

Full-thickness endoscopic resection of nonintracavitary gastric stromal tumors: a novel approach

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Abstract

Background Until now, the conventional treatment of stromal tumors has been primarily open surgery or laparoscopic excision. The use of combined laparoscopic/endoscopic surgeries has been investigated, but endoscopic therapy alone has been limited to en bloc resection or nucleus removal of intracavitary tumors with diameters <2 cm. Nonintracavitary and intramural gastric stromal tumors preclude the use of endoscopic resection due to the risk of gastric perforation. This study was designed to show the safety and effectiveness of full-thickness endoscopic resection of nonintracavitary stromal tumors based on our direct experience. **Methods** A total of 109 consecutive patients with nonintracavitary gastric stromal tumors <4 cm in diameter underwent surgical treatment; 66 patients received endoscopic surgery and 43 patients received laparoscopic surgery. **Results** No significant differences existed between the two groups in terms of demographics and clinical characteristics, and no tumor exceeded 3.5 cm in size. Median operation times (endoscopic group, 53.6 min; laparoscopic group, 139 min) and hospitalization fees of the endoscopic group were significantly lower than those of the laparoscopic group with significant median hospital stays (8 days for endoscopic group; 6 days for laparoscopic group). No

intraoperative complications occurred in the laparoscopic group and complete removal of tumors was achieved in the endoscopic group. Postoperative complications occurred in 6 patients of 43 who underwent laparoscopic surgery and 17 patients of 66 who underwent endoscopic surgery, representing a significant difference; the size of the lesion correlated positively with the occurrence of complications. **Conclusions** Endoscopic resection is safe and effective for treating nonintracavitary stromal tumors. The endoscopic natural-cavity technique produced less surgical injury to the patients and preserved the anatomy of intra-abdominal structures. In addition, the endoscopic technique reduced operative times, postoperative bleeding, and costs.

Keywords Nonintracavitary gastric stromal tumor · Endoscopic resection · Laparoscopic resection

Diagnosis and treatment of stromal tumors has improved significantly along with the in-depth study of gastrointestinal stromal tumors. Currently, the conventional treatment of stromal tumors is primarily open surgery or laparoscopic excision [1–10]. Reports of both techniques, including, for example, en bloc removal of an extra-gastrointestinal stromal tumor (EGIST) of the greater omentum and laparoscopic intragastric approach for gastrointestinal stromal tumor (GIST) of the posterior gastric wall, show that conventional treatment can meet surgical challenges and achieve satisfactory outcomes [1, 3]. In recent years, many studies have addressed combined laparoscopic-endoscopic resection (laparoscopic and endoscopic cooperative surgery or LECS) [11–13], whereas endoscopic therapy alone has been limited to the en bloc resection or nucleus removal of intracavitary tumors with diameters <2 cm. Although studies have shown that the endoscopic dissection

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technique can directly remove gastric stromal tumors with a diameter >2 cm, these surgeries are performed only for intracavitary gastric stromal tumors, whereas nonintracavitary and intramural gastric stromal tumors are relative contraindications of the endoscopic treatment [14, 15]. Endoscopic resection has been considered unsuitable for treating the nonintracavitary gastric stromal tumor, and this is mainly because endoscopic resection may result in gastric perforation. However, the emergence of the titanium clip makes the endoscopic suture technique possible for small perforations [14, 16]. The titanium clip is a flexible metal clip that effectively occludes vessels or wounds through a special releasing endoscopic device. Our previous animal experiments showed that the endoscopic titanium clip was ideal and reliable for the suture of a dog's gastric wall. The experimental dog could be fed 24 h after the experiment, and no significant peritonitis resulted (unpublished data). These clues indicate that endoscopic resection can be performed for the nonintracavitary stromal tumor even considering possible risk of perforation after the resection, which is not actually viewed as a complication per se but as part of the surgical procedure when completely resecting a stromal tumor of the gastric wall. On the other hand, full-thickness endoscopic removal of the nonintracavitary gastric stromal tumor has been shown to produce less surgical injury to the patients. In addition, it does not affect the anatomy of intra-abdominal structures. Therefore, starting in September 2008, we began to apply full-thickness endoscopic gastric wall incision and suture technique in the treatment of nonintracavitary gastric stromal tumors. Our preliminary experience is retrospectively reviewed in this study, using the laparoscopic surgery cases performed in the same period as the control.

