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ABOUT COVER

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Retrospective Study

Clinical features of multiple gastrointestinal stromal tumors: A pooling analysis combined with evidence and gap map

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statement: This study was reviewed and approved by the Ethics Committee of the Peking University People's Hospital.

Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. The sample of informed consent had already uploaded.

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Abstract

BACKGROUND

Multiple gastrointestinal stromal tumors (MGISTs) are a very rare type of gastrointestinal stromal tumor (GIST) and are usually observed in syndrome.

AIM

The paper aimed to describe the clinical and oncological features of MGISTs and to offer evidence for the diagnosis and treatment.

METHODS

Data of consecutive patients with MGISTs who were diagnosed at Peking University People's Hospital (PKUPH) from 2008 to 2019 were retrospectively evaluated. Further, a literature search was conducted by retrieving data from PubMed, EMBASE, and the Cochrane library databases from inception up to November 30, 2019.

RESULTS

In all, 12 patients were diagnosed with MGISTs at PKUPH, and 43 published records were ultimately included following the literature review. Combined analysis of the whole individual patient data showed that female (59.30%), young (14.45%), and syndromic GIST (63.95%) patients comprised a large proportion of the total patient population. Tumors were mainly located in the small intestine

have no financial relationships to disclose.

Data sharing statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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(58.92%), and both CD117 and CD34 were generally positive. After a mean 78.32-mo follow-up, the estimated median overall survival duration (11.5 years) was similar to single GISTs, but recurrence-free survival was relatively poorer.

CONCLUSION

The clinical and oncological features are potentially different between MGISTs and single GIST. Further studies are needed to explore appropriate surgical approach and adjuvant therapy.

Key Words: Gastrointestinal stromal tumor; Multiple; Pooling analysis; Cross sectional study; Evidence and gap map

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Core Tip: The study retrospectively collected 12 patients of Peking University People's Hospital and 161 patients of literature research to illustrate the demographic, oncological, and surgical features of patients with multiple gastrointestinal stromal tumors (MGISTs). After analysis, MGISTs might have unique characteristics, such as lower morbidity, female predominance, young age, multiple organ involvement, and more likely to occur in syndrome. Although overall survival was similar to single gastrointestinal stromal tumor, the high rate of metastasis resulted in a poor recurrence free survival in MGISTs. Based upon evidence and gap map, gene detection and molecular biological analysis are necessary to explore the mechanism and provide appropriate therapy.

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INTRODUCTION

Gastrointestinal (GI) stromal tumor (GIST) is the most common mesenchymal tumor of the GI tract, with an estimated unadjusted yearly incidence of 1-1.5 per 100000 individuals^[1]. GISTs, with variable biological behavior ranging from benign to malignant types, usually occur in elderly individuals (age, 55-65 years; median age, 63 years) and are seldom observed in young individuals aged below 20 years (0.4%)^[2,3]. The tumors generally occur in the stomach (55%-60%) and small intestine (30%-35%) and rarely in the esophagus (< 1%) and colon/rectum (5%)^[1,2,4,5]. Particularly, GIST found elsewhere within the abdominal cavity, usually in the omentum, mesentery, or the retroperitoneum (accounting for < 5% of all GISTs), are referred to as extra-GI tract tumors (E-GISTs)^[2,6]; these are considered to have metastasized from the stomach and/or small intestine during their development^[2,7]. These tumors are derived from (or share a common stem cell with) intestinal Cajal cells^[8,9] and have histological features including spindle, epithelioid, and mixed. Several immunohistochemical (IHC) markers such as CD117 (95%), CD34 (70%), DOG-1 (96%), SMA (25%), desmin (< 5%), and S100 (rare) are observed in GISTs^[7,10]. Most GISTs show an oncogenic mutation in the KIT gene (80%-85%) or platelet-derived growth factor receptor alpha (PDGFRA, 5%-7%) gene^[11].

Multiple GISTs (MGISTs) are very rare and are commonly observed in cases of syndromic GISTs, such as type 1 neurofibromatosis (NF1)-associated GISTs^[12], familial GIST^[13], pediatric GIST^[14], Carney triad^[15], and Carney-Stratakis syndrome^[16]. Further, MGISTs are often misinterpreted as metastasis or recurrence using conventional diagnosis techniques^[12,13,17-20]. During the past decades, few studies have been conducted on MGISTs, and the guidelines from National Comprehensive Cancer Network^[21], European Society for Medical Oncology^[22], United Kingdom^[23], and France^[24] in addition to Asian^[25] and Chinese^[26] consensus fail to describe specific diagnosis, treatment, and follow-up strategies for MGISTs. Therefore, it is urgently

required to understand deeply these serious tumors and to determine whether single GIST diagnosis, treatment, and follow-up strategies are appropriate for diagnosing and treating MGISTs and whether they offer a worthwhile reference for precise and individualized medical measures in the future.

The present study was performed in accordance with Surgical Case Report (SCARE) Guidelines^[27] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement^[28], which provide the standard reporting guidelines for case reports and literature reviews, respectively.

MATERIALS AND METHODS

Definition

Multiple GISTs, also called multicentric or multifocal GISTs, do not have a formal definition at present. In our study, we defined MGISTs as no less than two GISTs located in the GI tract without any evidence of recurrence or metastasis despite one or more organs being involved^[17,29]. Especially, GISTs located in the extra-GI tract are usually considered to have metastasized, although a small portion of them are primary. Because patients with MGISTs comprise only a small proportion of patients with GISTs, we excluded multiple EGIST patients (or those with only one tumor located in the GI tract and the others in the extra-GI tract) to prevent the interference of metastatic EGIST.

Peking University People's Hospital patients

As shown in Figure 1, there were two inclusion criteria for patients at Peking University People's Hospital: (1) Diagnosis of GIST based on pathological results; and (2) Existence of multiple neoplasms (≥ 2 tumors). Patients were excluded if they: (1) Had only one tumor or none located in the GI tract and others were located in extra-GI tract sites, which are usually considered to have metastasized including mesentery, omentum, peritoneum, or abdomen; and (2) Substantial patient information such as baseline information or tumor features among others was missing.

