Ms.: "What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?" by Watari et al.

Point-by-Point responses

Dear Editor and Reviewers,

Thank you for your letter and the comments, which have helped us improve the manuscript. We have addressed the comments as follows. We revised numerous passages throughout the manuscript in addition to those that have been pointed out. The new text and revised text are shown in red font.

We appreciate the detailed review of our manuscript and have attempted to answer each of the comments raised. Thank you very much for your consideration of the revised version. We hope that it is now acceptable for publication in *World Journal of Gastrointestinal Endoscopy.*

Sincerely yours,

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Ms.: "What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?" by Watari et al.

Reviewer 1 (00503563)

Dear Reviewer 1,

Thank you for your comments, which have helped us improve the manuscript. We have addressed the comments as follows. We revised numerous passages throughout the manuscript in addition to those that have been pointed out. The new text and revised text are shown in red font.

Comment 1

How was the depth of tumor invasion judged by EUS in tumors with ulcerous finding (UL)?

Response:

According to the Reviewer's suggestion, we have now defined the EUS diagnosis for the lesions with UL(+) and provided this information in the Patients and Method section.

Comment 2

It is difficult to diagnose the depth of tumor invasion by EUS in tumors with UL. However, there was no significant difference in the inconclusive rate of EUS between tumors with and without UL. How do the authors discuss about this issue?

Response:

We described the definition of the inconclusive cases as a lesion in which at least five layers of the gastric wall, including the lesion, were unclear and the assessment by EUS was difficult due to the low-quality image, as mentioned in the Patients and Method section. The inconclusive rate indicates the incidence of low-quality EUS images but does not indicate the accuracy rate. Therefore, there was no significant difference in the inconclusive rate of EUS between tumors with and without UL, similarly to the rates of the other factors such as histology and the criteria for endoscopic resection.

Comment 3

The authors should indicate a flowchart regarding the endoscopic strategy as a Figure based on results obtained from this study.

Response:

In accord with the Reviewer's comment, we have added the flowchart of EUS diagnostic strategy for early gastric cancer, as Figure 3.

Ms.: "What types of early gastric cancer are indicated for endoscopic ultrasonography staging of invasion depth?" by Watari et al.

Reviewer 2 (70109)

Dear Reviewer 2,

Thank you for your comments, which have helped us improve the manuscript. We have addressed the comments as follows. We revised numerous passages throughout the manuscript in addition to those that have been pointed out. The new text and revised text are shown in red font.

Comment 1

"all 9 of the 0-I-type cancers (protruded-type) yielded low-quality EUS images, and thus were judged as inconclusive cases", the reason is just the use of a high-frequency ultrasound probe (20 MHz), if change a probe, what happens? The quality of EUS images will be proved? Or the conclusion will be changed?

Response:

As the Reviewer pointed out, the number of inconclusive cases among the protruded-type (0–I) cancers might have decreased if a low-frequency EUS or probe had been used. As the Reviewer knows, the mucosa is thick in those lesions and the muscularis mucosae elevates toward the mucosa from the submucosa, and thus it may be difficult to make an accurate diagnosis even if low-frequency EUS is performed. Indeed, although we tried to perform EUS using a low-frequency probe (12 MHz) for some protruded-type cancers, the result was the same. Additionally, as the spatial resolution by a low-frequency probe is low, a close examination may be difficult for those lesions. A description of this was added to the Discussion section as follows:

> “If a low-frequency EUS or probe had been used, the number of inconclusive cases among those types of cancers might have been lower. However, in 0–I-type cancer the mucosa is thick and the muscularis mucosae elevates toward the mucosa from the submucosa, and it may thus be difficult to make an accurate diagnosis even if low-frequency EUS is performed.”

Comment 2

"differentiated-type EGCs with a diameter ≤ 3 cm and SM2 invasion or undifferentiated-type EGCs that are determined by CE to meet the expanded-indication criteria for ER", How does the 3cm come from, why not 2 cm or 4 cm?

Response:

Thank you for the helpful advice. In our evaluation of the lesions ≤2 cm in size, two cases (20.0%, 2 of 10) that were misdiagnosed by CE were correctly diagnosed as M/SM1 lesions by EUS. Also, as the number of lesion >3 cm in size was only one, we re-evaluated a total of 14 cases including one lesion >3 cm. Thus, we revised the content of text, and the caption and number of Table 5.

