High bilirubin level has been clearly shown to be a risk factor of increased morbidity and mortality in patients undergoing surgical operations for malignancies or benign diseases [22-25]. Extended hepatectomy in case of bile obstruction and jaundice may be associated with an increased postoperative morbidity and mortality [26-28].

Use of PBD for the reduction of serum bilirubin and associated operative risks is controversial. Some authors suggest that presence of PBD may increase infection rate of the biliary system thus increasing the risk of postoperative infectious complications [29,30]. In 2009, Kloek et al. [9] demonstrated an altered coagulation profile and an inflammatory status in case of severe hyperbilirubinemia. Moreover, it has been shown that obstructive jaundice may be associated with renal and hepatic insufficiency [22-24,31-34]. Other studies showed that severe jaundice and related complications (renal and hepatic insufficiency, malnutrition, sepsis) might be potentially reversible by correcting hyperbilirubinemia [35,36].

In the event of severe complications related to obstructive jaundice, the majority of authors recommend urgent treatment of hyperbilirubinemia, regardless of the origin of the disease; conversely, isolated finding of elevated serum bilirubin may not be per se an indication to perform PBD particularly in the case of malignancies involving the distal portion of common bile duct [20,37,38]. However, as far as HC is concerned, poor evidence is available and data appear discordant.

Preoperative Bilirubin level

A preoperative bilirubin level lower than 3 mg/dl has been recommended by Makuuchi et al. [39] and Nimura et al [40], thus

suggesting an important role of PBD in managing HC. A recent single center retrospective study [41] reviewed a 10 years' experience of 105 patients treated for HC. Mean bilirubin levels at diagnosis and at surgery were 5.9 mg/dl (range 0.5-34.6 mg/dl) and 1.6 mg/dl (0.3-21.8 mg/dl) respectively. 84 patients of 105, those with bilirubin level greater than 2 mg/dl, were treated by PBD. After the procedure 72/84 (68.6% of total) had lowered their bilirubin level to less than 3 mg/dl before surgery. PTBD was the most frequently used approach. Thirty-nine patients (37.1%) were also treated for cholangitis. Persistence of cholangitis in the preoperative setting was found to be an independent predictor of mortality in univariate and multivariate statistical analysis. In multivariate analysis, a preoperative level greater than 3 mg/dl was found to be an independent prognostic factor of poor OS.

Grandadam et al. [42] showed that hepatic optimization of liver function in HC reduces postoperative morbidity; in their cohort of patients, mean preoperative bilirubin level was 4.4 mg/dl. A retrospective study by Nakayama et al. demonstrated a reduction in postoperative mortality from 28.3% to 8.2% in patients with malignancies undergoing curative or palliative surgery when preoperative serum bilirubin was lower than 5 mg/dl whereas mortality increased with bilirubin of 10 mg/dl or higher. The role of PBD in reducing postoperative mortality was evidenced in relation to decreasing preoperative bilirubin [22]. Findings by Denning et al. supported the hypothesis that postoperative morbidity and mortality rates are directly related to severity of preoperative hyperbilirubinemia [43]; also, considering preoperative bilirubin as the only predictor of postoperative morbidity and mortality in their analysis, no complications were reported among the 11 patients with values lower than 6 mg/dl.

Some authors describe the risk factors to look at in the decisional work up of HC, such as bilirubin lower than 10 mg/dl [44,45]. Su et al. [26] showed relationship between post-operative mortality and bilirubin level >10 mg/dl. On the other side, in a single center retrospective study made in 2009 Figure as et al., [46] reviewed data of 19 patients treated for HC during a 3 years period (2005-2008), suggesting PBD only for those patients with bilirubin level greater than 15 mg/dl or with preoperative cholangitis, severe malnutrition or hypoalbuminemia (<3 mg/dl).

Optimal drain duration

Reduction of hyperbilirubinemia usually occurs in 14 days [47,48]. This period must be used to control nutritional level, to correct an altered coagulation status, blood count, renal insufficiency and eventually to eradicate bile infection from multi-drug resistant bacteria.

In the cohort by Denning et al, external biliary drainage was left in situ up to 72 days in order to achieve optimal in-hospital and outpatient care; complications developed in 10% of procedures and drain replacement was necessary in 5 patients [43]. In other series, PBD was maintained up to 1 year postoperatively without major complications. [22,49]. Even if experimental data suggest that complete recovery of hepatic function occurs in 6 weeks [50], a 2 to 3 weeks period of biliary drainage is currently applied in clinical practice [51-53]. In case of cholangitis or long lasting drain, PBD tube should be periodically replaced. In order to achieve a rapid bilirubinemia reduction, some authors supports the use of PTBD as a standard technique for patients undergoing hepatic resection for HC [40,54].

