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# Clinicopathological features and prognosis of 276 cases of primary small (≤ 2 cm) gastric gastrointestinal stromal tumors: a multicenter data review

**Zifeng Yang[1] · Xingyu Feng[1] · Peng Zhang[2] · Tao Chen[3] · Haibo Qiu[4] · Zhiwei Zhou[4] · Guoxin Li[3] · Kai Xiong Tao[2] · Yong Li[1] · China Gastrointestinal Stromal Tumor Study Group (CN-GIST)**

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## Abstract

**Background** Till present, there are still controversies over the epidemiology, pathological features, types of surgical treatment, and prognoses of primary small gastric GISTs (gGISTs).

**Methods** From January 1998 to January 2015, patients with primary small gGIST admitted from four high-volume medical centers of the Southern China were enrolled and their data were analyzed to evaluate their clinicopathological features, treatment and prognostic factors to provide evidence-based medical experience for clinical practice.

**Results** A total of 276 primary small gGIST cases over a period of 18 years were investigated and had a median age of 60 years (range 27–91 years old). Regarding the tumor sites, 24 (8.7%) cases were in the cardia of the stomach, 107 (38.8%) in the fundus, 117 (42.4%) in the gastric body, and 28 (10.1%) in the gastric antrum. Eleven patients (4.0%) underwent a preoperative biopsy. A total of 137 (49.6%), 75 (27.2%), and 64 (23.2%) patients underwent laparoscopic, open resection, and endoscopic resection, respectively. Sixty-four patients (23.2%) had local endoscopic resection, 172 (62.3%) had wedge resection, 7 (2.5%) had proximal gastrectomy, 19 (6.9%) had distal gastrectomy, and 14 (5.1%) had total gastrectomy. Mitotic counts were ≤ 5/50, (5–10)/50, and > 10/50 per HPF in 259 (93.8%), 7 (2.5%), and 10 (3.6%) cases, respectively. There were 259 cases (97.1%) of spindle cell type, 7 (2.5%) epithelial cell types and one case (0.4%) of mixed type. Immunohistochemistry showed 74.6% (206/276), 98.2% (271/276), and 97.4% (269/276) of the patients had co-expression of CD34+, CD117+, and DOG-1+, respectively. Thirty-nine patients underwent genetic testing (39/276, 14.1%). Three patients (1.1%) had positive resection margin. Five high-risk patients received follow-up treatment with imatinib with a median follow-up time of 38 months (range 3–156 months). The overall 1-, 3-, and 5-year overall survival rates were 100%, 99.6%, and 99.1%, respectively.

**Conclusion** Though the incidence of primary small gGISTs increased per annum, the overall survival prognoses were high. Surgery or endoscopic resection was the primary mode of treatment. Pathological features of primary small gGISTs were similar to large gGISTs, and to achieve a timely surgical intervention, the identification of intermediate- and high-risk cases should be a future focus of study.

Zifeng Yang, Xingyu Feng, and Peng Zhang have an equal contribution to this article.

✉ Kai Xiong Tao
tao_kaixiong@163.com

✉ Yong Li
yuan821007@126.com

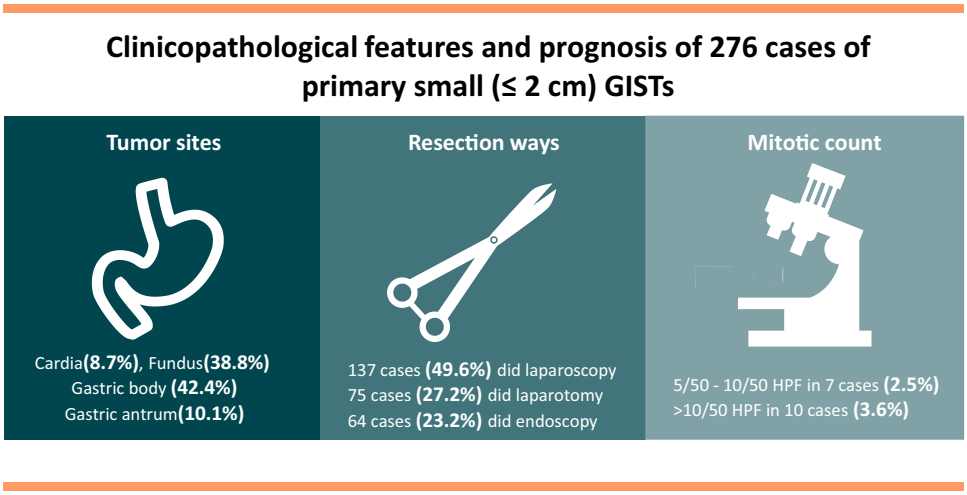
[1] Department of General Surgery, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, People's Republic of China

