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Original Article

Clinical features and prognosis of extragastrointestinal stromal tumors

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Abstract: Objective: To investigate the prognostic factors of extragastrointestinal stromal tumors (EGISTs). Methods: A retrospective analysis of the clinical data of 464 gastrointestinal stromal tumor (GIST) cases and 22 EGIST cases that underwent surgical treatment at our hospital during the period of 1999-2011 and that received pathological confirmation was conducted. The Kaplan-Meier method was adopted for survival analysis, and the Cox proportional hazards model was used for multivariate regression analysis. Results: The 1-, 3-, and 5-year overall survival rates of EGIST were 91.7%, 61.1% and 48.9%, respectively; the 1-, 3-, and 5-year recurrence-free survival rates were 72.2%, 28.9% and 19.3%, respectively. The overall survival rate of EGIST was significantly lower than that of GIST (with 1-, 3-, 5-year overall survival rates of 94.0%, 88.1%, and 82.4%, respectively; P = 0.008), but EGIST and GIST did not show a statistically significant difference in recurrence-free survival (P = 0.299). Kaplan-Meier univariate analysis revealed that the primary tumor site, tumor size, and tumor cell nuclear pleomorphism are important factors affecting the overall survival of EGIST patients after surgery. Multivariate analysis did not identify independent risk factors affecting the prognosis of EGIST patients. Conclusion: Compared with GIST patients, EGIST patients had a lower disease onset age, relatively larger tumors and a poorer prognosis. Survival analysis showed that the primary tumor site, tumor size, and tumor cell nuclear pleomorphism are important prognostic factors for patients with EGIST.

Keywords: Gastrointestinal stromal tumors, extragastrointestinal stromal tumors, prognosis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal mesenchymal tumors, and the incidence rate is 10-14/1 million [1-3]. A GIST mostly originates in the gastrointestinal tract, and the most frequently affected sites are, in descending order, the stomach (50-60%), small intestine (20-30%), colorectal region (10%) and esophagus (5%) [4]. However, mesenchymal tumors located in extragastrointestinal stroma are also frequently found in clinical practice, and the morphology, immune phenotype and molecular characteristics of this type of tumor are similar to those of GISTs. These non-gastrointestinal stromal tumors are called extragastrointestinal stromal tumors (EGISTs). EGISTs are relatively rare, accounting for only 5-10% of GISTs [5]. The purpose of this study was to investigate the prognostic factors of EGISTs.

Patients and methods

A total of 22 EGIST cases between January 1999 and December 2011 in our department were enrolled in this study. Additionally, 464 GIST cases were also selected for comparison. Among the EGIST patients, 13 were male (59.1%), and 9 were female (40.9%), with a median age of 45.5 years. Abdominal pain and abdominal discomfort (8 cases, 36.8%) were the most important first symptoms in EGIST patients (**Table 1**). Among the GIST patients, there were 248 males (53.4%) and 216 females (46.6%), with a median age of 58.0 years. Abdominal pain and abdominal discomfort (164 cases, 35.4%) are also the most important first symptoms in GIST patients. The study was con-

Table 1. Comparison of the two groups

Characteristic	GIST (%)	EGIST (%)	*P*-value
Number of samples	464	22	—
Male/Female	248/216	13/9	0.604[a]
Median age (range)	58.0 (23.0-87.0)	45.5 (28.0-79.0)	0.028[b]
Family history	18.5 (26/464)	4.5 (1/22)	1.000[a]
Tumor's median size (range)	5.5 (0.4-30.0)	8.0 (4.0-25.0)	0.004[c]
Median mitotic counts	3	4.5	0.486[c]
Chief complaint (%)			0.368[a]
Abdominal mass	10.8 (50/464)	13.6 (3/22)	
Abdominal pain/abdominal discomfort	35.4 (164/464)	36.4 (8/22)	
Physical examination	24.3 (113/464)	4.5 (1/22)	
Hematemesis/hematochezia	15.5 (72/464)	0.0 (0/22)	
Others	14.0 (65/464)	45.5 (10/22)	
Pathological and immunohistochemical analysis			
Tumor necrosis	35.8 (100/279)	18.2 (4/22)	0.094[a]
Tumor Hemorrhage	37.9 (77/203)	18.2 (4/22)	0.067[a]
CD117 positive	93.3 (433/464)	81.8 (18/22)	0.106[a]
CD34 positive	82.1 (331/403)	61.1 (11/18)	0.054[a]
S100 positive	45.8 (175/382)	66.7 (12/18)	0.083[a]
Treatments			0.727[a]
Radical resection	90.9 (422/464)	86.4 (19/22)	
Palliative resection	8.1 (42/464)	13.6 (3/22)	
Median survival time	132.0	50.0	0.008[d]
Median relapse-free survival time	12.0	20.0	0.299[d]

