Gastrointestinal stromal tumors in a cohort of Chinese patients in Hong Kong

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Abstract

AIM: To investigate the prevalence and clinical pattern of gastrointestinal stromal tumors (GISTs) in Hong Kong Chinese, and to assess the impact of introduction of CD117 on the disease incidence.

METHODS: From the database of the Department of Pathology of Yan Chai Hospital, 47 patients, with GISTs from September 1995 to December 2003 were included in this study. Ten GISTs were diagnosed before the introduction of CD117. The clinical features, tumor characteristics, and treatment were analyzed. Factors predicting tumor related death or recurrence were studied with Cox proportional hazard model.

RESULTS: The patients included 26 males and 21 females, with a mean age of 66.6 years (SD 13.1, range 29-87 years). The estimated prevalence of GISTs was 13.5-15.6 per 100 000 people, with an annual incidence of 1.68-1.96 per 100 000 people. The annual incidence of GISTs before and after the introduction of CD117 was 1.1 per 100 000 people and 2.1 per 100 000 people respectively. Stomach (34 patients, 72.3%) was the most common location for the tumor, followed by the small intestine (8 patients, 17.0%), esophagus (2 patients, 4.3%), omentum (2 patients, 4.3%) and colon (1 patient, 2.1%). Thirty-one patients (66%) had complete tumor resection. Eleven out of 16 deaths (23%) were tumor-related. The median survival time was 26 mo. Five-year survival rate was 61.3%. The significant factors associated with tumor-related death or recurrence were incomplete resection, tumor size 5 cm or above, invasion to the adjacent organ or presence of metastasis.

CONCLUSION: The incidence of GIST in Hong Kong is comparable to that in the United States but lower than that in Finland. The true incidence of GISTs could be underestimated before the introduction of CD117. Incomplete resection, tumor size 5 cm or above, invasion to the adjacent organ or presence of metastasis are factors predicting tumor-related death or recurrence.

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Key words: Gastrointestinal tumor; GIST; Prognostic factors; Clinical features; Incidence

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors that have been a controversial topic since their first description by Golden and Stoot in 1941[1]. In the past three decades, there has been considerable debate regarding its nomenclature, cellular origin, diagnosis, and prognosis[2]. Before the discovery of gain-of-function mutations in the c-KIT proto-oncogene in GISTs by Hirota and colleagues in 1998[3], most GISTs were thought to be smooth muscle neoplasm, and were classified as leiomyosarcoma due to their similar appearance by light microscopy. At present, GISTS are defined as spindle-cell, epithelioid, or occasionally pleiomorphic mesenchymal tumours of the gastrointestinal tract that express the protein c-KIT[4]. The precise cellular origin of GISTs recently has been proposed to be the interstitial cell of Cajal, an intestinal pacemaker cell[5]. The definition of c-KIT-negative GISTs remains a focus of research. In this study, we analyzed 47 Chinese patients with GISTs in Yan Chai Hospital to study their clinical, pathological characteristics, survival pattern and recurrence. The impact of introduction of CD117 on the incidence of this tumor was assessed, as well.
MATERIALS AND METHODS

Patient selection

From the database of the Department of Pathology of Yan Chai Hospital, we selected patients with the diagnoses of gastrointestinal stromal tumors (GISTs), leiomyoma, leiomyoblastoma and leiomyosarcoma from September 1995 to December 2003. Their histology slides were reviewed by a separate pathologist of the Department of Pathology. Patients with the diagnosis of GISTs were recruited to our study.

Clinical information including age, sex, comorbidity of the patients and presentation status of the tumor were recorded. The presentation status of the tumor reflected the extent of disease and the history of prior treatment when the patient was first seen in our hospital. The tumor was categorized as primary, metastatic or locally recurrent. Acute gastrointestinal haemorrhage was defined as significant blood loss requiring transfusion or haemodynamically significant blood loss. The criteria for chronic gastrointestinal haemorrhage were intermittent melena, guaiac-positive stool or iron deficiency anaemia. Ranges of diagnostic tests were used in these patients. They involved evaluating the gastrointestinal tract with contrast such as barium studies, endoscopies or ultrasound of abdomen. Computerized tomography scan and mesenteric angiography were used in some patients. Histology with or without adjacent organ involvement was also recorded. Histological subtype was determined by examination of light microscopy applying different staining methods. Immunohistochemistry stain included vimentin, alpha-smooth muscle actin, desmin, neuron-specific enolase (NSE), S100 protein and CD 34. CD117 was introduced to our Department of Pathology since October 1998. Electronic microscopy was also performed.