[2] Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

[3] Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, People's Republic of China

[4] Department of Gastric and Pancreatic Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, People's Republic of China

**Graphical Abstract**




**Keywords** Primary small gGIST · Epidemiology · Clinicopathological features · Overall survival · Prognosis

Gastrointestinal stromal tumors (GISTs) are tumors originating from the mesenchymal tissues having malignant tendencies [1]. The incidence of GIST is 1–2 person per 10 million in worldwide. Additionally, approximately 20% of soft tissue sarcomas are GISTs, and 60% occur in the stomach [2]. According to the modified National Institutes of Health (NIH) risk classification system, the postoperative recurrence and metastasis risk factors are based on the tumor site, tumor size, mitotic count, and tumor rupture, which are used to classify patients into very low-, low-, intermediate-, and high-risk groups. In recent years, with the progress in imaging and endoscopic techniques, and the improvement of health awareness, the detection rate of primary small gGISTs (≤ 2 cm) has increased by nearly 20–30% [3]. In fact, primary small gGISTs have a significantly higher detection rate than large gGISTs (> 2 cm). Primary small gGISTs have therefore recently gained the attention of clinicians [4]. However, unlike large gGISTs, the clinical diagnosis, treatment and prognoses of primary small gGISTs are still without consensus. This study aims to evaluate the clinicopathological features, treatment and prognostic factors of primary small gGISTs and to provide evidence-based medical experience for clinical practice.

## Methods

### Patient information and ethics

From January 1998 to January 2015, the data of patients with primary small gGISTs (≤ 2 cm) treated at four high-volume medical centers of the Southern China, namely the Guangdong General Hospital, Guangdong Academy of Medical Sciences, Union Hospital Tongji Medical College, Southern Medical University Nanfang Hospital, and Sun Yat-sen University Cancer Center, were collected and analyzed (Fig. 1). The enrollment criteria for this study were a complete record of clinicopathological data and pathological confirmation diagnosis, either pre- or post-operative, of gGIST. Patients were excluded if they succumbed to other diseases apart from GISTs. All the four participating medical centers provided ethical approvals for this case series study and all patients provided informed consents for participation.

### Observations and follow-up

Based on the initial time of diagnosis, the data collected were classified into six 3-years' time periods: 1998–2000, 2001–2003, 2004–2006, 2007–2009, 2010–2012 and 2013–2015. Age, gender, tumor site, tumor size, surgical and pathological outcome, adjuvant therapy after surgery and other clinical and pathological factors were retrospectively analyzed. Additionally, the tumor site was allocated to one of the four anatomic subsites, namely the gastric cardia, fundus, body, or antrum. Primary small gGIST was defined as ≤ 2 cm according to the National Comprehensive Cancer Network (NCCN) guidelines [5] and was further subdivided into < 1 cm and 1–2 cm gGISTs. Surgical methods included laparoscopic, open resection or endoscopy resection. The resection scope included local endoscopic tumor excision, wedge resection, proximal gastrectomy, distal gastrectomy, and total gastrectomy. Based on the modified NIH risk

