



Clinicopathological Features and Prognosis of Small Gastric Gastrointestinal Stromal Tumors (GISTs)

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Abstract

Background The aim of the present study was to evaluate the safety of endoscopic surgery, the clinicopathological features, and prognoses of small gastric gastrointestinal stromal tumors (GISTs).

Methods Small gastric GIST patients (diameter: 0.10–2.00 cm) resected endoscopically in Zhongshan Hospital were retrospectively identified and clinicopathological features and outcomes were collected. The relationship between clinicopathological characteristics and tumor recurrence was analyzed. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal tumor diameter for predicting malignant potential.

Results All lesions were completely removed by endoscopy and En bloc resection was 98.5%. The most frequent location was the gastric fundus (60.3%) and the average diameter of all lesions was 1.20 cm (range: 0.10–2.00 cm). Mitoses were calculated as more than 5/50 HPF in 44 (6.8%) patients and nuclear atypia was moderate in 243 (37.5%) patients, severe in 1 (0.2%). Necrosis, mucosal infiltration, and vascular infiltration were detected in 8 (1.2%), 5 (0.7%), and 3 (0.5%) patients, respectively. Tumor size was positively correlated with mitotic index ($P < 0.001$) and nuclear atypia ($P < 0.001$). After a median follow-up of 54 months, four patients were confirmed local recurrence. ROC curve analysis identified 1.45 cm as the best cut-off value to predict malignant potential (95% CI: 0.694–0.774). Survival analysis showed that patients with tumor diameters larger than 1.45 cm were associated with more local recurrences after resection ($P = 0.011$).

Conclusions Endoscopic surgery is feasible and safe for small gastric GISTs, especially those in favorable locations. Small gastric GISTs bear a good prognosis as a whole but those with diameters larger than 1.45 cm should receive more intensive surveillance or undergo endoscopic surgery.

Keywords Gastrointestinal stromal tumors · Endoscopic surgery · Malignant potential · Prognosis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and are supposed to originate from the interstitial cells of Cajal—the

pacemaker cells of the gastrointestinal tract.¹ Most GISTs harbor activating mutations in c-kit or platelet-derived growth factor receptor alpha (PDGFRA) genes, both of which encode receptor tyrosine kinases.^{1, 2} Despite a reported incidence of only about 0.0014% clinically, GISTs, especially small GISTs, are actually more common as reported in autopsy studies, which range from 2.9 to 35%.^{3, 4} In 2010, small GISTs were defined for the first time by the National Institute of Health (NIH) as lesions with a diameter smaller than 2 cm.⁵ With the increasing popularity of endoscopy, particularly the application of endoscopic ultrasonography (EUS), small GISTs are easier to be detected than before. For GISTs larger than 2 cm, there has been a consensus that curative surgery should be applied if possible; however, management of small GISTs is still in controversy. The National Comprehensive Cancer Network (NCCN) recommended conservative follow-up for

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small gastric GISTs lacking high-risk EUS features⁶ while the European Society for Medical Oncology (ESMO) suggested that standard treatment for histologically proven small gastric GISTs is surgery.⁷ Some researchers also maintained that all GISTs have malignant potential and should be resected once detected.^{8, 9} Another hotspot issue in the treatment of small gastric GISTs is the application of endoscopic surgery. Endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR) have been reported as minimally invasive treatments for submucosal tumors.^{10, 11} Endoscopic resection maintains the integrity of gastrointestinal tract and is advantaged by fewer postoperative complications; however, endoscopic resection is not recommended as a routine treatment for the fear of positive residual tumor margin and gastric perforation.^{6, 7, 12, 13} In the current study, we evaluated the safety of endoscopic surgery, the clinicopathological features and prognoses of small gastric GISTs.

Materials and Methods

Patients

We retrospectively enrolled patients with gastric submucosal tumors resected endoscopically at Zhongshan Hospital between January 2009 and December 2016. Patients were included if lesions were 2 cm or smaller in diameter and proven as GISTs histopathologically. Exclusion criteria were as follows: (1) Patients coexisted with other malignant tumors; (2) Patients had received previous gastric surgery and/or endoscopic resection; (3) Patients had chronic gastric ulcer and were receiving chronic medicine; (4) Patients who were younger than 18 years. Finally, 648 patients were eligible for analyses. This study was approved by the Ethics Committee of Zhongshan Hospital (Approval No. HGBB-201804002) and written informed consent was obtained from all patients.

