Enhancement of liver regeneration and liver surgery

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CHAPTER 11

External biliary drainage following major liver resection for perihilar cholangiocarcinoma: impact on development of liver failure and biliary leakage

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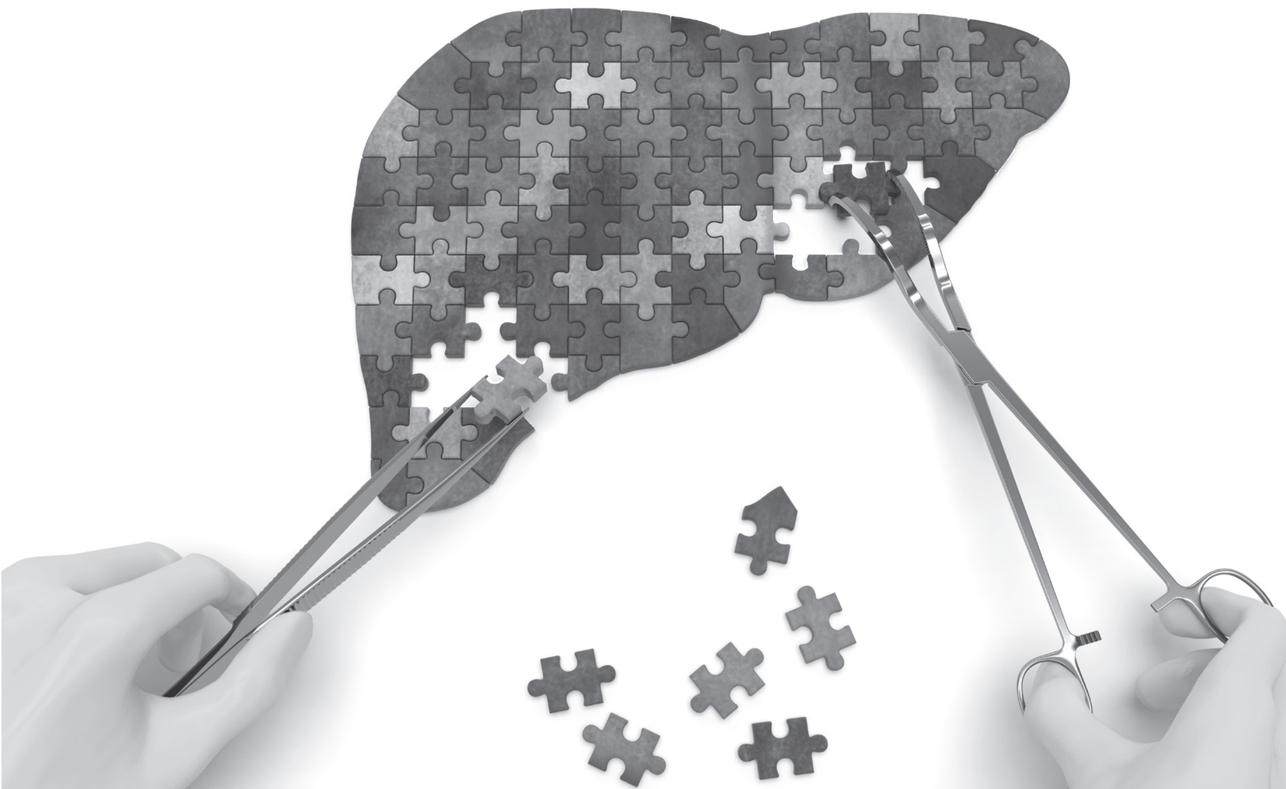

ABSTRACT

Background: Preoperative biliary drainage is considered essential in perihilar cholangiocarcinoma (PHC) requiring major hepatectomy with biliary-enteric reconstruction. However, evidence for postoperative biliary drainage as to protect the anastomosis is currently lacking. This study investigated the impact of postoperative external biliary drainage on the development of post-hepatectomy biliary leakage and liver failure (PHLF).

