Research Article

Risk Factors and Prognostic Analysis of Gastrointestinal Stromal Tumor Recurrence-Metastasis

Shan Chen,1 Kanru Sang,1 Wenjing Chen,2 Jinji Jin,2 Xiaolei Chen,2 Guanbao Zhu,2 Pengfei Wang,2 and Yiqi Cai2

1First Clinical College of Wenzhou Medical University, Wenzhou, China
2Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Correspondence should be addressed to Yiqi Cai; caiyiqi908123@sina.com

Received 16 May 2022; Revised 27 June 2022; Accepted 1 July 2022; Published 18 July 2022

Academic Editor: Ahmed Faeq Hussein

Copyright © 2022 Shan Chen et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. Gastrointestinal stromal tumors (GISTs) are potential malignancies that occur in the digestive tract. This study aimed to investigate the risk factors and prognosis of recurrence and metastasis of gastrointestinal stromal tumor (GIST).

Methods. From January 2018 to December 2019, 422 patients with GIST who received surgery in the First Affiliated Hospital of Wenzhou Medical University were enrolled. Their clinical data were retrospectively analyzed, and their follow-ups were continued until March 31, 2022. Subsequently, univariate and multivariate Cox analyses, survival curves, and nomograms were adopted to explore the relationship between clinicopathological characteristics and recurrence or metastasis in patients with GIST.

Results. Univariate and multivariate Cox analysis exhibited that the prognosis of patients was affected by tumor rupture ($P=0.040$), tumor location ($P<0.001$), tumor diameter ($P=0.016$), mitotic figures ($P<0.001$), and risk grade ($P<0.009$). The above variables were selected to create the nomogram for 3-year disease-free survival (DFS). The 3-year the ROC (receiver operating characteristic) curves of the nomogram were (0.878 95% confidence interval [CI]: 0.871–0.939).

Conclusion. Collectively, risk factors affecting postoperative recurrence or metastasis of GIST consist of primary site of tumors, tumor rupture, tumor diameter >10 cm, high-risk tumor classification, and mitotic figures $\geq 10$ per 50 HPFs. And the application of nomogram may help physicians provide individualized diagnosis and treatment for patients with GISTs following surgical resection.

1. Introduction

Gastrointestinal stromal tumor (GIST) is a rare tumor arising from the gastrointestinal tract, with an incidence of 0.1%–3% of all gastrointestinal malignancies [1]. However, in gastrointestinal tract, GIST is the most common mesenchymal tumor [2] and small intestinal malignant tumor, affecting 10–20 people per million [3]. Notably, GIST shows an increasing trend to its incidence in recent years [4]. GIST originates from interstitial cells of Cajal and their stem cells, and their mainly histological types enroll spindle, epithelioid, and mixed cells. The dominating biological characteristics of GIST are KIT gene (75%) activation or PDGFRα gene (15%) mutations, which result in continuous activation of tyrosine kinase receptors and continuous proliferation of tumor cells [5]. In addition, 50% to 70% GIST occur in the stomach (70% in the body of stomach, 15% each in the antrum and cardia), 30% in the small intestine, and occasionally in other parts of the abdominal cavity (colon, rectum, appendix, esophagus, and liver) [6].

The clinical manifestations of GIST lack specificity, so its diagnosis largely relies on imaging tests and pathological biopsy [7]. Despite adopting complete surgical resection as a mainstay treatment for localized and primary GIST [8], the 5-year recurrence rate of patients after treatment is estimated as high as 29.5% [9]. At present, important independent factors predicting GIST recurrence include the tumor mitotic rate, size, location, and tumor rupture [10], and postoperative adjuvant tyrosine kinase inhibitor (TKI) treatment may delay recurrence [11]. Therefore, an evaluation of the recurrence and progression risks of GIST has become more and more important for patients; also, an exploration to additional prognostic factors of recurrence risk stratification might increase the prognostic accuracy [12].
2.2. Relevant Indicators of Risk Stratification of Gastrointestinal Stromal Tumors. According to the modified National Institutes of Health (NIH) classification proposed by Joensuu in 2008 [15], patients with GIST were classified as very low risk, low risk, intermediate risk, and high risk (Table 1).

