

## ANSWERING REVIEWERS

June 24, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 18394-review.doc).

**Title:** Histological diagnosis of gastric submucosal tumors: EUS-guided fine-needle aspiration biopsy versus mucosal cutting biopsy

**Author:** Hisatomo Ikehara, Zhao Liang Li, Jiro Watari, Masato Taki, Tomohiro Ogawa, Takahisa Yamasaki, Takashi Kondo, Fumihiko Toyoshima, Tomoaki Kono, Katsuyuki Tozawa, Yoshio Ohda, Toshihiko Tomita, Tadayuki Oshima, Hirokazu Fukui, Ikuo Matsuda, Seiichi Hirota, Hiroto Miwa

**Name of Journal:** *World Journal of Gastrointestinal Endoscopy*

**ESPS Manuscript NO:** 18394

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

### Point-by-Point responses

#### Reviewer 00503857

**Comment 1:** In page 6, EUS-FNAB procedure section, please describe how the histological diagnosis of certain submucosal tumor was made. (i.e., the histological diagnosis of certain submucosal tumor was made by typical histological features and immunohistochemical staining)

**Response:** Thank you for all of your comments and suggestions. All obtained materials were assessed by hematoxylin-eosin (HE) staining. If the material was diagnosed as a mesenchymal tumor, an additional immunohistochemical staining assessment was performed. We have mentioned this in the "EUS-FNAB procedure" section.

**Comment 2:** In Mucosal cutting biopsy section, please describe how you processed the biopsy specimens for histopathological examination. Furthermore, you also should describe how the histological diagnosis of certain submucosal tumor was made.

**Response:** The mucosal cutting biopsies (MCBs) were all performed using conventional biopsy forceps (Radial Jaw™ 4: Boston Scientific, Natick, MA). After mucosal cutting, the submucosa was directly observed endoscopically through the mucosal defect. Subsequently, the biopsy samples were obtained. We have provided a detailed description of the MCB procedure in the "Mucosal cutting biopsy" section.

**Reviewer 02542408**

**Comment 1:** In the Intro, the authors state that all GISTS need to be resected, but this is not true. Small GISTS can be followed with standardized protocols.

**Response:** Thank you for all of your comments and suggestions. According to the Japanese GIST guidelines, SMTs that are 2–5 cm in diameter should be confirmed histopathologically. As you indicated, small SMTs without malignant findings can be observed followed by scheduled EUS or CT, etc. We have revised the manuscript (page 4, line 8) as suggested.

**Comment 2:** Please cite the statistics for the statement that “SMT for cytology has been reported to be relatively high, but the success rate for histology is not”.

**Response:** In accord with this comment, we have added the statistics on the success rate in the Introduction section.

**Comment 3:** I would move your later comments on endoscopist experience to the methods section to establish the experience level much earlier in the manuscript.

**Response:** We have moved those sentences to an earlier part of the Methods section.

**Comment 4:** In the methods section, can you clarify if a cytologist was intentionally not available as part of the protocol, or if this is just the way things standardly happen for your practice.

**Response:** A cytologist was intentionally not available in this study. As we had noted regarding this point in the Method section (page 5, line 33) and the Discussion section (page 8, line 11), it was difficult to gain the cooperation of cytologists due to their busy schedules in daily medical practice, as is true in many hospitals in Japan.

**Comment 5:** Methods. Please state where you injected into the submucosa. Your figures suggested that you injected directly over the lesion to create your submucosal cushion but this should be stated.

**Response:** In the “Mucosal cutting biopsy” section, we have mentioned that saline was injected into the submucosal layer.

**Comment 6:** Methods: please list your brand of clips.....these look like Olympus clips from the figure.

**Response:** We used EZ clips (Olympus Optical) for closing the incision hole. We have added the name of the hemoclips used (page 6, line 4).

**Comment 7:** Results. Please list the mean number of clips used to close the defect.

**Response:** The mean number of clips was 3.4 (range, 1–6 clips). We have added text regarding the number of hemoclips in the “Complications in both procedures” section (page 7, line 17).

