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Comparison of Endoscopic and Open Resection for Small Gastric Gastrointestinal Stromal Tumor[1,2]

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Abstract

The National Comprehensive Cancer Network recommends conservative follow-up for gastric gastrointestinal stromal tumors (GISTs) less than 2 cm. We have previously reported that the mitotic index of 22.22% of small gastric GISTs exceeded 5 per 50 high-power fields and recommended that all small gastric GISTs should be resected once diagnosed. The aim of the present study is to compare the safety and outcomes of endoscopic and open resection of small gastric GISTs. From May 2010 to March 2014, a total of 90 small gastric GIST patients were enrolled in the present study, including 40 patients who underwent surgical resection and 50 patients who underwent endoscopic resection. The clinicopathological characteristics, resection-related factors, and clinical outcomes were recorded and analyzed. The clinicopathological characteristics were comparable between the two groups except for tumor location and DOG-1 expression. Compared with the surgical resection group, the operation time was shorter ($P = .000$), blood loss was less ($P = .000$), pain intensity was lower ($P < .05$), duration of first flatus and defecation was shorter ($P < .05$), and medical cost of hospitalization was lower ($P = .027$) in the endoscopic resection group. The complications and postoperative hospital stay were comparable between the two groups. No *in situ* recurrence or liver metastasis was observed during follow-up. Endoscopic resection of small gastric GISTs is safe and feasible compared with surgical resection, although perforation could not be totally avoided during and after resection. The clinical outcome of endoscopic resection is also favorable.

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract [1] and are believed to originate from the interstitial cells of Cajal, the pacemaker cells of the gastrointestinal tract [2]. GISTs can occur anywhere throughout the gastrointestinal tract; the most common locations are the stomach, small intestine, duodenum, and colorectum. Rare cases have been reported out of the gastrointestinal tract [3].

According to the National Comprehensive Cancer Network guideline [4], gastric GISTs less than 2 cm and with a mitotic index less than 5 per 50 high-power fields (HPF) are considered as very low risk, and conservative follow-up is suggested for small gastric GISTs [5]. However, it is believed that small gastric GISTs also have malignant potential, and we have previously reported that the mitotic index of 14 out of 63 small gastric GISTs (22.22%) exceeded 5 per 50 HPF [6]. Moreover, it was reported that the size of small gastric GISTs increased significantly during follow-up [7], and one case of small gastric GIST showed rapid growth and early metastasis to the liver [8].

Given this situation, we proposed that small gastric GISTs should be resected immediately once diagnosed. However, little is known about the safety and clinical outcomes between endoscopic resection

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and surgical resection for small gastric GISTs. Thus, the present study was carried out to investigate the safety and clinical outcomes of endoscopic resection in comparison to surgical resection for small gastric GISTs.

Materials and Methods

Patients

This study was performed in the Xijing Hospital of Digestive Diseases affiliated to the Fourth Military Medical University. From May 2010 to March 2014, a total of 90 patients were enrolled in the present study, including 40 small gastric GIST patients who underwent surgical resection and 50 small gastric GIST patients who underwent endoscopic resection. This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgical or endoscopic resection.

Resection Procedures

For the surgical resection group, all patients received general anesthesia with tracheal intubation. The procedure started with a traditional left side transrectus upper abdominal incision. The incisal margin was 2 cm beyond the tumor margin, and frozen slices of the incisal margin were performed during surgery. The detailed operation method depended on the location of tumor. For the endoscopic resection group, all patients received intravenous anesthesia. Marking dots were made with hook knife 3 mm outside the tumor margin. A 10% glycerin solution containing epinephrine (0.005 mg/ml) was injected into the submucosal layer. The tumor was completely

