Endoscopic Full Thickness Resection compared to Submucosal Tunnel Endoscopic Resection for Treatment of Gastric Gastrointestinal Stromal Tumor

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:

Introduction
Submucosal tunnel endoscopic resections (STER) had been increasingly performed for treatment of gastric GIST, while STER was limited by close dissection within tunnel and risking breach of tumor capsule. Endoscopic full thickness resection (EFTR) allowed resection of GIST with margins to prevent recurrence. This study aimed to compare EFTR against STER for treatment of gastric GIST.

Method
We retrospectively reviewed clinical outcomes of patients with gastric GIST who received either STER or EFTR. Gastric GIST less than 4cm were recruited. The clinical outcomes including baseline demographics, perioperative and oncological outcomes were compared between two groups.

Results
From 2013 to 2019, 46 patients with gastric GIST were treated by endoscopic resection, 26 received EFTR and 20 received STER. Most of the GISTs were in proximal stomach. There was no difference in operative time (94.9 vs 84.9 mins; p = 0.401), while endoscopic suturing was applied more for closure after EFTR (p < 0.0001). Patients after STER had earlier resumption of diet and shorter hospital stay while there was no difference in adverse event rate between two groups. The en-bloc resection rate for EFTR was significantly higher than STER (100% vs 80%; p = 0.029) while there was no difference in the local recurrence.

Conclusion
This study demonstrated that although patients who received EFTR had longer hospital stay and slower resumption of diet compared to STER, EFTR achieved significantly higher rate of en-bloc resection compared to STER for treatment of gastric GIST.

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Endoscopic Full Thickness Resection (EFTR) compared to Submucosal Tunnel Endoscopic Resection (STER) for Treatment of Gastric Gastrointestinal Stromal Tumors

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data analysis as well as writing of manuscript. HC Yip is responsible for performance of the
procedures and edition of the manuscript. SM Chan, S Ng, A Teoh and E Ng are responsible
for quality assurance and critical comment of the manuscript.
Abstract

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Conclusion

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Introduction

Gastric subepithelial tumors are usually considered as benign neoplasm. The commonest pathology for gastric subepithelial tumors included gastrointestinal stromal tumor (GIST), leiomyoma, Schwann cell tumor, pancreatic heterotopia as well as neuroendocrine tumor. Current guidelines stated that for surgical resection should be performed for GIST larger than 2cm, while endoscopic surveillance should be conducted for GIST of low risk and less than 2cm [1,2]. The determination of risks from these small gastric GIST depends on suspicious features on endoscopic ultrasonography (EUS), while fine needle aspiration or biopsy could be challenging due to the small size of these GISTs [3].

Endoscopic submucosal dissection (ESD) was established as standard of treatment for intramucosal early gastrointestinal neoplasia [4]. Recently, studies demonstrated the feasibility of applying techniques of ESD for treatment of gastric subepithelial tumors [5,6,7]. Despite the success in achieving resection of these tumors, various cohort studies demonstrated high risk of full thickness perforation during resection by ESD as majority of these tumors arise from or adherent to muscularis propria [5,6,7,8,9]. Submucosal tunnel endoscopic resection (STER) and per-oral endoscopic tumor resection (POET) were developed aiming to achieve endoscopic resection of submucosal tumors of the gastrointestinal tract without inducing full layer perforation [10,11,12]. However, during dissection of the tumor within the submucosal tunnel, the space for manipulation was quite narrow which might lead to close dissection to the tumor causing breach of the tumor capsule [13].