### Table 1: Risk stratification of gastrointestinal stromal tumors.

| Risk stratification | Tumor diameter(cm) | Mitotic count (per 50 HPFs) | Primary location of tumor | The number of cases |
|---------------------|--------------------|-----------------------------|---------------------------|---------------------|
| Very low            | <2.0               | ≤5                          | Any location              | 152                 |
| Low                 | 2.1-5.0            | ≤5                          | Any location              | 119                 |
|                     | 2.1-5.0            | >5                          | Gastric                   | 44                  |
| Intermediate        | <5.0               | 6-10                        | Any location              |                     |
|                     | 5.1-10.0           | ≤5                          | Gastric                   |                     |
|                     | Any size           | Any mitotic rate             | Tumor rupture             | 107                 |
|                     | >10.0              | Any mitotic rate             | Any location              |                     |
| High                | >5.0               | >5                          | Any location              |                     |
|                     | 2.1-5.0            | >5                          | Nongastric                |                     |
|                     | 5.1-10.0           | ≤5                          | Nongastric                |                     |

Note: HPF, high-power field.

In this study, we analyzed the risk factors of metastasis and recurrence in patients with GIST. Specifically, nomograms were plotted with 3-year disease-free survival (DFS) to provide theoretical guidance for individualized postoperative prognosis analysis and intervention. And area under the curve (AUC) of nomograms reached 0.878 (95% confidence interval [CI]: 0.871–0.939), indicating that the reliability of clinical use was relatively strong.

2. Materials and Methods

2.1. General Information. A total of 422 patients diagnosed with GIST in the First Affiliated Hospital of Wenzhou Medical University from January 2018 to December 2019 were included in this study. Baseline data and clinical characteristics of patients were recorded. This study was a retrospective analysis requiring no informed consent, and all procedures were approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Inclusion criteria: (1) the age of patients ≥ 18 years; (2) with the primary tumor diagnosed in 2018-2019, and regular chemotherapy drugs for GIST were used according to the guidelines of the Chinese Society of Clinical Oncology (CSCO) [13, 14]. And there were no cases of preoperative neoadjuvant therapy in the included patients; (3) with GIST confirmed by test results of biopsy specimens which were obtained during laparotomy or laparoscopic, endoscopic resection; (4) complete outpatient/emergency follow-up data could be obtained after surgery. The exclusion criteria were as follows: (1) primary tumor occurring before 2018, and recurrent tumor occurring in 2018-2019; (2) confirmed as leiomyoma, fibroma, and other nonstromal tumors by intraoperative immunohistochemical results; and (3) lost to follow-up cases.

2.2. Relevant Indicators of Risk Stratification of Gastrointestinal Stromal Tumors. According to the modified National Institutes of Health (NIH) classification proposed by Joensuu in 2008 [15], patients with GIST were classified as very low risk, low risk, intermediate risk, and high risk (Table 1).

2.3. Disease-Free Survival. After surgery, patients with GIST were followed up for 36 months, and the prognosis and disease-free survival (DFS) were recorded. To be specific, follow-up was conducted in the outpatient clinic or by telephone, and the follow-up duration was calculated from the date of surgery to the date of finding recurrence and metastasis. Besides, patient prognosis included whether recurrence and metastasis occurred, and the site of tumor recurrence and metastasis, and DFS included the time from initiation of treatment to recurrence or metastasis of GIST. By the way, all data were finally censored at the last follow-up for the living patients.

2.4. Statistical Analysis. SPSS 26.0 statistical software was used for data analysis. Enumeration data were expressed as n (%); χ² test was adopted for statistical analysis; measurement data were expressed as mean ± standard deviation (SD); and t-test was applied for statistical analysis. Univariate and multivariate Cox regression was performed to analyze the factors of tumor recurrence and metastasis. Survival curves were plotted using the Kaplan-Meier method, and nomograms of associated risk factors were generated using the R language. The receiver operating characteristic (ROC) analysis was used to evaluate the predictive ability of the nomogram of risk stratification systems. P < 0.05 served as the criterion of significant difference.

3. Results

3.1. General Clinical Data. Among 422 included patients, 199 (47.2%) were male, and 223 (52.8%) were female, aged from 25 to 82 years. Baseline data of patients are shown in Table 2. And in this paper, 12 patients suffered postoperative recurrence, with stomach as the common site; 31 patients had metastasis, with the liver as the common site (Table 3).

3.2. Correlation of Primary Tumor Location with Clinical Symptoms. To provide guidance for clinical diagnosis of GIST, 2 patients with multiple primary tumors were excluded, and the relationship between the chief complaints of the remaining 420 patients with GIST and their primary
tumor sites was explored in this study. According to the results, a significant difference was identified in the complaints among patients with different primary sites ($P < 0.001$). Primary tumors in the stomach and other sites were mainly discovered by physical examination, and those in the small intestine presented with gastrointestinal bleeding (Table 4).

