Gastrointestinal Stromal Tumors: A 19 Year Experience

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ABSTRACT: **Background:** Gastrointestinal stromal tumors are the most common mesenchymal neoplasms of the human gastrointestinal tract.

Objectives: To review our accumulated experience using surgery to treat gastrointestinal stromal tumors.

Methods: We reviewed all patient charts and histological diagnoses of leiomyomas, leiomyosarcomas, leiomyoblastomas and schwannomas. Only tumors that displayed c-kit (CD117) immunopositivity were defined as GISTs.

Results: The study group comprised 40 female and 53 male patients (age 26–89 years); 40.8% of the tumors were classified as malignant, 39.8% as benign, and 19.4% as of uncertain malignancy. Fifty-six GISTs were located in the stomach (60.2%), 29 in the small bowel (31.2%), 4 in the duodenum (4.3%), 2 in the colon (2.1%) and 2 in the rectum (2.1%). Incidental GISTs were found in 23.7% of our patients. Mean overall survival time for malignant gastric GISTs was 102.6 months (95% confidence interval 74.2–131.1) as compared to 61.4 months mean overall survival for malignant small bowel GISTs (95% CI 35.7–87) ($P = 0.262$). The mean disease-free survival period for patients with malignant gastric GISTs was 97.5 months (95% CI 69.7–125.2) as compared to only 49.6 months (95% CI 27.4–71.7) for patients with small bowel malignant GISTs ($P = 0.041$).

Conclusions: We found a high percentage of incidental GISTs. Gastric GISTs are more common than small bowel GISTs. Patients with malignant gastric GISTs have a significantly better prognosis than patients with malignant small bowel GISTs. A statistically significant correlation was found between age and malignant potential of the GIST.

IMAJ 2009;11:98–102

KEY WORDS: stromal tumors, GIST, gastrointestinal cancer; surgery

Gastrointestinal stromal tumors, rare neoplasms arising from the gastrointestinal wall, are the most common mesenchymal neoplasms of the human gastrointestinal tract [1,2]. This group of tumors accounts for about 0.1% to 3% of all gastrointestinal tumors [3-5] with an incidence of 10–20 cases per million [2]. Previously, these tumors were classified as leiomyomas, leiomyosarcomas, leiomyoblastomas or schwannomas, based predominantly on their histological features. More recently, most of these tumors have been termed GISTs and have been distinguished immunohistochemically from the above-mentioned morphologically similar neoplasms of the gastrointestinal tract. Clinical and histopathological experience has shown that there are typical immunohistochemical markers enabling the identification of different types of mesenchymal tumors. It has been shown that positive immunohistochemical staining for CD34 and CD117 enables the identification of tumors arising from Cajal (pacemaker) cells. CD34 protein is present in around 40–70% of all GISTs while CD117 protein is present in nearly all cases [6-10]. Other markers, such as alpha-smooth muscle actin, show variable expression in 20–30% of GISTs and S100 in about 10% of GISTs, whereas desmin is weakly expressed in about 2% of cases only.

According to the literature, GISTs occur predominantly in people over the age of 40, with a small male predominance [2,5,11-13]. The stomach is the most common site of involvement, followed by the small intestine, colon, rectum and esophagus [2,4,9,11]. Clinical presentation is usually characterized by gastrointestinal bleeding, abdominal pain, weight loss and a palpable mass [4,10,14]. The biological behavior of GISTs is complex and unpredictable. Tumor size and mitotic counts are considered to be two important parameters for predicting the clinical course and chance of recurrence [1-6,15-17]. A consensus conference held at the U.S. National Institutes of Health in 2001 provided both an evidence-based definition and a practical scheme for the assessment of risk in the critical course of this disease. This risk categorization is based on the evaluation of the size and mitotic rate of the tumors [18]. Herein we present our experience of surgically treating 93 patients suffering from GISTs.

