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Malignant Gastrointestinal Stromal Tumors of the Small Intestine: A Review of 50 Cases From a Prospective Database

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Background: Malignant gastrointestinal stromal tumors (M-GIST) are rare mesenchymal tumors originating in the wall of the gastrointestinal (GI) tract. Previous studies have included limited numbers of patients, and most included malignant and benign cases from throughout the GI tract. We reviewed the experience of a single tertiary cancer care center with M-GIST of the small intestine only.

Methods: A prospective database identified all patients seen from 1989 to 1998. Clinical and pathological data, treatment, and outcome were analyzed. Overall median follow-up time was 24 months (range, 1-176 months).

Results: Fifty patients (31 male, 19 female) were identified. Mean age at diagnosis was 55 years. Disease was localized in 11 patients, locally advanced (invasion into adjacent organs/peritoneum) in 24 patients, perforated in 4 patients, multiple primary lesions in 2 patients, and distant metastases in 9 patients. All patients underwent resection, which was complete in 70%. Locoregional recurrence (LR) developed in 43% (median, 25 months), and distant metastases in 59% (median, 21 months) of patients at risk. At last follow-up, 14 patients were alive (6 disease-free), 2 had died disease-free, and 34 died with recurrent disease. Overall survival (OS) was similar for localized and locally advanced disease; OS also was similar for patients with multiple primaries and distant metastases at diagnosis. Patients were grouped into three stages: (I) patients with localized and locally advanced disease; (II) patients with perforated; and (III) patients with multiple primaries and distant metastases. Actuarial OS at 5 years was 41% ($n = 50$)—42% for those with complete resection and 8% for incomplete resection. Univariable analysis showed that earlier stage at diagnosis ($P = .001$) and completeness of resection ($P = .004$) predicted for longer OS.

Conclusions: Most patients with M-GIST of the small intestine relapse following resection, but survival may be prolonged. In univariable analysis, stage at presentation and complete resection were significant prognostic variables for OS; grade was not significant. Localized and locally advanced M-GIST of the small intestine have a mean OS > 5 years. Complete resection should be the goal of initial surgical treatment.

Key Words: GIST—Gastrointestinal stromal tumors—Intestinal sarcoma—Small intestinal neoplasms.

Gastrointestinal stromal tumors (GIST) are uncommon mesenchymal tumors that arise in the wall of the gastrointestinal (GI) tract. They account for approximately 0.1% to 3% of all gastrointestinal neoplasms, with about 150 new cases per year diagnosed in the United States.[1] The term GIST, first used by Mazur and Clark in 1983, encompasses a heterogeneous group of nonepithelial neoplasms composed of spindle or epithelioid cells, which display a range of differentiation.[2] There has been considerable debate in the literature regarding the nomenclature, origin, differentiation, and clinical behavior of these tumors. Mesenchymal tumors of the GI tract previously were thought to be smooth muscle neoplasms (leiomyomas and leiomyosarcomas); however the clinical behavior of GISTs differs from classical smooth muscle tumors in other locations. In the 1980s, immunohistochemical studies demonstrated that

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most of these tumors do not show complete differentiation toward smooth muscle.[3] GISTs may have either well-developed or incomplete myoid, neural, autonomic nerve/ganglionic, or mixed myoid/neural differentiation, or may remain undifferentiated.[4] The cell of origin of these tumors is thought to be a stem cell that differentiates toward the interstitial cell of Cajal. This theory was first proposed by Kindblom in 1998, supported by the finding that positivity for unique markers such as CD117 is common to the two cell types.[5] Other reports have concurred with these observations.[6–9] Investigators also have characterized the mutations seen in the c-*kit* protooncogene and found an association between the presence of c-*kit* mutation and prognosis in human GISTs.[10–15]

Numerous authors have reported on the clinical behavior and prognostic factors of GISTs. Because these tumors are uncommon, most series are composed of cases accumulated over long periods, or from sites throughout the entire GI tract,[16–21] although it is known that they differ according to site.[21,22] Furthermore, many of the case series in the literature contain a substantial proportion of tumors that were clinically or histologically benign (e.g., leiomyomas or schwannomas).[19,21,23,24] There have been three studies of GISTs of the small intestine only, all of which included both clinically benign and malignant tumors in an attempt to retrospectively identify pathologic predictors of malignant clinical behavior. In these three series, there were 25, 15, and 15 cases, respectively, of malignant GIST, collected over lengths of time that varied from 11 to 25 years.[25–27]

Currently, there is no widely accepted method of staging for GISTs, although systems have been proposed by Ng,[17] who suggested one based on a TGM (tumor, grade, metastases) system, and by Horowitz,[28] whose proposal was based on combinations of adverse prognostic factors. A proposed classification system that included tumor size, regional nodal status, metastases, and histopathological grading was reviewed by the UICC in 1993.[29] However, GISTs seldom metastasize to regional lymph nodes, and grade as a prognostic variable is controversial. Thus, this classification has not yet been accepted for use by the UICC.