Procedures of Endoscopic Resection

ESD or EFTR techniques were performed with a single-channel gastroscopy or dual-channel endoscopy (GIF-H260 or GIF-2T240, Olympus). The surgery consisted of six major procedures: (1) Marker dots were made about 5 mm from the lesions; (2) Several milliliters of solution (100 mL saline solution, 5 mL 0.8% indigo carmine, and 1 mL epinephrine) were injected around the lesions; (3) The mucosa was incised outside the marker dots using the needle-knife; (4) ESD: The insulation-tipped knife was used to peel the muscularis propria layer along the capsule of the lesions; EFTR: The insulation-tipped knife incised into serosal layer around the lesions; (5) ESD: The lesions were resected completely from the muscularis propria layer with the needle-knife; EFTR: The dual-channel endoscopy was used with forceps grasping the

lesions into the gastric cavity, and the lesions including the serosal layer were resected completely. (6) The gastric wall defect was closed with metallic clips. En bloc resection was defined as excision of a tumor in one piece without fragmentation.

Pathology and Immunohistochemistry

All specimens were fixed in formalin immediately after endoscopic resection and embedded in paraffin routinely for histologic examination. Immunohistochemical staining of CD34, CD117, and DOG-1 was performed according to the manufacturer's instructions. All slides were reviewed by two experienced pathologists. Mitotic index was counted as the number of mitoses per 50 high power fields (HPF) and cellular type was classified as spindle, epithelioid, and mixed. Positive margin was defined as the presence of tumor cells in the dissected margin. Biological behaviors were also assessed according to the criteria proposed by Professor Hou from our institute.¹⁴ Nuclear atypia, necrosis, mucosal infiltration, vascular infiltration, nerve infiltration, and fat infiltration were defined as malignant biological parameters. All patients were classified into different risk groups according to the modified NIH consensus criteria and morphological classification system. The evaluated criteria were listed in Table 1.

Postoperative Complications

Postoperative bleeding was defined as hematemesis or melena requiring an endoscopic hemostatic procedure in 14 days from endoscopic resection. Perforation was defined as gastric wall penetration detected by abdominal plain radiography or computed tomography (CT). Post-ESD electrocoagulation syndrome (PEECS) was defined

Table 1 The Modified NIH and the Morphological classification systems to evaluate the risk and biological behaviors of small gastric GISTs

	Classification	Parameters
Modified NIH	Very-low	Size ≤ 2 and mitotic ≤ 5
	Intermediate	Size ≤ 2 and $5 < \text{mitotic} \leq 10$
	High	Size ≤ 2 and mitotic > 10
Morphological	Non-malignant	Parameters of mitotic index (≤ 10) and no necrosis, mucosal infiltration, vascular infiltration, nerve infiltration and fat infiltration
	Low-malignant	One or two parameters of mitotic index (> 10), necrosis, mucosal infiltration, vascular infiltration, nerve infiltration, and fat infiltration

as postoperative fever (>37.7 °C) and abdominal pain without evidence of abdominal free air in 7 days .

Follow-up Strategy

We conducted postoperative follow-up via outpatient service review or by telephone. Endoscopic surveillance was performed to observe healing of the wound at 1, 3 or 6, and 12 months for the first year and annually thereafter. Abdominopelvic enhanced CT was carried out once per year.

Statistical Analyses

Statistical analyses were performed by SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean \pm standard deviation (SD) and categorical data were displayed as number (*n*) or percentage (%). Chi-square test was applied for intergroup comparisons. Recurrence-free survival (RFS) was defined as the interval from endoscopic surgery to radiologic and/or endoscopic evidence of recurrence. RFS was analyzed using Kaplan-Meier curve and Log-Rank test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal tumor diameter for predicting malignant potential, and lesions with moderate/severe nuclear atypia or mitoses more than 5/50 HPF were defined as true positives. *P* value <0.05 was considered statistically significant.

Results

Clinical and Pathological Features of Small Gastric GISTs

The study included 235 males and 413 females, with an average age of 58.5 years (range: from 29 to 83 years) at diagnosis. The most frequent locations were the gastric fundus (60.3%) and gastric body (28.9%) and the average diameter of all lesions was 1.20 cm (range: 0.10–2.00 cm). Microscopically, 97.1% of lesions showed a cellular phenotype of predominant spindle. Mitoses were calculated as more than 5/50 HPF in 44 (6.8%) patients and equal or less than 5/50HPF in 604 (93.2%). Nuclear atypia was absent or mild in 404 (62.3%) patients, moderate in 243 (37.5%) patients, and severe in 1 (0.2%) patients. Necrosis, mucosal infiltration, and vascular infiltration were detected in 8 (1.2%), 5(0.7%), and 3(0.5%) patients, respectively. Calcification was observed in 51 (7.9%) lesions. Immunohistochemically, the positive rate of CD34, CD117, and DOG-1 expressions was 99.5%, 99.5%, and 96.4%, respectively.