Literature search

We searched the following electronic databases from inception up to November 30, 2019: PubMed, EMBASE, and the Cochrane library. All published studies were searched without any language restriction. Search items including *gastrointestinal stromal tumor*, *multiple*, *multicentric*, and *multifocal* were searched using Medical Subject Headings terms combined with free text terms. We also performed a supplemental literature search through *Google Scholar* and identified two studies by manual search.

Study selection

Endnote software (version X9.2, Thomson Reuters, Philadelphia, PA, United States) was used for removing duplicates and facilitating the screening process. After two reviewers independently screened the titles and abstracts, unsuitable studies were excluded; further, observational studies were excluded after reading the full text, and the eligible trials were finally identified. Disagreements between reviewers were resolved through discussions. In some cases, case reports may be used as a part of patients group in same author's or other author's studies, and we excluded these patients' data from the latter and reserved the case reports.

Data extraction

Two reviewers independently extracted the following data after literature search: Titles, years of publication, demographics and baseline characteristics, perioperative information, tumor features, pathological results, and follow-up duration. Meanwhile, methodological and reporting qualities were assessed by two reviewers as well.

Literature-based patients

As shown in Figure 2, we retrieved studies focusing on patients with MGISTs from PubMed, EMBASE, and the Cochrane library using keywords mentioned before. After screening titles and abstracts, studies such as case reports, case series, or retrospective studies with detailed patient information were included. Following this, full-text articles were assessed for eligibility: Studies with either metastatic GIST or incomplete patient information (such as lack of tumor location data) were excluded. Finally, combined with two articles shortlisted by manual search, the evaluation of studies for

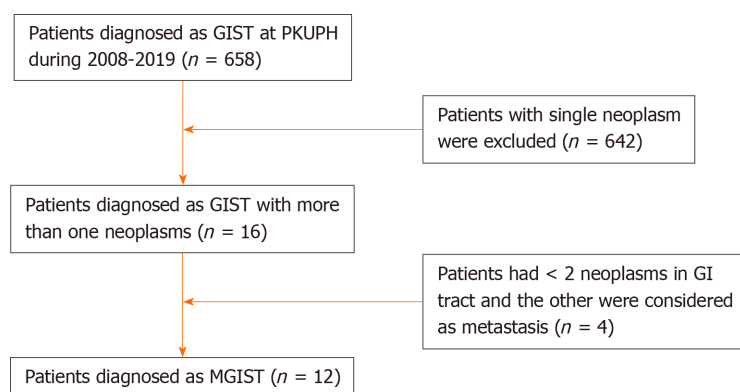


Figure 1 Flowchart of patient inclusion and exclusion criteria at Peking University People's Hospital. GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; MGIST: Multiple gastrointestinal stromal tumor; PKUPH: Peking University People's Hospital.

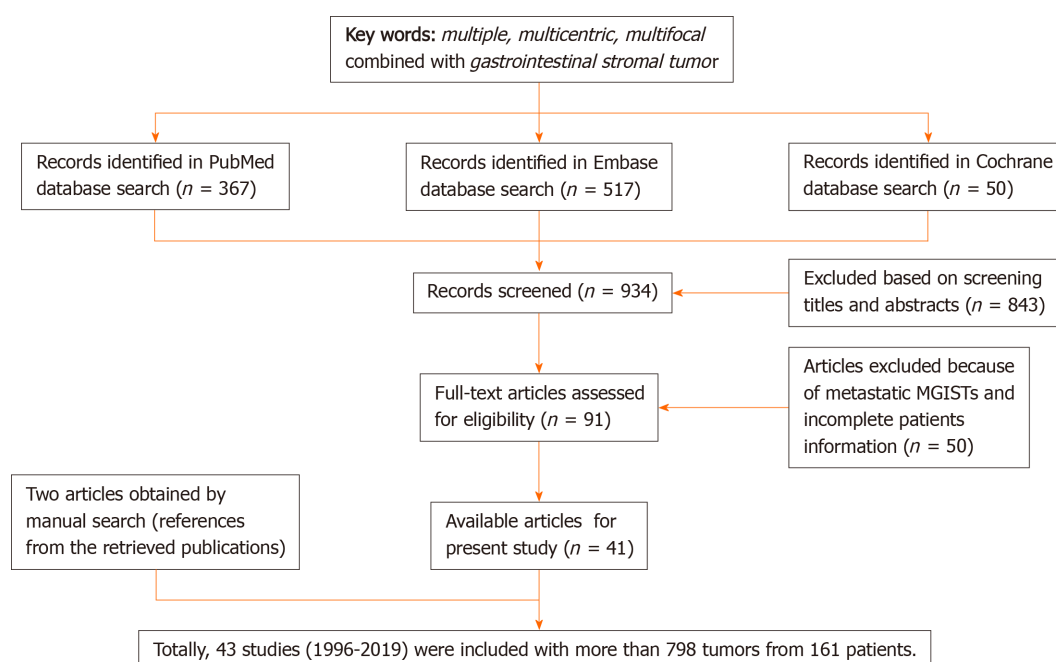


Figure 2 Flowchart of literature selection.

inclusion was completed.

During full-text article assessment, data of literature review-based patients were included if they were diagnosed with GIST based on pathological results and if they had ≥ 2 tumors. Accordingly, studies were excluded if patients had only one tumor in the GI tract and others were located in sites that are usually considered as metastasis sites and if explicit patient and tumor information was missing.

Assessment of reporting and methodological quality of including studies

The SCARE guideline is a consensus-based surgical case report guideline^[27]. Another tool, Joanna Briggs Institute (JBI) model, was used to enable the assessment of evidence-based healthcare and its role in improving global health^[30]. We assessed the methodological and reporting quality of the included studies on the basis of the SCARE guideline and JBI model for quality evaluation. We recorded the issues, and each of the criteria was assigned different scores including "1 = Yes," "0 = No," and "0.5 = Unclear" to estimate the quality of the included studies. Particularly, some items were not applicable to certain articles; these were marked as "NA". Subsequently, we classified the JBI model (case report/case series) and SCARE guideline points as follows: JBI-I (high, 6-8/8-10), JBI-II (intermediate, 3-5/5-7), JBI-III (low, 0-2/0-4); SCARE-A (very high, 28-30), SCARE-B (high, 21-27), SCARE-C (intermediate, 14-20), SCARE-D (low, 7-13), and SCARE-E (very low, 0-6). A detailed rating scale for the JBI model and SCARE guidelines is available in [Supplementary Tables 1 and 2](#). Each

study was subjected to quality assessment by two reviewers, and discrepancies were resolved by a discussion.