[a]X^2 text, [b]independent-samples T test, [c]rank sum test, [d]Kaplan-Miere.

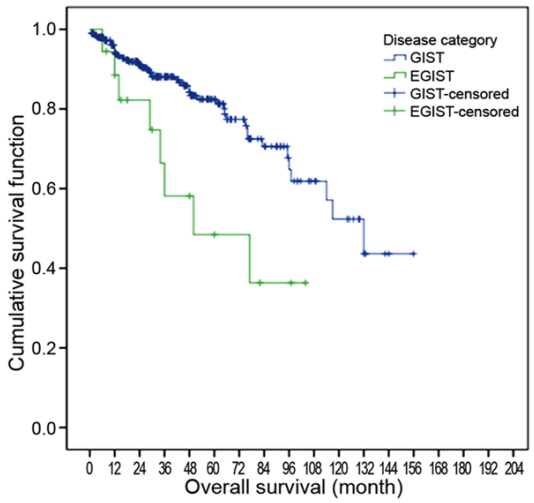

Figure 1. Comparison of postoperative overall survival rate between EGIST and GIST (n = 486, Log-rank P = 0.008).

ducted with the approval of the institutional ethics board of our institute.

SPSS software for Windows (version 20.0; SPSS, Chicago, IL, USA) was used for statistical analysis. Count data were analyzed using χ^2 test; and measurement data were analyzed using t-test. Survival analysis was performed using SPSS software, Kaplan-Meier survival curves were plotted, followed by performance of the log-rank test, and Cox regression analysis was performed for multivariate analyses. *P* value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

All patients were pathologically confirmed to have stromal tumors. For EGIST cases, the median tumor size was 8.0 cm (range, 4.0-25.0 cm), 18.2% (4/22) of cases had necrosis, and 18.2% (4/22) of cases had simultaneous tumor hemorrhage. Immunohistochemistry showed that 81.8% (18/22) of cases were CD117 positive, 61.1% (11/18) of cases were CD34 positive, and 66.7% (12/18) of cases were S100 positive. For GIST, the median tumor size was 5.5 cm (range, 0.4-30.0 cm), 35.8% (100/279) of cases had necrosis, 37.9% (77/203) of cases

Table 2. The univariate analysis of prognostic factors in EGIST group

Factors	Median relapse-free survival time (month)	*P*-value	Median overall survival time (month)	*P*-value
Tumor location		0.234		0.045
Omentum	48		-	
Intra-abdominal	12		77	
retroperitoneal	12		29	
Tumor size (cm)		0.408		0.017
≤10	20		77	
>10	24		29	
Gender		0.514		0.100
Male	12		36	
Female	20		95	
Age		0.367		0.720
≤60	20		36	
>60	30		50	
Tumor necrosis		0.840		0.813
Yes	12		58	
No	20		50	
Nuclear atypia		0.241		0.014
Yes	3		12	
No	20		77	
CD117		0.504		0.359
Positive	20		36	
Negative	7		77	
CD34		0.349		0.643
Positive	8		77	
Negative	24		50	
SMA		0.649		0.242
Positive	12		77	
Negative	24		34	
S100		0.462		0.660
Positive	24		50	
Negative	12		77	
Postoperative Imatinib Mesylate		0.242		0.426
Yes	30		50	
No	12		34	

had simultaneous tumor hemorrhage; immunohistochemistry results showed that 93.3% (433/464) of cases were CD117 positive, 82.1% (331/403) of cases were CD34 positive, and 45.8% (175/382) of cases were S100 positive.