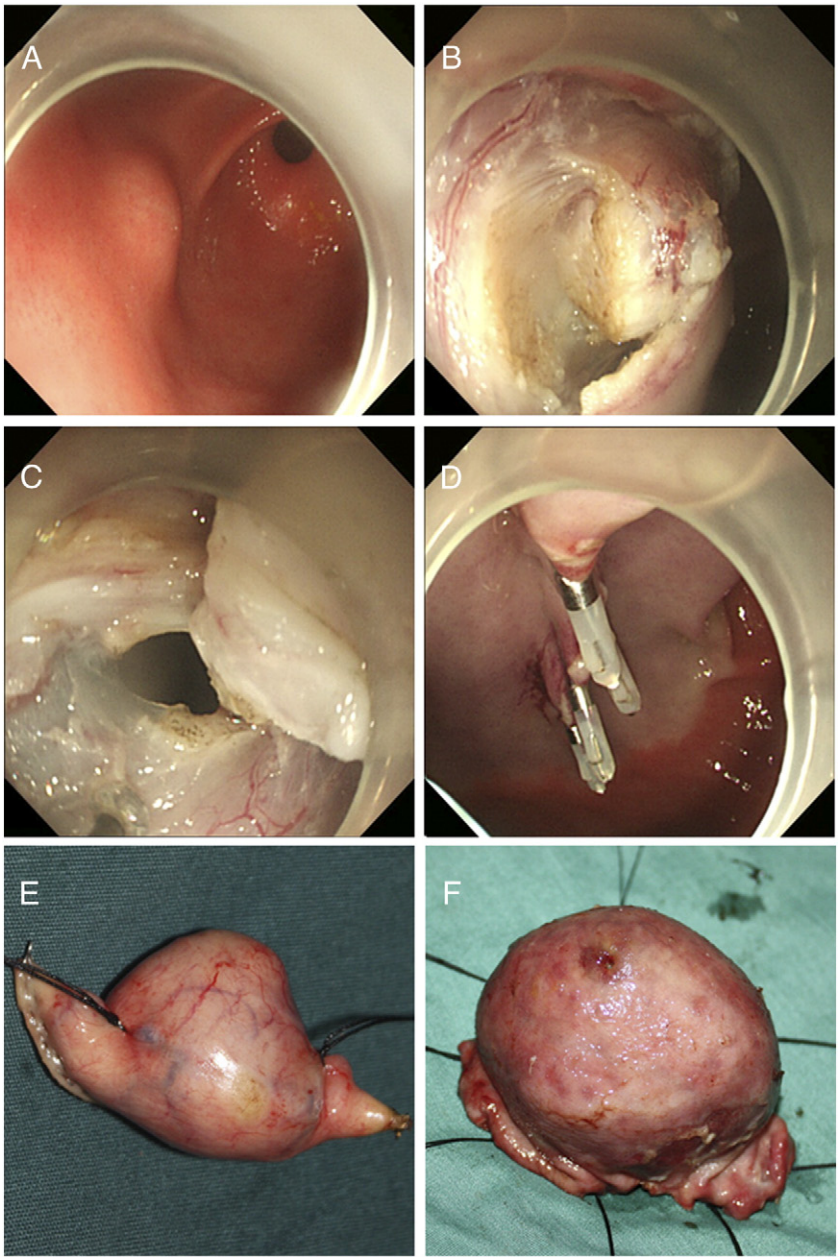

Figure 1. Endoscopic and surgical resection of small gastric GISTs. (A) Endoscopic view of small gastric GIST with intragastric type pattern. (B) Endoscopic resection of small gastric GIST. (C) Gastric perforation occurred during endoscopic resection. (D) Perforation was closed with clips after endoscopic resection. (E and F) Surgical resection of small gastric GISTs.

separated from the surrounding normal tissue using a needle knife, and squeezed out of the gastric wall without rupture. Clips were used to close the incision to avoid bleeding and perforation. All the endoscopic resections and surgical resections were performed by skilled doctors (Figure 1).

Pathology

All the specimens after surgical or endoscopic resection were treated routinely for histologic examination in the Pathology Department in the Xijing Hospital of digestive diseases. Histological type and mitotic index were detected by hematoxylin and eosin stain. Immunohistochemistry was performed on 3-μm sections according to the manufacturer's instructions and the following antibodies: CD117, CD34, DOG-1, and Ki67.

Follow-Up

The patients after resection were followed up through endoscopic ultrasound and computed tomography every 6 months to evaluate tumor recurrence and distant metastasis.

Data Collection

We recorded the preoperative data including age, gender, tumor location, tumor ulceration, tumor bleeding, tumor margin, growth type, and tumor size. The pathological characteristics including histological type, intratumoral bleeding, intratumoral necrosis, mitotic index, Ki-67, CD117, CD34, and DOG-1 were also recorded. The surgical and endoscopic resection–related data including operation time, blood loss, first flatus, first defecation, pain intensity, postoperative hospital stay, medical cost of hospitalization, and postoperative complications were also recorded. Pain intensity was evaluated from postoperative day (POD) 1 to POD 3 using a visual analog scale.

Statistical Analysis

Data were processed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). Numerical variables were expressed as the mean ± SD unless otherwise stated. Discrete variables were analyzed using the chi-square test or Fisher's exact test. The *P* values were considered to be statistically significant at the 5% level.

Results

The clinical and pathological characteristics were comparable between the two groups except for tumor location and DOG-1 expression (Table 1). Compared with the surgical resection group, the operation time was shorter (113.60 ± 14.02 vs 50.00 ± 4.96 minutes, $P = .000$), blood loss was less (56.67 ± 9.77 vs 2.96 ± 0.48 ml, $P = .000$), and medical cost of hospitalization was lower (32,600.39 ± 2267.51¥ vs 27,210.46 ± 869.62¥, $P = .027$) in the endoscopic resection group. The patients in the endoscopic resection group also showed significantly accelerated recovery of gastrointestinal function in terms of time to first flatus and first defecation ($P < .05$).The postoperative hospital stay was comparable between the two groups (Table 2). Visual analog scale analysis showed that pain intensity of patients in the endoscopic resection group was significantly lower than that of patients in the surgical resection group on POD 1 to 3 ($P < .05$) (Table 3).