Methods: All patients who underwent major liver resection for suspected PHC between 2000 and 2015 were retrospectively analyzed. Biliary leakage and PHLF were defined as grade B or higher according to the International Study Group of Liver Surgery criteria.

Results: Eighty-nine out of 125 (71%) patients had postoperative external biliary drainage. PHLF was more prevalent in the drain group (29% versus 6%; *P*=0.004). There was no difference in the incidence of biliary leakage (32% versus 36%). On multivariable analysis, postoperative external biliary drainage was identified as an independent risk factor for PHLF (Odds-ratio 10.3, 95% confidence interval 2.1-50.4; *P*=0.004).

Conclusions: External biliary drainage following major hepatectomy for PHC was associated with an increased incidence of PHLF. It is therefore not recommended to routinely use postoperative external biliary drainage, especially as there is no evidence that this decreases the risk of biliary anastomotic leakage.

INTRODUCTION

Perihilar cholangiocarcinoma (PHC) is a tumor that originates at or near the confluence of the bile ducts which typically obstructs the central bile ducts causing cholestasis and jaundice.[1] Radical surgical resection is considered the only potentially curative treatment and entails a major liver resection with hilar resection and biliary-enteric anastomoses. Liver regeneration is essential for patients recovering from major hepatectomy. However, obstructive cholestasis hampers the regenerative capacity of the liver and hereby increases postoperative morbidity and mortality.[2] Therefore, preoperative biliary drainage is mostly used to treat cholestasis prior to surgery for PHC.[3]

Preoperative biliary drainage can be achieved using internal/external percutaneous transhepatic biliary drainage (PTBD) or by endoscopic stenting. PTBD is often needed after a failed endoscopic attempt to achieve the required therapeutic effect of biliary decompression.[4, 5] These percutaneous drains can subsequently be left in situ during resection as trans-anastomotic drains with the intent to protect the biliary-enteric anastomosis. In case of endoscopic stents, the stents are removed and a retrograde trans-anastomotic external drain may be placed during the operation. However, evidence for the use of postoperative external biliary drains in the prevention of biliary leakage is currently lacking in patients with PHC. Furthermore the identification of bile acids as mediators of liver regeneration might advocate against postoperative external biliary drainage, as external loss of bile by the biliary drainage will reduce the regenerative response after hepatectomy.[6] Notwithstanding the ongoing debate on the effects of preoperative biliary drainage, there is currently little evidence for the use of external biliary drainage after major hepatectomy for biliary drainage.

The current study investigated the impact of postoperative external biliary drainage in PHC patients undergoing curative resection on the development of complications, mainly post hepatectomy anastomotic biliary leakage and liver failure (PHLF).

METHODS

Data were retrospectively collected from a database including all consecutive patients submitted to exploratory laparotomy for PHC between January 2000 and July 2015 at the Academic Medical Center, Amsterdam. Inclusion criteria included curative-intent major liver resection, defined as either left or right (extended) hemihepatectomy or central liver resection of at least three segments for PHC.

Preoperative optimization and surgical strategy were performed as previously reported.[7] Briefly, preoperative biliary drainage of the future liver remnant (FLR) is considered standard practice in the presence of obstructive cholestasis with jaundice in our center. Preoperative biliary drainage was most often initiated at the referring center and attempted endoscopically. Additional drainage in our center was indicated when prior endoscopic drainage had failed to obtain adequate drainage with ongoing cholestasis in the FLR and/or elevated total bilirubin level. The optimal method (endoscopically or percutaneously) for additional drainage procedures was decided at the multidisciplinary team meeting, based on the cause of failure of drainage and biliary anatomy. Bile ducts that were unintentionally opacified upstream from the obstruction were always drained. In the case of a percutaneous approach, 10 Fr internal/external drains, with side holes from the tip towards the intrahepatic part were used and after crossing the biliary stricture, were positioned with the tip in the duodenum. Computed tomography volumetric data of the FLR were available in all patients and calculated as the percentage of FLR volume of the total liver volume. The presence of an intra-operatively placed postoperative external biliary drain through the biliary-enteric anastomosis was determined according to the operative report. The attending surgeon decided whether to use such a drain or not. Postoperatively, external biliary drains were allowed free drainage. Drains were closed when drainage was <50 cc/day or after 5 days postoperatively and left in situ for 2-6 weeks. Using the external drain, cholangiography was performed to check the anastomosis when considered indicated. Postoperative abdominal drains were standard in all patients and were removed when postoperative production was below 100 cc/day.

