

Peer Review File

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Comment 1: In the study design, the authors have excluded the lesions resected by conventional EMR and those with prior biopsy. I think including those treated by conventional techniques adds merit to the study by providing comparison within the same cohort. Similarly, those with prior biopsy must be retained. It is understood that these cases are likely to be excluded based on exclusion criteria of ulceration and bleeding. If these lesions did end up undergoing endoscopic resection (with any residual disease), the challenges and pitfalls should be described so that readers are aware of the inherent problems with such cases. In practical situations, these cases cause more technical and interpretation problems.

Reply 1: We would like to thank the reviewer for the suggestions for our manuscript. **Most rectal neuroendocrine tumors originate in the deep mucosal and submucosal layers, and have the potential to infiltrate into the submucosa. Conventional EMR techniques can only remove lesions of mucosal origin, such as colorectal polyp lesions. However, conventional EMR for lesions locating in the submucosal layer, often results in a high rate of residual lesions and requires further endoscopic or surgical treatment. Therefore, according to the recommendations of most current guidelines, modified EMR or ESD is recommended for rectal neuroendocrine tumors to improve the rate of histologically complete resection and reduce the rate of tissue residue. In fact, most of the cases in this study that underwent EMR were due to inaccurate assessment of the lesion before endoscopic resection and mistaken removal by conventional EMR. Therefore, we excluded such cases to reduce the bias of our study.**

We agree with the reviewer that the cases undergoing biopsy before endoscopic resection, may provide higher research value for endoscopic resection. However, our research mainly focuses on patients with initial diagnosis of rectal endocrine tumor, since these patients have complete clinical data. In contrast, most of the patients with previous biopsy were examined outside our hospital, and the authenticity of the information is difficult to determine. More importantly, the size and shape of the lesion after biopsy would change, which was not suitable to be compared with the lesion without biopsy, and therefore they were excluded.

Changes in the text:

1. In the introduction, we add some comment : “Currently, most guidelines recommended modified EMR or ESD for the endoscopic treatment of rectal NETs to improve histologically complete resection of the lesion and to reduce the rate of residual tissue(1,2).”(see Page 3, Line 18 to 20)

2. In the discussion section, we add the content as follows: “Most rectal NETs originate in the deep mucosal and submucosal layers, and have the potential to infiltrate into the submucosa. Conventional EMR techniques can only remove lesions of mucosal origin, for example, colorectal polyps. However, conventional EMR for lesions located in the submucosal layer often results in a high rate of residual lesions and requires further endoscopic or surgical treatment. Therefore, according to the recommendations of most of the current guidelines, a modified EMR or ESD is recommended for rectal NETs to improve the rate of histologically complete resection and to reduce the rate of tissue residue.” (see Page 11, Line 2 to 10)

References :

1. de Mestier L, Lepage C, Baudin E, et al. Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). *Dig Liver Dis.* May 2020;52(5):473-492.
2. Basuroy R, Haji A, Ramage JK et al. Review article: the investigation and management of

rectal neuroendocrine tumours. *Aliment Pharmacol Ther.* Aug 2016;44(4):332-345.

Comment 2: In the results section, the authors mention 13 patients had positive margins, 3 who had deep margins positive underwent additional resections. Does this mean, the remaining 10 patients had positive lateral margins? What was the follow up strategy for these patients? Did they receive confirmed endoscopic follow up 3 months (vs telephone follow up).

Reply 2: We sincerely thank the reviewer for the thorough analysis and critical evaluation of our manuscript. We appreciate the reviewer's suggestions. Three of the 13 patients with positive tumor margins had additional surgery (two with positive vertical margins, one with positive lateral and vertical margins). Nine of the remaining 10 patients had positive vertical margins, while one patient was with positive lateral and vertical margin. Our follow-up strategy had been described in the previous manuscript: "For patients who underwent complete resection but had vascular invasion or patients who underwent incomplete resection and refused additional surgery, colonoscopy was recommended 3, 6 and 12 months after the operation and once a year afterward if no local recurrence was shown."

Changes in the text:

The content of histopathological manifestations are added as follows: "Three patients with positive tumor margins had additional surgery (two with positive vertical margins and 1 with positive lateral and vertical margins), and no residual tumor cells were found at postoperative microscopic examination; 9 of the remaining 10 cases had positive vertical margins, while 1 had a positive lateral and vertical margin." (see Page 8, Line 16 to 19)

Comment 3: Why was 7 mm chosen as the cut off; I assume it based on prior studies, It should be clarified in Methods.

Reply 3: Thanks for the reviewer's insightful comments and suggestions. The diameter for 7 mm as a cut-off was based on the findings of previous relevant studies. In the discussion section of the original article, it was stated that "Yang et al. [30] showed that for rectal neuroendocrine tumors of 6-8 mm in diameter, there was no significant difference in the However, none of study has investigated the efficacy and safety of modified EMR and ESD for treating rectal neuroendocrine tumors. neuroendocrine tumors larger than or equal to 7 mm in diameter. " Therefore, we chose a mean value of 6-8 mm as the cut-off, aiming to further investigate the differences in safety and efficacy between modified EMR and ESD.

Changes in the text: We had clarified the cut-off in the method.

Minor correction

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1. Line 149 - G1 Ki-67 cutoff should be <3%
 2. Line 151-152 - The sentence should be re-phrased - Vascular invasion was evaluated using D2-40 and CD34 immunohistochemical stains.
 3. Table 1 - delayed hemorrhage rate. Delayed spelling error should be corrected.

Reply : Thanks to the reviewer's for correcting the errors in manuscript. Your comments will greatly improve the accuracy of the manuscript and make the article more standardized. (see Page 6, Line 15, Line 17 and Table 1)