PATIENTS AND METHODS

This study is based on our accumulated experience of 19 years (1988–2007). Since 2000, all data were collected prospectively into a computerized database. All patient charts and histological diagnoses of leiomyomas, leiomyosarcomas, leiomyoblastomas and schwannomas were reviewed and the following data were retrieved: age, gender, clinical presentation, diagnostic evaluation, tumor location, size, treatment modalities, complications, and long-term follow-up. The histological material was re-reviewed by the senior pathologist (J.S.).

GISTs = gastrointestinal stromal tumors
CI = confidence interval

Ninety-three GISTs were diagnosed, either originally or retrospectively, following the review of all pathological reports dealing with GI spindle cell tumors. All tumors were defined as GISTs only if they displayed c-kit (CD117) immunopositivity. Additional immunohistochemistry studies were performed (CD34, CD117, Ki67, P53, Bcl2, MSA, Calponin, S100) to corroborate the diagnosis. The tumors were subdivided into three categories: spindle cell, epithelioid, and mixed type [9]. Tumor size was recorded as the largest diameter of the primary tumor and stratified according to the following diagnostic/prognostic criteria:

PROBABLY BENIGN

- Intestinal tumors: Maximum diameter ≤ 2 cm *and* no more than 5 mitoses per 50 high power fields.
- Gastric tumors: Maximum diameter ≤ 5 cm *and* no more than 5 mitoses per 50 HPFs.

PROBABLY MALIGNANT

- Intestinal tumors: Maximum diameter ≥ 5 cm *or* more than 5 mitoses per 50 HPFs
- Gastric tumors: Maximum diameter ≥ 10 cm *or* more than 5 mitoses per 50 HPFs.

UNCERTAIN OR LOW MALIGNANT POTENTIAL

- Intestinal tumors: Maximum diameter > 2 cm but ≤ 5 cm *and* no more than 5 mitoses per 50 HPFs
- Gastric tumors: Maximum diameter > 5 cm but ≤ 10 cm *and* no more than 5 mitoses per 50 HPFs.

The mitotic count was performed on 50 HPFs, with a microscope with wide field oculars (the area of a single HPF being approximately 0.5 mm^2). According to the results of the histological evaluation, tumors were classified as probably benign, of uncertain malignant potential, or probably malignant GISTs [16].

RESULTS

The study group comprised 93 patients diagnosed with GISTs – 40 females and 53 males with a ratio of 1:1.3. Age ranged between 26 and 89 years (mean 62 years, median 63 years).

Of all the GISTs in this series, 40.9% (38 patients) were classified as probably malignant, 39.8% (37 patients) as probably benign tumors and 19.4% (18 patients) as of uncertain malignancy. Fifty-six neoplasms were located in the stomach, accounting for 60.2% of all GISTs, 29 tumors originated in the small bowel (31.2%), 4 in the duodenum (4.3%), 2 in the colon (2.1%) and 2 in the pelvis (2.1%) most probably of rectal origin [Table 1].

GI = gastrointestinal
HPF = high power fields

Table 1. Clinical presentation

Symptom	Stomach: (n=56)	Duodenum: (n=4)	Small bowel: (n=29)	Large bowel: (n=2)	Rectum: (n=4)
Bleeding	27	4	10		1
Abdominal pain					
Acute (including perforation)	4		11		
Chronic (with and without palpable abdominal mass)	9		3	1	1
Asymptomatic (incidental finding)					
Diagnostic studies	9		2		
During surgery	5		2	1	
Histological	2		1		

A statistically significant correlation was found between age and the malignant potential of the GIST. By dividing the patients into three age groups it was clearly shown that the GISTs were malignant in 64.7% (11 patients) in the younger age group (26–49 years old), in 45.5% (20 patients) in the age group 50–69 years, and in only 21.9% (7 patients) of those aged 70 years and over were the GISTs malignant ($P = 0.010$). The mean age of the patients in the malignant GIST group was 56.9 years as compared to 62.3 in the group with tumors of uncertain malignant potential and 67.4 in the group with benign tumors.

