The Effect of Surgery and Grade on Outcome of Gastrointestinal Stromal Tumors

Jean-Pierre E. N. Pierie, MD, PhD; Umar Choudry, MD; Alona Muzikansky, MA; Beow Yong Yeap, ScD; Wiley W. Souba, MD, ScD, MBA; Mark J. Ott, MD

Hypothesis: Gastrointestinal stromal tumors (GIST) are aggressive, rare, and difficult-to-cure gastrointestinal tumors. We believe that the clinical behavior of these tumors can be predicted by reproducible prognostic factors.

Design and Setting: A retrospective review of all patients (N=70) with GIST treated at a tertiary care center from 1973 to 1998.

Patients: Adequate data for evaluation were available for 69 patients. Male-female distribution was 40:29. Median age was 60 years. Median follow-up duration was 38 months.

Main Outcome Measures: Tumor grade, stage, and histologic subtype at presentation; effect of grade, surgery and adjuvant therapy on recurrence, salvage, and survival.

Results: Tumor distribution included 61% in the upper, 23% in the middle, and 16% in the lower digestive tract, with a median tumor size of 7.9 cm (range, 1.8-25 cm). Tumors with more than 1 mitosis per 10 high-power fields constituted 57% of neoplasia in the series. Distant disease at initial visit occurred in 49% of patients. Complete gross resection occurred in 59% of patients. After complete resection, the 5-year survival rate was 42%, compared with 9% after incomplete resection (hazard ratio = 0.27, P<.001). Neither radiation nor chemotherapy demonstrated any significant benefit.

Among 39 patients who were disease free after complete resection, 2% developed lymph node recurrence, 25% developed local recurrence, and 33% developed distant recurrences (54% liver, 20% peritoneum). By multivariate analysis the risk of local and/or distant metastases was significantly increased for tumors with more than 1 mitosis and size larger than 5 cm (P<.05). Multivariate analysis in all 69 patients revealed that incomplete resection, age greater than 50 years, non–smooth muscle histological feature, tumor with more than 1 mitosis, and tumor size larger than 5 cm significantly decreased survival.

Conclusion: Complete gross surgical resection is presently the only means of cure for GIST. Tumors with more than 1 mitosis and a size larger than 5 cm have an especially poor prognosis, with decreased survival, and increased local and/or distant recurrence.


Gastrointestinal stromal tumors (GIST) are uncommon tumors, constituting 1% to 3% of all gastrointestinal malignant neoplasia in the United States.1-3 There has been considerable debate regarding the proper nomenclature, cell of origin, and pathological classification of this tumor of mixed phenotypes.4 The cell of origin has recently been postulated to be the interstitial cell of Cajal, an intestinal pacemaker cell of mesodermal descent.5-8 Gastrointestinal stromal tumors are known for wide variability in clinical behavior and for difficulty in determining malignancy and prognosis.9 Along with variability in the management of these patients, this difficulty in classifying GIST contributes to a wide variation in reported 5-year survival rates ranging from 19% to 56% overall, and from 32% to 63% following complete resection.1,3,10

To date, surgery remains the primary treatment modality for patients with GIST, but the extent of the resection, including regional lymph nodes or adjacent organs, remains unclear.3,11 The benefit of adjuvant radiotherapy and chemotherapy has been inconclusive, probably owing to the rarity of the disease, the indolent course of low grade tumors, and the dose-limiting tolerance of neighboring organs.12

Several prognostic factors have been reported in the literature, but there has been no consistency.3,13 The main objective of this study was to identify factors that...
SUBJECTS AND METHODS

From January 1973 to August 1998, 70 consecutive patients were treated for primary GIST at the Massachusetts General Hospital (MGH), Boston. The data of the 70 patients with GIST were prospectively collected at the MGH Cancer Registry. Adequate data for analysis were available for 69 (99%) of the 70 patients. The median follow-up duration for survivors was 38 months (range, 1-159 months). We defined a GIST as any sarcoma of the gut, since they originate as primitive mesenchymal tumors that are capable of divergent differentiation.6,14 Tumors of lymphoid origin were excluded.

