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Original Article

Clinico-pathological characteristics and prognostic factors of gastrointestinal stromal tumors among a Chinese population

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Abstract: Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumors of the digestive tract. GISTs include a group of heterogeneous tumors with different morphology, biologic behavior, and genetic characteristics, so their epidemiology, clinico-pathological features and prognosis is distinct in different countries. The objective of this study is to analyze clinico-pathological characteristics and prognostic factors of GISTs among Chinese population. We investigated 112 GIST patients were diagnosed between July 2008 and January 2013 at the First Affiliated Hospital of Guangxi Medical University. Histologic evaluation and immunohistochemistry analysis was performed on paraffin-embedded tissue from the 112 GISTs. Overall survival analysis was carried out using the Kaplan-Meier method and the log-rank test. Multivariate analysis was performed according to Cox's proportional hazards model. Three and 5-year OS rates were 71.4 and 58.6% respectively. Univariate analysis showed that the following factors were significant in predicting OS: tumor site, tumor size, metastasis, resection margin status, cell type, invasion of adjacent organ, invasion of smooth muscle, mitotic rate, P53 and adjuvant therapy with imatinib ($P<0.05$). Multivariate analysis showed that tumor size, metastasis, resection margin status, mitotic rate, P53 and adjuvant therapy with imatinib were independent prognostic factors associated with OS. This may aid in the prediction of clinical evolution and guide treatments in patients with GIST in China.

Keywords: Gastrointestinal stromal tumor, clinical features, pathologic features, prognostic factors

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal tumors of the gastrointestinal tract [1]. Gastrointestinal stromal tumors (GISTs) arise from precursor cells shared with the interstitial cells of Cajal (ICC) [2]. GIST has an estimated annual incidence worldwide of approximately 10-20 per million individuals [3]. GIST has been shown to affect men more than women [4]. The most frequent location is the stomach, followed by the small intestine, colon and rectum and abdominal cavity. Clinical presentations are diverse and largely dependent on tumor size and location. GISTs demonstrate any of the 3 main histologic cell types: spindle cell type, epithelioid cell type, and the mixed spindle-epithelioid type [5]. Estimated 85% of GIST tumors were found to have an active mutation in the *kit* protooncogene while only 3-5% mutation in PDGFRA [6]. Surgery resection remains the primary way of therapy for localized GISTs. In some cases, surgery can be used for advanced metastatic disease after neoadjuvant treatment [7]. Imatinib mesylate is competitive inhibitor of KIT and PDGFRA [8], and inhibits phosphorylation and downstream KIT signaling activation. Most GIST patients will achieve the clinical benefits with imatinib.

GISTs are clinically and morphologically diverse, ranging from benign to malignant, so their biologic behavior is difficult to predict. Tumor size, location, and mitotic index remain the main variables used in risk stratification systems [9]. Surgery resection is the mode of therapy in primary resectable tumors, but all GISTs are still associated with a risk of recurrence. The prognosis for patients with GISTs has improved

