

April 21, 2023

Andrzej S Tarnawski
Editor-in-Chief
World Journal of Gastroenterology

Dear Dr Tarnawski,

I wish to submit the revised version of our original article, titled “Hot snare polypectomy versus endoscopic mucosal resection using bipolar snare for intermediate size colorectal lesions: propensity score matching,” for publication in *World Journal of Gastroenterology*.

The insightful comments of the reviewer have been helpful for our revision process. We provide here point-by-point responses to the questions raised by the associate reviewer. We appreciate your willingness to review the revised manuscript and look forward to working with you and the reviewer to move this manuscript closer to publication in the *World Journal of Gastroenterology*.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewer #1:

Specific Comments to Authors: This is a single center retrospective study using propensity score matching method to compare the treatment outcomes of bipolar polypectomy with hot snare polypectomy (HSP) to those with endoscopic mucosal resection (EMR). Author concluded that Using bipolar snare, ER of nonpedunculated 10–15 mm colorectal lesions may be performed safely and effectively, even without submucosal injection. I have some comments.

RESPONSE: We wish to express our appreciation to the reviewer for these insightful comments, which have helped us significantly improve the paper.

Major Comments 1. I think it's very hard to show the equality between two groups in those small sample size. This is limitation of this study. Please show your results with 95% CI. And if you prove inferiority, how many cases would be needed or what rate would be appropriate in this sample size? And please show this is limitation of this study.

RESPONSE: Thank you for your suggestion. We have added the results with 95% CI to Tables 2 and 3. The sample sizes required to prove non-inferiority for each outcome were calculated by the statistician and are shown below: 704 cases for en bloc resection rate, 1556 cases for R0 resection rate, 460 cases for delayed bleeding rate, and 2206 cases for perforation rate. In this study, the sample size was not large enough to prove non-inferiority for any of the outcomes, and this has been added to the Discussion section as a limitation.

2. How did investors select HSP or EMR? Investors selected treatment methods with indication of themselves. Could the indication of those two methods be different? And those factors included in propensity matching variables? It could be another limitation of this study.

RESPONSE: We appreciate the reviewer's comment on this point. As stated in the Materials and Methods section, the treatment choice (HSP or EMR) was at the

endoscopist's discretion for a lesion with a preoperative diagnosis of JNET Type 2A. Therefore, the skill of a specific endoscopist or any confounding characteristics of the lesion may have affected the outcomes. We have already been mentioned this limitation in the Discussion section. Since there was no difference in the indication criteria between EMR and HSP, it was not a variable in propensity score matching.

3. Please show the detailed diagnostic performance of JNET type 2A especially in difference between non-expert and expert. Is there no potential of including T1 cancers? How do you think about HSP for T1 cancers? And also, those diagnostic methods can become standard or generalized in the world because HSP would be allowed for patients with type 2A?

RESPONSE: The original cohort included only 1 (0.2%) T1 cancer in the HSP group and 2 (1.6%) in the EMR group, while the PSM cohort included no T1 cancer. In other words, most of the lesions analyzed in this study were LGD/HGD, indicating that the diagnostic performance of JNET Type 2A was good regardless of non-expert or expert status. With regard to HSP for T1 cancer, we cannot draw any conclusions because of the very small number of cases in this study. Therefore, we suggest that HSP for lesions 10-15 mm in size is currently indicated for intramucosal lesions and that the finding of JNET Type 2A is a useful diagnostic criterion for adopting HSP.

4. Standardized difference of histological findings is over 0.1. Please mention it and show the influence of it.

RESPONSE: We hypothesize that the standardized difference of histological findings exceeded 0.1, which was influenced by only 3 cases of SSL being in the HSP group. Although SSL has been reported to have a higher rate of positive margins compared to LGD/HGD,¹ we think that only 3 cases of SSL had minimal impact on the treatment outcomes in this study.

1. Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (care) study. *Gastroenterology* 2013; **144**: 74-80.e1.

