Responses to the Reviewers' Comments

Dear editor，

Re: "Ligation after endoscopic mucosal resection using a transparent cap：a novel method to treat small rectal carcinoid tumors" to World Journal of Gastroenterology (Manuscript NO: 45393).

Thank you very much for the decision and advice. We have carefully studied the comments and made corrections accordingly. The modifications are showed using the track changes mode. Point by point responses to the reviewers' comments are listed below in this letter.

We hope that this resubmitted version is acceptable for publication in your journal. Looking forward to hearing from you,

With kind regards,

Sincerely yours,

Jun Yao, M.D. OR Ding-Guo Zhang, M.D.

Department of Gastroenterology

Shenzhen People's Hospital,

First Affiliated Hospital of Southern University of Science and Technology，

Second Clinical Medical College of Jinan University，

1017 East Gate Road, Shenzhen 518020, Guangdong Province, China

Tel: 0086-755-25533018

Fax: 0086-755-25533497

Email: jun.yao@szhospital.com OR zdg8012@sina.com

REVIEWERS' COMMENTS TO THE AUTHOR

1st Reviewer:

SPECIFIC COMMENTS TO AUTHORS

This report is a retrospective study about the utility of endoloop ligation after ESD using a transparent cap. It is interesting. However, this report has some major problems, so it is considered that this paper is inappropriate for publication as it is.

Major 1) The authors do not address the follow-up method and period. In particular, detailed description of follow - up method and period are required for the patients with remnant tumor after LC-EMR or ESD.

A:Previous studies showed patients presenting with small (≤1.0 cm), non-metastatic rectal carcinoids are unlikely to develop local or distant recurrence after resection. Aggressive surveillance with repeat endoscopies or other imaging studies after resection may be unnecessary. Generally，we review colonoscopy and observe post-operation scar and recurrence six months after resection，and then interval of 1 to 2 years .For 2 patients with remnant tumor after LC-EMR or ESD who didn't choose further surgery, we review colonoscopy and observe post-operation scar and recurrence 3 months after resection，and then repeat colonoscopy and abdominal CT scan every interval of 1 year .

1.Murray SE, Sippel RS, Lloyd R, Chen H. Surveillance of small rectal carcinoid tumors in the absence of metastatic disease. *Ann Surg Oncol*. 2012;19(11):3486-90.

2.Kwaan MR, Goldberg JE, Bleday R. Rectal Carcinoid Tumors: Review of Results After Endoscopic and Surgical Therapy. Arch Surg . 2008;143(5):471–475.

3. Tsai BM, Finne CO, Nordenstam JF, et al. Transanal Endoscopic Microsurgery Resection of Rectal Tumors: Outcomes and Recommendations. Dis Colon Rectum. 2010;53(1):16–23.

2) In figure 1, the authors should show the scar after endoscopic therapy.

A:Figure 1 describes the patient with residual pathological findings after endoscopic resection, and no tumor cells were found in the final further surgery. The patient's postoperative scar was surgical scar and non-endoscopic scar.

Minor 1) In the paragraph of Introduction, is "… the use of nylon ligation in the treatment of rectal carcinoma after endoscopic resection …." wrong? Is "…rectal carcinoid…" a correct description?

A:Although rectal carcinoid should be accurately described as rectal neuroendocrine tumors (NET), most of the literature still use the old terminology.

1.Lee HJ, Kim SB, Shin CM.A comparison of endoscopic treatments in rectal carcinoid tumors.Surg Endosc,2016 ;30(8):3491-8
2.Li X,Gui Y,Han W,et al.Application value of endoscopic submucosal dissection and endoscopic mucosal resection for treatment of rectal carcinoids.J Cancer Res Ther,2016 ;12(Suppl):43-46

2nd Reviewer:

SPECIFIC COMMENTS TO AUTHORS

This is an interesting single center study on local endoscopic treatment of small <1cm rectal carcinoid tumor comparing ESD v/s EMR-LC methods. Both methods had similar good results. The study is interesting. However some issues: 1. Although the authors stated that EMR-LC is easier sometimes the position of the endoloop is difficult. Did the authors face any complications such as difficulty in position of the endoloop in the inner end of cup?

A:Frankly speaking, endoloop has been used for the ligation of esophageal varicose veins in our unit for more than 10 years, and the surgeons and assistants have cooperated with each other skillfully. Moreover, most rectal carcinoids are located in the lower part of the rectum, so we have not encountered any difficulty in placing endoloop.

