Surg Endosc (2018) 32:1787–1792
https://doi.org/10.1007/s00464-017-5862-9

Endoscopic resection of gastric gastrointestinal stromal tumors originating from the muscularis propria layer in North America: methods and feasibility data

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Received: 3 May 2017 / Accepted: 22 August 2017 / Published online: 15 September 2017

Abstract
Introduction Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. In recent years, endoscopic procedures such as endoscopic enucleation (EN) and endoscopic full-thickness resection (EFTR) have been used to resect GISTs. This study aimed to investigate the clinical efficacy, safety, and feasibility of endoscopic resection of GISTs in a North American population.
Methods A total of 25 patients with gastric submucosal lesions (SML) underwent endoscopic resection from December 2014 to April 2016. Data from cases with histologically proven GISTs originating from the muscularis propria layer (MP-GIST) were collected. The main outcome measures were complete resection rate, operative time, postoperative complications, length of hospital stay, narcotic analgesic requirement, and follow-up outcomes. Surveillance was performed with CT abdomen, and/or EGD along with oncology follow-up at 6- to 24-month intervals.
Results Out of 25 gastric SML, there were 12 histologically proven MP-GIST. Five endophytic MP-GIST were removed by EN, and seven exophytic MP-GIST were removed by EFTR. All lesions were removed en bloc except for one hard to localize exophytic lesion which was completely removed piecemeal. The mean removal time was 79.7 min (range 17–180 min). Nine out of twelve patients required inpatient admission for observation with a mean length of stay of 2.08 days (range 1–4 days). No complications were noted and no narcotic analgesics were required. Pathology reports showed that one GIST was intermediate risk but all others were low-risk lesions. No recurrence has been noted thus far.
Conclusion Endoscopic removal of MP-GIST by a trained endoscopist appears to be safe and feasible in North American population. Further studies with greater sample size are necessary to compare endoscopic versus surgical resection of MP-GIST. Comparison of outcomes may support wider use of endoscopic techniques for GIST removal.

Keywords GIST · Gastrointestinal stromal tumor · ESD · Endoscopic submucosal dissection · EFTR · Endoscopic full-thickness resection · Endoscopy · Laparoscopy

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Manifestations of GISTs range from symptomatic bleeding to incidental detection during endoscopy [1]. Approximately, 10–30% of GISTs are clinically malignant but all GISTs can have some malignant potential [1, 2]. Even small tumors with low mitotic rates have been observed to be malignant. The European Society of Medical Oncology guidelines state, all GISTs >2 cm in size should be resected [3]. Endoscopic surveillance is an option for GISTs <2 cm without high-risk endoscopic ultrasonography (EUS) features. However, optimal surveillance

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management has not been defined [4]. Due to the unpredictable malignant potential of GISTs which requires long-term surveillance, many patients and physicians may decide on elective resection of GISTs <2 cm as well.

The primary method of resecting these neoplasms is via laparoscopic or open surgery. The primary goal of surgery is complete tumor removal with clear resection margins. Guidelines suggest that laparoscopic wedge resection can be used for tumors ≤5 cm [5, 6]. In recent years, less invasive endoscopic procedures (EP) such as endoscopic enucleation (EN) and endoscopic full-thickness resection (EFTR) have been used to remove GISTs. Endoscopic removal has several advantages, such as an intact stomach after GIST removal, a relatively short hospital stay, decreased sedation and analgesic requirement, relatively low cost, and fewer human resources required compared with surgery. Multiple studies have demonstrated the safety and efficacy of EP to resect GISTs [7, 8]. Even in tumors up to 5 cm, endoscopic resection is noted to be safe and feasible [9]. A recent analysis of 733 cases of endoscopic resection of upper gastrointestinal subepithelial tumors originating from the muscularis propria layer showed that EP for GIST removal is relatively safe and efficacious.

