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ORIGINAL ARTICLE

The risk factors about prognosis of 142 GIST patients with recurrence or metastasis: A retrospective study of single centre in Northern China

Yong Li, Bibo Tan, Haifeng Wu, Haisong Xin, Liqiao Fan, Qun Zhao, Zhixue Ma, Yü Liu

Department of General Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei 050011, P.R.China

Summary

Purpose: *In this retrospective study, we investigated the clinicopathologic features, prognosis as well as the factors contributing to prognosis of patients with metastatic or recurrent gastrointestinal stromal tumors (GISTs).*

Methods: *A total 142 GIST patients with confirmed metastasis or recurrence with complete clinicopathologic and prognostic data were enrolled as research group, and 278 GISTs patients without metastasis or recurrence as control group between June 2003 and June 2013.*

Results: *Significant differences between research group and control group were revealed, including gender, age, primary tumor sites, tumor diameter, mitosis rate, CD117 expression, risk level, treatment methods and surgical types ($p<0.05$). Univariate survival analysis suggested that factors with significant influence on prognosis were tumor primary site, tumor diameter, mitosis rate, tumor progression (recurrence or metastasis), and treatment methods ($p<0.05$). Multivariate survival analysis demonstrated that mitosis and treatment methods were independent prognostic factors for GIST patients with metastatis or recurrence.*

Conclusion: *Some factors contributed significantly to the prognosis of GIST patients with metastatis or recurrence, and the combination of surgery and targeted agent should be selected for these patients to improve prognosis.*

Key words: *gastrointestinal stromal tumor, metastasis, prognosis, recurrence, risk factors, treatment*

Introduction

GISTs are the most common digestive mesenchymal tumors with various degrees of malignant potential in different risk levels [1]. Since GISTs have unique clinicopathological features [2,3], which are different from other tumors, most current researches for GIST treatment have been focusing on the GIST clinicopathological features and have made significant progress. Especially, the use of the targeted agent Imatinib mesylate has significantly improved the GIST prognosis [4]. With increasing numbers for GISTs, researchers have now more comprehensive understanding of primary biological characteristics and prognosis of GISTs [5,6], resulting in comprehensive GIST treatments including surgery and targeted agent Imatinib based on the pathology reports [7,8].

However, a number of GIST patients still suffer from recurrence and/or metastasis, which leads to patients' death despite this comprehensive treatment [9].

In this study, we retrospectively analyzed the biological characteristics and prognosis of 142 GIST patients with recurrence or metastasis in our hospital and the prognostic risk factors were also investigated, which provided clues for the appropriate treatment for the recurrent or metastatic GIST patients.

Correspondence to: Yong Li, PhD. Department of General Surgery, the Fourth Hospital of Hebei Medical University, 12 Jiankang Rd, Shijiazhuang, Hebei 050011, P.R. China.
Tel: +86 311 86095678, Fax: +86 311 86077634, E-mail: li_yong_hbth@126.com, 1223041227@qq.com
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Methods

Patients

A total of 420 patients confirmed as GIST were collected between June 2003 and June 2013 in the Fourth Hospital of Hebei Medical University, and all of these patients had complete clinical and pathological records. 142 GIST patients with metastasis or recurrence composed the research group, while 278 GIST patients without recurrence or metastasis composed the control group. The biological characteristics and the follow-up of both groups were recorded and a database was created. Informed consents were obtained from all participants and this study has been approved by the Medical Ethics Committee of the Fourth Hospital, of Hebei Medical University.

Data collection

The data of research and control group, including general patient condition, clinical manifestations, tumor biology characteristics, risk levels, the sites of tumor recurrence and metastasis and treatment methods, were documented. Meanwhile, the clinical features, prognosis and risk factors of the research group were recorded and analyzed.

Follow-up

After surgery, patients were followed-up once per month, and the closing date of the follow up was June

Table 1. Biological characteristics of research and control group

Characteristics	*Research group (142)* *n*	*Control group (278)* *n*	x^2	*p*
Gender				
Male	85	131	6.104	0.014
Female	57	147		
Age, years				
≥55	76	178	4.342	0.037
<55	66	100		
Locations of primary lesions				
Stomach	42	193	61.615	<0.001
Small intestine	52	40		
Colorectum	6	8		
Other sites	42	37		
Diameter (cm)				
<5	8	122	95.562	<0.001
5-10	58	116		
>10	76	40		
Mitotic number (HPF)				
<5/50	27	142	52.685	<0.001
05/10-10/50	66	105		
>10/50	49	31		
Results of immunohistochemistry				
CD34 (positive/negative)	131/13	248/30	0.322	0.570
CD117 (positive/negative)	135/9	235/43	7.460	0.006
DOG1 (positive/negative)	43/0	82/1	0.522	0.470
Risk degree (NIH)				
Very low	0	44	112.455	<0.001
Low	3	49		
Intermediate	6	76		
High	130	109		
Therapeutic methods				
Operation	120	199	17.048	<0.001
Targeted drug	2	0		
Operation + Targeted drug	19	79		
Other	1	0		
Operative methods				
Radical	113	278	59.159	<0.001
Non- radical	28	0		