Tumor size was tabulated based on actual measurement of the gross surgical specimen or imaging when the tumor was inoperable. It was recorded as the largest diameter in any dimension of the primary tumor and was classified into < 5 cm, 5 to 10 cm, or >10 cm. Resection margins were checked closely for presence of microscopic disease. Tumors were also grouped according to their mitotic numbers as no mitosis (0/10 HPF), low mitotic index (1-4/10 HPF) and high mitotic index (>5/10 HPF). Tumor cellularity, presence or absence of invasive growth, tumor necrosis and the presence or absence of haemorrhage were also examined.

Complete resection was defined as the excision of all gross disease regardless of microscopic margins. Resections were classified as incomplete when gross residual disease was present after resection. Inoperable was defined as when the tumor was unresectable at surgical exploration. Patients with incompletely resected tumor, metastatic or unresectable tumor were referred to oncology units for chemotherapy and radiation therapy as indicated. In total, 47 patients satisfied the diagnosis of GISTs.

Survival analysis

All times were calculated from the first presentation to the date of last follow-up or death. Time of last follow-up of dead patient was recorded as the time of certification of death. Others were censored at the time of last follow-up in specialist outpatient clinic or admission (clinical or emergency) whichever was later. Clinical variables, tumor characteristics, as well as modality of treatment were analyzed against tumor recurrence or death.

Statistic analysis

Statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, USA). Influence of the factors in predicting tumor recurrence or death was assessed by univariate analyses. Multivariate analysis was performed with the Cox proportional hazards model to identify significant prognostic factors. P<0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between September 1995 to December 2003, 47 patients (26 men and 21 women) were diagnosed with GIST. Mean follow up time in this cohort was 31 mo (range 0-99 mo). Mean age was 66.6 years (SD 13.1, range 29 to 87). Stomach (34 patients, 72.3%) was the most common site for the tumor, followed by the small intestine (8 patients, 17.0%), esophagus (2 patients, 4.3%), omentum (2 patients, 4.3%) and colon (1 patient, 2.1%). Gastrointestinal bleeding was the most common presenting symptom (28 patients, 60%), followed by epigastric pain (21 patients, 45%), and the presence of an abdominal mass (10 patients, 21%). Three patients (6%) with GIST were diagnosed incidentally. Endoscopically, the most common finding was a round tumor mass, either pedunculated or sessile, resembling a leiomyoma. Huge tumor usually presented as submucosal mass bulging into the lumen. Active bleeding ulcer or ulcer with stigmata of recent haemorrhage was present in 5 cases (71%) (Table 1). Radiological imaging including computerized tomography (CT) scan of the abdomen and barium studies were employed in most of our patients to identify the site and to assess the size of the lesions as well as the presence of any local invasion or distant metastases (Figure 1). Two patients had metastases delineated by CT scan, one in liver and one in omentum respectively, which precluded any curative surgical intervention.

Tumor characteristics

Tumor size ranged from 0.3 to 24 cm (median 4.5 cm, inter-quartile range 3-7.5 cm). Twenty-seven (57%) patients had tumor size less than or equal to 5 cm, 14 (30%) patients with tumor size between 5 cm to 10 cm, whereas 6 (13%) patients presented with tumor size greater than 10 cm. Seven (15%) patients had high mitotic index (>5/10 HPF), 18 (38%) patients low (1-4/10 HPF) and 22 (47%) no mitotic index (0/10 HPF). Necrosis inside the tumor was found in 15 patients (32%) with GISTs. Seven out of 47 patients (15%) had presence of tumor metastases or invasion to adjacent organs. Immunohistochemical analyses were performed in all cases. Eleven (23%) GISTs had markers for neuronal and neuroendocrine tumors,
8(17%) demonstrated immunohistology markers for myoid series. Twenty-eight (60%) GISTs were undifferentiated tumors (Table 2).

**Treatment**

All patients were assessed for tumor resection either endoscopically or surgically. Thirty-one patients (66%) had complete resection of the tumor, and 7 patients (15%) underwent incomplete resection. In 5 patients (10%), resection of tumor was impossible because of extensive tumor metastases or poor general condition at the time of diagnosis. Endoscopic resection was possible only in 7 patients (15%) (5 gastric, 1 oesophageal and 1 colonic GISTs). All small bowel GISTs required surgical resection. Adjuvant chemotherapy by Imatinib (Glivec) was given in 2 patients post-operatively.