Recently, advancement of endoscopic resection led to development of techniques for endoscopic full thickness resection (EFTR) [14]. ASGE Technology Committee established
guideline for EFTR and STER, and EFTR is classified into exposed and non-exposed procedures. The exposed EFTR is performed with a tunnelled or non-tunnelled technique and subsequent closure of defect, while for the non-exposed EFTR a secure serosa-to-serosa apposition is achieved before full thickness resection. Recent ESGE guidelines on management of gastrointestinal subepithelial lesions recommended endoscopic resection as an option for gastric subepithelial lesions smaller than 20mm [15]. Meanwhile, the evidence to support the type of endoscopic resection to achieve en-bloc resection of these lesions is lacking. This study aimed to compare the clinical and oncological outcomes of tunnelled resection (STER) against non-tunnelled exposed EFTR of gastric GIST.
**Method**

This is a retrospective cohort study conducted at the endoscopy center of a University-affiliated tertiary referral hospital. The objective was to compare the clinical outcomes of Submucosal Tunnel Endoscopic Resection (STER) against exposed Endoscopic Full Thickness Resection (EFTR) for treatment of gastric GIST. The case records of patients with diagnosis of gastric GIST who received endoscopic resection by STER and exposed EFTR collected in were recruited into a prospectively collected database were retrospectively reviewed.

All patients would receive preoperative investigation of the gastric submucosal tumors including endoscopic ultrasonography (EUS) and contrast CT abdomen. The decision to EUS guided fine needle aspiration cytology depend on the decision of individual endoscopist. The size of the gastric submucosal tumors would be determined by OGD, EUS, CT or combination. Patients with gastric GIST located at the gastric cardia, lesser curvature and antrum with size between 15mm to 40mm upon preoperative investigations were recruited for endoscopic resection by STER or EFTR. The study was conducted with standards according to the principles of Declaration of Helsinki. All the procedures were performed by two endoscopists who had vast experience in performance of advanced endoscopic procedures including ESD, POEM, STER and EFTR. All the procedures were performed under general anaesthesia at the endoscopy suite with CO2 insufflation.

**Intervention**

**Submucosal Endoscopic Tumor Resection (STER)**

The procedure of STER was described in a previous publication [16]. Briefly, after endoscopic location of the gastric GIST and pre-injection, a 2 to 3cm mucosal entrance would be created 2cm proximal to the tumor border. A short submucosal tunnel would be developed until
identification of the tumor. The lateral borders of the subepithelial tumor would be
dissected, and subsequently a 2cm pocket would be created distally for manipulation.
Subsequently, the tumor would be dissected away from muscularis propria layer to the
subserosal layer. Upon completion of the dissection, the tumor would be retrieved per
orally. The mucosal entrance would be closed by primary clip closure method.

Endoscopic Full Thickness Resection (EFTR)
The procedure steps of EFTR for treatment of gastric subepithelial tumors were illustrated in
Figure 1, 2 and video. The procedural planning would depend on the location of the gastric
GIST. For gastric GIST located over the proximal stomach, cardia and fundus, EFTR would be
performed with the endoscope in retroflexed position, while for those located at the antrum
and prepyloric canal, the endoscope would be in antegrade position.

After adequate lifting of the submucosa, mucosal incision would be performed using Dual
Knife jet (Olympus Co Ltd, Japan). Upon trimming of the mucosal incision and exposure of
submucosal plane on the surface of the muscularis propria, the tumor would be identified.
To ensure en-bloc margin negative resection, the dissection plane should aim at preserving
an intact tumor pseudo-capsule while dividing the muscularis attachment 1-2mm away from
the capsule. The serosal layer would often be breached upon deep dissection of the
muscularis propria and resulted in full thickness resection. After adequate mobilization of
the GIST, transoral clip-string countertraction would be applied to retract the GIST and
expose the serosal plane. Upon full thickness incision to peritoneum, insufflation of CO2
should be reduced to minimum manually. As the tumor and covering mucosal layer was still
attached to the luminal wall, we could reduce the full thickness defect and thus reducing the
CO2 leakage through pulling of transoral clip-string. Percutaneous needle decompression of
the intraperitoneal CO2 could be performed in occasions when the pressure is too high that impaired adequate mechanical ventilation. At this juncture, the serosal border of the GIST could be clearly identified by recognizing abnormal tumor vessels, and the dissection over normal serosa and muscularis propria would ensure adequate resection margins. During serosal dissection in close proximity to adjacent intraperitoneal organs such as colon, inadvertent damage could be avoided by the use of insulated tip knife (IT2, Olympus Co Ltd, Japan). Once the tumour was fully mobilized and pulled inside the stomach, the resection could be completed by placing the endoscope in antegrade manner. The tumor would then be retrieved using Roth Net® retrieval device to avoid slippage of the tumor to peritoneal cavity.

