

Endoscopic full thickness resection for gastric tumors originating from muscularis propria

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Abstract

AIM: To do systematic review of current literature for endoscopic full thickness resection (EFTR) technique for gastric tumors originating from muscularis propria.

METHODS: An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered. For the purpose of review, data from individual studies was combined to calculate mean. No other statistical test was applied.

RESULTS: A total of 9 original articles were identified. Four articles were from same institute and the time frames of these studies were overlapping. To avoid duplication of data, only the study with patients over the longest time interval was included and other three were excluded. In total six studies were included in the final review. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%. The mean procedure time varied from a minimum of 37 min to a maximum of 105 min. There was no reported mortality from the technique itself. The most common histological diagnosis was gastrointestinal stromal tumors and leiomyoma. Gastric wall defect closure by either metallic clips or over the scope clip (OTSC) had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm).

CONCLUSION: EFTR is a minimally invasive technique to resect gastric submucosal tumors originating from muscularis propria with a high success rate and low complication rate.

Key words: Endoscopic full thickness resection; Gastric tumor; Muscularis propria; Over the scope clip

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Core tip: Endoscopic submucosal dissection success for gastric submucosal tumors arising from muscularis propria has remained limited. Authors have reported success with endoscopic full thickness resection (EFTR) in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of patients. Careful selection of candidates by preoperative imaging and endoscopy including endoscopic ultrasound to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

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INTRODUCTION

Over the last decade, therapeutic options for gastric submucosal tumor (SMT) resection have drastically evolved. Gastric SMTs are mostly asymptomatic when small (< 2 cm) and are discovered incidentally on endoscopy or radiological investigations done for other indications but larger lesions are more likely to be symptomatic^[1]. The usual symptoms are bleeding, abdominal pain or obstruction. Abdominal mass and weight loss may be present especially if malignant^[2].

Gastrointestinal SMTs can be broadly classified in 4 main groups - gastrointestinal stromal tumors (GIST) which should be considered potentially malignant; smooth muscle derived SMTs like leiomyoma, leiomyosarcoma; SMTs of neurogenic origin like schwannoma, granular cell tumor, neurofibroma and vascular tumors like hemangioma, lymphangioma, kaposi sarcoma, etc^[3]. GISTs are further classified into groups based on their potential of recurrence and metastasis; very low risk, low risk, intermediate risk and high risk or overtly malignant with metastasis at diagnosis^[4]. Most of the tumors arising from muscularis propria are GISTs^[5]. National Comprehensive Cancer Network Guidelines recommend resection of GISTs larger than 2 cm^[6]. Gastric SMTs smaller than 2 cm without clinical

signs of malignancy can be managed conservatively with frequent follow up by endoscopic ultrasonography (EUS)^[7]. However, conservative management is limited by patient's anxiety about diagnosis and follow-up compliance. In addition, EUS cannot differentiate between benign and malignant tumor reliably and EUS-guided fine-needle aspiration is not always accurate since histology is not available^[8]. Due to these reasons some physicians and patients may prefer resection of these tumors over conservative management.

Surgically, gastric SMTs can be resected either by laparoscopic approach or open procedure. However, less invasive endoscopic techniques have been considered and used more often in the last few years. The endoscopic techniques include snare polypectomy or endoscopic submucosal dissection (ESD). Not all SMTs arising from muscularis propria may be luminal to be suitable for snare polypectomy and the success rate for complete resection of tumors originating from muscularis propria by ESD has been reported to vary from 68% to 75%^[9,10]. As tumors from muscularis propria are deep and are associated with risk of perforation and incomplete resection with ESD, newer techniques like full thickness resection followed by endoscopic closure of defect have evolved.

In this review article, we have summarized the studies describing endoscopic full thickness resection (EFTR) of gastric SMTs originating from muscularis propria. Indications, procedure techniques, outcomes and complications reported are discussed.

MATERIALS AND METHODS

An extensive English literature search was done till December 2015; using PubMed and Google scholar to identify the peer reviewed original and review articles using keywords-EFTR, gastric tumor, muscularis propria. Human only studies were included. The references of pertinent studies were manually searched to identify additional relevant studies. The indications, procedural details, success rates, clinical outcomes, complications and limitations were considered.