Evidence and gap map

Evidence and gap map (EGM) is a method of systematically identifying, reporting, and visualizing a body of evidence on a specific topic, which may show high-quality studies and the emphasis of studies. The scope of the EGM in our study was to cover the different types of MGISTs and their clinical and pathological information. The EGM adopted in our study was classified into five categories: Baseline characteristics, tumor features, pathological characteristics, perioperative information, and follow-up results. Further, the population was classified into six categories: Sporadic MGISTs, NF1-associated MGISTs, familial MGISTs, pediatric MGISTs, Carney triad syndrome, and Carney-Stratakis syndrome. A bubble diagram was used to visualize the EGM *via* Excel (Microsoft, 2016, Redmond, WA, United States). The size of a bubble represented the sample, and the color indicated whether the clinical characteristic was fully or partly reported in each study.

Statistical analysis

The statistical methods of this study were reviewed by Tian JH from Evidence-Based Medicine Center of Lanzhou University. Continuous variables are expressed as means, and categorical variables are expressed as numbers (%). Kaplan-Meier survival function and statistical analyses were performed using the SPSS software (version 25.0, SPSS Inc., Armonk, NY, United States), unless indicated otherwise.

RESULTS

Peking University People's Hospital patients

During the period between January 2008 and November 2019, 12 identified individual patients (males, six; females, six) aged 53 to 88 years (mean age, 65.33 years) were admitted to the Peking University People's Hospital. All detailed information is available in [Supplementary Table 3](#). Based on the patient age groups, we could determine that patients aged between 61 and 80 years comprised the major proportion of patients (9/12). With regard to the common symptoms, incidental finding without any subjective discomfort occurred in seven patients, and GI bleeding and abdominal pain were the most common symptoms (both 2/12). Sporadic MGISTs (10/12) were predominant and the others were NF1-associated type; no patient had familial history of GIST. Only one in 12 patients had a secondary malignant tumor (breast cancer). All patients at the Peking University People's Hospital underwent computed tomography (CT), and half of them underwent an endoscopy; only two patients underwent magnetic resonance imaging. During the surgery, laparoscopy was performed in seven patients, and nine patients received *en bloc* (R0) resection. Among the 40 tumors of 12 patients, 22 tumors were located in the stomach and 17 in the small intestine. Three quarters of patients showed the involvement of only a single organ. With regard to the pathological results, minimal and maximum sizes were 0.10 cm and 8.00 cm, respectively. All tumors showed spindle morphology, and > 90% had a low mitosis rate (≤ 5), with a mean tumor size of 3.86 cm. Interestingly, more than half of the tumors were micro-GIST (sized < 1 cm). Because of the small size of tumors, the risks were predominantly low or very low (more than 85%). On immunohistochemical analysis, CD117 was extensively positive in 12 patients, and only one-third of the tumors were positive for CD34. Desmin, smooth muscle actin (SMA), and S-100 were almost negative, and Ki-67 level ranged from 0% to 20% with a mean value of 3.83%. After a mean 33.75-mo follow-up in the form of telephonic conversations and outpatient visits, imatinib was administered as an adjuvant therapy in seven patients, and all patients were alive without any evidence of metastasis or recurrence.

Literature-based patients

After literature retrieval, 43 published records were included in the study ([Supplementary Table 4](#)). Of these, 21 showed high-quality (level I) methodology, and the other 22 were of the intermediate level based on the JBI model. Meanwhile, level C (23/43) and level D (15/43) comprised the main proportion of the identified records with regard to reporting quality (according to SCARE guidelines). Finally, 161 patients with more than 798 tumors were recorded in total. Accordingly, SCARE guidelines ([Supplementary Table 5](#)) and PRISMA statement ([Supplementary Table 6](#)) were

adopted in the present study for improving the reporting quality.

On observing the bubble diagram (Figure 3), we could see that the baseline characteristics and tumor features showed high-level evidence, and perioperative information showed a lower level. In contrast, sporadic and NF1-associated MGISTs were reported more frequently than other types. In correspondence, partially reported articles were more frequently observed. Compared with the abovementioned types, familial type MGISTs showed a lack of evidence with regard to pathological characteristics and perioperative information. Further, pediatric and Carney triad syndromic MGISTs showed a weak evidence level, and evidence gaps were observed with regard to perioperative information in Carney triad syndromic and Carney-Stratakis syndromic MGISTs.

As shown in Supplementary Tables 7 and 8, there was a female predominance in literature-based patients (96/160, one patient's gender is unknown), with a mean age of female patients being 48.70 years. The highest number of patients were admitted to the hospital after GI bleeding as the first symptom, followed by abdominal pain and incidental findings. Apart from sporadic GISTs, NF1-associated MGISTs were the most common in the 161 patients. Unlike patients from Peking University People's Hospital, literature-based patients underwent endoscopy more frequently than CT and predominantly underwent laparotomy. Referring to tumor features, 201 tumors were located in the small intestine and 121 in the stomach. Of these, most tumors were spindle type and had a low mitosis rate ($< 5/50$ high-power fields). Accordingly, low and very low risk tumors comprised the highest proportion among all tumors. Both CD117 and CD34 were extensively positive in tumors; further, the mean value of Ki-67 was similar between literature review patients and Peking University People's Hospital patients, and desmin, SMA, and S-100 were almost negative, although 29.63% tumors were S-100 positive. After a mean 83.01-mo follow-up, 62.60% patients were alive without any evidence of recurrence, and seven patients died of MGISTs. The frequency of recurrence was 2.75% and in all, 16 patients showed evidence of metastasis. Peritoneum, liver, and lymph nodes were the common sites of metastasis.

Individual patient data

Among the 173 patients shown in Table 1, 102 (59.30%) were females and 70 (40.70%) were males, with a mean age of 49.85 years. Patients between 41 to 60 years ($n = 53$; 30.81%) and 61 to 80 years ($n = 60$; 34.88%) comprised the majority among patients with MGISTs.