**Survival**

Totally 16 deaths were recorded in the study period, and 11 deaths were tumor related. The overall median survival was 26 mo. Five-year survival probability was 61.3% (SE 8.0%). The median survival time for completely resected GISTs was longer than that for incompletely resected or inoperable patients, 37 mo versus 10 mo respectively (log rank test, $P = 0.0013$) (Figure 2). Two patients receiving imatinib were still alive at the end of the study, with liver metastasis. Their survival time censored at the end of the study was 26 mo and 37 mo respectively.

**Prognostic factors**

By univariate analyses, the significant factors predicting tumor recurrence or tumor related death included tumor size 5 cm or above ($P = 0.003$), presence of significant mitotic figures (1/10 HPF or above) ($P = 0.021$), presence of necrosis ($P = 0.005$), invasion to adjacent organ and/or presence of metastases at the time of diagnosis ($P < 0.001$),

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**Table 1** Characteristics of patients with GISTs

| Characteristics                  | n (%)          |
|----------------------------------|----------------|
| Number of patients               | 47             |
| Male/Female (ratio)              | 26:21 (1.23:1) |
| Mean age at the time of diagnosis (SD) | 66.60 (SD 19.1) |
| Median follow up time in months (IQR) | 26.00 (10-43)  |
| Presenting symptoms              |                |
| GI bleeding                       | 28 (60%)       |
| Epigastric pain                   | 21 (45%)       |
| Abdominal mass                    | 10 (21%)       |
| Incidental finding                | 3 (6.3%)       |
| Locations                         |                |
| Stomach                           | 34 (72.3%)     |
| Small bowel                       | 8 (17.0%)      |
| Esophagus                         | 2 (4.3%)       |
| Colon                             | 1 (2.1%)       |
| Omentum                           | 2 (4.3%)       |
| Resection$^1$                     |                |
| Complete                          | 31 (66%)       |
| Incomplete                        | 7 (14.9%)      |
| Inoperable                        | 5 (10.6%)      |
| Recurrence (after initial surgery)|                |
| Total                             | 4 (8.5%)       |
| Local recurrence                  | 1 (2.1%)       |
| Distal metastasis                 | 3 (6.4%)       |
| Death                             |                |
| Total                             | 16 (34%)       |
| Tumor related                     | 11 (23.4%)     |
| Tumor unrelated                   | 5 (10.6%)      |

$^1$Two patients refused resection of tumor. Two GISTs were discovered incidentally during autopsy. IQR: Inter-quartile range.

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**Table 2** Tumor characteristics of 47 patients with GISTs

| Characteristics                  | n (%)          |
|----------------------------------|----------------|
| Number of patients               | 47             |
| Median tumor size in cm (IQR)    | 6.05 (3-7.5)   |
| ≤5 cm                            | 24 (51)        |
| >5-10 cm                         | 13 (28)        |
| >10 cm                           | 4 (9)          |
| Mitotic index                    |                |
| High                             | 7 (15)         |
| Low                              | 18 (38)        |
| No                               | 22 (47)        |
| Presence of distal metastasis or local invasion | 7 (15) |
The true incidence of GISTs could be underestimated before the introduction of CD117. In our hospital, all gastrointestinal tract tumors suspected to be GISTs were routinely tested for CD 117 marker since October 1998. Interestingly, only 10 patients out of 47 (21%) were diagnosed as GISTs before the introduction of CD117. The annual incidence of GISTs after the introduction of CD117 increased from 1.1 per 100,000 people to 2.1 per 100,000 people (Figure 3). Similar trend was also noted in the United States. The estimated incidence of GISTs in the United States was around 0.6 per 100,000 people in the 1980s. The incidence increased to approximately 1-2 patients per 100,000 people after 2000.

There existed some conflicting evidence on male predominance, however, most studies indicated no sex predilection[18, 21, 24, 31]. In our study, the occurrences of GISTs were similar in both sexes (1.2 male to 1 female). The age of presentation had a unimodal distribution, similar to the published data where the majority of patients presents in the fifth to seventh decade of life[34], the mean age of presentation of our patients was 66 years. GISTs are occasionally found in young adults, but they are very rare in children[7].

The vast majority of GISTs arise as a result of somatic mutation, but rare familial cases associated with mutated c-KIT have been identified[8, 10-12]. In our study, we could not identify any patient with familial relation. All the patients with GISTs were sporadic, and the predisposing factors were unknown.

