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ORIGINAL ARTICLE

Imatinib therapy after resection of high-risk gastrointestinal stromal tumors in Chinese patients: a median follow-up of 48 months

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Summary

Purpose: *Adjuvant imatinib can be given for gastrointestinal stromal tumors (GISTs), but adequate risk stratification is necessary to select patients who will benefit from this therapy. We aimed to investigate the treatment methods and prognostic factors of high risk GISTs.*

Methods: *This retrospective study included 108 patients who underwent tumor resection for high-risk GISTs between January 2003 and February 2017. The patients were divided into two groups: a group of patients received postoperative imatinib adjuvant therapy (Adjuvant therapy group), and the other group was not treated with imatinib until they were found to have disease progression (Follow-up observation group). The progression-free survival (PFS) and overall survival (OS) were compared between the two groups, and the risk factors of prognosis were analyzed by Cox regression model.*

Results: *The median PFS was 45 months (range 23-67). The 1-, 3-, and 5-year PFS was 88.6, 70.4 and 59.0%, respectively. The PFS in the adjuvant therapy group was longer than in the follow-up observation group (p<0.001). The median OS was 117 months (range 93-141). The 1-, 3-, and 5-year OS was 97.0, 87.7 and 77.4%, respectively. There was no difference in OS between the two groups (p=0.737). Intra-operative tumor integrity (p=0.003) and postoperative adjuvant treatment (p<0.001) were independent prognostic factors of PFS. R0 resection (p=0.019) and low mitotic count (≤5/50 HPF) (p=0.031) were independent prognostic factors of OS.*

Conclusions: *Avoiding intra-operative tumor rupture and administering postoperative adjuvant imatinib treatment improved PFS in patients with high-risk GISTs. Low mitotic count and R0 resection were associated with better survival.*

Key words: *gastrointestinal stromal tumor, imatinib, overall survival, progression-free survival, surgery*

Introduction

Gastrointestinal stromal tumors (GISTs) are rare tumors of gastrointestinal mesenchymal (non-epithelial) origin [1]. GISTs may also arise from other intra-abdominal soft tissues [2]. About 50-60% of the GISTs are in the stomach and 30-35% in the small intestine [1,2]. Men and women are equally affected and 80% of the patients with GISTs are over 50 years old (median 63 years) [1,3]. The global prevalence is around 130 per 1,000,000 people, but geographical variations are noted: the incidence is 10 per 1,000,000 person-year in Europe and 16-22 per 1,000,000 person-year in Korea and China [1]. Most cases of GISTs are sporadic, but they may be associated with some familial multitumor syndromes like neurofibromatosis type 1, familial GIST syndrome, Carney-Stratakis

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syndrome, and Carney triad [1]. Activating mutations of KIT and PDGFRA could play some role in the pathogenesis of GISTs [2].

An important problem for GIST management is that their malignant potential may vary from benign tumors to aggressive sarcomas associated with disseminated metastases [2,4]. The traditional method for risk assessment is based on tumor size and mitotic count (NIH consensus classification system) [5]. Novel risk factors (including tumor histology, high cellularity, tumor ulceration, mucosal invasion, presence of KIT/PDGFRA mutations, tumor necrosis, and tumor rupture, among others [4,6-8]) are being described and could improve tumor classification and risk assessment, but studies are necessary to assess their exact contribution to prognosis [4].

Imatinib, a tyrosine kinase inhibitor (TKI), has been shown to improve survival in patients with unresectable or metastatic GISTs [9,10]. The ACOSOG Z9001 trial showed a better recurrence-free survival for patients who received adjuvant imatinib 400 mg/d for 1 year after surgery [10]. Nevertheless, because of the high cost of the drug and adverse effects, adequate risk stratification is necessary to select patients who will benefit the most from the therapy.