The dominant symptom was GI bleeding (33/67), followed by incidental finding and abdominal pain. NF1-associated (42.77%) and sporadic type (36.42%) MGISTs were the predominant types among patients; pediatric-type MGISTs comprised 16.18% of all cases, followed by familial MGISTs (4.62%). With regard to secondary malignant tumors, the breast (4.62%), genitourinary tract (2.89%), and gastrointestinal tract (1.73%) were the three common sites.

Among 218 tumors located in the small intestine (58.92%), the jejunum (19.46%) was the most common site compared with the ileum (7.57%) and duodenum (7.57%). The stomach was the second most common site, comprising 38.65% of all tumors. In addition to the tumors in the stomach and small intestine, tumors at rare sites such as the colon (case 5, 6, 9, 14 and 124) and rectum (case 5, 145) were also observed (2.43%). Approximately 69.64% patients had only a single organ involved. Tumors sized ≤ 1 cm and 2-5 cm were the most common, accounting for 32.68% and 30.70% of all tumors, respectively; the mean tumor size was 3.12 cm.

As shown in Table 2, most tumors had a spindle morphology (80.46%), low mitosis rate ($< 5/50$ high power fields, 87.34%), and low or very low risk classification (69.36%). Among the resected specimens, 179 (97.28%) and 126 (72.00%) were positive for CD117 and CD34, respectively. Further, Ki-67 value ranged from 0% to 33.8% with a mean value of 3.91%; simultaneously, positivity for desmin, S-100, and SMA was rare, accounting for 1.50%, 23.08%, and 15.48% of all specimens.

On considering the Peking University People's Hospital and literature review-based patient data (Table 3), CT (31/41) was the most commonly used detection method for patients with MGISTs, followed by endoscopy (27/41). A traditional open surgery was conducted in 23 (23/37) patients, and 31 (31/42) patients underwent a radical operation. After surgery, imatinib was administered to 32 (32/49) patients as adjuvant therapy.

After a mean 78.32-mo follow-up, 65.93% (89/135) patients were alive without any evidence of recurrence or metastasis. Unfortunately, 5.19% patients died of MGISTs. Of 121 patients with clear follow-up results, 2.48% patients had a relapse, and 13.22% patients were metastatic. Common sites of metastasis were the peritoneum (7.44%), liver (6.61%), and lymph nodes (4.13%). As shown in Figure 4 and Figure 5, all patients

Table 1 Baseline characteristics of patients with multiple gastrointestinal stromal tumors, *n* (%)

	PKUPH patients, <i>n</i> = 12 ¹	Literature-based patients, <i>n</i> = 161 ¹	Total patients, <i>n</i> = 173 ¹
Sex	<i>n</i> = 12	<i>n</i> = 160	<i>n</i> = 172
Female	6 (50.00)	96 (60.00)	102 (59.30)
F/M	1.00	1.48	1.46
Age in yr	<i>n</i> = 12	<i>n</i> = 161	<i>n</i> = 173
Range	53-88	8-84	8-88
≤ 20	0 (0.00)	25 (15.63)	25 (14.45)
21-40	0 (0.00)	29 (18.12)	29 (16.86)
41-60	2 (16.67)	51 (31.88)	53 (30.81)
61-80	9 (75.00)	51 (31.88)	60 (34.88)
> 80	1 (8.33)	5 (3.13)	6 (3.49)
Mean (SD)	65.33 (9.48)	48.70 (21.17)	49.85 (20.99)
Symptoms	<i>n</i> = 12	<i>n</i> = 55	<i>n</i> = 67
GI bleeding	2 (16.67)	31 (56.36)	33 (49.25)
Hematochezia	1 (8.33)	13 (24.07)	14 (21.21)
Anemia	0 (0.00)	11 (20.37)	11 (16.67)
Hematemesis	1 (8.33)	2 (3.70)	3 (4.55)
Incidental finding	7 (58.33)	15 (27.27)	22 (32.83)
Abdominal pain	2 (16.67)	14 (25.45)	16 (23.88)
Palpable mass	0 (0.00)	2 (3.64)	2 (2.99)
Others	1 (8.33)	11 (20.00)	12 (17.91)
Classification	<i>n</i> = 12	<i>n</i> = 161	<i>n</i> = 173
Sporadic multiple GIST	10 (83.33)	53 (32.92)	63 (36.42)
NF-1 associated GIST	2 (16.67)	72 (44.72)	74 (42.77)
Primary familial GIST	0 (0.00)	8 (4.97)	8 (4.62)
Pediatric GIST	0 (0.00)	25 (15.53)	25 (14.45)
Carney-Stratakis syndrome	0 (0.00)	0 (0.00)	0 (0.00)
Carney triads	0 (0.00)	3 (1.86)	3 (1.73)
Combined diseases	<i>n</i> = 12	<i>n</i> = 161	<i>n</i> = 173
GI tumors	0 (0.00)	3 (1.86)	3 (1.73)
GU tumors	0 (0.00)	5 (3.11)	5 (2.89)
Breast tumors	1 (8.33)	7 (4.35)	8 (4.62)
Other tumors	0 (0.00)	5 (3.11)	5 (2.89)

¹*n* For total number of patients, other *n* for number of patients with relevant data. GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; GU: Genitourinary tract; PKUPH: Peking University People's Hospital; SD: Standard deviation.

at the Peking University People's Hospital showed an estimated median overall survival (OS) duration of 11.5 years (138 mo, 95% confidence interval: 8.7-14.3) and estimated 5-year, 10-year, and 15-year recurrence-free (RF) survival rates of 89.4%, 76.3%, and 50.8%, respectively.