Demographic features (sex and age at initial visit), clinical symptoms (pain or discomfort, palpable mass or increased girth, bowel obstruction or constipation, weight loss, and intestinal bleeding), the extent of the disease (lymph node, distant metastases, and intraperitoneal seeding), the tumor location (upper digestive tract: esophagus, stomach, duodenum; middle digestive tract: jejunum, ileum; or lower digestive tract: colon, rectum), the size of the tumor as determined by gross pathological examination (greatest diameter), histologic features (leiomyosarcoma and epithelioid leiomyosarcoma vs fibrosarcoma, spindle cell sarcoma, neurolemma, and reticulum cell sarcoma), and histologic grade (low, intermediate, and high, defined as 1, 2-5, and >5 mitoses, respectively, per 10 high-power fields [HPF])13 were recorded to describe the population under study. These factors were then analyzed as possible prognostic factors for survival and both local and distant recurrence. To formulate a simpler grading classification, the effects of the 3 different histologic grades on survival and recurrence were compared.

The influence of different treatment modalities was assessed. The surgical treatment was defined as a complete resection when no gross disease was left behind and no tumor spillage had occurred. Any other type of surgery was defined as an incomplete resection. The extent of surgery (whether additional organs were resected) and the status of the closest resection margin (microscopically negative or positive) were similarly analyzed.

The administration of radiation therapy and/or chemotherapy was recorded to assess their influence on both survival and on the development of local and/or distant recurrences. Although the use of adjuvant therapy has changed throughout the period of study, radiation therapy was generally considered for high or intermediate grade tumors and/or after incomplete resections when no distant disease was present. When administered, dosage depended on the site and volume of the tumor remnant. Chemotherapy generally was considered when metastatic disease was detected.

Survival rate was calculated from the time of diagnosis until death, or censored at the time of latest follow-up, and survival curves were estimated using the method of Kaplan and Meier. Rate of recurrence was calculated from the time of surgery until the first evidence of recurrence, either distant or local, or both. Recurrence-free rates were also estimated using the Kaplan-Meier method. Univariate and multivariate analyses of prognostic factors were based on the Cox proportional hazards model. The decision regarding the inclusion of variables in the multivariate model was based on the P values of the Wald statistics from the univariate analysis.

RESULTS

Table 1 presents the effect of patient and tumor characteristics on the outcomes of all 69 patients, and the time to recurrence for the 39 patients who underwent complete tumor resection and did not have any metastatic disease at the time of initial surgery. There were no perioperative deaths. The median age at presentation was 60 years (range, 1-93 years). The male-female ratio was 58:42. At the time of initial visit, 48% of the patients had pain or discomfort, 40% had intestinal bleeding, 35% had a palpable mass or increased girth on physical examination, 28% experienced malaise, 22% had weight loss, and 19% had a history of obstruction or constipation.

Metastatic disease at initial visit was present in 41% of patients (21% hepatic, 15% hepatic and intraperitoneal seeding, 1% intraperitoneal seeding only, and 4% with lymph node metastases). The GIST arose in the upper, middle, and lower digestive tracts in 61%, 23%, and 16% of patients, respectively. Median tumor size was 7.9 cm (range, 1.8-25 cm). Smooth muscle histologic differentiation predominated (83% of patients). High and intermediate grade tumors occurred in 57% of the patients. There was no difference in survival or recurrence between patients with high and intermediate grade tumors. Patients with low grade tumors had a significantly better survival rates (hazard ratio=2.62, P=.002) and fewer recurrences (HR=4.14, P=.02) than either high or intermediate grade tumors.

The overall 3- and 5-year survival rates were 38% and 29%, respectively. In 59% of patients, complete gross resection of the tumor was possible. After complete resection, 3- and 5-year survival rates were 54% and 42%, respectively, compared with 13% and 9% after incomplete resection (Figure 1) (HR=0.27, P<.001). The microscopic status of the closest margin did not influence survival or recurrence (Table 2).