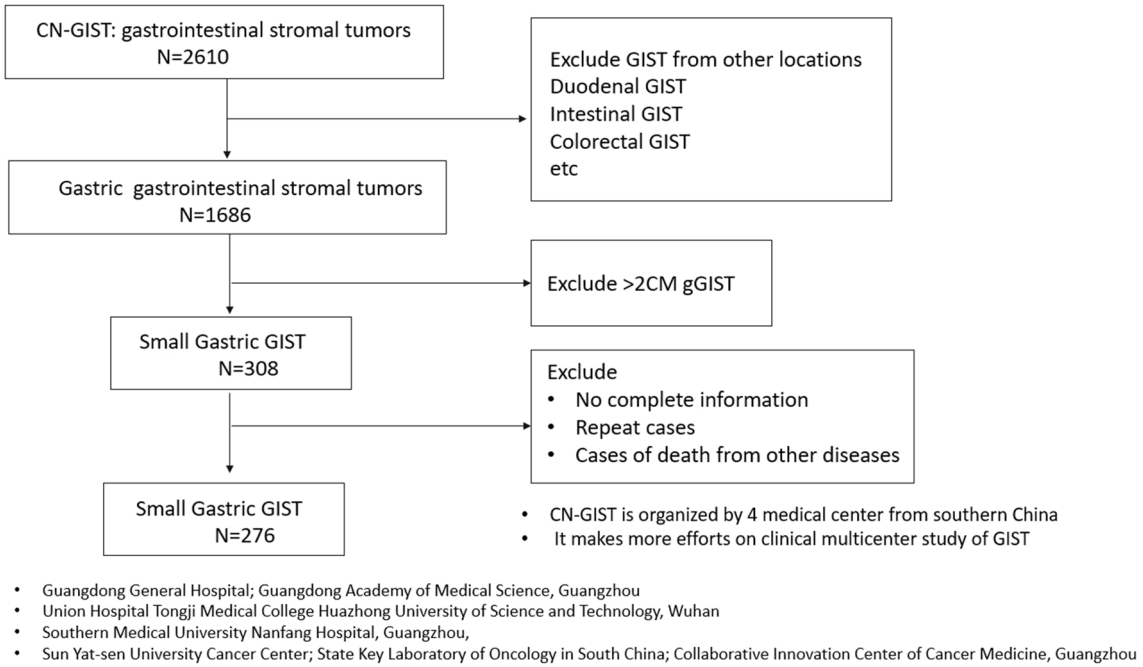



**Fig. 1** Study flowchart

stratification system, all the curative resected cases were classified into either a very low-, low-, intermediate-, or high-risk group. The mitotic count was assessed per 50 high-power field (HPF). Pathologic examination was approved by four experienced pathologists. All patients were followed up by gastroscopy, ultrasound gastroscopy or CT examination every 6 months. The last follow-up visit was 15 February 2016.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 19.0 for Windows; SPSS, Chicago, IL, USA). All data were analyzed by descriptive statistics. Survival curves were derived from Kaplan–Meier estimates.

## Results

### Cases descriptions

A total of 276 patients with primary small gGISTs were eligible for this study and consisted of 56 cases from the Guangdong General Hospital, 80 cases from the Sun Yat-sen University Cancer Center, 71 cases from the Southern Medical University Nanfang Hospital, and 69 cases from the Union Hospital Tongji Medical College (Fig. 1). There were 130 male (47.1%) and 146 female (52.9%) patients aged between 27 and 91 years old at the time of diagnosis. The median age was 60 years, and there were 139 cases (50.4%) older than 60 years. There were no obvious clinical symptoms in 23.2% of the cases; the remaining 76.8% demonstrated symptoms of gastrointestinal bleeding, abdominal distension, or abdominal pain. Preoperative examination of the patients was done by CT (computer tomography) (231 cases, 83.7%), endoscopy (197 cases, 71.4%), endoscopic ultrasonography (182 cases, 65.9%), or a combination of the above (138 cases, 50%) (Table 1).

### Prevalence of cases over time

Based on the six 3-year intervals, there were two cases from 1998 to 2000, two cases from 2001 to 2003, 13 cases from 2004 to 2006, 69 cases from 2007 to 2009, 85 cases from 2010 to 2012, and 105 cases from 2013 to 2015 (Fig. 2; Table 2).

### Tumor site and biopsy

Based on the preoperative CT, gastroscopy or intraoperative exploration, there were 24 (8.7%) small gGISTs in the cardia, 107 (38.8%) in the fundus, 117 (42.4%) in the body and 28 (10.1%) in the antrum of the stomach (Table 1). Eleven patients (4.0%) underwent preoperative biopsy.