In this study, we document the clinical behavior of GISTs of the small intestine as a specific group and analyze the extent of tumor at presentation, patient outcome, predictors of survival, and patterns of recurrence.

METHODS

The prospectively collected sarcoma database created in 1989 at Princess Margaret Hospital (PMH) in Toronto was searched to identify all patients with a diagnosis of malignant GIST referred from 1989 to 1998. Inclusion in this series was based on review of the operative specimen by one of the pathologists associated with PMH, performed at the time of referral. For the present study, all patients whose tumors were classified as sarcoma of the small intestine (1989–1996) or malignant GIST of the small intestine (1993–1998) were included ($n = 50$). Clinical and pathologic data were taken from the database, and the information was augmented with a chart review and follow-up with the patient's family physician.

Patient data collected included age, sex, details of diagnosis, clinical presentation, investigations, treatment, and outcome. Details of clinical presentation included symptoms, extent of disease at presentation, date of diagnosis, and history of treatment before referral to our center, if any. Treatment and outcome data collected included type of resection, adjuvant treatment, development of locoregional recurrence or distant metastases, and status at last follow-up. No analysis of the effect of adjuvant therapy was attempted, because only 20% of patients had received it.

Pathologic data included tumor size (largest diameter classified as < 5 cm, 5 to 10 cm, or > 10 cm), cellularity, presence or absence of nuclear pleomorphism and/or necrosis, mitotic counts (number of mitoses per 10 high-power fields), and invasion into the mucosa. For patients who had presented initially to another institution, a Princess Margaret Hospital pathologist reviewed the original specimen at the time of referral. As part of the present study, all retrievable cases ($n = 29$) were independently reviewed by a single pathologist (R.K.) to confirm the diagnosis of GIST and to allow regrading of the tumors according to the most current pathologic standards. Our analysis of grade as a prognostic factor was based on the 29 retrievable cases, using the grade assigned by R.K. Mitotic count (number of mitoses per 10 high-power fields) was analyzed based on counts recorded in the original PMH pathology review. The current pathological review ($n = 29$) identified one case in which pathologic confirmation of the diagnosis of malignant GIST was problematic and one in which the patient had a concurrent gastric carcinoma. The details of these two cases were carefully reviewed. For one case originally diagnosed as epithelioid GIST, review of immunohistochemical stains revealed some focal staining for low-molecular-weight keratin, raising the possibility that the tumor was a spindle cell carcinoma. However, the clinical behavior of the tumor was consistent with GIST. The second case involved a patient with multiple GISTs of the jejunum and ileum who had a concurrent small, localized, node-negative adenocarcinoma of the stomach

resected at the same time as his GIST. This patient developed symptomatic tumor progression and underwent debulking of a mass, which had become incarcerated in a ventral hernia. This recurrent tumor was histologically identical to his primary GIST, and there was no evidence of recurrent adenocarcinoma. Based on the considerations described, both cases were included in the present analysis.

Resection was considered to be complete when all grossly evident disease was resected at the initial operation, and incomplete when there was residual locoregional or distant metastatic disease. Locoregional recurrence was defined as an intra-abdominal relapse localized to a single site. Multiple or diffuse peritoneal implants (sarcomatosis) were classified as distant metastatic disease, as were recurrences at other intra- or extra-abdominal sites (e.g., liver, lung, or bone).

Patient, tumor, treatment, and outcome variables were analyzed. Descriptive statistics were calculated using frequencies, means, standard deviations, and medians as appropriate to the type of data. All times were calculated from the date of diagnosis until the particular end point examined (recurrence, patient death, or date of last follow-up), reported in months. The a priori hypothesis was that tumor size, stage at presentation, and type of resection would predict for overall survival (OS) and disease-free survival (DFS). All figures for overall survival refer to disease-specific survival.

Survival was calculated using the Kaplan-Meier[30] and life table methods.[31] Univariable and multivariable analyses were conducted using the Cox model.[32] A P value of $\leq .05$ was considered significant. Variables with a P value of $\leq .10$ in univariable analysis were maintained for analysis in the step-wise, multivariable Cox model.

