

## ANSWERING REVIEWERS



February 5, 2022

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 74256\_Auto\_Edited.docx).

**Title:** Clinical outcomes of endoscopic resection of sporadic, nonampullary, duodenal neoplasms: a 10-year retrospective, single-center study

**Author:** Joon Hyun Cho, Ki Young Lim, Eun Jung Lee, Si Hyung Lee

**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**ESPS Manuscript NO:** 74256

Thank you very much for your kind comments.

We tried to revise the manuscript as much as possible according to the suggestions made by the reviewers and the Editorial Office's comments and suggestions, and enclosed revision detail and revised manuscript.

We hope all these revisions will be satisfactory.

The manuscript has been improved according to the suggestions of reviewers and the Editorial Office's comments and suggestions:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

### Answers to Reviewer No. 05155415

(highlighted by yellow and sky blue colors in the updated version of the manuscript)

The authors demonstrated the safety and efficacy of EMR including piecemeal resection, for superficial duodenal neoplasms. I would like to express my opinion after carefully pursuing this report.

1. The long-term efficacy of EMR for superficial duodenal neoplasms has already been shown (Nonaka S, et al. *Endoscopy* 2015; 47: 129-135), and there is little novelty in this study. It is preferable to indicate the hemostasis method performed for EMR-related intraoperative bleeding and to add detailed management methods in the discussion column.

Answer) Thanks for your delicate remarks. As your comment, we indicated the hemostasis method performed for EMR-related intraoperative bleeding in the "EMR and complications" part of the RESULTS section (at the top of the page 9 of the revised manuscript) and added management methods in the DISCUSSION section. (at the bottom of the page 13 of the revised manuscript). However, there is no standardized definition of intraprocedural bleeding, it is hard to know whether the reported bleeding cases in various studies were clinically significant or not, therefore, the discussion for the management of intraprocedural bleeding during duodenal EMR was so difficult.

2. Recently, the usefulness of underwater EMR for superficial duodenal neoplasms has been reported, if duodenal EMR which requires difficult submucosal injection is to be the first choice, its advantages over UEMR should be described in the discussion column.

Answer) Thank you very much for your important comment. As your comment, conventional EMR technique is sometimes difficult to obtain successful results due to insufficient lifting after the submucosal injection. We mentioned this and added the results of a study comparing UEMR and EMR in the DISCUSSION section. (at the page 11-12 of the revised manuscript)

3. The thin muscular layer of the duodenum can be perforated by hemostasis procedure, and intraoperative bleeding is considered an undesirable complication. Rate of intraoperative bleeding in this study was higher than previously reported in UEMR (Clin Gastroenterol Hepatol. 2021; S1542-3565(21)00707-2.), and the management of intraoperative bleeding should be discussed.

Answer) Thank you very much for your detailed insight.

In the study you presented, intraoperative bleeding was defined as spurting bleeding. Reported rates of bleeding during or after endoscopic resection of duodenal tumors vary because of the different definitions of bleeding used in different studies, therefore, it is very difficult to compare research results in terms of intraprocedural bleeding. We described this with your comment in the DISCUSSION section. (at the bottom of the page 13 of the revised manuscript)

4. It is likely that adjunctive coagulation was performed in some cases of En bloc resection. However, it is confusing to consider the cases with adjunctive coagulation and without adjunctive coagulation as the same En bloc resection group. The criteria for adjuvant coagulation should be clarified, or cases of En bloc resection with adjuvant coagulation should be treated as a separate group.

Answer) Thank you very much for your attentive point.

We reviewed the data again and found that the adjunctive coagulation was performed in 10 lesions out of 39 lesions with en bloc resection and in all of 19 lesions with piecemeal resection. Although performing the adjunctive coagulation may affect relapse, no further analysis was necessary because there were no relapse cases in this study. All 3 lesions of incomplete resection with a positive lateral margin were the lesions in which the adjunctive coagulation was performed. We have added this in the "EMR and complications" part (at the bottom of the page 8 of the revised manuscript) and "Long-term outcomes" part (at the top of the page 10 of the revised manuscript) of the RESULTS section.

5. Analysis of risk factors for EMR-related bleeding should be performed by dividing intraoperative and delayed bleeding. In addition, the multivariate analysis in this study requires about 70 cases of EMR-related bleeding. It is inappropriate to analyze the results of multivariate analysis in this study.

Answer) We very much agree with your point.

As your comments, EMR-related bleeding should be analyzed separately for intraprocedural bleeding and delayed bleeding. However, in this study, there was only one case of delayed bleeding among all 17 cases of EMR-related bleeding, and there were some reports that analyzed without separating these two groups. (Tomizawa Y, Ginsberg GG. Clinical outcome of EMR of sporadic, nonampullary, duodenal adenomas: a 10-year retrospective. *Gastrointest Endosc* 2018; 87: 1270-1278 [PMID: 29317270 DOI: 10.1016/j.gie.2017.12.026])

If you have any additional comments about this, we will gladly revise the paper accordingly.

