Answer to reviewers

1. To editoral office

Thanks for everything you have done for our manuscript. We have made corrections as you and reviews recommendations. There are 165 patients enrolled in our manuscript. All patients have signed informed consent. We just submited the informed consents of 5 patients with esophageal SMTs and 5 patients with cardial SMTs this time, because the files are to large if we submit all patients' content. We don't know whether that meet your requirement. If not, we could provide all informed content.

2. To Reviewer 1

Dear authors,

As a whole, this paper is well written, but I have two suggestions about this article.

1) Authors presented some pictures of two esophageal cases in Figure 3

The pictures of the former case seems to be better in the endoscopic ultrasound (EUS) image, because SMT seems to be derived from the muscle layer in EUS image. On this point, the latter case is difficult to understand it. In addition, other endoscopic images are similar to the former ones. I think it is better to delete the latter case.

Answer

We very appreciate your kind suggestions. As you suggested, we deleted the latter case. Thank you.

2) Instead of deleting the pictures of the latter esophageal case, authors should add the endoscopic images of cardiac SMT. They performed STER for 59 cases of cardiac SMT. Those pictures will be helpful for the readers to understand the procedure of STER.

Answer

Thanks for your suggestion. The STER procedures for SMTs located in cardia were added as you suggested.

3. To Reviewer 2

The authors investigated efficacy and safety of STER, that is third space endoscopy, for SMTs originating from MP layer in the esophagus and cardia. The study was retrospectively reviewed and had a relatively large number of the patients. There were several concerns which should be addressed by the authors.

Major comments

1. The authors mentioned that the criterion of the endoscopic treatment for gastric GIST was the size with less than 4 cm in diameter. However, the authors concluded that the tumor size was the only risk factor associated with a high mitotic index (≥

5/50 HPF) of GISTs. It should be clearly addressed how many cases showed a high mitotic index. It may suggest that some of the enrolled cases are not indicative of the endoscopic treatment.

Answer

Thanks for your suggestion. Only 3 GISTs were enrolled in our study, and these accounted for 1.8% of all SMTs. One was located in the oesophagus and 2 were located in the cardia. The sizes of each of these 3 GISTs were 10.0*10.0 mm, 24.0*11.0 mm and 25.2*13.2 mm. No GIST in our study was larger than 4 cm in diameter. Moreover, the mitotic rates of these 3 GISTs were no more than 5/50 HPF. As suggested, we added this detailed information to the manuscript.

2. The enrolled cases were defined as their tumors originated from the muscularis propria layer. When, and how were the histological diagnoses done? Were all the cases derived from MP? It seems doubtful.

Answer

Thanks for your comments. The histological diagnoses were made after resection. At present, EUS-FNA and biopsy are considered the most reliable methods for the histological diagnosis of SMTs. Considering the challenges of preoperative tissue collection for SMTs that originate deep within the GI tract, pathological examination is not easy or necessary for easily resectable tumours. Therefore, most of these SMTs had no preoperative diagnosis.

If an SMT did not originate in the MP layer, the surgery cannot be called STER. Several cases demonstrated origins in the MP layer by preoperative EUS, but during surgery, they were confirmed to have originated in the submucosal layer. Although a tunnel was created during the procedures, we cannot regard those surgeries as STER, which was initially named by Xu et al. to describe the resection of SMTs originating in the MP layer. We eliminated all SMTs originating from the submucosal layer. In our study, the 165 SMTs originated in the MP layer.

3. This study was retrospective study. Therefore, the term of “retrospective” should be indicated in the abstract.

Answer

As you suggested, we added “retrospective” to the “methods” section of the abstract.

4. In the patients and methods, there were no comments for the rest of five excluded patients. Please describe them.

Answer

Thanks for your advice. We have added this information to the “patients and methods” section, as you recommended.

5. Why was the maximum diameter of the tumor defined less than 35mm. According to the other reports, the tumor was should be limited less than 3cm [1]. Otherwise, there are some reports for the resectable tumor up to 4cm. What do you consider the resectable size of the tumor using STER technique? Please describe in the discussion.

[1] Xu et al. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). GIE 2012;75:195-199.