Closure of the luminal defect after EFTR

The luminal defect of gastric wall should be re-examined to determine the optimal method of safe closure. The option of luminal defect closure included: 1. Primary through the scope (TTS) clip closure; 2. Clip-Loop closure (Crown technique) and 3. Endoscopic suturing device closure. The choice of closure would depend on – 1. Size of the luminal defect; 2. Proportion of the full thickness segment. For small luminal defect of 10mm or less with minimal full thickness segment, we could use primary clip closure method with multiple TTS clips. However, for majority of defect of larger than 10mm, clip-loop closure would be performed if the full thickness segment was less than 50% [Figure 3]. If the full thickness segment was larger than 50% of the luminal defect, endoscopic suturing would be the preferred closing method [Figure 2]. The endoscopic suturing device employed was the Overstitch endoscopic suturing system including the OverStitch and OverStitch Sx (Apollo Endosurgery Inc., Austin, United States). The OverStitch would be attached to the end of double channel endoscope.
while the OverStitch Sx would be attached along the side of a single channel endoscope. The procedure of closure was similar between these two systems [Figure 2]. First, the needle would be passed over the whole thickness of one side of the luminal defect. The detachable needle would be caught by anchor exchange catheter, and after opening of the needle driver the tissue would be disengaged. After passage of needle back to needle driver, the needle would be driven as full thickness suture to the opposite side of the gastric wall. After repeating this procedure of suturing in “Figure of 8” manner, the needle would be detached and cinching procedure performed to achieve full thickness suture closure. The procedure would be repeated as necessary until the defect was completely closed as evidence by full distension of stomach upon insufflation without gas leakage and visual confirmation of closure without remnant defect.

The specimen would be sent to dedicated pathologist for analysis with immune staining as well as observation of resection margins.

**Outcome measures and statistical analysis**

The primary outcome is the en-bloc resection rate of GIST, while secondary outcomes included the need of conversion to other procedures for resection, operative time, hospital stay and the rate of complication. The oncological outcomes including the en-bloc resection rate of the gastric GIST as well as rate of tumor recurrence would be assessed. En-bloc resection was defined upon histopathological examination as resection of the GIST in one piece with clear resection margins.

The statistical analyses comparing clinical outcomes between the two groups were performed using Student t-tests for parametric data, Mann-Whitney U test for non-parametric data when appropriate. Categorical data were analysed using Chi-square test or
Fisher exact’s test. Statistical analyses of the data were performed using the SPSS 27.0 statistical software. P values of less than 0.05 were considered statistically significant.
Results

From 2013 to 2019, 46 patients with gastric GIST received endoscopic resection at our institution, including 26 patients who received non-tunnelled exposed EFTR while 20 who received tunnelled exposed EFTR / STER (Table 1). All patients recruited into this study were confirmed to have gastrointestinal stromal tumor (GIST) upon histopathology after resection. When compared between the two groups there was no difference in basic demographics. The mean size of GIST was 22.0 ± 9.79 mm for EFTR group and 20.9 ± 12.4mm for STER group (p = 0.757). Most of the gastric GISTs were located at the cardia and proximal stomach, and there was no difference in the distribution of locations between the two groups. Apparently, EFTR was applied for resection of GIST at fundus - a location which usually contraindicated for submucosal tunnel development in STER group.