**Table 1** Clinical information of small gastric GIST

| Clinical information | No. of cases (%) |
|---|---|
| Median age | 60 (27–91) |
| Age | |
| >60 years | 139 (50.4%) |
| ≤60 years | 137 (49.6%) |
| Gender | |
| Male | 130 (47.1%) |
| Female | 146 (52.9%) |
| Presenting symptom | |
| Yes | 212 (76.8%) |
| No | 64 (23.2%) |
| Diagnostic workup | |
| CT | 231 (83.7%) |
| UGIE | 197 (71.4%) |
| EUS | 182 (65.9%) |
| All three | 138 (50.0%) |
| Tumor location | |
| Cardia | 24 (8.7%) |
| Fundus | 107 (38.8%) |
| Body | 117 (42.4%) |
| Antrum | 28 (10.1%) |
| Biopsy | |
| Yes | 11 (4.0%) |
| No | 266 (96%) |
| Postoperative adjuvant therapy | |
| Yes | 5 (1.8%) |
| No | 271 (98.2%) |
| Recurrence | |
| Yes | 2 (0.7%) |
| No | 274 (99.3%) |

Presenting symptom contains gastrointestinal bleeding, abdominal distension and abdominal pain. Adjuvant therapy is postoperative imatinib treatment. Imatinib is only required for intermediate-risk and high-risk cases that defined by modified National Institutes of Health (NIH) risk categories

*CT* computer tomography, *UGIE* upper gastrointestinal endoscopy, *EUS* endoscopic ultrasound

## Surgical outcomes

All patients underwent surgical or endoscopic resection, of which 137 (49.6%) had laparoscopic, 75 (27.2%) open resection and 64 (23.2%) endoscopic resection. Sixty-four patients (23.2%) underwent a local endoscopic excision, 172 (62.3%) had wedge resection, 7 (2.5%) had proximal gastrectomy, 19 (6.9%) had distal gastrectomy, and 14 (5.1%) had total gastrectomy. Postoperative complications (30 days postoperatively) occurred in eight cases (2.9%) and included abdominal infection (3 cases), bleeding (2 cases), gastroplegia (2 cases), leakage (1 case); all these cases were treated by drug and never had a surgical intervention (Table 3).

## Pathological outcomes

The postoperative pathology report identified that there were 137 cases (50.4%) of < 1 cm gGISTs and 139 cases (49.6%) of 1–2 cm gGISTs (Table 4). The mitotic counts were ≤ 5/50, (5–10)/50, and > 10/50 per HPF in 259 (93.8%), 7 (2.5%), and 10 (3.6%) cases, respectively. Based on the histopathological classification, 259 (97.1%) cases were classified as spindle cell type, 7 (2.5%) as epithelial cell type and 1 (0.4%) as a mixed type. Immunohistochemistry demonstrated that 74.6% (206/276), 98.2% (271/276), and 97.4% (269/276) of the patients had co-expression of CD34+, CD117+, and DOG-1+, respectively and an additional four cases had tumor necrosis (1.5%).

Furthermore, 39 patients had genetic testing (14.1%). In this study, there were three cases (1.1%) with positive margins after local endoscopic resection on follow-up pathology examination. These three patients subsequently received an open or laparoscopic resection, which resulted in a negative margin. According to the modified NIH risk classification system [5], there were 259 cases (93.9%) of very low risk, 7 cases (2.5%) of intermediate risk and 10 cases (3.6%) of high risk (Table 4). Five high-risk patients received follow-up treatment with imatinib (postoperative adjuvant therapy).

## Survival information

All patients were followed up by gastroscopy, ultrasound gastroscopy or CT examination every 6 months. The median follow-up time was 38 months (range 3–156 months). There were two high-risk cases of recurrence (currently receiving imatinib treatment, survival status), and an additional two high-risk patients succumbed due to their disease. All the four high-risk cases recurred within 2 years after surgery, but the years of diagnosis and treatment were different. Two cases were diagnosed before 2003, and imatinib was not taken after surgery, recurrence, and metastasis, resulting in death at 37 months and 40 months after surgery, respectively. However, the other two cases with recurrence were diagnosed in 2012 and 2014. Postoperative imatinib treatment was performed in both cases, and increasing imatinib dosage (600 mg/d) was taken after recurrence and continue to take until the last follow-up time. The overall 1-, 3-, and 5-year survival rates were 100%, 99.6%, and 99.1%, respectively (Fig. 3). Due to the lack of tumor progression data and death cases, we could not perform a Kaplan–Meier univariate or Cox multivariate survival analysis.

