

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79484

Title: Diagnostic evaluation of endoscopic ultrasonography with submucosal saline injection for differentiating between T1a and T1b early gastric cancer

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00503563

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Staff Physician

Reviewer's Country/Territory: Japan

Author's Country/Territory: South Korea

Manuscript submission date: 2022-08-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-08-24 04:50

Reviewer performed review: 2022-08-26 05:20

Review time: 2 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The authors demonstrated the clinical utility of endoscopic ultrasonography with submucosal saline injection (EUS-SSI) for discriminating T1a and T1b in patients with early gastric cancer (EGC). Although this study has the clinical importance, there are several comments. Comments 1. In the present study, 24 patients with EGC who underwent EUS during March-April 2019 were enrolled. Why did the authors select these patients? If patients who have undergone EUS from 2019 to 2022 are enrolled, this study may be conducted by a large sample size. 2. This was a clinical study conducted at a single institution, and the sample size was small. These findings indicate limitations of the present study. Consequently, these findings should be shown in the manuscript. 3. The presence or absence of ulcerative findings (UL) may have an impact on the clinical utility of EUS-SSI. UL should be indicated in Table 1. How do the authors discuss about this suggestion? 4. According to Table 3, the rate of overstaging in EUS alone and EUS-SSI was 4.2% and 20.8%, respectively. These results show the high rate of overstaging in EUS-SSI. The authors should discuss about these results.

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Title: Diagnostic evaluation of endoscopic ultrasonography with submucosal saline injection for differentiating between T1a and T1b early gastric cancer

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06074316

Position: Peer Reviewer

Academic degree: MD

Professional title: Medical Assistant

Reviewer's Country/Territory: Brazil

Author's Country/Territory: South Korea

Manuscript submission date: 2022-08-24

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-08-24 13:48

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Review time: 2 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This is an interesting paper about the use of submucosal injection to improve endoscopic ultrasonography (EUS) in the differentiation between T1a and T1b early gastric cancer. This innovative technique could improve the current way it is done. Twenty-three patients underwent EUS during this case series, with an improvement in accuracy rates (37,5 to 75%). As an initial study, the authors suggest that more extensive and randomized studies must be done to confirm the hypothesis, but the results are promising. The writing is concise and clear, and the text is organized. I have the following comments: 1. In previous studies, higher rates of accuracy were found. Does just the beginners' endoscopist explain this finding? Were they under supervision of a senior? 2. A higher procedure time was cited in the discussion. Was it measured? How long does the procedure take?

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Title: Diagnostic evaluation of endoscopic ultrasonography with submucosal saline injection for differentiating between T1a and T1b early gastric cancer

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06285350

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: South Korea

Manuscript submission date: 2022-08-24

Reviewer chosen by: AI Technique

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Review time: 3 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Diagnostic evaluation of endoscopic ultrasonography with and without submucosal saline injection for differentiating between T1a and T1b early gastric cancer Even though pre-evaluation using EUS is not recommended for the management of superficial gastric tumors (Endoscopy. doi:10.1055/a-1811-7025), this method will be beneficial if the submucosal saline injection clarifies the submucosal tumor invasion. However, there are many critical problems in this article, as bellows. Major comments: #1 Please state the aim and outcome of this study in the method section with a heading. Major comments: #2 About the following sentence, "Subsequently, they underwent endoscopic or surgical resection within 7 days". Why did you carry out EUS just before ESD? Is there a risk of submucosal fibrosis caused by submucosal saline injection? It seems like this study is in a retrospective fashion (recruitment in 2019, approval number SGPAIK"2021"-10-019). The results of EUS-SSI did not influence on treatment (Case 6, 7, 23, 24). Should be clarified. Also treatment flow and decision making flow for your institute should be shown. Major comments: #3 About the following sentence, "All recruited patients agreed to be enrolled in this clinical trial patients and provided informed consent." Please revise this manuscript under a native speaker of English. Also, should be thoroughly checked again for abbreviations including table and figure legends. Major comments: #4 About the following sentence, "...by one endoscopist with only 6 months' experience with EUS." Was this study conducted by only a 'trainee'? Please disclose those data under an 'expert'. In addition, please show the concordance rate between both endoscopists. Major comments: #5 About the following sentence, "The puncture points were located 0.5 cm beyond the edge of the lesion, and saline injection

