

Round-1

Dear Editor,

We would like to thank you and the reviewers for the positive evaluation of our manuscript. We have carefully read all comments and suggestions and have revised the manuscript accordingly. The constructive suggestions provided to us have helped improve both the quality and clarity of the manuscript. We hope that the revised paper is now acceptable for publication in *World Journal of Gastroenterology*. Our point-by-point responses to the reviewers' comments follow.

1. Abstract: The abstract is too long, please shorten it.

Response: The abstract has been shortened. The revised abstract is below:

BACKGROUND

Endoscopic submucosal dissection to treat mucosal and submucosal lesions often results in low rates of microscopically margin-negative (R0) resection. Endoscopic full-thickness resection (EFTR) has a high R0 resection rate and allows for the definitive diagnosis and treatment of selected mucosal and submucosal lesions that are not suitable for conventional resection techniques.

AIM

The aim of the study was to evaluate the efficacy and safety of EFTR using an over-the-scope clip (OTSC).

METHODS

This prospective, single-center, non-randomized clinical trial was conducted at the endoscopy center of Shengjing Hospital of China Medical University. The study included patients aged 18-70 years who had gastric or colorectal submucosal tumors (SMTs) (≤ 20 mm in diameter) originating from the muscularis propria based on endoscopic ultrasound (EUS) and patients who had early-stage gastric or colorectal cancer (≤ 20 mm in diameter) based on EUS and computed tomography. All lesions were treated by EFTR combined with OTSC for wound closure between November 2014 and October 2016. We analyzed patient demographics, lesion features, histopathological diagnoses, R0 resection (negative margins) statuses, adverse events, and follow-up results.

RESULTS

A total of 68 patients (17 men, 51 women) with an average age of 52.0 ± 10.5 years (32-71 years) were enrolled, which included 66 gastric or colorectal SMTs and 2 early-stage colorectal cancers. The mean tumor diameter was 12.6 ± 4.3 mm. The EFTR procedure was successful in all cases. The mean EFTR procedure time was 39.6 ± 38.0 minutes. The mean OTSC defect closure time was 5.0 ± 3.8 minutes, and the success rate of closure for defects was 100%. Histologically complete resection (R0) was achieved in 67 patients (98.5%). Procedure-related adverse events were observed in 11 patients (16.2%). The average post-procedure length of follow-up was 48.2 ± 15.7 months. There was no recurrence during follow-up.

CONCLUSION

EFTR combined with OTSC is an effective and safe technique for the removal of select subepithelial and epithelial lesions that are not amenable to conventional endoscopic resection techniques.

2. The indication for EFTR using OTSC is SMT originating from muscularis propria less than 2cm in diameter. Why was the size less than 2cm in diameter? I think that it is not necessary to resect small SMT such as benign tumor. How is the indication for this procedure decided? Are change of tumor size and/or shape or histological findings considered?

Response: The use of an OTSC to close a 2-cm (diameter) gastric wall defect has been proven to be safe and effective. Thus, we chose the lesions with a diameter of less than 2 cm in the study.

Whether small GISTs require endoscopic resection remains controversial. The National Comprehensive Cancer Network guidelines recommend that in the case of small GISTs (≤ 2 cm) lacking high-risk EUS features (e.g., irregular border, lobulation, internal heterogeneous echogenicity, anechoic [cystic] spaces, hyperechoic foci, and tumor extraluminal growth), conservative follow-up should be performed. However, the European Society for Medical Oncology indicates that surgery should be the standard treatment for small histologically confirmed GISTs. Furthermore, some researchers have even proposed that all GISTs have malignant potential and, thus, surgical or endoscopic resection should be performed on detected GISTs.

Since endoscopic resection is a simple and minimally invasive method of obtaining histological samples, this method is recommended even for small gastric tumors original from the

muscularis propria. In this way, patients not only avoid the burden of survival and follow-up with a tumor, but also obtain accurate diagnosis.