Small GISTs are usually treated with resection alone if they present high-risk endoscopic ultrasound features or are followed-up if they do not present these features [11]. In resectable GISTs >2 cm, surgery can be performed if there is no significant risk of morbidity or if the patient is bleeding or symptomatic, followed by adjuvant therapy for high- or intermediate-risk GISTs [11]. Guidelines agree that GISTs with mutated KIT or PDGFRA (excepted the D842V mutation) should receive adjuvant TKI, but there is no consensus for GISTs with wild-type KIT or PDGFRA [3,11]. Currently, for patients who received neoadjuvant imatinib, it is recommended to continue the treatment after surgery. In addition, adjuvant TKI is recommended only for intermediate- or high-risk GISTs, or in case of recurrence or metastasis [3,11]. Nevertheless, better risk stratification and patient selection are necessary.

Therefore, the aim of the present study was to examine the survival and risk factors of Chinese patients with high-risk GISTs. The results of this study could help plan a better selection of patients for adjuvant TKI administration.

Methods

This was a retrospective cohort study of 108 patients diagnosed with high-risk GIST. The patients were enrolled between January 2003 and February 2017 at the Department of Gastrointestinal Surgery of the affiliated Cancer Hospital of Xinjiang Medical University. According to the revised NIH risk classification system by Joensuu et al. [4], the primary tumor site and tumor rupture were both considered as the basic evaluation indexes for prognosis. Patients were included if they met the following criteria: 1) age over 18 years; 2) diagnosed with primary GIST by histopathology and immunohistochemistry; 3) absence of distant metastasis; 4) postoperative high-risk; and 5) complete available follow-up data. The exclusion criteria were: 1) 5 years medical history of any other malignancy; or 2) any serious concomitant diseases that might affect survival.

This study was approved by the ethics committee of the affiliated Cancer Hospital of Xinjiang Medical University. Informed consent was waived by the committee because of the retrospective nature of the study.

The patients were divided into two groups according to whether they received adjuvant therapy after surgery or not: 1) adjuvant therapy group (69 patients received adjuvant imatinib within one month after surgery); and 2) follow-up observation group (39 patients did not receive imatinib until they were found to have disease progression). Disease progression was defined as the emergence of new lesions in the surgical area and/or distant organ, as confirmed by imaging examinations.

In the adjuvant therapy group, the patients received oral imatinib for at least 3 years with an initial dose of 400 mg/d. Once the patient suffered recurrence or metastasis, the dose of imatinib was increased to 600 mg/d, or changed to sunitinib as second-line treatment. In the follow-up observation group, the patients were followed up. When the patient suffered from recurrence or metastasis, they received imatinib with an initial dose of 400mg/d. In case of disease progression, the dose was increased to 600 mg/d or changed to sunitinib for second-line treatment.

The baseline characteristics of the patients were collected, including demographic characteristics (gender and age) and clinical/pathological features (symptoms at admission, tumor location, radical resection, tumor diameter, mitotic count, and intra-operative tumor rupture).

The patients were followed up every 3 months during the first year after surgery, then every 6 months from the second to fifth year, and once every year thereafter. Follow-up was censored in March 2017. Patients were followed up by outpatient visit, hospital review treatment, or telephone. Patient survival and disease progression were collected during follow-up. PFS was defined as the time from surgery to the date of disease progression or death caused by any reason. OS was defined as the time from surgery to death or follow-up completion. Patients were examined by B-mode ultrasound, CT or MRI, according to their condition during follow-up.

Statistics

Continuous variables were presented as mean± standard deviation (SD). Categorical variables were expressed as n (%) and analyzed by the chi-square test or

the Fisher exact test, as appropriate. The Kaplan-Meier method was used to analyze PFS and OS. Differences in PFS and OS between groups were detected using the log-rank test. Multivariate Cox regression analysis was used to identify the independent factors associated with prognosis. SPSS 21.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Two-sided p-values <0.05 were considered to indicate statistical significance.