Answer

Thanks for your comments. The inner diameter of the tunnel is approximately 3.5 cm, and therefore, the transverse diameter of the SMT treated by STER should not be greater than 3.5 cm (> 3.5 cm)[1, 2]. Several studies that included large SMTs that were greater than 3.5 cm (> 3.5 cm) have concluded that STER is feasible even for large tumours[3-6]. Chen et al.[1] demonstrated that the longest diameter for which STER is efficient is 7 cm. However, previous studies reported that STER was performed for SMTs that were no larger than 5.5 cm in diameter (≤ 5.5 cm)[2, 3]. The most suitable size for a successful STER remains controversial.

We have added “STER was not indicated for SMTs with a transverse diameter larger than 35.0 mm because the inner diameter of the tunnel is approximately 3.5 cm; however, the upper limit of the longest tumour diameter remains unknown. A 7 cm SMT was successfully resected by Chen et al. However, larger size is associated with a high risk of malignancy and may result in loss of endoscopic visualization.” This was added to the “Discussion” section, as you suggested.

6. What kind of the endoscopists did perform STERs? Experts or novice who were supervised by experts? Please describe it.

Answer

We have added “STER procedures were performed by experts with POEM experience in more than 100 cases” to the “methods” section, as you suggested.

Minor comments

1. In the table, the median of the tumor size was needed to describe precisely.

Answer

We have described the size in terms of the median and range. We used the mean (±SD) because we believe the sample size is fairly large, while the distribution of the size of the SMTs is not normal. As you kindly reminded us, it is more suitable to describe the size in terms of the median and range. We have corrected this in the manuscript.

2. When did the administration of antibiotics begin? Please describe it.

Answer

We have added “Intravenous antibiotics were administered from the day STER was performed and were stopped after 2 to 3 days if no signs of infection were observed”, as you suggested.

3. There are several mistakes of spelling in the manuscript. Please submit by the native English editing.

Answer

We apologize for the spelling errors. We have resent the manuscript to AJE for editing by a native English speaker. We selected the premium editing service to guarantee the high quality of editing. Thanks again for your suggestions.

1. Chen T, Zhang C, Yao LQ, Zhou PH, Zhong YS, Zhang YQ, Chen WF, Li QL, Cai MY, Chu Y, Xu MD (2016) Management of the complications of submucosal tunneling endoscopic resection for upper gastrointestinal submucosal tumors. Endoscopy 48 (2):149-155. doi:10.1055/s-0034-1393244

2. Chen T, Zhou P-H, Chu Y, Zhang Y-Q, Chen W-F, Ji Y, Yao L-Q, Xu M-D (2017) Long-term Outcomes of Submucosal Tunneling Endoscopic Resection for Upper Gastrointestinal Submucosal Tumors. Annals of Surgery 265 (2):363-369. doi:10.1097/sla.0000000000001650

3. Liu H, Wei LL, Zhang YZ, Sha QM, Huang Y, Qin CY, Xu HW (2015) Submucosal tunnelling endoscopic resection (STER) for the treatment of a case of huge esophageal tumor arising in the muscularis propria: a case report and review of literature. International journal of clinical and experimental medicine 8 (9):15846-15851

4. Maydeo A, Sharma A, Bhandari S, Dhir V (2015) Submucosal tunneling and endoscopic resection of a large, esophageal leiomyoma. Gastrointestinal endoscopy 82 (5):954. doi:10.1016/j.gie.2015.05.037
5. Tan Y, Liu D (2015) En bloc submucosal tunneling endoscopic resection for a giant esophageal leiomyoma. Gastrointestinal endoscopy 82 (2):399. doi:10.1016/j.gie.2015.03.1904
6. Tan Y, Lv L, Duan T, Zhou J, Peng D, Tang Y, Liu D (2016) Comparison between submucosal tunneling endoscopic resection and video-assisted thoracoscopic surgery for large esophageal leiomyoma originating from the muscularis propria layer. Surgical endoscopy 30 (7):3121-3127. doi:10.1007/s00464-015-4567-1

4. To Reviewer 3

I am interested in this manuscript for the efficiency and safety of STER.
This manuscript is almost acceptable in my insight.
However, I have some comments for this paper, please see below.