Table 1. Clinico-pathological characteristics and results of univariate analysis

	Total cases N (%)	3-year OS (%)	5-year OS (%)	Median Survival Time (months)	χ^2 values	*P* values
Age (years)					0.555	0.456
≥60	29 (25.9)	72.4	65.2	67		
<60	83 (74.1)	71.1	56.5	65		
Sex					0.355	0.551
Male	64 (57.1)	67.2	54.3	64		
Female	48 (42.9)	77.1	64.6	67		
Tumor site					9.141	0.01
Stomach	55 (49.1)	81.8	72.6	69		
Small intestine	42 (37.5)	59.5	42.2	44		
Colorectum	15 (13.4)	66.7	53.3	66		
Tumor diameter (cm)					109.409	<0.001
≤2	18 (16.1)	100	100	83		
>2≤5	21 (18.8)	95.2	95.2	83		
>5≤10	49 (43.8)	75.5	46.1	59		
>10	24 (21.4)	20.8	20.8	14		
Metastasis					80.318	<0.001
Yes	17 (15.2)	11.8	5.9	14		
No	95 (84.8)	82.1	68.1	67		
Operation					97.511	<0.001
R0	83 (74.1)	90.4	75.7	69		
R1or R2	29 (25.9)	17.2	8.6	19		
Cell type					13.589	0.001
Spindle	82 (73.2)	73.2	61.8	67		
Epithelioid	13 (11.6)	84.6	76.9	69		
Mixed	17 (15.2)	52.9	29.4	37		
Invasion of adjacent organ					51.12	<0.001
Yes	15 (13.4)	20	10	14		
No	97 (86.6)	79.4	65.9	67		
Invasion of smooth muscle					6.837	0.009
Yes	101 (90.2)	69.3	46.3	63		
No	11 (9.8)	90.9	90.9	77		
Invasion of mucosa					3.241	0.072
Yes	50 (44.6)	68	51.2	61		
No	62 (55.4)	74.2	64.5	68		
Mitotic rate (/50 HP)					52.637	<0.001
≤5	65 (58.0)	84.6	75.3	73		
6~10	23 (20.5)	73.7	46	51		
>10	24 (21.4)	33.3	23.3	22		
P53					8.9	0.003
Positive	51 (45.5)	58.8	44.6	53		
Negative	61 (54.5)	81.9	70.2	72		
Desmin					0.679	0.41
Positive	17 (15.2)	88.2	75.1	78		
Negative	95 (84.8)	67.4	55.7	65		
SMA					1.876	0.171
Positive	42 (37.5)	71.4	51.6	61		

Negative	70 (62.5)	71.4	62.7	67		
S100					0.828	0.363
Positive	17 (15.2)	82.4	76	72		
Negative	95 (84.8)	69.5	55.7	65		
CD34					1.952	0.162
Positive	82 (73.2)	73.2	61.9	67		
Negative	30 (26.8)	66.7	50	59		
CD117					0.384	0.536
Positive	97 (86.6)	74.2	60.5	66		
Negative	15 (13.4)	53.3	46.7	44		
Adjuvant therapy					75.154	<0.001
Yes	60 (53.6)	91.7	84.8	80		
No	52 (46.4)	48.1	28.8	30		

observably because of clinical practice of targeted therapy with tyrosine kinase inhibitors (TKI). The objectives of the current study were to identify prognostic factors for primary GISTs of different clinical and pathological data among Chinese population.

Materials and methods

This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University and written informed consent was obtained from every participant.

Patient information

112 GIST patients were diagnosed between July 2008 and January 2013 at the First Affiliated Hospital of Guangxi Medical University. The samples were anonymous and without identifying any personal information. All patients underwent surgical resection through an open or laparoscopic approach and the final diagnosis was obtained from the analysis of clinicopathological findings. Surgical excision was the primary treatment in all of the cases. Patient demographics, clinico-pathological characteristics, nature of surgical and medical treatment and postoperative course were reviewed. According to the International Union Against Cancer (UICC) criteria, R0 was defined as a complete macroscopic and microscopic resection, R1 as microscopic evidence of tumor at resection margins and R2 as macroscopic residual tumor at surgery. Follow-up information was collected through direct interview with patients and by review of electronic inpatient records. The complete follow-up was recorded for 108 of the 112 patients. The follow-up period was calculated from the date of primary surgery until tumor-related death. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (No. 2011 KY-022).

Histologic evaluation and immunohistochemistry

112 embedded paraffin blocks of GIST taken from the First Affiliated Hospital of Guangxi Medical University. Hematoxylin and eosin (H&E)-stained of each tumor were evaluated for cell shape. Tumor cells were classified as spindle, epithelioid, or mixed cell type. Mitoses were counted in 50 consecutive highpower fields (HPFs) from the most cellular and mitotically active area. Immunohistochemical staining was performed using the following primary antibodies: P53, CD117, CD34, α-smooth muscle actin (SMA), desmin and S100 protein.

Statistical analysis

Overall survival analysis was carried out using the Kaplan-Meier method and the statistical difference between groups was evaluated using the log-rank test. Multivariate analysis of prognostic factors related to overall survival was performed according to Cox's proportional hazards model. Values of $P<0.05$ were considered to be statistically significant. The statistical analysis was performed using SPSS 17 software (IBM, USA).