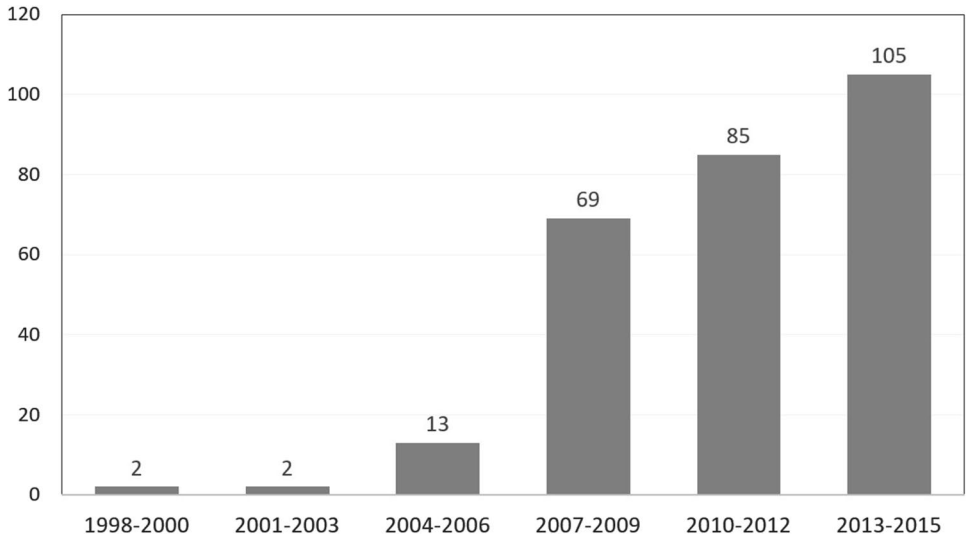



**Fig. 2** Cases of primary small gastric GISTs in six different time periods. There was an increasing tendency to perform the resection for small gastric GIST

**Table 2** Clinical information of small gastric GIST in six different time periods

| Time period (year) | Cases | Micro-surgery[a] | Laparotomy | Extensive resection[b] | Genetic test | Intermediate and high risk (NIH) | Adjuvant therapy[c] |
|---|---|---|---|---|---|---|---|
| 1998–2000 | 2 | 0 | 2 | 0 | 0 | 0 | 0 |
| 2001–2003 | 2 | 1 | 1 | 0 | 0 | 1 | 0 |
| 2004–2006 | 13 | 2 | 11 | 4 | 0 | 1 | 0 |
| 2007–2009 | 69 | 49 | 20 | 9 | 1 | 1 | 1 |
| 2010–2012 | 85 | 66 | 19 | 13 | 18 | 7 | 1 |
| 2013–2015 | 105 | 83 | 22 | 14 | 20 | 7 | 3 |
| Total | 276 | 201 | 75 | 40 | 39 | 17 | 5 |

[a]Micro-surgery = endoscopy + laparoscopy

[b]Extensive resection = proximal gastrectomy + distal gastrectomy + total gastrectomy

[c]The intermediate- and high-risk cases accepted postoperative adjuvant therapy

## Discussion

### Definition of small gGIST

The GISTs originate in the mesenchymal tissue and its predominant site is the stomach. It is a relatively rare disease for which the prognosis can be made based on indicators such as the tumor site, tumor size, mitotic count, and rupture. This is suggested by the modified NIH classification system for gGISTs [5]; however, there is currently no consensus for defining small GISTs. Based on the tumor size, there are two groups of GIST, small or large. The umbrella term 'small GISTs' includes very small or minute GISTs ($\leq 2$ cm), GIST tumorlets, microscopic GISTs ($\leq 1$ cm) or interstitial cells of Cajal. 'Large GISTs' are usually only referred to as "big" or "large." In clinical practice, 1–2 cm is generally used as the cut-off size for small gGISTs, which is important for the correct classification of patients into low risk or intermediate- to high-risk groups [6–9]. The present study used the current and most widely used NCCN guidelines, in which a primary gGIST of $\leq 2$ cm is considered a primary small gGIST [10].