Overall survival

Among the 22 EGIST cases, 15 had tumor recurrence and metastasis, including 8 cases of liver metastases, 5 cases of local recurrence, and 2 cases of lung metastases. Among the patients with recurrence, seven patients accepted intervention therapies, four patients received radiotherapy, and eight underwent secondary surgery, and seven patients received imatinib treatment after relapse.

The 1-, 3-, and 5-year overall survival rates for EGIST patients were 91.7%, 61.1% and 48.9%, respectively; the 1-, 3-, and 5-year recurrence-

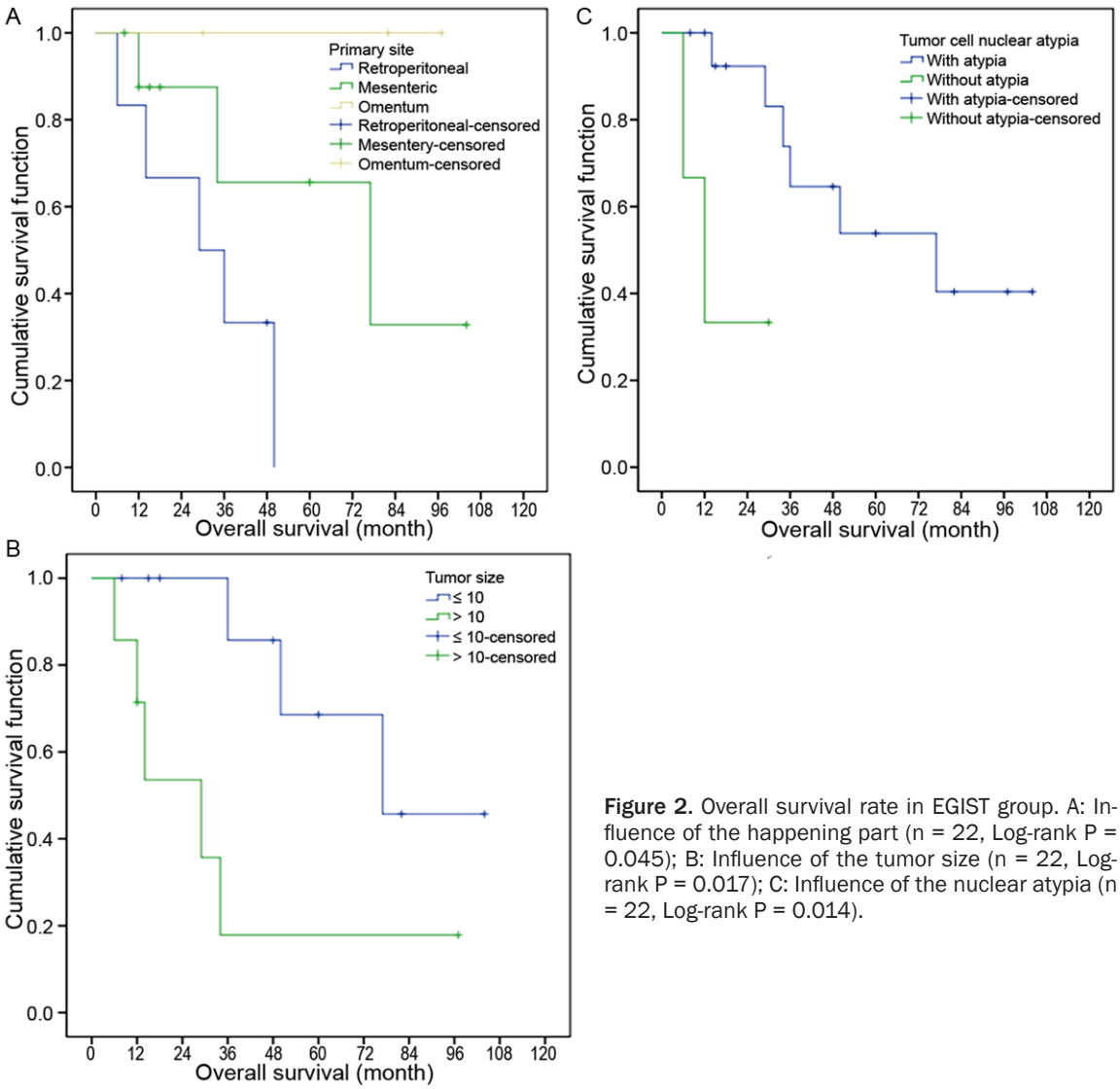

Figure 2. Overall survival rate in EGIST group. A: Influence of the happening part (n = 22, Log-rank P = 0.045); B: Influence of the tumor size (n = 22, Log-rank P = 0.017); C: Influence of the nuclear atypia (n = 22, Log-rank P = 0.014).

free survival rates were 72.2%, 28.9% and 19.3%, respectively. The overall survival rates of patients with EGIST were significantly lower than those with GIST (with 1-, 3-, and 5-year overall survival rates of 94.0%, 88.1%, and 82.4%, respectively) (P = 0.008); however, there was no statistically significant difference in recurrence-free survival between the two groups (P = 0.299) (**Figure 1**).

Kaplan-Meier univariate analysis (**Table 2**) revealed that the primary tumor site, tumor size, and tumor cell nuclear pleomorphism are important factors affecting the overall survival of EGIST patients after surgery. Multivariate analysis did not identify independent risk factors affecting the prognosis of EGIST patients (P>0.05).

Discussion

In 1999, Miettinen first defined soft tissue tumors that originate outside of the gastrointestinal tract and that presented clinicopathological features, immunohistochemical phenotypes and molecular characteristics similar to those of GISTs as EGISTs [6]. Additionally, Miettinen found that the incidence of EGISTs accounted for approximately 5-10% of GISTs and approximately 4~7% of soft tissue tumors in the abdominal cavity. The data from our hospital showed that EGISTs accounted for 4.5% of all stromal tumors (22/486), with a male to female ratio of 1.4:1 and a median onset age of 45.5 years, values that are consistent with those of previous reports [7]. In addition, we found that the onset age for EGIST patients was

