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Clinicopathological characteristics and prognostic factors of gastrointestinal stromal tumors in Chinese patients

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Abstract. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms in the gastrointestinal tract, exhibiting wide variability in their biological behavior. The aim of the present study was to investigate the clinicopathological characteristics and prognostic factors of GISTs in Chinese patients. All GIST cases (n=182) retrieved from the pathology database and the archived files in Shanghai Changzheng Hospital between January 2011 and December 2014 were reviewed. The clinical symptoms, preoperative investigations, treatments, pathological characteristics and follow-up data of these patients were reviewed, and univariate and multivariate survival analyses were performed. A total of 73.1% of the GISTs were located in the stomach, and the most common three symptoms included abdominal pain (30.2%), dyspepsia (23.1%) and gastrointestinal bleeding (21.4%). Univariate analysis revealed that larger tumor size (P<0.001), higher mitotic rate (P<0.001), aggressive behavior (P<0.001), negative smooth muscle actin expression (P=0.009) and palliative resection (P<0.001) contributed toward poor overall survival (OS). In addition, non-gastric disease location (P<0.001), larger tumor size (P<0.001), higher mitotic rate (P=0.004), aggressive behavior (P<0.001) and palliative resection (P<0.001) were associated with poor relapse-free survival (RFS). Multivariate analysis indicated that mitotic rate [hazard ratio (HR=3.761, P=0.015)] and aggressive behavior (HR=3.916, P=0.010) were independent risk factors for OS, while non-gastric location (HR=4.740, P=0.002) and aggressive behavior (HR=4.009, P=0.004) were independent risk factors for RFS. The present study provided information on the clinicopathological characteristics and epidemiology of GISTs in the Chinese population. Non-gastric disease location, higher mitotic rate and tumor metastasis or local invasion prior to treatment were identified as predictors of a poor prognosis.

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Key words: gastrointestinal stromal tumor, clinical symptoms, clinicopathological characteristics, immunohistochemistry, prognosis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, accounting for 80% of all digestive mesenchymal tumors. It is widely accepted that GISTs arise from the interstitial cells of Cajal, and the term 'stromal tumor' was first introduced by Mazur and Clark in 1983 (1). The incidence of GISTs has been reported to range between 11 and 15 per million annually (2-4), and 60% of GISTs are located in the stomach, 30% in the jejunum or ileum, 5% in the duodenum and 4% in the colorectum. Extragastrointestinal GISTs (EGISTs) have been reported in the liver, omentum, mesentery, gallbladder and urinary bladder (5-7).

The diagnosis of GISTs is based on morphology, positive immunohistochemistry (IHC) results for CD117 and DOG1, and mutation analyses of KIT and platelet-derived growth factor receptor α polypeptide gene (PDGFRA) (7-9). With increasing use of abdominal computed tomography (CT), magnetic resonance imaging (MRI) and endoscopy, an increasing number of asymptomatic GISTs are diagnosed at an early stage, although the effect of early detection of GIST on the prognosis remains unclear. The National Institutes of Health (NIH) and Armed Forces Institute of Pathology (AFIP) risk classification criteria are commonly used to predict the prognosis of GISTs (10-12). Large tumor size, high mitotic rate, non-gastric tumor location and tumor ulceration are commonly accepted to be associated with a poor prognosis in patients with GIST. Other factors, including sex, age, symptoms and IHC results are also reported to be associated with patient outcomes (13,14). However, the biological behavior of GISTs varies widely, with unclear risk predictors, and it is difficult to predict their malignant potential with the currently available risk classification criteria (15).

The number of studies on the clinicopathological characteristics of GIST in China is limited. The aim of the present study was to update the clinicopathological and immunophenotypic characteristics of GISTs in mainland China, and to investigate the prognostic factors of GISTs based on these patients.

Materials and methods

Patients and diagnosis. The present study was approved by the Institutional Review Board of Changzheng Hospital. Written informed consent was obtained from all patients involved for the publication of any associated data and accompanying images. The clinicopathological and survival data of 182 patients with GIST treated surgically at Shanghai Changzheng Hospital between January 2011 and December 2014 were retrospectively reviewed. A total of 94 males and 88 females were included. The mean age of the patients was 59.2±12.6 years (range, 26-88 years). The diagnosis of each patient with GIST was established based on the results of the histopathology and IHC. Pathological samples were collected during surgical interventions. If the diagnosis of GIST was uncertain based on pathology, mutation analysis for the KIT and PDGFRA genes was performed. For 136 patients with mitotic rate data, the tumors were categorized into different risk groups according to the modified NIH and AFIP risk classification criteria.

