

Manuscript NO: 39338 (R1)

Title: Long-term outcomes of endoscopic resection for small (≤ 4.0 cm) gastric gastrointestinal stromal tumors originating from the muscularis propria layer

Dear Pro. Xue-Jiao Wang,

Thank you for your letter and the reviewer's comments about our manuscript (WJG Manuscript NO: 39338). The comments by the reviewers are very constructive and helpful for improving the manuscript. We have modified the manuscript in line with the reviewer's comments. Hereby we submit the revised manuscript for your consideration for publication. We think that we have addressed reviewer's comments to the best degree we could, and we hope this has met the reviewers' requests.

If you have any questions, please feel free to contact us. We appreciate your support very much. Our detailed point-by-point responses to the comments are as following pages.

Yours sincerely,

Li-Ping Ye

Responses to the reviewers' comments:

Reviewer #1:

Q1. There is a recently published paper of the same authors, a technical review, that pose the size limit for endoscopic resection up to 3.5 cm. In this paper they increase the limit up to 4 cm. It would be clarify the reason.

Thank you for raising this question. Although gastric subepithelial tumors (SETs) less than 4.0 cm could be removed en bloc in our endoscopic center before 2015, very few cases of gastric SETs > 3.5 cm were reported in the published literature at that time, and some resulted in partial or piecemeal resection. Therefore, in that review, we stated that the optimal indication for endoscopic resection in gastric SETs might be less than 3.5 cm in tumor diameter. Recently, other publications have reported that gastric SETs greater than 3.5 cm in diameter can be removed from the stomach using an endoscopic approach [1-5]. Although in these published literature, the maximum size of the lesions resected by endoscopic approaches was ranged 5.0 to 7.6 cm, endoscopic resection of larger tumor is associated with narrower endoscopic view, higher complication rate, longer endoscopic resection time and more difficult removal of the tumor. Therefore, in this article, we have described that the optimal indication for endoscopic resection in gastric SETs might be less than 4.0 cm, which will increase the rate of indication for endoscopic resection, but not increase the adverse events associated with endoscopic resection.

Reference:

1. An W, et al. Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. *Surgical endoscopy* 2017; 31(11): 4522-4531.
2. Yu C, et al. Long-term outcomes of endoscopic resection of gastric GISTs. *Surg Endosc.* 2017;31(11):4799-4804.
3. Clinical impact of submucosal tunneling endoscopic resection for the treatment of gastric submucosal tumors originating from the muscularis propria layer (with video). *Surg Endosc.* 2015;29(12):3640-6.
4. Mori H, et al. Establishment of the hybrid endoscopic full-thickness resection of gastric gastrointestinal stromal tumors. *Mol Clin Oncol.* 2015;3(1):18-22.
5. Andalib I, et al. Endoscopic resection of gastric gastrointestinal stromal tumors originating from the muscularis propria layer in North America: methods and feasibility data. *Surgical endoscopy* 2018; 32(4): 1787-1792.

Q2. I completely disagree to use piecemeal technique for larger lesions because the danger of dissemination. An expert would not use and propose this technique for larger , maybe HIGH-RISK , lesions.

Thank you for raising this question. In our hospital, for patients with large gastric lesions, options will be discussed with our interdisciplinary tumor board, and the advantages and disadvantages of each treatment method will be explained to the patients and their family members before operation. The patients' interests and wellbeing will always be put first. We agree with reviewer's comment. We also agree that surgical resection is the main and standard therapeutic method for patients with large gastric lesions, which should be considered first. [Therefore, in our study, we have described that](#)

surgical resection still is the first choice of treatment for patients with gastric GISTs > 4 cm in diameter. (page 16, line 1 – 2). However, for certain patients who are contraindicated for surgical resection or prefer not to undergo a scarring surgical procedure, endoscopic resection provides a alternative therapeutic method for these patients.

Q3. Finally i completely disagree with the statement - laparoscopic resection of GIST near esophagi-gastric junction or antrum altered gastric function - : the antrum is quite large and only resection that are strictly close to cardias or pylorus could be at risk of altered function. Personally I have performed laparoscopic resection of GIST in the gastric fundus until to 1 cm close to cardia.

First of all, We do apologize that we have not expressed the meaning of this sentence well. The sentence in the introduction section should be: “Especially when the tumor is located near or in the gastric cardia or pylorus, resection of the gastric cardia or pylorus might lead to irreparable damage to the cardioesophageal sphincter or pylori sphincter, leaving patients prone to certain diseases associated with digestive fluid reflux.” (page 5, line 10 – 14)

Reviewer #2:

Q1. Please make some emphasis on the difference your study with other published ones.

Thanks for your suggestion. We have added these descriptions in the discussion section:” Currently, endoscopic resection is being increasingly used for gastric MP-GIST removal. However, additional evidence is required to support the long-term effectiveness of endoscopic resection for the treatment of gastric GISTs. Compared with the published studies, our study included a larger sample size with a longer follow-up period to assess the long-term safety and efficacy of ER for gastric MP-GIST, which would increase evidence and support for the use of endoscopic resection to treat/remove gastric MP-GISTs”. (page 14, line 8 – 14)

Q2. Please describe the contraindication of endoscopic resection in your study.

Thanks for your suggestion. We have added these descriptions in the discussion section:” Third, the tumor should be assessed by EUS and CT before ER. For some lesions with high risk features (irregular border, cystic spaces, echogenic foci, and internal heterogeneity) identified on EUS or metastasis confirmed by CT, ER is absolutely contraindicated”. (page 16, line 7 – 10)

Q3. Did some patients receive adjuvant therapy (Imatinib) after endoscopic resection?