To drain or not to drain

Laurent work [55] shows that there is no difference in terms of post-operative mortality and hepatic insufficiency after hepatic resection between patients with or without jaundice. Despite this conclusion, postoperative morbidity and pre-operative transfusion rate were higher in patients with obstructive jaundice. The most remarkable post-operative complications were bile leaks and subphrenic abscess, which occur more frequently in patients having pre-operative jaundice, increasing the number of days of hospitalization. Overall morbidity rate in icteric and non-icteric group were 50 and 15%, respectively.

The authors do not recommend routinary use of PBD in HC. However, there might be some cases where it is still advised: these are patients with a FRL less than 40%, patients with cholangitis, long-time lasting jaundice, malnutrition or severe hypoalbuminemia. If we decide to use PBD, FLR should be drained and surgery should be performed with a bilirubin level of less than twice the normal range. In case of cholangitis or long lasting drain, PBD tube should be periodically replaced. When FLR doesn't allow a safe resection, preoperative portal vein embolization (PVE) should be performed in order to achieve FLR hypertrophy, and in these cases preoperative PBD is usually necessary. PBD may be avoided in the following situations: short-time onset of jaundice (<2-3 weeks), total bilirubin level < 200 mmol/l, absence of sepsis, future liver remnant >40%. These criteria include most patients requiring left hepatic resection and selected patients needing right hepatectomy. In other cases, PBD is required, alone or in association with PVE in case of small FLR [55].

In a retrospective study on 71 patients treated for HC, Hochwald et al. [29] reported an increased risk of biliary infections (69%, p 0.001) and overall infectious complications (66%, p 0.03) in the drained group (42 patients) compared to the non-drained group (29); bile contamination was found in 100% and 69% of patients drained with endoscopic or percutaneous approach respectively. Conversely, there were no significant differences in terms of postoperative non-infectious complications, hospital stay and rate of reoperations. It has to be noted that postoperative mortality was lower (although not statistically significant) in drained compared to non-drained patients, with a rate of 5% versus 14% respectively.

Ferrero et al. [56] retrospectively reviewed outcomes of 30 combined hepatic and biliary resection for malignancies (mostly HC) over a 17 years period. Overall mortality, morbidity and major complications rate were not significantly different between drained and non-drained group (3% vs. 10%, p 0.612; 70% vs. 63%, p 0.583; 37% vs. 53%, p 0.194 respectively); notably, mortality rate of non-drained group was in fact three times higher than drained group. Patients with PBD showed a significant higher risk of infections (40% vs. 17%, p 0.044) whereas no significant difference was found between the two groups in non-infectious complications and hospital stay. PBD was the only independent risk factor associated with postoperative infectious complications (RR 4.411, 95% CI 1.216-16.002, p 0.024).

Figueras et al. [46] reviewed a single center experience in treating 19 patients for HC over a 3 years period (2005-2008): preoperative PBD was indicated in those patients having a preoperative level greater than 15 mg/dl, if presenting with cholangitis or severe preoperative malnutrition or hypoalbuminemia (<3 mg/dl). Bile duct drainage was necessary in 7 cases (37%) and no significant differences were found between the two groups.

In a series of 38 patients operated for type III HC by the group in Rennes [42], preoperative liver optimization was achieved in 15 patients (12 received drainage), reducing intra-abdominal abscess rate; no difference was found in terms of overall morbidity and survival. However, 4 non-drained patients (among which 3 developed an abscess) accounted for the 10.5% mortality. At multivariate analysis, preoperative jaundice was found to be associated with poor outcome.

Interestingly, a recent multicentric retrospective French study [57] suggested that PBD may be beneficial in particular for patients undergoing right hepatectomy (OR 0.29, 95% CI 0.11-0.77, p 0.013) because of higher mortality rate related to liver failure for this procedure. Conversely, drainage might increase mortality due to infectious complications in left hepatectomy for HC (OR 4.06, 95% CI 1.01-16.30, p 0.035).

According to our review of literature, a definitive recommendation for routinary use of PBD in HC is not supported by the current evidence; however, drainage of the biliary system may be indicated in specific conditions: long-lasting jaundice with significant hyperbilirubinemia, cholangitis, malnutrition and severe hypoalbuminemia. PBD might be avoided in recently developed jaundice (less than 2-3 weeks), serum bilirubin < 200 mmol/l, absence of sepsis; these criteria include most patients requiring left hepatic resection and selected patients needing right hepatectomy [55]. Ratti et al. [8] showed that percutaneous biliary drainage placement is mandatory in candidates for PVE but also have may advantages in other subsets of patients. In a recent review of the literature, Iacono et al. [20] recommend biliary drainage, limited to FLR, in the majority of cases of jaundiced patients who are candidates for major liver resection.