The overall complication rate in the surgical resection group was 5.00% compared with 12% in the endoscopic resection group ($P = .292$). In the surgical resection group, two patients (5.00%) suffered from pneumonia. In the endoscopic resection group, three patients (6.00%) experienced perforation and suffered from fever after resection; the fever of two patients was controlled by antibiotics, and the remaining patient underwent reoperation because of abdominal infection. One patient (2.00%) in the endoscopic resection group experienced tardive postoperative hemorrhage 1 month after resection, and the hemorrhage was controlled by conservative treatment (Table 4). All the patients after surgical resection and endoscopic resection were followed up using endoscopic ultrasound and abdominal computed tomographic

Table 1. Comparison of Clinicopathological Characteristics between Two Groups

Characteristics	Surgical Resection	Endoscopic Resection	*P* Value
Age (years)			
≤60	18	28	.300
>60	22	22	
Gender			
Male	25	24	.170
Female	15	26	
Tumor location			
Cardia	4	4	.018
Fundus	9	27	
Body	23	17	
Antrum	4	2	
Tumor ulceration			
Yes	8	2	.021
No	32	48	
Tumor bleeding			
Yes	2	0	.195
No	38	50	
Tumor margin			
Regular/smooth	37	48	.652
Irregular	3	2	
Growth type			
Intracavity	38	50	.195
Extracavity	2	0	
Histological type			
Spindle	40	50	–
Epithelioid	0	0	
Mixed	0	0	
Intratumoral bleeding			
Yes	1	0	.444
No	39	50	
Intratumoral necrosis			
Yes	1	0	.444
No	39	50	
Mitotic index			
≤5	31	41	.596
>5	9	9	
Ki-67			
≤5	37	46	1.000
>5	3	4	
CD117			
Positive	38	50	.195
Negative	2	0	
CD34			
Positive	38	50	.195
Negative	2	0	
DOG-1			
Positive	34	50	.006
Negative	6	0	

Table 2. Comparison of Perioperative Characteristics between Two Groups.

Characteristics	Surgical Resection	Endoscopic Resection	*P* Value
Operation time (min)	113.60 ± 14.02	50.00 ± 4.96	.000
Blood loss (ml)	56.67 ± 9.77	2.96 ± 0.48	.000
First flatus	62.43 ± 7.67	42.29 ± 5.27	.034
First defecation	78.37 ± 9.48	53.06 ± 6.28	.029
Postoperative hospital stay (day)	5.87 ± 0.29	5.80 ± 0.30	.883
Medical cost of hospitalization (RMB)	32600.39 ± 2267.51	27210.46 ± 869.62	.027

Table 3. Comparison of Postoperative Pain Intensity between Two Groups

Time	Surgical Resection	Endoscopic Resection	*P* Value
POD1	3.154 ± 0.154	0.551 ± 0.131	<.001
POD2	1.941 ± 0.135	0.184 ± 0.063	<.001
POD3	1.231 ± 0.122	0.102 ± 0.044	<.001

examination. The median follow-up time was 32 months (range from 12 to 65 months), and no *in situ* recurrence or liver metastasis was observed during follow-up.

Discussion

The aim of the present study was to evaluate the safety and clinical outcomes of endoscopic resection of small gastric GISTs in comparison with conventional surgical resection. The data of the present study showed that the endoscopic resection group had shorter operation time, less intraoperative blood loss, shorter time to first flatus and defecation, lower postoperative pain intensity, and lower cost of hospitalization. The complications in the two groups are comparable, and no recurrence and distant metastasis were observed in the endoscopic resection group.

The National Comprehensive Cancer Network recommends that small gastric GISTs less than 2 cm can be conservatively followed up [9]. However, every GIST is now regarded as potentially malignant, including small gastric GISTs. It was reported that the tumor size of small gastric GISTs could increase significantly during follow-up [10], and our previous study showed that the mitotic index of approximately 22.22% of small gastric GISTs exceed 5 mitotic figures per 50 HPF [6]. This highlights the fact that even if the gastric GIST is small, the tumor could show rapid growth, potential for metastasis, and poor prognosis. Thus, resection of small gastric GIST should be taken into consideration once diagnosed.