Table 2 Tumor and pathological features of patients with multiple gastrointestinal stromal tumors, *n* (%)

	PKUPH patients, <i>n</i> = 12 [†]	Literature-based patients, <i>n</i> = 161 [†]	Total patients, <i>n</i> = 173 [†]
Site	<i>n</i> = 40	<i>n</i> = 330	<i>n</i> = 370
Stomach	22 (55.00)	121 (36.67)	143 (38.65)
Small intestine	17 (42.50)	201 (60.91)	218 (58.92)
Duodenum	1 (2.50)	27 (8.18)	28 (7.57)
Jejunum	4 (10.00)	68 (20.61)	72 (19.46)
Ileum	3 (7.50)	25 (7.58)	28 (7.57)
Other sites	1 (2.50)	8 (2.42)	9 (2.43)
Involving organ	<i>n</i> = 12	<i>n</i> = 156	<i>n</i> = 168
Single	9 (75.00)	108 (69.23)	117 (69.64)
Two or more	3 (25.00)	48 (30.77)	51 (30.36)
Size in cm	<i>n</i> = 40	<i>n</i> = 315	<i>n</i> = 355
Range	0.10-8.00	0.05-27.00	0.05-27.00
≤ 1	22 (55.00)	94 (29.84)	116 (32.68)
1-2	4 (10.00)	65 (20.64)	69 (19.44)
2-5	11 (27.75)	98 (31.11)	109 (30.70)
5-10	3 (7.50)	45 (14.29)	48 (13.52)
> 10	0 (0.00)	13 (4.13)	13 (3.56)
Mean (SD)	2.00 (2.16)	3.26 (3.50)	3.12 (3.40)
Cellular type	<i>n</i> = 40	<i>n</i> = 180	<i>n</i> = 220
Spindle	40 (100.00)	137 (76.11)	177 (80.46)
Epithelial	0 (0.00)	23 (12.78)	23 (10.46)
Mixed	0 (0.00)	20 (11.11)	20 (9.09)
Mitosis, /50 HPFs	<i>n</i> = 35	<i>n</i> = 202	<i>n</i> = 237
Range	0-9	0-48	0-48
≤ 5	33 (94.29)	174 (86.14)	207 (87.34)
5-10	2 (5.71)	15 (7.43)	17 (7.17)
> 10	0 (0.00)	13 (6.44)	13 (5.49)
Mean (SD)	3.86 (1.87)	3.32 (5.91)	3.40 (5.50)
Risk classification	<i>n</i> = 35	<i>n</i> = 249	<i>n</i> = 284
Very low risk	20 (57.14)	54 (21.69)	74 (26.05)
Low risk	10 (28.57)	113 (45.38)	123 (43.31)
Median risk	3 (8.57)	26 (10.44)	29 (10.21)
High risk	2 (5.71)	56 (22.49)	58 (20.42)
CD117	<i>n</i> = 35	<i>n</i> = 149	<i>n</i> = 184
Positive	35 (100.00)	144 (96.64)	179 (97.28)
CD34	<i>n</i> = 35	<i>n</i> = 140	<i>n</i> = 175
Positive	12 (34.29)	114 (81.43)	126 (72.00)
Ki-67	<i>n</i> = 35	<i>n</i> = 47	<i>n</i> = 82
Range	0-20	1-33.8	0-33.8
Mean (SD)	3.83 (4.85)	3.96 (5.11)	3.91 (4.97)

Desmin	<i>n</i> = 35	<i>n</i> = 98	<i>n</i> = 133
Positive	1 (2.86)	1 (1.02)	2 (1.50)
S-100	<i>n</i> = 35	<i>n</i> = 108	<i>n</i> = 143
Positive	1 (2.86)	32 (29.63)	33 (23.08)
SMA	<i>n</i> = 35	<i>n</i> = 120	<i>n</i> = 155
Positive	5 (14.29)	19 (15.83)	24 (15.48)

¹*n* For total number of patients, other *n* for number of patients with relevant data. HPFs: High-power fields; PKUPH: Peking University People's Hospital; SD: Standard deviation.

DISCUSSION

The majority of GISTs occur as sporadic solitary neoplasms resulting from somatic mutations in KIT or PDGFRA genes^[8]. MGISTs are rare and were often misinterpreted previously as a recurrent or metastatic disease^[20], leading to inappropriate treatment. Until now, there are no established criteria for confirming the diagnosis and treatment of MGISTs. Given the lack of clinical trials, single GIST therapy has conflicts in MGIST patients with regard to factors such as surgical excision and perioperative adjuvant therapy. KIT or PDGFRA mutation analysis and pattern of muscularis involvement can contribute to differential diagnosis^[13,17,20]. As molecular analysis is generally not available in routine practices, basic clinical characteristics, distinctive syndromic manifestation, and pathological features of MGISTs are required to be known in routine examination.

In this study, unlike the similar prevalence of men and women in GISTs^[31], female prevalence (F/M = 1.46) was higher in MGISTs, which may because of female predominance in syndromic GIST. GIST can develop at any age, but no less than 80% of these were reported in middle-aged and elderly patients (mean age, 64-69 years)^[5,32,33]. Compared with single GIST, MGISTs were usually observed in younger individuals (mean, 49.85 years) and showed a variant age predominance in different types. Sporadic MGISTs comprise the highest proportion of cases among all types and have similar demographics with single GIST^[5,12,19,29,34,35]. According to published studies, NF1-associated GIST patients were younger (49 years) than single GIST patients without obvious sex predominance^[12]. Similarly, familial GISTs equally appear in men and in women and are observed in younger patients, with a mean age of 46 years^[13]. Moreover, pediatric, Carney triad, and Carney-Stratakis syndromic GIST often occur in young patients (approximately 80% being women) who are < 20-years-old^[36-38]. Because of the lack of department of pediatric surgery and Grade 3A classification of the Peking University People's Hospital, fewer young female patients and more elderly patients may have been included in the study.

On MGISTs classification, NF1-associated GIST and sporadic GIST were found to be the main types. Although multiplicity is very rare (1.1%-1.6%) in sporadic GIST^[20,29], it was the second frequent type due to the large cardinal number. In contrast, multiple growth patterns are a characteristic feature of NF1-associated GIST and familial GISTs^[13] (up to 70% NF1-associated GIST patients have multiple lesions^[36,39,40]). Pediatric, Carney triad, and Carney-Stratakis syndromic GISTs showed multiplicity in approximately 23%-81%, 40%, and 80% cases, respectively, and GIST may be the first sign in the latter two syndromes^[41-43]. In particular, Armed Forces Institute of Pathology (Washington, DC, United States) revealed that GIST in young patients who lack other features of the Carney triad syndrome are clinically, phenotypically, and molecularly similar to those in patients with Carney triad syndromic GIST and might represent an attenuated manifestation of the triad^[19]. We could infer that pediatric MGIST patients may be heterogeneous and may include Carney triad syndrome, Carney-Stratakis syndrome, or an attenuated manifestation of them. Hereinafter, we use "pediatric-type MGISTs" to represent pediatric, Carney triad syndromic, and Carney-Stratakis syndromic MGISTs. Interestingly, some previous studies^[38,44] indicated that some adult GIST patients also have clinical and pathological characteristics similar to those of pediatric GIST patients, and these special groups are also included under pediatric-type GISTs. However, these may have been classified under sporadic GISTs in our study because of the ambiguous diagnosis criteria, and this may have led to an increase in the number of sporadic MGIST cases.