Results

Patient Characteristics

From February 1989 through October 1998, 50 patients were referred to PMH with malignant GIST of the small intestine. This represented 3.9% of all patients referred to PMH with any sarcoma, and 28% of all visceral sarcomas seen over the same time period. Referral regarding management of malignant GIST was made at the time of primary diagnosis in 78% and at the time of recurrence in 22%. Referrals were made by a tertiary care center in 20 cases (19 from University of Toronto teaching hospitals) and from community hospitals in 26 cases. In 4 cases patients had their initial surgery at a hospital outside of Canada. There were 31 men (62%) and 19 women (38%). The mean and median age of patients were both 55 years (range, 36–76 years) (Table 1). Prior or concurrent malignancy was documented in 3 patients: one patient had ovarian cancer diagnosed 7 years prior to GIST; one patient had cervical cancer diagnosed 27 years prior to GIST; and one patient had gastric adenocarcinoma diagnosed concurrently with GIST (see Methods).

All patients in this series had one or more signs or symptoms, most commonly abdominal pain (74%), abdominal mass (72%), GI bleeding (44%), and partial or complete small bowel obstruction (44%). Other patients developed weight loss (16%), fever or abscess (14%), and urinary symptoms (12%).

Tumor Characteristics

All tumors were located in the small intestine: 10% in the duodenum; 34% in the jejunum; 30% in the ileum; and 18% in a location described only as small bowel. In 8% of cases there were tumors in multiple discrete locations within the small intestine. Both mean and median tumor size were 11.0 cm (range, 2.5–27 cm). In the 29 cases retrievable for re-review, tumor grade was rated as high in 21 cases (72%) and low in 8 cases (28%). Mean mitotic count per 10 high-power fields ($n = 41$) was 6.8 (median 7.6, range 0–33) (Table 1). Regional lymph node status was documented in only 15 cases: nodes were involved in 4 cases (27%) and uninvolved in 11 cases (73%). Because lymph node status was not re-

TABLE 1. *Clinical and pathologic characteristics*

	No. (%)	Mean	Median
Sex	50		
Male	31 (62)		
Female	19 (38)		
Age (y)	50	54.9	55.0
36–45	12 (24)		
46–55	14 (28)		
56–65	11 (22)		
66–76	13 (26)		
Tumor size (cm)	49	11.0	11.0
<5	5 (10)		
5–10	19 (39)		
>10	25 (51)		
Tumor grade	29		
Low	8 (28)		
High	21 (72)		
Mitotic count (per 10 high-power fields)	41	6.8	4.0
Type of resection	50		
Complete	35 (70)		
Incomplete	15 (30)		
Margins (in patients with complete resection)	35		
Negative	22 (63)		
Microscopic positive	9 (26)		
Unknown	4 (11)		

ported for 35 of the 50 patients, the true lymph node positivity rate could not be determined.

Extent of Disease Classification

In 11 cases (22%) the tumor was confined to the site of origin (small intestine and adjacent mesentery); we classified this as localized disease (Table 2). In 24 cases (48%) the tumor invaded into adjacent organs or peritoneum; we classified this as locally advanced disease. The most common sites of direct local extension were adjacent peritoneum or omentum (with no other tumor implants), a noncontiguous segment of small bowel, bladder/ureter, colon, and abdominal wall. Four patients (8%) had perforation of their tumor discovered at laparotomy. In 2 patients (4%) multiple primary lesions within small bowel (without distant metastases) were seen. Nine patients (18%) presented with distant metastatic disease. We included patients with multiple peritoneal implants (sarcomatosis) in this category. In these 9 patients, the sites of distant metastases were as follows: liver only ($n = 2$); omentum or peritoneum only (n = 5); and liver plus omentum or peritoneum ($n = 2$).

Surgical Management

All patients underwent surgical resection. Complete gross resection was achieved in 70% of cases, with 30% of patients having gross residual local or distant metastatic disease. Of the 35 patients who underwent complete resection, microscopic margins were recorded as negative in 22 patients (63%) and positive in 9 patients (26%); they were not recorded in the other 4 patients (11%). However, most of the margins examined were axial on the small bowel or resected adjacent organs, and very few comments were made regarding the circumferential margin. All 11 patients presenting with localized primary tumors had complete resection, as did 19 of 24 patients with locally advanced disease and all 4 patients with perforations. Neither of the 2 patients with multiple primary lesions and only 1 of 9 patients with distant metastases (omental and peritoneal nodules) had complete resection (Table 2).