Results

Table 1 presents the characteristics of the patients and shows no differences between the two groups. Among the 108 patients with high-risk GIST, there were 51 males and 57 females; median age was 58 years (range 27-82). The locations of the tumors were: 41 (38.0%) in the stomach, 8 (7.4%) in the duodenum, 40 (37%) in the jejuno-ileum, 4 (3.7%) in the rectum, 9 (8.3%) in the mesentery, 3 (2.8%) in the retroperitoneum, and 3 cases in the omentum major, colon, and esophagus, respectively (0.9%). Of them, tumor types included 80 (74.1%) cases of fusiform cells, 20 (18.5%) cases of epithelioid cells, and 8 (7.4%) cases of mixed cell types of fusiform and epithelioid cells. Mean tumor size was 11.1±5.9 cm with a range of 2.5-37.0 cm. There were 44 (40.7%) cases with mitotic counts ≤5 from 50 randomly selected high-power fields (HPF), 64 (59.3%) cases with mitotic counts >5 from 50 random HPF. Immunohistochemistry showed that the positive rate of CD117 expression was 95.4% (103/108), the positive rate of CD34 expression was 71.3% (77/108) and the positive rate of DOG1 was 89.3% (42/47).

All patients completed the follow-up. The median follow-up time was 48 months (range 1-161). Fifty-eight (53.7%) patients developed postoperative recurrence and/or metastasis; 20 (18.5%) patients had hepatic metastasis, 25 (23.1%) had abdominal and pelvic metastases, and 13 (12%) had hepatic, abdominal, and pelvic metastases. In the adjuvant therapy group, 24 patients (34.8%) developed recurrence and metastasis. In the follow-up observation group, 34 patients (87.2%) developed recurrence and metastasis, and the recurrence rate was higher than that in the adjuvant therapy group (p<0.001).

Table 1. Patient characteristics

Characteristics	*Adjuvant therapy group n (%)*	*Follow-up observation group n (%)*	*p value*
Gender			0.815
Male	32 (46.4)	19 (48.7)	
Female	37 (53.6)	20 (51.3)	
Age (years)			0.780
<60	37 (53.6)	22 (56.4)	
≥60	32 (46.4)	17 (43.6)	
Symptom on admission			0.624
Abdominal pain	32 (46.4)	20 (51.3)	
Non-abdominal pain	37 (53.6)	19 (48.7)	
Tumor site			0.246
Stomach	27 (39.1)	14 (35.9)	
Small intestine	33 (47.8)	15 (38.5)	
Others	9 (13.0)	10 (25.6)	
Degree of radical surgery			0.832
R0	61 (88.4)	35 (89.7)	
R1 and R2	8 (11.6)	4 (10.3)	
Tumor diameter, cm			0.373
≤5	7 (10.1)	4 (10.8)	
>5 and ≤10	34 (49.3)	14 (35.9)	
>10	28 (40.6)	21 (53.8)	
Mitotic count (/50HPF)			0.964
≤5	28 (40.6)	16 (41.0)	
>5	41 (59.4)	23 (59.0)	
Intra-operative tumor rupture			0.331
Yes	22 (31.9)	9 (23.1)	
No	47 (68.1)	30 (76.9)	

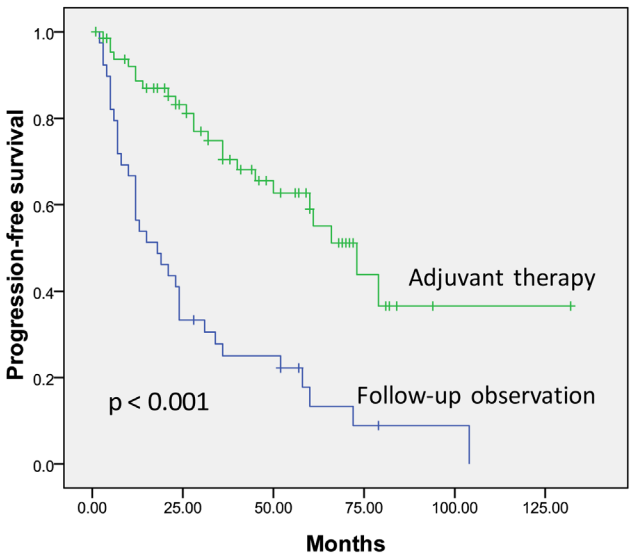

Figure 1. Comparison of the progression-free survival of patients in the adjuvant therapy group and follow-up observation group (p<0.001).

