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Prognostic Factors of Gastrointestinal Stromal Tumors: A Single Institutional Retrospective Experience with Surgical Management over 20 Years

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OBJECTIVE To analyze the pathological features and prognosis factors of gastrointestinal stromal tumor (GIST) after primary resection.

METHODS Medical records of the diagnosis, surgery, and follow-up of 327 patients with GISTs who underwent surgery between 1988 and 2007 were retrospectively reviewed. The predictive factors for the survival of these patients were identified using multivariate analysis.

RESULTS In the 327 tumors, 152 (46.5%) were located in the stomach, 89 (27.2%) in the small intestine, 33 (10.1%) in the colon and rectum, and 43 (13.1%) in other sites including the omentum and mesentery. The 3-year and 5-year overall survival rates of the 327 GIST patients were 74.4% and 62.7%, respectively, and univariate survival analysis demonstrated that factors, such as tumor size, mitotic index, NIH categories, Ki-67 index, tumor location, surgical margins, tumor bleeding, and tumor necrosis have significant effect on survival of the patients ($P < 0.05$). Multivariate analysis demonstrated that the NIH categories, surgical margins, and Ki-67 index were independent prognostic factors for the survival rate. In the group of patients with postoperative recurrence or metastasis, the median survival time of patients who did not receive imatinib treatment was 30 months and that of patients who received imatinib treatment was 59 months. Their 5-year survival rates were 16.4% and 39.4%, respectively, and the difference was statistically significant ($P = 0.017$).

CONCLUSION Complete resection is the first choice of treatment for GISTs. It is reasonable to evaluate the prognosis of resectable GISTs and guide the adjunctive therapy with NIH categories and Ki-67 index. Imatinib treatment can significantly increase the survival rate of patients with recurrent and metastatic GISTs.

KEY WORDS: gastrointestinal stromal tumors, prognostic factors, surgical management, survival, adjuvant therapy.

Introduction

Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the gastrointestinal tract. Most gastrointestinal soft tissue neoplasms, previously referred to as leiomyomas, schwannomas, leiomyoblastomas or leiomyosarcomas, are today

classified as GIST on the basis of molecular and immunohistological features. GIST are characterized by over expression of the tyrosine kinase receptor KIT, mutations of the tyrosine-kinase c-Kit have been related to GIST oncogenesis as well as PDGFRA (platelet derived growth factor receptor-α) mutations[1]. Over the past 10 years, there have been breakthroughs in the study of the etiology, pathology, and treatment of GISTs, the optimal management of localized and advanced GIST in terms of histological diagnosis, surgery, imaging, medical treatment and molecular biology, which has been an active scientific area. This study reported on a retrospective analysis of 327 GIST patients who were evaluated the prognostic factors and results of adjunctive therapy. The aim of our study was to analyze the value of the NIH criteria and other prognostic factors, as well as clinicopathologic features, in relationship to disease recurrences in a large sample of primary GIST patients enrolled into our tumor registry. To our knowledge, it represents the biggest study from a single centre in china.

Materials and Methods

Clinical data

A retrospective analysis was performed on the clinical data of 327 patients with GISTs whose diagnosis was confirmed by pathological examination in the Cancer Hospital between January 1988 and December 2007. Among them, 162 cases were male and 165 were female. The median patient age was 56 years (range, 9 to 81 years). Primary tumor locations included 152 in the stomach, 89 in the small intestine, 31 in the rectum, 31 in the abdominal cavity, 9 in the retroperitoneal space, 2 in the colon, 2 in the esophagus, and 1 case with an unknown primary location. The diameter of the tumors ranged from 1 cm to 30 cm, with a median diameter of 7 cm. The symptoms in these patients included abdominal pain in 49.5% (162/327), abdominal mass in 18.0% (59/327), and bleeding in the digestive tract in 15.5% (51/327). The GIST was found by chance in 40 patients during routine physical examination or during treatment for other diseases.