Univariate and multivariate analyses of the 69 patients demonstrated that besides incomplete resection, an age older than 50 years, non-smooth muscle differentiation, a high or intermediate tumor grade, and a tumor size greater than 5 cm significantly decreased survival. Survival data of the patients by tumor grade and tumor size are depicted in Figure 2 and Figure 3, respectively. No beneficial effect could be recorded after administration of radiation and/or chemotherapy (Table 2).

There were 39 patients who had no distant disease, peritoneal seeding, or lymph node metastases at the time of diagnosis, and they were subsequently able to undergo a complete resection. Recurrent disease occurred...
in 41% (16 of 39) of these patients and was resectable for cure in 2 (13%) of these patients. Among these patients, the tumor recurred at a distant site in 35% (18% in the liver only; 9% in the liver and another distant site such as the lung, bone, or skin; 6% intraperitoneal only; and 2% developed lymph node metastases) and locally in 25% (8% had no concurrent distant metastasis). Local recurrences could be completely resected in 31%, hepatic recurrences in 17%, and intraperitoneal recurrences in 0% of cases.

The overall time to local and/or distant recurrence was 19 months (range, 8-300 months). Univariate and multivariate analyses of these 39 patients demonstrated that a high or intermediate tumor grade and a tumor size larger than 5 cm significantly increased local and/or distant recurrences (Table 1 and Table 3). Recurrence-free rates of the patients by tumor grade and tumor size are depicted in Figure 4 and Figure 5, respectively.

Gastrointestinal stromal tumors are uncommon malignant tumors that occur throughout the entire alimentary tract. These tumors appear most commonly during the sixth and seventh decades of life, but they can also occur in the pediatric population, as seen in the 2 infants in our series. There is limited anecdotal information on the natural course of GIST in pediatric patients, but they seem to have a behavior similar to that seen in adults.15
The most frequent initial symptoms in this series are pain, discomfort, a palpable mass, and bleeding. Patients who had intestinal bleeding were the most likely to undergo a complete resection of the tumor, suggesting that bleeding might be a fortuitous event leading to an earlier diagnosis. However, the patients' initial signs were generally nonspecific, and even after endoscopy and radiological imaging, the surgeon did not know the diagnosis prior to surgery in more than half of the cases. This implies that an adequate therapy for a rare disease needs to be formulated at the time of surgery. It is therefore important for surgeons to have an understanding of the clinical behavior and routes of metastatic spread of GIST to optimize therapy. The symptoms and tumor distribution in the digestive tract as described in this series are similar to those of other series. Although it has been reported that clinical behavior may be variable in GIST of different sites within the gastrointestinal tract, our data could not confirm this.16,17

Since smooth muscle is the predominate mesenchymal tissue of the alimentary tract, it is not surprising that most GIST (83% in this series) demonstrate smooth muscle histological features and were previously classified as (epithelioid) leiomyosarcomas.1,9,13 Other histologic lines of differentiation include autonomic nerve/ganglionic, neural, and mixed neural/myoid.4 Of importance, the non–smooth muscle histological features had a significantly worse prognosis in this series. This is in contrast with the recent assumption that the different phenotypes of GIST, all deriving from the same stem cell of Cajal, do not influence clinical behavior.14

Table 2. Impact of Different Treatment Modalities on Possible Prognostic Factors for Disease-Specific Death and Both Local and Distant Recurrence*

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>All Patients (n = 69), Time to Death From Disease</th>
<th>After Complete Resection (n = 39), Time to Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, No.</td>
<td>Events, No.</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>41</td>
<td>29</td>
</tr>
<tr>
<td>Incomplete (debulking)</td>
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<td>25</td>
</tr>
<tr>
<td>Complete with negative margin</td>
<td>36</td>
<td>25</td>
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<td>Complete with positive margin</td>
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<td>4</td>
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<tr>
<td>Additional organs resected</td>
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<td></td>
</tr>
<tr>
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<td>34</td>
</tr>
<tr>
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<td>Radiation therapy</td>
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<tr>
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<tr>
<td>Yes</td>
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</tr>
</tbody>
</table>

*Univariate analysis was used to obtain values. Events indicates deaths, or both distant and local recurrences; HR, hazard ratio; and ellipses, not applicable.