### Epidemiology and diagnosis

Studies have shown that the incidence of primary gGISTs is high in the elderly and that there is no gender difference [2]. This is in agreement with the results of our study, where the median age of the investigated patients was 60 years of age and the approximate proportion of male to female cases was at a ratio of 1:1.12. In recent years, there has been an increase in health awareness of patients, which have contributed to improvements in the diagnosis and therapeutic progress of gGIST and at the same time, this has increased the detection rate of gGISTs, also considering that the number of asymptomatic-, autopsied- and accidentally discovered cases has also increased, thereby enhancing the clinicians as well as patients' perception and knowledge for the willingness of undergoing and abiding to GISTs treatments protocols.

**Table 3** Surgical outcome of small gastric GIST

| Surgical outcome | No. of cases (%) |
|---|---|
| Surgical method | |
| Laparoscopy | 137 (49.6%) |
| Open resection | 75 (27.2%) |
| Endoscopy | 64 (23.2%) |
| Resection scope | |
| ER | 64 (23.2%) |
| WR | 172 (62.3%) |
| PG | 7 (2.5%) |
| DG | 19 (6.9%) |
| TG | 14 (5.1%) |
| Complication | |
| Yes | 8 (2.9%) |
| Bleeding | 2 |
| Leakage | 1 |
| Abdominal infection | 3 |
| Gastroplegia | 2 |
| No | 268 (97.1%) |

*ER* endoscopic resection, *WR* wedge resection, *PG* proximal gastrectomy, *DG* distal gastrectomy, *TG* total gastrectomy

Complication—30 days complication postoperatively

**Table 4** Pathological outcome of small gastric GIST

| Pathological outcome | No. of cases (%) |
|---|---|
| Tumor size | |
| 1–2 cm | 139 (50.4%) |
| <1 cm | 137 (49.6%) |
| Mitotic count | |
| ≤5/50 HPF | 259 (93.8%) |
| >5/50 HPF ≤10/50 HPF | 7 (2.5%) |
| 10/50 HPF | 10 (3.6%) |
| Histopathological classification | |
| Spindle | 268 (97.1%) |
| Epithelioid | 7 (2.5%) |
| Mixed | 1 (0.4%) |
| IHC | |
| CD34(+) | 206 (74.6%) |
| CD117(+) | 271 (98.2%) |
| Dog-1(+) | 269 (97.4%) |
| Tumor necrosis | |
| Yes | 4 (1.5%) |
| No | 272 (98.5) |
| Surgical margin | |
| + | 3 (1.1%) |
| – | 273 (98.9%) |
| NIH criteria | |
| Very low | 259 (93.8%) |
| Intermediate | 7 (2.5%) |
| High | 10 (3.6%) |
| Genetic test | |
| Yes | 39 (14.1%) |
| No | 237(85.9%) |

*HPF* high-power field, *IHC* immuno-histo-chemistry, *NIH* National Institute of Health

As such, to date, the detection rate of small gGISTs ranges between 3 and 35% [11, 12] and as demonstrated in this study, the number of gGIST cases rapidly increased over the six 3-year periods. Additionally, in agreement with Giuliano et al. [13], 76.8% (212/276) of our enrolled patients had symptomatic, including abdominal discomfort (abdominal distension, abdominal pain) and gastrointestinal bleeding. At present, the diagnosis of small gGISTs mainly relies on CT, endoscopy, and endoscopic ultrasonography. The combined-modality examinations help to clarify the site, origin, and depth of the tumor, and provides better evidence for assisting the decision-choice of treatment(s) to be undertaken [4, 14].

The NCCN guideline states that because the tissue of GIST is soft and fragile, it is recommended that biopsies should only be performed for gGIST cases that require preoperative adjuvant therapy. Small gGISTs (≤2 cm) are generally considered benign and exhibit an inert biological behavior for which a preoperative biopsy is not suggested, as this may increase the risk of abdominal spreading [5]. Therefore, at present, the clinical diagnosis is mainly based on CT examination, UGIE (upper endoscopic ultrasound) and EUS (endoscopic ultrasound) to improve the clinical diagnosis of GIST. This explains the reason for the 11 (4%) cases of primary small gGISTs to have a preoperative biopsy, which may have been related to either their tumor mucosal surface being ulcerated or difficulty in differential diagnosis from other tumors such as lymphadenoma, thus requiring the biopsy for a differential diagnosis.