Materials and methods

Between September 2008 and May 2009, 109 consecutive patients with nonintracavitary gastric stromal tumors <4 cm in diameter underwent surgical treatment in our hospital. After fully explaining the surgical rationales and potential risks to the patient, the decision to undergo endoscopic or laparoscopic surgery was made by the patient in each case. As a result, 66 patients underwent endoscopic surgery and 43 patients underwent laparoscopic surgery. Among 66 patients in the endoscope group, 31 were men and 35 were women; the mean age was 44 (range, 38–52) years. Among 43 patients in the laparoscope group, 23 were men and 20 were women; the mean age was 41 (range, 35–48) years. This retrospective study was approved by the Internal Review Board (IRB) of our hospital. Informed consent was obtained from all patients to take part in this study. No patients were excluded from the study.

Surgical procedure

Endoscopic surgery

Before the operation, repeated gastric lavage was performed with saline and then with 100 ml of 0.2% metronidazole. The patient was placed in a lateral recumbent position. After intravenous injection of propofol (15 mg/kg), a gastroscope (GIF 260 series; Olympus, Tokyo, Japan) was applied. Endoscopic submucosal injection of normal saline with adrenaline 1:10000 was administered. Linear resection of the superficial mucous membrane of the lesion (Fig. 1A) was performed with a needle-knife along with the longitudinal axis of the gastric cavity. The lesion was dissected and exposed with an argon beam coagulator (ERBE ICC-20) (Fig. 1B, C) and then it was suctioned by a transparent suction set (Olympus, MAX-139). The root of the lesion was ligated with a nylon ring (Fig. 1D) and bilateral gastric walls were clamped by a titanium clip (Olympus HX-610-090, HX-610-135, HX-610-090L). The nylon ring was prepared before surgery by bending a ~ 10 mm length of nylon thread (0.168 or 0.2 mm in diameter) into a circular shape and gluing it with plastic adhesive to form a circle measuring approximately 3 mm in diameter [17]. The ring was placed into a ventilated environment for 24 h to dry and fix the adhesive. Suturing was performed by using a double-channel endoscope (MAX-330, Olympus, Tokyo, Japan). When used during surgery, the nylon ring was introduced through one channel and the titanium clamp was inserted through the other channel, fixing the nylon ring at the surrounding tissue of the incision and suturing by tightening the nylon ring. A snare (Olympus MAJ-339, MAJ-340) was then applied to remove the lesion. Linear suture was performed with titanium clips for the stump remaining after the excision (Fig. 1E, F). After the operation, antibiotics were routinely used to prevent infection and a proton pump inhibitor (40 mg omeprazole) was intravenously injected twice daily for 3 days to prevent stump ulcer. A video link can be accessed at: <http://202.105.179.239/pic/1/1.mpg>

Laparoscopic surgery

After conventional general anesthesia with endotracheal intubation, the patient was placed supine and the table was tilted to head-up position. Aspiration was performed to establish an observation hole at the inferior margin of the umbilicus (the observation hole was made on the umbilicus for patients with obesity and deep abdominal cavity). Three manipulation incisions were made below the left and right costal margins and xiphoid. Conventional pneumoperitoneum was created and then a laparoscope (Olympus XLS, Japan) was inserted into the abdominal cavity to locate the