Safety of Endoscopic Surgery for Small Gastric GISTs

En bloc resection was performed in 638 lesions (98.5%), with only 10 lesions (1.5%) managed by piecemeal. Complete resection was achieved in all patients with no residual tumor microscopically. The overall incidence of postoperative complication was 7.2%, with 6 (0.9%) postoperative bleeding, 10 (1.5%) perforations, and 31 (4.8%) PEECS. Postoperative bleeding and perforation were all successfully managed by endoscopic procedures without severe consequences. Patients with PEECS recovered uneventfully following conservative treatment including fasting and intravenous antibiotics. There were no treatment-related deaths. The median postoperative hospital stay was 3 days (range 0–25 days). The clinicopathological characteristics were listed in Table 2.

Prognoses of Small Gastric GISTs

Follow up data was available for all patients with a median of 54 months (range: 12–107). In general, small gastric GISTs had a favorable prognosis (Fig. 1a). Only four patients developed local recurrence and no distant metastases were discovered. Detailed clinicopathological features of four relapses were summarized in Table 3. In all, only two patients died during the follow-up period, one of pancreatic cancer and the other of mediastinal neoplasm. According to the modified NIH risk stratification,¹⁵ 7 (1.1%) patients were classified as high risk, 37 (5.6%) as intermediate risk, and the rest as very low risk. Three patients (0.4%) with high risk of recurrence were administered imatinib mesylate (IM) 400 mg daily for 24–36 months. No malignant biological behaviors were detected in 638 patients and the remaining 10 patients were low-malignant by the grading parameters of Professor Hou.¹⁴ Survival analysis between groups divided by modified NIH criteria showed no significant difference. (Fig. 1b). Though patients with malignant biological behaviors appeared to have shorter RFS, the number of patients between groups was extremely imbalanced (Fig. 1c).

ROC Curve Analysis

To determine the optimal cut-off value for predicting malignant potential of small gastric GISTs, aggressive biological behaviors were expanded to mitoses more than 5/50HPF or moderate/severe nuclear atypia. Lesions with mild/severe nuclear atypia or mitoses more than 5/50 HPF were defined as true positives. 1.45 cm was finally identified as the optimal cut-off value, with the area under the curve (AUC) being 0.734 (95% confidence interval [CI], 0.694–0.774, *P* <0.01) (Fig. 2). Subsequently, 399 patients fell into the group of \leq 1.45 cm and 249 into the group of $>$ 1.45 cm. The comparison of clinicopathological characteristics between two groups are

Table 2 Clinicopathological characteristics of the patients

Characteristics	Cases (<i>n</i> = 648)	Cases of recurrence
Age (year)	58.5 ± 9.4	4
Sex		
Male	235 (36.3%)	2
Female	413 (63.7%)	2
Tumor location		
Cardia	41 (6.3%)	0
Gastric fundus	391 (60.3%)	2
Gastric body	187 (28.9%)	1
Gastric antrum	29 (4.5%)	1
Endoscopic resection		
ESD	491 (75.8%)	2
EFTR	157 (24.2%)	2
Excavation procedure		
En bloc	638 (98.5%)	4
Piecemeal	10 (1.5%)	0
Tumor size (cm)		
≤ 1.45	399 (61.6%)	0
1.45–2.00	249 (38.4%)	4
Morphology		
Spindle	629 (97.1%)	4
Epithelioid	9 (1.4%)	0
Mixed	10 (1.5%)	0
Mitotic index (/50HPF)		
≤ 5	604 (93.2%)	3
> 5	44 (6.7%)	1
Nuclear atypia		
No	80 (12.3%)	1
Mild	324 (50.0%)	0
Moderate	243 (37.5%)	3
Severe	1 (0.2%)	0
Calcification		
Yes	51 (7.9%)	0
No	597 (92.1%)	4
Modified NIH classification		
Very-low	604 (93.2%)	3
Low	0 (0%)	0
Intermediate	37 (5.7%)	1
High	7 (1.1%)	0
Morphological classification		
Non-malignant	638 (98.5%)	0
Low-malignant	10 (1.5%)	4
Margin		
Positive	0 (0%)	0
Negative	648 (100%)	4
Complication		
Bleeding	6 (0.9%)	0
Perforation	10 (1.5%)	0
PEECS	31 (4.8%)	0

Table 2 (continued)

Characteristics	Cases (<i>n</i> = 648)	Cases of recurrence
Postoperative hospital stay (range)	3d (0–25d)	–

Data are *n* (%) or mean ± standard deviation

ESD endoscopic submucosal dissection, *EFTR* endoscopic full-thickness resection, *HPF* high power fields, *PEECS* post endoscopic submucosal dissection electrocoagulation syndrome

presented in Table 4. Patients with larger tumor diameter tended to display severer nuclear atypia and more active cell division. Kaplan-Meier survival analysis suggested that tumor diameter larger than 1.45 cm reflected a relatively poorer prognosis (Fig. 1d, *P* = 0.011).

