Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors

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Background: GI stromal tumors (GISTs), with their potential for malignant transformation, are usually treated by surgical intervention. Endoscopic treatment remains controversial.

Objective: The aim of this study was to investigate clinical outcomes associated with use of endoscopic ligation and resection for diagnosis and treatment of small EUS-suspected gastric GISTs.

Design: Prospective case series.

Setting: Academic medical center.

Patients: Eight patients with submucosal gastric tumors <2 cm in diameter suspected to be GISTs.

Interventions: Endoscopic ligation and resection.

Main Outcome Measurements: Clinical/technical feasibility, success, and adverse events.

Results: Seven patients with small EUS-suspected gastric GISTs were successfully treated by endoscopic ligation, with sloughing of residual tissue within 1 month. All were diagnosed pathologically with GISTs of low malignant potential. One additional patient required a second ligation to remove residual tumor, also diagnosed as a GIST with low malignant potential. No perforation, massive hemorrhage, or other complication requiring endoscopic or surgical intervention occurred.

Limitations: Small number of patients (n = 8) and limited follow-up; risk of microscopically positive margins, which limits application to lesions strongly suspected to be benign.

Conclusions: Endoscopic ligation and resection shows promise as a safe and feasible technique to treat small EUS-suspected gastric GISTs. Controlled clinical trials with more subjects and longer follow-up are needed to confirm the value and limitations of this method.

GI stromal tumors (GISTs) are common submucosal tumors of the stomach with the potential for malignant transformation, which are usually treated surgically.[1-3] Asymptomatic GISTs <2 cm in diameter are considered to be of low malignant potential; however, the management of these small GISTs remains uncertain. Small lesions may gradually grow, produce symptoms, and undergo malignant transformation.[4-6] Moreover, the presence of a GIST, which necessitates lifelong follow-up, can be a source of psychologic stress. An endoscopic approach is less invasive than open surgical or laparoscopic interventions; however, endoscopic treatment of GISTs has not been well established.[7,8] A minimally invasive technique that can diagnose and remove small GISTs with a low incidence of procedure-related complications would be a useful new option for physicians and patients. Here, we report development of a new method of combined endoscopic ligation and resection that shows promise for the diagnosis and treatment of patients with small EUS-suspected gastric GISTs. The aim of this study was to prospectively evaluate both the feasibility and the safety of the method.

Abbreviations: GIST, GI stromal tumor.

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PATIENTS AND METHODS

Patients

A total of 8 patients (2 men, 6 women; median age, 54 years; range, 45-71 years) who were scheduled to undergo

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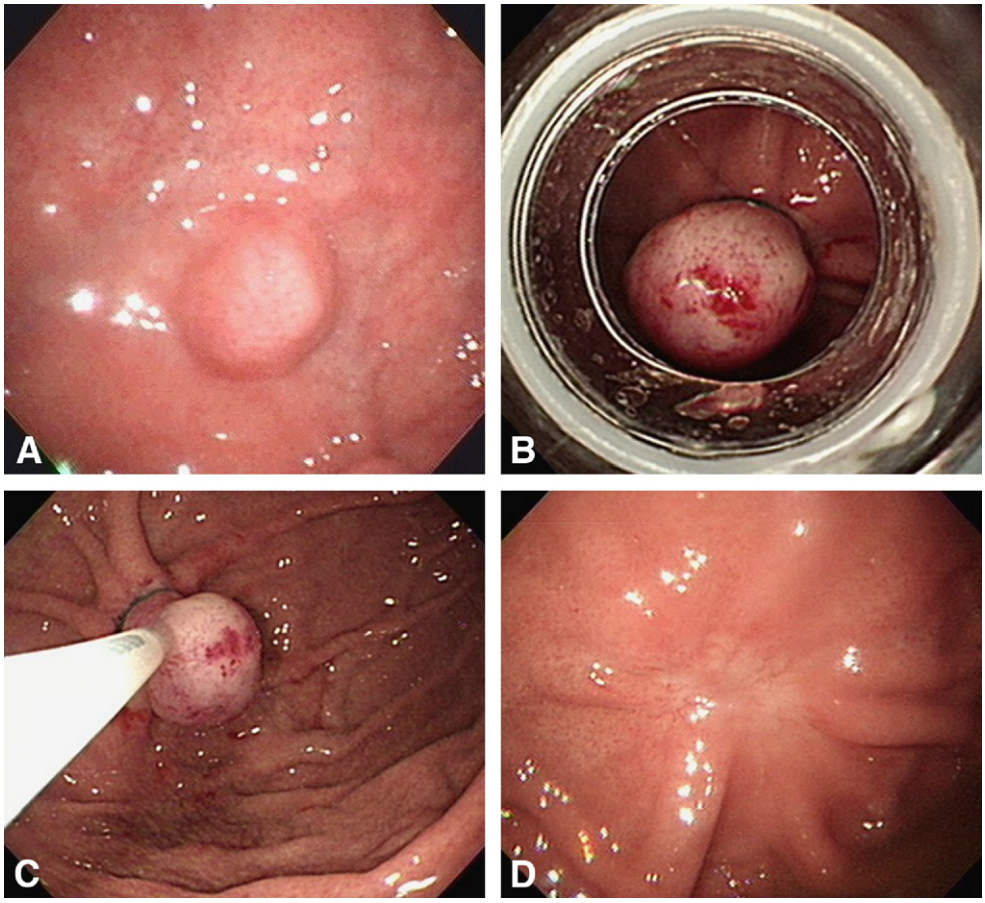