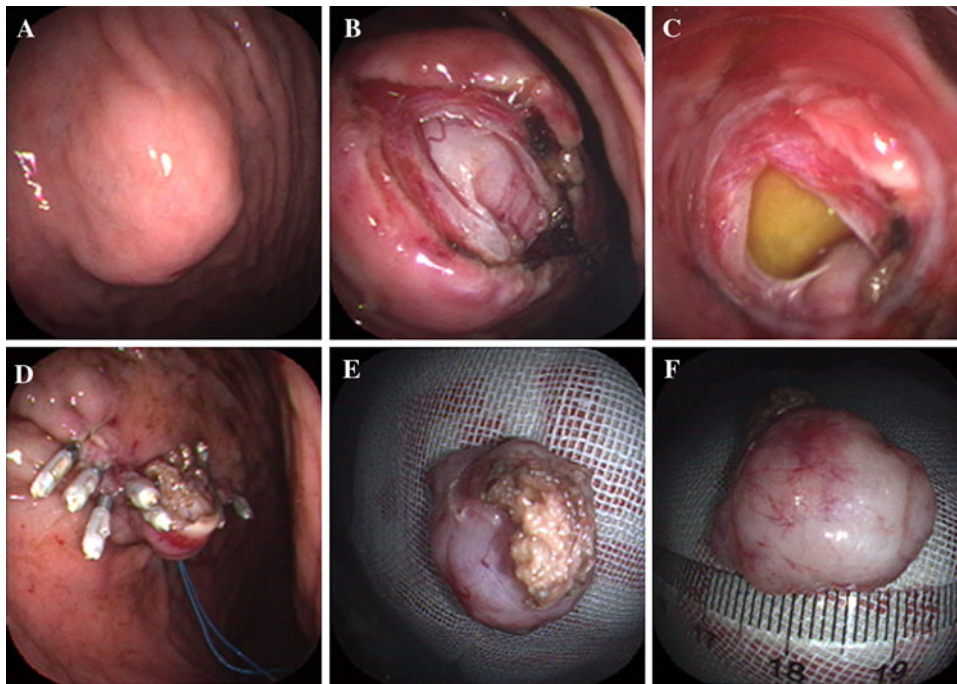


Fig. 1 Procedure of gastroscopic resection of the lesion. **A** Endoscopic view showed a flat and elevated mass, which could be observed at the greater curvature of the stomach, the surface was smooth, and the aeration was not apparent. **B** White bulging mass was seen after needle-knife longitudinal incision of mucosal layer, submucosal layer, and partial muscle layer. **C** After cutting off

partial gastric wall, it was found that the white mass was located between the outside of the gastric wall and the yellow greater omentum. **D** A rubber band is applied by a transparent suction sets to ligate the lesion from the root; the stump left was closed by titanium clips. **E–F** Diameter of the residual serous mass was 2.3 cm in the lesion removed

tumor. The gastroscope was applied during the operation if the localization of the tumor was difficult, either because of the relatively small tumor size or its intraluminal growth. Local wedge resection of tumor and partial gastric wall was directly performed with an endoscopic stapler for tumors located at the anterior wall of the stomach. Small or large omentum was opened with an ultrasonic knife beforehand for tumors growing extraluminally in the posterior wall. Then, the gastric wall was turned over to expose the tumor for local resection. The anterior gastric wall was opened to expose the tumors growing intraluminally in the posterior wall, and the anterior wall was closed by sutures after the tumor resection. The large omentum was dissected along with the vascular arcade for the tumors located at the fundus or antrum of the stomach, and local wedge resection of the tumor was performed after it was turned over and exposed. Laparoscopic gastrectomy was performed if gastric stenosis was anticipated after the resection. Antibiotics were routinely used to prevent infection after the operation.

Outcome measurement

Parameters, such as the operation time, intraoperative bleeding, intraoperative and postoperative complications,

duration of hospitalization, hospital cost, etc., were collected and comparative analysis was performed.

Statistical analysis

All statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as median with first and third quartiles [Q1, Q3] by group due to not following normal distribution, whereas categorical data were tabulated as numerical percentages by group. For comparison, the nonparametric Wilcoxon Mann–Whitney *U* test was performed for continuous and ordinal data, whereas the chi-square test was performed for categorical data. All statistical assessments were two-tailed and the significance level was set as less than $p = 0.05$.

Results

Table 1 shows the demographics and other characteristics by group. The median age was 44.0 years (37.8, 52.0) in group 1 and 41.0 years (35.0, 48.0) in group 2, percentage of males was 47% (31/66) in group 1 and 53.5% (23/43) in

Table 1 Demographics and other patient characteristics by group

Variables	Group 1 (n = 66)	Group 2 (n = 43)	p value
Age (yr)	44 (37.8, 52)	41 (35, 48)	0.083
Gender, male (%)	31 (47)	23 (53.5)	0.506
Tumor site			
1 Antrum of stomach	2 (3)	4 (9.3)	0.4
2 Body of stomach	26 (39.4)	16 (37.2)	
3 Fundus of stomach	38 (57.6)	23 (53.5)	
Tumor size (cm)	1.5 (0.8, 1.7)	1.1 (0.7, 1.7)	0.49
Range of tumor size			
0.5–1.0	23 (34.8)	21 (48.8)	0.32
1.0–2.0	32 (48.5)	14 (32.6)	
2.0–3.0	8 (12.1)	6 (14)	
3.0–3.5	3 (4.5)	2 (4.7)	
Patients with full-thickness resection of lesion, yes (%)	31 (47)	43 (100)	<0.001*

Data are expressed as median (Q1, Q3) for age and tumor size with a nonparametric Mann–Whitney *U* test; and *n* (%) for gender, tumor site, stratification of tumor size, and patients with full-thickness resection of lesion with a person Chi-square test, and a nonparametric Mann–Whitney *U* test