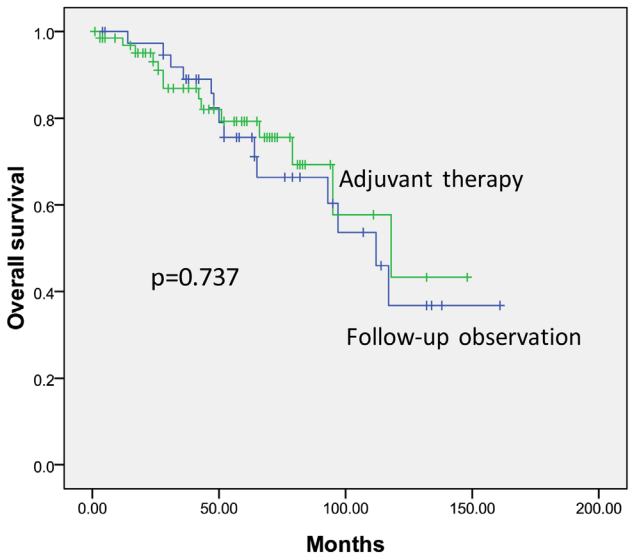

Figure 2. Comparison of the overall survival of patients in the adjuvant therapy group and follow-up observation group (p=0.737).

Table 2. Univariate analysis of progression-free survival

Characteristics	*n (%)*	*Median survival (months)*	*p value*
Gender			0.055
Male	51 (47.2)	36	
Female	57 (52.8)	60	
Age (years)			0.923
<60	59 (54.6)	45	
≥60	49 (51.9)	50	
Symptom on admission			0.154
Abdominal pain	52 (48.1)	45	
Non-abdominal pain	56 (51.9)	61	
Tumor site			0.155
Stomach	41 (38.0)	72	
Small intestine	48 (44.4)	40	
Others	19 (17.6)	28	
Degree of radical surgery			0.001
R0	96 (88.9)	58	
R1 and R2	12 (11.1)	21	
Tumor diameter, cm			0.213
≤5	11 (10.2)	34	
>5 and ≤10	48 (44.4)	73	
>10	49 (45.4)	36	
Mitotic count (/50HPF)			0.392
≤5	44 (40.7)	52	
>5	64 (59.3)	40	
Intra-operative tumor rupture			0.005
Yes	31 (28.7)	31	
No	77 (71.3)	58	
Postoperative adjuvant therapy			<0.001
Yes	69 (63.9)	73	
No	39 (36.1)	18	

Among the 108 patients, the median PFS was 45 months (range 23-67). The 1-, 3-, and 5-year PFS was 76.2, 52.0, and 40.0%, respectively. In the adjuvant therapy group, the median PFS was 73 months (range 52-94). The 1-, 3-, and 5-year PFS was 88.6, 70.4, and 59.0%, respectively. In the surgery+follow-up group, the median PFS was 18 months (range 7-29). The 1-, 3-, and 5-year PFS was 56.4, 25.0, and 13.3%, respectively. The difference between the two groups was significant (p<0.001; Figure 1). The median OS of the 108 patients was 117 months (range 93-141). The 1-, 3-, and 5-year OS was 97.0, 87.7, and 77.4%, respectively . In the adjuvant therapy group, the median OS was 118 months (range 69-167). The 1-, 3-, 5-, and 5-year OS was 96.8, 86.9, and 79.3%, respectively. In the follow-up observation group, the median OS was 112 months (range 89-135). The 1-, 3-, and 5-year OS was 97.3, 89, and 75.6%, respectively. There was no difference of OS between the two groups (p=0.737; Figure 2).