Treatment

All 327 patients underwent surgical treatment. Among them, 6 patients underwent exploration and biopsy; 261 patients underwent partial resection of organs for removal of the primary tumor; 16 underwent resection of tumor and their draining lymph nodes; 42 underwent combined resection of related organs; and 2 underwent combined resection of related organs and metastasis. The resected tumor margin was negative in 299 cases and positive in 28 cases (including cases receiving exploration and biopsy). Among the 16 patients who underwent lymph node removal, 2 cases had metastases in 1 to 2 lymph nodes. Fifteen patients received adjuvant chemotherapy with carboplatin, cisplatin, fluorouracil, hydroxycamptothecin, or mitomycin for 1 to 4 cycles. Five patients received 400 mg imatinib mesylate (IM) once daily. Among the 105 patients with postoperative recurrence or metastasis, 28 received IM treatment.

Pathological and immunohistochemical examinations

Pathological diagnosis was made with standard immunohistochemical examinations according to the World Health Organization (WHO) pathological classification of digestive system tumors and the standard of histological examination recommended by the European Society for Medical Oncology (ESMO) symposium on soft tissue carcinomas and GIST[2]. In CD117 negative cases, diagnosis was made by combined evaluation of the expression of CD34, SMA, desmin, and S-100 and cell morphology with the exclusion of neurogenic or myogenic tumors.

All patients in the current study were diagnosed with GISTs by pathological and immunohistochemical examinations. The medical records of patients with mesenchymal neoplasm that arose the gastrointestinal tract and abdomen diagnosed and treated between June 1988 and December 2007 were retrieved from the Cancer Hospital. Tumor slides stained with hematoxylin and eosin (H&E) from these patients were assessed. Immunohistochemistry staining were performed using antibodies to c-kit protein (CD117), CD34, smooth muscle actin, Desmin and S-100 protein. Among them, 298 (91.1%) were CD117 positive; 273 (83.4%) were CD34 positive, 43 (13.2%) were SMA positive; 16 (4.8%) were S-100 positive, 17.7% of patients (58/327) were desmin positive, 44.2% (147/327) were KI-67 positive, and 25.0% (82/327) were Ki-67 $\geq$ 10%. Tumor bleeding occurred in 137 cases, and tumor necrosis was present in 145 cases. Spindle cells were predominant in 296 cases (90.5%); epithelial cells were predominant in 22 cases (6.6%); and mixed cell types were found in 9 cases (2.7%).

Risk of malignancy

GISTs were classified into risk categories according to NIH categories system[3]. Eighteen cases were in very low risk; 75 cases were in low risk; 79 cases were in intermediate risk; and 155 cases were in high risk.

Follow-up

Follow-up was completed for 318 patients and included visits to the outpatient department, follow-up calls or letters. The deadline for completing and submitting follow-up reports was March 2009. The rate of follow-up was 93%, and the duration of follow-up was between 10 months and 15 years. The median follow-up time was 85 months.

Statistical analysis

SPSS 13.0 software was used for statistical analysis. The Kaplan-Meier method was used for the univariate

analysis of prognostic factors. Log rank test was used for statistical comparison. A P value of < 0.05 was considered statistically significant. Stepwise regression was applied to introduce variables which may influence the prognosis into a Cox proportional hazard model one-by-one, and multivariate analysis was carried out.

Results

Surgical complications

Postoperative complications occurred in 18 cases (5.50%) with postoperative bleeding in 3, wound infection in 8, pulmonary infection in 4, intestinal obstruction in 2, and 1 patient died in the perioperative period.

Recurrence and metastasis

The postoperative rate of metastasis was 32.1% (105/327), with liver metastasis in 40 patients, abdominal cavity implantation metastasis in 31, abdominal cavity implantation and liver metastasis in 19, local recurrence in 9, abdominal implantation, liver, and lung metastases in 4, and wound implantation metastasis in 2. The rate of recurrence and metastasis was 53.5% (83/155) in the high risk group, and the median time to recurrence or metastasis was 23 months (Table 1).

Table 1. The site and frequency of metastasis.

Site of metastasis	Frequency
Liver	40
Incisal opening	2
Peritoneal cavity	31
Peritoneal cavity and liver	19
Local recurrence	9
Peritoneal cavity, liver and lung	4
Total	105

Survival analysis

The 1-year, 3-year, and 5-year overall survival rates of the 327 GIST patients were 94.6%, 74.4% and 62.7%, respectively. Univariate survival analysis showed that tumor size, mitotic index, NIH categories , Ki-67 index, tumor site, surgical margins, tumor bleeding, and tumor necrosis had a statistically significant effects on survival ($P < 0.05$), see Figs.1-8. Univariate analysis showed that age, CD117 and CD34 expression, cell type, and adjunctive chemotherapy did not exhibit a statistically significant effect on the survival rate. Univariate analysis showed that, in the group with recurrence or metastasis, the median survival time of patients who did not receive imatinib treatment was 30 months, and that of patients who did receive imatinib treatment was 59 months. Their 5-year survival rates were 16.4% and 39.4%, respectively, and the difference was statistically significant ($P = 0.017$).