TABLE 2. *Extent of disease at presentation and rate of complete resection*

	Total per group	Complete resection
	No. (%)	No. (%)
Localized to intestinal site of origin	11 (22)	11 (100)
Locally advanced (invasion of adjacent organs and/or peritoneum)	24 (48)	19 (79)
Perforation at diagnosis	4 (8)	4 (100)
Multiple primary lesions	2 (4)	0 (0)
Distant metastases at diagnosis	9 (18)	1 (11)
Total	50	35

Adjuvant Therapy

Adjuvant treatment was administered in approximately 20% of patients. Ten patients received adjuvant radiotherapy. Two patients were treated preoperatively, one for a fixed pelvic mass, and the other for a fixed left upper quadrant mass. One had treatment terminated at 28 Gy due to sepsis, and the other received 50 Gy in 2-Gy fractions. Postoperative radiotherapy was given to eight patients, all of whom had well-defined and fixed areas of tumor adherence that could be encompassed with a radiation field postoperatively. This included the pelvis in six cases, the anterior abdominal wall in one case, and the retroperitoneum in another. The median postoperative dose given was 45 Gy in 1.8-Gy fractions (range, 45 Gy–60 Gy). Adjuvant chemotherapy was not given. Palliative radiotherapy was given to 1 patient, and palliative chemotherapy was given to 16 patients, all for symptomatic recurrences. Twelve of these 16 patients had distant metastases, 3 had local recurrence, and 1 had both distant and local metastases.

Outcome

Median follow-up time for the 50 patients was 24 months (mean 38, range 1–176). For the 16 patients alive at last follow-up or dead of other causes, median follow-up time was 20 months (mean 35, range 8–101 months). All patients had complete follow-up, with documentation of the time to radiologic or symptomatic recurrence. At last follow-up, 14 patients were alive (28%), 6 with no evidence of disease. Thirty-six patients were deceased (72%), 2 with no evidence of disease, 8 with locoregional recurrence, 26 with distant metastases, and 10 with both locoregional and distant metastases.

Overall disease-specific actuarial survival for the total group ($n = 50$) was 84% at 1 year, 51% at 3 years, and 41% at 5 years (Fig. 1). Disease-free actuarial survival was 59%, 24%, and 18% at 1, 3, and 5 years, respectively. The median disease-specific overall survival for the total group was 29.9 months (mean, 36.6; range, 1–176 months), with a median disease-free survival of 16 months (mean, 23.3; range, 0–91 months). When analyzed by type of resection, 5-year actuarial survival was 42% for patients with complete resection, but only 8% for patients with incomplete resection (Fig. 2). The complete resection group had a median overall survival of 50 months (mean, 60; range, 4.5–176 months) compared to the patients with incomplete resection who survived a median of 20 months (mean, 29; range, 1–157 months). This difference was statistically significant ($P = .004$).

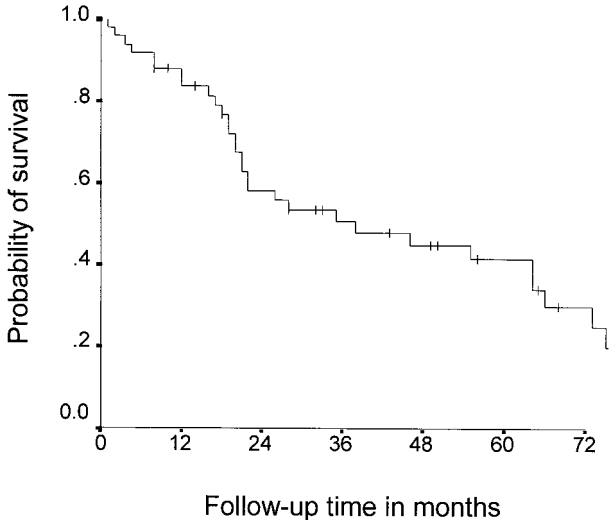

FIG. 1. Overall disease-specific actuarial survival in 50 patients with malignant small intestinal GIST.

There was no significant difference in disease-free survival between these two groups.

Comparison of survival data according to extent of disease at presentation found no difference in overall or disease-free survival between patients with localized ($n = 11$) and locally advanced ($n = 24$) disease. Similarly, there was no difference in survival between patients with multiple primary lesions ($n = 2$) and those who presented with distant metastases ($n = 9$). For all further analysis, patients were re-grouped into the following clinical stages (Fig. 3): stage I, localized or locally advanced disease, 35 patients; stage II, patients who presented with perforated tumors at diagnosis, 4 patients; and stage III, patients with multiple primary lesions or distant metastases at diagnosis, 11 patients. When analyzed according to clinical stage at presentation, actuarial overall 5-year disease-specific survival was 46% for stage I, 24% for stage II, and 0% for stage III ($P = .001$) (Fig. 4). Patients with stage I disease had a median overall survival of 55 months (mean, 62.5; range, 1–176, months).

