Format for ANSWERING REVIEWERS

October 19, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5274- Review.doc).

Title: Preoperative biliary drainage in patients with hilar cholangiocarcinoma undergoing major hepatectomy

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **1.1** ***It must be really precise, even if the study is retrospective, the selection criteria for drainage. If the populations are similar, what were the authors' choice criteria for drainage in the same jaundiced patients with bilirubin level greater than 170 before major resections.***

This is a retrospective study. The selection criteria for drainage in patients were jaundice of more than 4 weeks duration or poor nutritional status (serum albumin <3 g/dL) or signs of cholangitis.

1.2 ***There must be a paragraph concerning the presence of a bias according to highly variable procedures in terms of biliary drainage which include surgical drainage, patients treated in other centers, patients with failure of a primary drainage.***

We agree with the reviewer's comment and have outlined this in the revised manuscript. However, as the baseline characteristics of the 2 groups were comparable, we hope that the variable effect of the various drainage methods on postoperative outcomes has been minimized.

1.3.1 ***The inclusion of 5 patients with arterial resection (although harmoniously distributed in the two groups) is annoying since we know that they are very special patients.***

We agree with the reviewer's comments. Patients undergoing arterial resection are 'special', with increased surgical complications. However, in our study, vascular resection was not identified to be a risk factor in the univariate and multivariate analysis.

1.3.2 ***The article by Olivier Farges cited three times (reference 14) has not been adequately analyzed because it is not a series that showed no difference in patients drained or not drained. It is one of the first series that shows a difference in terms of morbidity and mortality in patients who have had a right liver resection and who were drained versus undrained whereas this difference didn't not appear for the left liver resections. The originality of these new data must be precised. It may therefore be specified in this series (although subgroup analysis but using adapted statistical methods to small sample) results of : - the 13 drained patients with right hepatic resection versus the 12 undrained patients who underwent right hepatic resection, - idem for the 14 drained patients with left hepatic resection versus the 32 undrained patients who underwent left hepatic resection. Do we find the same results or not than the series of Farges et al? It is surprising that no patient who had complications of drainage has been cons - indicated for surgery. This is not a study in intention to treat but there is a real morbidity and mortality of biliary drainage as it has already been shown in a series of more simple drainage represented by drainage before PD.***

We undertook a subgroup analysis in patients who had a right-sided hepatectomy and those who had a left-sided hepatectomy (PBD *vs.* no PBD) and our results were similar to the study by Farges. There was a higher morbidity (84.6% vs 35.7%, $P = 0.028$) in patients undergoing right-sided hepatectomy without PBD (n = 13) as compared to those with a PBD (n = 14). In patients undergoing left-sided hepatectomy, patients in the drained group (n = 19) had a higher morbidity (78.9% vs 40.6%, $P = 0.018$) as compared to the undrained group (n = 32). This has now been included in the revised manuscript. All the patients who had complications of drainage in our study proceeded to have surgery.

1.3.3 ***Surgical procedure paragraph must described the surgical procedure of the present article and not all the procedures performed in the autors' department for hilar cholangiocarcinoma resection because the presence of intrahepatic cholangiojejunostomy associated with minor resections is disturbing since they are only major liver resections in this article.***

We agree with the reviewer's comment and have now only included procedures undertaken as part of this study in the paragraph on 'surgical procedures' namely Roux-en-Y hepaticojejunostomy.

1.3.4 ***The 15.3 days delay between drainage and surgery is short. Is this delay includes patients who have been previously drained out of the department?***

The time between drainage and surgery of 15.3 days in our study is short. Some studies

have suggested 3-6 weeks of preoperative drainage for obstructive jaundice, with even longer periods proposed for prolonged biliary obstruction before decompression. In light of the above, it is plausible that postoperative outcomes in our study may have improved further, had we kept the PBD catheter *in situ* longer, with a lower preoperative serum bilirubin level. We have already endeavored to explain this limitation in the manuscript. This (15.3 days) includes few patients who had been previously drained out of the department.