There was no difference in the operative time between two groups (94.9 vs 84.9 mins; p = 0.401), while endoscopic suturing was applied more frequently for closure after EFTR compared to STER (p < 0.0001). Patients who received STER was able to resume on full diet one day earlier than those who received EFTR (mean 2.92 vs 2.0 days; p = 0.0002).

Moreover, the STER group had significantly shorter hospital stay than EFTR group (mean 4.38 days vs 3.50 days; p = 0.015). The commonest complication was fever after the procedure for both groups, meanwhile there was no leakage after closure of the mucosal incision or full thickness defect. There was no difference in overall complication rate between two groups (p = 0.593). 92.3% of the patients in the EFTR group required release of the CO2 pneumoperitoneum which developed during the procedure compared to only 35.0% of patients who received STER (p < 0.0001).
All the histopathology confirmed gastrointestinal stromal tumors (GIST) with c-kit and CD117 positive. There was no difference in the proportion of GIST larger than 20mm in size as well as mitotic figures between two groups [Table 1]. Upon histopathological examination of the resected specimen, en-bloc resection rate for EFTR was 100%, which was significantly higher than for STER (100% vs 80%; p = 0.0297). Meanwhile, there was no difference in the local recurrence rate between two groups. The mean follow-up period was significantly longer for STER group compared to EFTR group (21.15 vs 50.50 months; p < 0.0001).
Discussion

Gastric GIST are increasingly recognized during diagnostic endoscopy [15,17]. The malignant potential of GIST can be assessed by size, location as well as mitotic figures through EUS, CT and EUS guided FNB [15,18]. The NCCN guidelines recommended surgical resection for treatment of gastric GIST larger than 20mm or those with high-risk features upon EUS [2]. For small gastric GIST of less than 20mm in size without high-risk features, periodic endoscopic or radiographic surveillance is recommended. Recently, ESGE guidelines for management of GI subepithelial lesions suggested that surveillance for gastric subepithelial lesions without definite diagnosis should be conducted with EGD at 3 to 6 months intervals. Afterwards, surveillance EGD at 2 to 3 years intervals for lesions < 10mm in size and at 1 to 2 years intervals for lesions 10 to 20mm in size [15]. Meanwhile for pathologically confirmed gastric GIST of less than 20mm in size, ESGE recommended management by either regular endoscopic surveillance or endoscopic resection as an acceptable alternative [15].

Although endoscopic surveillance is both feasible and safe in managing gastric GIST smaller than 20mm, the long-term compliance is usually suboptimal. In a cohort study of 65 patients with foregut subepithelial lesions on endoscopic follow-up over 30 months, 25% of these lesions demonstrated growth in size. However, less than 50% of patients underwent surveillance EUS as recommended [19]. The authors suggested that endoscopic surveillance is a poor strategy since the compliance is very low. On contrary when technically feasible, tissue acquisition should be pursued as tissue diagnosis will reassure patients, provide guidance to surveillance recommendation, and in some case eliminate the need for follow-up. However, a meta-analysis of 17 studies on use of EUS guided tissue acquisition for upper GI subepithelial tumours only achieved a diagnostic yield of 59.9% [20].
Endoscopic resection served as an alternative approach for definite treatment for small gastric GIST. Endoscopic resection will not only provide tissue diagnosis but also as a curative treatment and alleviate patients' need for surveillance. Endoscopic resection can be considered for small gastric GIST to avoid the burden of surveillance among young patients and those which demonstrated high risk features upon EUS [14,15]. Endoscopic submucosal dissection (ESD) was first explored as treatment of gastric GIST in a cohort of 33 patients [21]. The mean size of GIST was only 14.5mm while 93.9% of these were resected in one piece. However, vertical resection margin was insufficient in 4 of the 33 GISTs. As GIST originated from interstitial cell of Cajal which located at muscularis propria, endoscopic resection would likely result in full thickness perforation during procedure [22]. Submucosal Tunnel Endoscopic Resection (STER) was developed to avoid full thickness perforation during resection of gastric GIST through a submucosal tunnel [10,11,12,13]. In a retrospective cohort comparing STER against ESD for treatment of gastric GIST at cardia demonstrated similar clinical outcomes including en-bloc resection and complication [22]. However, the en-bloc resection rates for STER and ESD were only 70.2% and 67.5% respectively. One of the major technical issues for STER is the dissection within limited space of submucosal tunnel, which may lead to breaching of the tumor capsule during dissection and increased risks of local recurrence. Secondly, as most of the gastric GIST are usually located in proximal stomach, cardia and fundus, there may be major difficulty in developing a tunnel to reach the target GIST [23].