However, most studies of endoscopic resection of GISTs have been performed in Asia, where advanced endoscopy training is more extensive and use of EP is more widespread. To our knowledge, there is relatively scant research completed in North America regarding EP for GIST resection. In this study, we have retrospectively reviewed the data of patients who underwent endoscopic resection of GISTs originating from the muscularis propria (MP-GIST), and we aim to demonstrate the safety and efficacy of EP for MP-GIST resection in a North American population. Demonstrating efficacy of EP by a trained endoscopist in North America may allow for increased use of less invasive EP in the management of GISTs in this region.

Methods

Study design

This single-center retrospective study included a total of 25 patients with gastric submucosal lesions (SML) who underwent endoscopic resection from December 2014 to April 2016 in a tertiary care hospital in Brooklyn, NY. The inclusion criteria were patients with gastric SML originating from the muscularis propria layer determined by computed tomography (CT) and/or endoscopic ultrasound who underwent endoscopic resection and were found to have histologically proven GIST. All procedures were performed with the patient under general anesthesia in the operating room by one experienced endoscopist who had prior training in EN and EFTR. Prophylactic antibiotic was administered in all cases. We recorded all data including demographic information, pathologic characteristics, risk classification, operative times, complications, length of hospital stay, narcotic analgesic requirement, and data on follow-up surveillance including recurrence rate. The main outcome measures were complete resection rate, operative time, perioperative complications, length of hospital stay, narcotic analgesic requirement, and follow-up outcomes. Surveillance was performed with abdominal CT and/or esophagogastroduodenoscopy (EGD) along with oncology follow-up at 6- to 24-month intervals. The institutional review board at our institution approved the study protocol.

Study procedures

Patients that were identified as having gastric lesions on endoscopy and/or radiologic imaging were consented to undergo endoscopic ultrasound (EUS). In all cases, upper EUS was used to characterize the layer of origin, lesion size, location, and growth pattern i.e., endophytic (projecting into the gastric lumen and/or arising from the superficial MP) versus exophytic (projecting into the peritoneal cavity and/or arising from the deeper MP). GISTs often appear as round, hypoechoic lesions with a ground-glass appearance on ultrasound, and diagnosis was confirmed by pathology. Main equipments and accessories are detailed in Table 1.

Endophytic lesions were removed by EN with the following technique: (a) the perimeter of the lesion was marked with cautery; (b) submucosal solution was injected in most of the cases to lift the overlying mucosa, followed by circumferential mucosal incision (endocut) using a Dual Knife; (c) the overlying mucosa was removed (endocut) by either hot snare polypectomy or continued submucosal dissection (endocut) using a Dual knife in order to expose the MP-GIST; (d) the MP-GIST was enucleated using a combination of Dual and IT-2 knives dissection (endocut); (e) any visible vessels were coagulated (soft coag) using a coag grasper; (f) to prevent any delayed bleeding or perforation, the dissection site was closed using either a combination of endoscopic clips and endoloop or over-the-scope endosutures. We solely used endosuturing when it became available at our institute in the later part of the study. After endosuturing, all such patients were discharged home the same day. Any intra-procedural bleeding was managed by using a coag grasper (Fig. 1).

With exophytic lesions which originated from the deeper layers of the muscularis propria, there was high risk of iatrogenic perforation. It was necessary to resect the entire lesion with EFTR. The subsequent gastric wall defect was closed using either a combination of endoscopic clips and endoloop or over-the-scope endosutures. We solely used endosuturing when it became available at our institute in

Table 1 Main equipment and accessories used

Upper endoscopes	Olympus GIF-H190
	Olympus GIS-2TH180 (for closure of the defect)
Submucosal solution	500 ml of 6% hetastarch mixed with 0.5–1 ml of methylene blue and 10 ml of 1:10,000 epinephrine
Injection needles	25 or 23 gauge
Electrocautery knives	Dual 2.0 mm (for mucosal incision and dissection)
	IT-2 (for dissection around the GIST)
	Hot snare (to remove the overlying mucosa in some cases)
Electrocautery unit	ERBE Vio300
Electrocautery settings	Endocut (for mucosal incision and dissection)
	Forced coagulation (used instead of endocut in vascular areas)
	Soft coagulation (for hemostasis using a 5 mm coagulation forceps)
Closure	Metallic hemoclips along with an endoloop
	Over-the-scope endosuture