* $p < 0.05$ indicated the distribution of patients with full-thickness resection of lesion was significantly different between two groups

group 2. Among patients in groups 1 and 2, the majority of tumors (57.6% and 53.5%, respectively) occurred in the fundus of the stomach compared with the body and antrum of the stomach. The overall median tumor size in group 1 was 1.5 cm and most tumors (48.5%; 32/66) were within 1.0–2.0 cm in size, with only a few (4.5%; 3/66) within 3.0–3.5 cm. The overall median tumor size in group 2 was 1.1 cm and most tumors (48.8%; 21/43) were within 0.5–1.0 cm in size, with only a few (4.7%; 2/43) within 3.0–3.5 cm. No statistically significant differences were found in demographics and characteristics between groups 1 and

2. In addition, full-thickness resection of lesions was performed for all 43 patients in group 2, but only 47% (31/66) of patients in group 1 received full-thickness resection of lesions.

Table 2 shows the comparison of operation times, hospitalization periods, and hospitalization fees of patients by group. Among these, it was found that the median operation times and hospitalization fees of group 1 were significantly lower than those of group 2, but the hospitalization period was significantly higher ($p < 0.001$). For patients who received full-thickness resection of the lesion, similar to all endoscopy and laparoscopy patients, the median operation time and hospitalization fee for group 1 was significantly lower than those of group 2; the hospitalization period was the exception with no significant differences between groups ($p \leq 0.001$).

No intraoperative complications occurred in the 43 laparoscope-treated patients. Tumors were completely removed in 65 of 66 patients in the endoscope group. In one patient, the endoscope could not obtain an excellent operative field and manipulation plane because the lesion was located at the fundus near the dome of the stomach. The bilateral walls could not be clamped with the titanium clip during the operation, endoscopic suture was not obtained successfully, and open surgery was performed. Stump perforation occurred in 15 patients after the tumor resection and it was repaired by the titanium clip in each case. Significant bleeding occurred in five patients during the operation and successful hemostasis was achieved by using the argon plasma coagulator and titanium clip under the guidance of the endoscope.

In the laparoscope group, localized peritonitis occurred in three cases and gastrointestinal bleeding happened in three cases, 1–2 days after the operation. Patients were treated by gastrointestinal decompression and intravenous injections of omeprazole. In the endoscope group, abdominal distension was found in three cases, 11–16 h

Table 2 Comparison of operation times, hospitalization periods, and hospitalization fees of patients by group

Variables	Group 1 (n = 66)	Group 2 (n = 43)	p value
All patients	n = 66	n = 43	
Operation time (min)	53.6 (51, 57.1)	139 (135, 142)	<0.001*
Hospitalization period (days)	8 (7, 8)	6 (6, 7)	<0.001*
Hospitalization fee (\$)	6,847.5 (6,756, 6,885)	17,354 (17,246, 17,544)	<0.001*
Patients with full-thickness resection of lesion	n = 31	n = 43	
Operation time (min)	54 (52, 58)	139 (135, 142)	<0.001*
Hospitalization period (days)	8 (7, 8)	6 (6, 7)	<0.001*
Hospitalization fee (\$)	6,852 (6,756, 6,877)	17,354 (17,246, 17,544)	<0.001*

Data are expressed as median (Q1, Q3) with a nonparametric Mann–Whitney *U* test

* $p < 0.05$ indicated the distribution was significantly between two groups

Table 3 Summary of intraoperative and postoperative complications by group

Complications	Group 1 (<i>n</i> = 66)	Group 2 (<i>n</i> = 43)	<i>p</i> value
Wound disruption	2 (3)	0 (0)	
Wound disruption, pneumoperitoneum, and localized peritonitis	1 (1.5)	0 (0)	
Localized peritonitis	0 (0)	3 (7)	
Gastrointestinal bleeding	0 (0)	3 (7)	
Pneumatoxis	5 (7.6)	0 (0)	
Pneumatoxis and localized peritonitis	9 (13.6)	0 (0)	
Total	17	6	<0.001*

Data are expressed as *n* (%) with a Pearson Chi-square test

* *p* < 0.05 indicated the distribution was significantly different between two groups

after the operation. Abdominal X-ray showed loss of sub-phrenic free air in the abdominal cavity. Further endoscopic examination found local disruption of the wound in the operation site. A nylon ring (as described in the procedure above) was fixed to the wound bilaterally with the titanium clip under the guidance of endoscope and the wound was closed by tightening the nylon ring; the patient recovered fully after this treatment. Abdominal pneumatoxis and localized peritonitis occurred in 14 patients, 12 h after the operation. Symptoms disappeared within 48 h after local peritoneal drainage. Table 3 shows the postoperative complications by groups.