RESULTS

A total of 9 original articles were identified. Four articles^[11-14] were from same institute and the time frames of these studies were overlapping. Only, the study^[11] which included the patients over the longest time interval was included in our review. Other three were excluded to avoid duplication of data^[12-14]. Out of the final 6 studies included, one was a prospective study^[15] from Germany and other 5 were retrospective studies^[11,16-19] from China. One study^[15] reported results for all gastric sub epithelial tumors. However, we included only those patients from this study who had tumors originating from muscularis propria^[15]. All studies have been summarized in Table 1.

Table 1 Descriptive summary of all studies

Ref. and location	Study type	Inclusion criterion	Exclusion criterion	No. of subjects	No. of lesions	Tumor location	Mean size of lesion (range) (cm)	Mean procedure time (range) (min)	Complications	Success rate (%)	Follow up
Ye <i>et al</i> ^[11] , 2014 China	Retro-spective Single Centre	(1) CT/EUS confirmation of MP origin (2) No extraluminal growth	(1) Size > 3.5 cm (2) Coagulation disorders (3) Unfit for GA (4) High risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity)	51	51	(1) Fundus = 22 (2) Corpus = 28 (3) Antrum = 1	2.4 (1.3-3.5)	52 (30-125)	None	98	(1) Surveillance endoscopy for healing at 1, 3 and 6 mo PP (2) For GIST = Endoscopy/EUS/abdominal ultrasound/CT/chest radiography every 12 mo, indefinitely
Schlag <i>et al</i> ^[15] , 2013 Germany	Retro-spective Single Centre	(1) Age > 18 yr (2) Confirmed SET originating from MP on EUS	(1) Size > 3.0 cm (2) ASA class 4 or 5 (3) Coagulopathy (4) Pregnancy	EFTR group = 6 Lap group = 5	6 5	(1) Corpus = 4 (2) Antrum = 1 (3) Cardia = 1 (1) Fundus = 1 (2) Corpus = 4	1.3 (0.7-2.0) 1.88 (0.8-2.6)	37.3 (26-45) 55 (30-95)	None None	83.3 80	(1) Telephone interview or outpatient visit at 1 mo PP (2) Endoscopy at 3 mo PP
Feng <i>et al</i> ^[16] , 2014 China	Retro-spective Single Centre	(1) MP originating tumor confirmed on EUS or CT if size > 2.0 cm	(1) Size > 5.0 cm (2) Coagulopathy (3) Patients not suitable for GA	48	52	(1) Fundus = 40 (2) Corpus = 7 (3) Antrum = 1	1.59 (0.50-4.80)	59.72 (30-270)	(1) Abdominal distension = 5	100	(1) Endoscopy at 2, 6, 12 and 24 mo PP
Guo <i>et al</i> ^[17] , 2015 China	Retro-spective Single Centre	(1) CT and EUS confirming origin of tumor from MP	(1) Size > 2.0 cm (2) Enlarged lymph nodes (3) Malignant disease	23	23	(1) Fundus = 11 (2) Corpus = 9 (3) Antrum = 3	1.21 (0.6-2.0)	(1) Mean ETFR time = 40.5 (16-104) (2) Mean closure time = 4.9 (2-12)	(1) Localised peritonitis = 2 (managed conservatively) (2) Post op fever = 4	100	(1) Endoscopy at 1 wk, 1 and 6 mo PP
Wu <i>et al</i> ^[18] , 2015 China	Retro-spective analysis of clinical control study	(1) Single tumor (2) Absence of metastasis	(1) Size > 5.5 cm	EFTR group = 50 Lap group = 42	50 42	(1) Fundus = 14 (2) Corpus = 23 (3) Antrum = 13 (1) Fundus = 8 (2) Corpus = 19 (3) Antrum = 15	3.4 (2.5-5.0) 3.8 (3.0-5.0)	85 (55-155) 88 (45-215)	None (1) Gastroparesis = 2 (managed conservatively)	100 93	(1) Endoscopy at 1 mo PP
Zhou <i>et al</i> ^[19] , 2011 China	Retro-spective Single Centre	(1) MP originating tumors confirmed on EUS	(1) Size > 5.0 cm (2) Patients not fit for GA (3) Known abdominal adhesions	26	26	(1) Fundus = 12 (2) Corpus = 14	2.8 (1.2-4.5)	105 (60-145)	None	100	(1) Endoscopy at 2, 4 and 6 mo PP and then every 6 mo (2) EUS or CT scan was performed if tumor residual or recurrence was suspected

GA: General anesthesia; MP: Muscularis propria; PP: Post procedure; SET: Subepithelial tumor; EFTR: Endoscopic full thickness resection; Lap: Laparoscopic; CT: Computed tomography; EUS: Endoscopic ultrasonography; GIST: Gastrointestinal stromal tumors; ASA: American society of anesthesiologists.