Up to now, surgery is the main treatment of GISTs, and complete surgical resection with an adequate margin and without rupture and spillage remains the definitive treatment for gastric GISTs [11]. As lymphatic metastasis is rare in gastric GISTs and with the rapid advances in the development of minimally invasive technology and endoscopic skill, there are more choices for treatment of local GISTs, including laparoscopic resection [12], endoscopic resection [13], and combination of laparoscopic and endoscopic resection [14]. Previously, it was thought that endoscopic resection was not appropriate for GIST considering that GIST originated from the muscular layer. However, endoscopic resection of GIST has been accepted for its satisfied safety and outcome [15]. Compared with surgical resection, endoscopic resection has many advantages, such as an intact stomach after resection, a relatively short postoperative hospital stay, a relatively low cost of hospitalization, and fewer human resources required [16]. Moreover, endoscopic resection has more advantages for elderly patients and patients who could not tolerate surgical resection or patients with small size tumors. In our present study, the endoscopic resection group had shorter operation time, less blood loss, earlier flatus and defecation, lower pain intensity, and lower medical cost. However, endoscopic resection remains controversial because of major complications including perforation and bleeding. Furthermore, the risk of tumor rupture and spillage and positive margins is also a huge concern [17].

Table 4. Comparison of Postoperative Complications between Two Groups

	Surgical Resection	Endoscopic Resection	*P* Value
Total cases	2	6	.292
Pneumonia	2	0	.195
Abdominal infection	0	1	1.000
Gastric retention	0	0	
Perforation and fever	0	3	.251
Postoperative hemorrhage	0	1	1.000
Deep-vein thrombosis	0	0	
Ileus	0	0	
R1 resection	0	0	
Reoperation	0	1	1.000
Mortality	0	0	

Perforation is a common and important complication in endoscopic resection [18]. The direction of tumor growth is one of the reasons that result in perforation. It was reported that the perforation rate was 73.68% in extracavity growth type and 18% in intracavity growth type [19]. The location of the gastric GISTs is another factor that contributed to perforation. It was reported that the rate of perforation was higher for the fundus than for other location [20]. In our present study, intraoperative perforation occurred in 17 patients, which was closed well using titanium clips with no conversion to open surgery. Only 3 of 17 patients suffered from fever after endoscopic resection due to application of antibiotics. Unfortunately, one patient suffered from tardive perforation and abdominal infection 1 month after endoscopic resection and finally received open surgery for perforation repair. Perforation is usually accompanied by pseudocapsule injury, which increases the possibility of peritoneal seeding, and peritoneal seeding is accompanied by a high recurrence rate. Waterman et al. reported a case of a patient who underwent endoscopic resection of small gastric GIST resulting in incomplete excision and gastric perforation, and the patient had tumor recurrence in the pelvis 3 years later [21]. However, to date, no comparative data with surgical resection about long-term follow-up exist.

Bleeding is also a common complication after endoscopic resection, and severe postoperative bleeding sometimes needs reoperation. In our present study, one patient after endoscopic resection experienced tardive postoperative hemorrhage 1 month after resection, and the hemorrhage was controlled by conservative treatment. R1 resection is another important issue which should be paid enough attention to. There have been no data showing whether or not there was remnant GIST tissue at dissection surface when R1 resection was confirmed through pathological examination [22]. Although there is no evidence that patients who have positive microscopic margin require further resection [23] and several studies have shown that a microscopically positive margin was not a significant adverse factor [24], one of the latest studies reported that a 5.8% local recurrence was observed even though R0 resection was achieved [16]. In our present study with limited follow-up, no *in situ* recurrence was observed in patients who received endoscopic resection.

Small GISTs normally do not recur after surgical removal of tumor, and the prognosis of small GISTs is generally good [25]. According to expert consensus, most of the small gastric GISTs are extremely low risk or low risk based on National Institutes of Health risk factor classification; therefore, imatinib was unnecessary after resection [26]. Thus, none of the patients in our study were administered with imatinib after resection, and no *in situ* recurrence or liver metastasis was observed with the median follow-up of 32 months. However, Shen et al. reported that one patient of small gastric GIST after surgical resection and one patient after endoscopic resection experienced recurrence or liver metastasis at 23 and 31 months [27]. It should also be noticed that the exact duration of follow-up is

uncertain because of the limited existing experience on the endoscopic resection of small gastric GSITs. A 5-year follow-up may be appropriate according to surgery follow-up duration.

There are some limitations in the present study. First, it was a retrospective analysis, and the sample size was not big enough. A randomized controlled trial should be carried out to evaluate the safety and prognosis of small gastric GIST patients who underwent endoscopic resection. Second, the duration of follow-up was not long enough to evaluate *in situ* recurrence and liver metastasis. Third, no patients received adjuvant therapy with imatinib after resection. The necessity of adjuvant therapy with imatinib after resection of small gastric GISTs needed further investigation.

In summary, endoscopic resection of small gastric GISTs is safe and feasible compared with surgical resection, although perforation could not be totally avoided during and after resection. The clinical outcome of endoscopic resection is also favorable.

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