Study variables included baseline patient characteristics, details of surgery, postoperative complications and mortality. Postoperative morbidity was defined as any severe complication (i.e. Clavien-Dindo Grade III and higher) within 30 days after surgery. Complications were further stratified into post-hepatectomy liver failure (PHLF), biliary (anastomotic) leakage, hemorrhage and infectious complications. Post-hepatectomy liver failure, biliary leakage and hemorrhage were scored and graded according to the International Study Group of Liver Surgery (ISGLS) criteria, with grade B and C being considered as clinically relevant.[8-10] Infectious complications were scored when a patient showed clinical and/or laboratory signs of infection (e.g., fever, malaise, or leukocytosis) that necessitated an intervention such as antibiotic treatment or percutaneous drainage. Postoperative mortality was defined as death within 90 days after surgery or within the same hospital admission.

Statistical analysis

Univariable analyses of differences in baseline and postoperative outcomes between the drain and no-drain group were tested using Pearson's chi-squared or Fisher's exact test for categorical variables and using Mann-Whitney *U* or unpaired *t*-test for continuous variables. The association between an external bile drain and grade B/C PHLF was assessed in multivariable analysis by logistic regression, which was adjusted for demographic data (age, gender), and previously described risk factors such as FLR volume,[11] preoperative bilirubin level[12] and preoperative cholangitis.[13] All analyses were performed using IBM SPSS Statistics for Windows (Version 22.0, IBM Corp., Armonk, NY, USA). Two-tailed *P*-values of <0.05 were considered to indicate statistical significance.

RESULTS

A total of 126 consecutive patients underwent a major liver resection for PHC during the study period. One patient was excluded from the analysis due to insufficient data. Eighty-nine out of 125 (71%) patients had postoperative external biliary drainage. A preoperatively placed PTC drain was used as postoperative drain in 46 patients and the other 43 patients received a new external drain during surgery. Patient and operative characteristics of the drain and no-drain group are provided in **Table 1**. A higher preoperative bilirubin level was observed in the drainage group, although only 5 patients in the study cohort (4 with external bile drain) had a preoperative bilirubin level above 50 µmol/L and the median preoperative bilirubin levels were in the normal range. Preoperative suspicion of PHC was microscopically confirmed postoperatively in 83 out of 89 patients (93%) in the external bile drain group and in 26 out of 36 (72%) in the group without postoperative drainage ($P = 0.002$). R0 resection rate was similar in both groups, 69% in the external drain group and 78% in the no drain group ($P = 0.976$). Data on the amount of drainage of postoperative external biliary drains was only available starting from 2013. Since 2013, fourteen patients received a postoperative external bile drain. Of these patients, one had no bile drainage, 8 patients had 125 to over 1000 mL (median 400) drainage in the first days postoperatively, and data was missing in 5 patients. Due to the insufficient data available this variable was not included in the analysis.