**Comment 8:** Results: please clarify....in some locations it appears as if only one case was non-diagnostic, but in others it seems as though there were three non-diagnostic cases.

**Response:** We could not follow this comment well, but we suspect that you are asking about the location of the tumors that could not be diagnosed by either the EUS-FNA or MCB methods. We have addressed this point in the Results section.

**Comment 9:** Discussion: as we move into an era of full thickness endoscopic resection, I think it is important that you mention whether your method would preclude any future procedures to remove the lesion. I believe firmly, no, your method would still permit future therapeutic resection, but this

should be noted.

**Response:** The mucosa incised by the MCB method was completely closed by hemoclips in all cases. Therefore, the risk of peritoneal dissemination was extremely low. We mentioned this in the “Mucosal cutting biopsy” section (page 6, line 5). Recently, a laparoscopic and endoscopic cooperative surgery (LECS) is being accepted for the treatment of gastrointestinal SMT, following its introduction by Dr. Hiki et al. in 2008. However, the MCB method for the histological diagnosis of SMTs is unlikely to preclude LECS for the treatment of those lesions. We have added these sentences in the Discussion section.

**Comment 10:** Discussion: can you briefly comment on any cost difference between the two methods.

**Response:** We have now addressed the costs of the two methods in the Discussion section (page 7, lines 29-35).

**Comment 11:** Discussion. The discussion is too long and doesn't focus on all the topics that should be noted. The discussion about GISTs and the recommendations for resection are not relevant to the manuscript.....this is not about GIST it is about SMTs. This paragraph can be removed and the remainder shortened.

**Response:** Based on this comment, we have deleted a paragraph in the Discussion section.

**Comment 12:** In table 2, it is not clear to the reader what is being compared for the P values....for example, I cant tell if you are comparing all of Location 1 between diagnostic/non-diagnostic, or just the Upper portion of Location one.

**Response:** We have revised Table 2.

**Comment 13:** Figures are great.

**Response:** Thank you for the kind word.

#### **Reviewer 00183658**

**Comment 1:** This study is a low sample size study.

**Response:** Thank you for all of your comments and suggestions. As you pointed out, the sample size of this study is small and drawn from a single institution. We are well aware of this issue and had mentioned it at the end of the Discussion section as one of the study's limitations. We also now note that a randomized control trial comparing the capabilities of MCB with those of EUS-FNAB is needed.

**Comment 2:** Several factors influence the outcome of the study. Some limitations might be occurred.

**Response:** There may be several limitations of this study, but we countered the limitations as much as possible by performing both diagnostic modalities simultaneously for the same patients with SMTs, as noted in the text.

**Comment 3:** This procedure needed experienced endoscopist and special equipment. It could not apply in the other hospitals.

**Response:** Some expensive equipment including the echoendoscope, its observing system, and the FNA needle are needed in the EUS-FNA procedure, and thus this method can be performed at only a limited number of institutions. On the other hand, MCB can be performed using common devices such as a needle knife, injection needle and EZ clip. We have mentioned these points in the Introduction and

Discussion sections.

**Question 4:** Unfortunately, the authors did not show the cost-effectiveness of the study.

**Response:** This is similar to a comment raised by reviewer 02542408. We have added a description regarding the cost-effectiveness of the study.

**Comment 5:** The clinical application of the study is very important. The authors should to recommend the readers to apply this knowledge into routine clinical practice.

**Response:** Thank you; we also hope that our message is understood by its *World Journal of Gastrointestinal Endoscopy* audience.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Jiro Watari' with a stylized flourish at the end.

Jiro Watari, MD, PhD

Division of Gastroenterology,

Department of Internal Medicine,

Hyogo College of Medicine,

1-1, Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan

Tel: +81-798-45-6662, Fax: +81-798-45-6661

E-mail: watarij@hyo-med.ac.jp