Results

112 GIST patients with a median age of 68 years were included in this study. The rate of

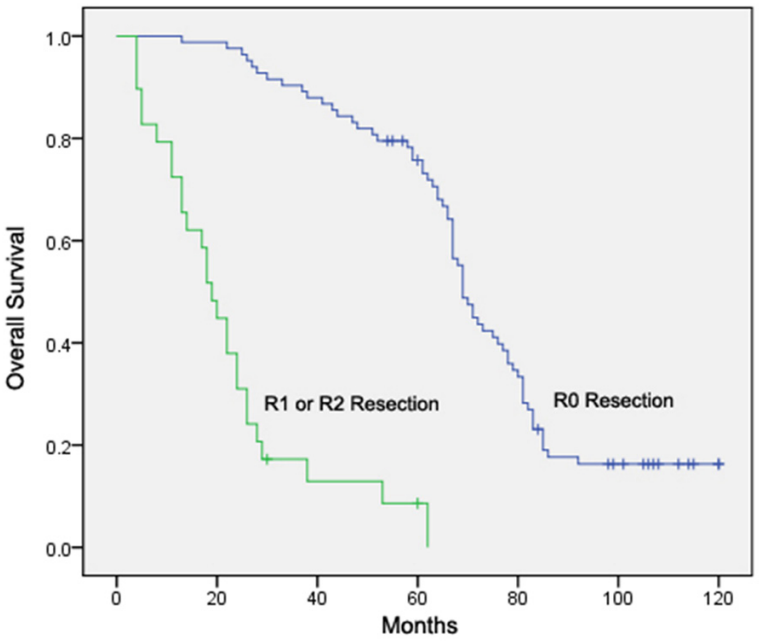

Figure 1. Overall survival analysis according to the resection margins.

male and female patients were 57.1%% (n=64) and 42.9%% (n=48) respectively. The most common presentation is abdominal pain in 35 patients (31.3%) and GI bleeding in 35 patients (31.3%), followed by incidental findings in 24 patients (21.4%), intestinal obstruction in 10 patients (8.9%), weight loss in 10 patients (8.9%) and vomiting in 8 patients (7.1%) respectively. 88% of patients underwent a preoperative endoscopy, and 74% had a preoperative computerized tomography scan to investigate for locally invasive or metastatic disease. 17 patients (15.2%) presented with metastatic disease at initial diagnosis, and the most common site of metastases was liver (n=10), followed by peritoneal cavity (n=6) and intraabdominal lymph nodes (n=1) respectively. 15 patients were found to have an invasion of adjacent organs. 83 patients (74.1%) had R0 resection, 29 patients (25.9%) had R1 or R2 resection. 60 patients (53.6%) received postoperative treatment with imatinib mesylate (Gleevec, Novartis Oncology, USA) (**Table 1**). The usual starting dose of Imatinib is 400 mg per day.