DISCUSSION

Indications

All studies included patients with gastric SMTs originating from the muscularis propria confirmed on pre procedure imaging. Endoscopic EUS was the standard imaging technique used in all the studies to determine the layer of origin and size of tumor. Most studies^[11,17-19] also included computed tomography (CT) imaging to further assess the tumor and look for any metastasis. In one study, CT scan was performed only if the tumor size was > 2.0 cm on EUS^[16]. Small size gastric tumors arising from MP can be either benign or malignant. EUS does not allow definite discrimination of benign from malignant lesions^[20,21]. Even tissue sampling by EUS guided fine needle aspiration, trucut biopsy or other biopsy techniques fails to reliably differentiate between benign and malignant lesions^[22-29]. Hence, the only accurate way is complete resection of the target lesion. Nonetheless, authors from each study have used any potential sign of malignancy like large regional lymph nodes, metastatic disease on CT scan, large tumor size, high risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci or heterogeneity) as an exclusion criteria. In addition, subjects with coagulopathy and those unfit for endotracheal intubation or general anesthesia were also excluded.

The inclusion and exclusion criteria for subjects across each study have been summarized in Table 1.

Technique

Ye *et al*^[11], Feng *et al*^[16], Guo *et al*^[17], Wu *et al*^[18] and Zhou *et al*^[19], used similar technique with little variations to resect the gastric SMTs from muscularis propria. Both single and dual channel endoscopes were used to resect the tumor. Dual chamber endoscope was especially used for the broad based tumors. A transparent cap was applied to the tip of the endoscope to provide a constant endoscopic view during the procedure. The area around the lesion was marked either by needle knife^[11,19] or argon plasma coagulation^[18]. Submucosa in the area around the lesion was injected with a solution containing normal saline, 1% indigo carmine and epinephrine to make dissection easier. A hook knife^[11,16,18], IT knife^[16] or a triangle tipped knife^[17] was used to make incision in mucosa over the tumor. Dissection down to the serosa was done using hook knife and IT knife. Gastric fluid was aspirated and an active perforation was made through with a hook knife or IT knife. The tumor was dissected out *en bloc*. A needle paracentesis was often performed for decompression if there were signs of pneumoperitoneum.

Schlag *et al*^[15] performed EFTR *via* slightly different technique. EFTR was performed under the laparoscopic control in general anesthesia unless contraindicated, in which scenario procedural sedation was used. A 5 mm optic was used for laparoscopic control. A double channel endoscope was used in all cases. The tumor was grasped by the tissue anchor and lifted into the

snare. The snare was secured and resection performed using blended electrosurgical current. Some of the cases developed perforation during resection, which was treated with tissue twin grasper and over the scope clip (OTSC).

Sarker *et al*^[30] attempted EFTR for gastric tumors ($n = 2$, both were less than 2 cm in size) using OTSC. Although the study was excluded from the review secondary to the site of tumor origin (above the level of muscularis propria), the technique used by the author deserves a mention. The target gastric lesion was suctioned into the cap, followed by deployment of OTSC. Following clip application the scope was removed and reintroduced to snare the lesion above the closed clip. In both cases, author was able to achieve tumor free margin but was unable to achieve full thickness resection. With further improvisation, OTSC holds a promising future for achieving EFTR for local gastric tumors. For larger defects post resection two OTSC placed side by side can be helpful^[31].

Closure

It is extremely important and challenging to achieve effective closure of the gastric perforation for the success of procedure to prevent peritonitis and surgical intervention. There were two main methods for gastric defect closure-metal clips^[11,16,18,19] and OTSC^[15,17].

Metal clips have been commonly used to close the gastric wall defect. They can be easily applied when the perforation is small. For wider defects, air suctioning was used to narrow the size of defect and then clips were applied to close the defect^[11,18,19]. In few cases across the studies, omental patch method^[18,19] was used in which the omentum was sucked into the gastric cavity and clips were used to seal the wound by clipping the omentum to the gastric mucosa. This technique is useful especially for larger defects. Ye *et al*^[11] used endoloop to further strengthen the closure with clips. The endoloop was placed to trap all clips, the loop was tightened and all the clips were tied together with a ligature^[11]. The number of clips used for gastric wall closure were higher for the tumors located in the gastric corpus^[16].