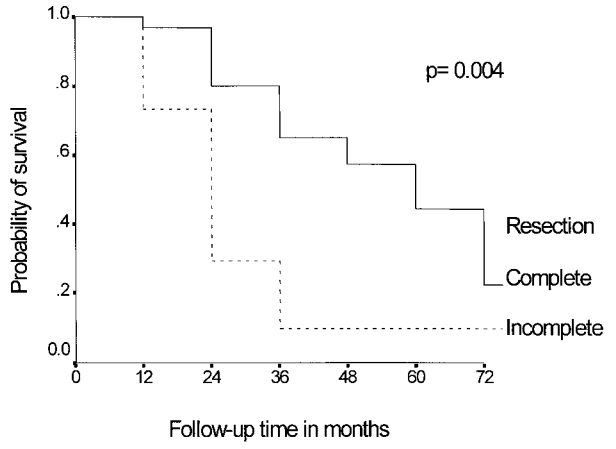

FIG. 2. Overall disease-specific actuarial survival according to type of surgical resection: complete vs. incomplete.

Analysis of Prognostic Variables

Potential prognostic variables were evaluated. On univariable analysis only stage at presentation ($P = .001$) and type of resection ($P = .004$) were significant predictors of overall survival. Age, gender, tumor size, tumor spill (including patients with either preoperative tumor perforation [$n = 4$] or tumor spill during the course of resection [$n = 8$]) and histologic grade were not predictive of survival. Mitotic count, stratified as less than 2 versus 2 or more showed a trend toward predicting survival with a P value = .09, but was not significant (Table 3). On multivariable analysis, neither stage nor type of resection remained significant, although stage at presentation showed a trend toward longer survival ($P = .07$). None of the variables analyzed were significant predictors of disease-free survival by univariable analysis, although lower stage trended toward longer disease-free survival ($P = .09$).

Pattern of Recurrence

Thirty-five patients underwent complete resection and thus were at risk for locoregional recurrence; 15 of these patients (43%) recurred at a median of 25 months (mean, 25.5; range, 4–81 months). In the 41 patients presenting without distant metastases, 24 patients (59%) developed metastases at a median of 21 months (mean, 31; range 2–91 months). In these 24 patients, the most common sites of distant metastases were the liver and the peritoneum or omentum (sarcomatosis) (Table 4). Only 2 patients developed extra-abdominal metastases, to bone and lung in one patient, and to bone and subcutaneous site, as well as liver, in the other patient.

All patients who received adjuvant radiotherapy subsequently relapsed. In six cases, relapse was outside the radiation field, in three cases it was inside the radiation field, and in one case the site of relapse relative to the radiation field could not be determined.

Seven of the 15 patients who developed locoregional recurrence underwent complete gross resection of recurrent disease. One of these patients had peritoneal implants completely resected along with the locally recurrent lesion. One patient was alive at last follow-up, 40 months post re-resection, but developed liver metastases 8 months after re-resection. The other 6 patients relapsed

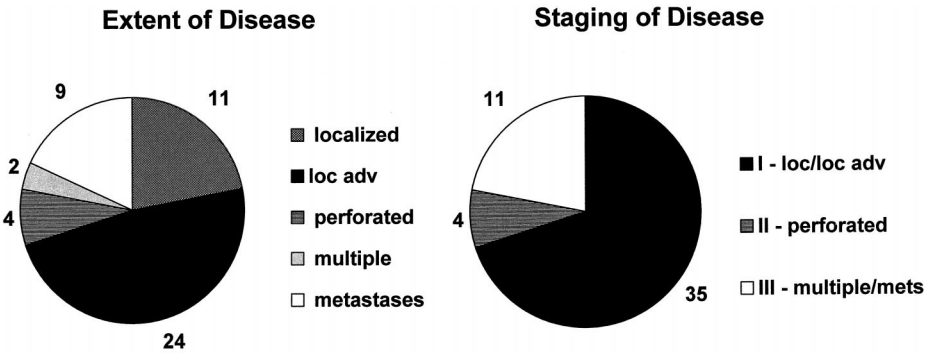

FIG. 3. Reclassification of 50 patients with malignant small GIST into three stages, according to extent of disease at presentation.

again (2 locoregional, 4 metastatic) and died at a median of 33 months post re-resection (mean, 39; range, 20–83 months) and a median of 68 months from initial diagnosis (mean, 73; range, 33–157 months).