Overall survival analyses

Median overall survival (OS) was 66 months (range 4~120 months, 95% CI) in the study. Three and 5-year OS rates were 71.4 and 58.6% respectively. Survival time did not differ according to age and gender groups (P=0.456 and P=0.551). Gastric tumors was significantly associated with longer survival when compared with small intestine tumors and/or colorectal tumors (69 months vs 44 months for small intestine tumors, 66 months for colorectal tumors; 95% CI; P=0.01). The patients with tumors larger than 10 cm had significantly shortened survival as compared to the patients with smaller tumors (95% CI; P<0.001). The 5-years OS rate for patients with metastasis was 5.9%, which was significantly lower than the 5-years OS for patients without metastasis (68.1%, P< 0.001). Patients who underwent R1 or R2 resection had worse prognosis (3-year OS rate of 17.2%; 5-year OS rate of 8.6%) compared to patients with R0 (3-year OS rate of 90.4%; 5-year OS rate of 75.7%; R0 vs R1 or R2 P<0.001) (**Figure 1**). Patients who received post-operative adjuvant therapy with imatinib mesylate had better outcome than patients who did not (3-year OS rate of 91.7% and 5-year OS rate of 84.8% vs. 3-year OS rate of 48.1% and 5-year OS rate of 28.8%; P<0.001) (**Figure 2**). Epithelioid morphology had significantly longer survival as compared to spindle cell and/or mixed histology (69 months vs 67 months for spindle cell, 37 months for mixed histology; 95% CI; P=0.001). The 5-years OS rate for patients with invasion of adjacent organ was 10.0%, which was significantly lower than the 5-years OS for patients without invasion of adjacent organ (65.9%, P<0.001). Median OS was 63 months in patients with invasion of smooth muscle while it was 77 months in patients without invasion of smooth muscle (P=0.009). Although the 5-year survival rate was lower for patients with invasion of mucosa (51.2 *vs.* 64.5%), were not found statistically significant differences. The patients with tumors with high mitotic rate survived significantly shorter than the patients with tumors with low mitotic rate (95% CI; P<0.001). The three and 5-year OS was significantly worse for

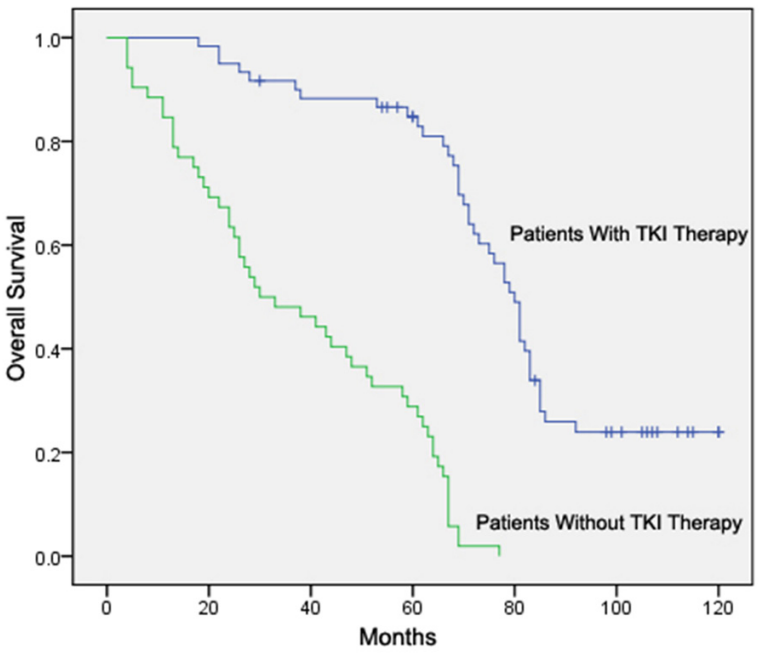

Figure 2. Overall survival analysis according to the adjuvant therapy with imatinib mesylate.