Discussion

Application of endoscopic submucosal dissection and ongoing development of related accessory techniques have made the en bloc resection of mucosal and submucosal lesions possible. In the current study, our goal was to show the safety and effectiveness of full-thickness endoscopic resection of nonintracavitary stromal tumors based on our experience with 66 patients for whom we had applied the endoscopic gastric wall incision and suture technique. Our experience challenged the prevailing idea that the risk of gastric perforation precluded use of this application, and our study is the first to report results of full-thickness endoscopic resection for non-intracavitary stromal tumors.

We retrospectively reviewed details of two groups of surgery cases in which the first group (group 1) had received endoscopic surgery and a second control group (group 2) had received laparoscopic surgery during the same time period. No significant differences existed between the two groups in terms of demographic profiles

and clinical characteristics and the patients themselves determined which type of surgery they would undergo. The tumors in both groups were in the fundus, body, and antrum of the stomach, with median tumor size 1.5 for group 1 and 1.1 for group 2. No tumor was greater in size than 3.5 cm.

Our main findings were that the median operation times and hospitalization fees of the endoscopic group were significantly lower than those of the laparoscopic group; the hospital stays were different but similar, a median of 8 days for endoscopic patients and 6 days for laparoscopic patients. Intraoperative complications did not occur in the laparoscopic group and tumors were removed completely in the endoscopic group, although one patient was converted to open surgery because of an endoscopically inaccessible tumor location (at fundus near dome of stomach). Postoperative complications occurred in 6 of 43 patients who underwent laparoscopic surgery and 17 of 66 patients who underwent endoscopic surgery, representing a significant difference. Regarding this issue, it is important to note that our results show positive correlation between the size of the lesion and the occurrence of complications.

Regarding postoperative complications, the present study suggests that the size and location of the lesion are the main factors influencing the endoscopic resection of nonintracavitary stromal tumors; our results show that complications increased significantly along with the increased size of lesion. Suturing is relatively difficult for large or irregular wounds produced by bulky lesions under the existing conditions, and sometimes it is impossible to close the wound. Furthermore, the location of a lesion makes the surgery difficult as well. Procedures involving the dome of fundus and the upper part of the lesser curvature are especially difficult to perform; however, we believe that large nonintracavitary tumors also can be successfully removed under the guidance of the endoscope because of great improvements in suture devices, although this requires further investigation. In the present study, the combined titanium clip and nylon ring technique was applied for those large and irregular lesions that could not be closed by the titanium clip directly and for lesions located at some special areas difficult to reach, and with this technique, most surgical wounds were closed successfully. This compares favorably with the success of other investigators, such as Hiki et al., who report successful closure of operative wounds using the endoscopic stapler in extragastric approaches [12].

In the present study, the perforation rate of endoscopic excision of the intracavitary or intramural stromal tumors was 22.7% (15/66); however, use of the titanium clip can completely close the perforation to avoid complications. We do not necessarily consider perforation itself as a complication but accept it as a part of the complete

resection of a stromal tumor of the gastric wall. Full-thickness gastric resection initially opens the gastric wall and incision in this case is more appropriate than perforation. However, when the incision cannot be sutured, it is described as “unable to be sutured” and employing the titanium clip as in our technique precludes further complications. In fact, when we treat stromal tumors originating within the muscularis propria of the gastric wall, we believe that the titanium clip should be applied as one step of the surgical procedure rather than just be reserved as a remedial measure for postoperative perforation. This is because we know that gastric wall perforation may happen if we want to perform en bloc resection of these lesions. If the titanium clip is used in advance to clamp the root of the lesion, it will be more aligned with the gastric wall if perforation occurs and will make the suture easier. When the perforation is too large to be closed by conventional titanium clips, elongated clips can be selected for the closure, and once the first clip is successfully placed, then the subsequent procedure is easily performed.