Figure 1. A, Endoscopic view of a GI stromal tumor (GIST) in the gastric fundus. **B,** Endoscopic view of the ligated GIST. **C,** Snare placed around the GIST just above the band. **D,** Endoscopic view of an ulcer scar without tumor recurrence at the ligation site 7 months later.

EUS for suspected small gastric GISTs between June 2007 and July 2008 were enrolled in the study. All lesions eligible for participation based on EUS examination were ≤2 cm in diameter, and were well circumscribed hypoechoic homogeneous masses originating in the muscularis propria layer of the stomach. All patients in this series had a normal complete blood count and prothrombin time. No participant took aspirin, clopidogrel, or a nonsteroidal antiinflammatory drug for at least 1 week before endoscopy. The Ethics Committee of the China Medical University Hospital approved the study protocol. Informed consent for endoscopic ligation and resection was obtained from each patient before the procedure.

Procedure

EUS was done while the patient was under conscious sedation with intravenous meperidine and bolus titration of midazolam. The EUS was done using a radial echoendoscope at a frequency of 7.5 or 12 MHz (Olympus GF-UM 2000; Olympus Medical Systems Corp, Tokyo, Japan); an ultrasonic miniprobe at a frequency of 12 MHz (Olympus UM-2R) was introduced through the conventional endoscope. The procedure for endoscopic ligation and resection was as follows.

1. If the EUS-suspected GIST was ≤12 mm in diameter, endoscopic ligation was carried out with a conventional endoscope and an attached band ligator device (EVL device; Akita Sumitomo Bakelite Co, Akita City, Japan). The lesion was aspirated into the transparent cap of the band ligator device, followed by deployment of an elastic rubber band (Fig. 1, case no. 3).
2. If the size of the EUS-suspected GIST was >12 mm, the EVL device–assisted endoscopic ligation failed, or the lesion was pedunculated, a ligating device (Olympus HX-20U-1) with a detachable endoloop (Olympus MAJ-254) was used (Fig. 2; case no. 2). For sessile lesions >12 mm in size, tumor ligation was carried out with a large-sized transparent cap (distal attachment, 20 mm × 18 mm, Olympus D-206-06) attached to the tip of a 2-channel therapeutic endoscope (Olympus GIF-2T240) with endoloop assistance. Briefly, after placing an endoloop around the lesion and a large-sized cap attached to the endo-