Stepwise regression was applied to introduce clinical factors, such as gender, tumor size, mitotic index, NIH categories, Ki-67 index, surgical margins, tumor bleeding, and tumor necrosis into the Cox proportional hazard model, and the results showed that the NIH categories ($P = 0.000$, OR = 2.408, 95% CI = 1.631-3.556), surgical margins ($P = 0.000$, OR = 0.407, 95% CI = 0.254-0.653), and Ki-67 index ($P = 0.000$, OR = 3.351, 95% CI = 2.108-5.327) were independent prognostic factors for survival .

Discussion

With the improvement of imaging techniques and histological diagnostic methods, the discovery and diagnosis of GISTs has increased. It is very important in clinical practice to accurately differentiate benign from malignant tumors, and predict the prognosis of malignancies; however, this is difficult for GISTs because their biological behavior is very complicated, and GISTs of any size can exhibit malignant behavior[4]. In this study, the rates of postoperative recurrence and metastasis were 19.0% (4/21), 22.0% (24/109), and 39.0% (77/197) in the 3 groups with tumors < 2 cm, 2-5 cm, and > 5 cm in size, respectively. Therefore, it can be assumed that every GIST is potentially malignant, and should be classified according to malignant potential rather than simply being divided into benign and malignant groups. A consensus conference held at the National Institute of Health (NIH) provided both an evidence-based definition and a practical scheme for the assessment of the risk in the clinical course of this disease. The risk categorization is based on evaluation of the size and mitotic rate of the tumors as the most reliable prognostic factors, and its use is strongly advocated. However, the design of trials assessing adjuvant treatment in GIST patients with imatinib has raised debate about the accuracy of the NIH consensus criteria for the risk of disease recurrence after surgical treatment of primary tumors[5].

The 5-year survival rate after resection of GISTs ranged from 50%-70%. The tumor size, tumor location, necrosis, mitotic activity, PCNA index > 10%, and the presence of metastasis were reported to correlate with patient survival in previous studies[4-6]. The grading standard suggested by Fletcher who divided patients with GISTs into very low, low, intermediate, and high risk groups according to the tumor size and mitotic count. In the present study, patients were classified according to NIH categories: 18 were in very low risk; 75 were in low risk; 79 were in intermediate risk; and 155 were in high risk, and their corresponding 5-year survival rates were 100%, 73.8%, 65.8%, and 38.3%, respectively. The differences between the various groups were statistically significant ($P < 0.001$). This suggests that Fletcher's criteria is effective in determining the malignant potential of GISTs and useful for guiding treatment.

