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Original Article

Prognosis and clinicopathological characterization of small gastrointestinal stromal tumors (GISTs) in a Chinese population

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Although generally responsive to treatment, tumors measuring less than 2 cm in diameter can recur or metastasize. The aim of the current study was to analyze the clinicopathological characteristics, molecular biological changes and prognosis of small GISTs. The clinical records of 76 patients who underwent resection for pathologically confirmed small GISTs, were analyzed retrospectively. Sixty-three cases were localized to the stomach, 5 small intestine, 4 colon-rectum, 2 pelvic cavity, and 2 to esophagus. There were 67, 0, 4 and 5 cases that were classified very low, low, moderate and high risk, respectively. The numbers of mitoses and Ki67 indexes were significantly associated with NIH risk grade. During follow-up, 1 patient with a single rectum small GIST recurrence, and 1 stomach small GIST patient developed liver metastases. All cases had CD117 and DOG1 protein positivity. KIT and PDGFRA mutations were detected in 41 cases, while 9 cases expressed wild-type KIT and PDGFRA. Generally, the prognosis of small GISTs is favorable. A high Ki67 index may be a predictive sign of poor prognosis in cases of small GISTs. Small GISTs of the lower gastrointestinal tract appear to be more malignant than those in other areas. It is necessary for close follow-up of small GISTs, at least once after the initial discovery.

Keywords: Small gastrointestinal stromal tumors, prognosis, mutation

Introduction

Gastrointestinal stromal tumors (GISTs) originate from Cajal cells or mesenchymal stem cells in the GI tract, and are the most common mesenchymal neoplasms of the GI tract [1, 2]. The annual incidence of GIST in Western countries is 14.5 per million, while the prevalence in western Sweden is 129 per million [3]. In 2010, the NCCN guidelines defined, for the first time, GISTs less than 2 cm in diameter as small GISTs. Most studies have reported that the small GISTs respond to therapy [4, 5]. However, some GISTs show a high rate of recurrence, metastasis, and poor clinical outcome. Recent reports suggest that even small GISTs can recur or metastasize, and therefore, are not necessarily benign tumors [6, 7].

Small GISTs are not uncommon. Some pathological studies have reported the incidence of small GISTs at autopsy to be 2.9%-35.0%, which is much higher than that reported in clinical studies [8, 9]. The management of small GISTs is difficult because these tumors are often only identified incidentally. Only a few series have been published so far. Therefore, an accurate understanding of the biological behavior of small GISTs is lacking. The aim of this study was to retrospectively analyze 76 cases of small GISTs in terms of their immunohistochemistry, clinical pathology and molecular biology, and follow-up status.

Materials and methods

Patients

Seventy-six patients underwent resection of pathologically confirmed small GISTs from January 2003 to May 2014 at Guangdong General Hospital (Guangzhou, China). No patient had

Table 1. Characteristics of the Study Population

	n (%)
Sex	
Male	43 (56.6)
Female	33 (43.4)
Age	
Range	26-80
Median	58
<58	36 (47.4)
≥58	40 (52.6)
Tumor diameter	
≤1 cm	46 (60.5)
>1 cm, ≤2 cm	30 (39.5)
Tumor location	
Esophagus	2 (2.6)
Stomach	63 (82.9)
Small intestinal	5 (6.6)
Colorectal	4 (5.3)
Pelvic cavity	2 (2.6)
Cell morphology	
Spindle cell	74 (97.4%)
Epithelioid	1 (1.3%)
Mixed	1 case (1.3%)
Number of mitoses	
≤5	67 (88.2)
>5, ≤10	4 (5.3)
>10	5 (6.6)
Ki67 index (percent positive for tumor cells)	
0-2%	53 (69.7)
3-5%	19 (25.0)
≥6%	4 (5.3)
NIH risk classification	
Very low	67 (88.2)
Low	0 (0)
Moderate	4 (5.2)
High	5 (6.6)

undergone preoperative radiotherapy neoadjuvant chemotherapy or therapy targeting selective tyrosine kinase inhibitors during follow-up. Patient consent and approval was obtained from a sub-committee of Guangdong General Hospital Ethics Committee before using the clinical materials for research purposes. Follow-up studies were continued up to November 30, 2015.

