ANSWERING REVIEWERS

July 22, 2014

Dear Editor,

To begin with, we would like to express great appreciation for your showing interest and helpful criticisms on our meta-analysis article. We tried to incorporated reviewer's comments and advices into our new revised version of manuscript.
Please find enclosed the edited manuscript in Word format (file name: 11760-review.doc).

Title: Clinical Characteristics of Incidental or Unsuspected Gallbladder Cancers Diagnosed During or After Cholecystectomy: A Systematic Review and Meta-Analysis

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Name of Journal: *World Journal of Gastroenterology*

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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

Reviewer 1

(1) Would change language in conclusion about additional imaging "might" be necessary for revisional surgery to something more definitive.

→We ppreciate the reviewer's comment. We change "might be necessary" to "are necessary" as follows.

→P16, line 4

Furthermore, even though these GB cancers were found incidentally, some incidental GB cancers were unresectable when attempting revisional surgery. Therefore, additional imaging studies to determine the extent of disease and resectability are necessary before performing revisional surgery.

Reviewer 2

The authors present a meta-analysis of incidentally found gallbladder cancer following cholecystectomy. They evaluated a total of 26 studies with over 2,100 patients included in their analysis. Because cholecystectomy is such a common surgical entity, this study provides some basis and weight to the fact that benign surgical diseases can present as malignancies with dire outcomes.

(1) one major missing piece of data and discussion from this paper is the actual survival length & mortality of the patients included in the analysis. While the incidence of GB cancer found incidentally is important, how this impacts patients' survival seems a necessary component that merits results & discussion.

→We appreciate the reviewer's comment. The reviewer's comment is right. However, actual survival length is described as different style among the studies, for example, according to stage, or according to whether to perform revisional surgery, according to suspected or unsuspected, and so on, therefore we extracted the survival data at first, but it is difficult to describe and show manifestly. And mortality was not described clearly. Therefore, we did not mention about the survival and mortality.

(2) Figure 2 does not provide much information, other than to show the very low incidence of incidental GB cancer, 0.7%, which you state in multiple places in the manuscript. This figure may be left out.

→We removed the figure 2 in the revised version of manuscript according to reviewer's comment

(3) While you describe some of the definitions of TNM staging in your results, the paragraph is a bit confusing (e.g. you don't describe T1a vs b or T2). Please clarify the current guidelines for Tis through T4 (each) in addition to some of the modifications you list over the various AJCC editions. ?

→We appreciate the reviewer's comment. We incorporated the definition of Tis, T1a, T1b and T2 in the revised version of manuscript. The definition of Tis, T1 and T2 are obviously the same among the AJCC staging system. Although the definition of T3 and T4 were somewhat different as described in the manuscript, they are similar among the AJCC staging systems. Therefore we regarded the T3 in each addition as T3 and also T4 in each addition as T4 throughout the addition without modification of the stage.

→P9, line 8

For T stage, Tis, T1, and T2 are the same from the 3rd to 7th editions of AJCC stage. Tis is carcinoma in situ. T1a tumor invades mucosa and T1b invades muscle layer. T2 invades perimuscular connective tissue, without extension beyond the serosa or into the liver [34-38]. T3 tumors are those that perforate the serosa, or directly invade one adjacent organ, or both (extension 2cm or less into liver) whereas T4 tumors extend more than 2cm into the liver and/or into two or more adjacent organs in the 4th and 5th editions. [35, 36] In the 6th and 7th editions of AJCC, [37, 38] T3 tumors perforate the serosa or directly invade the liver and/or one other adjacent organ or structure, and T4 tumors invade the main portal vein or hepatic artery, or two or more extrahepatic structures. Although T3 and T4 stage are somewhat different among the versions of AJCC stage, we regarded T3, T4 in each edition as the same T3, T4 respectively throughout the editions.

(4) The Results paragraph "Revisional Surgery for Radical Chole" contains mostly discussion and, as such, should be moved from Results to the Discussion section of the manuscript. ……

→We appreciate the reviewer's comment. We removed the paragraph and moved to the discussion in the revised version of the manuscript

→P13, line 5

The most important clinical problem related to incidentally found GB cancers is the decision of

whether to proceed with revisional surgery for radical cholecystectomy. If the GB cancer is found during the operation, conversion to radical surgery is relatively easy. However if GB cancers are found after the operation, reoperation for revisional surgery is both necessary and critical.

5)Additional extrapolation and impact on society would add some weight to the study, such as including the total number of cholecystectomies performed in the world/US/Korea/etc, which may result in ___ number of GB cancers found incidentally.

→We appreciate the reviewer's helpful comment. However, there is no clear data of incidence of incidental GB cancers in the world/US/Korea.

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

With best regards,
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