Answer) The results of multivariate analysis were interpreted very carefully under statistical consulting. However, your concerns are very appropriate. As you pointed out, we deleted the results of multivariate analysis and added the reason why multivariate analysis was not possible in the DISCUSSION section. (at the top of the page 14 of the revised manuscript) (highlighted by sky blue)

6. The number of EMR-related bleeding cases in Table 4 does not match the number of cases per size (19 cases).

Answer) I am very sorry for making you confuse. We corrected the mistake in the data summary thanks for your comments.

#### Answers to Reviewer No. 00188995

(highlighted by green and sky blue colors in the updated version of the manuscript)

The authors report clinical outcomes of endoscopic resection of sporadic, nonampullary, duodenal neoplasms by performing a retrospective study. The paper is well written.

1. Similar studies have been reported earlier as well. In fact, a study from USA reported on more than 150 cases of duodenal EMR (Gastrointestinal Endoscopy 2018 May;87(5):1270-1278). The current study has only 56 patients and hence the novelty of data is limited.

We really appreciate your valuable comment. We have tried to describe as much as possible what you have pointed out.

2. How was the depth of lesion determined? Was it based on NBI findings or EUS? Did the patients also have cross sectional imaging of abdomen like CT scan, etc.

Answer) Although some researchers advocate the use of EUS in the evaluation of the depth of duodenal polyps larger than 20 mm (Al-Kawas FH. The significance and management of nonampullary duodenal polyps. Gastroenterol Hepatol (N Y) 2011; 7: 329-332 [PMID: 21857835]), there is very little information regarding the use of EUS and ME-NBI for the evaluation of invasion depth of superficial nonampullary duodenal epithelial tumors (SNADETs) before endoscopic resection. The patients included in this study were the cases that endoscopic resections were attempted because it was judged not to be invasive mainly based on the results of biopsy and high-definition WLE. NBI was used only in order to allow better delineation of the margins of the lesion in the initial evaluation of SNADETs, potentially reducing incomplete resection rates. CT scan was not performed routinely before endoscopic resection, but CT scan was performed when the biopsy diagnosis was HGD or CIS.

3. How was the findings on NBI interpreted to assess depth of the lesion and do the authors have any reference for this?

Answer) Due to the limitations of the retrospective study, it is very difficult to know how the NBI findings were interpreted, but it did not play a role in judging the depth of the lesion and NBI was used only in order to allow better delineation of the margins of the lesion in the initial evaluation of SNADET.

(Kikuchi D, Hoteya S, Iizuka T, Kimura R, Kaise M. Diagnostic algorithm of magnifying endoscopy with narrow band imaging for superficial non-ampullary duodenal epithelial tumors. Dig Endosc 2014; 26 Suppl 2: 16-22 [PMID: 24750143 DOI: 10.1111/den.12282])

4. Please describe the lesion morphology based on Paris classification.

Answer) As your comment, we modified the lesion morphology based on Paris classification.

5. In Table 5, the authors have presented the data for multivariate analysis. However, with only 17 outcome events (bleed), it may not be appropriate to do a multivariate analysis using five predictors and the result has to be interpreted with caution.

Answer) Other reviewer had also pointed out the multivariate analysis. The results of multivariate analysis were interpreted very carefully under statistical consulting. However, your concerns are very

appropriate. As you pointed out, we deleted the results of multivariate analysis and added the reason why multivariate analysis was not possible in the DISCUSSION section. (at the top of the page 14 of the revised manuscript) (highlighted by sky blue)

6. The median follow up was 23 months only and negative lateral margin was noted in 62.1% patients. A longer follow up may be needed to be certain of the low risk of recurrence. What was the follow up duration in patients with inconclusive or positive margin?

Answer) Thank you for the very important and so intellectual comment.

We reviewed and analyzed our data again, and found that all 22 patients (22 lesions) with the histopathologic results of inconclusive or positive resection margin were followed for more than 6 months (median follow-up duration 28 months; range 12 - 101 months). What you pointed out was described in the "Long-term outcomes" part of the RESULTS section. (at the bottom of the page 9 of the revised manuscript)

7. Please provide a table categorizing patients based on the number of follow up endoscopies done.

Answer) We reviewed and analyzed our data again, and as your good comment, described the number of follow-up endoscopies at "Table 6 Long-term outcomes"

8. Did the patients undergo colonoscopy to screen for colonic adenomas?

Answer) Thank you for the important comment.

We reviewed and analyzed our data again, and found that colonoscopy was performed for screen for colonic adenomas in 69.6% of our patients with SNADETs, and colorectal adenomas were found in 46.2% of the cases with SNADETs that underwent colonoscopy. We described this in the "Patient characteristics" part of the RESULTS section and added this in the Table 1.

9. 10 patients had pedunculated lesion - EMR is generally done for sessile lesions? Why did the authors consider removal of these lesions using EMR as they are managed with snare polypectomy?

Answer) Thank you for the important comment. We reviewed and analyzed our endoscopic picture again, and found that 9 patients had a very short peduncles. Our general approach is that pedunculated lesions and sessile lesions >1.0 cm in diameter were treated with an attempt at submucosal injection-assisted EMR.

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

Sincerely yours,

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