

Format for ANSWERING REVIEWERS

August 31, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 12599-review.docx).

Title: Comparison of clinical outcome of small cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder

Author: Sung Pil Yun, Nari Shin, Hyung Il Seo

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12599

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 editor

- (1) We revised conclusion of the abstract.
- (2) Comments have been included.
- (3) The decomposable figures (Figure 1 & 2) are provided as a PPT format in the manuscript. The PPT files also have been uploaded separately.
- (4) We added table 4 "Small cell neuroendocrine carcinoma of the gallbladder of literature".

3 Revision has been made according to the suggestions of the Reviewer 1

- (1) Are there differences between GB-NEC-SCCs and large cell neuroendocrine carcinomas of the gallbladder? If there are, it need be discussed

Answer: We explained the differences between GB-NEC-SCCs and large cell neuroendocrine carcinomas of the gallbladder to the discussion.

- (2) Compared with GB-adenocarcinoma group, there is smaller sample size for GB-NEC-SCCs. Is it reliable for the conclusion of similar clinicopathological features and prognosis between GB-NEC-SCCs and GB-adenocarcinomas?

Answer: We also agree about the comment as well. We made a change to the conclusion of the abstract and added table 4 (Small cell neuroendocrine carcinoma of the gallbladder of the literature) for comparison to previous studies.

4 Revision has been made according to the suggestions of the Reviewer 2

- (1) The sample size is too limited to conclude a reliable conclusion, can you add some patients than do the comparison?

Answer: Unfortunately, there are no cases to add at this point. Instead to make up for it, we added a table to compare with previous study and made some adjustment to result in regard to the abstract. Additionally, we are in the process of preparing a multi-center study for its lack of number in GB-NEC-SCC cases.

- (2) There are some typing errors. The authors should carefully read again, and correct them

Answer: typesetting were corrected

5 Revision has been made according to the suggestions of the Reviewer 3

- (1) Since the number of cases with small cell neuroendocrine carcinoma are small (n=4), most of the statistical analyses may not be effective, and final conclusions are difficult to be drawn. For instance, the prognosis of patients with small cell neuroendocrine carcinoma might be better than that of adenocarcinoma (Fig. 2), if the number of the patients would be more than this study

Answer: Having agreed with your comment about that final conclusion is difficult to be drawn; we revised our conclusion of the abstract. According to previous studies, we also think that the prognosis of patients with GB-NEC-SCC may not be better even if additional cases are included. Nonetheless, due to the lack of comparison studies between GB-adenocarcinoma and GB-NEC-SCCs (after radical resection), it was valuable to assess the clinical course of patients with GB-NEC-SCCs after curative surgery.

- (2) The four patients with small cell neuroendocrine carcinoma might be divided into two groups, because two of the patients showed different immunostaining patterns (positivity of synaptophysin and chromogranin A) as shown in Table 3. The authors should discuss on a possibility of heterogeneity of small cell neuroendocrine carcinoma

Answer: In the Niigata registry for gut-pancreatic endocrinomas (Bull Coll Biomed Technol Niigata University.), immunohistochemical evaluation was done in 77 cases, and two peptides most commonly identified were CgA (91%) and NSE (84%). In our study, when synaptophysin and chromogranin A were negative (in two cases, 50%), mitosis was shown to be high, but we did not think this result represented heterogeneity of small cell neuroendocrine carcinoma nor reflected much of relationship between heterogeneity of GB-NEC-SCC and prognosis, due to small number of cases of GB-NEC-SCCs. In order to get a more accurate conclusion, we believe either more cases need to be collected or multi-center studies are required.

6 In order to assist identifying the requested changes made to the manuscript, all changes made have been highlighted in **yellow** within revised version of the paper.

7 References and typesetting were corrected.

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

Sincerely yours,

A handwritten signature in black ink, appearing to be 'H. Seo'.

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