### 3.3. Analysis of Factors Associated with Recurrence-Metastasis in Patients with Gastrointestinal Stromal Tumors

#### 3.3.1. Recurrence-Metastasis Is Not Related to Blood Tumor Markers in Patients with Gastrointestinal Stromal Tumors.

A total of 44 patients with GIST had tumor metastasis or recurrence during follow-up at 36 months after surgery. To investigate the relationship between postoperative metastasis or recurrence and blood tumor markers, patients were divided into recurrence-metastasis group ($n = 36$) and nonrecurrence-metastasis group ($n = 386$). Relationship between five blood tumor indicators carcinoembryonic antigen (CEA, $P = 0.405$), alpha-fetoprotein (AFP, $P = 0.459$), cancer antigen 199 (Ca199, $P = 0.461$), Ca125 ($P = 0.732$), and Ca153 ($P = 0.147$) between the two groups.

#### 3.3.2. Correlations of Recurrence-Metastasis with Clinicopathological Characteristics in Patients with Gastrointestinal Stromal Tumors.

To further investigate the relationship between recurrence-metastasis and clinical characteristics in patients with GIST, univariate and multivariate Cox regression analysis was performed. The results of univariate analysis suggested that postoperative recurrence and metastasis were closely correlated with tumor rupture, primary tumor site, tumor size, mitotic count, and risk classification ($P < 0.05$), but not with age, gender, body mass

### Table 2: Baseline data of patients.

| Item                                | Category | n (%       |
|-------------------------------------|----------|------------|
| Gender                              | Male     | 199 (47.2%)|
|                                     | Female   | 223 (52.8%)|
|                                     |          | 25-82 (median: 60) |
| Age (year)                          | <60      | 205        |
|                                     | ≥60      | 217        |
| Smoking history                      | Yes      | 84         |
|                                     | No       | 338        |
| Drinking history                     | Yes      | 86         |
|                                     | No       | 336        |
|                                     | <18.5    | 14         |
|                                     | >18.5    | 167        |
| Body mass index                     | Not detected | 74     |
| Accompanied by malignant tumors *   | Yes      | 76         |
|                                     | No       | 346        |
| Primary location of tumor           | Stomach  | 298 (70.9%)|
|                                     | Small intestine | 93 (22.1%)|
|                                     | Other locations | 29 (6.9%)|
|                                     | Multiple primaries | 2 (0.5%)|
| Pathological results                | ≤5 per 50 HPFs | 337       |
|                                     | >10 per 50 HPFs  | 29        |
|                                     | Not detected | 56         |
| Tumor diameter                       | 0.2–23 cm (median: 4 cm) |      |
| Immunohistochemical results         | CD117-positive | 93.4% (394/422) |
|                                     | CD34-positive | 90.8% (383/422) |
|                                     | DOG-1-positive | 93.1% (393/422) |
|                                     | Ki-67-positive | 81.75% (345/422) |
|                                     | S-100     | 5.7% (24/422) |
|                                     | SMA       | 19.4% (82/422) |
| Other parameters                    | Very low  | 152        |
|                                     | Low       | 119        |
| Risk stratification                 | Intermediate | 44        |
|                                     | High      | 107        |
| Treatment method                    | Laparotomy | 161        |
|                                     | Laparoscopic resection | 133    |
|                                     | Endoscopic resection | 128    |
| Follow up results                   | Recurrence and metastasis | 7     |
|                                     | No recurrence or metastasis | 386    |

Note: * accompanied by malignant tumors such as gastric adenocarcinoma, primary malignant tumor of liver, and colorectal malignant tumor.

### Table 3: Postoperative recurrence-metastasis location and proportion of patients with gastrointestinal stromal tumors.