## Surgical treatment

Further, in agreement with previous literatures [15], 89.9% (248/276) of the primary small GISTs were found in the middle and upper part of the stomach. The NCCN guidelines (2010) for the treatment of ≤2 cm gGISTs (referred to as very small gastric GIST) have been developed and applied thus far. The guidelines suggest that, if there are no high-risk endoscopic ultrasound-guided features (irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity), the patient only requires a follow-up with endoscopic ultrasound every 3–6 months. However, in practice, this approach has raised some concerns. Endoscopist specialists have argued that, for ultrasound endoscopy to be used to screen for such factors, the clinician needs adequate experience to avoid misdiagnosis or to discourage resection when there is no immediate requirement (as per the guidelines).

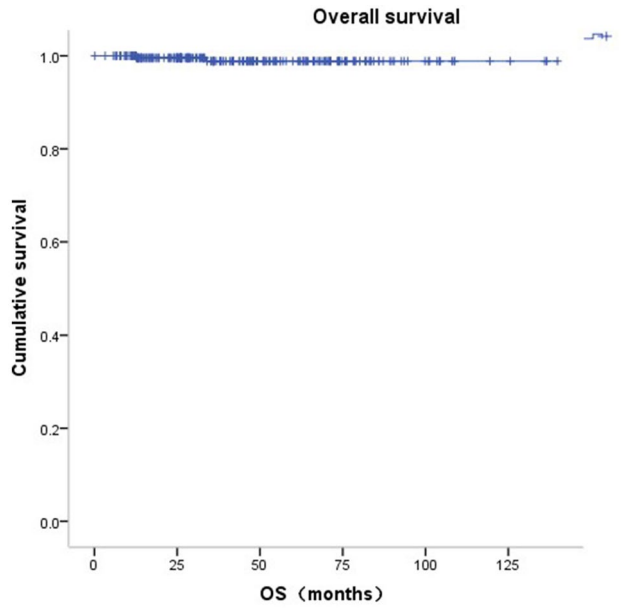



**Fig. 3** Survival curves of the 229 small gastric GIST patients. The 1-, 3-, and 5-year overall survival rates were 100%, 99.6%, and 99.1%, respectively

Surgeons have also disputed that because of the unique and difficult initial tumor sites (gastric cardia or antrum) of small gGISTs, R0 resection may affect organ function. Moreover, for cases with gastrointestinal bleeding, conservative treatment is often poor. The preoperative diagnosis experience of intermediate- to high-risk cases of small gGIST is also still limited.

Further, there is patient's discomfort to consider, as such, persistent abdominal discomfort or psychological stress may compel patients for earlier clinical visits to undermine the cause and to favor early resection rather than performing additional confirmatory diagnostic preoperative tests. For these reasons, the detection rate and treatment of clinically small gGIST resections has gradually increased in recent years [16, 17]. Regarding the surgical method, the frequently used methods are endoscopy, laparoscopy, or open resection. The resection standard only needs to ensure that the tumor margin is negative and that there is no need for lymph node dissection [10]. Studies have shown that endoscopic and laparoscopic resection, compared to open resection, were significantly less invasive and could meet the requirements of negative margins. These are, therefore, the two recommended methods [15, 16, 18]. In this study, the number of microsurgeries (endoscopic and laparoscopic surgery combined) increased gradually over the years. Although endoscopic treatment of a non-invasive muscular submucosal mass is safe, the GISTs that originate from muscle lesions have a potential risk of perforation. Further, endoscopic resection of the cardia and fundus is difficult and can easily result in tumor-residual resection margins and increasing the risk of postoperative complications. Indeed, the three cases with positive margins in our study followed an endoscopic resection. The NCCN guidelines do not suggest endoscopic treatment for small gGISTs [5, 19, 20]. However, there is still prospects for endoscopic technology in the treatment of gGISTs as endoscopic platforms improve, the experience of doctors' increases and multidisciplinary team meetings provide further insights.