Of the 15 patients who developed locoregional recurrence, only 4 did not ultimately develop distant metastatic disease. Three of these 4 patients with locoregional recurrence only have died of disease at a median of 6 months following diagnosis of recurrence (mean, 9; range, 1–20 months). Eighteen of the 24 total patients who developed distant metastases died, with a median time from diagnosis of metastases to death of 17.5 months (mean, 19.3; range, 2–85 months).

Of the 35 patients at risk for any type of recurrence, only 8 patients (23%) remained free of disease at the last follow-up; 2 patients were dead of other causes with no evidence of disease.

DISCUSSION

GISTs are infrequently encountered mesenchymal tumors of the GI tract. We identified 50 cases of malignant GIST of the small intestine from a prospective database at a tertiary care cancer center. Follow-up, undertaken at our institution, was complete in all cases. The strengths of our study compared to other series include the number of cases, the uniformity and completeness of follow-up, and the relatively short time frame over which the cases were collected.

The present study focuses specifically on GIST of the small intestine. There are three previous series in the literature reporting on GIST of the small intestine specifically, comprised of 25, 15, and 15 patients with malignant GIST.[25-27] These series divided the patients according to outcome ("adverse versus non-adverse"), and looked retrospectively for prognostic factors that discriminated between the two groups. The first two series did not report data on survival times or time to development of recurrence. A series of sarcomas of the large and small bowel reported by the group at Roswell Park included 32 patients with sarcomas of the small bowel; however, there was no separate analysis of small versus large bowel tumors.[28] Of the nine other reports in the recent literature that include substantial numbers of small bowel sarcomas, two do not give a specific sub-

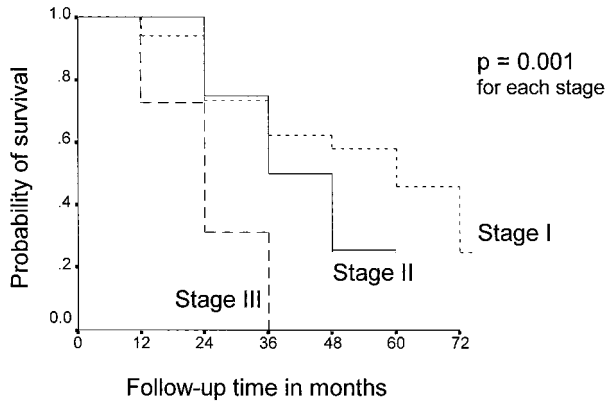

FIG. 4. Overall disease-specific actuarial survival according to stage of disease at presentation.

TABLE 3. *Univariable analysis of prognostic variables*

	Beta coefficient	*P* value	Hazard ratio	Confidence interval
Type of resection Complete Incomplete	1.052	0.0042	2.86	1.39–5.89
Stage at presentation Localized/locally advanced Perforated Multiple primaries/metastases	0.758	0.0012	2.13	1.35–2.27
Tumor size <5, 5–10, or >10 cm	−0.02	0.61	0.98	0.91–1.06
Mitotic count <2 or ≥2	−0.786	0.09	0.46	–
Tumor spill	−0.162	0.69	0.85	–
Histologic grade	0.615	0.29	1.85	–

TABLE 4. *Patterns of distant recurrence in malignant small intestinal gastrointestinal stromal tumors*

Site of recurrence	Number with distant metastases	% of all patients with distant metastases
Total developing metastases	24	100
Liver only	12	50
Sarcomatosis only (peritoneal and/or omental deposits)	3	13
Liver + sarcomatosis	7	29
Extra-abdominal	2	8
Lung + bone	1	4
Liver + bone + subcutaneous	1	4

group analysis of the survival, patterns of recurrence, and prognostic factors for small intestinal GIST.[33,34] Ng et al.[17] reported on prognostic factors for GI sarcomas throughout the GI tract, but gave some subgroup analysis on small intestinal tumors. The other six papers include fewer than 20 cases or present limited information regarding small bowel tumors.[21,35–39]

Our recent analysis of GISTs at all sites in the GI tract suggested that the clinical behavior of small intestinal GISTs differ from that of gastric or colorectal GISTs.[40] This is a controversial topic, however, and some other authors have concluded that the behavior of GISTs is similar regardless of site.[16,35] On the other hand, there is considerable evidence in the literature that anatomic site does have prognostic implications, with small bowel GIST having a worse prognosis than gastric.[36,39] A study published by Emory et al. in 1999 examined 1004 cases of GIST. Anatomic site was a highly significant independent predictor of survival in a multivariable analysis; patients with small intestinal tumors had poorer survival than those with gastric tumors. However, both benign and malignant tumors were included in their series, and the precise number of benign lesions at each site is not clear.[21]

All patients in the present series were symptomatic, likely reflecting the large median tumor size of 11 cm. This is in agreement with the findings of Ludwig et al.[23]: in their series, GISTs detected incidentally at laparotomy and had a mean size of 1.5 cm, whereas the mean size of symptomatic tumors was 6 cm. The spectrum of symptoms documented in our series is similar to that reported by other investigators[16,23,26,28,36,41] We were unable to determine whether there was significant delay or difficulty in reaching a diagnosis.