2013. The research group follow-up period was 1-120 months with a 29-month median follow-up period. The control group follow-up period was 2-120 months with a 34-month median follow-up period. The follow-up rate was 100%. All patients were followed-up with regard to postoperative treatment, metastasis, recurrence and survival via phone, mail and outpatient visits. Tumor recurrence, metastasis, the timing of metastasis or recurrence and the survival were recorded.

Statistics

SPSS 21.0 statistical software package was utilized. The continuous data (PFS and OS) are shown as mean±standard deviation (SD) and numerical data (eg, gender, age, primary tumor site, tumor diameter, mitotic index) are shown as percentages. Univariate survival analysis investigated the association between research data and patients' prognosis, then the independent prognostic risk factors were investgated using Cox's proportional hazards regression model. $p<0.05$ was considered to be significant.

Table 2. Locations of recurrence, metastasis and therapeutic measures in research group

	Cases n (%)
Locations of recurrence (34)	
Stomach	4 (11.76)
Small intestine	13 (38.24)
Colorectum	3 (8.82)
Other sites	14 (41.18)
Locations of metastasis (108)	
Liver	56 (51.85)
Abdominopelvic cavity	32 (29.63)
Liver + abdominopelvic cavity	16 (14.82)
Other sites	4 (3.70)
Therapeutic measures (142)	
Operation	3 (2.11)
Operation + targeted drug	16 (11.27)
Targeted drug	76 (53.52)
Follow-up only	47 (33.10)

Results

Clinicopathologic features of the research group patients after the initial treatment

The research group included 85 males and 57 females and their ages ranged from 23 to 84 years (median 55.6). The control group included 131 males and 147 females with ages ranging from 14 to 82 years (median 58.0). Abdominal discomfort, abdominal distension, abdominal mass, hematemesis, melena and anemia appeared in both patient groups. There were significant differences between the 2 groups in terms of gender, age, primary tumor site, tumor diameter, mitoses, CD117 expression, risk level (National Institutes of Health Classification 2008), treatment method and types of operation ($p<0.05$) (Table 1).

Data for GISTs with metastasis or recurrence in the research group

According to CT imaging results, the research group could be divided into two subgroups with 34 cases of local recurrence and 108 cases of distant metastasis. Among of the local recurrence subgroup, the sites were stomach (4 cases) small intestine (13 cases), colorectal (3 cases) and other sites (13 cases). For the distant metastasis subgroup, 56 cases had liver metastasis, 32 abdominal-pelvic cavity metastasis (7 cases of peritoneal, 21 cases of abdominal organs, 4 cases of pelvic metastasis, 16 cases with combination of liver and abdominal pelvic-cavity metastasis and 4 cases with other metastases (1 case with bone metastasis, 1 with neck metastasis, 1 with mediastinal metastasis, 1 with combination of neck and brain metastases).

In the research group, after metastasis or recurrence, 76 cases (53.52%) were treated with oral Imatinib mesylate only, 3 cases (2.11%) were subjected to surgery alone, 16 cases (11.27%) were treated with surgery and Imatinib mesylate combined, and 47 cases (33.10%) had only follow-up (Table 2).

Table 3. Results of multivariate analysis for survival of GIST patients

Variables	*B*	*SE*	*Wald*	*df*	*Sig*	*Exp(B)*	*95%CI for Exp(B)*	
							Lower	*Upper*
Locations of primary lesions	0.256	0.136	3.521	1	0.061	1.292	0.989	1.688
Diameter	0.225	0.320	0.494	1	0.482	1.252	0.669	2.342
Mitotic number	0.494	0.251	3.858	1	0.050	1.638	1.001	2.681
Recurrence or metastasis	1.027	0.433	5.633	1	0.018	2.794	1.196	6.527
Therapeutic measures	0.773	0.157	24.153	1	0.000	2.166	1.592	2.948