Compared with laparoscopic resection, endoscopic resection of stromal tumors has demonstrated certain advantages, as follows: (1) endoscopic resection utilizes the natural cavity of the patient and leaves no scars on the abdomen. At one time, surgery without scars was unheard of and considered to be impossible. Now, we are essentially performing incisionless surgery. Today’s minimally invasive techniques, especially natural orifice transluminal endoscopic surgery (NOTES), which has been performed successfully even for cholecystectomy [18], minimize bodily trauma and virtually eliminate abdominal scarring. (2) Surgical injury is minor for patients who undergo endoscopic resection compared with those who undergo laparoscopic resection. This means not only avoiding the scars of abdominal incisions but reducing inflammatory response associated with surgical trauma. According to the report by McGee et al., immune response, including secretion of inflammatory factors, such as IL-1, IL-2, and TNF- α , is significantly lower in surgery performed through the natural cavity of human body compared with laparoscopic surgery [19]. (3) Avoiding an abdominal incision may have the advantage of reducing perceived pain in patients. According to the report by Marescaux et al., the subjective perception of pain is milder in patients who undergo surgery utilizing the natural cavity of the human body compared with laparoscopic surgery [18]. (4) Surgery utilizing the natural cavity of the human body has also been shown to have a lower incidence of postoperative methicillin-resistant *Staphylococcus aureus* (MRSA) infection and hospital-acquired infection [20]. (5) Compared with those who undergo laparoscopic resection of gastric stromal tumors, the cost of hospitalization in patients who undergo endoscopic resection of gastric stromal tumors is

significantly lower; in our study, the costs associated with laparoscopic surgery were nearly three times higher than those associated with endoscopic surgery. Although in our study the hospital stay of endoscopic surgery was significantly higher than that of laparoscopic surgery, their difference was not so big. Hiki et al. reported that the mean operation time in their series was 168 min in the combined endoscopic and laparoscopic resection; the average amount of bleeding was 7 ml, and the operation time was similar to that of our laparoscopic resection group [12]. Although the diameter of the lesion was more than 5 cm in two cases in their study, their mean operation time was significantly longer than that of our simple endoscopic resection group. (6) Compared with laparoscopic resection, endoscopic resection has no significant bleeding and also has higher manipulation ability. Two patients in the laparoscopic group in our study experienced postoperative gastrointestinal bleeding and none in the endoscopic group.

Partial resection of the gastric cavity is needed during laparoscopic surgery and it changes the structure of the stomach; esophagogastric anastomosis is required near the cardia of the stomach, which usually provokes reflux. However, endoscopic resection, which only performs local excision of the lesion, has the advantage of not changing the anatomical structure of the gastric cavity. The traditional surgical treatment for gastric stromal tumors is open partial gastric resection, and because most of these tumors are located at or near the fundus, partial cardia and fundus resection or fundus resection alone often is required. The esophagus and residual stomach are anastomosed together in these cases, resulting in compromised cardiac function. On the other hand, if the tumor is in the middle or lower part of the gastric body, distal partial gastric resection and Billroth II gastrointestinal anastomosis will be done. However, because lymph metastasis is rare with stromal tumors, local resection can be performed to achieve greater preservation of gastric function.

According to the results of the present study, the incidence of postoperative complications was significantly higher in the endoscopic resection group than in the laparoscopic resection group. The most serious complication was postoperative wound disruption, which was quickly repaired by secondary endoscopic treatment. Other complications can be resolved by endoscopic procedures or conservative treatment without affecting hospitalization time and the cost of hospitalization. Therefore, even though the incidence of complications is higher in the endoscopic resection group than the laparoscopic resection group, the types of complications that occur can be successfully managed by endoscopic and conservative treatment.

Our study was limited by the small sample size. Results of our initial experience indicate that a larger prospective study of endoscopic resection for nonintracavitary gastric stromal

tumors would be of value to clinical practice. In particular, more studies are needed to evaluate the relationship between tumor size and postoperative complications.

In conclusion, we consider that in the treatment of the nonintracavitary gastric stromal tumor, full-thickness endoscopic resection is not only safe, but also cost-efficient and able to reduce the medical cost greatly. In our experience, applying the endoscopic natural-cavity technique produced less surgical injury to the patients and did not affect the anatomy of intra-abdominal structures. Tumor size in our cases did not exceed 3.5 cm; at present, we feel that excessively large tumors are not suitable for endoscopic resection. We suggest that it should be applied more widely in clinical practice to convey advantages that include reduced operative times, reduced postoperative bleeding and infection, and reduced costs. However, we also acknowledge that this technique has a steep learning curve and the cooperation of the surgical department is necessary.

Disclosures Drs. Lei Wang, Wei Ren, Chao-qiang Fan, Yi-hui Li, Xia Zhang, Jin Yu, Guo-ce Zhao, and Xiao-yan Zhao have no conflicts of interest or financial ties to disclose.

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