Gastrointestinal stromal tumors (GISTs), 10-year experience: Patterns of failure and prognostic factors for survival of 127 patients

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KEYWORDS
Tumor; Stromal; Gastrointestinal; GIST; Survival

Abstract  Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract (GIT) and are believed to originate from the interstitial cell of Cajal. Management of GIST has evolved very rapidly in the last decade.

Aim: To report our surgical experience in the treatment of GIST patients, to evaluate the prognostic factors and to discuss some controversial issues about the role of target therapy.

Patients and methods: One hundred and twenty seven consecutive patients who underwent surgical resection for GISTs at Nasser Institute (98 patients) and NCI, Cairo University (29 patients) from January 2000 to December 2009 were reviewed retrospectively. The clinical and pathological features of patients were collected. Also data about treatment variables, patterns of failure and factors that predict survival were collected and analyzed.

Results: Of the 127 patients, 81 (64%) had primary disease without metastasis, 11 (9%) had metastatic lesions at presentation, and 35 (27%) presented with recurrence (isolated, metastasis or both). Patients with primary disease underwent complete resection of gross disease. The 5-year overall survival was 53.4% and disease free survival (DFS) was 46.5%. The median DFS was 43.0 months (95% CI: 21.2–64.9). On multivariate analysis, survival was affected by mode of...
Introduction

Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal (GI) mesenchymal tumor, which accounts for 0.2% of all GI tumors [1]. Gastrointestinal stromal tumors (GISTs) have been recognized as a biologically distinctive tumor type, different from smooth muscle and neural tumors of the gastrointestinal tract. It is now believed that GISTs originate from gastrointestinal pacemaker cells known as interstitial cells of Cajal that control gut, or from a precursor of these cells [2]. The identification of mutations mostly in exon 11 and to a lesser extent in exons 9 and 13 of the c-kit proto-oncogene coding for c-kit (CD117) in many GISTs, has resulted in a better understanding of their oncogenic mechanism [3].

The term was first coined by Mazur and Clark in 1983 to describe a heterogeneous group of gastrointestinal non-epithelial neoplasms [4]. In 1998, Hirota and co-workers reported that GISTs contained activating c-kit mutations, which play a central role in its pathogenesis [5]. Furthermore, GISTs express the KIT protein CD117 and often also CD34 on immunohistochemistry [7]. Over 90% of GISTs occur in adults over 40 years of age, with a median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence does not differ with sex, though a study reported that there is a slight predominance of males [8].

The prediction of malignant potential of GISTs based on clinico-pathological features is often difficult. Large mitotically active tumors with necrosis predictably behave aggressively [9]. The two main methods of spread of malignant GISTs are liver metastases and intra-abdominal spread [10]. It is now accepted that categorizing GISTs into low, intermediate and high-risk tumors based on an estimation of their potential for recurrence and metastases is more appropriate than dividing them into benign and malignant categories [11].

This study reports our experience in the surgical treatment of GIST patients with evaluation of the prognostic factors.

Patients and methods

From January 2000 to December 2009, 127 patients with GIST (different nationalities, mainly Palestinians, 57%) were operated upon at the department of surgery, National Cancer Institute, Cairo University and Nasser Institute, Cairo, Egypt. All patients had full laboratory workup, chest radiogram and computed tomography (CT) of the abdomen and the pelvis for surgical planning. Upper or lower GIT endoscopies were performed when indicated with biopsy (if feasible). Our policy discourages CT or ultrasound guided biopsy as it may cause tumor rupture, hemorrhage and peritoneal seeding with negative impact on final outcome.

The treatment philosophy with regard to GIST emphasizes complete gross removal of the tumor (R0). Resections are classified as incomplete (R2) when the tumor is unexcetable at exploration or when gross residual disease is present after resection and complete (R1) when all gross diseases are excised regardless of microscopic margins. Resection of metastases is performed in selected patients in whom the primary tumor is controlled. Systemic chemotherapy and radiation therapy were excluded from the analyses in this report because they were used sporadically.

An experienced pathologist reviewed all tumors for histological confirmation of diagnosis and evaluation of morphological and immune-histochemical characteristics including expression of CD117 and CD34. Patient and tumor characteristics were evaluated as well as treatment variables with special emphasis to study patterns of failure and prognostic factors that predict survival. Risk factors including tumor size, mitotic count/50 high power field (HPF) and resection margin were assessed.

Statistical methods

Data were analyzed using SPSS win statistical package version 15. Quantitative data were presented as median and range. Qualitative data were expressed as frequency and percentage. Survival was calculated by the Kaplan–Meier method. Overall survival (OS) was calculated from the date of pathological diagnosis to date of death or last follow up. Disease free survival (DFS) was calculated from date of surgical intervention to date of recurrence or death or last follow up. The relations of patient, tumor and treatment characteristics to outcome (DFS, OS and recurrence) were tested by univariate analysis using the Log rank test. Cox regression is used for multivariate analysis of significant factors affecting survival in univariate analysis. A $p < 0.05$ was considered significant.

Results

Patient characteristics

Patients were 81 males (63.8%) and 46 females (36.2%), with median age of 54 years (range, 18–77 years). Table 1 shows that 81 patients (63.8%) presented with primary tumors, 11 patients (8.7%) had metastatic lesions in addition, whereas and 35 patients (27.6%) presented with recurrent disease either isolated recurrence, metastasis or both.

Tumor characteristics

Tumor sites are shown in Table 2. The most common site of tumor was gastric in 41.7% of cases followed by small intestinal in 31.5%. The median tumor size was 18 cm (range: 5–42 cm). The histopathological and immunologic tumor
Characteristics are shown in Table 3. Spindle cell tumors were the main histopathological type.

