

Preoperative biliary drainage in hilar cholangiocarcinoma: When and how?

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Abstract

Hilar cholangiocarcinoma is a tumor of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence. Biliary drainage in hilar cholangiocarcinoma is sometimes clinically challenging because of complexities associated with the level of biliary obstruction. This may result in some adverse events, especially acute cholangitis. Hence the decision on the indication and methods of biliary drainage in patients with hilar cholangiocarcinoma should be carefully evaluated. This review focuses on the optimal method and duration of preoperative biliary drainage (PBD) in resectable hilar cholangiocarcinoma. Under certain special indications such as right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended. Generally, selective biliary drainage is enough before surgery, however, in the cases of development of cholangitis after unilateral drainage or slow resolving hyperbilirubinemia, total biliary drainage may be considered. Although the optimal

preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended. Endoscopic nasobiliary drainage seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions.

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Key words: Klatskin's tumor; Management; Jaundice; Endoscopic biliary drainage; Percutaneous biliary drainage; Preoperative biliary drainage

Core tip: In selected patients, optimal preoperative management will improve the morbidity and mortality of hilar cholangiocarcinoma. Endoscopic nasobiliary drainage seems to be the most appropriate method of preoperative biliary drainage (PBD) in terms of minimizing the risk of tract seeding and inflammatory reactions. Percutaneous transhepatic biliary drainage could be a better option in certain cases such as advanced hilar cholangiocarcinoma or segmental cholangitis. Total biliary drainage is not usually recommended except in certain situations when the surgical technique is difficult without PBD or when patients develop cholangitis after unilateral drainage or a slow-resolving hyperbilirubinemia. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended.

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INTRODUCTION

Hilar cholangiocarcinoma (also known as a Klatskin tu-

mor) is an adenocarcinoma of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence^[1]. Hilar cholangiocarcinoma has an extremely poor prognosis with a 5-year survival rate of less than 10%^[2,3], and it is one of the most common causes of malignant biliary obstruction in the Asia-Pacific region^[4]. Surgical resection is the only potentially curative treatment for hilar cholangiocarcinoma. Bile duct resection in combination with major hepatectomy is the standard treatment for hilar cholangiocarcinoma. This treatment modality achieves a higher cure rate compared to that with bile duct resection alone^[5]. The morbidity and mortality of liver resection are significantly higher in patients with obstructive jaundice than in patients with normal liver function^[6]. Therefore, preoperative biliary drainage (PBD) has been widely performed to reverse cholestasis-associated liver dysfunction and impaired hepatic regeneration^[7,8]. The studies that analyzed PBD in hilar cholangiocarcinoma patients undergoing surgical resection are described in Table 1^[8-15]. There are still controversies regarding the necessity of routine PBD since it can be associated with an increase in procedure-related adverse events^[4]. A recently published meta-analysis on PBD in hilar cholangiocarcinoma revealed no clinical benefit and there were significant increases in postoperative adverse events, mainly infectious complications^[16], which represent the most common complications after PBD^[9,12]. Another recent multicenter retrospective study showed that PBD did not decrease postoperative morbidity and mortality in hilar cholangiocarcinoma^[8]. However, in a subgroup analysis, PBD was noted to significantly decrease postoperative mortality in patients undergoing right hepatectomy by reducing postoperative liver failure. On the contrary, PBD tends to increase sepsis after surgery in patients undergoing left hepatectomy.

PBD may have some additional benefits in selected patients with severe malnutrition or biliary sepsis and in those undergoing delayed surgery due to portal vein embolization or chemoradiation therapy^[17]. In addition, PBD may be indicated in patients with severe pruritus or renal failure^[4]. Selective biliary drainage of preoperative intrahepatic segmental cholangitis plays an important role in reducing complications after major hepatic resection^[18]. Moreover, cholangiography obtained by percutaneous transhepatic biliary drainage (PTBD) or endoscopic nasobiliary drainage (ENBD) can provide more precise information regarding the complicated segmental anatomy of the intrahepatic bile ducts and the extent of cancer along the separated ducts.

To date, the optimal serum bilirubin level for surgery is yet to be determined. Additionally, the optimal duration of PBD has not been clearly determined. Prolonged duration of biliary drainage would increase the risk of drainage malfunction, tract seeding, and secondary inflammatory changes to the bile duct. However, incomplete biliary drainage may increase the perioperative risks of liver resection^[6]. Although biliary drainage differs between proximal and distal biliary obstructions, most studies analyzed the various levels of biliary obstruction

as a single entity^[19]. The patients heterogeneously showed a variety of serum bilirubin ranges and underwent different types of surgery. Despite the limitations, we focused on the optimal method and duration of PBD in resectable hilar cholangiocarcinoma. We searched electronic databases with the following keywords: “hilar cholangiocarcinoma”, “Klatskin tumor”, and “biliary drainage”. The studies about preoperative biliary drainage in hilar cholangiocarcinoma from 1999 were reviewed and listed in this study.

