

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **6740-review.docx**).

Title: Endoscopic submucosal dissection for undifferentiated-type early gastric cancer:

Do we have enough data to support this?

Author: Choong Nam Shim, Sang Kil Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6740

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

(1) Referee: 1

Comments to Authors

Excellent review on endoscopic submucosal dissection

Response:

Thank you for your favorable criticism concerning our manuscript. The present study reviewed the safety and therapeutic efficacy of endoscopic submucosal dissection (ESD) for undifferentiated early gastric cancer (UD-EGC) with reference to risks for lymph node (LN) metastasis within the proposed criteria as well as the short-term and long-term outcomes of ESD for UD-EGC. Moreover, we addressed the limitations of current diagnostic modalities for defining the appropriate lesions to obtain the curability after ESD. We hope that our review article can expound on the fine prospects of ESD for UD-EGC. We appreciate your comments.

(2) Referee: 2

Comments to Authors

Dear authors, thank you very much for this interesting manuscript. This is an important issue for all endoscopists performing ESD. I am convinced that if the manuscript would be shortened, including the very long list of references, it would be more easy to read. Also, e.g. on page 4, you have mentioned that the role of ESU is mainly to differentiate between mucosal and submucosal lesions. I would not support this comment. In daily practice, EUS is mainly used to rule out deep wall invasion or at least proper muscle layer invasion. Because after that, ESD can be carried out without a high risk of perforation. The role of EUS is primarily to rule out LN metastasis. Please change the text accordingly or at least discuss.

Response:

We would like to thank the reviewer for raising this point, as this is an important one.

As you mentioned above, endoscopic ultrasound is an important imaging modality for preoperative assessment to exclude LN metastasis as well as to confirm deeper wall invasion including the proper muscle layer. Therefore, we revised the role of EUS in ESD for EGC, as you recommended.

(3) Referee: 3

Comments to Authors

I would like to ask you that you should add the references about NBI findings on esrly poorly adenocarcinoma. It is important factor recently to diagnose accuracy.

Response:

We would like to appreciate your comments. We fully agree with your comments, since the magnifying endoscopy with narrow-band imaging (ME-NBI) is a supporting tool to enhance the diagnostic accuracy through more precise determination of tumor margin and depth of invasion in EGC. As you mentioned, we revised the role of ME-NBI, particularly during ESD for UD-EGC and added the references on ME-NBI findings of UD-EGC.

(4) Referee: 4

Comments to Authors

This review by Shim et al summarizes the current clinical routine and state of research regarding the endoscopic resection of undifferentiated early gastric cancers. In sum, this is a comprehensive and important review about the different approaches to treat UD-EGC.

The review is mostly clearly written and the figures nicely summarize the literature and current knowledge.

I have only a few minor comments that should be considered: Page 6, lower paragraph: "Concerning lesion, add: Concerning lesion size, The Section "Risk factors for LN metastasis and proposed criteria for ESD" : Please consider subheadings in this paragraph, as this will enable the reader to clearly understand the different points: e.g. i) Lesion size, ii) invasion, iii) ulceration, iv) lymphovascular invasion

Response:

Thank you for your comments. We fully agree with your comments, and therefore, we revised and added the subheadings in the RISK FACTORS FOR LN METASTASIS AND PROPOSED CRITERIA FOR ESD section, as you recommended.

p7: "Ulceration within the lesion is the representative index regarding heterogeneity in definition. More than moderate heterogeneity was identified at previous meta-analysis" I do not understand these two sentences. This should be re-formulated. Do the authors mean that ulcerations appear heterogeneously and are therefore often misjudged by the observer?

Response:

We would like to appreciate your comments. As you mentioned above, ulceration in EGC revealed more than heterogeneity in terms of different definitions in addition to the

interobserver variability for the assessment of ulcerations through meta-analysis^[1] and other several earlier studies^[2-5]. Thus, we clarified the meaning of heterogeneity in ulceration in EGC, as you recommended.

The authors should mention and discuss the current recommendations for endoscopically resected UD-EGC where lymphovascular invasion has been detected histologically. Surgical resection? Second endoscopic resection, or surveillance? What time interval if surveillance?

Response:

We would like to thank the reviewer for raising this point, as this is an important one. Since the lymphovascular invasion is the most critical finding predictive of LN metastasis in EGCs treated by ESD, EGCs with lymphovascular invasion in endoscopically resected specimen should be treated by further surgery according to numerous previous studies and the Japanese gastric cancer treatment guidelines. As you recommended, we further mentioned this point on the section of lymphovascular invasion.

The authors should briefly mention the recommended surveillance/observation follow-up after successful resection of UD-EGC, is there a difference to well differentiated early gastric cancers?

Response:

We appreciate your comments. Although the clinical importance of scheduled endoscopic

surveillance after curative resection are recently evaluated through large-volume multicenter study^[6], there is no evidence-based consensus for the endoscopic surveillance follow-up. Thus, further studies on surveillance follow-up after curative ESD for UD-EGC, compared with curative cases in differentiated EGC, are warranted. We discussed this area in the LONG-TERM OUTCOMES section, as you recommended.

The authors should also discuss the clinical decision making (endoscopy versus surgery) regarding patient age and co-morbidities. Are there data comparing quality of life and complication rates between endoscopy and surgery. Along these lines, is there any evidence that younger patients or even sex determines the invasiveness of early gastric cancer. Interestingly, table 3 shows the highest rate of SM invasion and ulcers in relatively young patients (56.7 years). Should younger patients therefore receive a more aggressive treatment approach?

Response:

We would like to appreciate your comments. As you mentioned above, the decision of treatment strategy for EGC (ESD *vs.* surgery) regarding patients' age and co-morbidities is an important issue in the management of patients with EGC. In addition, the data comparing the quality of life and complication rates between endoscopic resection and surgery can provide the clinical support for therapeutic decision making. However, these are not under the focused area of this review article. We tried to deal with the arguments in the ESD for UD-EGC with reference to the therapeutic efficacy and safety based on the short-term and long-term outcomes of ESD for UD-EGC.

Is there a reason why table 2 does not include European papers that are cited in the reference section otherwise (e.g. ref 20 and 21)? The references need corrections, e.g. author names (see ref 1), some include PMID numbers, or PMID numbers and DOI, others neither of them.

Response:

We appreciate your comments. Although the studies conducted in Europe are excellent, these did not focus on the feasibility of ESD for UD-EGC in particular. Therefore, we could not include the European data for analysis, because these included heterogeneous compositions including differentiated EGC, UD-EGC, and adenoma as well as the small number of enrolled UD-EGCs. In addition, we corrected the errors of references, as you recommended.

3 References and typesetting were corrected

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

Sincerely yours,

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- 4 Lee HL, Choi CH, Cheung DY. Do we have enough evidence for expanding the indications of ESD for EGC? *World J Gastroenterol* 2011; **17**: 2597-2601 [PMID:21677826 DOI:10.3748/wjg.v17.i21.2597]
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- 6 Kato M, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62**: 1425-1432 [PMID:22914298 DOI:10.1136/gutjnl-2011-301647]