3. Were those tumors made a pathological diagnosis before EFTR?

Response: There is a clear preoperative pathological diagnosis of mucosal lesions; however, no pathological diagnoses for SMTs were made.

4. The indication for EFTR using OTSC includes gastric cancers and colonic cancers. However, ESD has recently become as standard therapy. If ESD is difficult to resect the lesions, not only lesions but also lymph node should be resected for complete curability.

Response: ESD has recently become a standard therapy. Therefore, there were few early-stage cancer cases included in this study. However, for the lesions at difficult anatomical sites or lesions that are non-lifting due to scarring, EFTR is an alternative resection technique that expands the possibilities of endoscopic resection.

5. EFTR procedure time for some lesion was too long (236min). Why did it take more time?

Response:

1. The case was at the beginning of the learning curve;
2. The location of the lesion was difficult to operate;
3. Intraoperative hemostasis takes a long time.

6. Was follow up endoscopy performed after EFTR? Were resected sites in some lesions open after EFTR?

Response: Patients were scheduled for endoscopy follow-up at 3 months and at 1 year, 2 years, and 3 years after the initial EFTR, in order to observe local healing and determine if the OTSC had disintegrated. There were no cases of perforation due to early OTSC shedding.

5. What is the criteria of mild adverse events?

Response: Mild adverse events included events that did not require medical or repeated endoscopic intervention and did not prolong hospital admission. The mild adverse events included post-procedural abdominal pain, discomfort, and elevated body temperature.

6. Was bleeding, fever, or local peritonitis included into moderate adverse events?

Response: Yes. Bleeding, fever, or local peritonitis were included as moderate adverse events because these conditions required medical or repeated endoscopic intervention and/or prolonged hospital admission.

7. Authors mention in Discussion section EMR or ESD are associated with a low rate of R0-resection and high perforation rate. However, ESD recently shows high rate of R0-resection and low perforation rate.

Response: This passage has been removed.

Minor

8. Abstract: Please change “52±10.54” to “52±10.5”. please change “12.56±4.26” to “12.6±4.3”.

Response: These values have been changed, as requested.

9. Please unify the form of references.

Response: The references have been formatted and are not in a uniform style.

Yours sincerely,

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Round-2

Dear Editor,

We would like to thank you and the reviewers for the positive evaluation of our manuscript. We have carefully read all comments and suggestions and have revised the manuscript accordingly. The constructive suggestions provided to us have helped improve both the quality and clarity of the manuscript. We hope that the revised paper is now acceptable for publication in World Journal of Gastroenterology.

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I think that major revision is necessary for this manuscript. Authors revised the manuscript, however, it has not been fully revised yet. Please mention the responses to reviewer's comments No. 2, 5 in Discussion section. Authors did not unify the form of references at all. For example, in No 5, please correct “2018 Jun;32(6):” to “2018;32:”.

Response: I have added the modification of No.2,5 to the discussion section and unify the form of references.

EFTR lasted 236 minutes in one case. The specific reasons are as follows: 1. The case was at the beginning of the learning curve; 2. The location of the lesion was difficult to operate; 3. Intraoperative hemostasis takes a long time.

The use of an OTSC to close a 2-cm (diameter) gastric wall defect has been proven to be safe and effective. Thus, we chose the lesions with a diameter of less than 2 cm in the study.

Whether small GISTs require endoscopic resection remains controversial. The National Comprehensive Cancer Network guidelines recommend that in the case of small GISTs (≤ 2 cm) lacking high-risk EUS features (e.g., irregular border, lobulation, internal heterogeneous echogenicity, anechoic [cystic] spaces, hyperechoic foci, and tumor extraluminal growth), conservative follow-up should be performed. However, the European Society for Medical Oncology indicates that surgery should be the standard treatment for small histologically confirmed GISTs. Furthermore, some researchers have even proposed that all GISTs have malignant potential and, thus, surgical or endoscopic resection should be performed on detected GISTs.

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