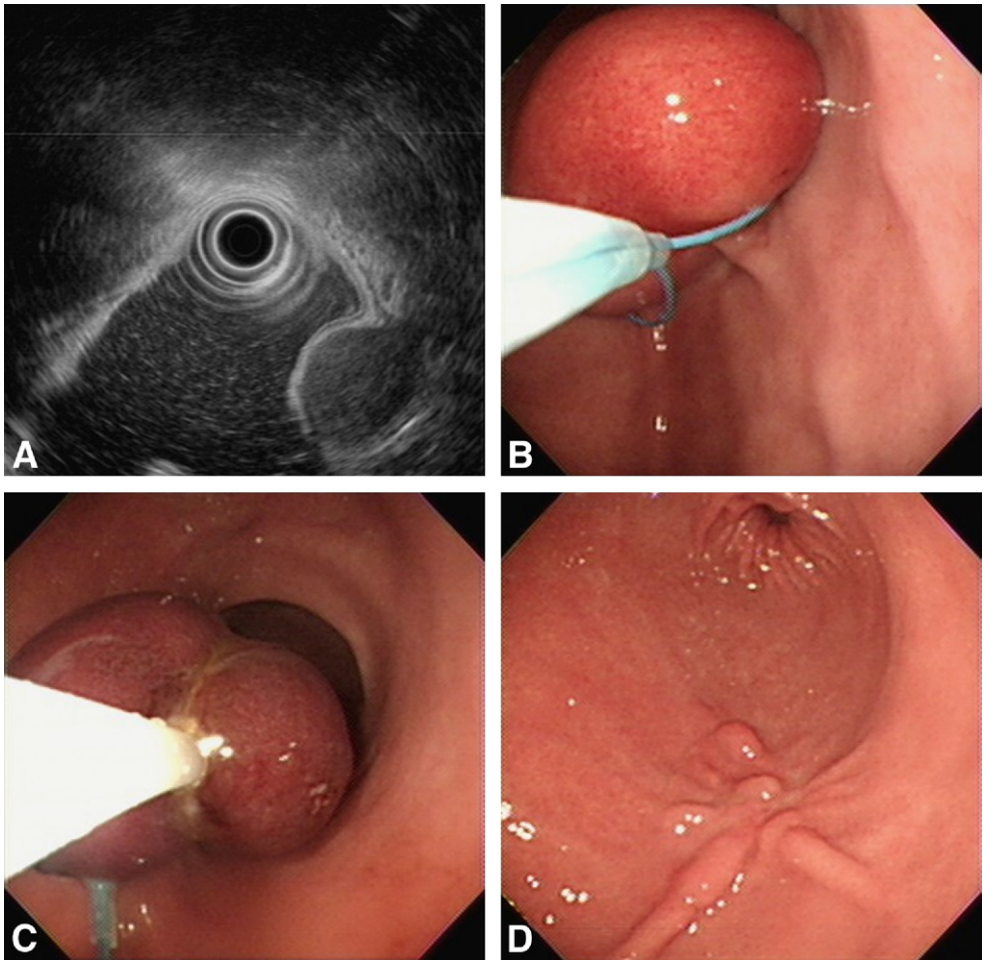

Figure 2. A, EUS image of a GI stromal tumor (GIST) in the gastric antrum. **B,** Endoscopic ligation with an endoloop. **C,** Snare placed around the upper portion of the ligated GIST. **D,** Endoscopic view of an ulcer scar at the ligation site 1 month later.

scope over the lesion, maximum sustained suction was applied while the endoloop was tightened at the base of the lesion (Fig. 3; case no 8).

3. After an elastic rubber band or endoloop was successfully applied to the base of the lesion, EUS examination was performed to confirm that the lesion was located above the band or endoloop, and that the band or loop had been properly tightened.
4. Endoscopic resection of the upper portion (unroofing technique) of the lesion was carried out using an electrocautery snare with electrosurgical current at 30-40 W on the coagulation setting (Olympus UES-30 unit). The resected specimen was retrieved using a snare or grasping forceps and was sent for pathologic study. A schematic presentation of the method is summarized in Figure 4.

All procedures were performed on an outpatient basis. Patients were discharged about 1 hour after the procedure was completed, and were followed in the outpatient clinic for any procedure-associated complications. In addition, all patients underwent follow-up EUS at 1 month and 6 months after the procedure, and every 12 months thereafter to document clinical outcomes after endoscopic treatment.