| Recurrence-metastasis location | Number of cases (n) | Proportion (%) |
|-------------------------------|---------------------|----------------|
| Stomach                       | 5                   | 41.6           |
| Small intestine               | 2                   | 16.7           |
| Abdominal and pelvic cavity   | 2                   | 16.7           |
| Colon and rectum              | 2                   | 16.7           |
| Anal canal                    | 1                   | 8.3            |
| Total                         | 12                  | 100%           |
| Metastasis location           |                     |                |
| Liver                         | 11                  | 35.4           |
| Abdominal and pelvic cavity   | 9                   | 29.0           |
| Bone                          | 1                   | 3.2            |
| Pleura                        | 1                   | 3.2            |
| Multiple                      | 9                   | 29.0           |
| Total                         | 31                  | 100%           |
Further results of multivariate analysis showed that tumor rupture, primary tumor site, tumor size, mitotic count, and risk classification were independent risk factors for recurrence or metastasis of GIST ($P < 0.05$) (Table 6). After that, nomograms were plotted to qualify and analyze the effect of independent risk factors on prognosis. As shown in Figure 1, for patients with the primary site of tumors in the stomach, the tumor diameter $\leq 2$ cm, the mitotic count $\leq 5$ per 50 HPFs, the risk stratification as low/intermediate, and without tumor rupture, the 3-year DFS rate is higher than 90%, and the prognosis is better. By contrast, for patients with tumor rupture, nongastric primary site, tumor diameter $> 10$ cm, mitotic count $> 10$ per 50 HPFs, and high-risk grade, their total score was 290 points, and the 3-year DFS rate was less than 40%. ROC analysis for 3-year prognostic accuracy of the nomogram was performed, and according to the results, the 3-year AUC was nomogram, 0.878 (95% CI: 0.871–0.939).

### 4. Discussion

In spite of the occurrence at any age, GIST is more common in adults, and the median age ranges from 60 to 65 years [16]. A survey and analysis from America showed that the incidence of GIST was similar in men and women [17]. In our study, the median age of patients was 60 years old, with a male-to-female prevalence ratio of 1:1.12, in line with previous literature reports.

The primary site of most mesenchymal tumors is in the stomach (60%–65%), followed by the small intestine (20%–30%), rare in the rectum, colon, and esophagus [18]. Besides, some studies have reported primary GIST in the liver [19]. As for mesenchymal tumor patients in our study, there were
Table 6: Univariate and multivariate COX regression analysis of recurrence and metastasis in patients with gastrointestinal stromal tumors.

|                  | Total (N) | Nonrecurrence-metastasis group (n = 386) | Recurrence-metastasis group (n = 36) | Univariate analysis | Multivariate analysis |
|------------------|-----------|------------------------------------------|--------------------------------------|---------------------|-----------------------|
|                  |           |                                          |                                      | Hazard ratio        | Hazard ratio          |
|                  |           |                                          |                                      | (95% CI)            | (95% CI)              |
|                  |           |                                          |                                      | P value             | P value               |
| Age              | 422       |                                          |                                      |                     |                       |
| ≤60              | 190       | 15                                       |                                      | 1.266 (0.646-2.480) | 0.493                 |
| >60              | 196       | 21                                       |                                      |                     |                       |
| Gender           | 422       |                                          |                                      |                     |                       |
| Male             | 178       | 21                                       |                                      | 1.999 (0.994-4.021) | 0.052                 |
| Female           | 208       | 15                                       |                                      |                     |                       |
| BMI              | 381       |                                          |                                      |                     |                       |
| <18.5            | 12        | 2                                        |                                      | 0.727 (0.392-1.349) | 0.312                 |
| 18.5-23.9        | 183       | 17                                       |                                      |                     |                       |
| >23.9            | 154       | 13                                       |                                      |                     |                       |
| Drinking history | 420       |                                          |                                      |                     |                       |
| Yes              | 82        | 4                                        |                                      | 0.648 (0.226-1.859) | 0.420                 |
| No               | 304       | 30                                       |                                      |                     |                       |
| Smoking history  | 419       |                                          |                                      |                     |                       |
| Yes              | 75        | 9                                        |                                      | 1.686 (0.772-3.682) | 0.190                 |
| No               | 311       | 24                                       |                                      |                     |                       |
| Gastrointestinal bleeding | 422 | 54                                      | 8                                    | 1.976 (0.887-4.401) | 0.096                 |
| Yes              | 54        | 8                                        |                                      |                     |                       |
| No               | 332       | 28                                       |                                      |                     |                       |
| Tumor rupture    | 422       |                                          |                                      |                     |                       |
| Yes              | 62        | 16                                       |                                      | 1.810 (1.245-2.631) | 0.002                 |
| No               | 324       | 20                                       |                                      | 1.556 (1.020-2.375) | 0.040                 |
| Complicated with other tumors | 422 | 72                                      | 4                                    | 0.601 (0.210-1.718) | 0.342                 |
| Yes              | 72        | 4                                        |                                      |                     |                       |
| No               | 314       | 32                                       |                                      |                     |                       |
| Tumor location   | 422       |                                          |                                      |                     |                       |
| Gastric          | 287       | 11                                       |                                      | 0.262 (0.127-0.541) | 0.000                 |
| No-gastric       | 99        | 25                                       |                                      | 1.786 (1.261-2.5892) | < 0.001               |
| Tumor size (cm)  | 422       |                                          |                                      |                     |                       |
| ≤2.0             | 161       | 2                                        |                                      | 2.466 (1.743-3.490) | <0.001                |
| 2.1-5.0          | 141       | 6                                        |                                      | 1.693 (1.102-2.602) | 0.016                 |
| 5.1-10.0         | 59        | 21                                       |                                      |                     |                       |
| >10.0            | 25        | 7                                        |                                      |                     |                       |
|                | Total (N) | Nonrecurrence-metastasis group (n = 386) | Recurrence-metastasis group (n = 36) | Univariate analysis | Multivariate analysis |
|----------------|-----------|----------------------------------------|-------------------------------------|--------------------|-----------------------|
|                |           | Hazard ratio (95% CI)                  | Hazard ratio (95% CI)               | P value            | P value               |
| Mitotic count (per 50 HPFs) | 415       | 324                                    | 13                                  | 3.208 (2.171-4.740) | <0.001                | 2.196 (1.421-3.392)  | < 0.001               |
| ≤5             |           | 324                                    | 13                                  |                    |                       |                       |                       |
| 6-10           |           | 42                                     | 7                                   |                    |                       |                       |                       |
| >10            |           | 14                                     | 15                                  |                    |                       |                       |                       |
| Ki67 (n%)      | 403       | 298                                    | 24                                  | 1.327 (0.606-2.906) | 0.479                 |                       |                       |
| <5             |           |                                        |                                     |                    |                       |                       |                       |
| >5             |           |                                        |                                     |                    |                       |                       |                       |
| Risk classification |          |                                        |                                     |                    |                       |                       |                       |
| Low/intermediate | 422     | 301                                    | 14                                  | 3.865 (1.937-7.712) | <0.001                | 1.163 (0.527-2.568)  | 0.009                 |
| High           | 85        |                                        |                                     |                    |                       |                       |                       |