The following details of these patients were collected: Age, sex, symptoms and signs, preoperative investigations, surgical details, pathology and follow-up data. The tumor site was analyzed according to previous classification methods (16,17). Preoperative investigations comprised radiological and endoscopic examinations, including gastroscopy, abdominal CT, MRI, colonoscopy, small intestinal endoscopy, capsule endoscopy and positron emission tomography (PET)-CT.

Pathology and IHC. Tissues were fixed in formalin for 12-24 h at room temperature then paraffin-embedded. Sections of 4 μM were stained with Hematoxylin & Eosin at room temperature (3-5 min for hematoxylin and 5-10 sec for eosin) (18). Tissue sections were deparaffined in xylene and rehydrated in a descending alcohol series. Antigen retrieval was performed by heating the sections for 30 min at 95˚C in 1 mM EDTA buffer (pH 8.0). Endogenous peroxidase activity was eliminated by treating sections with 3% methanolic hydrogen peroxide solution for 10 min. Thereafter, the slides were blocked in 1/100 diluted goat serum (cat. no. kit-9710; Fuzhou Maixin Biotech Co., Ltd., Fuzhou China) for 20 min at room temperature. IHC analysis included common biomarkers for the diagnosis of GISTs, including CD117 (dilution, 1:400; cat. no. kit-0029; Fuzhou Maixin, Co., Ltd., Fuzhou, China), DOG1 (dilution, 1:400; cat. no. kit-0035; Fuzhou Maixin Biotech Co., Ltd.), CD34 (dilution, 1:600; cat. no. kit-0004; Fuzhou Maixin Biotech Co., Ltd.), smooth muscle actin (SMA) (dilution, 1:600 dilution; cat. no. kit-0006; Fuzhou Maixin Biotech Co., Ltd.), S-100 protein (dilution, 1:500; cat. no. kit-0007; Fuzhou Maixin Biotech Co., Ltd.), Ki-67 (dilution, 1:500; cat. no. kit-0005; Fuzhou Maixin Biotech Co., Ltd.) and desmin (dilution, 1:600; cat. no. kit-0023; Fuzhou Maixin Biotech Co., Ltd.). The sections were incubated with the aforementioned antibodies at 4˚C overnight. Following 3 washes in PBS, the sections were incubated with biotin-conjugated secondary antibody (ready-to-use; 50 μl for each section; goat anti-mouse IgG secondary antibody for CD34, SMA, S-100, Ki-67 and desmin; goat anti-rabbit IgG secondary antibody for CD117 and DOG1) (cat. no. kit-9710; Fuzhou Maixin Biotech Co., Ltd.) for 10 min at room temperature, followed by incubation with peroxidase-conjugated biotin-streptavidin complex (Fuzhou Maixin Biotech Co., Ltd.) for 10 min at room temperature, and finally stained with diaminobenzidine at room temperature for 2 min, and counterstained with hematoxylin at room temperature for 3-5 min. Mitoses were counted in 50 high-power fields (HPF). Two professional pathologists reviewed these results under a light microscope (x100 and x400, magnification).

Treatment methods and follow-up. For localized primary GISTs, radical resection, including open surgical resection and minimally invasive techniques, were selected as the primary treatments (19). Minimally invasive techniques included laparoscopic surgery, endoscopic surgery and endoscopy-assisted laparoscopic surgery (20,21). For locally advanced unresectable or metastatic GISTs, palliative surgery and/or imatinib treatment were recommended, and imatinib adjuvant therapy following radical resection was recommended for patients with intermediate-to-high-risk GISTs (22). The final treatment decision was made with the consent of the patients. The records of all surgical procedures were reviewed. Patient follow-up was conducted by regular hospital visits at 3, 6 and 12 months, and annually thereafter. Each visit included a medical review, physical examination and associated investigations. The patients' status was confirmed by telephone communication at the end of the study. Survival outcomes were assessed in terms of overall survival (OS) and relapse-free survival (RFS). OS was defined as the time from the date of initial treatment to the date of the last follow-up or mortality, and RFS was defined as the time from the date of initial treatment to the time of clinical or radiological evidence of disease relapse or the date of the last follow-up.