was stopped once the gastric mucosa had been elevated by approximately 1 cm.” With this injection around the lesion, is it impossible to inject the submucosal saline under the SM invasion at the central site appropriately, especially for a widely spread or fibrotic lesion? How did you measure this 1 cm mucosal elevation? Major comments: #6 In the result, the author should exclude the patient with T2 cancer before analysis. Please describe the inclusion/exclusion criteria in the method session. “endoscopically diagnosed EGC lesions” is unclear. Does this mean EGC diagnosed by white light or combined with NBI (and magnifying)? Were there any cases of endoscopically diagnosed T2 or more lesions turned out to be T1 by surgical exploration? Please draw the flow chart of the included patients. Major comments: #7 In the third paragraph in the result session. The EUS feature with and without SM invasion should be defined in the methods session. Major comments: #8 All EUS figures are poor. What do those markers indicate? Please explain them in the figure legends. Please magnify them and indicate the first, second, third, fourth, and injected saline layers with arrowheads for readers. Figures should be composed of endoscopic, EUS, and pathological images. Major comments: #9 To my knowledge, maximum Hz available for UE-260 is 12MHz. Is 20MHz correct? Also, I do not know any injection needle applicable for UE-260 (with instrumental channel 2.2mm). What did the authors use? Or did they used other scopes prior to EUS for injection? Major comments: #10 Usually, the problem with EUS for diagnosing tumor depth is underdiagnosing due to the difficulty of visualizing the pin-pointed (may be larger in cases) SM invasion (T1b) of tumor. Why are there so many cases of overdiagnosis (33.3%). Should be discussed or noted in limitation. Minor comments: #1 About the disclosure of the equipment. Please add the city and country. Minor comments: #2 Introduction “with metastasis” not necessary in the 1st sentence. Minor comments: #3 SM1 refers to submucosal invasion to <500 μ m Minor comments: #4 SM3 should be defined.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79484

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00503563

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Staff Physician

Reviewer's Country/Territory: Japan

Author's Country/Territory: South Korea

Manuscript submission date: 2022-08-24

Reviewer chosen by: Ji-Hong Liu

Reviewer accepted review: 2022-09-24 01:03

Reviewer performed review: 2022-09-24 01:13

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors sufficiently responded to the reviewer's comments. The paper seems to be ready to be accepted.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: South Korea

Manuscript submission date: 2022-08-24

Reviewer chosen by: Ji-Hong Liu

Reviewer accepted review: 2022-09-24 07:14

Reviewer performed review: 2022-10-11 00:52

Review time: 16 Days and 17 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

ESD has a bilateral character, including a minimally invasive therapy to maintain gastric function and a maximally accurate approach for investigating T-1 stage. Therefore, ESD is carried out unless there is a contraindication of massive invasion: rupturing of the SM layer. However, EUS scanning of the stomach layer invasion is very difficult even for the expert because of the bursiform stomach shape, tumor location, infiltrative growth, air bubble interference, and muscle shrinking effect. This paper's result is only by trainee hands. So, the author should disclose the result of the interobserver agreement (trainee vs. supervisor) with kappa coefficient. With your data, the diagnostic yields of EUS-SSI for SM invasion (T1b) are as follows: Sn=60%, Sp=92.3%, PPV=85.7%, NPV=75%, and AC=78.2%. I never perform this EUS-SSI with this low sensitivity. I definitely chose ESD unless contraindication under endoscopic findings. Major comments: #1 Please state the aim and outcome of this study in the method section with a heading. -> We do not think it is appropriate to include the aim and outcome of this study in a method session. The aim of the study was revealed in the introduction session and the outcome was shown in the results session. > OK. Please refer to the author's guidelines. Major comments: #2 About the following sentence, "Subsequently, they underwent endoscopic or surgical resection within 7 days". Why did you carry out EUS just before ESD? Is there a risk of submucosal fibrosis caused by submucosal saline injection? It seems like this study is in a retrospective fashion (recruitment in 2019, approval number SGPAIK"2021"-10-019). The results of EUS-SSI did not influence on treatment (Case 6, 7, 23, 24). Should be clarified. Also, treatment flow and decision making flow for your institute should be shown. -> Our hospital conducts EUS before deciding how to treat stomach cancer. EUS was performed during the diagnosis process, and surgery or ESD is