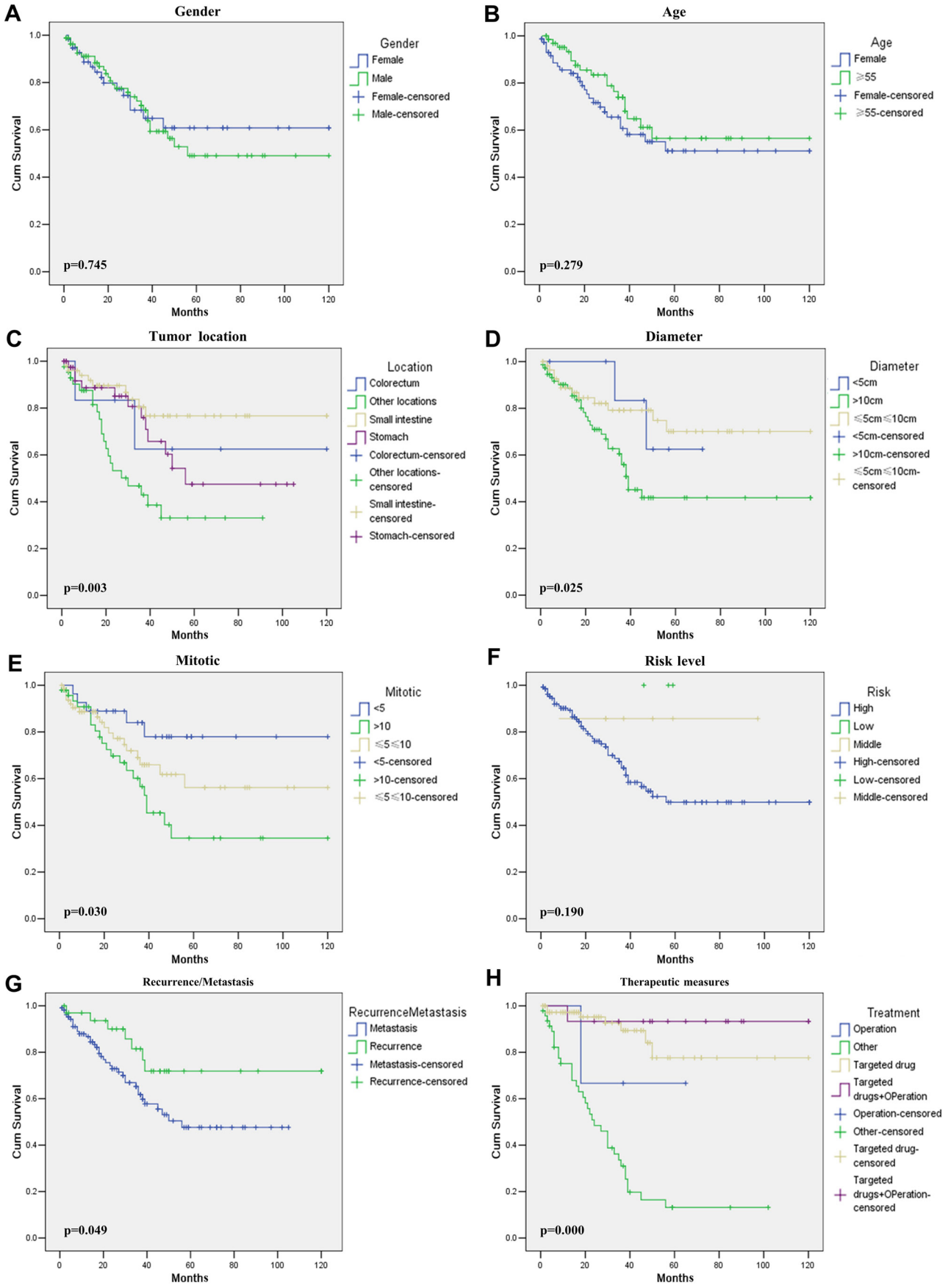

Figure 1. Result of the univariate survival analysis about factors contributing to prognosis of patients with metastatic or recurrent GIST. Results of Kaplan-Meier curve analysis indicated that factors contributing to prognosis are described in this Figure. It was demonstrated that primary tumour site, tumour diameter, mitotic number, tumor progression (recurrence or metastasis) and therapeutic measures were factors contributing to prognosis ($p<0.05$).

Survival analysis in the research group

Forty-four out of 142 patients passed away after a median of 19.5 months at the end of follow-up, with a death rate of 30.99% (44/142). Progression-free survival (PFS) ranged from 0 to 0.9 months (median 11.61). Overall survival (OS) ranged from 1-120 months (median 48).

Univariate survival analysis

The results showed that gender, age, and risk level were not related to patients' prognosis (p=0.745, p=0.279, p=0.190, respectively). The factors contributing to prognosis were: primary tumor site, tumor diameter, mitotic index, tumor progression (reccurence or metastasis) and treatment method (p=0.003, p=0.025, p=0.030, p=0.049, and <0.001, respectively) (Figure 1).