BMI: body mass index. Tumor rupture; tumor location; tumor size; mitotic count; and risk classification.
298 patients whose primary site in the stomach (70.9%), 93 patients in the small intestine (22.1%), and 29 patients in other sites (6.9%), and two cases had multiple primary tumors. The primary tumor site was associated with the risk of the tumor. Under the condition of tumor diameter of 2.1–5.0 cm and 6–10 mitoses per 50 HPFs, the tumor with primary site in the stomach was graded as intermediate risk and that in nongastric primary tumor was graded as high risk. In this paper, univariate and multivariate Cox regression analysis showed that tumor rupture, tumor site, tumor size, and mitotic count were independent risk factors for recurrence or metastasis of GIST (P < 0.05). After predicting prognosis using nomogram, the score difference could reach 20 points between patients with primary tumor in the stomach and those in the small intestine, suggesting that patients with nongastric primary site (small intestine) had a higher risk of recurrence and metastasis. Gender is also an important risk factor affecting the prognosis of mesenchymal tumors [5]. Patryk Zemaca et al. concluded that male patients had a lower survival rate regardless of age [20]. Most of patients with mesenchymal tumors have no obvious symptoms, especially for GIST less than 1 cm in diameter, and the autopsy rate can reach 25% [21]. Most patients with mesenchymal tumors less than 2 cm in diameter are diagnosed by endoscopy, while larger GIST can invade blood vessels, and patients are usually accompanied by gastrointestinal bleeding and other clinical symptoms [22]. In our study, the first three reasons for hospital visits were physical examination, abdominal discomfort, and gastrointestinal bleeding, basically in line with the characteristics of mesenchymal tumors. In addition, some cases have perianal discomfort, nausea, anemia, and other clinical manifestations. Gastrointestinal bleeding was the main reason for patients with primary GIST in the small intestine to visit the hospital, while physical examination was the main reason for those with primary GIST in the stomach, and a correlation could be suspected between the primary tumor site and clinical symptoms. For patients with gastrointestinal bleeding, if mesenchymal tumor is suspected, but the tumor lesions cannot be discovered by gastroscopy and colonoscopy, the possibility of small intestinal GIST should be considered. Mesenchymal tumor located in small intestine has higher risk of recurrence or metastasis, and segmental intestinal resection is recommended to obtain negative resection margins [9, 23]. Imatinib, a preferred chemotherapeutic drug [22], can help advanced GIST patients obtain longer DFS and prevent metastatic adverse events when applied as adjuvant radiotherapy [24]. Unfortunately, given the limited number of samples and observation time in this study, it keeps unknown whether gastrointestinal bleeding is related to the clinical manifestations at the time of recurrence and metastasis of GIST.