Histological of tissue samples

Tissue samples of small GISTs were sliced into 4 μm thick sections, and subjected to immunohistochemical analysis using a Dako EnVision System (Dako, Carpentaria, CA, USA) according to the manufacturer's recommendations. All the samples were stained with anti-CD117 (1:400, DAKO Biotechnology, clone A4502, Denmark), anti-DOG1 (1:400, DAKO Biotechnology, clone H-300, Denmark), and anti-Ki67 (1:100, DAKO Biotechnology, clone MIB1, Denmark). Briefly, the intensity of staining was scored as negative (-), weak (+), moderate (++), or strong (+++). Any signal was considered to be positive. To evaluate Ki67 protein expression, based on the ratio of Ki67 positive cells, the results were graded as follows: Ki67+ (1-2%), Ki67++ (3-5%), and Ki67+++ (≥6%). Two pathologists who were blinded to the clinicopathological information evaluated the immunohistochemical staining.

Biological behavior of GISTs

According to the National Institutes of Health (NIH) consensus 2008 risk evaluation standard [10], tumors with fewer than 5 mitoses per 5 mm^2 and diameter less than 2 cm have very low-risk lesions. Low-risk lesions include those tumors with fewer than 5 mitoses per 5 mm^2, and measuring less than 5 cm. Intermediate-risk lesions include those less than 5 cm in size with 6 to 10 mitoses and those measuring 5 to 10 cm with fewer than 5 mitoses. High-risk lesions are larger than 5 cm with more than 5 mitoses and all lesions greater than 10 cm or with more than 10 mitoses. We graded the small GISTs based on tumor size and mitotic count.

Molecular analysis

Purified genomic DNA was isolated from formalin-fixed, paraffin-embedded blocks with adequate tumor tissue using a DNeasy Tissue Kit according to the manufacturer's instructions. We used single-strand conformational polymorphism analysis to identify mutations in KIT exons 9, 11, 13, 17 and platelet-derived growth factor receptor, alpha polypeptide (PDGFRA) exons. Specific PCR primers were designed for the exons: (KIT exon 9) forward: 5'-AGTATGCCACATCCCAAGTGTTTTATG-3', reverse: 5'-ATCATGACTGATATGGTAGACAGAGCC-3'; (KIT exon 11) forward: 5'-CCAGAGTGCTCTAATGACTG-3',

Table 2. NIH Risk Grade and Location of Small GISTs

	NIH risk grade				
	Very low	Low	Intermediate	High	Total
Esophagus	2	0	0	0	2
Stomach	57	0	3	3	63
Small intestinal	5	0	0	0	5
Colorectal	2	0	0	2	4
Pelvic cavity	1	0	1	0	2
Total	67	0	4	5	76

reverse: 5'-AGCCCCTGTTTCATACTGAC-3'; (KIT exon 13) forward: 5'-CTTGACATCAGTTTGCCAGTTGT-3', reverse: 5'-GACAGACAATAAAAGGCAGCTTG-3'; (KIT exon 17) forward: 5'-TGGTTTTCTTTTCTCCTCCAA-3', reverse: 5'-GCAGGACTGTCAAGCAGAGA-3'; (PDGFRA exon 12) forward: 5'-ATTTATTTTCCTAGAGTAAGCCAGGG-3', reverse: 5'-ATCATGACTGATATGGTAGACAGAGC-3'; and (PDGFRA exon 18) forward: 5'-CCAGAGTGCTCTAATGACTG-3', reverse: 5'-AGCCCCTGTTTCATACTGAC-3'.

PCR was carried out in an ABI Veriti thermal cycler [11]. We used an ABI PRISM 3100 sequencer to sequence the PCR products according to the manufacturer's instructions.

Statistical analysis

Kaplan-Meier analysis was used to determine overall survival (OS). OS was measured from the date of diagnosis to the date of death or last contact. We performed statistical analysis using IBM SPSS Statistics Version 20 software.

Results

Clinicopathological results

Patient characteristics are listed in **Table 1**. The patient age ranged from 26 to 80 years, with an average of 58 years. Tumor size ranged from 0.1 to 2 cm, with an average diameter of 1.02±0.53 cm. Forty-six lesions were 0.1 to 1 cm, and 30 lesions were 1.1 to 2 cm. Sixty-three cases were localized to the stomach, 5 small intestine, 4 colon-rectum, 2 pelvic cavity, and 2 to esophagus. Nineteen cases had GIST coexisting with other benign or malignant tumors. The major types of GIST-associated cancers were gastric adenocarcinoma (n = 9, 47.4%), esophageal squamous cell carcinoma (n = 7, 36.8%), lung squamous cell carcinoma (n = 1, 5.3%) and colorectal adenocarcinoma (n = 1, 5.3%). In 74 cases (97.4%) GIST was of the spindle cell type, 1 case (1.3%) mixed spindle and epithelioid cells, and 1 case (1.3%) epithelioid. In one case, the stroma was myxoid and there was necrosis. Cases that were classified very low, low, moderate and high risk were 67, 0, 4 and 5, respectively. The relationship between NIH risk grade and the location is displayed in **Table 2**, two of the 4 cases of colorectal small GISTs occurred in the high-risk group. Small GISTs that were very low-risk were always spindle-shaped, whereas high-risk tumors were always of epithelioid cell or mixed histology.