Miner comments
1: How many cases did you perform EUS-FNA before STER?
And if there are EUS-FNA cases before STER procedure, please describe the number and the accuracy rate of the examination in your study. Because even if STER is safety procedure however targeted disease is mostly benign lesion, such as leiomyoma. I think that it is better to narrow down to attempt cases with more malignant potential lesions such as GIST. If you only performed few cases of EUS-FNA, please describe the reason without EUS-FNA before STER in the discussion.

Answer

We are so sorry that few of our enrolled patients have undergone EUS-FNA. We have made an explanation in “Discussion” part as you suggested.
SMTs are covered by intact mucosa, making the EUS-FNA and biopsy difficulty, especially when they originate from the MP layer. Considering limited diagnostic values and the challenge of preoperative tissue collection especially when SMTs are easily resected and the accuracy of biopsy seems low, preoperative EUS-FNA was not conducted in our study. In our experience, preoperative biopsy seems not necessary for SMTs originating from the MP layer, because the inflammatory causing by biopsy will make the procedures, especially tunnel procedures, more difficult. Inflammatory will affect the creation of tunnel.

2: It was written that the author performed to use a single-accessory channel scope (GIF Q260J/GIF 290J; Olympus) in Materials and methods. However I cannot find GIF 290J in Olympus web site, please confirm it.

Answer

We are so sorry that we made a mistake. We have correct GIF 290J to GIF 290. Very

appreciated you very much.

1) Title. Does the title reflect the main subject/hypothesis of the manuscript?
Yes

2) Abstract. Does the abstract summarize and reflect the work described in the manuscript?
Yes

3) Key words. Do the key words reflect the focus of the manuscript?
We have updated the key words as WJG instruction.

4) Background. Does the manuscript adequately describe the background, present status and significance of the study?
Yes

5) Methods. Does the manuscript describe methods (*e.g.*, experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail?
Yes

6) Results.
Are the research objectives achieved by the experiments used in this study?

Yes. The research objectives of this manuscript are the safety and effectiveness of STER.

I think these objectives achieved in this study. Even though this study was designed by single-center and retrospective study, the number of underwent STER patients are more than one hundred in this institution, it is not small number compared with the previous papers.

What are the contributions that the study has made for research progress in this field?

There is no severe complication in this study. SMTs of the area, especially esophageal lesions are almost benign neoplasms, so it is important to need to achieve very few complications. I think this aim is at least achieved in this study.

7) Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently?

8) Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends?
Yes, it is no problem.

9) Biostatistics. Does the manuscript meet the requirements of biostatistics?
Yes.

10) Units. Does the manuscript meet the requirements of use of SI units?
Yes.

11) References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references?
Yes.

12) Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate?
There is no problem for the language issues.

13) Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting?
Yes.

14) Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics?
It is already checked by the attached file.

5. To Reviewer 4
In this retrospective study, authors describe the effectiveness and safety of STER for gastrointestinal (GI) SMTs originating from the MP layer in a large population and compare the feasibility of STER for resection of oesophageal and cardial SMTs.
This result with a large number provides us an important information in the management of small SMT.

However, I would like to suggest some issues of this article with several comments and criticisms as following.

Major comments

1)What is the preoperative diagnosis for included SMTs?
EUS-FNA is generally recommended. Authors should mention it.

Answer

We appreciate your kind advice. The preoperative diagnosis was primarily made based on CT, MRI, or EUS. Few patients underwent EUS-FNA in our study. We have added an explanation to the "Discussion" section as you suggested. We hope our explanation is satisfactory.

I would like to discuss with you the necessity of EUS-FNA. EUS-FNA and biopsy are considered the most reliable methods for the histological diagnosis of SMTs [1, 2]. SMTs are covered by intact mucosa, which increases the difficulty of EUS-FNA biopsy, especially when they originate in the MP layer. Considering their limited diagnostic value and the challenge of preoperative tissue collection [3-7], EUS-FNA is not necessary, especially when SMTs are easily resected and the accuracy of biopsy seems low [8, 9]. In our experience, preoperative biopsy does not appear to be necessary for SMTs originating in the MP layer because the inflammation induced by biopsy will increase the difficulty of these procedures, especially the tunnel procedure. Inflammation may also affect the creation of the tunnel.