Discussion

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the gastrointestinal tract, with an estimated incidence of around 1–2/100000/year.^{1, 16} Compared with GISTs larger than 2 cm, the incidence of small GISTs is obviously higher,^{4, 17} but their management policy has been controversial.^{12, 18} In addition, it is a hotspot issue whether to apply endoscopic resection to treat small GISTs. Therefore, researches should be conducted to investigate the malignant potential and the appropriate treatment of small GISTs. The current study retrospectively recruited 648 patients with small gastric GISTs resected endoscopically and analyzed their clinicopathological features and prognoses.

GISTs generally exhibit a broad range of biological behaviors and prognoses, but small GISTs, gastric ones in particular, tend to be less malignant and even benign. Five recurrences were observed in 20 small non-gastric GISTs as reported by Wang et al.¹⁹ while no recurrence was reported in all gastric small GISTs according to Feng and Wang et al.^{20, 21} Of all the 648 patients with small gastric GISTs included in our study, mitoses were calculated as equal or less than 5/50 HPF in 604 (93.2%) patients and nuclear atypia was absent or mild in 404 (62.3%) patients. Necrosis, mucosal infiltration, and vascular infiltration were detected in 8 (1.2%), 5 (0.7%), and 3 (0.5%) patients, respectively. After a median follow-up of 54 months, only four patients developed local recurrences. This low probability of recurrence reported above renders surgery too radical but makes gastroscopy treatment of choice for patients with small gastric GISTs. Gastroscopy, sometimes combined with ultrasonography, is widely recommended to evaluate and follow-up submucosal lesions. However, when GISTs are highly suspected and regular gastroscopy is infeasible, endoscopic surgery is a choice.