The most common clinical presentation was gastrointestinal bleeding: 45.2% of all patients (n=42) presented with this clinical picture, most in the gastric GIST group (27 patients, 48.2% of all gastric GISTs) compared to 14 patients in the small bowel group (including the duodenum), comprising 42.4% of all small bowel and duodenal GISTs. The second most common form of presentation was acute or chronic abdominal pain, a leading symptom in 31.2% of all patients [Table 1]. The duration of symptoms varied between 1 week or less in 44% of our patients to as long as 1 year in 8% of the patients.

Of 85 patients with stomach and small bowel GISTs, 45 (52.9%) were admitted on an emergency basis, 12 of whom (26.7%) were operated upon urgently, with the other 33 patients undergoing surgery upon stabilization but during the same admission. Nine patients (31%) with small bowel GISTs required urgent surgery as compared to only three patients (5.4%) with gastric GISTs.

Only 3 of 19 patients (15.8%) with malignant gastric GISTs presented with synchronous metastases as compared to 8 of 15 patients (53.3%) with malignant small bowel GISTs.

Surgery was performed in 92 patients, while one patient with a huge GIST of the small bowel, who presented with simultaneous lung metastases, was medically managed with surgery being deferred. A variety of surgical procedures was performed [Table 2].

Table 2. Operations performed

	Overall	B	UM	M
Stomach – 56 patients				
Wedge resection	28	10	4	7
+ Nissen fundoplication		2		
+ TAH + BSO		1		
+ Lt colectomy due to carcinoma of colon		1		
+ Rt colectomy due to carcinoma of colon		2		
+ Distal pancreatectomy				1
Distal gastrectomy	12	7	3	
+ splenectomy			1	
+ abdominal wall resection				1
Proximal gastrectomy	14	2	1	5
+ splenectomy			2	1
+ splenectomy + distal pancreatectomy				2
+ RFA of liver metastases				1
Total gastrectomy (due to carcinoma of stomach)	2	1		
+ cholecystectomy		1		
Duodenum – 4 patients				
Segmental duodenectomy (wedge resection)		1	1	1
Whipple's operation + transverse colectomy				1
Small bowel – 28 patients				
Resection	25	5	5	8
+ colectomy		2		1
+ Nissen fundoplication			1	
+ colectomy + partial nephrectomy + wedge resection of duodenum				1
+ cholecystectomy + 2 liver metastases resection				1
+ colectomy + partial cystectomy + right salpingoophorectomy				1
Whipple's operation	1	1		
Enucleation of multiple tumors from abdominal cavity	2			2
Large bowel – 2 patients				
Rt hemicolectomy		1		
Lt hemicolectomy				1
Rectum – 2 patients				
Anterior resection + TAH + BSO				1
Abdominal mass biopsy				1

B = benign, UM = uncertain malignant potential, M = malignant, TAH + BSO = transabdominal hysterectomy and bilateral salpingoophorectomy, RFA = radiofrequency ablation.

As previously stated, positive immunohistochemical staining for CD117 was an absolute criterion for establishing the diagnosis of GIST. Bcl-2 – one of the anti-apoptotic cellular factors – was strongly expressed in 90% of all GISTs, malignant as well as benign, and CD34 was observed in 78% of cases. P53, on the other hand, was very weakly immunopositive or absent altogether in about 90% of all GISTs. The smooth muscle markers, muscle-specific actin and calponin, were mostly negative or very focal and weakly positive.

The size of gastric benign tumors and gastric tumors of uncertain malignancy ranged from 1.7 to 6 cm with a mean of 3.5 cm; in benign tumors and tumors of uncertain malignancy of the small bowel the sizes ranged from 0.9 to 2.5 cm with a mean of 1.7 cm. The size of malignant GISTs in the stomach ranged from 3 to 22 cm with a mean of 9.2 cm, and in the small bowel tumor group the range was 3–24 cm with a mean of 10 cm.