1 Zhang D, Shi R, Yao J, Zhang R, Xu Z, Wang L.Treatment of massive esophageal variceal bleeding by Sengstaken-Blackmore tube compression and intensive endoscopic detachable mini- loop ligation: a retrospective study in

83 patients. Hepatogastroenterology 2015 ;62:77-81

2. One major disadvantage of EMR is that it is performed blindly in contrast to ESD, which to our opinion is the standard method of choice for some submucosal tumors.

A：It is true that compared with ESD, EMR has operation blindness, but the technical requirements of ESD are relatively high, and not every unit had carried out routinely. Previous studies have shown that EMR-cap had a satisfactory effect in the treatment of rectal carcinoid.

1.Choi HH, Kim JS, Cheung DY,et al.Which endoscopic treatment is the best for small rectal carcinoid tumors?World J Gastrointest Endosc,2013 ; 5(10): 487–494.

2.Yang DH, Park Y,Park SH, et al.Cap-assisted EMR for rectal neuroendocrine tumors: comparisons with conventional EMR and endoscopic submucosal dissection (with videos).Gastrointest Endosc,2016 ;83(5):1015-22

3. ESD was more time consuming and demanding. However, time is not a tamboo, but efficacy is the issue. Obviously high quality ESD has been proved more efficient for en bloc resection in one specimen (R0) than EMR.

A：Previous studies have shown that EMR-cap had a satisfactory effect in the treatment of rectal carcinoid.

1. Nagai T, Torishima R, Nakashima H, et al. Saline-assisted endoscopic resection of rectal carcinoids: cap aspiration method versus simple snare resection. Endoscopy, 2004;36:202–205.

2.Yang DH, Park Y,Park SH, et al.Cap-assisted EMR for rectal neuroendocrine tumors: comparisons with conventional EMR and endoscopic submucosal dissection (with videos).Gastrointest Endosc,2016 ;83(5):1015-22

3.Pan J, Zhang X,Shi Y,et al.Endoscopic mucosal resection with suction vs. endoscopic submucosal dissection for small rectal neuroendocrine tumors: a meta-analysis.Scand J Gastroenterol,2018 ;53(9):1139-1145

4. The authors gave as the sense that ESD resulted in remnant tumors and not EMR. However, none of the three cases with histologically positive margins proved to have remnant tumor during follow up. A comment is necessary. I think this technique is useful in case of absence of ESD availability.

A: We have added comment as suggested.

3rd Reviewer:

SPECIFIC COMMENTS TO AUTHORS

The authors investigated treatment strategies for small <1cm rectal carcinoid tumor comparing ESD with EMR-LC methods. Both methods had similar good results. There were major comments as follows;

1. Essentially, they should compare EMR (not ESD) with EMR-LC for investigating the efficacy of EMR-LC more accurately. A comment is necessary.

A:The previous literature showed that the residual rate of traditional EMR lesions was relatively high, so I think it was unwise to still choose such a treatment method.

1.Lee HJ, Kim SB, Shin CM.A comparison of endoscopic treatments in rectal carcinoid tumors.Surg Endosc,2016 ;30(8):3491-8

2.Li X,Gui Y,Han W,et al.Application value of endoscopic submucosal dissection and endoscopic mucosal resection for treatment of rectal carcinoids.J Cancer Res Ther,2016 ;12(Suppl):43-46

2. Rate of negative margin in cases of EMR-LC was relatively lower than that in ESD. Some cases, which was not resected en-bloc, may invade into deeper layer, therefore they should discuss about this issue more in detail.

A:We have revised it as suggested.

3. For investigating the efficacy of EMR-LC, they should mention about ”the burn effect” by electrocautery after EMR. Is LC after EMR really needed? They should compare LC with clip closure.

A:Considering the possible residual problems of EMR, we chose wound ligation instead of titanium clip closure. The reason is that even if there is residual, post- ligaton can make the residual tumor tissue ischemic necrosis and achieve the purpose of complete resection.EMR-LC is not LC after EMR,it means Ligation after EMR-cap

1 **Zhang D**,Lin Q,Shi R, Wang L, Yao J, Tian Y.Ligation-assisted endoscopic submucosal resection with apical mucosal incision to treat gastric subepithelial tumors from the muscularis propria. Endoscopy 2018;50:1180-1185

4. They should show the rate of closure in Table. Closing an endoloop after EMR will need some time, therefore they should mention about the procedure time including the closure time.

A:we have added relevant content in the discussion section.