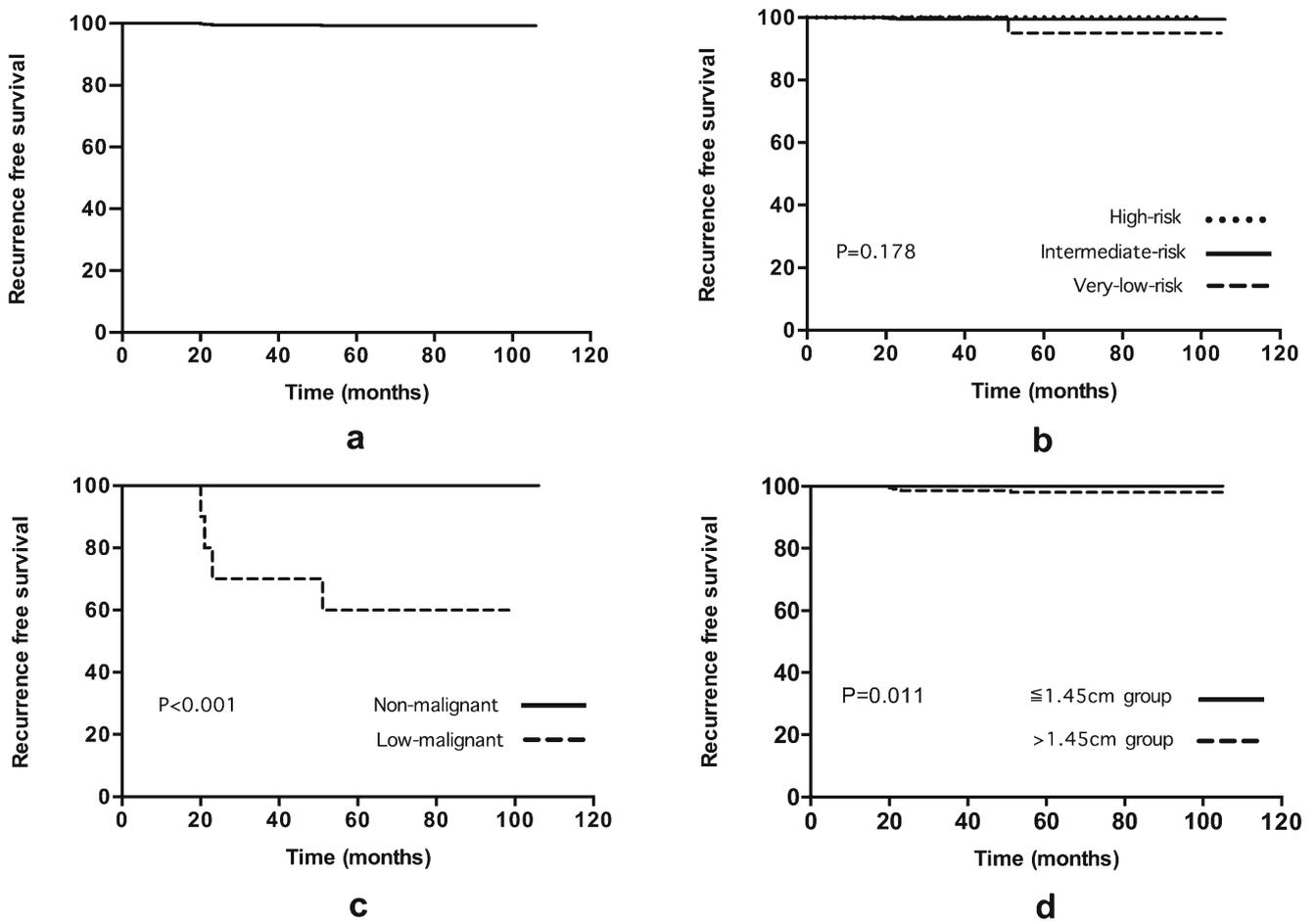


Fig. 1 Kaplan-Meier survival curve of the RFS. **a** The RFS of the small gastric GISTs patients. **b** There was no statistical difference of RFS among very-low-risk group, intermediate-risk group, and high-risk group

($P=0.178$). **c** There was significant difference of RFS between two groups ($P<0.001$). **d** There was statistical difference of RFS between ≤ 1.45 cm group and > 1.45 cm group ($P=0.011$)

Surgery is the only possible way to eradicate GISTs when resectable, but with the development of endoscopic techniques, complete removal has become possible via endoscopy. Application of endoscopic surgery in treating small GISTs has received increasing attention; however, positive tumor margin may result in local recurrence and perforation increases the possibility of peritoneal seeding, both which limit the application of endoscopic surgery. Many institutions have carried out relevant researches and suggested that endoscopic resection of small GISTs by a trained endoscopist appears to be safe and feasible.^{22–26} In the present study, the En bloc resection rate was 98.5%, consistent with previous ones ranging from 93 to 100%.^{10, 11, 27–29} All of the lesions were completely resected endoscopically and no residual tumor was observed on any surgical margins. The incidence of postoperative bleeding and perforation were low, manifested by 0.9% and 1.5%, respectively. Although laparotomy and laparoscopy are advantaged by more precise tumor margin, we believe that endoscopic resection is worth trying in view of comparable safety and less injury, especially for small gastric GISTs in favorable locations.

Although small gastric GISTs seem to have a considerably favorable prognosis after resection, retrospective investigations of small sample size suggested that 23.2% (16/69) of small gastric GISTs do progress during follow-up³⁰ and Coe et al. reported that up to 11% small gastric GISTs had regional or distant metastases at diagnosis.³¹ Previous studies proposed heterogeneous echogenicity, irregular borders, echogenic foci or ulceration under EUS as predictors of malignancy,^{32–34} but intensive surveillance with EUS poses an economic and psychological burden on patients. Tumor size is associated with progression and easy to access.^{30, 32} In our study, we generated a ROC curve based on two potential malignancy predictors, mitoses more than 5/50HPF and moderate/severe nuclear atypia, to determine the optimal cut-off value of tumor size. A tumor diameter of 1.45 cm was identified as the optimal cut-off value, with a sensitivity of 62.0% and a specificity of 76.4%. Survival analysis showed that tumor diameter larger than 1.45 cm was associated with local recurrence after endoscopic resection. We thus proposed that patients with gastric GISTs larger than 1.45 cm should be followed-up more

