Preoperative Management of Patients Undergoing Liver Resection for Perihilar Cholangiocarcinoma

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ABSTRACT

Surgical resection with negative margins is the standard treatment for perihilar cholangiocarcinoma whenever possible. Patient's frequent low performance status at presentation and need of extended resections require optimization of the patient's condition in the preoperative setting. Biliary drainage is mandatory in case of cholangitis, jaundice-related liver insufficiency, malnutrition or renal failure. Drainage is also necessary in case of portal vein embolization (PVE), in order to improve regeneration of the future liver remnant (FLR). Unilateral drainage of the FLR should be obtained, while bilateral drainage is required in case of cholangitis, slow reduction in bilirubin and uncertainty about the side of resection. The technique for biliary drainage should be decided according to the local expertise and other factors (need of further evaluation of tumour extension, patient's compliance, necessity of bilateral drainage). Preoperative symbiotics-reduce postoperative infections. PVE is safe and increases the safety of surgery in case of extended liver resections. It is indicated in case of low FLR volume (<40%), low FLR function or in case of previous cholangitis. ALPPS is not recommended in case of PHC.

Key words: perihilar cholangiocarcinoma, Klatskin, biliary drainage, portal vein embolization, preoperative management

INTRODUCTION

Surgical resection with negative margins is the preferred treatment for patients with Perihilar cholangiocarcinoma (PHC). PHC often requires complex surgical resections with high rates of morbidity and mortality (1). Despite improvements in the recent years, postoperative mortality remains high and represents one of the highest among abdominal surgical procedures (1).

Patients with PHC often present with a poor performance status, which increases surgical risk. Optimal management of these patients in the preoperative setting can, therefore, have a significant impact on postoperative

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outcomes. This review will focus on available interventions to optimize patients condition prior to surgery for PHC.

BILIARY DRAINAGE VS NO DRAINAGE

Jaundice is the most common symptom of presentation in patients with PHC (2). The necessity of routine pre-operative biliary drainage (PBD) in these patients has been a topic of controversial debate.

Theoretic advantages of PBD include improved liver function and regeneration with decreased risk of post hepatectomy liver failure (PHLF) (3, 4), reduction of systemic toxicity (5) and reversal of impaired immune function to reduce subsequent risk of infections (6). These experimental data are supported by clinical data showing increased morbidity and mortality in patients undergoing extended liver resections without PBD (7-9). Many authors, mostly from Asia, routinely perform PBD in jaundiced patients undergoing major liver resection. Of note, Nagino et al. reported PBD even in 69 non-jaundiced patients showing only intrahepatic biliary dilatation (10).

On the other side, PBD carries some risks, which could delay or prevent surgical treatment (e.g. cholangitis, pancreatitis) and compromise patients outcomes (e.g. drain track tumor seeding) (11, 12). These risks should be taken into account, especially considering some series showing the safety of liver resections for PHC without PBD (13, 14).

A number of randomized controlled trials has analyzed the impact of PBD in jaundiced patients undergoing surgery for malignancy. However, these studies focused mainly or exclusively on patients undergoing pancreateoduodenectomy, making their findings not applicable to those undergoing liver resection (15, 16). Hence, high-level evidence on this topic is missing, while lower-level evidence remains controversial (15). This becomes evident even in national guidelines from different countries (17), where pre-operative PBD for PHC is recommended (8) or not recommended (18).

Nonetheless, mostly all authors recommend PBD in selected group patients with cholangitis, hepatic insufficiency, jaundice-related malnutrition or renal failure, and in patients undergoing neoadjuvant chemotherapy (19, 20). PBD is also recommended when portal vein embolization (PVE) is needed in presence of a small future liver remnant (FLR) (20).

ENDOSCOPIC VS PERCUTANEOUS DRAINAGE

There are currently 3 options for PBD, which include percutaneous transhepatic biliary drainage (PTBD), endoscopic biliary drainage (EBD) and endoscopic nasobiliary drainage (ENBD) (table 1, fig. 1).

Percutaneous transhepatic biliary drainage

PTBD has been associated with a high success rate in relieving cholestasis with a percentage ranging from 58% and 100% of patients undergoing the procedure and a median time from the first attempt to normal bilirubin level of 41 days compared to 61 days in the EBD (21-24). Furthermore, a lower risk of cholangitis compared to the other available options has been reported with rates between 8% and 22% and an overall incidence of 16.6% compared to 30.5% in EBD (22, 23, 25, 26). However, PTBD is associated with complications related to its invasiveness. Aside from patient discomfort, the risk of hemorrhage should be considered as this is reported with an incidence of 2-15% in major series (21, 23). Furthermore, some cases of cancer dissemination along the catheter tract have been reported, with rates up to 6% (12, 23, 27). An advantage of PTBD is that it can provide better delineation of the tumor extent within the liver for a more accurate operative planning (20).