The results of the nomogram in this study showed that the total score was 290 points and the 3-year DFS rate was less than 40% for patients with tumor rupture, nongastric primary site, tumor diameter >10 cm, mitotic count >10 per 50 HPFs, and high-risk grade. Additionally, survival curve analysis exhibited that different mitotic count (P < 0.0001), tumor rupture (P = 0.0003), risk classification (P < 0.0001), tumor location (P = 0.0006), and tumor diameter (P < 0.0001) all affected DFS in patients with GIST. Generally, the diameter of GIST ranges from 0.6 to 25.5 cm, with an average diameter of 8.78 ± 5.6 cm and a median diameter of 6.8 cm; however, giant GIST with a diameter of 34 cm have also been reported [25]. Therefore, some studies have selected 10 cm as the cut-off value.

**Figure 1:** Nomogram of statistically significant variables in multivariate Cox proportional hazards model. (a) Nomogram of statistically significant variables in multivariate Cox proportional hazards model: (1) rupture: 1; intraluminal rupture of digestive tract; 2 extraluminal rupture of digestive tract; (2) site: 0; no gastric; 1, gastric; (3) size: 0, ≤2.0; 1, 2.1–5.0; 2, 5.1–10.0; 3, >10.0; (4) mitotic index (per 50 HPFs): 1, ≤5; 2, 6–10; 3, >10; (5) classification of risks: 0, low/intermediate; 1, high. (b) Receiver operating characteristic curves for risk model to predict the PFS of patients with GISTs.
affecting the prognosis [26]. Miettinen et al. believed that GIST with a diameter of more than 10 cm had a higher risk of recurrence and metastasis [27]. In our study, the diameter of GIST was 0.2–23 cm, with a median diameter of 4 cm. Among the 36 cases with recurrence and/or metastasis, 19.4% patients (7/36) had a tumor diameter of more than 10 cm. Nevertheless, among the cases without recurrence and metastasis, only 6.5% (25/386) had a diameter of more than 10 cm.

Mitotic count is considered to be the most powerful predictor of recurrence and metastasis of GIST [20, 27]. According to our analysis, the mitotic count greater than 5 per 50 HPFs accounted for 61.1% (22/36) of the recurrent and/or metastatic cases, with a statistically significant

Figure 2: Kaplan–Meier survival curves for RFS of patients with gastrointestinal stromal tumors. (a) Mitotic count (group A: mitoses <5 per 50 HPFs; group B: 5 per 50 HPFs ≤ mitoses <10 per 50 HPFs; group C: mitoses ≥5 per 50 HPFs). (b) Tumor rupture (group A: no rupture; group B: with rupture). (c) Risk classification (group A: low risk-intermediate risk; group B: high risk). (d) Tumor location (group A: nonstomach; group B: stomach); (e) Tumor diameter (group A: tumor diameter ≤ 2.0 cm, group B: 2.0 cm < tumor diameter ≤ 5.0 cm; group C: 5.0 cm < tumor diameter ≤ 10.0 cm; group D: tumor diameter > 10.0 cm).
difference compared with that of nonrecurrent and metastatic cases [14.5% (56/386)]. Mitotic count is positively correlated with tumor volume, which affects the malignant potential of tumors together [20]. Univariate and multivariate Cox regression analysis showed that the mitotic count was an independent risk factor for recurrence or metastasis of GIST, and nomogram and survival curve analysis also revealed that the more mitoses, the smaller the 3-year DFS rate of GIST.