OPTIMAL PREOPERATIVE DRAINAGE METHOD

In general, three methods in PBD are used in hilar cholangiocarcinoma: PTBD, endoscopic retrograde biliary drainage (ERBD) and ENBD. Yet, no randomized controlled trial has compared PTBD, ERBD and ENBD to identify the optimal method for PBD in hilar cholangiocarcinoma. ERBD has some advantages as it is more physiologic, improves nutritional status, reduces endotoxemia, normalizes dyslipidemia, and improves immune functions^[19]. The endoscopic biliary drainage of hilar cholangiocarcinoma is often more challenging and complex. ERBD has the drawback of complicating the intraoperative evaluation of the longitudinal tumor extension and delaying the surgery^[12,15]. The procedure-related morbidity and mortality rates of ERBD in proximal bile duct obstructions were 25%-50% and 3%-5%, respectively^[12,20].

The procedure-related morbidity rates for percutaneous drainage were reported to be lower than those of endoscopic drainage^[12]. PTBD was preferred to ERBD because of the reduction in both post-procedural cholangitis and the number of procedure sessions^[12]. In particular, the success of biliary decompression is significantly higher with percutaneous stent insertion than with ERBD in advanced hilar cholangiocarcinoma^[21]. Cholangiography obtained *via* the PTBD tube is helpful in determining the tumor extent and classification (Bismuth) before surgery. However, PTBD is an invasive technique in which is the tube penetrates through the liver parenchyma. The tumor seeding risk of this procedure is reported to be 5%-20%^[22,23]. Gerhards *et al.*^[23] suggested that preoperative radiotherapy in patients with a resectable proximal bile duct cancer who underwent PBD, might decrease the risk of tumor dissemination. Further studies are required on the prevention of tract seeding after PBD.

In a recently published retrospective study, ENBD in the future remnant liver was considered the most suitable method for initial PBD management as compared with ERBD and PTBD^[14]. ERBD had more frequent complications and PTBD was associated with serious complications such as vascular injuries and cancer dissemination. The inflammatory reaction around the bile duct would be less severe in ENBD because unlikely ERBD, ENBD does not cause duodenobiliary reflux^[24]. Furthermore, ENBD is preferred to PTBD because it has no risk of

Table 1 Studies which have analyzed preoperative biliary drainage in hilar cholangiocarcinoma patients undergoing surgical resection

Ref.	Total number of patients with PBD	PBD-associated morbidity	Serum bilirubin before surgery (mg/dL)	Duration of PBD (d)	Postoperative morbidity	Postoperative complications	Infectious complications	5-year survival rate
Hochwald <i>et al</i> ^[9] , 1999 ¹	42 (PTBD 23; ERBD 13; intraoperative 3; ENBD 1; PTBD and ERBD 1; ERBD and ENBD 1)	-	5.6 ± 0.9	-	90%	5%	52%	-
Figueras <i>et al</i> ^[10] , 2000 ¹	11 (PTBD 11)	-	11.0 ± 9.4	16 ± 10	100%	9%	18%	25%
Ferrero <i>et al</i> ^[11] , 2009 ¹	30 (PTBD 18; ERBD 7; ERBD and PTBD 3; intraoperative 2)	23%	3.1 (0.3-14.1)	27.5 (10-90)	70%	3%	11%	-
Kloek <i>et al</i> ^[12] , 2010 ¹	101 (PTBD 11; ERBD 90)	76%	PTBD 1.1 ± 0.8; ERBD 1.3 ± 1.2	PTBD 11 (3-21); ERBD 15 (4-29)	-	-	48%	-
Grandadam <i>et al</i> ^[13] , 2010 ¹	12 (PTBD 12)	25%	4.1 ± 2.5	32 ± 9	13%	0	-	42%
Kawakami <i>et al</i> ^[14] , 2011 ¹	128 (PTBD 48; ERBD 20; ENBD 60)	Total 40% (PTBD 31%; ERBD 65%; ENBD 38%)	10.5 (2.2-29.3)	11.4 (1-154)	13%	3%	-	-
Ratti <i>et al</i> ^[15] , 2013 ¹	55 (PTBD 51; ERBD 4)	18%	3.4 ± 1.5	24 (10-36)	46%	5%	7%	29%
Farges <i>et al</i> ^[9] , 2013 ¹	180 (PTBD 104; ERBD 63; PTBD and ERBD 13)	33%	2.8 (1.2-5.6)	32	68%	9%	-	-

¹All reports were retrospective studies. Data are expressed as mean ± SD or median (range). PBD: Preoperative biliary drainage; PTBD: Percutaneous transhepatic biliary drainage; ERBD: Endoscopic retrograde biliary drainage; ENBD: Endoscopic nasobiliary drainage.