RESULTS

Patient demographic characteristics, lesion features, endoscopic techniques, and clinical outcomes are summarized in Table 1. The mean size of EUS-diagnosed gastric GISTs was 13 ± 3 mm (range, 8-20 mm). Eight lesions were found, 1 in each patient. Four lesions were in the fundus, 2 in the high body, 1 in the cardia, and 1 in the antrum. Seven of 8 patients were successfully treated with 1 tumor removal procedure. One patient required a second ligation to remove residual tumor. The upper portions of all 8 lesions were successfully resected with the unroofing technique and sent for pathologic study. The histologic diagnosis of all specimens was GIST with very low risk of malignant potential (≤5 mitoses/50 high-power fields). There were no significant procedure-related complications, such as massive hemorrhage or bowel perforation. One patient had 2 days of melena that spontaneously resolved. Two patients complained of epigastric pain after the procedure; in both

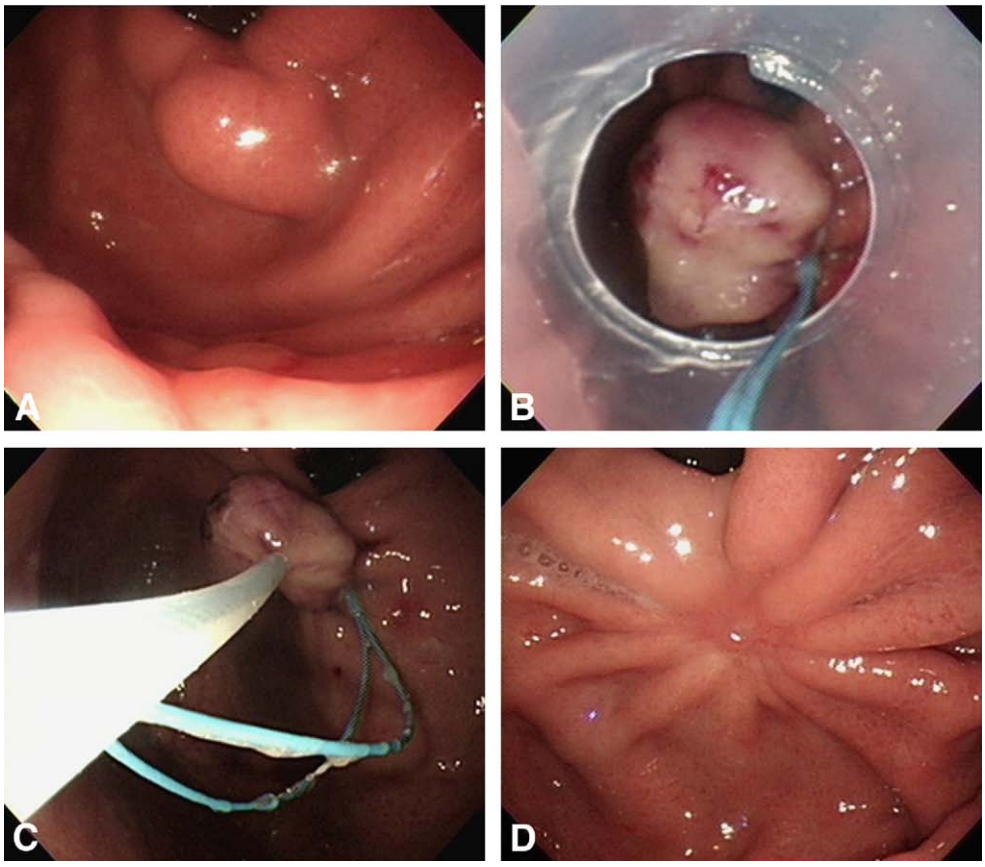

Figure 3. A, Endoscopic view of a GI stromal tumor (GIST) in the gastric cardia. **B,** Endoscopic ligation with assistance of an endoscope fitted with a large-sized cap plus an endoloop. **C,** Snare placed around the upper portion of the ligated GIST. **D,** Endoscopic view of a healed ulcer at the ligation site 1 month later.