Statistical analysis. SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA) and SPSS 23.0 (IBM Corp., Armonk, NY, USA) were used for statistical analysis. Continuous variables are expressed as mean ± standard deviation and were compared using an unpaired, two-tailed Student's t-test. Categorical variables were compared using the χ^2 test or Fisher's exact test. The Kaplan-Meier method and the log-rank test were used for survival analysis. Independent factors were identified in multivariate analysis using the Cox proportional hazard model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological characteristics. A total of 182 patients with GISTs were analyzed in the present study. The stomach was the most common site, accounting for 73.1% of the cases, followed by the jejunum and ileum (14.3%), duodenum (5.5%), colorectum and anus (4.94%), esophagus (1.1%), and EGISTs (1.1%). Abdominal pain, dyspepsia and gastrointestinal bleeding were the main presenting complaints, reported in 30.2, 23.1 and 21.4% of the patients, respectively. The symptoms varied according to the primary location. Patients with esophageal GISTs often presented with dysphagia (2/2 patients), whereas patients with GISTs of the colorectum or anal canal usually reported altered bowel habits (4/9 patients; Table I).

Gastroscopy and abdominal CT were used in 83 (54.6%) and 87 (57.2%) patients, respectively, with a high diagnostic accuracy of 62.7 and 74.7%, respectively. Other investigations,

Table I. Clinical characteristics of 182 patients with gastrointestinal stromal tumor.

Factor	n
Sex, n (%)	
Male	94 (51.6)
Female	88 (48.4)
Age, years	
Median	60
Range	26-88
Location, n (%)	
Esophagus	2 (1.10)
Stomach	133 (73.1)
Duodenum	10 (5.50)
Jejunum and ileum	26 (14.3)
Colon, rectum and anus	9 (4.94)
Other (liver and omentum)	2 (1.10)
Immunohistochemistry, n (%)	
CD117	179 (98.4)
DOG-1	177 (98.3)
CD34	171 (94.5)
Desmin	24 (13.9)
S-100	25 (14.2)
SMA	100 (57.5)
Symptoms, n (%)	
Abdominal pain	55 (30.2)
Dyspepsia	42 (23.1)
Gastrointestinal bleeding	39 (21.4)
Regurgitation	11 (6.04)
Palpable mass	8 (4.40)
Altered bowel habit	8 (4.40)
Weight loss	4 (2.20)
Fever	3 (1.65)
Dysphagia	2 (1.10)
Vomiting	2 (1.10)
Pre-operation examinations, n (%)[a]	
Gastroscopy	83 (54.6)
Abdominal CT scan	87 (57.2)
Endoscopic ultrasonography	23 (15.1)
Abdominal MRI	13 (8.6)
Abdominal ultrasound	32 (21.1)
Colonoscopy	8 (5.3)
Small intestine endoscopy	7 (4.6)
PET-CT	5 (3.3)

[a]n=152, 30 patients with co-existing diseases excluded. CD, cluster of differentiation; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

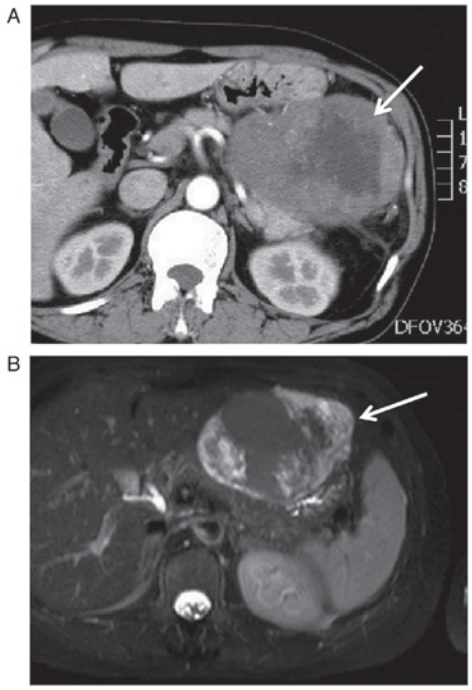

Figure 1. Radiological characteristics of GISTs. (A) Computed tomography scan (arterial phase): The lesion is indicated by the arrow. GIST of the stomach demonstrating a thickening of the gastric wall, with slight to moderate inhomogeneous enhancement following contrast agent injection. Lymph nodes around the mass exhibited reactive hyperplasia. (B) Magnetic resonance imaging (T2-weighted): The lesion is indicated by the arrow. GIST of the stomach sized ~9x7 cm and exhibiting heterogeneous hyperintense T2 signals. GIST, gastrointestinal stromal tumor.

including endoscopic ultrasonography, MRI, abdominal ultrasound, colonoscopy, small intestinal endoscopy (or capsule endoscopy) and PET-CT were used in 23 (15.1%), 13 (8.6%), 32 (21.1%), 8 (5.3%), 7 (4.6%) and 5 (3.3%) patients, respectively (Table I and Fig. 1). In addition, 30 patients (16.5%) were diagnosed with GIST by pathological examination following surgery for other conditions.