Atypia was observed in 86% of the malignant GISTs versus only 6.4% of the benign tumors or tumors of uncertain malignancy. The epithelioid component was observed in 51.6% of the malignant cases (22.6% of which were composed entirely of the epithelioid population, the other cases consisting of a mixed spindle cell/epithelioid population). In the benign tumors and those of uncertain malignant behavior, the epithelioid component was observed in only 29% of cases, 55% of which consisted entirely of epithelioid cells.

The mitotic index in the benign and uncertain malignant potential cases ranged from virtually no mitotic activity to 5 mitotic figures/50 HPF in several cases. The mean mitotic activity was 1.31 MF/50 HPF. The mitotic activity in the malignant GISTs ranged from occasional cases with no mitotic activity to 190 MF/50 HPF, with a mean of 33 MF/50 HPF. Necrosis was observed in 74.2% of the malignant GISTs and in only one of the GISTs diagnosed as benign or of uncertain malignant potential.

These results confirm the previously published criteria for malignancy, showing a prominent difference between the malignant and benign/uncertain malignant potential cases regarding size, presence or absence of the epithelioid component, atypia, mitotic activity and presence or absence of tumor necrosis. Ki-67 showed a wide range of positivity, from 0.01% to 51% and no correlation with other factors.

The follow-up period for patients with malignant GISTs and with tumors of uncertain malignancy ranged between 4 and 153 months. Mean overall survival time for malignant gastric GISTs was 102.6 months (95% confidence interval 74.2–131.1) as compared to 61.4 months mean overall survival for malignant small bowel GISTs (95% CI 35.7–87) (P = 0.262, Kaplan-Meier survival analysis) [Figure 1].

The mean disease-free survival period for patients with malignant gastric GISTs was 97.5 months (95% CI 69.7–125.2) as compared to only 49.6 months (95% CI 27.4–71.7) for patients with malignant GISTs in the small bowel (P = 0.041) [Figure 2].

DISCUSSION

Although Mazur and Clark [19] introduced the term GIST in 1983, it is only in the last few years that this particular group of neoplasms has gained interest. In reviewing the literature on GISTs it becomes clear that classifications and terminologies are continuously being revised and redefined [9,16].

MF = mitotic figures

Figure 1. Overall survival for malignant gastric and small bowel GISTs

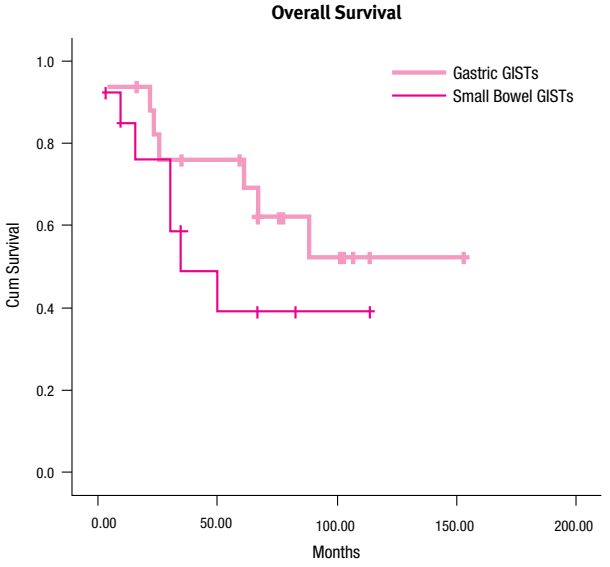
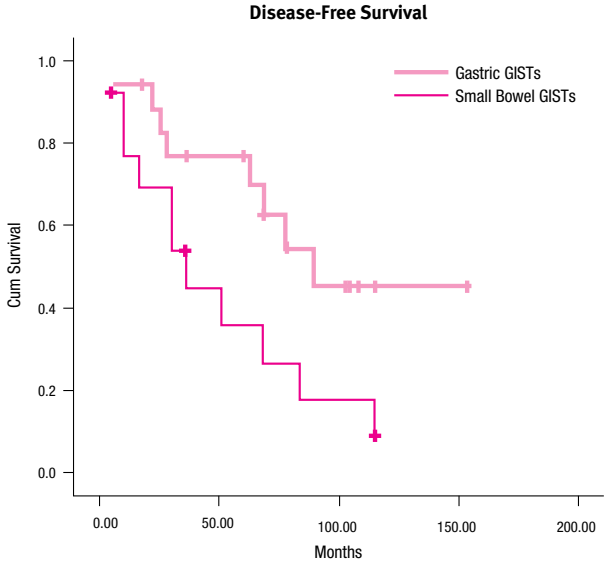