lower than that for GIST patients (45.5 years vs. 58.0 years, respectively) (**Table 1**).

Kaplan-Meier univariate analysis (**Figure 2**) showed that the primary tumor site, tumor size, and tumor cell nuclear pleomorphism are important factors affecting the prognosis of EGIST patients. Tumor size is widely considered to be an important factor affecting the prognosis of stromal tumors, and therefore has been included in the risk rating system for stromal tumors. We will discuss in detail below the relationship between primary tumor sites and prognosis. It has been previously reported in the literature that EGISTs are often found in the mesentery, omentum and retroperitoneum and that they can also occur in the pancreas, bladder and female reproductive system [8]. The data from our hospital showed that the incidence of tumors in the mesentery was 50% (11/22), that in the retroperitoneum was 36.4 (8/22), and that in the omentum was 13.6 (3/22). Stratified survival analysis showed that EGISTs that originated from the omentum had the best prognosis and that those from the retroperitoneum had the worst prognosis. After reviewing the previous literature, we believe that the above observation may be due to the following reasons. First, this observation could be due to the biological characteristics of EGISTs in the lesser omental sac being similar to those of gastric stromal tumors, and the morphological and biological characteristics of mesenteric stromal tumors being similar to those of small intestinal stromal tumors; therefore, GISTs with the origin in the mesentery have a poor prognosis [9, 10]. Second, it could be related to the thoroughness of surgical treatment. The omentum is a free intraperitoneal organ, which facilitates complete tumor resection, whereas the distribution of blood vessels and nerves inherent to the mesentery can affect complete resection of the tumor [11]. Furthermore, the data from our hospital data showed that the median diameter of tumors in the retroperitoneum (10 cm) was significantly greater than those of tumors originating from the mesentery (8 cm) and omentum. This result suggests that the symptoms of EGISTs originating from the retroperitoneum appear at a late stage, leading to larger tumors and more advanced staging.