The majority of GIST samples were positive for CD117 and DOG1 according to the IHC analysis (98.4 and 98.3% cases, respectively). In addition, 94.5% of the samples were positive for CD34. Positive SMA, S-100 protein and desmin expression was also detected in 57.5, 14.2 and 13.9% of the GISTs, respectively. The Ki-67 index was 0-65%, with a mean of 7% (Table I and Fig. 2).

The malignant potential of 136 GISTs with data on mitotic rate was evaluated. The distribution of risk groups was 17 (12.5%) in the very low-risk, 35 (25.7%) in the low-risk, 31 (22.8%) in the intermediate-risk and 53 (39.0%) in the high-risk groups according to the NIH criteria. In addition, 72 cases (52.9%) were classified in the benign group, 5 (3.68%) in the malignant potential group and 59 (43.4%) in the malignancy group according to the AFIP criteria. It was also demonstrated that larger GISTs exhibited a higher mitotic rate ($P<0.001$). The NIH risk classification of GISTs at different sites was significantly different ($P=0.006$), with GISTs in the stomach or duodenum exhibiting a lower risk of malignancy. However, the AFIP risk classification and mitotic rate of GISTs did not differ significantly by primary location ($P=0.0996$ and $P=0.1203$, respectively). Based on the symptoms of the 136 patients when they were admitted to Changzheng Hospital, the patients were divided into the asymptomatic GIST group (asymptomatic patients and patients accidentally diagnosed with co-existing disease; n=46) and the symptomatic GIST group (n=90).

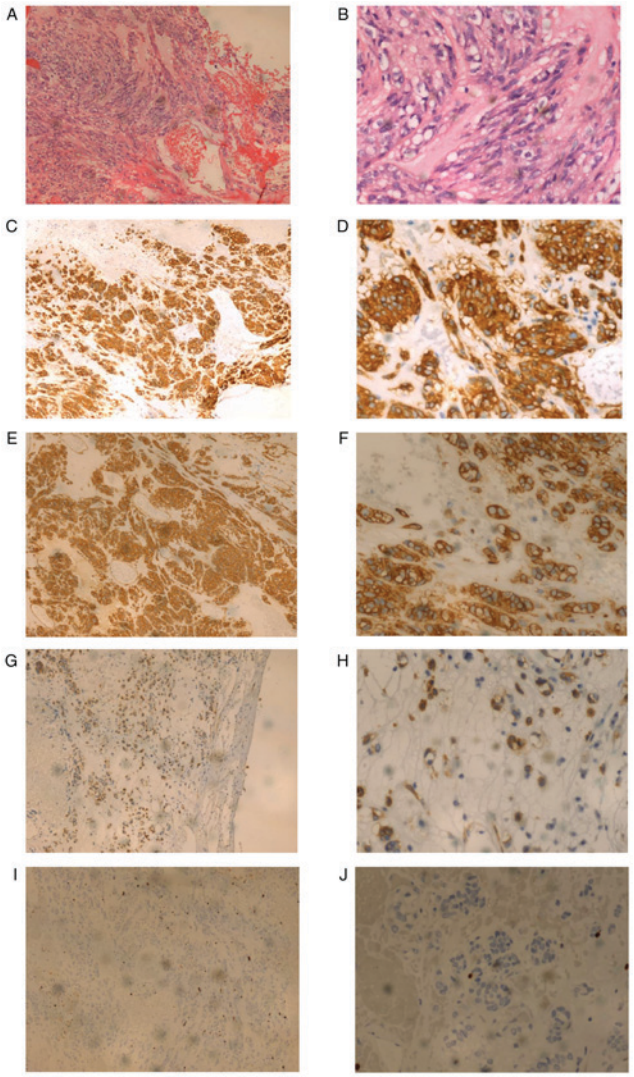

Figure 2. Histological and immunohistochemical characteristics of GISTs. H&E staining; magnification, (A) x100 and (B) x400. Strong and diffuse staining for CD117; magnification, (C) x100 and (D) x400. Strong and diffuse staining for CD34; magnification, (E) x100 and (F) x400. Staining for DOG1; magnification, (G) x100 and (H) x400. Staining for Ki-67; magnification, (I) x100 and (J) x400. GIST, gastrointestinal stromal tumor; CD, cluster of differentiation.