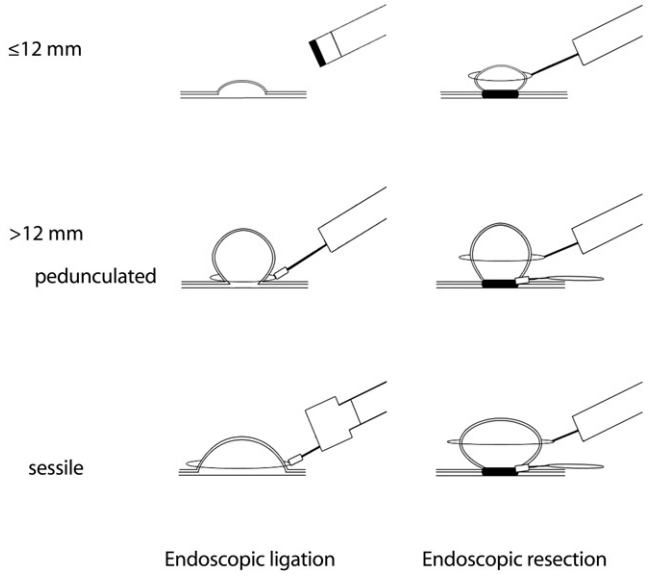

Figure 4. Schematic presentation of endoscopic ligation and resection (unroofing technique).

cases the pain resolved within 2 days. During follow-up (mean, 11 ± 9 months; range, 7-20 months), no recurrent tumor was found on EUS examination.

DISCUSSION

Endoscopic treatment of GISTs has been reported, but the role of endoscopy has remained controversial owing to the increased risk of procedure-related complications. Recently, advances in endoscopic techniques and devices have improved the ability to safely remove submucosal tumors. Endoscopic band ligation for resection of gastric submucosal tumors was first reported by Chang et al[9] in 1996. A small gastric leiomyoma was successfully resected by EUS-assisted band ligation. Sun et al[10] reported a new technique involving endoscopic band ligation without electrosurgery for excision of small upper GI leiomyomas. The authors found that 61 out of 64 leiomyomas sloughed spontaneously within 3.6 to 4.5 weeks after endoscopic band ligation. Complications related to electrosurgical resection were avoided in that study because they directly applied the ligating elastic band. Martinez-Ares et al[11] reported EUS-assisted endoscopic band ligation and resection for 3 patients with GI submucosal tumors. However, the majority of tumors involved only the muscularis mucosa or the submucosal layer of the stomach. After a report by Sun et al in 2007,[7] endoscopic band ligation was applied to submucosal tumors originating from the muscu-

TABLE 1. Characteristics and results for patients with small EUS-suspected GI stromal tumors (GISTs) undergoing endoscopic ligation and resection

Case no.	Gender/age (y)	Features of the lesions			Endoscopic treatment			Pathology (mitoses/HPF)
		Size (mm)	Site	Type	Technique	Session	Complications	
1	F/52	11	Body	Sessile	Band + resection	1	—	<5/50
2	M/58	20	Antrum	Pedunculated	Endoloop + resection	1	—	<5/50
3	M/45	11	Fundus	Sessile	Band + resection	1	—	<5/50
4	F/49	20	Fundus	Sessile	Endoloop* + resection	1	Bleeding	<5/50
5	F/49	9	Fundus	Sessile	Band + resection	1	Pain	<5/50
6	F/67	10	Fundus	Sessile	Band + resection	1	—	<5/50
7	F/55	8	Body	Sessile	Band + resection	1	—	<5/50
8	F/71	15	Cardia	Sessile	Endoloop* + resection	2	Pain	<5/50

HPF, High-power field.
*Large-sized cap-fitted 2T endoscope.

laris propria of the stomach. Only GISTs ≤12 mm in diameter could be managed by the EVL device. In the present case series, smaller GISTs were treated by endoscopic band ligation with an EVL device. Larger GISTs (ie, those >12 mm in diameter) could be managed by endoscopic ligation with a detachable endoloop (for pedunculated GISTs), or with an endoscope fitted with a large-sized cap plus an endoloop (for sessile GISTs).