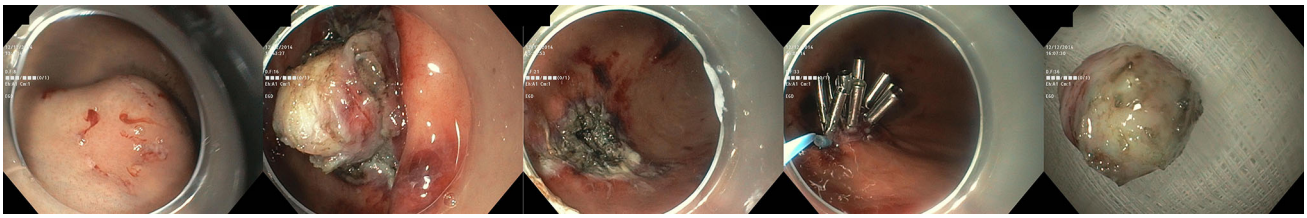

Fig. 1 Endoscopic submucosal dissection. **A** Endoscopy showed a submucosal tumor located in the gastric body. Submucosal solution was injected. **B** The MP-GIST was identified by removal of the overlying mucosa. **C** The tumor was excavated from the MP layer and removed. **D** The dissection site was closed with several clips and endoloop. **E** The resection specimen was 1.7 cm

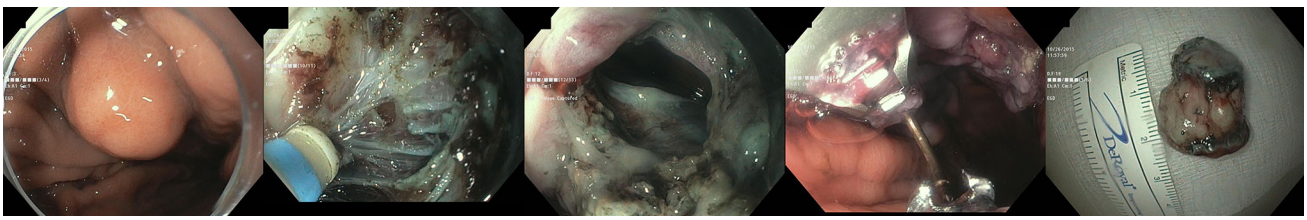

Fig. 2 EFTR. **A** Endoscopy showed a submucosal tumor located in the gastric body. **B** The lesion is being dissected from the deeper fibers of the MP using dual knife. **C** The entire lesion is removed by EFTR, leaving an iatrogenic defect. **D** The gastric wall defect is closed with over-the-scope endosutures. **E** The 2.7-cm MP-GIST was removed en bloc

the later part of the study (Fig. 2). The resulting capnoperitoneum was decompressed by passing an 18-gauge needle attached to half-filled normal saline syringe in the right middle quadrant. All such cases were admitted to the hospital for observation. Per-oral feeding was started if abdominal CT did not show any gastrografin contrast extravasation the following day.

Pathology assessment

Immunohistochemical staining of CD117 (c-KIT), DOG-1, CD34, and S-100 was performed on all resected specimens and positive reactions were considered diagnostic of a GIST. Tumor size and margins were evaluated by experienced pathologists. The mitotic index was determined with 50 high power fields (HPF). Using the mitotic index, tumors were categorized as low risk (<5 mitosis/50 HPF), intermediate risk (6–10 mitosis/50 HPF), and high risk (>10 mitosis/50 HPF) [7].