Postoperative complications are shown in **Table 2**. Incidence of bile leakage did not differ between groups, nor did infectious complications or postoperative hemorrhage. However, 26 (29%) patients in the drain group developed PHLF compared to only 2 out of 36 patients (6%) without an external bile drain ($P = 0.004$). Independent risk factors for clinically relevant PHLF are shown in **Table 3**. No risk factors were identified for the incidence of postoperative biliary leakage. Out of 41 patients with biliary leakage, 17 patients (41%) had leakage of (one of) the hepaticojejunostomies confirmed by injecting contrast though the PTBD which was either in situ or placed in response to the suspected biliary leakage. The other 24 patients had suspected leakage of the hepaticojejunostomy, however were managed by percutaneous abdominal drainage only and contrast imaging was not performed.

Table 1. Comparison of patient and operative characteristics between the drain and no-drain group

	Postoperative external bile drain (n=89), *n* (%)	No postoperative external bile drain (n=36), *n* (%)	*P* value
Age, years, median (range)	62 (36-79	63 (40-81)	0.360
Gender, male	56 (63%)	25 (69%)	0.489
BMI, kg/m², median (range)	24 (18-37)	25 (18-32)	0.429
Jaundice at presentation	69 (78%)	27 (75%)	0.680
Preoperative bilirubin, µmol/L, median (range)	16 (5-70)	11 (4-55)	0.015
Preoperative biliary drainage			0.003
None	6 (7%)	6 (17%)	
EBD	37 (42%)	24 (67%)	
PTBD	11 (12%)	2 (6%)	
Both	35 (39%)	4 (11%)	
Preoperative cholangitis	35 (39%)	16 (44%)	0.598
ASA classification			0.906
1	19 (21%)	9 (25%)	
2	57 (64%)	22 (61%)	
3	13 (15%)	5 (14%)	
Bismuth-Corlette stage			0.324
I	1 (1%)	0	
II	4 (5%)	5 (14%)	
IIIa	39 (44%)	11 (31%)	
IIIb	18 (20%)	9 (25%)	
IV	19 (21%)	6 (17%)	
Left or right hepatic duct	8 (9%)	5 (14%)	
Surgical procedure			0.085
Left hemihepatectomy	27 (30%)	11 (31%)	
Extended left hemihepatectomy	14 (16%)	6 (17%)	
Right hemihepatectomy	9 (10%)	10 (28%)	
Extended right hemihepatectomy	36 (40%)	9 (25%)	
Central hepatectomy	3 (2%)	0	
CBD resection			0.063
No	0	2 (6%)	
1 biliary anastomosis	60 (67%)	27 (75%)	
2 biliary anastomoses	26 (29%)	7 (19%)	
3 or 4 biliary anastomoses	3 (3%)	0	
Portal vein reconstruction	26 (29%)	6 (17%)	0.146
No. of postoperative external drains			
1	55 (62%)	-	
2	31 (35%)	-	
3	2 (2%)	-	
>3	1 (1%)	-	
Operation time, minutes, median (range)	499 (346-1011)	425 (280-738)	<0.001
Portal vein embolization	3 (3%)	4 (11%)	0.105
FLR volume, % of total, median (range)	52 (16-90)	49 (20-92)	0.899
FLR <40%	30 (34%)	13 (36%)	0.848

Table 2. Postoperative complications and mortality in the drain and no-drain group

	Postoperative external bile drain (n=89), *n* (%)	No postoperative external bile drain (n=36), *n* (%)	*P* value
Hospital stay, days, median (range)	15 (6-95)	12 (5-28)	0.002
Any complication, Clavien-Dindo Grade ≥III	47 (53%)	20 (56%)	0.844
Biliary leakage	28 (32%)	13 (36%)	0.616
Hemorrhage	9 (10%)	3 (8%)	1.000
Infectious complications	42 (47%)	14 (39%)	0.433
PHLF	26 (29%)	2 (6%)	0.004
Relaparotomy	18 (20%)	3 (8%)	0.122
90-day mortality	17 (19%)	5 (14%)	0.608

Biliary leakage, hemorrhage and PHLF were defined according to the ISGLS criteria (grade B and C)