Table 3 Clinicopathological characteristics of four recurrent patients

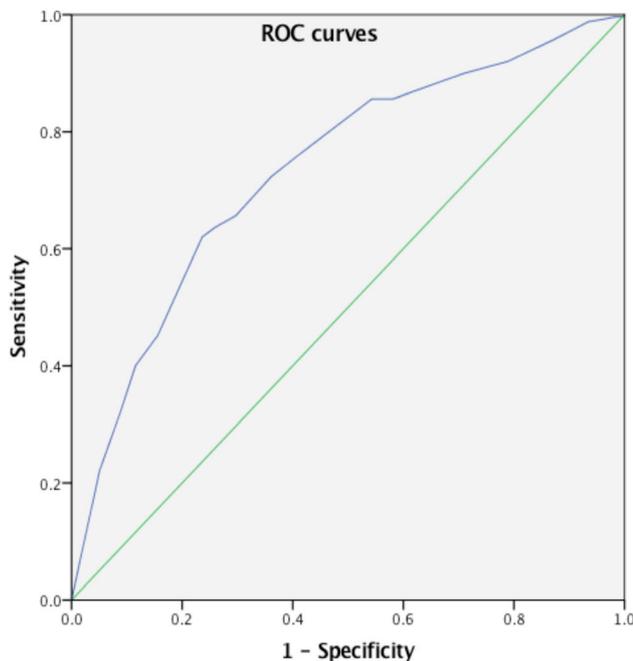
Characteristics	1	2	3	4
Sex	Male	Female	Male	Female
Age (year)	74	58	69	53
Endoscopic resection	ESD	ESD	ESD	EFTR
Tumor location	Fundus	Fundus	Antrum	Body
Tumor size (cm)	1.50	1.70	1.55	1.60
Morphology	Spindle	Spindle	Spindle	Spindle
Mitotic index (/50HPF)	2	6	1	3
Nuclear atypia	No	Moderate	Moderate	Moderate
Calcification	No	No	No	No
Margin	Negative	Negative	Negative	Negative
Modified NIH classification	Very-low	Intermediate	Very-low	Very-low
Morphological classification	Low-malignant	Low-malignant	Low-malignant	Low-malignant
Malignant parameters				
Ulceration	No	Yes	Yes	No
Coagulative necrosis	Yes	No	Yes	Yes
Mucosal infiltration	Yes	Yes	No	No
Vascular infiltration	No	No	No	Yes
Nerve infiltration	No	No	No	No
Fat infiltration	No	No	No	No
Imatinib mesylate	No	No	No	No
Recurrence free time (months)	20	51	23	21

ESD endoscopic submucosal dissection, EFTR endoscopic full-thickness resection

frequently and think about endoscopic surgery as an option when regular follow-up is not feasible.

There are several limitations in our study. First, the cut-off value to predict malignancy were based on two pathological

features after resection, which may not accurately reflect their real aggressive behaviors, but large-scale study to observe tumor progression in vivo is difficult to carry out. Second, EUS was performed in a relatively small portion of population



Test Result Variable (s)	Tumor size	Positive if \geq cm ^d	Sensitivity	1 - Specificity
		-.900	1.000	1.000
		.150	.996	.997
		.250	.996	.982
		.350	.992	.960
		.450	.988	.935
		.550	.956	.869
		.650	.920	.789
		.750	.900	.711
		.850	.856	.580
		.950	.856	.543
		1.050	.756	.405
		1.150	.724	.362
		1.250	.656	.296
		1.350	.636	.259
		1.450	.620	.236
		1.550	.452	.156
		1.650	.400	.116
		1.750	.320	.088
		1.850	.220	.050
		1.950	.164	.038
		3.000	.000	.000

Fig. 2 Receiver operating characteristic curve. The results showed that the tumor size cut-off was 1.45 cm

Table 4 Comparison of clinicopathological characteristics between ≤ 1.45 cm group and > 1.45 cm group

Characteristics	Tumor size		P value
	≤ 1.45 cm group	> 1.45 cm group	
Age (year)	58.2 ± 9.0	58.7 ± 10.2	0.514
Sex			0.111
Male	135	100	
Female	264	149	
Tumor location			< 0.001
Cardia	14	27	
Fundus	261	130	
Body	115	72	
Antrum	9	20	
Morphology			0.024
Spindle	393	236	
Epithelioid	3	6	
Mixed	3	7	
Mitotic index (/50HPF)			< 0.001
≤ 5	394	210	
> 5	5	39	
Nuclear atypic			< 0.001
No or mild	307	97	
Moderate or severe	92	152	
Other*			< 0.001
Yes	4	12	
No	395	237	

Other*: Lesions that had one or more parameters of necrosis, mucosal infiltration, vascular infiltration, nerve infiltration, and fat infiltration

and the correlation between EUS features and pathological characteristics was not analyzed. Third, endoscopic surgeries were all performed by experienced endoscopists who formed a tertiary hospital renowned for its superb surgical techniques, which may improve the resectability and safety.

Conclusion

Endoscopic surgery by experienced endoscopists is feasible and safe for small gastric GISTs, especially those in favorable locations. Small gastric GISTs bear a good prognosis as a whole but those with diameters larger than 1.45 cm should undergo more intensive surveillance. Endoscopic surgery can be regarded as a choice as well if regular follow-up is infeasible.

