

Dear Editors and Reviewers:

On behalf of my co-authors, we are very grateful to you for giving us an opportunity to revise our manuscript. We appreciate you very much for your positive and constructive comments and suggestions on our manuscript entitled “Endoscopic mucosal resection-precutting vs conventional endoscopic mucosal resection for sessile colorectal polyps sized 10-20 mm: a multicenter randomized controlled trial” (Manuscript NO.: 78694).

We have studied the reviewers’ comments carefully and tried our best to revise our manuscript according to the comments. The following are the response and revisions we have made in response to the reviewers’ questions and suggestions on an item-by-item basis. Thanks again to the hard work of the editor and reviewers!

Response to the comments of Reviewer #1:

Major items:

1.As stated by the authors, several improved EMR techniques have been developed, such as EMR-P, underwater EMR, and tip-in EMR. What is the reason that made the authors focus on EMR-P? Please state the reason in the INTRODUCTION section compared with other EMR techniques.

Answer: Thanks for your kind suggestion that we didn’t discuss this part in our manuscript. “Theoretically, EMR-P does have some advantages over the above two alternative treatments of CEMR. Because it does not need to fill the entire lumen only with fluid, compared with UEMR, EMR-P saves a lot of time in deflating the lumen completely, moreover, its visual field during operation is less affected by poor intestinal preparation or intraprocedural bleeding. In comparison with tip-in EMR, circumferential incision of EMR-P allows the snare to be closer to the vertical margins of the lesions when snaring the polyps, which may conducive to a better R0 resection rate.” To simplify the introduction, we have put this part into DISSCUSSION section.

Moreover, as we described in INTRODUCTION section, most of the study concerning about EMR-P were retrospective study, with a small sample size, involving large lesions (≥ 20 mm) or difficult lesions (en bloc resection could not be achieved by CEMR), and the quality of evidence was relatively poor.

These are the reasons why we focus on EMR-P rather than other improved EMR techniques.

2. In the MATERIALS AND METHODS section, the authors stated that the polypectomy snares were chosen at the discretion of each institution. As the snare used is crucial for the success of EMR; please describe exactly what kind of snare has been used in this study. In addition, please describe the injection needle and injection solution used.

Answer: We have listed the model types of snare, injection needle and injection solution used in each institution in Supplementary material 1.

3. Given the importance of the high-frequency generator in snaring, please elaborate on the high-frequency generator used here. In addition, mention the settings, both for the precut and during snaring.

Answer: We have also listed the model types of high-frequency generator used in each institution in Supplementary material 1.

4. No histological definition was provided in this study. As shown in Table 2 (histological type), tubular adenomas were classified into three subtypes: tubular, tubular adenoma with low-grade dysplasia, and tubular adenoma with high-grade dysplasia. However, based on the WHO classification, tubular adenomas should be classified into two types: low-grade and high-grade. Villous adenomas or tubular villous adenomas should be classified into two types as well. Furthermore, “cancer” had an ambiguous expression. Did it include intramucosal and submucosal invasive carcinomas? Thus, these two factors should be clearly separated.

Answer: I'm sorry that this part was not clear in the original manuscript. We have used the “The 2019 WHO Classification of Tumors Editorial Board. WHO Classification of Tumors. Digestive System Tumors” to redefine histological type of our study. The histological types included in our study are presented as follows: tubular adenoma with low-grade dysplasia; tubular adenoma with high-grade dysplasia; villous adenoma with low-grade dysplasia; villous adenoma with high-grade dysplasia; tubular villous adenoma with low-grade dysplasia; tubular villous adenoma with high-grade dysplasia; hyperplastic polyp; serrated lesions; intramucosal adenocarcinoma; submucosal invasive adenocarcinoma; and others. We have modified relevant part and table 2.

5. In this study, EMR-P (9.1%) had a higher intraoperative bleeding rate than C-EMR (6.4%), although the occurrence of intraprocedural bleeding was not significantly different between these groups. This may be due to the limited case numbers included in this study. Furthermore, did bleeding occur during the precut? Elaborate about the intraoperative bleeding in detail.

Answer: Thank you for your good suggestion. In the EMR-P group, 10 case of intraprocedural bleeding occurred in our study, among them, 4 cases had bleeding during pre-cutting, while 6 cases had bleeding during snaring and removing procedure. However, all of them were addressed successfully by endoscopic coagulation and endoscopic clips. We also have modified the presentation of the RESULTS part in our article.

6. EMR-P is still a technically challenging protocol, but not as much as ESD. In this analysis, the experts performed the EMR-P procedure in all but one case.

This is one of the limitations of the present study.

Answer: EMR-P is more challenging than CEMR but simpler than ESD, so it may require endoscopists have rich experience to perform EMR-P. Since one case of polyp larger than 20mm was included in the study, it was then excluded during analysis. But notably, this case was also successfully achieved en bloc and R0 resection. However, this situation is indeed one of the limitations of this study.

7. The authors concluded that the potential benefits of EMR-P are promising in clinical practice, particularly for lesions >15 mm in size. I think that this is an overstatement. EMR-P is technically challenging and a time-consuming practice, but not much compared to ESD. Therefore, EMR-P should definitely be considered as an alternative treatment for non-pedunculated colorectal polyps sized 10-20 mm.