Table 3. Univariate and multivariable analysis for risk factors of post-hepatectomy liver failure (ISGLS Grade B or C)

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age	1.01 (0.97-1.06)	0.561	1.03 (0.98-1.09)	0.224
Male gender	1.48 (0.59-3.69)	0.406	1.70 (0.54-5.34)	0.362
Jaundice at presentation	1.89 (0.59-6.02)	0.281	1.27 (0.31-5.22)	0.736
Preoperative bilirubin (μmol/L)	1.02 (0.99-1.05)	0.233	1.00 (0.96-1.04)	0.956
Postoperative external bile drain	7.02 (1.57-31.36)	0.011	10.07 (1.84-55.1)	0.008
Preoperative cholangitis	2.86 (1.21-6.81)	0.017	3.65 (1.16-11.48)	0.027
FLR volume (%)	0.28 (0.00-0.27)	0.002	0.01 (0.00-0.15)	0.009

DISCUSSION

This study shows that a postoperative external bile drain is an independent risk factor for development of clinically relevant postoperative liver failure in patients who underwent major liver resection for PHC. No risk factors for postoperative biliary leakage could be identified in this cohort.

Liver resection for PHC is associated with considerable morbidity and mortality of 68% and 5-18%,[7, 14] respectively. Decreasing the perioperative risk in patients with PHC by preoperative biliary drainage is a subject of debate and has been the focus of numerous reports and clinical trials. In PHC, the benefits of preoperative biliary drainage have been demonstrated especially in patients undergoing right hepatectomy. In a French multicenter study, mortality after right hepatectomy was 22% and 8.9% in non-drained and drained patients, respectively.[12] However, there is no evidence for postoperative biliary drainage although many surgeons will leave the PTBD in situ postoperatively in an effort to decompress the biliary-enteric anastomoses. Some studies have addressed postoperative biliary drains in related procedures. In a cohort of all patients who underwent a hepaticojejunostomy, the incidence of biliary leakage was 15.2%.[15] The incidence of a clinically relevant bile leak was associated with simultaneous liver resection, preoperative biliary drainage and the presence of a transanastomotic stent. These results suggest an increased risk of HJ leakage in PHC patients, without any beneficial effects of the use of intra-operatively placed transanastomotic drains. The latter report, however, includes only 19 liver resections and a variety of 95 other procedures. Six of 15 biliary leakage events occurred in the liver resection group; this study is therefore, underpowered and results cannot be adequately translated to the setting of liver resection for PHC.

A systematic review and meta-analysis of the use of a trans-choledocho-choledochostomy t-tube for the prevention of biliary leakage following orthotopic liver transplantation, could not demonstrate a protective effect on anastomotic leakage.[16] Another report in the same patients reported a potential benefit of t-tubes in risky anastomoses and anastomoses of small bile ducts.[17] Although these biliary reconstructions differ from the hepaticojejunostomies in PHC patients, such a recommendation might apply to PHC as well. A cystic duct tube (C-tube) was reported to prevent biliary leakage following hepatectomy, however, no data on liver failure was provided.[18] Therefore, results should be interpreted with caution as this report did not include biliary reconstructions nor the use of transanastomotic drains.[18]

The abovementioned studies cannot reliably recommend or disapprove the use of transanastomic drains for the prevention of biliary leakage in PHC patients after resection. In the current study, no risk factors for postoperative biliary leakage were identified. Patients with a postoperative biliary drain had a similar incidence of biliary leakage compared to patients without a drain. The patients with a postoperative drain might have had higher-risk biliary-enteric anastomoses and therefore might have received a transanastomotic external bile drain. However, no differences were found between groups, the number of hepatojejunostomies were similar between groups and no other differences could be detected. Future prospective studies should examine the place of biliary drainage in the prevention of biliary leakage following major liver resection for PHC.