Figure 2. Estimated cumulative percentage of patients surviving with low grade histological features (n=28) (solid line) or high or intermediate grade histological features (n=38) (dashed line). Survival is improved with low grade histological features (P=.002).

Figure 3. Estimated cumulative percentage of patients surviving with a tumor size of 5 cm (n=19) (solid line) or greater than 5 cm (n=49) (dashed line). There is a trend toward improved survival with tumors 5 cm or smaller (P=.08).
study, the 5-year survival rate for all patients was 29%, but failed to demonstrate a plateau effect. This finding is in agreement with other large series, and indicates that with adequate long-term follow-up, a high incidence of recurrences and death can be anticipated. This further emphasizes the importance of follow-up extended to well beyond the typical 5-year end point.

It is generally appreciated that surgical resection is the most effective treatment for GIST and that appropriate surgical management involves complete resection of all gross tumor. Complete resection of all tumor was possible in 59% of our patients according to the intention-to-treat principle. This is consistent with the reported spectrum of 48% to 89%. The data from this series confirm that complete resection had a major effect on survival. This was true even when achieving a complete resection involved the resection of multiple adjacent organs (Table 2). After complete resection, 3- and 5-year survival rates were 54% and 42%, respectively, as compared with 13% and 9% after incomplete resection (P<.001, Figure 1). This 5-year survival rate was in the range that was seen in most series (32%-63% following complete resection). Our series was composed of a high number of large grade and high grade tumors, both of which are negative prognostic factors. Seventy-two percent of patients had a tumor larger than 5 cm, and 57% had high grade tumors at the time of diagnosis. In this disease, as opposed to most other solid organ malignant neoplasia, whether the final microscopic margins were positive or negative seemed to have no effect on survival or even recurrence. However, the number of microscopic positive margins after complete gross surgical excision in this series was relatively small, and might, therefore, not be sufficient for making firm statistical conclusions. Given the low rate of initial lymph node involvement (4%) and/or subsequent lymph node recurrence (2%), the resection should encompass enough bowel to resect the tumor grossly. There seems to be no added survival benefit to wide resections of additional bowel or extensive lymphadenectomies.

Tumor grade was the second major factor that had an effect on survival and recurrence. Many grading systems have been devised based on different cutoff points for the number of mitoses per 10 HPF and other histopathologic features. Since the high and intermediate grade tumors in this study did not differ in terms of survival and recurrence, as opposed to low and intermediate grades, we propose to simplify the classification for tumor grade to high (formerly high or intermediate) and low grade tumors only. Although any division of a continuous biological variable is arbitrary, the cutoff point in this classification would be 1 mitosis per 10 HPF (low grade) vs more than 1 mitosis per 10 HPF (high grade). This correlated well with both survival and recurrence rates (Figure 2 and Figure 4). This grading system also supports the emerging evidence that all GIST are to be considered malignant tumors on a scale from low to high grade, and it eliminates the confusion created by the older terminology of “benign” and “malignant” GIST, or “leiomyoma” vs “leiomyosarcoma.” Although the number of patients is relatively small, especially in the recurrence group, these data may be a first step toward a simple and reproducible bimodal grading classification. In a rare cancer such as GIST, any study of
new treatment modalities will require multicenter involvement. A simple and reproducible grading system would facilitate stage standardization and improve outcome analysis between centers.

The pattern of recurrence predominantly involved the liver and peritoneal surface, as demonstrated by others. Lymph node metastases are rare, indicating that not much benefit is to be expected from regional lymph node dissection. This implies that when local recurrence is discovered with no evidence of distant disease, resection can be considered with curative intent since lymph node metastases are seldom an issue.

