

March 5, 2018

Dear Editor,

**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 38317

**Title:** Intraoperative frozen section diagnosis of bile duct margin for extrahepatic cholangiocarcinoma

**Author:** Takayuki Shiraki, Hajime Kuroda, Atsuko Takada, Yoshimasa Nakazato, Keiichi Kubota, Yasuo Imai

Thank you for your kind and constructive reviewing of our manuscript. Please find enclosed the edited manuscript.

We responded to each comment raised by the reviewers. Responses to the comments are in the separate sheets. In addition, we modified our manuscript in accordance with the instructions by the editor.

We hope you find this revised manuscript appropriate for publication in *World Journal of Gastroenterology*.

Sincerely yours,

Yasuo Imai, M. D.

Department of Diagnostic Pathology  
Dokkyo Medical University  
880 Kitakobayashi, Mibu, Shimotsuga,  
Tochigi 321-0293, Japan  
Phone 81-282-87-2130; Fax 81-282-86-1681  
E-mail; ya-imai@dokkyomed.ac.jp

Enclosures

1. Reviewer 00053888

We greatly appreciate the favorable comments by the reviewer.

Thank you very much.

2. Reviewer 02529835

We greatly appreciate the constructive comments on our manuscript by the reviewer. We described our responses point by point below.

(C1) I found your nomenclature of borderline is confusing. Borderline includes case with biliary intraepithelial neoplasia, so basically it means dysplasia, not invasive cancer. The diagnosis is better classified into negative, dysplasia and malignancy.

(A1) As the reviewer has pointed out, the borderline lesion primarily indicates dysplasia. In the clinical practice, however, we sometimes encounter such cases as cannot be determined whether neoplastic or reactive. Dysplasia is a neoplastic lesion, but some non-neoplastic/reactive lesion may be included in our borderline lesions. This may be partly due to the difficulty in distinguishing very low-grade dysplasia from reactive atypia and partly due to the artifact during sampling and processing. We called such lesions indefinite for neoplasia and included them in the borderline lesion. We therefore preferred the nomenclature of borderline.

(C2) Adding a reference at the end of the 1st paragraph in Introduction.

(A2) We revised the manuscript according to the reviewer's comment (p.7, l.12).

(C3) What is the follow-up time of your study group?

(A3) The overall follow-up period of the 74 patients from surgery to disease-related death or censoring were 4 to 2343 days (Median, 623 days). We added these sentences to the text (p.14, ll.9-10).

(C4) Adding figures including frozen pictures of biliary intraepithelial neoplasia 1 - 3.

(A4) We added representative figures of BilIN-1, 2, and 3 on FSD as Figure 1 according to the reviewer's suggestion.

(C5) There is a lining error in Table 1.

(A5) We revised Table 1 according to the reviewer's comment.

### 3. Reviewer 01588404

We greatly appreciate the constructive comments on our manuscript by the reviewer. We described our responses point by point below.

(C1) The authors have not mentioned the impact of prior stenting instrumentation especially in light of almost 40% borderline epithelial margins which significantly decreases on PSD. This might be due to the above mentioned reasons as the subepithelial borderline rate is low and does not change on PSD.

(A1) As the reviewer has pointed out, we thought that a significantly higher rate of borderline in the epithelial layer than in subepithelial layer on FSD may be partly due to the impact of preoperative biliary drainage tube insertion. We added information on preoperative biliary drainage in Table 1, and added the following sentences in the discussion:

1. In this study, the rate of borderline was significantly higher in the epithelial layer than in the subepithelial layer on FSD, and borderline epithelial margins significantly decreased but borderline subepithelial margins did not change on PSD. This may be partly explained by the fact that almost all patients underwent biliary drainage tube insertion preoperatively (Table 1). (p.17, ll.21-24, p.18, l.1)

2. (3) impact of preoperative biliary drainage tube insertion. (p.19, ll.21-22)

(C2) Although the borderline epithelial lesions on frozen did not change to positive on PSD one borderline subepithelial lesion changed to positive. In a larger series with more diverse pathologist it is quite likely that some borderline margins may ultimately turn out to be positive. Hence the discussion and conclusion should emphasise the need for negative margins whenever positive especially if it is the first margin and additional margin can be safely obtained as the local recurrence is very high in positives.

(A2) We admit that the reviewer's comment is very reasonable and added several sentences emphasizing the need for achieving the negative margin in the discussion and conclusion (p.20, ll.5-10, ll.20-22).

(C3) The authors have not analysed proximal (hilar) and distal (periampullary) tumors to see if the concordance and outcomes change.

(A3) We added data describing the discordance between FSD and PSD in pCCA and dCCA separately (Tables 5 and 6). By investigating the data, we found no significant difference in diagnostic discordance rate between them. We added several sentences to the text (p.13, ll.20-23)