Immunohistochemical detection and molecular analysis

As shown in **Figure 1**, the CD117 and DOG1 were expressed primarily in the cytoplasm. All cases were positive for CD117 and DOG1, but there was a difference in the intensity of the expression. Ki67 were found primarily in nuclei. The numbers of cases positive for Ki67 staining were 53 (+), 19 (++), and 4 (+++). The Ki67 index was significantly associated with NIH risk grade (P = 0.000).

KIT and PDGFRA mutations were detected in 41 of the 76 cases (53.9 %). The overall mutation (KIT and PDGFRA mutation) rate was 78.0% (32/41). Three patients (9.3%) had mutations in KIT exon 9, 24 (75.0%) in KIT exon 11, and five (15.6%) in PDGFRA exon 18. Mutations were not detected in KIT exon 13 or 17 of or PDGFRA exon 12. All KIT exon 9 mutations were insertion mutations. Among the KIT exon 11 mutations (N = 24), 12 were deletions, 10 were missense (7 V560D, 2 V559A and 1 W557R), and 2 were insertions. Among the PDGFRA exon 18 mutations (N = 5), one was a deletion, and four were missense (D842V). The mutations and locations are listed in **Table 3**. GISTs that did not contain mutations in either KIT or PDGFRA were considered to be wild-type (WT) GIST. We did not detect any coexisting KIT and PDGFRA mutations in these cases.

Prognostic factors

Of the 76 patients examined, 68 (89.5%) had follow-up. The median follow-up was 929 d,