Patients in the asymptomatic group had a smaller tumor size (P=0.0245) and a lower risk of malignancy according to the NIH (P=0.0327) and AFIP (P=0.0198) risk classification criteria (Tables II and III).

Treatment. Numerous surgical procedures were performed, including partial gastric resection, total gastric resection, partial intestinal resection, hemicolectomy, sigmoid colon resection, abdomino-perineal rectum resection, pancreatoduodenectomy, distal pancreatectomy and endoscopic submucosal dissection. The choice of surgical procedure was individualized, depending on the tumor location, size and possibility of complete resection. Excluding the 30 patients who were incidentally diagnosed with GIST while treated for other conditions, 125 of the remaining 152 patients underwent radical resection of the primary tumor. Among these patients, 71 underwent open surgical resection; 47 underwent laparoscopic resection; 3 underwent endoscopic surgery; and 4 underwent endoscopic-assisted laparoscopic surgery. An additional 27 patients with unresectable tumors received palliative surgery, including 19 open surgery and 8 laparoscopic surgery. In 24 of the patients, the tumors displayed clear malignant characteristics during surgery, including local invasion and metastasis. Additionally, 5 patients were revealed to have tumor bleeding and ulceration. Imatinib as adjuvant therapy was administered to 15 patients with intermediate-to-high-risk GISTs, including 6 patients with advanced disease. No neoadjuvant imatinib therapy was used in the patients enrolled in the present study.

Survival analysis. Based on the 152 patients without co-existing diseases, the median follow-up time was 48 months (range, 3-81 months), and the 5-year OS and RFS rates were 85.4% (95% CI: 79.5-91.3) and 83.8% (95% CI: 77.5-90.1), respectively. A total of 21 patients succumbed during the follow-up period as a result of various causes (disease progression, other chronic diseases, including diabetes mellitus, cardiovascular and cerebral disorders, other malignancies and trauma). A total of 4 patients developed metastases in the abdominopelvic cavity and 3 in the liver during follow-up. The results of the univariate analysis of potential prognostic factors are presented in Table IV and Fig. 3. Larger tumor size (>10 cm; P<0.001), higher mitotic rate (>10/50 HPF; P<0.001), aggressive behavior, including tumor metastasis or local invasion prior to treatment (P<0.001) and negative SMA expression (P=0.009) contributed toward poorer survival of patients with GIST. In addition, non-gastric disease location (P<0.001), larger tumor size (>10 cm; P<0.001), higher mitotic rate (>10/50 HPF; P=0.004) and aggressive behavior (P<0.001) were associated with higher risk of recurrence. Patients receiving palliative tumor resection had a significantly shorter survival time (P<0.001) and a higher risk of recurrence (P<0.001). When therapeutic factors were included in the multivariate analysis, palliative surgical resection was the only independent risk factor for OS (HR=9.196, 95% CI: 3.327-25.417, P<0.001) and RFS (HR=16.42, 95% CI: 6.065-44.454, P<0.001). If the therapeutic factors were excluded, the multivariate analysis indicated that the mitotic rate (HR=3.761, 95% CI: 1.288-10.987, P=0.015) and aggressive behavior (HR=3.916, 95% CI: 1.389-11.044, P=0.010) were independent risk factors for OS. Non-gastric disease location (HR=4.740, 95% CI: 1.747-12.857, P=0.002) and aggressive behavior (HR=4.009, 95% CI: 1.538-10.449, P=0.004) were independent risk factors for RFS (Table V).

Discussion

The present retrospective study, based on 182 Chinese patients with GIST, aimed to investigate the clinicopathological and prognostic characteristics of this disease. The results are comparable with those of previous studies in other populations (23-27). The median age of the patients in the present study was 60 years. The stomach was the most common primary site of GISTs, while patients with GIST usually lack specific symptoms. In line with the results of a Japanese study that indicated that GISTs may be incidentally discovered during gastric cancer screening (28), 36 patients in the present study were asymptomatic without co-existing diseases and their GISTs were detected during their annual physical exam.

Table II. Association between tumor site, tumor size and mitotic rate.

Factor	n	0-5/50 HPF	5-10/50 HPF	>10/50 HPF
Location				
Stomach	101	59	33	9
Duodenum	9	7	1	1
Jejunum and ileum	21	10	7	4
Colon, rectum and anus	4	0	3	1
Omentum	1	1	0	0
Tumor size, cm				
0-2	15	14	1	0
2-5	59	36	18	5
5-10	40	22	16	2
≥10	22	5	9	8
Total	136	77	44	15

Table III. Association between symptoms, tumor site and NIH or AFIP risk classification criteria.