Figure 2. Disease-free survival for malignant gastric and small bowel GISTs



We reviewed all GI tumors previously diagnosed as leiomyomas, leiomyosarcomas, leiomyoblastomas and schwannomas and redefined them as GISTs only when the specific immunophenotype of these tumors was presented and in particular only when CD117 immunopositivity was given. According to criteria established by Newman et al. [20], 93 patients met these criteria and therefore entered the study.

Our study is similar to other reports regarding tumor location, male/female ratio, age, symptomatology and the process of diagnosis and treatment. However, our study differs in several aspects: 23.6% of the GISTs in our series were diagnosed as incidental findings during other operations or diagnostic procedures for varying complaints. We cannot be certain whether or not these small GISTs found incidentally were the precursor lesions for future large/malignant GISTs. A review of the literature did not reveal any study addressing this issue. Trupiano and co-workers [21] excluded the 1 cm incidental gastric GISTs from their study and as a result the number of benign GISTs equaled the number of malignant GISTs.

Another point adressed in our work was the correlation between age and the malignant potential of the GISTs – the younger the patients the higher the incidence of malignancy: 64.7% of patients in the age group 50 years and less were diagnosed with malignant tumors as compared to 45.5% in the age group 50–69 years and only 21.9% in the group aged 70 and over. This difference was statistically significant (P = 0.010). No similar data were found when reviewing other reports.

Another interesting finding was that in four patients the GISTs were located in the duodenum – a rare location for the development of primary neoplasms in general and GISTs in particular. Two of the GISTs were malignant, one was of borderline malignancy and one was a benign GIST.

Miettinen and colleagues [15] reviewed 3250 mesenchymal tumors based on the data accumulated during a 26 year period at the Armed Forces Institute of Pathology and the Haartman Institute of the University of Helsinki. Altogether, 156 neoplasms were located in the duodenum and defined as GISTs, based on the outcome of histological evaluation and CD117 expression. The authors concluded that the majority of duodenal mesenchymal tumors were GISTs, with a spectrum ranging from small indolent tumors to overt sarcomas. This study showed a correlation between size (> 5 cm) and mitoses (> 5/50 HPF) on the one hand and prognosis on the other, as was found in our three patients.

The finding that small bowel GISTs behave more aggressively than gastric GISTs has also been reported in other series [9,16,22,23]. However, the observation that a high percentage of these patients with small bowel tumors undergo emergency procedures has not been reported.

The golden standard treatment for GIST is surgical extirpation. Table 2 presents the procedures that we performed on our 92 patients. Our basic approach was extensive resection and multi-organ resection to achieve free tumoral margins.

To conclude, our study is similar to other studies with regard to the age of diagnosis, tumor location, clinical and morphological presentation of the tumor, immunohistological evaluation and biological behavior, based on the criterion of benign versus malignant characteristics. However, three points of interest were found: the higher percentage of malignant GISTs in patients under the age of 50, the rate of

emergency operations in the small bowel GIST group, and the high incidence of incidental GISTs. An aggressive surgical approach should be adopted as the treatment of choice. High risk GISTs are associated with increased disease recurrence and decreased survival despite complete surgical resection. These patients should be considered for adjuvant therapy with tyrosine kinase inhibitors [24,25].

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