After comparing the survival of EGIST patients to that of GIST patients, we found that the 1-, 3-, and 5-year overall survival rates of EGIST patients were 91.7%, 61.1% and 48.9%, respectively; the 1-, 3-, and 5-year recurrence-free survival rates were 72.2%, 28.9% and 19.3%, respectively. The overall survival rate of EGIST patients was significantly lower than that of GIST patients (with 1-, 3-, 5-year overall survival rates of 94.0%, 88.1%, and 82.4%, respectively) (**Figure 1**); however, EGIST and GIST patients did not show a statistically significant difference in recurrence-free survival. We believe that the explanation for the two groups showing significant differences in survival might be related to the following factors. First, tumor size is widely considered to be an important factor affecting the prognosis of stromal tumors. The present study found that the median tumor diameter of an EGIST was significantly greater than that of a GIST (8 cm vs. 5.5 cm, respectively), which may be due to the sites of EGIST occurrence having large gaps; thus, the clinical symptoms occur only when the tumor size becomes large, leading to the observation that the EGIST size is relatively larger. Second, compared with a typical GIST, an EGIST does not affect the digestive tract; therefore, it is relatively rare to identify early symptoms such as gastrointestinal bleeding that is observed in GISTs. The data from our hospital showed that none of the EGIST cases had the symptoms of vomiting blood/passage of blood in the stool or other gastrointestinal symptoms, while 15.5% (72/464) of GIST patients had these symptoms. This phenomenon is also an important factor causing the relatively larger size and more advanced staging upon the discovery of EGISTs.

In conclusion, compared with GIST patients, EGIST patients have a younger onset age, larger tumor size and poorer prognosis. The clinical symptoms of EGISTs are often manifested as abdominal pain/discomfort. Because it usually does not affect the gastrointestinal tract, an EGIST rarely causes gastrointestinal bleeding, obstruction and other typical clinical manifestations. Survival analysis showed that the primary tumor site, tumor size, and tumor cell nuclear pleomorphism are important factors affecting the prognosis of EGIST patients. Due to the low incidence of EGIST, multi-center collaborative investigations logically combining basic research with clinical studies are required to expand the sample size and further study the biological characteristics of EGISTs.

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Disclosure of conflict of interest

None.

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References

[1] Losada H, Villaseca M, Vivallo C, López M. Gastrointestinal stromal tumor as cause of hepatic mass. Hepatobiliary Surg Nutr 2016; 5: 388-389.

[2] Borczuk A, Paucar D, Halmos B. Has MET met its match? Ann Transl Med 2016; 4: 97.

[3] Phan K, Martires K, Kurlander DE, Gaddipati K, Xavier M. The incidence of second primary malignancies after gastrointestinal stromal tumor before and after the introduction of imatinib mesylate. Transl Cancer Res 2014; 3: 152-159.

[4] Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006; 130: 1466-1478.

[5] Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002; 33: 459-465.

[6] Miettinen M, Monihan JM, Sarlomo-Rikala M, Kovatich AJ, Carr NJ, Emory TS, Sobin LH. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Pathol 1999; 23: 1109-1118.

[7] Castillo-Sang M, Mancho S, Tsang AW, Gociman B, Almaroof B, Ahmed MY. A malignant omental extra-gastrointestinal stromal tumor on a young man: a case report and review of the literature. World J Surg Oncol 2008; 6: 50.

[8] Krokowski M, Jocham D, Choi H, Feller AC, Horny HP. Malignant extragastrointestinal stromal tumor of bladder. J Urol 2003; 169: 1790-1791.

[9] Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol 2000; 13: 577-585.

[10] Shetty N, Sirohi B, Shrikhande SV. Molecular target therapy for gastrointestinal stromal tumors. Gan To Kagaku Ryoho 2015; 4: 207-218.

[11] Trinh VA, You Y, Hwu WJ. Treatment of BRAF-mutated advanced cutaneous melanoma. Chin Clin Oncol 2014; 3: 28.