1.3.5 ***Patients have a mean bilirubin in the drainage group of 100 before surgery, therefore what is the purpose of drainage if it is not to normalize bilirubin?***

In this study, patients had a relatively high mean bilirubin (108.1±60.6 μmol/l) in the drainage group before surgery. Various studies have reported different cut-off levels of preoperative bilirubin that had a beneficial effect on surgical outcome. The purpose of drainage was to improve surgical outcome and to address complications such as cholangitis, poor nutritional status and further deterioration of liver function. Like most reported studies, it was not possible to normalize the bilirubin levels of all patients before surgery.

1.3.6 ***There are two patients who had Bismuth type I lesions, these patients had major resections?***

Indeed, there were 2 patients with Bismuth type I lesions who had major liver resection. According to medical records, these two patients were suspected of having a high T stage on the preoperative imaging. This was later disproved on the final pathology results. Major liver resection in Bismuth type I hilar cholangiocarcinoma has been reported in some studies [*Kondo S, et al. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study.Ann Surg. 2004;240(1):95-101 & Lim JH, et al. Liver resection for Bismuth type I and type II hilar cholangiocarcinoma. World J Surg. 2013;37(4):829-37*].

1.3.7 ***In Table II, it is precised bile leak and anastomotic leak. What is the difference?***

Bile leak was defined as the drainage of 50 ml or more of bile from a surgical drain or from drainage of an abdominal collection, over a period of three days. This could be either from the remnant liver or hepaticojejunostomy anastomosis. In our study, 6 patients had such a "bile leak" from the remnant liver. We were hoping to differentiate this from the leakage of bile from an anastomotic leak (hepaticojejunostomy). Three patients in our study had such an "anastomotic leak". While post-operative imaging was helpful in distinguishing between the 2, we appreciate that this may have caused some confusion, due to our inappropriate use of terminology in the table. We have therefore amended Table 2 appropriately to help clarify this.

1.3.8 ***Above 170, bilirubin was a risk factor of morbidity, while biliairy drainage does not. This is disturbing. What was the postoperative course of the subgroup of patients who had a very high pre-operative bilirubin level and who was brought to a bilirubin less than***

170 due to drainage?

In patients with a higher pre-operative bilirubin level (>170μmol/L) and PBD, the morbidity was lower than patients with a higher pre-operative bilirubin level (>170μmol/L) and without PBD. However, their morbidity was higher than the patients with PBD and lower pre-operative bilirubin level (≤170μmol/L) prior to drainage (data not shown). Koyama *et al* advised that adequate recovery of hepatic function depended not only on the duration of obstructive jaundice prior to decompression, but also on the duration of biliary decompression. Some studies have suggested 3-6 weeks of preoperative drainage for obstructive jaundice, with even longer periods proposed with a prolonged biliary obstruction before decompression. In our study, the PBD catheter remained *in situ* for a mean of 15.3 days. In light of the above, it is plausible that postoperative outcomes in our study may have improved further, had we kept the PBD catheter *in situ* longer with a lower preoperative serum bilirubin level. We have accepted this to be one of the possible reasons why we were not able to demonstrate a clear benefit of the use of PBD. Also, this is a retrospective single centre study with a small sample size. Ideally we would have liked to conduct a prospective study to validate the findings of our study. We accept these limitations of our study in the manuscript.