Endoscopic full thickness resection (EFTR) avoided dissecting close to tumor capsule as the tumor would be mobilized through endoscopic dissection at muscularis propria without space limitation. Moreover, the tumor could be retracted using clip and string technique.
which provided a clear observation to dissection plane, avoiding inadequate resection

margins over both muscularis and serosa. In our study, EFTR demonstrated significantly

higher rate of en-bloc resection compared to STER while there was no difference in the

overall adverse event rate. Though patients who received EFTR resumed diet later than

those who received STER, there was no leakage from full thickness defect after EFTR. The

preferred method for closure after EFTR included clip and loop technique and endoscopic

suturing. In a meta-analysis on endoscopic resection for gastric GIST less than 20mm, the

complete resection rate was 97% with adverse event rate of 8% [24]. However, in a study

comparing endoscopic resection against laparoscopic resection for 130 cases of GIST larger

than 20mm, endoscopic resection demonstrated a significantly lower R0 resection of 25.6%

compared to 85% for laparoscopic resection [25]. The methods of endoscopic resection

included ESD, STER, EMR, EFTR and polypectomy and noticeably numerous important

adverse events occurred, including bleeding, macroscopic perforation requiring laparoscopic

closure, as well as falling of specimen to peritoneal cavity after resection. In our study we

carefully applied techniques to avoid these adverse events including adjustment of energy

platform to achieve hemostasis, as well as various techniques for closure of defect.

Moreover, we always applied 1-2 per-oral clip suture traction to avoid dropping of specimen

into peritoneal cavity after dissection. The traction by per-oral clip suture during dissection

not only exposed the dissection plan but also served to minimize the full thickness defect

and reduce gas leakage during EFTR.

There are several limitations of the study. First, this is a retrospective cohort study

comparing EFTR against STER, where STER was first applied for treatment of gastric GIST

followed by EFTR. There could be improvement in endoscopic techniques over this
transition period which might explain partially the higher en-bloc resection rate. Secondly,
as all the procedures were performed by two endoscopists, there could be an operator bias
and the clinical outcomes may be not applicable in other centers.

In conclusion, our study demonstrated that EFTR achieved significantly higher rate of en-
bloc resection compared to STER for treatment of gastric GIST. Though patients recovery
was hastened by STER due to secure closure, there was no difference in adverse event and
procedure time. Hence EFTR should be recommended for treatment of gastric GIST
amendable to endoscopic resection.
References


Figure Legends

Figure 1 – Schematic illustration of Gastric Endoscopic Full Thickness Resection (EFTR) for treatment of Gastric GIST in proximal stomach. A – ½ circumferential mucosal incision from anal side of submucosal tumor (SMT); B – submucosal & muscular dissection for mobilization of SMT; C – Double retraction of SMT for full thickness & serosal dissection; D – Complete resection from oral side approach

Figure 2 – Endoscopic Full Thickness Resection of Gastric GIST; A – ½ circumferential mucosal incision and submucosal dissection to expose the gastric GIST; B – per oral clip string retraction to lift the submucosal GIST; C – full thickness resection with dissection at border of GIST; D – Exposure of the serosal margin for en-bloc dissection through pulling of the tumor by clip string retraction; E – Closure of luminal defect with Overstitch (Single Channel system; Apollo Surgical Co Ltd); F – complete closure of luminal defect evidence by full distension of stomach without gas leakage