The common sites of metastasis of GIST are liver, abdominal cavity, and lymph nodes [16, 19]. In the study by Jnnmniensuk et al., the metastasis of GIST also mainly occurred in liver and abdominal cavity, but some other articles have also reported bone metastasis [28]. In our study, the liver and abdominal cavity are the most common metastasis sites, occasionally with bone and pleural metastasis, suggesting that attention is needed to be paid on the possibility of extraperitoneal metastasis of GIST in clinical practice. In addition, this study revealed that postoperative recurrence-metastasis in patients with GIST was not related to blood tumor markers. Tumor rupture is an independent evaluation indicator of GIST and is closely related to recurrence and metastasis. The rupture caused by endoscopic biopsy or intraoperative resection easily induces tumor metastasis, and some patients with malignant ulcers should be alert to the possibility of tumor rupture and metastasis [29]. When the primary tumor ruptures spontaneously or due to surgery, the tumor can be metastasized to the retroperitoneum, and then, retroperitoneal mesenchymal tumors can be formed. Terribly, the traditional treatment methods, such as surgical resection, radiotherapy, and systemic chemotherapy, have little effect on retroperitoneal mesenchymal tumors, and patients have a poor prognosis [9]. Of the 10 patients with rupture outside gastrointestinal tract, 8 cases suffered recurrence and metastasis, including 5 cases of abdominal metastasis, in our study. Such results indicated that tumor rupture could increase the risk of metastasis; therefore, endoscopy and surgical procedures should be performed with caution to avoid tumor dissemination caused by iatrogenic factors.

Some limitations can be observed in this study. Firstly, this is a single-center retrospective study on GIST patients receiving surgical treatment, and the conclusion obtained still needs to be validated by a prospective and appropriately designed study. Secondly, follow-up in this study is not sufficient. On the one hand, follow-up duration is short; on the other hand, only 3-year DFS after surgery has been recorded. And both follow-up time and DFS of patients need to be prolonged. Thirdly, due to the small sample size, a detailed stratified analysis of GIST patients has not been performed in this paper; therefore, a large-scale multicenter trial must be conducted to validate our scoring system before adopting the system in routine practice.

5. Conclusion

There is a certain correlation between the primary site of GIST and the clinical manifestations of patients. Postoperative recurrence-metastasis in the patients is not associated with blood tumor markers, but closely with primary tumor site, tumor rupture, tumor risk grade, and mitotic figures. Therefore, individualized diagnosis and treatment for GIST should be performed based on clinicopathological characteristics and prediction of the risk of postoperative recurrence and metastasis.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study was a retrospective analysis requiring no informed consent but approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors’ Contributions

Shan Chen and Kanru Sang Contributed equally to this work.

Acknowledgments

This study was supported by the Department of Health of Zhejiang Province, China (Y2100660, 2016DTA006); the Zhejiang Provincial Health Department Medical Support Discipline-Nutrition (11-ZC24); the Wenzhou Municipal Science and Bureau (Y2020732); the Wenzhou Municipal Science and Technology Bureau (Y20170104); and the National Innovation and Entrepreneurship Training Program for College Students (202110343022).

References

[1] A. El-Menyar, A. Mekkodathil, and H. Al-Thani, "Diagnosis and management of gastrointestinal stromal tumors: an up-to-date literature review," Journal of Cancer Research, vol. 13, no. 6, pp. 889–900, 2017.
[2] C. P. Raut, J. A. Morgan, and S. W. Ashley, "Current issues in gastrointestinal stromal tumors: incidence, molecular biology, and contemporary treatment of localized and advanced disease," Current Opinion in Gastroenterology, vol. 23, no. 2, pp. 149–158, 2007.
[3] K. Søreide, O. M. Sandvik, J. A. Søreide, V. Giljaca, A. Jureckova, and V. R. Bulusu, "Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies," Cancer Epidemiology, vol. 40, pp. 39–46, 2016.
[4] M. Ahmed, "Recent advances in the management of gastrointestinal stromal tumor," World Journal of Clinical Cases, vol. 8, no. 15, pp. 3142–3155, 2020.
[5] S. Hirota, K. Isozaki, Y. Moriyama et al., "Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors," Science, vol. 279, no. 5350, pp. 577–580, 1998.
M. Miettinen and J. Lasota, "Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics," *Polish Journal of Pathology*, vol. 54, no. 1, pp. 3–24, 2003.

H. Joensuu, A. Vehtari, J. Riihimäki et al., “Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts,” *The Lancet Oncology*, vol. 13, no. 3, pp. 265–274, 2012.

M. L. Hemming, M. A. Lawlor, R. Zeid et al., “Gastrointestinal stromal tumor enhancers support a transcription factor network predictive of clinical outcome,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 115, no. 25, pp. E5746–E5755, 2018.

J. M. Sanchez-Hidalgo, M. Duran-Martinez, R. Molero-Payan et al., "Gastrointestinal stromal tumors: a multidisciplinary challenge," *World Journal of Gastroenterology*, vol. 24, no. 18, pp. 1925–1941, 2018.