Answer: In our analysis, EMR-P showed a better en bloc resection rate than CEMR for non-pedunculated colorectal polyps sized 10-20 mm, although it is more challenging than CEMR but simpler than ESD. Additionally, spending some three more minutes in clinical operation to increase en bloc resection rate seems to be acceptable. Thus, we concluded that EMR-P could serve as an alternative treatment for sessile colorectal polyps sized 10-20 mm.

8. Endoscopic images or schemas of the EMR-P procedure would help readers understand the EMR-P procedure. Please include the images/schematics.

Answer: Thank you for your good suggestion. We have added the images in the manuscript to help readers understand the process of EMR-P (Figure 1).

Minor items:

1. In the abstract, the authors concluded that EMR-P serves as an alternative to CEMR to remove non-pedunculated colorectal polyps sized 10-20 mm, particularly polyps >15 mm in diameter. However, sub-analysis for polyps >15 mm was not included in the RESULTS section of the abstract. Please include the relevant information.

Answer: Thank you very much for this proposal. We have added this part in the RESULTS section of the abstract.

2. In the MATERIALS AND METHODS sections, the Paris classification was used to classify the morphology of polyps with superficial appearance: pedunculated (0-1p), sessile (0-1s), or mixed (0-1sp), nonpolypoid (0-11a), flat (0-11b) or slightly depressed (0-11c). The Paris Classification uses Roman numerals. Please do the needful corrections.

Answer: Thanks for your good suggestion. We have modified this part in the MATERIALS AND METHODS sections.

3. In the MATERIALS AND METHODS section (histological examination), the authors stated that all the biopsy specimens were evaluated based on histologic types and involvement of the resection margin. The expression "biopsy" confuses readers. Please correct.

Answer: Thanks for your sincerely advise and we have changed the expression "biopsy" to "retrieved specimens" in our manuscript.

4. In the RESULTS section, the authors stated that four patients in the EMR-P group and three in the C-EMR group were excluded. Please briefly explain the reasons for this exclusion.

Answer: We have modified the expression in the RESULTS section as follows: three patients with pedunculated lesions in each group were excluded, while in the EMR-P group, one patient was excluded as the polyp was >20mm in size.

5. In the final paragraph on page 12, it is stated that, "although EMR-P also showed a higher R0 resection rate, a significant difference was found."—this is not that a "no significant difference"?

Answer: Thanks for your essential notification and we have revised the expression as followed: Although EMR-P also showed a higher R0 resection rate, no significant difference was found.

Response to the comments of Reviewer #2:

1. Introduction - Page 4, line 17, 'large lesions (≥ 2 mm)' seems to be a typographical error.

Answer: Thanks for your timely notification and we have revised the expression "large lesions (≥ 2 mm)" to "large lesions (≥ 20 mm)".

2. Materials and Methods, Results

1) Please, describe method to measure lesion's size because the size measured under endoscopy and gross measurement of resected specimen might be different.

Answer: Thanks for your kind suggestion. We have modified this part in our manuscript and we have presented it as follows: compared with the size of open (~7 mm) or closed (~2 mm) biopsy forceps according to its endoscopic appearance, the size

of the lesion was initially estimated and then was confirmed by comparison with an opened snare (20-30mm) during treatment.

2) The authors defined expert endoscopist as having more than 1000 colonoscopies and proficient experience of EMR and ESD. Could you explain in detail why this definition was used? In addition, please provide the characteristics of participating endoscopists in detail.

Answer: Actually, we didn't describe this part exactly since there seems to be no unified and clear standard for the definition of expert endoscopist. In our analysis, we had referred to Imai et al's definition (AM J GASTROENTEROL. 2021;116(7):1398-1405.) that endoscopists who have performed >1,500 colonoscopies, >100 polypectomies, and >5 ESDs could be define as experienced endoscopists. We had increased some requirements that endoscopists who have performed >1,000 colonoscopies, >300 EMRs, and >10 ESDs could be define as experienced endoscopists. We have modified the expression "expert" to "experienced endoscopists" in our manuscript to avoid misreading.

3. Discussion

1) Page 12, line 21, 'likely attributed to the only case of piecemeal resection in the EMR-P group during the removal of pedunculated polyp' What does the sentence mean? Randomization was appropriate?

Answer: we are sorry that this part was not clear in our original manuscript. Actually, in our study, we found that in EMR-P group, one case with pedunculated polyps was received piecemeal resection. However, if this case had achieved en bloc resection, in ITT analysis, the en bloc resection rates could be significantly different between groups (94.5% vs. 86.4%, $P=0.039$). Thus, we thought that there was no significant difference of en bloc resection rates in ITT analysis may be attributed to this special case and speculated that EMR-P may not be superior to CEMR in removing pedunculated lesions. However, to avoid misreading, we have deleted this sentence in our manuscript.

2) Although the study included the small portion of serrated lesion (SL), the endoscopic resection of SL shows somewhat different outcomes compared to that of conventional adenoma. Please, discuss regarding these points.

Answer: Thanks for your notification, and this issue is very important. According to The Paris Classification, in our study, the most type of morphology of serrated lesion was 0-IIa (10 cases), then was 0-Is (5 cases), and 0-IIb (1 case). Through using narrow band imaging (NBI) we could identify its boundary and then performed resection successfully. In our study, only once case didn't achieve R0 resection in EMR-P group, while one case didn't achieve en bloc resection in CEMR group. Because the numbers were too small, no statistical differences were shown between groups.