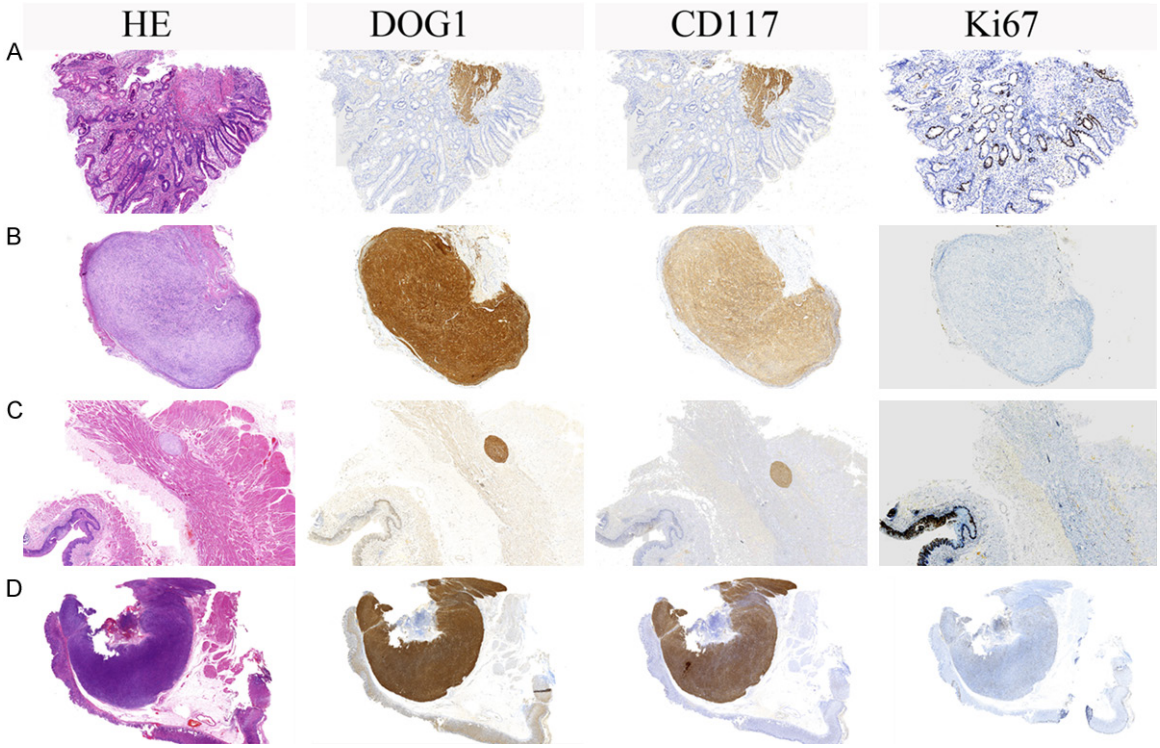

Figure 1. DOG1, CD117, Ki67 expression status of small GISTs. A: A 0.2 cm GIST, incidentally found in duodenum by endoscopy. B: A 0.6 cm GIST found in the ascending colon along with a resected colorectal adenocarcinoma. C: A 0.1 cm GIST in the *muscularis propria* of esophageal wall. D: A 1.0 cm gastric GIST.

Table 3. Mutation Status and Location of Small GISTs

	KIT exon 9	KIT exon 11	PDGFRA exon 18	Total
Esophagus	0	0	0	0
Stomach	3	20	5	28
Small intestine	0	1	0	1
Colon and rectum	0	2	0	2
Pelvic cavity	0	1	0	1
Total	3	24	5	32

with an estimated OS of 4011 days (**Figure 2**). During follow-up, 1 case died of esophageal squamous cell carcinoma, 2 cases from gastric adenocarcinoma. Only 1 patient with a recurrent solitary small GIST in rectum had a high NIH risk grade. One patient with metastasis had 20 mitoses per 50 high power fields, and the expression of Ki67 was 40% (+++). In addition, microscopy revealed necrosis. The remaining patients were found not to have recurrence or metastasis. Since tumor progression or death was rare, no univariate or multivariate survival analysis was performed.

Discussion

GISTs are more common in adults than in children, and occur anywhere in the digestive tract. The stomach is the most common location, accounting for 58% of the total number of these tumors [12, 13]. GISTs often grow submucosally [13]. The clinical manifestations are related to the tumor location, size and growth [14]. With small tumors there may be no clinical manifestations, so early diagnosis can be difficult [15]. Small GISTs are often incidentally found on physical examination or during surgery for other benign or malignant tumors such as gastrointestinal adenocarcinomas, esophageal squamous cell carcinomas, gastrointestinal lymphoma and hepatocellular carcinomas [16-18]. In 57 patients, GISTs were found during routine physical examination, and incidentally detected by endoscopic ultrasonography or during workup for abdominal discomfort. In the current study, 19 GISTs were found during surgery for other tumors. The most common accompanying neoplasm was gastric carcinoma, followed by esophageal carcinoma. The result was similar to that reported by Adim et al.

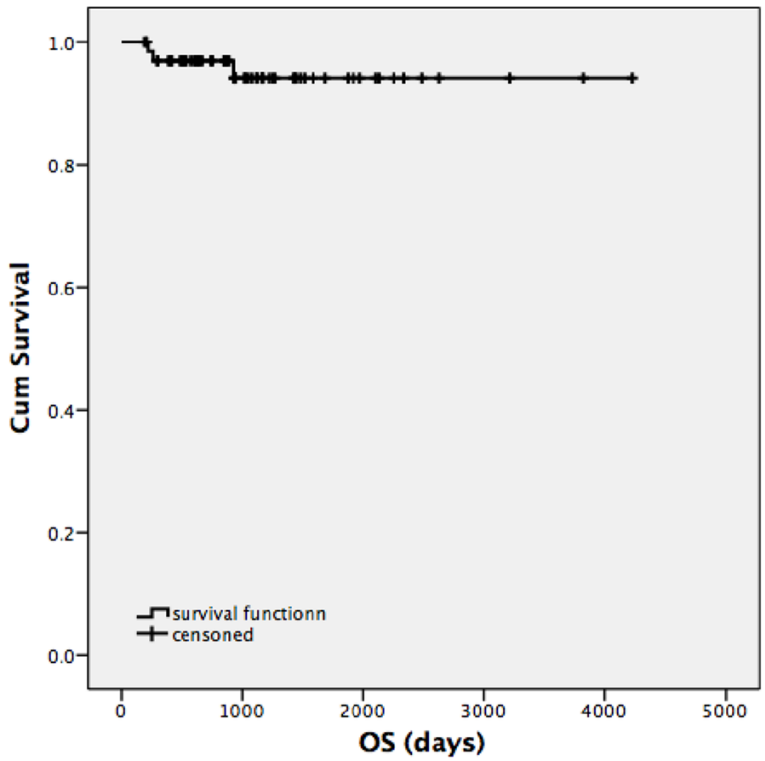

Figure 2. Overall survival (OS) of 68 cases. The median follow-up was 929 d, with an estimated OS of 4011 days.