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Reviewer 3 (2954023)

Dear Reviewer 3,

Thank you for your comments, which have helped us improve the manuscript. We have addressed the comments as follows. We revised numerous passages throughout the manuscript in addition to those that have been pointed out. The new text and revised text are shown in red font.

Comment 1

The proposals by authors "EUS should be performed" are overstated, since it would be insufficient to draw described conclusion. Please replace the phrases with a weaker expression (e.g. may be considered performing). (Page 13 line 24, Page 14, line 24)

Response:

We changed the phrases according to the Reviewer's suggestion.

Comment 2

In Fig. 1A, the reviewer could not agree with the diagnosis as SM2 assessed by the single author. Generally, the diagnostic accuracy of CE for tumor depth by experienced endoscopists has a tendency to overestimate tumor depth compared to EUS. Before comparing the diagnostic accuracy in assessing the invasion depth between chromoendoscopy and EUS, interobserver agreement in the endoscopic diagnosis should be assessed. Agreement between the two observers who graded the depth of the invasion should be determined by the κ statistic.

Response:

In accord with the Reviewer's comment, we calculated the κ statistics between the two endoscopists. We added text regarding the κ values for the interobserver agreement in the Results section as follows (page 10):

> "The κ-values for the interobserver agreement for the invasion depth diagnosis between the two endoscopists were 0.78 (95%CI 0.68–0.89) for EUS and 0.82

(95%CI 0.72–0.92) for CE. Thus the interobserver agreement for invasion depth diagnosis by EUS and CE was good to excellent. When the results of the diagnostic accuracy by one endoscopist whose accuracy rate was higher than that of the other endoscopist were used in both modalities, the accuracy rate of EUS was 71.2% (109 of 153 lesions) (Table 3)…"

Comment 3

Undifferentiated carcinomas should be further subdivided into sig or por types. EUS may be technically challenging because the optical control of such a large device for small lesions, especially signet-ring cell carcinomas, is not always feasible.

Response:

As the Reviewer mentioned, the biological behavior is actually different between signet-ring cell carcinoma (sig) and poorly differentiated-type adenocarcinoma (por) with/without sig cells. Thus, it is significant to subdivide the carcinomas into histologically sig or por types. However, we had to perform EUS with a thin probe (20 MHz) for all of the undifferentiated-type cancers under direct vision but not with a thick conventional EUS scope, even for small signet-ring cell carcinomas, in accord with the protocol of the Japan Clinical Oncology Group (JCOG) because our department belongs to the JCOG.

Comment 4

To help readers' better understanding, please consider explaining the advantages of EUS compared to NBI magnification for the diagnosis of EGC in "Discussion" or "Introduction" section.

Response:

We added the following sentences in the Discussion section (page 14):

"It has been reported that magnifying endoscopy with narrow-band imaging (ME-NBI) is useful for determining the invasion depth diagnosis of EGC [29,30]; however the diagnostic criteria for SM2 are complex [29] and the diagnostic specificity of ME-NBI may be relatively low [30]."

Comment 5

To draw described conclusion, differentiated-type cancers ≤ 2 cm in size should be analyzed in addition to differentiated-type cancers ≤ 3 cm in size.

Response:

When evaluating the lesions ≤2 cm in size, two cases (20.0%, 2 of 10) that were misdiagnosed by CE were correctly diagnosed as M/SM1 lesions by EUS. This is similar to a comment raised by Reviewer 1 (#70109). In accord with the comments by Reviewers 1 and 3, we revised the results and some descriptions throughout the text.

Comment 6

"152 EGCs" should be corrected to "153 EGCs" (Page 6, line 19).

Response:

We revised this on page 6.

Comment 7

Magnification should be written in figure legends (Fig. 1C and Fig. 2C). In addition, "H&E" should be written.

Response:

We added the term "H&E" and magnification to the legends of Figs. 1 and 2.

Comment 8

Please change "Histology" to "Surgical specimen histology" or something (Page 29, Figure 2C legend).

Response:

We changed the term "Histology" to "Surgical specimen histology" in Figure 2.