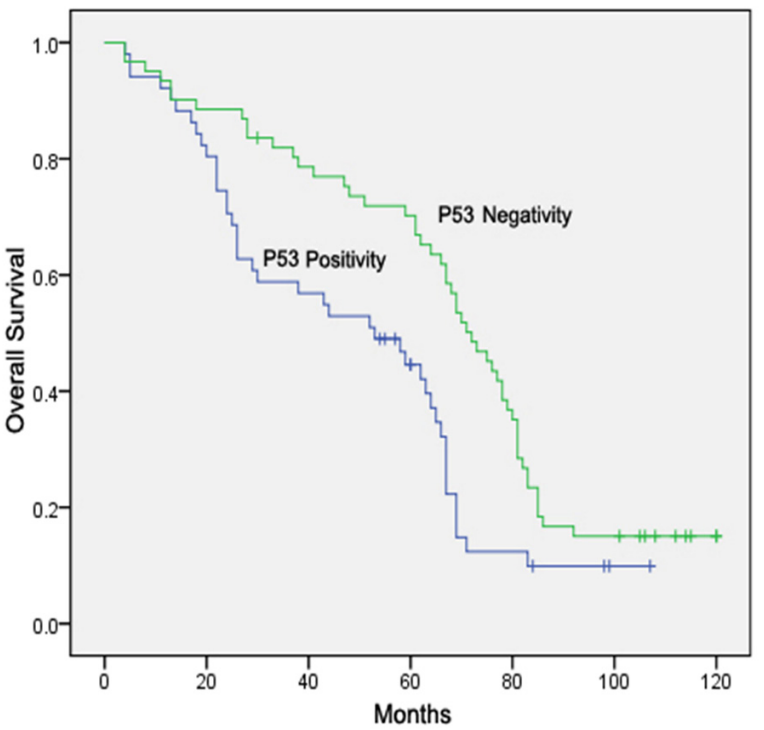

Figure 3. Overall survival analysis according to P53 expression.

patients with P53 positivity (95% CI; P=0.003) (**Figure 3**). No significant difference could be demonstrated statistically in Desmin, SMA, S100, CD34 and CD117 groups (**Table 1**).

The above variables with P<0.05 at univariate analysis (tumor site, tumor size, metastasis, resection margin status, cell type, invasion of adjacent organ, invasion of smooth muscle, mitotic rate, P53 and adjuvant therapy with imatinib mesylate) were included in the Cox's multivariate regression model. Tumor size, metastasis, resection margin status, mitotic rate, P53 and adjuvant therapy with imatinib mesylate were found as independent prognostic factors associated with OS (**Table 2**).

Discussion

GISTs include a group of heterogeneous tumors with different genetic characteristics morphology, and biologic behavior, so their epidemiology, clinical presentation, response to treatment and prognosis is diverse in different districts. The present study focused exclusively on clinico-pathological characteristics and prognostic factors of GISTs among Chinese population.

In our study, GIST predominantly occurred in patients of older age in China. Over 70% of GISTs occurred in old people over 60 years of age. The median age at diagnosis of 68 years was not consistent with that of 55~60 years reported in previous literature [4]. Patients over 60 years of age tended to survive longer than remainder patients, however no significant difference was demonstrated. In the present study, GIST had been shown to occur in men (57.1%) more than women (42.9%). Similarly, gender did not per-

Table 2. Results of multivariate overall survival analysis

	P values	Exp (B)	95% CI
Tumor site	0.344	0.865	0.641~1.168
Tumor size	<0.001	2.478	1.677~3.66
Metastasis	<0.001	0.121	0.039~0.381
Operation	0.004	3.159	1.431~6.976
Cell type	0.326	1.167	0.857~1.588
Invasion of adjacent organ	0.279	0.667	0.320~1.390
Invasion of smooth muscle	0.648	0.802	0.312~2.064
Mitotic rate	0.001	1.734	1.250~2.405
P53	0.025	1.945	1.089~3.476
Adjuvant therapy	<0.001	6.108	2.978~12.528

form a valuable difference in survival rates of GIST patients.