Thanks for your careful review, and we have added these descriptions in the

result section:" In this study, 2 patients with high-risk GISTs took imatinib mesylate to prevent recurrence or metastasis, whereas the other 8 patients with intermediate-risk GISTs were unable to take imatinib mesylate because they were unable afford the medication." (page 13, line 3 – 6)

Reviewer #3:

Q1. How about operative time?

Thanks for your suggestion. We have added these descriptions in the result section:" The mean time of ER procedure was 52.8 ± 16.1 min (range 23 – 118 min)." (page 11, line 17 – 18)

Q2. How about the mean times from endoscopic treatments to a solid diet?

Thanks for your suggestion. We have added these descriptions in the result section:" The median time from endoscopic treatment to a no-residue diet was 4 days (range 1–10 days, interquartile range 3–6 days)." (page 12, line 3 – 4)

Q3. In Figure 1G/1H and 2G/2H, scale bars should be indicated.

Thank you for your suggestion. We have added the scale bars in Figure 1 and Figure 2.

Q4. In the present study, patients with small (≤ 4.0 cm) gastric GIST were enrolled. How do the authors discuss about the indication of endoscopic

resection in patients with gastric GIST measuring > 4.0 cm?

Thank you for raising this question. In the discussion section, we have described “First, the tumor size of gastric MP-GISTs might be no more than 4.0 cm in diameter. When the tumor size is > 4 cm in diameter, it is very difficult to remove the tumor en bloc with an endoscopic approach, because of the limitations of the cardia and esophagus space. Meanwhile, larger tumor size is associated with certain disadvantages, such as a narrower endoscopic view, higher complication rate, and longer endoscopic resection time. Therefore, in our endoscopy center, surgical resection still is the first choice for patients with gastric GISTs > 4 cm.” (page 15, line 17 – page 16, line 2).

Reviewer #5:

Q1 In patients and methods section, the authors mentioned that they have undergone 1,021 cases of endoscopic resection for MP-SETs from 2005 to 2017. However, they evaluated only 229 cases of gastric MP-GISTs. First, they need to demonstrate the period of the treatment for the patients of 229 MP-GISTs. Second, they also should state the number of patients with MP-GISTs in the 1,021 MP-SETs. Without these information, the article can’t avoid the possibility of selection bias of this study.

First of all, We do apologize for a mistake in this sentence: “Up to December 2017, we had completed 1021 cases of ER for small (\leq 4.0 cm) gastric MP-SETs”. The sentence should be “Up to December 2017, we had completed

1021 cases of ER for small (≤ 4.0 cm) upper gastrointestinal MP-SETs". And then, we have revised in the introduction section" Since June 2005, our endoscopy center has been using ER for small (≤ 4.0 cm) upper gastrointestinal subepithelial tumors originating from the muscularis propria layer (MP-SETs). Up to December 2017, we had completed 1021 cases of ER for small (≤ 4.0 cm) upper gastrointestinal MP-SETs. Within those 1021 cases, we selected 229 consecutive patients who had gastric MP-GISTs less than 4.0 cm with at least 36 months of follow-up after ER, and demonstrated the long-term safety and efficacy of ER for this type of tumor." (page 5, line 18 – page 6, line 3)

Q2 In results section, the authors demonstrated 8 cases out of 229 tumors were removed without complete resection. In particular, 5 GIST tumors were resected piecemeal. In general, this is not acceptable procedure as treatment for malignant tumors. If these procedures were performed during EFTR, the risk of peritoneal dissemination will be increased. The authors should clearly state the places and the sizes of tumors regarding as the 5 tumors and if the procedures were ESD or EFTR or the others.

Thanks for your suggestion. We have added these descriptions in the result section:" Among the other 8 GISTs without complete resection, 3 GISTs were resected in one piece during EME technique, but the tumor margin could not be evaluated definitively because of electrocautery, and the other 5 GISTs were resected piecemeal during the EME procedure. Of the 8 GISTs, 5 were

located in the gastric fundus and 3 in the gastric body. The size of these GISTs in diameter was ranged 2.7 to 3.6 cm. According to the NCCN guidelines, these 8 GISTs were all low risk.” (page 11, line 19 – page 12, line 3)

Q3 In order to avoid peritoneal dissemination after treatment in particular in the case of piecemeal resection for treatment of gastric GIST, there is safe and reasonable laparoscopic endoscopic collaborative method. It is known as non-exposed endoscopic wall-inversion surgery (NEWS): Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. Gastric Cancer. 2014;17(3):594-9. At least, for the GIST whose growth pattern is extraluminal, laparoscopic endoscopic collaborative method seems safer than EFTR which is conducted by endoscopically.

Thank you for your recommendation of this article. In this article, the authors described a novel partial gastrectomy technique, called NEWS. Compared with pure endoscopic resection, NEWS has a significant advantage in terms of avoiding contamination and tumor dissemination into the peritoneal cavity. NEWS provides a feasible and efficacious approach for patients with gastric subepithelial tumors whose growth pattern is extraluminal, especially for some tumors with malignant potential. Therefore, we plan to invite several surgeons to join us to apply this technique in the proper cases.

Q4. Minor point: In discussion section, the authors stated that all

endoscopic operations were performed by an experienced endoscopist. I would like to confirm if only one endoscopist conducted all of 229 treatments.

Thank you for raising this question. We have confirmed these 229 ER procedures were performed by Dr. Ye. Before February 2015, another endoscopic operator (Dr. Mao, an author of this study) performed 17 cases of ER for upper gastrointestinal subepithelial tumors. However, according with the research criteria, these 14 cases were not included in this study.