		NIH				AFIP		
Factor	n	Very low	Low	Middle	High	Benign	Malignant potential	Malignancy
Location								
Stomach	101	16	25	29	31	56	3	42
Duodenum	9	1	5	1	2	7	0	2
Jejunum and ileum	21	0	5	0	16	8	1	12
Colon, rectum and anus	4	0	0	1	3	0	1	3
Omentum	1	0	0	0	1	1	0	0
Symptoms								
Asymptomatic	46	8	13	14	11	31	1	14
Symptomatic	90	9	22	17	42	41	4	45
Total	136	17	35	31	53	72	5	59

NIH, National Institutes of Health; AFIP, Armed Forces Institute of Pathology.

Radical tumor resection is the most important factor affecting patient prognosis. Furthermore, non-gastric disease location, higher mitotic rate and tumor metastasis or local invasion prior to treatment were revealed to be predictors of a poor prognosis.

For GIST patients with clinical symptoms and those with incidentally detected tumors during physical examination, further radiological and endoscopic examinations are required (29). In the present study, 52 patients were diagnosed with GIST by gastroscopy and 65 by abdominal CT. Gastroscopic and endoscopic ultrasonography can detect mostly intramural tumors and enable acquisition of cytological or histological samples, while the use of endoscopy is limited when evaluating metastasis outside the digestive tract (30). Abdominal CT can scan the whole abdomen and is able to detect small lesions, providing valuable information on the size, morphology, aggressiveness and metastasis of the tumors (31,32). Abdominal MRI and PET-CT also have high diagnostic sensibility, particularly in intestinal GISTs or EGISTs, and were used in 13 and 5 patients, respectively. MRI is affected by peristalsis of the gastrointestinal tract, which limits its applicability, although it has been reported that, for lesions of the rectum and liver, MRI may offer more detailed images compared with CT (33). PET-CT is applied for evaluating tumor metastasis and response following the initiation of targeted therapy (34). Among patients with intestinal GISTs, the diagnosis of 7 patients in the present study series was confirmed by small intestinal endoscopy or capsule endoscopy, as their tumors were relatively difficult to diagnose.

There are no standard criteria for assessing the aggressive behavior and predicting the clinical prognosis of GISTs, although the NIH and AFIP criteria are widely recommended (35). It is commonly accepted that all GISTs are considered to have malignant potential (36). Through multivariate analysis, higher mitotic rate and tumor metastasis or local invasion prior to treatment were revealed to be associated with poor survival in GIST patients, and non-gastric

Table IV. Univariate analysis of prognostic factors for OS and RFS in 152 GIST patients.

		OS		RFS	
Group	N	5-year OS	P-value	5-year RFS	P-value
Sex					
Male	69	84.0	0.724	81.8	0.361
Female	83	86.5		85.5	
Age (years)					
≤60	83	88.5	0.177	87.1	0.360
>60	69	81.3		79.5	
Disease location					
Gastric	106	87.8	0.192	90.8	<0.001[a]
Non-gastric	46	79.9		68.5	
Tumor size (cm)					
≤10	129	91.1	<0.001[a]	87.6	<0.001[a]
>10	23	55.3		60.1	
Mitotic rate (/50 HPF)					
≤10	107	89.3	<0.001[a]	87.3	0.004[a]
>10	14	54.5		58.9	
Metastatic disease or local invasion					
Yes	24	49.0	<0.001[a]	44.9	<0.001[a]
No	128	91.9		90.2	
Ulceration					
Yes	5	80.0	0.664	80.0	0.120
No	147	85.5		84.0	
Desmin					
Positive	19	82.6	0.841	85.9	0.539
Negative	130	85.7		83.3	
S-100					
Positive	23	85.6	0.907	95.5	0.132
Negative	126	86.0		82.1	
SMA					
Positive	89	91.4	0.009[a]	85.4	0.448
Negative	58	76.7		80.3	
Symptom					
Asymptomatic	36	91.2	0.301	93.0	0.077
Symptomatic	116	83.6		81.0	
Resection margin					
Radical	125	93.4	<0.001[a]	94.4	<0.001[a]
Palliative	27	46.6		28.4	
Surgical procedures					
Open	90	82.6	0.232	82.8	0.587
Minimally invasive	62	89.7		85.0	
Imatinib therapy[b]					
Yes	15	86.2	0.388	54.3	0.052
No	71	77.0		83.0	

[a]Statistically significant (P<0.05); [b]only including 86 patients with intermediate-high risk. SMA, smooth muscle actin, OS, overall survival, RFS, relapse-free survival; N, number.

disease location was associated with tumor recurrence, which is consistent with the results of previous studies (16). Similarly, one British study (17) identified high mitotic index as an independent poor prognostic factor in these patients.