The Kaplan-Meier analysis showed that the degree of radical resection (p<0.001), intra-operative tumor rupture (p=0.005), and postoperative adjuvant therapy (p<0.001) were the factors influencing PFS (Table 2). The multivariate Cox regres-

Table 3. Multivariate analysis of progression-free survival

Variables	*β*	*HR*	*95%CI*	*p value*
Degree of radical surgery (R0 vs R1 and R2)	-0.523	0.593	0.298-1.177	0.135
Intra-operative tumor rupture (no/yes)	-0.915	0.400	0.219-0.731	0.003
Postoperative adjuvant treatment (yes/no)	-1.392	0.249	0.144-0.429	0.000

HR: hazard ratio, CI: confidence interval

Table 4. Univariate analysis of overall survival

Characteristics	*n (%)*	*Median survival (months)*	*p value*
Gender			0.415
Male	51 (47.2)	95	
Female	57 (52.8)	117	
Age (years)			0.403
<60	59 (54.6)	117	
≥60	49 (45.4)	97	
Symptom on admission			0.801
Abdominal pain	52 (48.1)	117	
Non-abdominal pain	56 (51.9)	112	
Tumor site			0.954
Stomach	41 (38.0)	97	
Small intestine	48 (44.4)	112	
Others	19 (17.6)	117	
Degree of radical surgery, n (%)			<0.001
R0	96 (88.9)	>161	
R1 and R2	12 (11.1)	31	
Tumor diameter, cm			0.755
≤5	11 (0.2)	>148	
>5 and ≤10	48 (44.4)	112	
>10	49 (45.9)	117	
Mitotic count (/50 HPF)			0.012
≤5	44 (40.7)	>134	
>5	64 (59.3)	95	
Intra-operative tumor rupture			0.049
Yes	31 (28.7)	118	
No	77 (71.3)	112	
Postoperative adjuvant therapy			0.737
Yes	69 (63.9)	118	
No	39 (36.1)	112	

Table 5. Multivariate analysis of overall survival

Variables	*β*	*HR*	*95%CI*	*p value*
Degree of radical surgery (R0 vs R1 and R2)	-1.048	0.351	0.147-0.840	0.019
Mitotic count (/50 HPF) (≤5 vs >5)	-1.088	0.337	0.125-0.906	0.031
Intra-operative tumor rupture(no/yes)	-0.515	0.597	0.257-1.387	0.231

HR: hazard ratio, CI: confidence interval

sion analysis showed that intra-operative tumor integrity (HR:0.400; 95%CI:0.219-0.731; p=0.003) and postoperative adjuvant treatment (HR:0.249; 95%CI:0.144-0.429; p<0.001) were independent predictive factors of PFS (Table 3). Table 4 presents the factors associated with survival. The results showed that the survival of patients with R0 radical resection was significantly longer than for patients with R1 or R2 radical resection (>161 vs. 31 months, p<0.001). Mitotic count (p=0.012) and intra-operative tumor rupture (p=0.049) were factors influencing OS. The multivariate Cox regression analysis showed that R0 resection (HR:0.351; 95%CI:0.147-0.840; p=0.019) and low mitotic count (≤5/50 HPF) (HR:0.337; 95%CI:0.125-0.906; p=0.031) were independent predictive factors of OS (Table 5).

Discussion

Adjuvant imatinib can be given after surgery for GISTs, but adequate risk stratification is necessary to select patients who will benefit the most from this therapy [4]. Therefore, this study aimed to examine the survival and risk factors of Chinese patients with high-risk GISTs. The results suggest that avoiding intra-operative tumor rupture and administering postoperative adjuvant imatinib treatment improved PFS in Chinese patients with high-risk GISTs. Low mitotic count and R0 resection were also associated with better survival.