Figure 3 – Alternative closure of luminal defect with clip and loop technique (Crown technique); A – A relatively small portion of gastric luminal defect had involved full thickness resection; B – Application of first clip over detachable loop for fixation at proximal defect; C – further application of clips to attach the loop to mucosal border of the defect; D – Tightening of the detachable loop after application of multiple clips around the mucosal border; E – Complete closure of the defect after closure of the clip-loop; F – release of the detachable loop upon complete closure of the gastric luminal defect
Table 1 – Comparison of the clinical outcomes of EFTR against STER for treatment of gastric gastrointestinal stromal tumors (GIST)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>EFTR (26)</th>
<th>STER (20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>59.6</td>
<td>57.5</td>
<td>0.585</td>
</tr>
<tr>
<td>Male (%)</td>
<td>8 (30.7%)</td>
<td>8(40%)</td>
<td>0.548</td>
</tr>
<tr>
<td>Location of gastric GIST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Lesser curve</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Greater curve</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fundus</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Size of gastric GIST (mm)(mean)</td>
<td>22.0 ± 9.79</td>
<td>20.9 ± 12.4</td>
<td>0.757</td>
</tr>
<tr>
<td>Size &lt; 20mm</td>
<td>8</td>
<td>10</td>
<td>0.231</td>
</tr>
<tr>
<td>Size &gt; 20mm</td>
<td>18</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>26 (100%)</td>
<td>26 (100%)</td>
<td>1.0</td>
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<tr>
<td>Mean procedure time (mins)</td>
<td>94.9</td>
<td>84.9</td>
<td>0.401</td>
</tr>
<tr>
<td>Closure method</td>
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<tr>
<td>Clips / Clip-Loop</td>
<td>12</td>
<td>20</td>
<td>&lt; 0.0001*</td>
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<tr>
<td>Endoscopic suturing</td>
<td>14</td>
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<tr>
<td>Hospital stay (days)(mean)</td>
<td>4.38</td>
<td>3.50</td>
<td>0.015†</td>
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<tr>
<td>Days to resume full diet (mean)</td>
<td>2.92</td>
<td>2.00</td>
<td>0.0002†</td>
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<tr>
<td>Adverse event rate (overall)</td>
<td>1 (3.8%)</td>
<td>2 (10%)</td>
<td>0.593</td>
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<tr>
<td>Postoperative fever</td>
<td>1 (3.8%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>Leakage</td>
<td>0</td>
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<tr>
<td>Release of CO2 pneumoperitoneum</td>
<td>24 (92.3%)</td>
<td>7 (35.0%)</td>
<td>&lt;0.0001*</td>
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<tr>
<td>Conversion to laparoscopic surgery</td>
<td>2</td>
<td>0</td>
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<tr>
<td>En-bloc resection rate</td>
<td>26 (100%)</td>
<td>16 (80%)</td>
<td>0.0297*</td>
</tr>
<tr>
<td>Mitotic Figure (per HPF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 / 10 HPF</td>
<td>26</td>
<td>18</td>
<td>0.184</td>
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<tr>
<td>&gt; 1 / 10 HPF</td>
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<tr>
<td>Follow-up period (months)</td>
<td>21.15</td>
<td>50.50</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0</td>
<td>1</td>
<td>0.435</td>
</tr>
</tbody>
</table>

† - student T test with significant difference; * chi square test with significant difference; HPF – High Power Field
EFTR: mucosal incision from distal border of GIST

A. 1/4 circumferential mucosal incision from anal side of SMT

EFTR: Submucosal dissection around the border of GIST tumor

B. Submucosal & muscular dissection for mobilization of SMT

EFTR: Transoral retraction with dissection around tumor at muscularis propria to serosa

C. Double retraction of SMT for full thickness & submucosal dissection

EFTR: Complete en-bloc dissection after full thickness resection with complete retraction of GIST to within stomach

D. Complete resection from oral side approach