The most common location of GIST was the stomach (49.1%) and small intestine (37.5%), while 13.4% of GISTs occurred in the colon and rectum, in agreement with similar results published by other authors [10]. Tumor site is the leading features that have been widely approved as being predictive of clinical outcome for resected GIST patients [11]. In the present study, tumor origin had an impact on survival of GIST patients (69 months for gastric tumors vs 44 months for nongastric tumors); those originating in the small intestine expressed a more aggressive behavior and higher risk of recurrence. However the multivariate analysis showed that tumor location was not independent prognostic factors associated with OS in this study. In contrast, Miettinen et a. [12] and Demetri et al. [13] consider the tumor location as the basis for risk classification of these tumors. This was likely to be due to the limited number of patient included, not very high but all of them collected in one single center. The tumor size is widely known prognostic factor, as constitutes the basis of GIST risk classification systems. In this study, tumor size had an important negative effect on survival, and the patients with tumors larger than 10 cm survived significantly shorter than the patients with smaller tumors. Miettinen et al. demonstrated that tumor size was the only independent prognostic factor in multivariate analysis for disease-specific survival [14]. Similarly, our multivariate analysis demonstrated that tumor size was the strongest independent predictor for risk of death. Mitotic index is the main variable used in risk stratification systems first developed by the National Institute of health [5]. In this work, we found that the presence of more than 5 mitoses/50 HPF were clearly associated with worse outcome. Wong et al. demonstrated that mitotic rate was also an independent factor in multivariate analysis [15]. Consistent with the literature, our results confirm the importance of mitotic rate as an independent prognostic factor associated with OS. GISTs demonstrate any of the 3 histologic cell types: spindle cell morphology, epithelioid cell morphology, and mixed morphology [16]. The influence of tumor cell morphology on the prognosis was not definite from previous studies. Epithelioid cell type was associated with poor prognosis [17, 18]. In a study, the five-year survival rates were significantly higher in patients with spindle cell type when compared to epithelioid or mixed morphology [19]. However, the 5-years OS rate for patients with epithelioid cell morphology was significantly higher than that for patients with spindle cell or mixed type, in our study. These results could be explained by the relatively small cohort of patients with epithelioid cell morphology. The multivariate analysis showed that tumor cell type was not independent prognostic factors associated with OS. In our work, the most common site of metastases was liver, followed by peritoneal cavity and intraabdominal lymph nodes respectively. GISTs very rarely metastasize to the lymph nodes [20]. The overall survival of the patients with metastasis were significantly shorter than the patients without metastasis; and metastasis was significantly associated with poor outcome.

Surgery is used for tumor which is solitary and can be easily removed. It can be used for advanced metastatic disease for symptomatic relief as well [7]. Positive resection margin status (including R1 and R2 resections) was an adverse factor in OS [21, 22]. Consistent with the literature, we found that the patients with R0 resections had significantly longer survival as compared to those with R1 or R2 resections. However, McCarter et al. [23] observed that no statistically significant difference in OS between R0 resection and R1 resection subgroups. Adjuvant therapy with TKI may also influence OS. Our multivariate analysis demonstrated that resection margin status was still the strongest independent predictor for risk of death. Tyrosine Kinase Inhibitor (TKI) is competitive

inhibitor of KIT and PDGFRA [8], and inhibits phosphorylation and downstream KIT signaling activation. TKI is increasingly used as an adjunct to surgery to achieve dramatic improvements in long-term survival. TKI therapy became more prevalent. The 3 and 5-year OS rates of the patients with imatinib mesylate therapy in our study, which included many patients with metastasis, invasion of adjacent organ and R1 or R2 resection were 91.7% and 84.8% respectively. The patients with imatinib mesylate therapy survived significantly longer than those without TKI therapy. In a trial, the authors observed a 5-year OS of 77% for large primary tumors and 68% for metastatic tumors in patients with imatinib therapy [24]. The OS rates in our work were higher than that of above study. This was likely to be due to our study including many patients with lower risk tumors. Multivariate analysis confirmed that adjuvant therapy with imatinib was an independent prognostic factor associated with OS.

The influence of immunohistochemical markers on the prognosis were researched only in a few number of previous studies. These results were not clear. Liang et al. [25] observed CD34 positive tumors were significantly associated with aggressive behavior. Chirieac et al. [26] revealed no relationship between the expression of desmin, SMA, CD34, S-100 and OS. On our univariate analysis, no significant effect on OS was seen on the following immunohistochemical markers: Desmin, SMA, S100, CD34 and CD117. Conversely, GISTs with P53(+) was significantly associated with shorter survival when compared with the tumors with P53(-). The pathogenesis which GISTs with P53(+) have worse prognosis is not definite. This was likely to be due to P53 gene mutation and dysfunction of P53 protein like gastrointestinal cancer.

In summary, we demonstrated that besides the traditional risk factors of GISTs (tumor size, metastasis and mitotic rate), resection margin status, P53 and adjuvant therapy with imatinib mesylate were the strongest independent predictors for risk of death. We await further multicenter studies to confirm these findings. We envisage that these findings can be use in daily clinical practice, in the future.

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Disclosure of conflict of interest

None.

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