An endoloop-enabling endoscopic ligation at the base of an elevated lesion was first developed by Hachisu[12] in 1991. The loop is electrically nonconductive and consists of a heat-treated elliptically shaped nylon thread and a silicone rubber stopper, with the latter maintaining the tightness of the loop. Application of endoloop ligation to the treatment of GI submucosal tumors was first reported by Lee et al.[13] However, only pedunculated lesions could be treated by endoloop-assisted endoscopic ligation in that study. The method could not be applied to most sessile submucosal tumors of the stomach, a limitation that kept it from being applied more broadly. In the present study, sessile GISTs were aspirated by an EVL device or endoscope with a large-sized cap which created a "pedunculated" lesion that could be successfully ligated by an elastic band or endoloop. Iishi et al[14] found that bleeding during or after endoscopic polypectomy with a detachable endoloop occurred significantly less frequently than when the procedure was done without an endoloop. Thus, application of an endoloop or elastic band before endoscopic resection of a small GIST may reduce the probability of bleeding and make safe removal more likely.

Endoscopic resection of a submucosal tumor is technically difficult and is associated with an increased risk of bowel perforation.[15] Unroofing techniques, which were first introduced by Mimura et al[16] in 1997, only remove the upper portion of a submucosal tumor, and thus the possibility of bowel perforation is greatly reduced. The technique has been successfully applied to treatment of symptomatic lipomas of the duodenum.[17] In the present case series, only 3 patients experienced melena or dyspepsia, which resolved in all cases within a few days. No perforation or hemorrhage requiring endoscopic or surgical intervention developed after the use of our unroofing technique. Based on the findings of Lee et al,[13] endoscopic ligation without resection seems to be safe and feasible for treatment of large pedunculated submucosal tumors; however, only 60% of sloughed specimens in that study were retrieved for pathologic confirmation. Therefore, the authors suggested obtaining a definitive diagnosis before beginning the procedure. The pathologic diagnosis of a submucosal tumor, however, cannot be made on the basis of biopsy specimens obtained with a conventional forceps technique. Endoscopic resection with the unroofing technique allows acquisition of sufficient tumor tissue for histopathologic diagnosis. In the present study, endoscopic resection with unroofing allowed a definitive diagnosis of GISTs, with very low malignant potential in all of our patients.

In this case series, 7 patients were successfully treated by endoscopic ligation and resection, with complete sloughing of the remaining tumor within 1 month. Only 1 patient required a second session of endoscopic ligation. In that case, the endoloop loosened during the initial procedure. After the second ligation, residual tumor sloughed completely within 1 month. The looseness of the initial endoloop was probably due to the broad base of the lesion, insufficient tightness of the rubber stopper, and the inelasticity of the nylon loop, all of which contributed to the inability to maintain adequate tightness after endoloop

detachment. Therefore, the endoloop must be sufficiently tightened at the initial ligation for there to be a high likelihood of success. A second session of endoscopic ligation may be required for some sessile lesions, particularly larger GISTs with broad bases.

Follow-up in our patient series ranged from 7 to 20 months (mean, 11 ± 9 months), during which no tumor recurrence was observed in any patient on EUS examination. However, because of the limited number of patients and relatively short follow-up duration, we realize that longer follow-up is needed before one can conclude that the tumor has been completely removed. Another limitation of this method is the inability to provide en bloc resection of adjacent tissue. Surgical resection that removes the entire tumor as well as a margin of normal tissue can provide a clear histopathologic diagnosis regarding complete removal of the lesion. Although there was no macroscopic residual or recurrent tumor observed on EUS studies, an inherent risk of positive microscopic margins and tumor spillage is still a concern.[18] Therefore, a lesion suspected of being malignant should not be treated with this method. According to suggested guidelines for assessing malignant potential of gastric GISTs, small GISTs ≤2 cm are considered to have low malignant potential.[19] It is extremely rare for a small GIST to recur or cause death after the tumor has been removed surgically. However, we recommended to our patients that they have close follow-up, including periodic EUS studies, because GISTs are potentially malignant and residual stromal tumor cells may remain after the tumor has sloughed off. It will always be prudent and beneficial for patients to understand the need for sustained follow-up if GISTs are removed by a minimally invasive method.

In conclusion, endoscopic ligation and resection shows promise as a safe and feasible technique to treat small EUS-suspected gastric GISTs. In our series of patients, the technique allowed definitive diagnosis and probable complete lesion removal without significant procedure-related complications. However, because of the limited number of subjects and limited follow-up, controlled clinical trials involving a much larger number of subjects and a longer period of follow-up should be conducted.

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