Currently, most scholars consider the site of the pri-

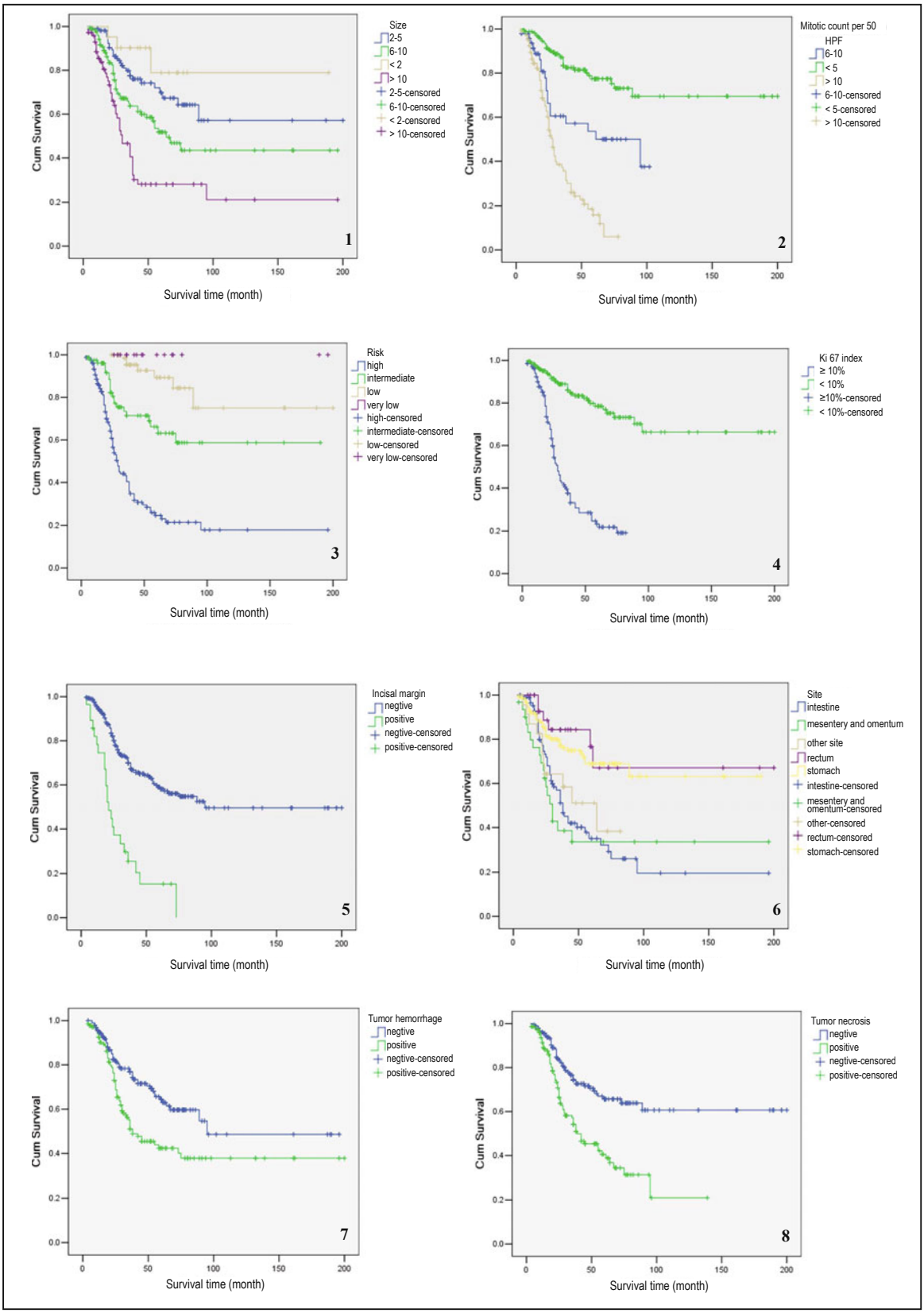

Fig.1. Survival curves of patients according to tumor size.
Fig.2. Survival curves of patients according to mitotic count.
Fig.3. Survival curves of patients according to Fletcher's risk .
Fig.4. Survival curves of patients according to Ki-67 index.
Fig.5. Survival curves of patients according to incisal margin.
Fig.6. Survival curves of patients according to tumor site.
Fig.7. Survival curves of patients according to tumor hemorrhage.
Fig.8. Survival curves of patients according to tumor necrosis.

mary tumor as a factor that influences the prognosis of GISTs[7]. Tumors arising from the small intestine, colon, rectum or mesentery are generally associated with a less favorable outcome than those arising from the stomach, and the risk of GIST recurrence in the colon and rectum is similar to that in the small intestine. In this study, 5-year survival rates of patients with GISTs of the stomach were 67.4%, and 5-year survival rates of patients with GISTs of the small intestine were 44.1%. Univariate analysis showed that there were significant differences between the survival rates of GISTs occurring at different locations ($P < 0.001$), which equates with the results of other studies[7,8].