OTSC closure system has been used in the past for the treatment of gastrointestinal bleeding, fistulas and perforations. Guo *et al*^[17] and Schlag *et al*^[15] used OTSC system to close the perforation after tumor resection. Gastric tissues adjacent to the perforation were clamped and then drawn into the transparent cap of the OTSC device. The OTSC system was then released to close the defect. Metal clips were used for any remaining perforation. Both closure methods-clips and OTSC have been found to be effective in the studies. OTSC system is simple to use, convenient and quick however the maximum tumor size for which it has been used till now is 3 cm in the study by Schlag *et al*^[15]. The use of OTSC for gastric perforations arising from EFTR of larger gastric SMTs originating from muscularis propria has not yet been reported.

The protocols to check for leak varied in different studies. Contrast roentgenography was routinely conducted on day 3 by Ye *et al.*^[11]. In the study where, EFTR was performed under laparoscopic control, methylene blue was used at the end of the procedure to perform leakage test^[15]. Feng *et al.*^[16] and Guo *et al.*^[17] did not report any routine post op investigations to check for the adequacy of closure. Two other studies reported use of contrast roentgenography on day 3 to check for contrast leakage in addition to abdominal and pelvic ultrasound to check for any fluid collections^[18,19].

As there is no uniform protocol, it needs to be established what type of investigations need to be performed routinely if any.

Procedure time

The mean procedure time varied from a minimum of 37 min^[15] to a maximum of 105 min^[19]. It was noted that EFTR for SMT > 2.0 cm and for gastric corpus located SMTs took longer time^[16]. Schlag *et al.*^[15] who used grasp and snare technique had shorter procedure time as compared to the other studies who used dissection for full thickness resection. Wu *et al.*^[18] had a mean time of 85 min for EFTR as compared to 88 min for laparoscopic surgery for gastric SMT originating from muscularis propria. A number of factors including size of tumor, location, technique used and experience of operator may effect the procedure time.

Post op care

The immediate post op care in most studies included GI decompression with nasogastric tube, NPO for 1 to 3 d, Proton Pump Inhibitors and antibiotics. Zhou *et al.*^[19] used hemocoagulase injections in addition to the above mentioned post op management.

Outcome

The success of procedure was considered as the complete resection of the tumor and closure of the perforation endoscopically without the need to convert into surgical operation during or after the procedure. R0 is complete resection of tumor with clear margins microscopically while R1 is macroscopic complete resection but positive margins on histology. In our systematic review, the mean success rate for EFTR of gastric tumors originating from muscularis propria was 96.8%.

Ye *et al.*^[11] reported a success rate of 98% for the 51 patients included in the study. One patient in this study needed laparoscopy to retrieve the tumor as it fell in the peritoneal cavity^[11]. Feng *et al.*^[16] reported a tumor free margin resection rate of 100%. A total of 52 lesions in 48 patients were resected in this study with a mean tumor size of 1.59 cm (0.50-4.80 cm)^[16]. Guo *et al.*^[17] also reported a success rate of 100% for tumor free margins for all 23 lesions. The mean size of the tumor was 1.21 cm (0.6-2.0 cm)^[17]. Wu *et al.*^[18] included 50 patients in their study who had EFTR of SMTs with

a mean size of 3.4 cm (2.0-5.0 cm) and 42 patients who had laparoscopic procedure for gastric SMTs with a mean size of 3.8 cm (3.0-5.0 cm). They reported a success rate of 100% for EFTR as compared to 93% for laparoscopic resection. In 3/42 patients, the laparoscopic procedure needed to be converted to laparotomy due to the location of the tumors^[18]. Zhou *et al.*^[19] also achieved a success rate of 100% for their 26 patients with a mean tumor size of 2.8 cm (1.2-4.5 cm). Schlag *et al.*^[15] who performed grasp and snare technique had 20 patients in their study. Eleven out of 20 patients had muscularis propria originating tumors with mean size of 1.56 cm (0.7-2.6 cm). In 5/11 patients, a pure endoscopic approach appeared impossible and a switch to laparoscopic gastric wedge resection was made. The main reasons were extraluminal growth and large size. So endoscopic resection was performed in 6/11 patients. Of these 6 patients, R0 resection was achieved in 5/6 patients (83.3%) and R1 in 1/6. R0 resection rate in laparoscopic group was 80% (4/5 patients). One patient had acute myeloid leukemia (AML) and histology showed diffuses infiltration of AML recurrence in gastric wall. Routine CT scanning in the pre procedure workup was not included in the protocol of this study. The high conversion rate to laparoscopy due to location and size of tumor may suggest the need of extensive pre procedure imaging to better define the size and location of the tumor to plan the resection modality.