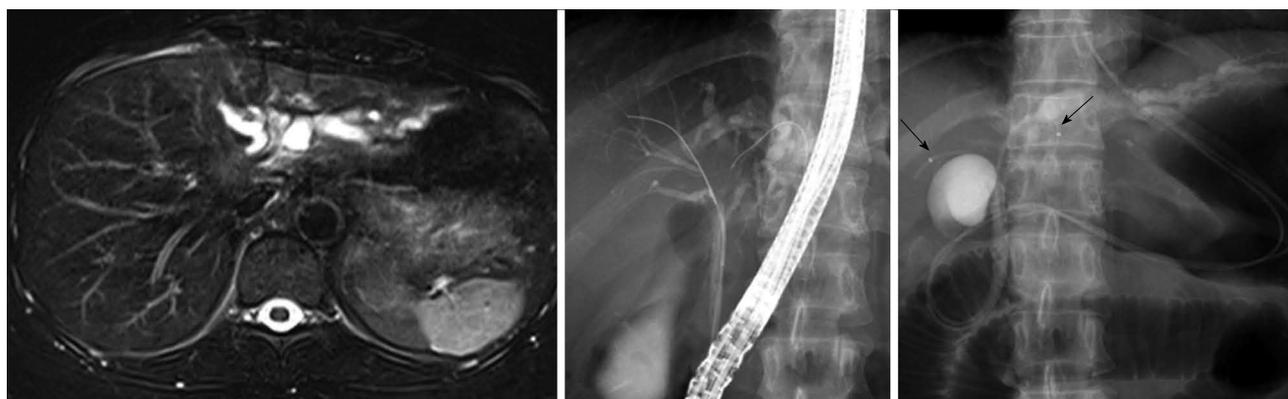


Figure 1 Forty-nine-year-old female with Bismuth type III B hilar cholangiocarcinoma. Since contrast media were injected into both intrahepatic biliary ducts, bilateral endoscopic nasobiliary drainage was performed to prevent post-procedural cholangitis (Black arrows indicate the tip of nasobiliary tubes).

tumor spread along the drainage tract^[14]. However, according to a recent report, ENBD was not effective in type IV hilar cholangiocarcinoma^[25]. Patient discomfort and the risk of self-removal are other problems associated with ENBD. ENBD also often requires longer preoperative hospitalization^[26]. The other disadvantage of ENBD is that it was previously impossible to drain both hepatic lobes^[26]. At present, however, bilateral drainage with ENBD is technically feasible (Figure 1).

In summary, ERBD may not be a suitable option for initial PBD in hilar cholangiocarcinoma. ENBD seems to be preferred over PTBD as there is no risk of tract seeding and less invasiveness. The risk of tract seeding after PTBD has recently been reported to be lower than that reported in previous studies^[27,28]. ENBD is less effective than PTBD in advanced hilar cholangiocarcinoma, in which there is a separation of the intrahepatic ducts.

Therefore, we suggest that ENBD may be considered as the first line for initial PBD management in hilar cholangiocarcinoma. PTBD could be considered in some cases involving advanced hilar cholangiocarcinoma, segmental cholangitis, or delayed resolution of jaundice.

SELECTIVE VERSUS TOTAL BILIARY DRAINAGE: WHICH IS BETTER?

According to both experimental and clinical evidence, unilateral hepatic duct obstruction results in atrophy of the affected lobe and compensatory hypertrophy of the contralateral lobe^[29]. Increased levels of hepatocyte growth factor due to biliary congestion might accelerate compensatory hypertrophy of the future remnant liver^[30,31]. Furthermore, an experimental study proved that

Table 2 Recommended indication for preoperative biliary drainage and total biliary drainage in hilar cholangiocarcinoma

