

ESPS Manuscript NO: 17068

Title: Endoscopic treatment for small gastric subepithelial tumors originating from muscularis propria layer

Dear Pro. Ma

Thank you for your letter and the reviewer's comments about our manuscript (ESPS Manuscript NO: 17068). The comments by the reviewer 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 entitled "Endoscopic treatment for small gastric subepithelial tumors originating from muscularis propria layer" 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. Our detailed point-by-point responses to the comments are as follow:

Responses to the reviewer 1:

This is a review article for SETs originating from the MP layer. The authors deal with recently advanced procedures. However, there are several issues to be considered.

(1) . There are no suggested indications for each technique. For example, in the case of STER, the preferred sites are cardia and antrum. And the upper size limit is usually less than 4 cm. Therefore, the indications for each technique (if it is difficult, the general indication for ER) should be added.

Thanks for the reviewer's suggestion. We have added "Indications of Endoscopic Procedure" in the new manuscript : "The optimal indication for endoscopic resection in gastric SETs should be less than 3.5 cm in diameter of tumor size. The reasons for this indication are as follows. First, because of the limitations of the cardia and esophageal cavity space, when a tumor > 3.5 cm in diameter, it is difficult to remove with an endoscopic approach after en bloc resection. Second, for the STER procedure, it is also difficult to excavate a large tumor during the narrow submucosal tunnel, which is often associated with an obscured endoscopic view and a high risk of tunnel mucosa perforation. Third, for the EFTR procedure, resecting a large tumor will leave a large gastric wall defect, which is also difficult to close by clips and associated with a potential risk of postoperative gastric leaks. Thus, at present, very few cases of SETs > 3.5 cm in diameter were reported in published literature and some of them resulted in partial or piecemeal resection. Partial or piecemeal resection, not an en-bloc resection, leads to tumor capsule rupture, a condition which obviously violates the principle of surgery. Therefore, only tumors less than 3.5 cm in diameter should be removed via endoscopic procedures. This is a relatively strict rule for endoscopic management. Note that tumors with high-risk EUS features, such as irregular borders, cystic spaces, ulcerations, echogenic foci, or heterogeneity, are not suitable for those endoscopic treatments." (Page 15, line 22-Page 17, line 5)

(2) . It is thought that ESD is nearly same to EME. Of course, although the authors suggested some difference between them, the real procedure is nearly same.

Therefore, it is recommended that EME will included in the section of ESD.

We agree with reviewer’s comment, and we have integrated the section of ESD and the section of EME.

(3) The last paragraph in ESD is not described properly. Please revise it.

Thanks for the reviewer’s suggestion. We have revised the statement about it in the section of Endoscopic Muscularis Excavation: “In a resent study focusing on the use of ESD to treatment gastric SETs, Bialek et al. reported that the complete resection rate was 100% when tumors had no connection to the underlying MP; yet when tumors presented with a narrow connection to the underlying MP, the complete resection rate was only 68.2% [10]. Therefore, ESD has some limitations for the treatment of gastric SETs with a tight connection to the underlying MP tightly.” (Page 7, line 8-13)

(4) As possible, please make a Table explaining pros and cons of each procedure.

Thanks for the reviewer’s suggestion. We have added 3 Tables in the new manuscript.

Table 1. Clinical Outcomes of Endoscopic Muscularis Excavation for Gastric Subepithelial Tumors Originating from the Muscularis Propria Layer

References	No. cases (tumors)	Location (details)	Mean Tumor size (mm)	Pathology	Complete resection rate,% (n)	Mean operating time (min) and range(min)	Complications (details)	Mean follow-up time (mo) and recurrence
Jeong et al.	64 (65)	23 cardia 8 fundus 30 body 4 antrum	13.8	26 GIST 32 leiomyoma 2 schwannoma 3 other	92.3 (60)	34.7	8 perforation	10 No recurrence

Chu et al.	16 (16)	1 cardia 3 fundus 9 body 3 antrum	26.1	14 GIST 2 leiomyoma	93.8 (15)	52	0	14.8 No recurrence
Liu et al.	31 (31)	14 esophagus 7 cardia 5 fundus 5 body	22.1	16 GIST 15 leiomyoma	96.8(30)	76.8	4 perforation	17.7 No recurrence
Ye et al.	212 (212)	93 fundus 104 body 15 antrum	16.5	97 GIST 115 leiomyoma	96.2 (204)	46.1	32 perforation 9 massive bleeding	26 No recurrence

Table 2. Clinical Outcomes of Endoscopic Full-Thickness Resection for Gastric Subepithelial Tumors Originating from the Muscularis Propria Layer

References	No. cases	Location (details)	Mean Tumor size (mm)	Pathology	Complete resection rate,% (n)	Mean operating time (min)	Complications (details)	Mean follow-up time (mo) and recurrence
Guo et al.	23	11 fundus 9 body 3 antrum	12.1	19 GIST 4 leiomyoma	100 (23)	40.5	2 localized peritonitis	3 No recurrence
Zhou et al.	26	12 fundus 14 body	28	16 GIST 6 leiomyoma 3 glomus tumors 1 schwannoma	100 (28)	105	0	8 No recurrence
Schmidt et al.	A 31	3 cardia 4 fundus 13 body 11 antrum	20.5	18 GIST 2 leiomyoma 2 adenomyoma 3 ectopic pancreas 1 lipoma 1 schwannoma 4 other	90.3 (28)	60.0	12 bleeding	7 No recurrence
Ye et al.	51	22 fundus 28 body 1 antrum	24	30 GIST 21 leiomyoma	98.0 (50)	52	0	22.4 No recurrence