T. Holmbeak, I. Hompland, B. Bjerkehagen et al., “Recurrence-free survival after resection of gastric gastrointestinal stromal tumors classified according to a strict definition of tumor rupture: a population-based study,” *Annals of Surgical Oncology*, vol. 25, no. 5, pp. 1133–1139, 2018.

B. Vincenzi, M. Nannini, G. Badalamenti et al., “Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors following progression with imatinib, sunitinib and regorafenib,” *Therapeutic Advances in Medical Oncology*, vol. 10, article 175883591879462, 2018.

B. K. Goh, A. Y. Chok, J. C. Allen Jr. et al., “Blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are independent prognostic factors for surgically resected gastrointestinal stromal tumors,” *Surgery*, vol. 159, no. 4, pp. 1146–1156, 2016.

M. Miettinen and J. Lasota, "Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis," *Archives of Pathology & Laboratory Medicine*, vol. 130, no. 10, pp. 1466–1478, 2006.

G. H. Kang, A. Srivastava, Y. E. Kim et al., "DOG1 and PKC-θ are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors," *Modern Pathology*, vol. 24, no. 6, pp. 866–875, 2011.

H. Jonesu, "Risk stratification of patients diagnosed with gastrointestinal stromal tumor," *Human Pathology*, vol. 39, no. 10, pp. 1411–1419, 2008.

B. Al-Share, A. Alloghbi, M. N. Al Hallak et al., "Gastrointestinal stromal tumour: a review of current and emerging therapies," *Cancer Metastasis Reviews*, vol. 40, no. 2, pp. 625–641, 2021.

N. Patel and B. Benipal, "Incidence of gastrointestinal stromal tumors in the United States from 2001–2015: a United States cancer statistics analysis of 50 states," *Cureus*, vol. 11, no. 2, article e4120, 2019.

J. Y. Blay, Y. K. Kang, and T. Nishida, “Gastrointestinal stromal tumours,” *Nature Reviews. Disease Primers*, vol. 7, no. 1, 2021.

B. Zhou, M. Zhang, and S. Yan, "Primary gastrointestinal stromal tumor of the liver: report of a case," *Surgery Today*, vol. 44, no. 6, pp. 1142–1146, 2014.

P. Zemla, A. Stelmach, B. Jabłońska, D. Golka, and S. Mrowiec, "A retrospective study of postoperative outcomes in 98 patients diagnosed with gastrointestinal stromal tumor (GIST) of the upper, middle, and lower gastrointestinal tract between 2009 and 2019 at a single center in Poland," *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, vol. 27, article e932809, 2021.

G. Mantese, “Gastrointestinal stromal tumor,” *Current Opinion in Gastroenterology*, vol. 35, no. 6, pp. 555–559, 2019.

K. Kawanowa, Y. Skuama, and S. Sakurai, "High incidence of microscopic gastrointestinal stromal tumors in the stomach," *Human Pathology*, vol. 37, no. 12, pp. 1527–1535, 2006.

J. A. Crosby, C. N. Catton, and A. Davis, "Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database," *Annals of Surgical Oncology*, vol. 8, no. 1, pp. 50–59, 2001.

R. Logroño, D. Jones, and S. Faruqi, "Recent advances in cell biology, diagnosis, and therapy of gastrointestinal stromal tumor (GIST)," *Cancer Biology & Therapy*, vol. 3, no. 3, pp. 251–258, 2004.

Y. Wang, J. Peng, and J. Huang, "Giant and high-risk gastrointestinal stromal tumor in the abdomino-pelvic cavity: a case report," *Oncology Letters*, vol. 11, no. 3, pp. 2035–2038, 2016.

F. Feng, B. Feng, and S. Liu, "Clinicopathological features and prognosis of mesenteric gastrointestinal stromal tumor evaluation of a pooled case series," *Oncotarget*, vol. 8, no. 28, pp. 46514–46522, 2017.

M. Miettinen, L. H. Sobin, and J. Lasota, "Gastrointestinal stromal tumors of the stomach," *The American Journal of Surgical Pathology*, vol. 29, no. 1, pp. 52–68, 2005.

C. Jumniensuk and M. Charoenpitakchai, "Gastrointestinal stromal tumor: clinicopathological characteristics and pathologic prognostic analysis," *World Journal of Surgical Oncology*, vol. 16, no. 1, p. 231, 2018.

Q. Y. Liu, Y. G. Wang, and L. Kong, "Study on clinicopathological features of gastrointestinal stromal tumor and relevant prognostic factors," *Cell Biochemistry and Biophysics*, vol. 73, no. 3, pp. 743–747, 2015.