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(VII) Final approval of manuscript: All authors

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References

1. Corless CL, Barnett CM, Heinrich MC: Gastrointestinal stromal tumours: origin and molecular oncology. *Nature Reviews Cancer* 2011, **11**(12):865–878.
2. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M *et al*: Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science (New York, NY)* 1998, **279**(5350):577–580.
3. Rossi S, Gasparotto D, Toffolatti L, Pastrello C, Gallina G, Marzotto A, Sartor C, Barbareschi M, Cantaloni C, Messerini L *et al*: Molecular and clinicopathologic characterization of gastrointestinal stromal tumors (GISTs) of small size. *The American Journal of Surgical Pathology* 2010, **34**(10):1480–1491.
4. Kawanowa K, Sakuma Y, Sakurai S, Hishima T, Iwasaki Y, Saito K, Hosoya Y, Nakajima T, Funata N: High incidence of microscopic gastrointestinal stromal tumors in the stomach. *Hum Pathol* 2006, **37**(12):1527–1535.
5. George D., Demetri M: NCCN Task Force Report: Update on the Management of Patients with Gastrointestinal Stromal Tumors. 2010.
6. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad EU, III, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ *et al*: Soft Tissue Sarcoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network : JNCCN* 2016, **14**(6):758–786.
7. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology : official journal of the European Society for Medical Oncology* 2014, **25** Suppl 3:iii21–26.
8. Melstrom LG, Phillips JD, Bentrem DJ, Wayne JD: Laparoscopic versus open resection of gastric gastrointestinal stromal tumors. *American Journal of Clinical Oncology* 2012, **35**(5):451–454.
9. Yang J, Feng F, Li M, Sun L, Hong L, Cai L, Wang W, Xu G, Zhang H: Surgical resection should be taken into consideration for the treatment of small gastric gastrointestinal stromal tumors. *World Journal of Surgical Oncology* 2013, **11**:273.
10. Zhou PH, Yao LQ, Qin XY, Cai MY, Xu MD, Zhong YS, Chen WF, Zhang YQ, Qin WZ, Hu JW *et al*: Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria. *Surgical Endoscopy* 2011, **25**(9):2926–2931.
11. Zhang Y, Ye LP, Zhu LH, Zhou XB, Mao XL, Ding JX: Endoscopic muscularis excavation for subepithelial tumors of the esophagogastric junction originating from the muscularis propria layer. *Digestive Diseases and Sciences* 2013, **58**(5):1335–1340.
12. Li J, Ye Y, Wang J, Zhang B, Qin S, Shi Y, He Y, Liang X, Liu X, Zhou Y *et al*: Chinese consensus guidelines for diagnosis and management of gastrointestinal stromal tumor. *Chinese Journal of*