In addition, the main reasons for having 40 cases (14.5%) of extensive resection in this study are as follows: First, some cases could not be differentiated from malignant tumors such as gastric carcinoma, and extensive resection (proximal gastrectomy or distal gastrectomy or total gastrectomy) was selected to achieve the radical effect on tumors. Second, the tumor was located in a risky and unfavorable site, such as the esophageal and gastric junction, pylorus, or small curvature. The resection of tumors in these sites often affects the digestive function of the gastric regions. To improve the quality of life in later days, extensive resection is often preferably performed.

## Risk grading and postoperative treatment

The diagnosis of primary small gGISTs mainly depends on histology, immunohistochemistry, and related-gene detection. Histopathological classification mainly includes spindle cell type, epithelioid cell type, and mixed type [9, 21]. This study demonstrated that the majority of small gGISTs (97.1%) were spindle cell type. Immunohistochemistry is an important means to diagnose GIST. Consistent with the literature [12], 76.4% of small gGISTs expressed CD34+, 98.2% expressed CD117+ and 97.4% expressed DOG-1+.

Only 39 (14.1%) cases in this study opted for genetic testing, and most of these cases were for patients diagnosed between 2010 and 2015 (Table 3). It is thought that this was related to the degree of patient awareness, as well as the patients' economic situation. The prognosis of small gGISTs is relatively good [22]; the 5-year survival rate in this study was 99.1% in this study for all the small gastric GIST. The mitotic count is a very important factor affecting prognosis. In our study, we identified 259 cases (93.8%) with a mitotic count lower than 5/50 per HPF, 7 cases (2.5%) with a count between 5/50 and 10/50 per HPF, and 10 cases (3.6%) with a mitotic rate higher than 10/50 per HPF. In reference to the modified NIH risk grading system, this meant that 259 cases (93.9%) were very low risk, 10 cases (3.6%) were intermediate risk, and 7 cases (2.5%) were high-risk. According to the findings of ACOSOG Z9001 [23] and SSG XVIII [24], intermediate- to high-risk patients can benefit from adjuvant therapy with imatinib, yet only five high-risk patients in this study received this treatment. The reason why only five high-risk patients had postoperative adjuvant imatinib therapy

was that before 2002 in China, there was no clear evidence or guideline of postoperative adjuvant therapy, before the data from ACOSOG Z9001 had been published [23]. Also, medical treatment is related to the financial situation of the patients [25] and few patients could not receive adjuvant treatment because imatinib was not covered by medical insurance due to its unaffordable price at that moment. Some of high-risk patients were elderly (> 65 years old) [26, 27], few of them did not receive adjuvant treatment as the following reasons: First, the lack of published data for the elderly, second, they may simultaneously have other diseases that may result in difficulties to tolerate drug treatment [28]. Third, elderly patients have more risk for drug side-effects, resulting in non-compliance to medication [28, 29]. However, we also believe that one of the most important reasons may have also been related to the degree of disease consciousness and economic level [30].

Despite elaborating on the different aspects of gGISTs, there are several limitations in this study that should be mentioned. First, this was a retrospective study and the results may contain some degree of unconscious selection bias. Second, because lack of detailed preoperative EUS results and other indexes or the reasons why patients underwent GIST removal. Third, the duration of follow-up was short in our study. Multicenter randomized controlled studies should be conducted to confirm the benefit of surgical resection of small gastric GISTs compared to conservative treatment.

## Conclusions

This study analyzed the clinicopathological features and prognostic factors of 276 patients diagnosed with small gGISTs, treated with endoscopic or surgical resection in four high-volume medical centers of the Southern China. The results have also highlighted that the epidemiology, definition, and treatment of small gGISTs are still controversial and that the identification of intermediate- to high-risk patients should become a priority.

**Author contributions** ZY, XF, PZ, TC, HQ, ZZ, GL, KXT, and YL have substantial contributions to the conception and design of this study, have revised its intellectual content, and have approved of the final submitted version.

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### Compliance with ethical standards

**Disclosure** Drs. Zifeng Yang, Xingyu Feng, Peng Zhang, Tao Chen, Haibo Qiu, Zhiwei Zhou, Guoxin Li, Kaixiong Tao, and Yong Li have no conflicts of interest or financial ties to disclose.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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