Endoscopic biliary drainage

EBD is considered a less invasive option for malignant obstructive jaundice and it is currently

Table 1 - Outcomes and complications of different methods for pre-operative biliary drainage

	Outcomes and complications				
	Success rate	Cholangitis	Pancreatitis	Bleeding	Cancerdissemination
Percutaneoustranshepaticbiliarydrainage	58-100%26	8-21.4%26	0-7%26	1-7%26	3-5.2%12, 26
Endoscopic biliary stenting	50-100%26	12.1-65%26	0-21%26	0-6.8%23,26	0%26
Endoscopicnasobiliarydrainage	39%28	15.3-29.4%26	0-14%26	0%22, 28, 29	0%26

Figure 1 - Preoperative biliary drainage in patients with peri-hilar cholangiocarcinoma
a. Endoscopic biliary drainage. A guide wire is advanced through the stenosis in the right biliary system
b. Percutaneous trans-hepatic biliary drainage. The left biliary system is opacified following double puncture in order to obtain double percutaneous drainage of the future liver remnant.

chosen as the first option in several centers. The success rate in resolving cholestasis ranges from 57% and 100% but despite this, a higher rate of cholangitis (12-65%) has to be considered because of ascending bacterial contamination (21-23). Furthermore, procedure-related complications such as duodenal perforation, hemorrhage (1%) and pancreatitis (4-21%) have been reported (21-23,28). It has to be mentioned that more than half of patients undergoing EBD will later require PTBD to achieve the required therapeutic effect (20).

Endoscopic nasobiliary drainage

ENBD is an alternative technique of EBD that allows reducing the rate of ascending cholangitis because of the limitation of bacterial contamination from the gut. In fact, the rates of cholangitis related to the procedure have been reported to be around 15-29% (22, 28, 29). Pancreatitis was reported to range between 0-14% and no hemorrhages related to the procedure were shown (22, 28, 29). A possible drawback of ENBD could be the related to the nasal catheter causing discomfort and nasopharyngeal irritation (22).

UNILATERAL VS BILATERAL DRAINAGE

Independently of the technique, unilateral drainage of the FLR is considered sufficient and is recommended by most of the authors (8, 30-32). This is possible as nowadays CT and MRCP allow planning the side of

resection in most of the cases before biliary drainage. PBD limited to the FLR facilitates also is hypertrophy, in case of PVE.

Bilateral drainage should be obtained when the type of hepatectomy (and thus FLR) cannot be established before PBD, when a cholangitis develops in the non-drained hemi-liver, or when, after unilateral drainage, the diminution of bilirubin is slow (15).

INTERNAL VS EXTERNAL DRAINAGE, BILE REINFUSION, SYMBIOTIC TREATMENT

In case PTBD is chosen, bile drainage can be either external or internal.

Internal drainage, with the catheter passing through the stenosis into the common bile duct or the duodenum, has the advantage of restoring physiological bile flow to the bowel, thus improving liver regeneration and function and maintaining the integrity of the intestinal barrier (33-35).

External drainage has the advantage of reducing the risk of ascending cholangitis. Eastern authors recommend bile reinfusion orally or through nasogastric tube (8, 35, 36), although the level of evidence supporting this recommendation is not high.

The preoperative oral administration of synbiotics (*Lactobacillus casei*, *Bifidobacterium breve*, and galacto-oligosaccharides) for two-weeks, has been shown to improve immune responses, attenuate postoperative inflammatory response and reduction of postoperative infectious complications (37).

FUTURE LIVER REMNANT EVALUATION AND RISK OF POSTOPERATIVE LIVER FAILURE

Nimura and colleagues introduced in the early '90s the concept of routine segment 1 resection for surgical treatment of PHC (38), demonstrating an improvement in the 5-year survival rate (40% vs 5%) (38, 39). Extended hepatectomies are nowadays considered the standard of treatment for PHC (40). A low-volume FLR is therefore often anticipated in these patients and a preoperative angio-CT for volumetric evaluation has to be part of the preoperative work-up for PHC.