usually performed within one week of diagnosis. Submucosal fibrosis due to submucosal saline injection was not identified as the final pathological finding in all patients. > OK. I understand it. In this study, the results of EUS-SSI were not directly applied in the treatment method decision. It was just a study to compare diagnostic accuracy of EUS and EUS-SSI. I think that more research is needed to apply the results of EUS-SSI to clinical practice. > Did the 24 patients be recruited consecutively? > The aim of this paper is to investigate the effectiveness of EUS-SSI. Why didn't the author disclose accuracy, sensitivity, specificity, NPV, and PPV? With your data (table 1,2), the diagnostic yields of EUS-SSI for SM invasion (T1b) are as follows: Sn=60%(6/10), Sp=92.3%(12/13), PPV=85.7%(6/7), NPV=75%(12/16), and AC=78.3%(18/23). Those of EUS-only are follows: Sn=30%(3/7), Sp=46.2%(6/13), PPV=30.0%(3/10), NPV=46.2%(6/13), and AC=39.1%(9/23). I never perform this EUS-SSI because the sensitivity is 60%. By the way, why are there only 22 cases in "EUS only" group in Table 2.? > As the author described in the introduction, assessing SM1 or SM2 is critical for decision-making: ESD or surgery. The cutoff point of T1a/T1b is not so crucial for decision-making. Although this study aim was to "confirm whether SSI could be a method to improve the accuracy of EUS in distinguishing T1a and T1b lesions", it should be refocused on distinguishing T1b1 (SM1) and T1b2 (SM2). > In addition, the number of T1b (EUS only Dx)-T1b (pathological Dx) should be 4, not 3. Please confirm the data analysis with your supervisor. > What is the terminology of accuracy? For example, in table 2, the accuracy of EUS-SSI for SM invasion is calculated as follows: $(12+6)/23 \times 100 = 78.3\%$. > Treatment /decision making flow for your institute should be shown. Major comments: #3 About the following sentence, "All recruited patients agreed to be enrolled in this clinical trial patients and provided informed consent." Please revise this manuscript under a native speaker of English. Also, should be thoroughly checked again for abbreviations including table and figure legends. -> We

re-examined these parts and made appropriate corrections. Modified parts are marked in bold. > OK. I understand it. Major comments: #4 About the following sentence, "...by one endoscopist with only 6 months' experience with EUS." Was this study conducted by only a 'trainee'? Please disclose those data under an 'expert'. In addition, please show the concordance rate between both endoscopists. -> This study was conducted only by beginners who had been in EUS for 6 months. > EUS scanning of the stomach layer invasion is very difficult even for the expert because of the bursiform stomach shape, tumor location, infiltrative growth, air bubble interference, and muscle shrinking effect. This paper's result is only by trainee hands. So, the author should disclose the result of the interobserver agreement (trainee vs. supervisor) with kappa coefficient. Major comments: #5 About the following sentence, "The puncture points were located 0.5 cm beyond the edge of the lesion, and saline injection was stopped once the gastric mucosa had been elevated by approximately 1 cm." With this injection around the lesion, is it impossible to inject the submucosal saline under the SM invasion at the central site appropriately, especially for a widely spread or fibrotic lesion? How did you measure this 1 cm mucosal elevation? -> We did not inject the needle directly at the center site of the the lesion because we were concerned about tumor spreading by the needle. We injected saline so that it swells by about 1 cm compared to the surrounding mucosa visually, and this was confirmed through EUS. > It is impossible to lift the central lesion enough when in a widely spread lesion. The author should discuss this point as limitation. Major comments: #6 In the result, the author should exclude the patient with T2 cancer before analysis. Please describe the inclusion/exclusion criteria in the method session. "endoscopically diagnosed EGC lesions" is unclear. Does this mean EGC diagnosed by white light or combined with NBI (and magnifying)? Were there any cases of endoscopically diagnosed T2 or more lesions turned out to be T1 by surgical exploration? Please draw the flow chart of the included patients. -> The patients