FLR and PBD

The importance of having a sufficient liver volume after hepatectomy to avoid liver failure is widely known. Hepatic optimization has been proposed with this purpose and the drain should be limited to the FLR [58]. Hepatectomies for HC are subjected to a higher risk of hepatic insufficiency due to the extent of the resection needed and due to the presence of preoperative hyperbilirubinemia. Recently, several series of hepatic resections for HC confirmed a decreased incidence of hepatic insufficiency when PBD was performed together with PVE [59, 60].

A retrospective single center study made in 2005 by Hemming [61] reviewed 80 patients affected by HC treated between 1997 and 2004. A total of 53 patients were subjected to curative resection, 14 underwent palliative surgery while 13 could not be surgically treated due to the extent of their disease or co-morbidities. The patients who underwent hepatic resection had a postoperative mortality of 9% with a morbidity of 40%. Patients having a compensatory FLR hypertrophy (due to PVE or tumor's PV invasion) were found to have a significant lower mortality compared to patients without hypertrophy. In the discussion with other authors at the end of the article, Hemming underlines that there should be some evidences that PBD improves the outcome of patients affected by resectable HC. The author suggests that for HC suitable to operation there is the risk of having up to 75% of viable liver resected. For this reason should be subjected to hepatic optimization prior the operation in order to avoid postoperative liver insufficiency. To drain FLR's bile duct is helpful to avoid residual hepatic function. The author concludes that there is no doubt that PBD augments bacterial colonization of the bile ducts and in some cases the rate of postoperative infections, but clinical implications of these findings are uncertain.

Conclusions

According to our review of the literature, ENBD might offer the greatest advantage for the initial management of hyperbilirubinemia in HC patients compared to other PBD techniques, because of minimal invasiveness, low risk of post procedural complications and virtually absent risk of tumour seeding. In case of inadequate decrease in serum bilirubin, additional tubes may be placed for optimizing drainage of FLR or bilateral liver lobes. However, ENBD demonstrated to be less effective and delay jaundice resolution in the event of advanced HC with complete or subtotal obstruction of bile ducts and in sub-lobar cholangitis; in these conditions, PTBD should be considered as a valid alternative treatment.

Despite the lack of prospective studies and data heterogeneity, we can define some principles which are common to many authors (Table 1).

It is a common and accepted opinion that preoperative bile drainage is mandatory in presence of obstructive jaundice if associated with renal insufficiency, malnutrition, cholangitis and sepsis.

Type of biliary drainage	Endoscopic Nasobiliary drainage (ENBD) as first approach
	Percutaneous transhepatic biliary drainage (PTBD) as second choice
	EBD in selected cases
Preoperative Bilirubin level	Biliary drainage probably useless below 3 mg/dl
	Biliary drainage advisable between 3-10 mg/dl
	Biliary drainage mandatory above 10 mg/dl
Optimal drain duration	2-6 weeks until optimal bilirubin level achieved
Post-drainage optimal bilirubin level	< 3 mg/dl
How to drain	Only the future liver remnant (except in cases of cholangitis or local complications)
Association with PVE	If FLR < 30%

Table 1: Recommendations for preoperative biliary drainage in resectable HC

Even if many Asiatic groups use bile drain routinely, PBD was shown to be helpful only in those patients having a bilirubin level greater than 3-10 mg/dl; we might conclude that PBD is probably useless with bilirubin level below 3 mg/dl, advisable between 3-10 mg/dl and mandatory above 10 mg/dl especially in patients undergoing an extended hepatic resection.

In the initial management of HC, ENBD should be preferred as it is characterized by a less invasive approach and less complications (lower morbidity). In case of suboptimal jaundice regression or in presence of complications PTBD might be combined, leaving EBD as last option. The number of drainages needed is chosen in relation with jaundice evolution and its complications. Drain should be limited to FLR. The optimal drain duration is debated: the drain should be left in place the time needed to reduce bilirubin level, meanly 2-6 weeks. This is the most variable datum, due to the wide spectrum of "normal" bilirubin level reported by the different groups.

PBD should be combined with PVE if estimated FLR is less than 30%. Some data suggest that PBD may be helpful only for those patients undergoing right hepatectomy, thus it is not advisable in other cases. Further studies are needed in order to confirm these assumptions.

Compliance with Ethical Requirements

1. For Conflict of Interest statements

   Francesco Caruso declares that he has no conflict of interest.

   Marco Nencioni declares that he has no conflict of interest.

   Arianna Zefelippo declares that he has no conflict of interest.

   Lucio Caccamo declares that he has no conflict of interest.

   Giorgio Rossi declares that he has no conflict of interest.

2. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

   Additional informed consent was obtained from all patients for which identifying information is included in this article.

3. All institutional and national guidelines for the care and use of laboratory animals were followed.

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