1 Hoda KM, Rodriguez SA,Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointestinal endoscopy 2009; 69(7): 1218-1223 [PMID: 19394006 DOI: 10.1016/j.gie.2008.09.045]

2 Polkowski M,Bergman JJ. Endoscopic ultrasonography-guided biopsy for submucosal tumors: needless needling? Endoscopy 2010; 42(4): 324-326 [PMID: 20354943 DOI: 10.1055/s-0029-1244070]

3 Nishida T, Kawai N, Yamaguchi S,Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society 2013; 25(5): 479-489 [PMID: 23902569 DOI: 10.1111/den.12149]

4 American Gastroenterological Association I. American Gastroenterological Association Institute medical position statement on the management of gastric subepithelial masses. Gastroenterology 2006; 130(7): 2215-2216 [PMID: 16762643 DOI: 10.1053/j.gastro.2006.04.032]

5 Levy MJ, Jondal ML, Clain J,Wiersema MJ. Preliminary experience with an EUS-guided trucut biopsy needle compared with EUS-guided FNA. Gastrointestinal endoscopy 2003; 57(1): 101-106 [PMID: 12518144 DOI: 10.1067/mge.2003.49]

6 Williams DB, Sahai AV, Aabakken L, Penman ID, van Velse A, Webb J, Wilson M, Hoffman BJ,Hawes RH. Endoscopic ultrasound guided fine needle aspiration biopsy: a large single centre experience. Gut 1999; 44(5): 720-726 [PMID: 10205212 PMCID: 1727480]

7 Cantor MJ, Davila RE,Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointestinal endoscopy 2006; 64(1): 29-34 [PMID: 16813799 DOI: 10.1016/j.gie.2006.02.027]

8 Xu MD, Cai MY, Zhou PH, Qin XY, Zhong YS, Chen WF, Hu JW, Zhang YQ, Ma LL, Qin WZ,Yao LQ. Submucosal tunneling endoscopic resection: a new technique for treating upper GI submucosal tumors originating from the muscularis propria layer (with videos). Gastrointestinal endoscopy 2012; 75(1): 195-199 [PMID: 22056087 DOI: 10.1016/j.gie.2011.08.018]
9 Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, Sundar HM, Trent JC,Wayne JD. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. Journal of the National Comprehensive Cancer Network : JNCCN 2010; 8 Suppl 2: S1-41; quiz S42-44 [PMID: 20457867 PMCID: 4103754]

2) Authors describe that leiomyomas are the most common SMTs in the esophagus while GISTs are more prevalent in the cardia and stomach in the discussion area. Whereas, STER is mostly indicated for esophageal SMTs, resulting in final diagnosis of mostly leiomyomas and rarely GISTs in this study.
Thus, authors should explain the clinical significance that STER is needed for esophageal SMTs.

Answer

Thanks for your suggestion. As you suggested, we have added an explanation to the "Discussion" section to explain the clinical significance of oesophageal STER. Several explanations are also included in the "Introduction" section. We hope our description explains the significance of STER, not only in the oesophagus but also in the cardia.

Leiomyomas are the most common SMTs in the oesophagus, but GISTs are the second most common SMTs in the oesophagus. Preoperative pathological diagnosis of SMTs is very difficult. Long-term surveillance may increase the financial burden and psychological stress in patients and may delay the diagnosis of malignancy and treatment. Early resection of SMTs allows confirmation of the pathological diagnosis and achieves a clinical cure. Therefore, STER is also important for oesophageal SMTs.

3)GISTs often occur in the body of the stomach. In this study, is this lesion included? If not, authors should mention the reason. Based on the incidental rate of GISTs on each organ, gastric SMT which often occurs in the body seems to be better lesion indicated for STER.

Answer

We did not enroll any patients with gastric SMTs except when the SMTs were located in the cardia. There were two reasons for this. One reason is mentioned in the "Materials and Methods" section, and we have now added the other reason as you

recommended.

The first reason is that “We excluded three patients with gastric antrum SMTs who underwent STER due to the small number of patients and because STER is less commonly performed in the antrum and requires further evaluation”.

The other reason we have added is that the bent anatomical orientation of the stomach makes it challenging to perform STER because of the difficulty in establishing a submucosal tunnel.

Therefore, few gastric SMTs were resected by STER in our study.