Table V. Multivariate analysis of prognostic factors for OS and RFS in 152 patients with gastrointestinal stromal tumors (therapeutic factors excluded).

	OS			RFS		
Factor	HR	95% CI	P-value	HR	95% CI	P-value
Disease location (gastric vs. non-gastric)	-	-	-	4.740	1.747-12.857	0.002[a]
Mitotic rate (≤10/50 HPF vs. >10/50 HPF)	3.761	1.288-10.987	0.015[a]	-	-	-
Metastatic disease or adjacent involvement (no vs. yes)	3.916	1.389-11.044	0.010[a]	4.009	1.538-10.449	0.004[a]

[a]Statistically significant. OS, overall survival; RFS, relapse-free survival; HR, hazards ratio; CI, confidence interval.

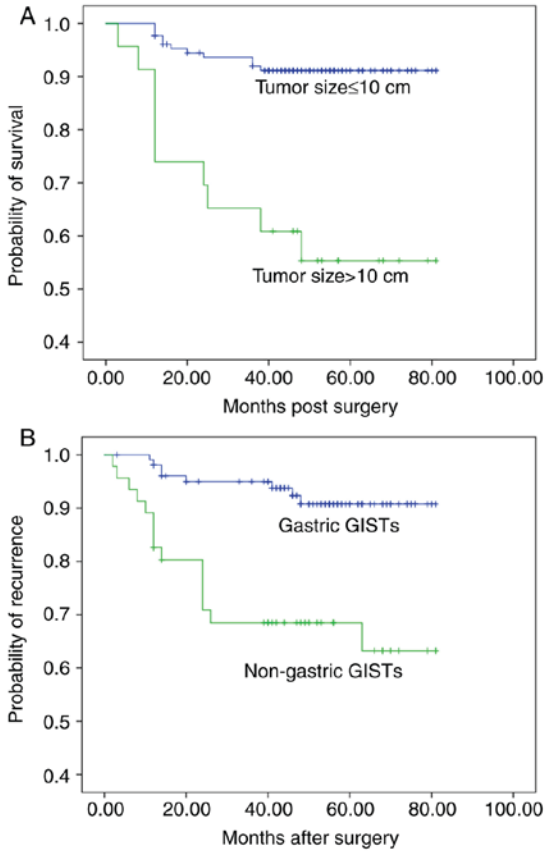

Figure 3. Survival analysis of 152 patients. (A) OS according to tumor size (P<0.001). (B) RFS according to tumor location (P<0.001). OS, overall survival; RFS, relapse-free survival.

Miettinen and Lasota (37) also demonstrated that small intestinal GISTs behave more aggressively than gastric GISTs, and small intestinal GISTs tend to be larger and more advanced at diagnosis. Liu *et al* (35) suggested that gastrointestinal bleeding is a prognostic factor. However, preoperative symptoms did not appear to affect the outcome of patients with GIST in our analysis. Large tumor size is considered to be a prognostic factor in the NIH and AFIP risk classification criteria. However, it failed to be an independent risk factor in the present study. Notably, patients with SMA-negative tumors exhibited a shorter survival time. Similarly, Demir *et al* (38) reported that patients with SMA-positive GISTs tended to survive longer and had significantly longer disease-free survival (DFS) times than the SMA-negative cases. Fujimoto *et al* (39) reported no association between SMA IHC analysis and the prognosis of patients with GIST. However, Bertin *et al* (40) reported that SMA positivity is significantly associated with a lower 5-year survival rate (39 vs. 100%). Differences in the selected population, tumor location, disease stage and treatment between these studies may affect these conclusions.