enrolled in this study were "EGC diagnosed by endoscopic gross findings". EUS findings are not included in the criteria for selecting or excluding patients. The macroscopic findings of the endoscopy were judged in combination with the NBI image. Patients diagnosed with gastric cancer with T2 or higher endoscopically were not included in this study. > Treatment /decision making flow for your institute should be shown. > If "EGC diagnosed by endoscopic gross findings" were enrolled, Case 18 (T2 case9 should be enrolled in calculating and else, nevertheless it may lower each variable. Major comments: #7 In the third paragraph in the result session. The EUS feature with and without SM invasion should be defined in the methods session. -> We added this to the method session. >Well-described. Major comments: #8 All EUS figures are poor. What do those markers indicate? Please explain them in the figure legends. Please magnify them and indicate the first, second, third, fourth, and injected saline layers with arrowheads for readers. Figures should be composed of endoscopic, EUS, and pathological images. -> As pointed out, markers are indicated by arrows in the figure. We thought that the pathologic findings were in agreement with the EUS findings, so it was not meaningful to include a pathological images. > I can not find the revised figure because the revised figure is not attached. > Comparison of EUS vs. pathology is critical. The author should show the representative pairs. Major comments: #9 To my knowledge, maximum Hz available for UE-260 is 12MHz. Is 20MHz correct? Also, I do not know any injection needle applicable for UE-260 (with instrumental channel 2.2mm). What did the authors use? Or did they used other scopes prior to EUS for injection? -> You are right. We fixed it to 12 MHz. Saline injection was performed through a gastroscope (Olympus GIF-HQ290 Endoscopic System, Olympus Co. Tokyo. Japan). >Well-responded. Major comments: #10 Usually, the problem with EUS for diagnosing tumor depth is underdiagnosing due to the difficulty of visualizing the pin-pointed (may be larger in cases) SM invasion (T1b) of tumor. Why are there so many



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cases of overdiagnosis (33.3%). Should be discussed or noted in limitation. -> This study was conducted by a endoscopist with only 6 months experience with EUS. Therefore, it is considered that there is a difference between the results of the examination by an experienced inspector. This study is not to investigate the accuracy of EUS EGC diagnosis, but to compare the diagnostic accuracy of EUS and EUS-SSI for EGC. > The author should disclose the result of the interobserver agreement (trainee vs. supervisor) with kappa coefficient. > What in the world do you think is the clinical impact of a EUS study performed by only trainee? None. At least the result of expert (in your institute) is necessary. Minor comments: #1 About the disclosure of the equipment. Please add the city and country. -> Yes, we added this. >Well-responded. Minor comments: #2 Introduction "with metastasis" not necessary in the 1st sentence. -> We deleted this. >Well-responded. Minor comments: #3 SM1 refers to submucosal invasion to $<500\ \mu\text{m}$ -> We corrected this part as pointed out. >Well-responded. Minor comments: #4 SM3 should be defined. -> It seems unnatural to mention the definition of SM3 in terms of the flow of content. SM3 was defined as an invasion depth of $\geq 1,000\ \mu\text{m}$ SI lowered the rate of overstaging. >Well-responded.