Similar to other published data[7,13,14], the stomach was the most frequent site of involvement in our patients (72%), followed by small intestine (17%). The large bowel, esophagus and omentum were least likely involved. Symptomatic lesions have manifestations that depend on tumor size, location and growth pattern[7,13,14]. Ludwig and Travero reported that GISTs with intraluminal nodule less than 2 cm was generally asymptomatic while tumors >4 cm were associated with symptoms[35]. In the literature approximately 50% of patients presented with acute or subacute gastrointestinal bleeding as the major symptom leading to diagnosis[29]. In our local patients, the most common presenting symptoms were gastrointestinal bleeding (60%), as results of overtly mucosal ulceration, followed by epigastric pain and abdominal mass. Other symptoms included fever, anorexia, dysphagia, obstruction and perforation of bowel were seldom seen in our series. Clinically palpable mass usually implies invasion to adjacent organs or distant metastasis, thus in turn predicts poor outcome of the patients. Surgical resection is the treatment of choice and should be performed with the intention to performing complete en bloc resection of the tumor, as it
is difficult or impossible to differentiate between benign or malignant lesions before or during operation\textsuperscript{[16]}. Tumor size and frozen section during operation are not conclusive \textsuperscript{[17,18]}. 

**Prognostic factors**

Gastrointestinal stromal tumors are unique in that their malignant potential is not always predictable. Most GISTs appear relatively low grade histologically, and it has been difficult to distinguish benign from malignant GISTs, especially at the low-grade end of the histological spectrum. Many previous studies suggest a single factor or even combinations of two factors are not sufficient to reliably predict the outcome of GISTs\textsuperscript{[19]}. Currently no accepted staging system exists. Most pathologists use a multiparametric approach to predict the biological behavior of GISTs. The most reproducible predictor of malignancy has been mitotic rate >1-5 mitosis per 10 HPF\textsuperscript{[20-22]}. Other poor prognostic factors include tumor size > 5 cm\textsuperscript{[23-27]}, mutation in the c-kit gene\textsuperscript{[28-30]}, necrosis\textsuperscript{[18,20,24,31]}, infiltration and metastasis to other sites\textsuperscript{[18]}. In our study, significant prognostic factors were tumor size 5 cm or above, invasion to adjacent organ and/or presence of metastases at the time of diagnosis as well as incomplete tumor resection. In contrast to previous studies\textsuperscript{[20,22]}, mitotic index did not appear as significant prognostic factor in our cohort. The different approaches to sample tissue from large tumors with considerable heterogeneity for microscopic assessment may explain such discrepancy between different studies. At present, the best method to adequately sample tumor tissue and report mitotic index is still controversial. In our hospital, our pathologists choose random sampling approach and report the highest mitotic index among different tissue samples. From the literatures, approximately 10% to 30% of all GISTs display malignant behavior\textsuperscript{[18,14]}. Our patients with GIST demonstrated similar ratio regarding malignant GISTs.

**Survival**

The overall survival appears to reflect the completeness of resection\textsuperscript{[7,18,32]}. In Roswell Park Cancer Institute (RPCI), the United States, the median survival rate was significantly higher in those who underwent complete resection (33 mo) as compared to those who underwent palliative surgery (15 mo)\textsuperscript{[13]}. Similarly in our center, the median survival time for completely resected GISTs was significantly longer than incompletely resected or inoperable patients, 37 mo versus 10 mo. The adjuvant therapy appeared to improve the survival and the quality of life in patients with incomplete tumor resections. Despite extensive metastasis, the 2 patients receiving imatinib were still alive at the end of the study. The survival times of 26 mo and 37 mo were much longer than the median 10 mo of other patients with incomplete tumor resection, although the number of patient in this group was too small for statistical analysis.

Recurrence is commonly local and peritoneal, often associated with liver metastasis. Peritoneal metastases are most probably a result of tumor cells seeding from the primary tumor directly into the peritoneal cavity. Liver metastases most probably result from hematogenous seeding into the portal vein\textsuperscript{[13]}. Extra-abdominal disease in the absence of peritoneal involvement is rare\textsuperscript{[13]}. There exist few reports in the literature describing a survival advantage after the resection of abdominal recurrence. In our hospital, local recurrence of GIST was not routinely operated again.

In conclusion, the incidence of GIST in Hong Kong is comparable to that of United States but lower than that in Finland. The true incidence of GISTs could be underestimated before the introduction of CD117. Incomplete resection, tumor size 5 cm or above, invasion to the adjacent organ or presence of metastases are factors predicting tumor-related death or recurrence. The survival of the completely resected tumor is good. The introduction of medical adjuvant therapy appears to improve the survival and the quality of life in the unresectable and incompletely resected GISTs patients.

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