4)Authors should mention the growth pattern of included SMTs (intra/extra/mixed) and the proportion.

If STER is indicated for only GI SMTs with intraluminal growth pattern, authors should describe this limitation in the discussion session.

Answer

Your advice is of great importance. As you stated, the growth pattern of SMTs is a predictive factor for en bloc resection. However, we apologize that we failed to mention the pattern of the 165 SMTs. Our study is a retrospective study, and EUS recordings are available for some SMTs, while for others, only EUS imaging is available. When the SMTs were evaluated, we pressed the EUS probe on the SMTs, which may have deformed the SMTs. I believe there will be great bias if we evaluate the growth pattern according to EUS imaging alone.

We are currently performing a prospective study of STER, and for this study, we will take the growth pattern into consideration. Thanks for the recommendation.

5) In the introduction session, digestive endoscopic tunnel technique (DETT) was firstly reported by Linghu et al. in 2009[10, 11].

Whereas, I have recognized that the first report regarding DETT was described by Sumiyama K. as follows:

Among the new endoscopic interventions based on endoscopic submucosal dissection (ESD) is the submucosal tunneling technique, which involves the introduction into the submucosa of tunnels that permit a safer offset entry into the peritoneal cavity for NOTES. This method, developed at the Mayo Clinic, was initially described as submucosal endoscopy with a mucosal flap safety valve (SEMF). (Ref.: Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Knipschield MA, Marler RJ. Submucosal endoscopy with mucosal flap safety valve. *Gastrointest Endosc*. 2007;65(4):688–694.)

Accordingly, the DETT is the same method with SEMF. Authors should investigate first-ever report on PubMed repeatedly.

10 Linghu E. Endoscopic resection for gastrointestinal pre-cancerous lesion and

early cancer. Electronic Image Press of the Chinese Medical Association; 2009
11 Endoscopy CSoD. Consensus on Digestive Endoscopic Tunnel Technique Chinese Journal of Gastrointestinal Endoscopy (Eletronic Edition) 2017; 4(4): 145-158

Answer

Thanks for the reminder. We have re-read the study by Sumiyama K et al., and we agree with you that DETT is similar to SEMF in some respects. For example, they can both prevent perforation and they both involve the creation of a space between the mucosal and MP layers. However, we insist that DETT is a new technique that differs from SEMF. There are three main reasons, which are discussed below.

First, the intentions of these two procedures are different. SEMF was designed to prevent perforation during NOTES. The mucosa overlying the dissected submucosal space serves as a safe flap valve, which prevents peritoneal leakage. However, the prevention of perforation is just one of its intentions. DETT, as reported by Linghu et al., aimed to isolate intra-luminal gas or fluid from the extra-luminal space, to resect lesions quickly, and to prevent infection. The creation of a tunnel was intended to provide a space for the endoscopic procedure (for example, for a better endoscopic view during resection of a larger tumour) and to allow a quick resection time.

Second, their application areas are different. SEMF is used in NOTES. However, DETT is used in a series of application areas. The DETT application range covers the following: (1) treatment of lesions originating in the mucosal layer, e.g., endoscopic submucosal tunnel dissection (ESTD) for large oesophageal or circular early-stage cancer or precancerous lesions; (2) treatment of lesions in the MP layer, peroral endoscopic myotomy (POEM), submucosal tunnelling endoscopic resection (STER), among others; and (3) diagnosis and treatment of lesions outside the GI tract, such as resection of lymph nodes and benign tumour excision in the mediastinum or abdominal cavity.

Third, DETT was initially named by Linghu et al., not by Sumiyama K. Now, DETT is well known worldwide, and the origin of DETT is attributed to Linghu et al.

In our opinion, SMEF and DETT have many differences. We hope our reasons are persuasive.

Minor comments

In the Discussion session, authors should revise the following mistakes:

Line 15:

few studies have enrolled a large population, making the results less convincing and g further studies necessary .

Answer

We apologize for this mistake. We have deleted the “g”. Thank you.

Line 47:

Creating a tunnel during STER for cardial SMTs was more difficult than for esophageal SMTs and took a longer amount of time. .

Answer

Thanks for your effort in helping us improve the quality of our manuscript. We have deleted the “.”