GIST, gastrointestinal stromal tumor

Table 3. Clinical Outcomes of Submucosal Tunneling Endoscopic Resection for Gastric Subepithelial Tumors Originating from the Muscularis Propria Layer

References	No. cases (tumors)	Location (details)	Mean Tumor size (mm)	Pathology	Complete resection rate,% (n)	Mean operating time (min)	Complications (details)	Mean follow-up time (mo) and recurrence
Xu et al.	15 (15)	9 esophagus 3 cardia 2 body 1 antrum	19	5 GIST 9 leiomyoma 1 glomus tumor	100 (15)	78.7	1 pneumoperitoneum 1 pneumothorax 1 SE	3.9 No recurrence
Liu et al.	12 (12)	7 esophagus 5 cardia	18.5	2 GIST 9 leiomyoma 1 schwannoma	100* (12)	78.3	2 pleural effusion 4 pneumothorax 8 SE	7.1 No recurrence
Wang et al.	57 (57)	57 esophago-gastric junction	21.5	7 GIST 46 leiomyoma 1 Intramuscular lipoma 1 granular cell tumor 2 schwannoma	100 (57)	47	8 pneumothorax 3 pneumoperitoneum 12 pneumothorax and SE 2 pleural effusion	12 No recurrence
Ye et al.	85 (85)	60 esophagus 16 cardia 9 stomach	19.2	19 GIST 65 leiomyoma 1 calcifying fibrous tumor	100 (85)	57.2	6 pneumothorax 4 pneumothorax 8 SE	8 No recurrence

GIST, gastrointestinal stromal tumor; SE, subcutaneous emphysem.

* 100% is en-bloc resection rates, no information on complete resection rate was given in this study.

(5) Other trivial things are marked in the attached file. Please revise them.

Thanks for your careful review, and we have revised them in the new manuscript.

Responses to the reviewer 2:

This is an excellent paper. I only suggest to better delucidate the relationship between the different techniques and tumor dimensions, if any exist .

Thanks for the reviewer's suggestion. We have added "Indications of Endoscopic

Procedure” in the new manuscript. (Page 15, line 22-Page 17, line 5)

Responses to the reviewer 3:

The authors have reviewed good studies for “Endoscopic treatment for small gastric subepithelial tumors originating from the muscularis propria layer” and have submitted a well-written manuscript. I have just minor comments;

1. Traditionally, the treatment of choice for GIST is surgical resection. However, the tyrosine kinase inhibitor imatinib has become an important additional management tool. Please discuss briefly treatment strategy for better clinical decision-making.

Thanks for raising the question. We have added these descriptions in the introduction:” According to the National Comprehensive Cancer Network (NCCN) guidelines, all GISTs >2 cm in diameter need to be resected, whereas treatment options for incidental tumors <2cm are resection or endoscopic surveillance. However, endoscopic surveillance involves known issues related to patient compliance as well as a potential risk for delayed diagnosis of malignancy.” (Page 5, line 6-10)

2. In the “Summary” section, please summarize the endoscopic operation procedures briefly.

Thanks for raising the question. We have added these descriptions in the summary:” Although there are some complications or adverse events associated with endoscopic operation, such as perforation, massive bleeding, and subcutaneous

emphysema, endoscopic operation provides a new option for the management of gastric SETs that originate from the MP layer, which has advantages over surgical resection in terms of maintaining the normal anatomic structure and function of the stomach and improving the quality of life.” (Page 17, line 8-13)

Responses to the reviewer 4:

The present paper by Yu Zhang et al. is a review on endoscopic treatment of gastric SETs originating from MP. I suggest that the authors include tables with the pros and cons of every technique and the possible clinical scenario that every one of them should be elected. It has to be analyzed in the text why a high risk endoscopic removal is superior to surgical removal. The relevant table with comparison of possible complications could be added.

Thanks for the reviewer’s suggestion. We have added 3 Tables in the new manuscript. These tables can be read in the responses to the reviewer 1. In addition, we have added the detailed description about the selection of endoscopic operation methods in the section of Indications of Endoscopic Procedure, it now reads:” There is no standard for the selection of endoscopic operation methods for small gastric SETs that originate from the MP layer. Endoscopist experience and tumor characteristics, such as the size, depth, location, and extraluminal or endoluminal growth of the tumor, are the main factors in deciding which surgical method to employ. Generally, for gastric SETs with endoluminal growth, ESE is a favorable choice, whereas for extraluminal growth, EFTR is another favorable choice. In areas suitable for

establishing a submucosal tunnel, such as in the cardia adjacent to the gastric fundus, the lesser curvature of gastric body, or the greater curvature of gastric antrum, STER is also applicable, yet it should be performed only by an experienced endoscopist.”(Page 16, line 18-Page 17, line 5)

In the summary section, we have explained why a high risk endoscopic removal is superior to surgical removal for small gastric subepithelial tumors, it now reads:” Although there are some complications or adverse events associated with endoscopic operation, such as perforation, massive bleeding, and subcutaneous emphysema, endoscopic operation provides a new option for the management of gastric SETs that originate from the MP layer, which has advantages over surgical resection in terms of maintaining the normal anatomic structure and function of the stomach and improving the long-term quality of life.” (Page 17, line 8-13)

We have revised the manuscript in line with all the reviewers’ comments and we hope that the manuscript is now acceptable for publication at WJG. If you have any questions, please feel free to contact us. We appreciate your support very much.

Yours sincerely,

Liping Ye