An FLR volume of >25–30% is considered a safe cut-off for patients with healthy liver parenchyma (41). However, in patients with compromised liver, as those with longstanding biliary obstruction or cholangitis, a higher risk of PHLF exists if the FLR is less than 40% (31, 42, 43). A precise cut off in terms of FLR experienced in patients with cholangitis has not yet been established. Indeed, Olthof et al. showed that liver volumetry alone has low negative predictive value towards PHLF (44). Indeed, liver volume has been shown to not fully represent its function (45). Other factors have been associated to PHLF, such as jaundice at presentation and pre-operative bilirubin level > 50 $\mu\text{mol/L}$ (2.9 mg/dl) (44) and cholangitis (46). Therefore, in addition to FLR volume, some scores have been proposed to identify patients undergoing surgery for PHC at risk of PHLF (44).

Liver functional tests as the clearance rate of the indocyanine green (ICG) and hepatobiliary scintigraphy with $^{99\text{m}}\text{Tc}$ -mebrofenin (HBS) are widely used in several centers to predict FLR function and the risk of PHLF.

ICG is the reference liver function test in the Eastern world. The safety of major liver resection planned on the base of preoperative ICG test has been shown in many series (47), even in case of PHC (48). An ICG clearance of the FLR less than 0.05 is associated with higher mortality after major liver resection for PHC (48).

HBS is gaining popularity as liver function test especially in the Western World (49, 50). HBS well correlates with ICG, providing additional information regarding the function of specific areas of liver parenchyma (51). An uptake <2.69 %/min/ m^2 of the FLR has been associated with the risk of PHLF and mortality after extended hepatectomy (52). Recently the Amsterdam Medical Centre has included HBS as part of the preoperative work-up for PHC (40). The authors believe that HBS could provide additional information on the liver quality, but results on the HBS impact on PHLF in patients with PHC are still awaited.

Both tests present, however, an important limitation. Indeed, bilirubin, $^{99\text{m}}\text{Tc}$ -mebrofenin, and indocyanine green share the same hepatocyte transporters (53). Hence, in patients with cholestasis, HBS and ICG could underestimate liver function, unless low bilirubin levels are obtained after adequate biliary drainage (54).

PORTAL VEIN EMBOLIZATION AND ALPPS

Since introduced by Makuuchi in 1982 (55), PVE is the standard technique to increase the FLR volume with minimal risks (56–58). Although PVE could promote tumor growth and influence oncological outcomes in case of metastases (59), it has been shown that PVE does not affect survival of patients with PHC (60). PVE seems to reduce significantly the risk of PHLF in case of extended hepatectomy, as reported by the Nagoya group (61).

Currently, indications for PVE include a FLR <40% of the total liver volume (40, 62) or low function of the FLR, quantified as an HBS function <2.7%/min/ m^2 (40) or an ICG clearance of the FLR < 0.0548). Recently, a score based on FLR volume, bilirubin level and cholangitis has been developed to select patients for PVE (44). Biliary drainage of the FLR should be obtained prior to PVE to improve its regeneration (58). In case of extended right hepatectomy, embolization of segment IV improves hypertrophy of the FLR (20). Following PVE, FLR hypertrophy less than 5% indicates a high risk for PHLF and liver resection should be contraindicated (58). The main drawback remains that PVE irreversibly determines the side of the resection, thus limiting the possibility of intraoperative changes in the surgical strategy (40).

Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) (63) has gained popularity for its ability to induce faster hypertrophy of the FLR. In addition, ALPPS could have an additional value in patients with PHC, allowing to decide the segments to resect and those that will remain on the base of an intraoperative assessment. However, the initial experience reported higher morbidity and mortality following ALPPS compared to major hepatectomies after PVE (63). In 2017, an analysis of from the international ALPPS registry specifically focusing on patients with PHC was published (64). ALPPS for PHC presented a higher 90-day mortality (48%) compared to major liver resection without ALPPS (13%). Moreover, even after matching for FLR volume, ALPPS presented worse mortality and survival rates (6 vs 29 months) (64). On the base of this evidence, ALPPS cannot be

recommended in a patient with PHC. Therefore, PVE has still to be considered the method of choice to increase the FLR volume in patients with PHC.

CONCLUSIONS

Preoperative management is pivotal for patients undergoing surgery for PHC with curative intent, although not high level of evidence is available. The operating surgeon should coordinate pre-operative interventions, which need to be patients-tailored and are in function of the surgical planning.

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None of the authors has potential conflicts to disclose.

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