The presence of a postoperative external bile drain was an independent risk factor for postoperative liver failure in this cohort of patients. The presence of such a drain itself appears not likely to be related to liver failure. Therefore, we hypothesized that the external loss of bile could explain the correlation found in the present study. Bile acids have been identified as promoters of liver regeneration and normal bile flow is necessary for adequate liver regeneration.[19, 20] The effects of bile acids are most likely mediated by the nuclear farnesoid X-receptor (FXR) in both liver and intestine.[21] Disruption of this gut-liver-axis by external biliary drainage was found to impede liver regeneration.[19] External biliary drainage following hepatectomy reduced liver regeneration when measured by CT volumetry.[6] However, no assessment of functional regeneration was performed in this study of only 46 patients which may be underpowered for relating the drains to clinical outcomes such as liver failure or mortality. Furthermore, the majority of patients in this report had hepatocellular carcinoma and received cystic duct tubes (C-tubes) for biliary drainage and therefore, are not translatable to PHC patients.

This retrospective study has several limitations. In the current study, no data on the amount of drainage of bile was available as the volume of drained bile was only included in the data collection since 2013. The majority of these patients had drains that produced a median of 400 mL per day. Considering the data from experimental studies in animals showing that external deviation of bile and bile-binding resin therapy impede liver regeneration, we hypothesize that the external loss of bile is a likely factor in the incidence of liver failure during postoperative biliary drainage. This notion however, needs further examination in prospective clinical studies.

A second limitation is the relatively low number of PHLF and biliary leakage events in this cohort. The consequent statistical uncertainty in multivariable analysis is reflected by the relatively wide confidence intervals. To reduce the risk of overfitting of the statistical model, only predefined and known risk factors along with age and gender were included in the analysis. FLR share was used as a variable, which is an accurate representation of the extent of the resection. The correction for FLR share adds weight to the other independent risk factors for PHLF.

Cholangitis is common after placement of an internalized PTBD and the cumulative incidence increases with the duration of a PTBD in situ. Furthermore, bacteria can be cultured in bile samples from patients with a PTBD in up to 77% of patients.[22] Considering that patients with a postoperative external biliary drain more often had a preoperative PTBD, cholangitis might have contributed to the increased incidence of postoperative liver failure. Preoperative cholangitis has been identified as an independent risk factor for postoperative morbidity and mortality,[23, 24] potentially by reducing expression of liver regeneration stimulating genes and upregulation of regeneration suppressive genes.[13] However, both incidence of preoperative cholangitis and postoperative infectious complications were similar in both groups in the present study. As an alternative, one might hypothesize the use of non-internalized external PTBD prior to surgery, but their use seems less attractive considering poorer quality of life and need for bile acid replacement.

The definition of postoperative liver failure used in this report was defined as grade B or C liver failure according to the ISGLS criteria. The 50-50 criteria do not allow grading of severity of liver failure and might not identify all patients with liver failure.[8] Therefore the ISGLS criteria for grading of liver failure were chosen over the 50-50 criteria. Grade A liver failure is defined as liver failure without the need for clinical intervention and was not included in the analysis.

In conclusion, postoperative biliary drainage after major liver resection for PHC was associated with an increased incidence of liver failure, without any difference in the incidence of postoperative biliary leakage. Since bile acids have recently been identified as mediators of liver regeneration, postoperative biliary drainage leading to loss of bile should be reconsidered. As the incidence of biliary leakage was similar between drained and non-drained groups, the assumed protective effect of a postoperative external biliary drain on the integrity of a biliary-enteric anastomosis is questionable. When external biliary drainage is considered indicated, for instance in patients with multiple, high-risk biliary anastomoses, bile acid replacement therapy should be considered. Until future studies provide definitive conclusions on the effects of postoperative biliary drainage in these complex patients with PHC, the routine use of external, transanastomotic biliary drains is not recommended.

