

December 31, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14618-review.doc).



Title: Biliary drainage strategy of unresectable malignant hilar strictures by computed tomography volumetry

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We are grateful to the reviewers for their critical comments and useful suggestions that have helped us to considerably improve our paper. We have carefully considered these comments and suggestions in the revised version of our paper, and have responses to the comments as follows.

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) Reviewer 02954726

Comment #1

Portal obstruction sometimes occurs in the patients with malignant hilar biliary stricture. The liver function of the segment of which portal vein is occluded relatively decreases. How do you deal with these liver segments in CT volumetry?

Response #1

Thank you for the comment. In multivariate analysis in the present study, portal obstruction was not found to be an independent factor contributing to effective drainage. Therefore, the liver segments affected by portal obstruction were assessed in a similar manner to unobstructed liver segments in CT volumetry.

Comment #2

Can you make a discussion on the reason for the result “smaller drained liver volume was associated with drainage-associated cholangitis”?

Response #2

An atrophied section is considered to be a likely cause of cholangitis due to the decreased bile excretory function (reference 28). We have added this statement to the Discussion section in the manuscript (page 11, line 3-4).

Comment #3

Placement of single stent is technically easier than that of multiple stents regardless of the type of stents.

Therefore, the information on the number of placed stent is important. How many cases of Bismuth IV strictures in which effective drainage was achieved via single stent placement do you have?

Response #3

We appreciate the comment of the reviewer, and we believe that this point is critically important in the present study.

In total, 33 patients with Bismuth type IV disease were treated with single stenting. The overall drainage response rate following single stenting of Bismuth type IV stricture was 42% (14/33); however, this response rate was 92% (12/39) for subjects with Bismuth type IV stricture who met the criteria ($\geq 33\%$ of the liver volume with preserved liver function and $\geq 50\%$ with impaired liver function).

Comment #4

Chemotherapy for the patients with unresectable malignant biliary stricture, especially biliary carcinoma, can improve their prognosis. The management of jaundice and cholangitis is important for continuous chemotherapy for malignant hilar biliary strictures. If the tumor becomes larger, the drainage volume becomes smaller, which will hinder continuous chemotherapy. Therefore, the minimum drainage is not always effective for continuous chemotherapy. Do you have information about this? And, please discuss about this.

Response #4

Thank you for the helpful comments. The management of jaundice and cholangitis is very important when administering continuous chemotherapy to cases with malignant hilar biliary strictures. In the present study, 40 patients (single stenting in 25 cases and multiple stenting 15 cases) received chemotherapy after stenting. The stent patency was longer in cases of single stenting (median, 354 days) than in cases of multiple stenting (210 days) ($P = 0.02$). Therefore, we believe that single drainage, which is technically simple and easy for re-intervention, is sufficient for the management of malignant hilar biliary strictures.

(2) Reviewer 01804189

Comment #1

Why was stenting done in these patients of unresectable hilar blocks? Were these patients having cholangitis or significant pruritis? or was stenting done just because of presence of jaundice?

Response #1

We appreciate the questions raised by the reviewer. Biliary drainage was performed in all patients with obstructive jaundice, if improvement of their prognosis was expected by drainage. Thirteen patients (16.7%) had a complication of cholangitis before biliary drainage.

Comment #2

According to this study all the patients were having compensated or decompensated cirrhosis how it is possible in all the cases.

Response #2

Thank you for the comment. Preserved liver function was defined as the presence of a normal liver or compensated cirrhosis in the present study. We have added this definition in the Methods section (page 7, line 1-5) to avoid any misunderstanding.

Comment #3

What was the life expectancy of patients with decompensated cirrhosis with hilar block?do they really need Stent placement?

Response #3

The median survival period of successfully drained patients with decompensated cirrhosis was significantly longer than that of undrained patients (77 days vs. 22 days, $P = 0.02$) (data not shown in the manuscript). If the patient's prognosis was expected to improve through biliary drainage, this treatment was performed for decompensated cirrhosis.

Comment #4 and #5

Majority of patients had Bismuth type 3 or 4 lesions and most of the patients were treated with plastic stents (it is not clear whether 7fr or 10fr) I think more patients will be harmed than benefited by this approach. Authors should very clearly mention in their discussion about indications for stenting in hilar block and which stent (plastic or metallic) in which situation.

Response #4 and #5

Thank you for the comments. Our policy for biliary drainage of malignant hilar stricture is as follows: The first drainage for hilar stricture is treated with a plastic stent. After the drainage effectiveness is confirmed, the plastic stent is replaced with a metal stent to achieve long-term patency.