With regard to clinical symptoms, some infrequent and specific symptoms require to be paid more attention. Patients with NF1 often present with specific subcutaneous

Table 3 Perioperative information and follow-up results of patients with multiple gastrointestinal stromal tumors, *n* (%)

	PKUPH patients, <i>n</i> = 12 ¹	Literature-based patients, <i>n</i> = 161 ¹	Total patients, <i>n</i> = 173 ¹
Preoperative I.E.	<i>n</i> = 12	<i>n</i> = 29	<i>n</i> = 41
CT	12 (100.00)	19 (65.52)	31 (75.61)
MRI	2 (16.67)	2 (6.90)	4 (9.76)
Endoscopy	6 (50.00)	21 (72.41)	27 (65.85)
Approach	<i>n</i> = 12	<i>n</i> = 25	<i>n</i> = 37
Laparotomy	5 (41.67)	18 (72.00)	23 (62.16)
Laparoscopy	7 (58.33)	7 (28.00)	14 (37.84)
Excision Extension	<i>n</i> = 12	<i>n</i> = 30	<i>n</i> = 42
Radical resection	9 (75.00)	22 (73.33)	31 (73.81)
Palliative resection	3 (25.00)	8 (26.67)	11 (26.19)
Imatinib	<i>n</i> = 12	<i>n</i> = 37	<i>n</i> = 49
Apply	7 (58.33)	25 (67.57)	32 (65.31)
Not apply	5 (41.67)	12 (32.43)	17 (34.70)
Follow-up time in mo	<i>n</i> = 12	<i>n</i> = 114	<i>n</i> = 126
Range	3-86	3-396	3-396
Mean (SD)	33.75 (27.28)	83.01 (82.26)	78.32 (79.96)
Outcome	<i>n</i> = 12	<i>n</i> = 123	<i>n</i> = 135
ANED	12 (100.00)	77 (62.60)	89 (65.93)
AWD	0 (0.00)	21 (17.07)	21 (15.56)
ATSU	0 (0.00)	2 (1.63)	2 (1.48)
DOD	0 (0.00)	7 (5.69)	7 (5.19)
DUC	0 (0.00)	9 (7.32)	9 (6.67)
DOPC	0 (0.00)	2 (1.63)	2 (1.48)
DUNC	0 (0.00)	5 (4.07)	5 (3.70)
Recurrence	0/12 (0.00)	3/123 (2.44)	3/135 (2.22)
Metastasis	<i>n</i> = 12	<i>n</i> = 123	<i>n</i> = 135
Lymph node	0 (0.00)	5 (4.07)	5 (3.70)
Liver	0 (0.00)	8 (6.50)	8 (5.93)
Peritoneum	0 (0.00)	9 (7.32)	9 (6.67)
Lung	0 (0.00)	1 (0.76)	1 (0.74)
Abdomen	0 (0.00)	1 (0.76)	1 (0.74)
Omentum	0 (0.00)	1 (0.76)	1 (0.74)

¹*n* For total number of patients, other *n* for number of patients with relevant data. CT: Computed tomography; I.E.: Imaging examinations; MRI: Magnetic resonance imaging; PKUPH: Peking University People's Hospital; SD: Standard deviation.

nodules and Cafe-au-Lait Spots; Carney triad patients manifest pulmonary chondroma and paraganglioma; and Carney-Stratakis syndrome patients present with only paraganglioma. Further, familial GIST patients normally suffer from skin pigmentation and dysphagia^[45]. Although most patients had symptoms or syndromes, approximately 30% patients were diagnosed incidentally during imaging or surgery for other disorders, and quite a few were diagnosed during autopsy. It is worth noting that specific symptoms and family history are vital information for our surgeons to make a correct clinical diagnosis.

CT is currently the preferred imaging examination^[46-49] because it can clearly show

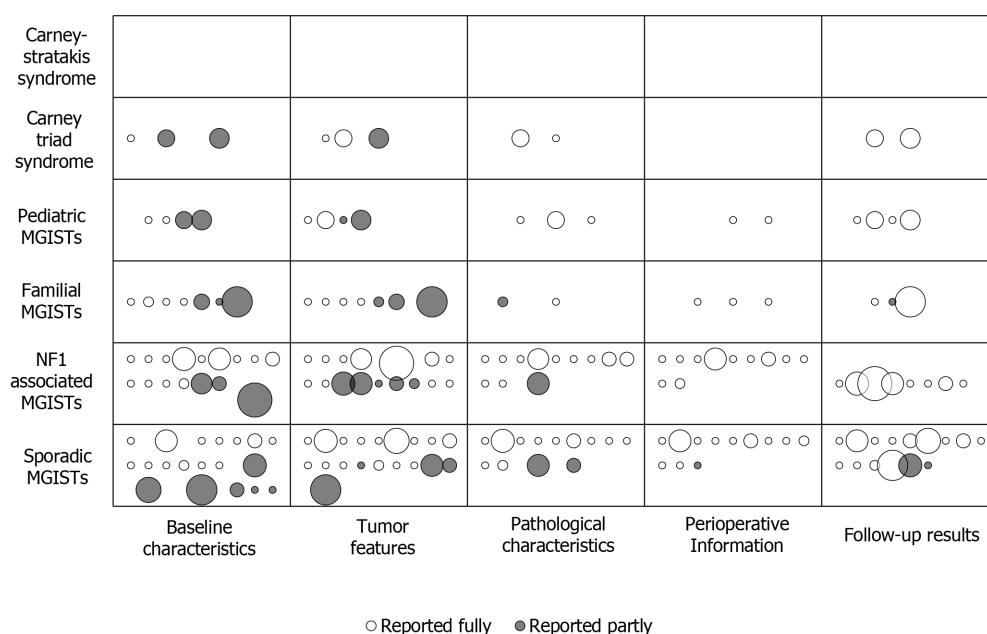


Figure 3 Evidence and gap map of multiple gastrointestinal stromal tumors (Bubble diagram). MGISTs: Multiple gastrointestinal stromal tumors; NF1: Type 1 neurofibromatosis.