REFERENCES

1. Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010.
2. Yokoyama Y, Nagino M, Nimura Y. Mechanism of impaired hepatic regeneration in cholestatic liver. *J Hepatobiliary Pancreat Surg*. 2007;14:159-166.
3. Iacono C, Ruzzenente A, Campagnaro T, et al. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg*. 2013;257:191-204.
4. Kloek JJ, van der Gaag NA, Aziz Y, et al. Endoscopic and percutaneous preoperative biliary drainage in patients with suspected hilar cholangiocarcinoma. *J Gastrointest Surg*. 2010;14:119-125.
5. Wiggers JK, Groot Koerkamp B, Coelen RJ, et al. Preoperative biliary drainage in perihilar cholangiocarcinoma: identifying patients who require percutaneous drainage after failed endoscopic drainage. *Endoscopy*. 2015;47:1124-1131.
6. Otao R, Beppu T, Isiko T, et al. External biliary drainage and liver regeneration after major hepatectomy. *Br J Surg*. 2012;99:1569-1574.
7. Coelen RJ, Wiggers JK, Nio CY, et al. Preoperative computed tomography assessment of skeletal muscle mass is valuable in predicting outcomes following hepatectomy for perihilar cholangiocarcinoma. *HPB (Oxford)*. 2015;17:520-528.
8. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713-724.
9. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. 2011;149:680-688.
10. Rahbari NN, Garden OJ, Padbury R, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)*. 2011;13:528-535.
11. Kennedy TJ, Yopp A, Qin Y, et al. Role of preoperative biliary drainage of liver remnant prior to extended liver resection for hilar cholangiocarcinoma. *HPB (Oxford)*. 2009;11:445-451.
12. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg*. 2013;100:274-283.
13. Watanabe K, Yokoyama Y, Kokuryo T, et al. Segmental cholangitis impairs hepatic regeneration capacity after partial hepatectomy in rats. *HPB (Oxford)*. 2010;12:664-673.
14. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*. 2007;245:755-762.
15. Suzuki H, Shimura T, Mochhida Y, et al. To Stent or Not To Stent Hepaticojejunostomy--Analysis of Risk Factors for Postoperative Bile Leaks and Surgical Complication. *Hepatogastroenterology*. 2014;61:920-926.
16. Sotiropoulos GC, Sgourakis G, Radtke A, et al. Orthotopic liver transplantation: T-tube or not T-tube? Systematic review and meta-analysis of results. *Transplantation*. 2009;87:1672-1680.
17. Lopez-Andujar R, Oron EM, Carregnato AF, et al. T-tube or no T-tube in cadaveric orthotopic liver transplantation: the eternal dilemma: results of a prospective and randomized clinical trial. *Ann Surg*. 2013;258:21-29.
18. Nanashima A, Abo T, Shibuya A, et al. Does the placement of a cystic duct tube after a hepatic resection help reduce the incidence of post-operative bile leak? *HPB (Oxford)*. 2013;15:517-522.
19. Naugler WE. Bile acid flux is necessary for normal liver regeneration. *PLoS One*. 2014;9:e97426.
20. Huang W, Ma K, Zhang J, et al. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. *Science*. 2006;312:233-236.

21. Zhang L, Wang YD, Chen WD, et al. Promotion of liver regeneration/repair by farnesoid X receptor in both liver and intestine in mice. *Hepatology*. 2012;56:2336-2343.
22. Nomura T, Shirai Y, Hatakeyama K. Bacteribilia and cholangitis after percutaneous transhepatic biliary drainage for malignant biliary obstruction. *Dig Dis Sci*. 1999;44:542-546.
23. Melendez J, Ferri E, Zwillman M, et al. Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. *J Am Coll Surg*. 2001;192:47-53.
24. Sakata J, Shirai Y, Tsuchiya Y, et al. Preoperative cholangitis independently increases in-hospital mortality after combined major hepatic and bile duct resection for hilar cholangiocarcinoma. *Langenbecks Arch Surg*. 2009;394:1065-1072.