Definition of complications

Complications were identified as blood loss requiring packed red blood cell transfusion, delayed bleeding,

localized peritonitis, postoperative infections, or perforation requiring surgical intervention.

Follow-up

Surveillance was performed with CT scan of the abdomen and/or EGD at 6- to 24-month intervals. All patients were also referred to oncology for subsequent follow-up. Recurrence was defined as suspected findings on CT or EGD and subsequent confirmation with biopsy.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation (SD) and categorical data were displayed as number (*n*) and percentage (%).

Results

Table 2 summarizes the demographic and clinical features of all included cases. Among 12 patients, 7 were female (58.3%). The mean age was 69.3 ± 12.1 years (range 51–85 years). Before the procedure, EUS and CT abdomen was performed for all patients to characterize lesions and to assess for any evidence of metastasis. The majority of tumors were located in the cardia and fundus of the stomach. There were five endophytic lesions removed by EN and seven exophytic lesions removed with EFTR. One GIST was removed piecemeal but all others were removed en bloc. One larger GIST was cut in few pieces after removal for per-oral retrieval. All but one GIST was characterized as low-risk tumors. One intermediate risk tumor was identified.

Table 3 demonstrates the outcomes of the twelve cases. All of the patients underwent successful endoscopic resection with a mean removal time of 79.7 min (range 17–180). Nine out of twelve patients required hospital admission for observation. The average length of stay was 2.08 days (range 0–4 days). None of the patients required blood transfusions. There were no other complications including delayed bleeding, postoperative infection or localized peritonitis, and need for surgical intervention.

All lesions were completely removed endoscopically. The inked tumor had positive microscopic margins in six cases. Out of those cases, one was removed piecemeal while another was cut during retrieval. Of the remaining four cases, three were removed by EN and one by EFTR. The follow-up period is limited in this study as EP for GIST resection at our institution only began in December 2014. Average follow-up period was about 12 months (6.5–24). All patients completed the follow-up studies except one who refused the follow-up studies. Thus far, there has been no recurrence.

Table 2 Demographic and clinicopathologic features for resected gastric GISTs

Parameters	Endoscopic group ($n = 12$)
Age	
Mean (range)	69.3 ± 12.1 (51–85)
Gender (%)	
Male	5 (41.6)
Female	7 (58.4)
Tumor size (range)	24 mm (10–50)
Tumor location (%)	
Cardia	5 (41.6)
Fundus	6 (50)
Body	1 (8.4)
Growth pattern (%)	
Endophytic	5 (41.6)
Exophytic	7 (58.4)
Excavation procedure (%)	
En bloc	11 (92)
Piecemeal	1 (8)
Closure method (%)	
Clip + endoloop	5 (41.6)
Endosuture	7 (58.4)
Risk classification (%)	
Low	11 (92)
Moderate	1 (8)

Table 3 Outcomes for endoscopic resection of GIST

	Endoscopic group ($n = 12$)
Operative time (min)	79.7
Days of hospital stay (range)	2.08 (0–4)
Complications	
Bleeding	0
Infection	0
Peritonitis	0
Surgical intervention	0
Months of follow-up (range)	12 (6.5–24)
Recurrence	0

Discussion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract [1]. Most often they are found incidentally with endoscopy or radiologic imaging. All GISTs

have some degree of malignant potential [1–3]. Thus, according to the size and clinical characteristics of the tumors and individualized evaluation of patients, resection of GISTs is advised [3, 4]. Surgical resection is considered to be the primary method of GIST resection. However, with continuous development of endoscopic devices and rapid advances in endoscopic technology, EP are being increasingly used for GIST resection [7, 10].

The discussed endoscopic resection techniques have been adopted widely in Asia for many years [11–16]. However, in North America and the rest of the Western world, there is a relative paucity of training resources for such advanced endoscopy procedures. Without more widespread use of EP for GIST resection in North America, evidence for true efficacy and safety in this population is limited. Our study presents increased evidence and support for using EP for GIST removal in North America.