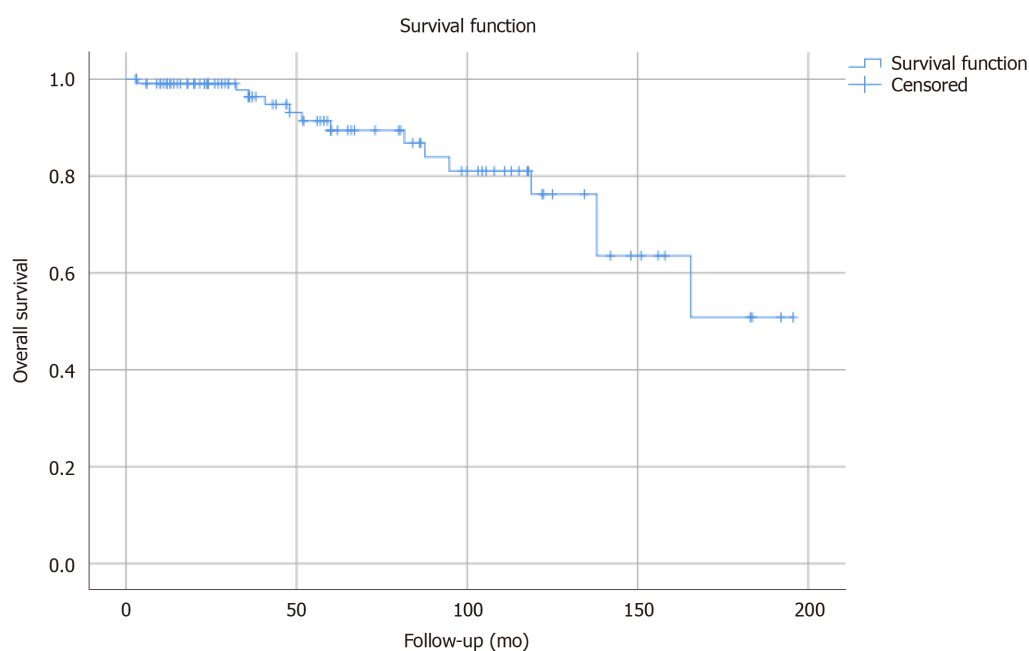


Figure 4 Overall survival of patients with multiple gastrointestinal stromal tumors.

GISTs in the small intestine. Small-sized GISTs in the small intestine usually show higher enhancement than those in the stomach^[50]. More remarkable, micro-GISTs that comprise the main parts of MGISTs are, however, difficult to detect by CT. Therefore, to avoid a misdiagnosis, preoperative endoscopy is necessary. However, we should factor in that small GISTs may have a large extra-extension that is not visible during endoscopy. Thus, CT and endoscopy are complementary to each other.

A previous systemic review showed that 49% of single GIST were measured to be 5-10 cm in size^[1,2]. In this study, groups of ≤ 1 cm (called as micro-GISTs) and 2-5 cm tumors were the main components of MGISTs, which may be because of satellite tumors. Roughly 30% of middle-aged and elderly general population may be detected with micro-GISTs, which have a high frequency of KIT mutation and almost no malignant potential, although they are considered to be a precursor lesion or the origin

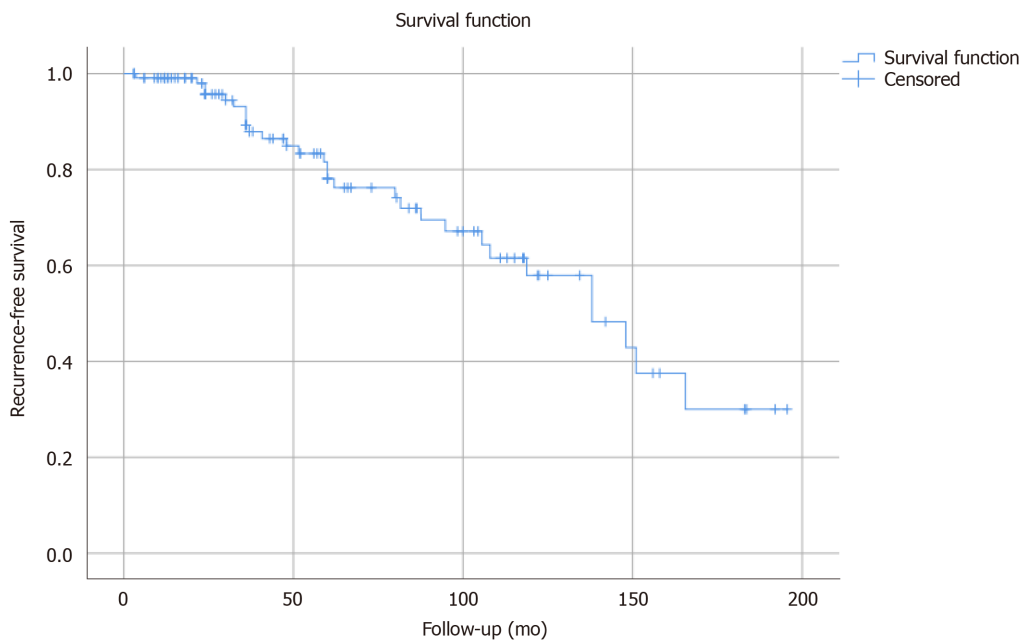


Figure 5 Recurrence-free survival of patients with multiple gastrointestinal stromal tumors.

of GIST^[31,34,51]. According to previous studies, sporadic, NF1-associated, and pediatric-type GISTs are mainly located in the stomach^[12,36,52,53]. Interestingly, we found that MGISTs in our study usually affected the small intestine, followed by stomach and other sites. On considering both Peking University People's Hospital and literature review, approximately 30% tumors were shown to affect two or more organs.