- Cancer Research = Chung-kuo yen cheng yen chiu 2017, **29**(4): 281–293.
13. Koo DH, Ryu MH, Kim KM, Yang HK, Sawaki A, Hirota S, Zheng J, Zhang B, Tzen CY, Yeh CN *et al*: Asian Consensus Guidelines for the Diagnosis and Management of Gastrointestinal Stromal Tumor. *Cancer Research and Treatment* : official journal of Korean Cancer Association 2016, **48**(4):1155–1166.
 14. Hou YY, Lu SH, Zhou Y, Qi WD, Shi Y, Tan YS, Zhu XZ: Stage and histological grade of gastrointestinal stromal tumors based on a new approach are strongly associated with clinical behaviors. *Modern Pathology* : an official journal of the United States and Canadian Academy of Pathology, Inc 2009, **22**(4):556–569.
 15. Miettinen M, Lasota J: Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Archives of Pathology & Laboratory Medicine* 2006, **130**(10):1466–1478.
 16. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, Sablinska K, Kindblom LG: Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. *Cancer* 2005, **103**(4):821–829.
 17. Muenst S, Thies S, Went P, Tornillo L, Bihl MP, Dirnhofer S: Frequency, phenotype, and genotype of minute gastrointestinal stromal tumors in the stomach: an autopsy study. *Hum Pathol* 2011, **42**(12):1849–1854.
 18. von Mehren M, Benjamin RS, Bui MM, Casper ES, Conrad EU, 3rd, DeLaney TF, Ganjoo KN, George S, Gonzalez R, Heslin MJ *et al*: Soft tissue sarcoma, version 2.2012: featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network: JNCCN* 2012, **10**(8):951–960.
 19. Wang YP, Li YI, Song C: Clinicopathological features and prognosis of small gastrointestinal stromal tumors outside the stomach. *Oncol Lett* 2015, **10**(5):2723–2730.
 20. Feng F, Liu Z, Zhang X, Guo M, Xu G, Ren G, Hong L, Sun L, Yang J, Zhang H: Comparison of Endoscopic and Open Resection for Small Gastric Gastrointestinal Stromal Tumor. *Translational Oncology* 2015, **8**(6):504–508.
 21. Wang H, Feng X, Ye S, Wang J, Liang J, Mai S, Lai M, Feng H, Wang G, Zhou Y: A comparison of the efficacy and safety of endoscopic full-thickness resection and laparoscopic-assisted surgery for small gastrointestinal stromal tumors. *Surgical Endoscopy* 2016, **30**(8):3357–3361.
 22. Meng FS, Zhang ZH, Hong YY, Li DJ, Lin JQ, Chen X, Ji F: Comparison of endoscopic submucosal dissection and surgery for the treatment of gastric submucosal tumors originating from the muscularis propria layer: a single-center study (with video). *Surgical Endoscopy* 2016, **30**(11):5099–5107.
 23. Andalib I, Yeoun D, Reddy R, Xie S, Iqbal S: Endoscopic resection of gastric gastrointestinal stromal tumors originating from the muscularis propria layer in North America: methods and feasibility data. *Surgical Endoscopy* 2017, **32**(4):1787–1792.
 24. An W, Sun PB, Gao J, Jiang F, Liu F, Chen J, Wang D, Li ZS, Shi XG: Endoscopic submucosal dissection for gastric gastrointestinal stromal tumors: a retrospective cohort study. *Surgical Endoscopy* 2017, **31**(11):4522–4531.
 25. Meng Y, Li W, Han L, Zhang Q, Gong W, Cai J, Li A, Yan Q, Lai Q, Yu J *et al*: Long-term outcomes of endoscopic submucosal dissection versus laparoscopic resection for gastric stromal tumors less than 2 cm. *J Gastroenterol Hepatol* 2017, **32**(10):1693–1697.
 26. Andalib I, Yeoun D, Reddy R, Xie S, Iqbal S: Endoscopic resection of gastric gastrointestinal stromal tumors originating from the muscularis propria layer in North America: methods and feasibility data. *Surgical Endoscopy* 2018, **32**(4):1787–1792.
 27. Zhang B, Huang LY, Wu CR, Cui J, Jiang LX, Zheng HT: Endoscopic full-thickness resection of gastric stromal tumor arising from the muscularis propria. *Chinese Medical Journal* 2013, **126**(13):2435–2439.
 28. Ye LP, Zhang Y, Mao XL, Zhu LH, Zhou X, Chen JY: Submucosal tunneling endoscopic resection for small upper gastrointestinal subepithelial tumors originating from the muscularis propria layer. *Surgical Endoscopy* 2014, **28**(2):524–530.
 29. Huang LY, Cui J, Lin SJ, Zhang B, Wu CR: Endoscopic full-thickness resection for gastric submucosal tumors arising from the muscularis propria layer. *World Journal of Gastroenterology* 2014, **20**(38):13981–13986.
 30. Gao Z, Wang C, Xue Q, Wang J, Shen Z, Jiang K, Shen K, Liang B, Yang X, Xie Q *et al*: The cut-off value of tumor size and appropriate timing of follow-up for management of minimal EUS-suspected gastric gastrointestinal stromal tumors. *BMC Gastroenterology* 2017, **17**(1):8.
 31. Coe TM, Fero KE, Fanta PT, Mallory RJ, Tang CM, Murphy JD, Sicklick JK: Population-Based Epidemiology and Mortality of Small Malignant Gastrointestinal Stromal Tumors in the USA. *J Gastrointest Surg* 2016, **20**(6):1132–1140.
 32. Fang YJ, Cheng TY, Sun MS, Yang CS, Chen JH, Liao WC, Wang HP: Suggested cutoff tumor size for management of small EUS-suspected gastric gastrointestinal stromal tumors. *J Formos Med Assoc* 2012, **111**(2):88–93.
 33. Huang Z, Li Y, Zhao H, Zhao JJ, Cai JQ: Prognostic factors and clinicopathologic characteristics of small gastrointestinal stromal tumor of the stomach: a retrospective analysis of 31 cases in one center. *Cancer Biology & Medicine* 2013, **10**(3):165–168.
 34. Nishida T, Goto O, Raut CP, Yahagi N: Diagnostic and treatment strategy for small gastrointestinal stromal tumors. *Cancer* 2016, **122**(20):3110–3118.

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