GISTs are usually asymptomatic until they reach a large size, at which point they may cause non-specific symptoms or be detected as a palpable mass (41). Compared with patients diagnosed with clinical symptoms, asymptomatic patients are considered to have early-stage disease. A total of 46 patients in the present study were asymptomatic or accidentally diagnosed with co-existing disease, and these GISTs were smaller in size and exhibited a lower risk based on the NIH and AFIP risk classification criteria, although no significant effect on OS and RFS was observed. A study by Yamamoto *et al* (28) reported that GISTs are incidentally observed during gastric cancer screenings in Japan. Over half of these patients are asymptomatic and have smaller tumors (P<0.001) and lower recurrence rates (P=0.017), compared with symptomatic patients. Therefore, the Japanese gastric cancer screening system contributes toward the early detection of gastric GISTs and favorable treatment outcomes by identifying asymptomatic patients. Scherubl *et al* (30) demonstrated that early asymptomatic GISTs have an excellent GIST-specific prognosis. The results of the present study also suggested that detecting GISTs at an early stage may improve patient outcome.

For resectable localized GISTs, radical surgery is the standard and first choice of treatment (42). Radical tumor resection significantly improved survival and reduced tumor recurrence, in univariate or multivariate analyses. Different surgical approaches, including open and laparoscopic surgery and endoscopic procedures, were performed in the present study. No statistically significant difference was observed in OS or RFS among these surgical strategies. A number of studies have been performed comparing the effect of minimally invasive and open surgery in the treatment of GISTs (42-44). It is generally accepted that minimally invasive surgery has similar or even superior perioperative outcomes, without compromising the oncological outcomes; it may also be safely used for larger tumors or tumors located in unfavorable sites. Imatinib serves an important role in the treatment of advanced GISTs and in the adjuvant setting, reducing the risk of recurrence and metastasis (16,45). In the

present study, not all the patients with intermediate-to-high risk GIST received imatinib as adjuvant therapy. However, there was no observed improvement in OS and RFS in the 15 patients who were administered adjuvant imatinib therapy. One possible reason may be that the selection of candidates for adjuvant therapy was not standardized and the sample size was limited. Imatinib was also recommended to patients receiving palliative surgery and those with disease progression. Advanced GISTs will inevitably progress and reduce the OS and RFS rates (16).

GISTs are widely considered to have a low risk of lymph node metastasis; therefore, lymphadenectomy is not deemed necessary during surgical resection (46,47). However, GIST cases with lymph node metastasis have been reported. Tashiro *et al* (48) and Shafizad *et al* (49) reported two cases of lymph node involvement in gastric GISTs. In addition, Gong *et al* (50) reported that 6 of 29 (20.7%) patients with GIST were revealed to have lymph node metastasis on PET-CT imaging. In the present study, lymph node metastasis was detected in only 1 patient with a history of intestinal GIST resection 2 years prior. Palliative surgery was performed and two main masses were removed from the small intestine. Tumor ulceration and bleeding were observed intraoperatively, and liver, peritoneal and pelvic cavity metastasis were confirmed. All 7 mesenteric lymph nodes resected during surgery were positive. Despite these reports, however, GISTs rarely metastasize to the lymph nodes, and regional lymph node resection is of unproven value (16).

There were certain limitations to the present study: The design of the study was retrospective; the selection of surgical approach and adjuvant therapy were not standardized; and the use of imatinib as an adjuvant therapy was limited to 15 patients with a potential selection bias; therefore, the benefit of using imatinib as adjuvant therapy cannot be evaluated based on this study. In summary, the present study updated the clinicopathological and immunophenotypic characteristics of GISTs in mainland China. Asymptomatic GISTs may be of smaller size and have a lower risk of malignancy according to the NIH and AFIP risk classification criteria. Clinical and immunohistochemical results were used for survival analysis, and positive SMA was associated with an improved survival in univariate analysis. Higher mitotic rate and tumor metastasis or local invasion prior to treatment were revealed to be independent risk factors for a poor OS, whereas non-gastric disease location and aggressive behavior were independent risk factors for a poor RFS. Large tumor size, a prognostic factor in the NIH and AFIP risk classification criteria, failed to reveal significant impact on OS and RFS in multivariate analysis. The present study may aid clinicians with an improved understanding of the diagnosis and treatment of GISTs.

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Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

YML analyzed and interpreted the patient data regarding GIST disease, performed statistical analysis and wrote the manuscript. WJC recorded the follow-up information, performed statistical analysis and wrote the manuscript. ZWB analyzed and interpreted the data and critically reviewed the manuscript. YDK designed the study and the quality control of data and algorithms, and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present retrospective study was approved by Changzheng Hospital Medical Committee. Written informed consent was obtained from all participating patients.

Patient consent for publication

The patient or parent, guardian or next of kin provided written informed consent for the publication of any associated data and accompanying images. All identifying information was removed.

Competing interests

The authors declare that they have no competing interests.

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