Currently there is no universally accepted staging system for GIST. Ng et al.[17] proposed a classification based on a TGM system: T1 = localized and <5 cm; T2 = localized and ≥ 5 cm; T3 = contiguous organ invasion or peritoneal implants; and T4 = tumor rupture. G was divided into low or high grade, and M into presence or absence of distant metastases. They found that survival correlated with stage as they defined it for GISTs throughout the GI tract (5-year overall survival decreased successively from 75% for stage I to 7% for stage IVB). Horowitz et al.[28] proposed a classification based on the number of the following adverse factors present: high grade; size larger than 5 cm; invasion or perforation; and sarcomatosis. They found stage (0 or 1 versus 3 or 4) to be a significant predictor of survival.

One study including 45 malignant GI smooth muscle tumors classified disease as either localized or advanced, placing those with direct extension to other organs in the same group as patients with metastases to liver or peritoneum. They found that patients with "locally advanced" disease have a poorer prognosis; however, we feel that this probably reflects inclusion of patients with distant metastatic disease in the same category.[34] McGrath et al.[16] also found invasion of other organs to be a significant prognostic variable for GISTs throughout the GI tract, including 14 small intestinal tumors. In our series, which reports on small intestinal GIST only, tumor size was not a significant prognostic factor, and locally advanced lesions had an overall survival similar to that for localized lesions. Analysis of our survival curves showed that patients with locally advanced disease (direct extension into adjacent organs, peritoneum, or omentum) have a better outcome than those with distant metastatic disease, possibly due to the fact that 79% were able to undergo complete resection (vs. 11% of those with distant metastases).

In the patients who underwent complete resection, microscopic margins were reported as negative in 63% and positive in 26%; they were not reported in 11%. The most commonly reported margins were those on the axial small bowel. A high proportion of intestinal GISTs directly invade other organs, and the margins on the invaded organ were less frequently reported. Also, because these tumors often extend through the serosa of the bowel wall, there is potential seeding of the peritoneal cavity despite complete resection and negative axial margins on the bowel. This may explain the substantial rate of peritoneal metastases that subsequently developed in our patients (10 of 24 of patients at risk) and is reported in the literature (16 of 24 and 10 of 15 small bowel GIST patients with peritoneal metastases in 2 studies).[25,26] We did not analyze microscopic margin status as a prognostic factor. The most recent series in the literature, by DeMatteo et al.,[33] which reports on 200 patients with GISTs at all sites, did not find microscopic margin status to be a predictor of survival.

Overall disease-specific survival in this series was 84% at 1 year, 51% at 3 years, and 41% at 5 years. Disease-free survival was much lower: 59%, 24%, and 18% at 1, 3, and 5 years, respectively. The only comparable data in series of small bowel GISTs is from Dougherty et al.,[36] who found a 5-year overall survival rate of only 17% in17 patients, and Ueyama et al.,[39] who, in 28 small bowel tumors documented a 10-year overall survival rate of 17%. Horowitz et al.,[28] in a series of 32 small bowel and 7 colorectal GISTs, reported a 20% overall 5-year survival rate. In 200 cases of GISTs of all sites, DeMatteo et al.[33] found the overall survival rates at 1, 3, and 5 years to be 69%, 44%, and 35%, respectively. In the latter series, patients without metastases at presentation who underwent complete resection had a 5-year OS rate of 54%. This is similar to our results in patients with small bowel GISTs without metastases who underwent complete resection, where 5-year OS was 42%.

Our univariable analysis of prognostic variables found that only stage of disease at presentation and type of resection (complete versus incomplete) were significant predictors of overall survival. Neither variable remained significant in multivariable analysis, but stage came close to significance ($P = .07$). This may reflect the fact that patients with low clinical stage were much more likely to undergo complete resection, and, therefore, these two variables were not independent.

Several previous studies have found that histologic grade or mitotic counts[16,21,26,34,36] were predictive of survival in GIST. One study that included subgroup analysis found that grade was a significant prognostic factor for GISTs of the stomach, but not for small bowel lesions.[17] Evans et al. showed that patients with low-grade GIST had a longer disease-free interval compared to high-grade tumors, but that over 10 years the recurrence rate was equivalent.[35] Similarly, we found no correlation between tumor grade and clinical behavior in our 50 patients.