(2) **2.1.** ***It is unclear how the authors arrived at the cut-off value of 170 μmol/L for bilirubin in their analysis of risk factors for peri/post-operative complications. Was an ROC-plot of preoperative bilirubin and postoperative morbidity made? A preoperative bilirubin >170 μmol/L was identified as an independent risk factor for postoperative complications. This is however not reflected in differences in postoperative complication rate in drained and non-drained patients, which have mean bilirubin levels well below and well above this cut-off, resp. Authors should perform a subgroup analysis to identify common and subgroup-specific risk factors. It should be explicated whether results of uni-/multivariate analysis are derived from the entire cohort, or from analysis of drained/non-drained subgroups.***

In this study, the preoperative mean bilirubin level was 108.1±60.6 (μmol/L) in the drained group and 265.7±69.1(μmol/L) in the undrained group. Previous studies have suggested that PBD should be performed when the preoperative bilirubin level was higher than 171 μmol/ L [10, 37]. So a cut-off of 170 μmol/L bilirubin was chosen. There were 48 patients with a bilirubin level of more than 170μmol/L and 30 patients with a bilirubin level of less than 170μmol/L. As per the uni-/multivariate analyses, bilirubin level of 170 μmol/L was an independent risk factor. Taking into account fewer patients, uni-/multivariate analysis were derived from the entire cohort in our study.

2.2. ***Authors studied short-term (up to 21 days) morbidity and mortality, while complications frequently develop after this period and, hence, a 90-day follow-up period that is common in surgical studies is more appropriate. Why do the authors deviate from this routine?***

We agree with the reviewer's comment and patients included in this study were indeed

followed up post-operatively for a longer period. However, as part of this study, we endeavored to investigate the effect of PBD on immediate postoperative outcomes prior to discharge from hospital (morbidity, mortality etc.). We have sought to clarify this in the revised manuscript.

2.3. ***Authors should grade (e.g. Clavien-Dindo) post-operative morbidity. Did some patients need ICU treatment?***
The Clavien-Dindo classification of surgical complications is an excellent quality assurance tool. We have now added this criterion in the text and Table 2. There were some patients who needed ICU treatment after operation.

2.4 ***In the Introduction the controversy about PBD in HCCA is focused on "to drain or not to drain", paying little attention to the type of drainage (e.g. internal/external, procedure), duration of drainage, and cut-off values for drainage and post-drainage surgery. This could be discussed in more detail.***

We have now discussed this in further detail in the introduction.

2.5 ***What were the criteria to perform (or not perform) PBD in patients? The author's recommendation of PBD with a preoperative bilirubin >170 µmol/L (p.12) appears to have not been applied in the present patient cohort.***

The selection criteria for drainage in patients were jaundice of more than 4 weeks duration or poor nutritional status (serum albumin <3 g/dl) or signs of cholangitis. This is a retrospective study and the recommendation of PBD with a preoperative bilirubin >170 µmol/L was not applied to the present patient cohort.

2.6 ***How do the authors define 'curative resection'?***

In our hospital, curative excision was defined as histologically negative surgical margins with a minimum tumour-free margin of 5 mm at the hepatic stump of the bile duct, the duodenal stump of the bile duct, and the excisional surface. We have clarified this in the revised manuscript.

2.7 ***No definition of (in)adequate PBD is given.***

Adequate PBD was evident by a relief of cholangitis, an improvement in the liver function and/or the nutritional status of the patient. We have now revised the text appropriately.

2.8 ***Were all patients presenting with HCCA during the enrolment period, operated at the author's center? (thus 78 patients in 10 years?)***

Yes, all the patients who presented with HCCA during the enrolment period (10 year) came from our center.

2.9 ***p7/Table 1. Authors should provide the number of days between blood sampling for***

serum biochemistry and drainage/surgery.

The blood sampling for serum biochemistry was completed in the 2 or 3 days before drainage or surgery. This has been included in the revised manuscript.

2.10 ***p10. What were the search criteria for the "systematic review" presented in the Discussion. Is the listing in Table 4 exhaustive? The respective studies identified in the literature search, agree that PBD has no effect on postoperative mortality. This should be acknowledged. A meta analysis of the available data on postoperative morbidity (for a given type of PBD) would be welcome, but is beyond the scope of this study.***

The existing literature was reviewed by performing a systematic search in PubMed, Medline and Embase from January 1990 to May 2013. The following search terms were used: "preoperative biliary drainage" or "percutaneous transhepatic biliary drainage" or "endoscopic biliary drainage or "endoscopic nasobiliary drainage" or "endoscopic biliary stenting" and ''hilar cholangiocarcinoma'' or "hilar bile duct cancer'' or ''proximal bile duct cancer'' or "Klatskin tumor'' or ''carcinoma of the hepatic duct confluence'' along with their synonyms or abbreviations. The search was restricted to comparative studies conducted on human subjects and in the English language only. The above has been included in the revised manuscript. We agree with the reviewer's comments on a meta analysis on the subject. However, it is beyond the scope of this study.