The original GIST risk classification was based on an expert consensus, but evidence accumulated over the years has shown large tumor size and high mitotic count are associated with poor prognosis [6-8,12-22]. Nevertheless, although some studies showed that tumor size was associated with GIST prognosis, the size cut-off varied among these studies: 5 cm [6,13,19,20], 8 cm [12], and 10 cm [7,14-18,21], while some other studies showed no association between tumor size and prognosis [8,22]. Most of these studies showed associations between mitotic count and prognosis, but once again with variable cut-off points [6-8,12-14,16,19-22], while some did not reveal such an association [15,17,18]. In the present study, mitotic count, but not tumor size, was independently associated with OS. Surgical resection is still the main treatment of GISTs, and the extend of radical surgery is undoubtedly an important factor in the prognosis of patients with GISTs. Wu et al. [23] showed that the 5-year survival rate for complete resection of GISTs (n=331) was higher than that of palliative resection (n=35) (73.4 vs 33.1%, p<0.05), and multivariate analysis showed that complete resection was an important predictive factor in the prognosis of GISTs (p=0.044). In the present study, the results also support such a conclusion.

Of course, the original NIH classification is somewhat limited since it does not include a long list of potential risk factors, such as tumor rupture, which has been shown to be a strong adverse prognostic factor [24]. Symptomatic patients at presentation have a poor 5-year disease-specific survival [25]. Singer et al. [8] showed that GISTs with mixed cell histology had a poor prognosis, while Koay et al. [18] showed that pure epithelioid histology had poor survival. Other small series suggested that high cellularity, tumor necrosis, mucosal invasion, non-gastric primary tumor site [7,21], and R1/R2 resection [8] were associated with poor prognosis. In the present study, tumor intra-operative rupture or not was independently associated with PFS. In our study, beside the classical NIH risk criterion of low mitotic count, R0 resection was independently associated with better OS, while adjuvant imatinib was independently associated with better PFS. These results are supported by a number of previous studies [6-8,12-14,16,19-22]. It has to be noted that R0 resection is possible in only about 85% of the cases, prompting the need for systemic treatments [15,26,27].

Concerning imatinib, phase II and III studies consistently reported high overall response rates and good PFS in patients with unresectable or metastatic GISTs, resulting in an objective response in >50% of the patients [9,28-31]. The S0033/CALGB trial showed that increasing the dose of imatinib upon disease progression showed disease stabilization that resulted in similar survival compared to patients who did not progress [31]. In the adjuvant setting, the B2222 trial confirmed that imatinib controls advanced GIST [32]. The ACOSOG Z9001 trial showed that imatinib 400

mg/d for 1 year resulted in improved recurrence-free survival (RFS) compared to the placebo arm [33]. The SSGXVIII/AIO trial examined imatinib treatment for 36 vs 12 months for patients with high-risk GISTs (according to the NIH criteria) and showed that patients who received the 36-month regimen had better RFS and OS [34]. In the present study, patients with high-risk GIST treated with imatinib after surgery had a better PFS compared to those who were not, which indicated that adjuvant therapy after surgery with imatinib could significantly improve PFS of patients with high-risk GISTs, while there was no difference in OS between the two groups, implying that intensive post-surgery follow-up and imatinib treatment immediately as soon as recurrence and/or metastases occurred for patients in the follow up observation group were crucial prognostic factors of survival.

Because imatinib is expensive and is associated with toxicities [35], adequate selection of patients is of prime importance. Additional studies are still necessary to address this issue.

The present study is not without limitations. The sample size was limited and from a single center. In addition, because of the retrospective nature of the study, some factors could not be assessed because they had not been evaluated as part of the clinical management of the patients. Finally, the *KIT* and *PDGFFRA* mutations could not be evaluated in the present study. Additional studies are still necessary to address these issues.

Conclusions

In conclusion, avoiding intra-operative tumor rupture and administering postoperative adjuvant imatinib treatment improved PFS in Chinese patients with high-risk GISTs. Low mitotic count and R0 resection were also associated with better survival. These results could provide further insights for the adequate selection of patients for adjuvant imatinib treatment.

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Conflict of interests

The authors declare no conflict of interests.

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