Studies comparing endoscopic and surgical resection of GISTs have shown that EP appear to be an effective, safe, and feasible treatment for GISTs in the esophagus and stomach. Shen et al. found that patients that underwent endoscopic resection of small GISTs (<2 cm) had significantly shorter hospital stay, less intraoperative blood loss, shorter nasogastric tube retention, shorter operative times, and less analgesic requirement compared to patients that underwent surgical resection [17]. In addition to these findings, other studies show that medical cost of hospitalization was lower in patients that underwent endoscopic resection when compared to surgical resection [10, 18].

Our study results were consistent with findings from prior studies demonstrating the safety and efficacy of endoscopic resection of MP-GISTs. In our study, most of the lesions were >2 cm. Based on the available evidence, it appears that EP are a safe method of MP-GIST removal. The major complication noted with endoscopic resection of upper GI tumors is perioperative perforation (12.1%) [19]. However, with endoscopic techniques such as endoscopic clip suturing by experienced endoscopists, perforation is increasingly considered to be a minor complication that rarely necessitates surgical intervention [20, 21]. In fact, EFTR, as implemented in seven out of twelve endoscopic cases in our study, involved perforation and subsequent endoscopic closure. None of the EFTR cases were associated with complications in our study.

There are limitations to our present study. First, this is a retrospective, single-center study so the results may not be generalizable to all patients who have undergone endoscopic resection for GISTs. Second, our study has a small sample size; therefore, larger prospective studies are required to reinforce our primary results. Also, the follow-up period is limited in this study as EP for GIST resection at our institution only began in December 2014. Longer duration of follow-up is needed to determine the long-term effects of endoscopic resection of GISTs. Furthermore, all procedures in our study were performed by an experienced endoscopist who had prior training in EN and EFTR so findings of subsequent studies in other centers may vary depending on the experience of the endoscopists.

With endoscopic resection, there is concern for the risk of tumor spillage into the peritoneum [22]. It is thus imperative to avoid pseudocapsule rupture to prevent intra-abdominal dissemination [5]. R0 resection rates are also lower with EP compared to surgical resection. In our study, 4 out of 10 cases removed and retrieved en bloc were reported to have positive margins. Out of those, only one was removed via EFTR. R0 resection rates can be improved with the use of EFTR. However, the significance of R0 margins for GISTs has been unclear. Some studies have shown that GIST recurrence was more dependent on tumor biology than microscopic margins [23]. There is also no evidence that positive microscopic margins require further resection [5]. Other studies have shown that a microscopically positive margin was not a significant factor in GIST recurrence and/or overall survival [23–27]. However, one study of 86 cases reported a 5.8% local recurrence rate even after complete endoscopic enucleation [28]. Thus, further follow-up studies with long-term surveillance data and assessment of the significance of resection margins will be necessary.

In conclusion, endoscopic resection of gastric muscularis propria GISTs up to 5 cm in size may be a safe and feasible method of removal by a trained endoscopist in a North American population. These lesions can be removed by either EN or EFTR. Increased training of advanced endoscopy techniques in North America is necessary for more widespread use of these endoscopic techniques. Further large-scale studies are necessary to confirm the efficacy of these endoscopic techniques as an acceptable alternative to surgical resection of MP-GISTs in centers with trained endoscopists in North America.

Author contributions I.A. and D.Y. drafted the manuscript and completed the statistical analysis for this study. S.X. reviewed the histopathology. R.R. provided surgical back-up, and reviewed the manuscript. S.I. conceived and designed the study, performed all the procedures, completed the paper review, and finalized the paper preparation. All authors read and approved the final paper.

Compliance with ethical standards

Disclosure Shahzad Iqbal, Iman Andalib, Daniel Yeoun, Ramesh Reddy, and Steve Xie have no conflicts of interest or financial ties to disclose.

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