Multivariate survival analysis

Multivariate survival analysis demonstrated that tumor progression pattern (recurrence or metastasis) and treatment method were independent risk factors influencing the prognosis of the research group patients (p=0.018, <0.001, respectively) (Table 3).

Discussion

GISTs are the most common mesenchymal tumors in digestive tract and can be found in any parts of the tract [10]. Since the GIST-related morbidity constantly increases [11], and all GISTs bear malignant potential, there is a high risk of metastasis or recurrence even after treatment [12]. Therefore, GISTs have become recently a focus in the gastrointestinal tumor research. Many reports have highlighted the prognosis [13] and treatment methods [14] of GISTs and suggested that GIST should be surgically removed, accompanied with targeted agents as necessary [15].

However, reports about the GIST biological characteristics, prognosis and treatment methods are still rare. Therefore, in this study we made a comprehensive investigation which concentrated on these aspects. Comparison of patients in the research and the control group showed that males and over 55-year-old with metastasis or relapse were more in the research group. The percentage of patients with gastric primary site was less than those in the control group. The results also showed that patients in the control group had larger tumor diameter, more mitoses and higher risk levels. Immunohistochemistry demonstrated that the positive rate of CD117 in the research group was higher than those in the control group. However, there was a similarity between the two groups regarding the positive rate of CD34 and DOG1. These results suggested that the risk factors related to recurrence and metastasis should be considered when GIST patients were diagnosed and treated because of the higher risk factors that the patients have and it seems more likely the tumor will recur and metastasize. Our study also found that the biological characteristics of the research group were consistent with the results of other reports [16,17]. Another result of this study was that the percentage of male and older patients in the research group was higher than in the control group, and this also was in accordance with the research result of Kramer et al. [18]. CD117 is a protein encoded by c-kit gene, and this research found that mutation may be one of the risk factors that can lead to poor prognosis of GIST patients [19,20]. This study also found that positivity of CD117 in the research group was higher than in the control group, which is consistent with other report [21].

In order to understand the prognosis of recurrent and metastatic GIST and the risk factors, this research analyzed the association between different factors and prognosis. The death rate of GIST patients with metastasis or recurrence was 30.99%, the median PFS was 11.61 months and the median OS was 48 months. The death rate of patients with recurrent or non-resectable GIST reported by Dip Borunda et al. [22] was 32.39% (23/71), which was similar to the result of this study. However, both our study and the study of Dip Borunda et al. [22] were single-centre studies with limited sample size and we believe it is apparent that larger sample studies are needed. The analysis of the present research about the relationship between the tumor site and patient prognosis suggested that GIST patients with primary small intestine lesion had an optimal outcome, followed by stomach, colorectal and gastrointestinal tract localizations. On the contrary, some other reports argued that the association between GIST prognosis and the tumor primary site was not significant [23-25]. We consider that this may be related to some influencing factors such as the research sample size, research period, demographic differences and research methods. More detailed analysis is needed to clarify this topic. Our research also showed that the larger the tumor diameter and the larger number of mitoses, the worse the patients' prognosis, a conclusion consistent with other reports [26-29]. It should be stressed that the tumor risk level of the research group (the standard set up by NIH in 2008 [30] was adopted in this research) was not related to patients' prognosis, which was not in accordance with another report [31]. We hypothesize that when

GIST metastasis or recurrence occur, tumor may have developed heterogeneity changes, which may could obscure the relation between the tumor risk level and prognosis. Further studies are needed to confirm this hypothesis.

Our study also suggests that tumor progression pattern can affect prognosis. The prognosis of patients with metastasis was worse compared to patients with recurrence. We consider that during tumor recurrences, the tumor was still confined in the original location which means patients still have a significant chance for cure. However, when metastasis occurs, there is no such possibility. Univariate and multivariate analysis suggested a relationship between prognosis and different treatment methods for the recurrent and metastatic GISTs. It was shown that the combination of surgery and imatinib mesylate was the most effective treatment method for GIST metastasis and recurrence. However, due to the high death rate of recurrent and metastatic GISTs, there is an urgent need for better and more effective treatment methods against recurrent and metastatic GISTs.

This study has confirmed that there was a significant difference between the biological characteristics of recurrent and metastatic GISTs. The risk factors included primary tumor site, tumor diameter, mitosis numbers, tumor progression (recurrence and metastasis) and the treatment method. In particular, tumor progression and treatment method were two independent risk factors of patients' prognosis. The results of this study can make a contribution for the prediction of recurrent and metastatic GIST prognosis. However, this study was a single-center research and the follow-up period of some patients was short. To obtain more accurate results, large-sized with long follow-up studies are necessary.

Conflict of interests

The authors declare no conflict of interests.

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