2.11 ***Table 1. The mean time between admission and surgery of non-drained patients should be provided.***

Time between admission and surgery were 20.7±2.1 days in the drained group and 3.8±1.6 days in the undrained group, respectively. We have now included these details in Table 1.

2.12 ***Table 2. The % of non-drained patients with GI bleeding has been left out.***

We apologise for this oversight. The % of non-drained patients with GI bleeding has now been included in Table 2.

2.13 ***Table 3 and 4 would greatly benefit from lines/shading to distinguish the various entries.***

We have now revised Table 3 and 4 appropriately.

2.14 ***Use of additional abbreviations for the surgical procedures/type of PBD could give***

Table 4 a more attractive, balanced lay-out. For easier comparison with the current study, studies included in Table 4 could be grouped as "curative resection" and "curative and palliative resection". Follow-up period should be included in the studies mentioned in Table 4.

We have included a column in table 4 to indicate "curative resection (CR)" and "palliative resection (PR)". Indeed, the follow-up period is important, however, as it was not stated in many studies, we did not include this in Table 4.

(3) **3.1** ***There is a contradiction between the no usefulness of PBD and the risk factor TBIL>170μmol/L. If we perform PBD to the cases with TBIL>170μmol/L, we could reduce the postoperative complications? Do these result show that cases showing higher TBIL even after PBD have a great risk for postoperative complications?***

The majority of patients with HCCA have obstructive jaundice at presentation, which increases the risk of complications, such as sepsis, bleeding and liver failure, especially in patients undergoing major hepatectomy. Our study has shown that TBIL>170μmol/L is a risk factor for developing postoperative complications. PBD affords us the potential to reduce the preoperative bilirubin and the complication rate post surgery. Koyama *et al* advised that adequate recovery of hepatic function depended not only on the duration of obstructive jaundice prior to decompression, but also on the duration of biliary decompression. Some studies have suggested 3-6 weeks of preoperative drainage for obstructive jaundice, with even longer periods proposed with a prolonged biliary obstruction before decompression. In our study, the PBD catheter remained *in situ* for a mean of 15.3 days. In light of the above, it is plausible that postoperative outcomes in our study may have improved further, had we kept the PBD catheter *in situ* longer with a lower preoperative serum bilirubin level. We have accepted this to be one of the possible reasons why we were not able to demonstrate a clear benefit of the use of PBD. Also, this is a retrospective single centre study with a small sample size. Ideally we would have liked to conduct a prospective study to validate the findings of our study. We accept these limitations of our study in the manuscript.

3.2 ***The χ2 test or Fisher's exact test is not appropriate to compare the differences of Bismuth–Corlette stage in Table1. Please use 2*4 table analysis.***

We have changed the statistical methods in Table1 for comparing the differences of Bismuth–Corlette stage. The RxC table analysis was used.

3.3 ***Please choose one term from PTBD and PTCD.***

In order to be consistent, we have now chosen PTCD and amended the manuscript accordingly.

3.4 ***Please check which is more appropriate endoscopic biliary stenting (EBS) or endoscopic biliary drainage (EBD)?***

Endoscopic biliary drainage (EBD) includes endoscopic biliary stenting (EBS), endoscopic nasobiliary drainage (ENBD), hence we have used this in the manuscript.

3.5 ***misspelling? Farges et al. [17] opined that in DISCUSSION***

We have changed the word 'opined' to 'advised' in the discussion.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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