En bloc (R0) resection and minimally invasive surgery are the first choice of treatment. For some local MGISTs (≥ 2 cm), a segmental or wedge resection instead of an extended anatomic resection is appropriate to obtain negative margins. Especially, unlike single GISTs, MGISTs may affect one or more long segments of the GI tract; therefore, segmental resection is performed more frequently. A multidisciplinary team (MDT, including experienced oncologists, gastroenterologists, and radiologists among others) are needed in all MGIST patients, especially in patients with multiple organ involvement, to assess surgical excision and perioperative adjuvant therapy. All 12 patients from the Peking University People's Hospital were assessed by MDT and underwent the most current appropriate individual-based treatment. Lymphadenectomy might not be required in most MGIST patients. A laparoscopic approach by experienced surgeons could be considered for select MGISTs located at favorable anatomic locations because of the fragile texture of tumors. Either laparotomy or laparoscopy must follow the basic oncological principles of GIST resection, and generally, multi-visceral resection and re-resection are not indicated. Imatinib was used as an auxiliary therapy in KIT/PDGFR mutation MGISTs^[29]. Gene detection is vital in precision therapy, as cases without KIT or PDGFR mutation, such as syndromic MGISTs cases, may not respond to Imatinib^[38,54,55], although some patients^[56] have reported contrasting outcomes.

The most important independent prognostic factor for GIST recurrence after surgery is a high tumor mitotic rate^[2,35,57,58]. Of note, IHC staining for Ki-67 antigen has been suggested as an alternative to mitosis rate counting, which is affected by subjective factors to some extent^[59,60]. As approximately 70% of overall tumors in this study were low or very low risk tumors compared with 30%-45%^[5,57,58] reported in previous studies, small satellite tumors may interfere with the results. Interestingly, pediatric-type GISTs are slightly unpredictable and have an indolent clinical progression; further, they may be more prone to be metastatic irrespective of the prognostic criteria used in adults, such as tumor site, size, and mitotic rate^[7,37,61,62].

With regard to IHC results, a number of previous studies have documented only one tumor's results, even though multiple lesions were observed; and this phenomenon was also observed in patients of the Peking University People's Hospital. Accordingly, it was difficult to determine the accurate IHC manifestation of each tumor and summarize the different marker expressions of the main large tumor and small satellite tumors in each MGIST patient. Therefore, we recommend that, if possible, appropriately detailed pathological examination should be conducted for

each tumor.

In an analysis including 10 population-based series and 2459 patients^[2], the estimated median OS duration was 12.4 years (95% confidence interval: 10.8-14.0), and the estimated 5-year, 10-year, and 15-year RF survival rates of patients with GISTs treated *via* surgery alone were 70.5%, 62.9%, and 59.9%, respectively. Only a few tumors relapsed after the first 10 years of follow-up, suggesting that most patients (approximately 60%) with operable GIST were probably cured by surgery^[31]. Tumor size, site, and rupture before or during surgery were independent prognostic factors recurrence^[2,57,58,63-66]. Despite the high tendency for metastasis and recurrence in syndromic MGISTs (particularly in pediatric-type MGISTs after up to 3-5 years, predominantly *via* a hematogenous pathway)^[38,67], the 5-year and 10-year clinical course is usually indolent with a favorable prognosis similar to that of (or even better than that of) single GISTs but 15-year RF survival rate is poorer.

As per the evidence gap map (Figure 3), most of the current studies mainly focus on the demographic and oncological characteristics, but few pay attention to perioperative and operative information. In other words, patients benefit from treatment strategies such as neoadjuvant chemotherapy, selection of operative extensions, or genetic detection. Furthermore, it is necessary to form a standard medical diagnosis and surgical procedures of the MGISTs

There were some limitations to the current study. First, inclusion bias existed among Peking University People's Hospital patients because of the hospital category and the lack of pediatric surgery at the hospital; this may have led to the recruitment of few young female patients and more elderly patients. Further, all 12 patients were unwilling to undergo gene detection because of the high cost and limited medical insurance coverage. Second, in the present study, we only included articles published in English; this may cause a language bias. Moreover, only case reports and series, as the current best evidence, were included, and SCARE and JBI data were not completely available for all included studies.

CONCLUSION

In conclusion, MGISTs may have unique characteristics such as lower morbidity, female predominance, young age, multiple organ involvement, and possible syndromic GIST. Although OS was similar between single GISTs and MGISTs, a high rate of metastasis in MGIST patients resulted in a poor long-time RF survival rate. Based on the current EGM, focusing on gene detection and molecular biological analysis can contribute to the determination of the mechanism underlying this special type of GIST in future studies. Furthermore, an appropriate surgical approach and auxiliary therapy are urgently need to be determined by prospective, multicenter, and large-scale studies.

ARTICLE HIGHLIGHTS

Research background

Multiple gastrointestinal stromal tumors (MGISTs) is a very rare type of gastrointestinal stromal tumor (GIST) and is usually misdiagnosed as metastatic tumors.

Research motivation

As physicians become more aware of MGISTs, researchers believed that it was imperative to describe MGISTs to help surgeons make appropriate diagnosis and treatment.

Research objectives

The study aimed to describe the clinical and oncological features of MGISTs and to offer evidence for MGISTs diagnosis and treatment.

Research methods

Data of consecutive patients with MGISTs who were diagnosed at Peking University People's Hospital (PKUPH) from 2008 to 2019 were retrospectively evaluated. Further, a literature search was conducted by retrieving data from PubMed, EMBASE, and the

Cochrane library databases from inception up to November 30, 2019.

Research results

In all, 12 patients were diagnosed with MGISTs at PKUPH, and 43 published records were ultimately included following literature review. Combined analysis of all the individual patient data showed that female (59.30%), young (14.45%), and syndromic GIST (63.95%) patients comprised a large proportion of the total patient population. Tumors were mainly located in the small intestine (58.92%), and both CD117 and CD34 were generally positive. After a mean 78.32-mo follow-up, the estimated median overall survival duration (11.5 years) was similar to single GISTs, but recurrence-free survival was relatively poorer.

Research conclusions

The clinical and oncological features are potentially different between MGISTs and single GIST, such as lower morbidity, female predominance, young age, multiple organ involvement, and possible syndromic GIST. Although overall survival was similar between single GISTs and MGISTs, a high rate of metastasis in MGIST patients resulted in a poorer long-time RF survival rate.

Research perspectives

In further studies, focusing on gene detection and molecular biological analysis can contribute to the understanding of the mechanism underlying this special type of GIST in future studies. Moreover, an appropriate surgical approach and auxiliary therapy are urgently need to be determined by prospective, multicenter, and large-scale studies.

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