Adjuvant radiation and/or chemotherapy were not beneficial in this study, and in fact, the patients receiving adjuvant therapy had much worse outcomes. There was almost certainly a selection bias toward patients with the worst tumors receiving radiation and/or chemotherapy. This makes interpretation of these data quite suspect. Although as many as 76% of patients with GIST in some series have received chemotherapy, this has not prolonged survival in patients with visceral sarcoma, including GIST, either by randomized trial or by meta-analysis. The effectiveness of external beam radiation therapy in GIST is limited by adjacent organ toxicity. Since these tumors arise in the digestive tract, it is difficult to deliver enough irradiation without significant toxic effect in the bowel. Given their histologic similarities to sarcoma, one would expect the treatment of these tumors to benefit from a combined scheme of external beam and intraoperative radiation therapy if it were technically feasible (U.C., R.A. Betensky, MD, J.P.E.N.P., et al, unpublished data, 2000). Unfortunately, the adjacent organ toxicity makes patients with GIST less likely to be eligible for intraoperative radiation therapy than patients with retroperitoneal sarcomas.

Gastrointestinal stromal tumors continue to present both a diagnostic and therapeutic dilemma. Most of the time, the operating surgeon will first become aware of the diagnosis on frozen section in the midst of surgery on a symptomatic patient. It is important that the surgeon understand the biological behavior of this rare tumor. The operation should be focused on complete resection of the tumor, including any involved adjacent organs. Only patients with a complete resection have any hope of long-term survival. There is little need for an extensive lymphadenectomy in this disease. Given the frequency of intra-abdominal metastases, a thorough exploration is mandatory. If the tumor is larger than 5 cm and/or the subsequent histologic features demonstrate a high grade (>1 mitotic figure per 10 HPF), the patient is at very high risk for recurrence and subsequent mortality. These simple and reproducible parameters identify patients in critical need of new adjuvant modalities, such as intraperitoneal chemotherapy, that should be recommended for multicenter experimental treatment protocols. Patients with GIST are at high risk for recurrence. Given that complete resection is at present the only chance for cure in these patients, close follow-up with abdominal and pelvic computed tomography scanning is mandatory, although in this series, only 13% of patients had isolated resectable recurrences. Nevertheless, we recommend that any recurrent disease that seems surgically resectable be aggressively pursued. Also, with the frequency of late recurrences, follow-up beyond the usual 5-year period is essential.


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Corresponding author: Mark J. Ott, MD, Division of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Cox Bldg, Room 626, 100 Blossom St, Boston, MA 02114 (e-mail: Ott.Mark@MGH.Harvard.edu).

REFERENCES


DISCUSSION

Samuel Singer, MD, Boston, Mass: Dr Ott and his colleagues present a comprehensive retrospective analysis of 70 patients with GI stromal sarcomas over a 25-year period. In the study, age at diagnosis, grade, histologic subtype, complete surgical resection, stage of disease, and size were prognostic for survival on univariate and multivariate analysis. Gastrointestinal stromal tumors (GISTs) have long been problematic in terms of classification and determination of prognosis. Recent studies by Hiroto and colleagues have suggested that GIST exhibit, as we heard in this talk, a phenotype similar to the interstitial cells of Cajal and possess activating mutations within the c-kit gene. Immunohistochemical analyses of large series of GIST have revealed that in contrast to smooth muscle and Schwann cell tumors, they consistently express the kit protein in virtually 85% to 100% of tumors, depending on the antibody used and the particular study that one cites. Importantly, GIST as defined by kit reactivity do not appear to express either desmin or S100 protein, although they commonly express smooth muscle actin and CD34. The authors define GIST as any sarcoma of the gut. This definition is problematic and may potentially contaminate their analysis due to inclusion of heterogeneous groups of tumors. In the past, these tumors have exhibited both smooth muscle and nerve sheath differentiation, and may have been difficult to distinguish from abdominal leiomyosarcoma and nerve sheath tumor. Over the last 2 to 3 years it has become evident that classifying GI stromal tumors based on clinical presentation and morphology alone is difficult and that immunohistochemistry using the kit antibody along with a panel of antibodies to S100 protein, smooth muscle actin, and desmin is essential to help delineate true GIST from smooth muscle tumors, neural tumors, desmoids, and other spindle cell neoplasia.