5. I didn't understand the meanings of 'RX/R1 resection were classified as HMX/VM0 in results section. Please explain more detail. You mean there were no patients with VM1 or VMx?

RESPONSE: We agree with your comment. All RX/R1 resected cases in this study were classified as HMX/HM1, and there were no patients with VMX/VM1. We have revised the en bloc and R0 resection rates in the Results section to clarify the meaning.

6. Recently, no electrical resection like cold polypectomy was known reducing the post-polypectomy bleeding. But you mentioned HSP with bipolar reduces bleeding. Please explain the mechanism of those.

RESPONSE: The detailed mechanism by which endoscopic resection with bipolar snare reduces delayed bleeding is not still unclear. Our speculation is that electrical resection using the coagulation mode may be related to the lower rate of delayed bleeding with bipolar resection in this study compared to monopolar resection in the previous reports.

7. EMR is high potential of perforation compare to HSP?

RESPONSE: As pointed out, one case of perforation was observed in the EMR group, but since it was a small cohort of cases, it is difficult to conclude that the EMR technique has a higher risk of perforation compared to HSP.

Reviewer #2:

Specific Comments to Authors: Dear Editor, Dear Author, I read with interest the manuscript entitled "Hot snare polypectomy versus endoscopic mucosal resection using bipolar snare for intermediate size colorectal lesions: propensity score matching" by Nobuhisa Minakata et al. This was a single-center retrospective study comparing the safety and efficacy of HSP and EMR by the use of a bipolar snare for non-peduncolated colo-rectal lesions of 10-15 mm. Although affected by its retrospective nature, I consider the manuscript innovative and relevant for the research context. However, I have the following major comments:

RESPONSE: Thank you for your valuable comments. We have revised our paper accordingly.

Major 1. Materials and methods: "Once removed, the lesions were fixed in formalin, embedded in paraffin, sectioned into 2-3 mm slices, stained with haematoxylin-eosin, and evaluated by two experienced pathologists blinded to the patient's clinical information." ◇ Given the retrospective nature of the study, this is unclear. How was blinded evaluation possible (pathological specimen revision by two blinded pathologists)? Please clarify.

RESPONSE: In clinical practice at our hospital, the pathological diagnosis is made by discussion between two pathologists only with reference to the pathological specimen. In this study, we extracted their pathology diagnosis from the medical record, so we did not re-evaluate the resection specimen retrospectively and revise the diagnosis.

2. Materials and methods: in the definition of perforation the onset of presentation is not specified (early versus late-onset perforation). Please clarify.

RESPONSE: Thank you for pointing this out. In this study, we defined both early and late-onset perforation together as "perforation." One case of perforation in the EMR group occurred intraoperatively. This information was added in the adverse events section of the Results.

3. Materials and methods: main adverse event associated with HSP is post-polypectomy syndrome due to excess coagulation and thermal injury of the colonic wall. Thus, this outcome should be properly defined and addressed by the current study.

RESPONSE: Because this was a retrospective study, it was difficult to accurately ascertain the cases of post-polypectomy syndrome. However, patients were informed to contact us or come to the hospital if symptoms such as severe abdominal pain and fever appeared after treatment, and no such cases were found in this study.

4. Materials and methods: were techniques to prevent delayed bleeding or perforation (i.e. post-resection clipping or other) applied? Please specify.

RESPONSE: Thank you for your comment. Prophylactic clipping after endoscopic resection was performed in some cases at the endoscopist's discretion, so we added a description in the Materials and Methods section. However, there is insufficient evidence that clipping prevents delayed bleeding or delayed perforation, so we did not consider this as a factor affecting the treatment outcomes in this study.²

2. Matsumoto M, Kato M, Oba K et al. Multicenter randomized controlled study to assess the effect of prophylactic clipping on post-polypectomy delayed bleeding. *Dig Endosc* 2016; **28**: 570-6.