Preoperative biliary drainage	Right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma Preoperative portal vein embolization and chemoradiation therapy Biliary infection of undrained bile duct Severe pruritus
Total biliary drainage	Development of cholangitis after selective drainage Slow resolution of hyperbilirubinemia Opacification of bilateral intrahepatic bile duct

the bile secretory capacity of the non-obstructed lobe is enhanced to compensate for the dysfunction of the obstructed lobes^[32]. Preoperative selective biliary drainage will reduce bile stasis and induce hypertrophy with the enhancement of future remnant liver function^[33,34]. The risk of segmental cholangitis might be a major weakness of selective biliary drainage^[18]. Therefore, in cases where the surgical technique is difficult without PBD or when patients develop cholangitis after unilateral drainage or a slow resolving hyperbilirubinemia, total biliary drainage is preferred as it reduces the risk of cholangitis and preserves preoperative liver function^[18,26,35,36]. Selectively applied and planned endoscopic drainage will reduce the use of contrast injections into atrophied and/or unintended multiple hepatic segments, which in turn reduces the incidence of post-procedural cholangitis^[37-39].

The main limitation of previous studies comparing selective and total biliary drainage is selection bias. Since most of the studies were retrospective in nature, the choice between selective and total biliary drainage could be influenced by the degree of bile duct separation and the physician's preference. A randomized controlled study would be needed to minimize this selection bias.

OPTIMAL DURATION AND TARGET LEVEL OF PREOPERATIVE DRAINAGE

Although PBD is widely performed in hilar cholangiocarcinoma, its optimal duration has not been established. The latest Asia-Pacific consensus on recommendations for endoscopic and interventional management of hilar cholangiocarcinoma included recommendations for the optimal palliative management of hilar cholangiocarcinoma; however, there were no recommendations on optimal preoperative management^[4]. In previous studies, the duration of PBD varied from 10 to 32 d^[9,10,19,40-44]. After biliary drainage, the normalization of hyperbilirubinemia was achieved in only two-thirds of treated patients. It took approximately 4 to 8 wk to achieve a complete resolution of jaundice^[26]. With respect to the duration of PBD, it was suggested that the adequate recovery of hepatic function depends on the duration of biliary decompression and the duration of obstructive jaundice before decompression^[45,46]. However, the long-term maintenance of biliary drainage increases the risk of drainage malfunction^[47,48]. Prolonged duration of PBD with ERBD

causes an extensive inflammatory reaction within the bile duct^[46,49,50]. It would cause bacterial translocation into the bile duct and the clogging of the stent, in addition to probably increasing the risk of post-operative leakage at the anastomosis site^[46]. These drainage-related problems would result in a delay of surgery, which cannot be justified for a potentially resectable cancer^[47]. Increased biliary drainage time was associated with a lower complete resection rate due to the possibility of tumor dissemination through the fistula tract^[48]. A recent study revealed that PBD of more than 2 wk duration was not beneficial in reducing postoperative complications, whereas, drainage-related complications and hospital stay increased^[48]. Therefore, a PBD duration of less than 2 wk would be more favorable in these jaundiced patients. Since most of the studies on the duration of PBD were retrospective in nature, the long duration of PBD might have caused the high rate of procedure-related adverse events and vice versa^[48].

To restore the hepatic function of jaundiced patients, reducing the bilirubin level by decompression of the biliary obstruction is necessary. However, the optimal preoperative bilirubin level is still a matter of debate. A preoperative bilirubin level of less than 3 mg/dL was recommended by Makuuchi *et al.*^[53] and Nimura *et al.*^[56]. Su *et al.*^[51] reported that a preoperative bilirubin level of more than 10 mg/dL was significantly associated with postoperative mortality. Grandadam *et al.*^[13] reported that preoperative optimization of the liver in hilar cholangiocarcinoma reduced postoperative morbidity, and that the direct bilirubin level before surgery was 4.4 mg/dL. In a recent single center study, a total preoperative bilirubin level of more than 3 mg/dL was a negative factor affecting overall survival (HR = 2.109, 95%CI: 1.026-4.335)^[52].

A longer period of PBD is required to achieve lower total bilirubin levels. However, to reduce procedure-related adverse events and to increase curative resections, surgery should not be delayed even if jaundice has not sufficiently resolved.

CONCLUSION

Optimal preoperative management for selected patients with hilar cholangiocarcinoma will improve morbidity and mortality. Under certain special indications such as right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended (Table 2). In most cases, selective PBD is adequate. Total biliary drainage is not usually recommended except in the development of cholangitis after unilateral drainage or slow resolving hyperbilirubinemia. Although the optimal preoperative bilirubin level is still a matter of debate, the shortest possible duration of PBD is recommended. ENBD seems to be the most appropriate method of PBD in terms of minimizing the risks of tract seeding and inflammatory reactions. PTBD could be a better option in certain cases such as advanced hilar cholangiocarcinoma or segmental cholangitis. A further

prospective randomized study comparing ENBD and PTBD is warranted.

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