What pathological analysis was used to verify patient inclusion in the study other than anatomical location of the tumor so that one could be assured that a homogeneous group of patients with true GIST was being analyzed in this study?

Regarding the criteria that were used to establish a histologic grade in the study, the mitotic count has been most widely accepted as the best prognostic indicator for GIST, and it has been shown that among clinically malignant tumors, a high mitotic count was associated with a shortened overall survival. Various cutoff levels separating GIST into benign and malignant categories or low and high grade subsets have been proposed. However, because of the overlap in mitotic activity between clinically benign and malignant GIST, and in view of the rare occurrence of metastasis in histologically bland mitotically inactive tumors, none of these have proven entirely reliable in the management of individual patients. It seems the grading criteria used in the present study were adopted from those used for leiomyosarcoma, which may not be applicable to GIST. How did the authors, though, arrive at their proposed grading criteria and mitotic count cutoffs? How did they choose the 1 mitotic count cutoff and those values, and how do they feel their prognostic scheme compares with the wide variety of grading classification schemes that have already been proposed in the literature?

In a recent mutational analysis of patients with GIST treated at the Brigham, we have demonstrated that a large majority of GIST contain oncogenic kit mutations, and that these mutations are heterogeneous both in their location within the gene and the type of mutation. I wanted to show 1 slide that summarizes this experience with 48 patients who have been treated during the past 6 years, from whom we have snap frozen tissue available for molecular analysis. From these data you can see that 92% have some kit mutation that we can detect, and in roughly 8% we did not detect any mutation even though they expressed high levels of c-kit activity by immunohistochemical examination. The most common mutation was a deletion/insertion in exon-11 followed by a point mutation in exon-11. The point exon-11 mutations were associated with improved survival on univariate analysis, and the exon-13 mutation was associated with an overall poorer survival rate. This is still a limited group of patients, and it remains to be determined if a molecular classification of GIST can provide improved prognostic information that is more predictive of clinical behavior when compared with conventional grading schemes.

Dr Pierie: With regard to c-kit, it is a marker that has only recently been found useful in the diagnosis of GIST. Most of these tumors, as you can see from the time frame from 1973 to 1998, were resected before the c-kit measurements were available. Furthermore, the c-kit measurement is not a perfect marker for GIST. For example, 10% of the retroperitoneal sarcomas have c-kit positivity, and not all GIST stain for c-kit, although this may be a specificity and sensitivity issue with the antibody. We could not do this in this study since it was not available at the time of the study.

The cutoff point for the grading system has been done in a practical manner since the old grading system was low, intermediate, and high grade, and the cutoff points were 0 to 1, 2 to 5, and more than 5, given by the pathologist during the period of study. That was the grading system that was most often used. In order to compare that grading system with the simple grading system we proposed, we just used our data to find an appropriate cutoff point by statistical analysis. This sorts out nicely with a bimodal grading system of low grade being 0 to 1 mitosis per HPF, and high grade being greater than 1 mitosis per HPF. We believe that this simplified system defines patients of high and low risk very clearly, and that it is an improvement on prior systems.

A fairly large number of patients with low grade GIST did have recurrences, and died of their recurrence. Nearly half of the low grade GIST had recurred by 3 years and the patients died of the disease (5-year survival rate was 52%). However, if you look at a curve, you can see that the survival rate after 10 years was much lower. It was about 20%, so that only 20% of the patients with low grade tumor survived their disease.

Another point to emphasize is that grade only affects the survival in the first 5 years, which is a phenomenon we see in retroperitoneal sarcomas as well. After 5 or 10 years, the 2 curves paralleled each other for low and high grade. Grade predicts who dies rapidly.

How many patients survived more than 15 years? The median follow-up was 38 months, but the range of follow-up was as long as 195 months. There were very few patients whom we followed that long; however, there were a few patients who lived that long.