[19]. However, Liszka et al. reported that the most common accompanying neoplasms were colorectal and gastric adenocarcinoma, as well as pancreatic adenocarcinoma [17]. The relationship between GISTs and other synchronous tumors requires further study. So endoscopic ultrasonography can increase the detection rate of asymptomatic small GISTs [9].

However, even GISTs with diameters less than 2 cm exhibit malignant behavior, with metastasis and recurrence [7, 20]. Therefore, accurate assessment of biological behavior of tumors is critical for evaluation of prognosis. Based on the current results, with a median follow-up of 929 days, the estimated overall survive (OS) was 4011 days which is significantly better than that reported for GISTs larger than 2 cm [21]. Miettinen et al. found 124 small GISTs in 1765 gastric GISTs cases, with no recurrences or deaths associated with GIST [22]. Rossi et al. examined 170 resected small GISTs, and found tumor progression in only 2 cases [5]. Overall, the prognosis for small GISTs is generally good. In our research, only 1 case with a high Ki67 index, the small GIST showed rapid growth, necrosis and metastasis. Ki67 is a nucleoprotein associated with cell proliferation, and is expressed in all cell proliferation cycles except G0. It reflects the status of cell proliferation accurately, and can be used as a marker of cell division and proliferation activity [23]. Selcukbiricik et al. [24] found that Ki-67 was a positive risk factor for GIST, and Ki67 positive patients had higher rates of recurrence and death. The current data showed that the number of mitoses, and the Ki67 index were significantly associated with NIH risk grade. Ki67 might reflect the biological behavior of GISTs. Ki-67 positive may be an indicator of high recurrence rate and poor prognosis.

GISTs are thought to originate from Cajal cells of gastrointestinal interstitium, which express CD117 and DOG1 in the gut [16]. Therefore, most GISTs show strong positive staining for CD117 and DOG1. DOG1 is a recently described protein found in GISTs irrespective of mutation status [16, 17]. In the current study, the CD117 and DOG1 expression rates were 100%, higher than that reported by Rossi et al., who examined 170 resected small GISTs, and found that CD117 was expressed in 90.6% tumors, while DOG1 was expressed in 96.2% cases [5]. Kawanowa et al. found 50 microscopic GISTs in 35 of the 100 whole stomachs, and all were positive for KIT and/or CD34 and negative for desmin [9]. There is growing evidence of phenotype-genotype (KIT, PDGFRA) and genotype-therapeutic (sensitivity to imatinib) correlations in GIST [18, 19, 25]. Rossi used *in silico* analysis to report that the correlation between molecular mutations and pathologic findings in small GISTs were relatively weak in terms of common KIT gene mutations. Non-classical site mutations might promote tumor cell regression [5]. We found that KIT exon 11 mutations were the most common, followed in frequency by PDGFRA exon 18 and KIT exon 9. This distribution is similar to what has

been described in the literature where exon 11 mutations were reported most frequently (50% to 77%) [26-28]. The pathogenicity of these mutations remains to be further defined. Small GISTs generally have a good prognosis, and therefore, the need for targeted therapy in patients with small GISTs is still under debate [29, 30].

In the current study, two of the 5 high-risk group GIST cases were found associated with colorectal tumors. In a 15 cases, incomplete resection, particularly in the area of the rectum, was also associated with a higher risk of recurrence of anorectal gastrointestinal stromal tumors [31]. Corless et al. also reported that GISTs in the rectum were also associated with a higher risk of recurrence [32]. It is possible that small GISTs in the lower gastrointestinal tract may be more aggressive than those in other areas of the GI tract. This suggests that careful surgical resection and follow-up may be advisable in these cases.

In general, all the data confirm that small GISTs have a benign biological behavior.

There were some limitations associated with the current study. The number of cases was small, and the follow-up time relatively short. Larger studies with longer follow-up times will be required to confirm the current observations. Accurate diagnosis and risk assessment of small GIST are still important issues. Although the indication for surgery is still not clear, improved indicators for the diagnosis and prognosis of small GIST is helpful. In addition to KIT and PDGFRA gene mutations, the role of other mechanisms underlying pathogenesis of GIST requires further study.

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Disclosure of conflict of interest

None.

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