Complete en-bloc resection of the tumor along with surrounding involved organs with negative tumor margins is the standard surgical treatment, and the resection rate of primary GISTs is approximately 85%[8]. The complete resection rate was 91% in this study. A tumor-free surgical margin is an important factor influencing the prognosis of GISTs. DeMatteo et al.[9] evaluated 200 GIST patients and found that the survival rate of patients who underwent total resection was 54% at 5 years with a median survival of 66 months; however, the postoperative median survival time was only 22 months for patients in whom resection was incomplete. Pierie et al.[10] evaluated 69 cases of GISTs and found that the 5-year survival rate of patients who underwent en-bloc resection was 42%, while that of patients who underwent palliative resection was only 9%. In the current study, surgical margins were negative in 299 cases (91.4%), and positive in 28 cases (8.6%), and the median survival time was 68 months in the group with negative surgical margins and 25 months in the group with positive surgical margins. Their 5-year survival rates were 65.4% and 19.1%, respectively. It is commonly believed that routine lymph node resection is not necessary because of the low rate of lymph node metastasis in patients with GISTS[11]. In this study, lymph node resection was performed in 16 cases, and among them, lymph node metastasis was found in 2 cases. There is increasing evidence that laparoscopic resection can be performed safely[12]. The feasibility of laparoscopic resection is now being addressed in the patient presenting with GIST in our unit, and an analysis paper on this will be published in the future.

Most GISTs arise due to a mutation in the proto-oncogene *C*-kit[13]. CD117 is the product of *C*-Kit, and CD34 is a hematopoietic precursor cell antigen, and both are widely expressed in GIST tissue. At present, most pathologists consider that identification of the presence of both CD117 and CD34 is an effective method for the diagnosis of GISTs. However, the expressions of CD117 and CD34 are not related with the risk of tumor malignancy. Ki-67 is a marker that reflects the activity of cell division and proliferation, and it is widely used for immunohistochemical examination for the diagnosis of GISTs. It has been shown that Ki-67 expression is an effective prognostic indicator for GIST patients[14]. Our results showed that 5-year survival rate in the high Ki-67 group was 46.5% and in the low Ki-67 group was 71.4%. The differences were statistically significant, and the results of multivariate analysis demonstrated that Ki-67 was an independent prognostic factor of survival, which is in accordance with other reports[15]. Thus, we find that it is reasonable to evaluate the prognosis of resectable GISTs and guide adjunctive therapy based on NIH categories and Ki-67 index.

Local recurrence, abdominal cavity implantation or liver metastasis occurs even after en-bloc resection in 40%-80% of GIST patients. The postoperative rate of recurrence and metastasis was 32.1% (105/327) shown in the current study. The therapeutic effect of conventional chemotherapy and cytotoxic drugs is poor and the response rate is estimated to be only 5% to 10%[16]. Surgery also has limited effectiveness as a treatment for patients with metastatic GISTs. The molecular-targeting drug IM, a tyrosine kinase inhibitor blocking most mutated-activated KIT and PDGFRa proteins of GIST, controlled tumor growth in up to 85% of advanced GIST in the phase I, II and III trials reported to date[17-20]. IM significantly improved the survival rate of patients with metastatic GISTs[21]. In the present study, IM was used for 28 of 105 patients with postoperative recurrence or metastasis, and the results of univariate analysis showed that in the group with recurrence or metastasis, the median survival time of patients who did not receive IM was 30 months and that of patients who received IM was 59 months, and their 5-year survival rates were 16.4% and 39.4%, respectively. The difference was statistically significant ($P = 0.017$). These results suggest that IM can improve survival in GIST patients with recurrence or metastasis. IM was used as an adjuvant treatment for 4 patients in the group with high risk of malignancy. The therapeutic effect is, however, uncertain because of the small number of patients. The latest research results show that assignment to 1 year of adjuvant imatinib improved recurrence-free survival after the complete resection of primary gastrointestinal stromaltumors compared with taking a placebo. Additionally, adjuvant imatinib was safe and well tolerated[22].

In conclusion, the limitations of this study included retrospective data analysis and the molecular classification of GISTs based on KIT and PDGFRa mutational status were not performed. However, it is reasonable to evaluate the prognosis of respectable GISTs and guide adjunctive therapy based on NIH categories and Ki-67 index. Complete resection and adjuvant imatinib use is clearly associated with improved survival in GISTs patients. Several other studies have also shown a correlation between exon 11 kit mutations and poor prognosis and suggested that exon 11 mutation may be one of the strongest prognostic factors. The molecular classification of GISTs based on KIT and PDGFRa mutational status may provide more exact prognostic estimates and

with the possibility of an individually tailored imatinib treatment[23-25].

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Conflict of interest statement

No potential conflicts of interest were disclosed.

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