Complications

Most studies^[11,15,18,19] did not report any major complications and the post procedure recovery was unremarkable. Feng *et al.*^[16] reported abdominal distension in 5 patients. It was relieved with paracentesis in 3 patients and resolved in 2 d in the rest of the patients. Guo *et al.*^[17] reported post op fever in 4 patients and localised peritonitis in 2 patients, which was managed conservatively. Overall, the complication rate was low with no mortality and no major complications.

Histopathology

The most common diagnosis was GIST and leiomyoma. Out of 51 total lesions, Ye *et al.*^[11] found 30 lesions to be GIST (7 - very low risk and 23 - low risk) and 21 to be leiomyoma. Schlag *et al.*^[15] removed 11 tumors arising from muscularis propria. The histopathologic examination showed GIST in 4, ectopic pancreas in 2, lipoma in 1, accessory spleen in 1, leiomyoma in 1, angioma in 1 and acute myeloid infiltration in 1 specimen. Feng *et al.*^[16] reported a diagnosis of GIST in 43 patients (29 - benign; 8 - very low risk and 6 - low risk), leiomyoma in 4 and schwannoma in 1. In the study by Guo *et al.*^[17] the histology of 23 cases revealed GISTs in 19 (18 - very low risk and 1 - high risk) and Leiomyoma in 4 cases. Zhou *et al.*^[19] resected 26 lesions. Of these 16 were GIST (2 - benign; 12 - low risk; 2 - malignant), 6 were leiomyoma, 3 were glomus tumor and 1 was schwannoma.

GISTs can be malignant but imaging techniques including EUS and CT scan cannot reliably estimate the malignant potential. Thus, resection of these gastric SMTs with minimal invasive techniques is necessary to make a histological diagnosis and estimate risk of malignancy without increasing the morbidity.

Follow up

All authors performed upper GI endoscopy on follow up visits, however timing varied across the studies^[11,15-19]. None of the authors reported any recurrence on the follow up visits. Currently, there is no uniform agreed follow up protocol after EFTR of gastric SMTs arising from muscularis propria. Although endoscopy alone is used in all studies for follow up, there may be a role of EUS to detect recurrence in deeper layers, which may be missed on routine endoscopy.

ESD success for gastric SMTs arising from muscularis propria has remained limited. Incomplete resection and high incidence of perforation seen with ESD is likely secondary to deep location of the tumor. Authors have reported success with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications. EFTR seems to be a reasonable replacement for laparoscopic technique for this subset of gastric SMTs. Careful selection of candidates by preoperative imaging and endoscopy including EUS to rule out metastatic disease and to confirm the size and location of lesion remains crucial. Gastric wall defect closure by either metallic clips or OTSC had similar outcomes although experience with OTSC was limited to smaller lesions (< 3 cm). Post resection follow up by EUS in addition to endoscopy is contemplated. The overall evidence for EFTR for gastric SMTs originating from muscularis propria is small but promising and more experience is awaited.

COMMENTS

Background

Minimally invasive resection of local gastric lesions has remained a challenge for endoscopists. Over the last decade, newer techniques like endoscopic mucosal resection (EMR), piecemeal EMR (EPMR), endoscopic submucosal dissection (ESD) have come up.

Research frontiers

For subset of gastric tumors originating from muscularis propria, the success of ESD remains limited due to deeper location resulting in incomplete resection and increased incidence of perforation. Endoscopic full thickness resection (EFTR) seems to have overcome these pitfalls.

Innovations and breakthroughs

Authors have reported high success rate with EFTR in achieving complete resection of gastric tumors (as large as 5 cm) originating from muscularis propria in the absence of major complications.

Applications

EFTR seems to be a reasonable replacement for laparoscopic technique for resection of gastric submucosal tumors. Careful selection of candidates by

preoperative imaging and endoscopy including endoscopic ultrasonography to rule out metastatic disease and to confirm the size and location of lesion remains crucial.

Terminology

EFTR is a minimally invasive method for *en bloc* resection of gastrointestinal lesions.

Peer-review

This is a good summarization of classification and option of therapeutic method of submucosal tumors (SMTs). The necessity of EFTR for SMTs is convincing and the outcome of EFTR is satisfactory and promising.

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