(3) Reviewer **00054001**

Comment

Disease entities included in this study are too varied. Disease entity must be limited to hilar cholangiocarcinoma which is the commonest and most problematic cause of malignant biliary obstruction.

Response

We appreciate the comments of the reviewer. Since the majority of previous reports for biliary drainage of unresectable malignant hilar stricture (UMHS) involved various diseases, the present study also included all cases of UMHS. When assessing only patients with cholangiocarcinoma, the patients with preserved liver function showed a similar result as that noted in the present study (39% in cases with $<33\%$ of drained liver volume vs. 88% in cases with $\geq 33\%$ of drained liver volume, $P < 0.01$). However, the patients with impaired liver function could not be appropriate assessed due to the small number of patients.

Comment #1

Reason(s) for being unresectable

Response #1

Thank you for your suggestion. Accordingly, we have included the reasons for non-resectable nature as the presence of distant metastasis, locally far-advanced tumors, and/or poor liver function (described in the Method section on page 6, line 9-11, of the revised manuscript).

Comments #2

Authors' policy for biliary drainage caused by unresectable hilar chlangiocarcinoma

Response #2

Our policy for biliary drainage in cases with UMHS supports the unilateral drainage of the predominant bile duct. We perform bilateral drainage only in cases where unilateral drainage is ineffective. Some previous reports (reference 8-11) have supported the use of unilateral drainage because of the associated technical simplicity and comparable patency time to bilateral drainage. There was no difference in the drainage effectiveness between unilateral drainage and bilateral drainage in the present study.

Comments #3

Evaluation for efficacy of stent(s) which was actually placed: It seems that the authors did not confirm the efficacy of stent(s) actually placed. If the placed stent(s) worked sufficiently, it can be confirmed by CT and/or US that dilatation of intrahepatic bile duct(s) is resolved in corresponding area(s). If not and jaundice is unresolved, additional drainage should be considered. I consider that required minimal volume must be calculated from post-procedural CT.

Response #3

Thank you for the comment. As the aim of the present study was to clarify the factors predicting the successful drainage in cases with UMHS, we determined the predictive drained liver volume from pre-drainage CT.

Comments #4

Clinical course of the study cohort: Related to the issues 2 and 3 above-stated, cases where single drainage is insufficient are often encountered and therefore plural attempts are needed in these cases. Authors should include summary of clinical courses of the study cohorts.

Response #4

A total of 78 patients with UMHS underwent biliary drainage. Effective drainage was achieved in 49 of these patients (63%) during initial drainage. Of the 21 patients who underwent additional drainage because of ineffective initial drainage, successful drainage was achieved in 17. Thus, eventually, 66 patients (85%) had effective drainage (page 8 line, 16-18).

(4) Reviewer 00923968

Comment #1

This is a relatively small study (n=78) on a very heterogeneous group of patients. The heterogeneities included the underlying pathologies, the drainage approach (percutaneous or endoscopic) and the type of stents used (nasobiliary drainage, metal stent or plastic stent). There are a lot of limitations in such a type of study.

Response #1

We appreciate the comments of the reviewer. It is true that such a heterogeneous group of patients is a limitation of the present study. Because of the retrospective nature of this study, the drainage procedures were not uniform; the procedures were chosen by the patient's attending physician, which might have led to bias. Second, because of the sample size, statistical subgroup analyses were not possible (page 11, line 11-15). However, this study is the first to select the drainage method by determining the required drainage volume based on liver function in cases with hilar biliary strictures. Although further prospective study is warranted, we believe that the results of the present analysis might be applicable in clinical practice.

Comment #2

It would be clearer to future potential readers to add the word biliary to the title of the paper making the title looks like “Biliary drainage strategy”.

Response #2

Thank you for the useful suggestion. According to the reviewer’s comment, we have changed the title to “Biliary drainage strategy of unresectable malignant hilar strictures by computed tomography volumetry”.

Comment #3

From previous studies, we know that the longer the history of obstructive jaundice is before drainage, the longer it takes for the liver to recover and the level of the bilirubin to drop. Did the authors study the duration of obstructive jaundice before drainage in this study group? If yes, did the duration have any impact on the effectiveness?

Response #3

I agree with the reviewer’s comment regarding the impact of the duration of obstructive jaundice on drainage effectiveness. However, due to the lack of information on the duration of obstructive jaundice before drainage, we could not assess its impact in the present study.

Comment #4

How did the author define decompensated liver cirrhosis in this study without a liver biopsy or at least a fibroscan?

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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