In our study, five patients had lesions that were felt to be of low rather than high grade on the pathological re-review by a single pathologist blinded to outcome. Four of these five patients have died of recurrent disease (3 metastases, 1 locoregional), and one is alive with metastases at 101 months postdiagnosis. This is consistent with previous reports showing that even patients with histologically benign lesions and no detectable mitotic figures can develop metastases and die of disease.[42–44] Taken together, these results support the conclusion that histologic grade does not correlate well with the clinical behavior of GIST, and suggests that patients with histologically benign GIST should, in fact, be treated and followed in the same way as those with histologic evidence of malignancy. The recent series from Memorial Sloan-Kettering Cancer Center did not include grade in the analysis of potential prognostic variables.[33,45]

For the present study, we defined locoregional relapse as a recurrence in the abdomen at a localized site, in contrast to sarcomatosis or diffuse peritoneal implants, which were classified as distant metastases. Our hypothesis was that the prognosis of patients with locoregional recurrence would be better than for those with sarcomatosis, particularly if the recurrence was resectable. The literature varies with regard to how these two types of recurrence are defined. In a study describing patterns of failure in GIST, Ng et al.[18] did not differentiate between the two, classifying peritoneal recurrence on the basis of resectability of tumor implants. Improved survival after relapse was seen with complete resection of peritoneal implants. Peritoneal implants were seen more often in patients with small bowel tumors than large bowel tumors, and there was no difference in the peritoneal recurrence rate between patients with localized or locally advanced disease in that study. Dougherty et al. considered locoregional recurrence and sarcomatosis separately, classifying the latter as distant metastatic disease. Of 51 patients analyzed, 15 developed liver metastases, and 8 recurred with sarcomatosis. Seven patients had isolated locoregional recurrence, and, despite resection of recurrent disease, all relapsed.[36] In 60 patients with recurrent gastrointestinal sarcoma described by Mudan et al.,[45] 23 patients presented with locoregional recurrence only, 23 patients had locoregional plus liver metastases, and 4 patients developed sarcomatosis. Thirteen of the 23 patients (57%) with locoregional recurrence only were resectable, but 10 failed again, and 7 had died of disease at last follow-up. They concluded that patients with locoregional recurrence fare no better that those with distant metastases. Our results lead us to conclude similarly that contrary to our prediction, patients with locally recurrent GIST of the small bowel have an equally poor outcome as those who relapse with distant disease. We concur with Mudan et al. that resection of recurrent disease should be directed principally at symptom control. There is some evidence that complete resection of isolated liver metastases in selected patients may improve survival, but statistically significant differences have not been documented, and most relapse again in the liver.[45]

Adjuvant radiotherapy was offered to a minority of our patients with small bowel malignant GIST. Many visceral sarcomas are not amenable to radiotherapy due to their mobility within the pelvic or abdominal compartments.[16,46] Accurate postoperative identification of the

field at risk is problematic, because contaminated loops of bowel or mesentery may relocate to remote areas. However, lesions fixed in the pelvis or attached to the abdominal wall may be suited to pre- or postoperative radiotherapy. Ten such patients in this series were treated with postoperative radiotherapy, and disease was controlled in the radiated field in six of nine evaluable cases. Typically, though, the vast size of the radiation fields needed to cover entire body cavities coupled with the very modest doses that can be administered to the abdominal viscera limits the usefulness of external beam radiotherapy as an adjuvant treatment.[36,47] No patients in this series received adjuvant chemotherapy. Gastrointestinal stromal tumors as a group appear to be very resistant to conventional cytotoxic agents.[16,38,48] However, intraperitoneal chemotherapy is currently being investigated as a treatment for intra-abdominal recurrence.[34,49]

In conclusion, GIST of the small intestine carries a high mortality rate, with only 28% of patients in our series alive at a median follow-up of 20 months, and only 12% without disease. The subgroups we identified with significantly longer overall survival in univariable analysis were those with localized or locally advanced disease at presentation (stage I) and those who underwent complete gross resection. Although most of these patients will eventually relapse and die of their disease, the mean overall survival in completely resected stage I patients is more than 5 years. We therefore advocate an attempt at preoperative diagnosis, careful surgical planning, and an effort to achieve complete gross resection in patients with malignant small intestinal GIST, even in the presence of local invasion. Because the overall and disease-free survival rates are poor for malignant GIST, novel strategies for therapy should be pursued in centers where substantial numbers of patients with malignant GIST are treated.

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