Surgical treatment

All patients underwent surgical exploration. Complete resection was accomplished in 94 patients (74%); 81 patients (63.7%) with primary disease, three patients (27.3%) with metastatic disease and 10 patients (28.6%) with recurrent disease. The details of the extent of surgical resection are shown in Table 4 and Figs. 1–9.

Postoperative complications

There were no postoperative mortalities. Postoperative morbidity was reported in nine patients (7.1%). Reoperation was resorted to in two patients (1.6%). The first patient had a subphrenic abscess that was surgically drained after failure of ultrasound guided aspiration. The second patient had been explored to relieve postoperative adhesive intestinal obstruction. Five patients had wound infection and two patients had wound dehiscence, but all were managed conservatively.
Recurrence

We followed up the 94 patients who underwent complete resection for the detection of recurrences. There were 43 cases of recurrence; 28 local recurrence, 9 distant metastases and 6 both local recurrence and metastases. Sites of distant metastases were liver ($n = 8$) and lung ($n = 7$). Patients who suffered metastatic or recurrent disease during the follow-up period were considered for surgical resection when all gross disease could be resected. This redo surgery was performed in 37/43 patients. Four mortalities (10.8%) have been encountered in this group within the first month after surgery.

Survival

Only those patients who had complete resection ($n = 94$) had survival chance. Those with inoperable lesions survived few weeks after presentation. For the 94 patients who underwent curative surgery, the median follow-up period was 57 months (range 14–108 months). At 5 years, the overall survival was 53.4% and disease free survival was 46.5%. The median DFS was 43.0 months (95% CI: 21.2–64.9).

On univariate analysis of the clinicopathological risk factors (Table 5), tumor size, mitotic index, gastric origin (Fig. 10) and primary presentation status (Fig. 11) predicted survival. Age, sex and the microscopic margin did not influence the outcome. On multivariate analysis using Cox regres-
Gastrointestinal stromal tumors (GISTs), 10-year experience: Patterns

Figure 6  (a and b) Postoperative specimens of gastric GIST.

Figure 7  A 32-years old male with recurrent GIST: (a) preoperative CT scan, (b) intra operative view, (c) postoperative specimen of showing part of small intestine transverse colon and part of stomach.

Figure 8  Recurrent small intestinal GIST with liver deposit: (a) intra-abdominal recurrence, (b) liver deposit, (c) specimen after wider resection and metastatectomy.
sion, recurrence or metastasis at presentation (OR: 2.3, 95% CI: 1.1–4.7), non-gastric origin (OR: 2.5, 95% CI: 1.3–4.8) and tumor size >10 cm (OR: 6.2, 95% CI: 1.9–20.0) were the independent variables predicting worse DFS (Table 6).

Discussion

We analyzed our results with 127 patients with GIST treated at the department of surgery, National Cancer Institute, Cairo University, and Nasser institute, Cairo, Egypt in the past 10 years. The present study reviewed the clinicopathological features appraising the results of treatment, patterns of failure and prognostic factors for survival.

In our series, tumor originated most frequently from the stomach (41.7%), the small intestine was the second most frequent tumor origin. These findings are similar to other reports[12]. All our patients were symptomatic at presentation. This could be explained by the large size of tumors ranging from 5 to 42 cm with a median size of 18 cm. In contrast, a Western study reported that only 50–70% of patients are symptomatic[13]. Among 94 patients who underwent complete resection (CR), those with tumor size ≤5 cm had a median DFS of 78 months compared to 38 months in those with tumor size 5–10 cm. The median disease free survival dropped significantly to 6.6 months when tumors were larger than 10 cm (p = 0.015).

Yao et al.[16] demonstrated that tumor size has a significant impact on overall survival.

Table 5  Disease free survival of the patients with GIST who underwent complete resection in relation to the risk factors (n = 94).

<table>
<thead>
<tr>
<th>Item</th>
<th>No.</th>
<th>Median DFS (months)</th>
<th>Cumulative DFS (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>13</td>
<td>31.6 (0.0–71.8)</td>
<td>47.9</td>
<td>0.689</td>
</tr>
<tr>
<td>≥40</td>
<td>81</td>
<td>43.0 (25.8–60.2)</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>37.1 (7.6–66.6)</td>
<td>50.3</td>
<td>0.263</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>a</td>
<td>56.9</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>81</td>
<td>66.1 (31.5–100.8)</td>
<td>56.6</td>
<td>0.028</td>
</tr>
<tr>
<td>Recurrent or metastases</td>
<td>13</td>
<td>31.6 (15.6–47.5)</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>49</td>
<td>a</td>
<td>56.4</td>
<td>0.027</td>
</tr>
<tr>
<td>Others</td>
<td>45</td>
<td>20.3 (2.2–38.3)</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>13</td>
<td>77.5 (59.1–95.8)</td>
<td>84.6</td>
<td>0.015</td>
</tr>
<tr>
<td>5–10</td>
<td>56</td>
<td>38.6 (20.9–56.3)</td>
<td>40.7</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>25</td>
<td>6.6 (0.0–15.4)</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>Surgical margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative microscopic margin</td>
<td>66</td>
<td>23.5 (0.5–58.2)</td>
<td>49.3</td>
<td>0.513</td>
</tr>
<tr>
<td>Positive microscopic margin</td>
<td>28</td>
<td>45.4 (22.8–67.9)</td>
<td>48.1</td>
<td></td>
</tr>
<tr>
<td>Mitosis per 50 HPF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>11</td>
<td>77.5 (0.0–128.0)</td>
<td>81.8</td>
<td>0.046</td>
</tr>
<tr>
<td>5–10</td>
<td>58</td>
<td>38.6 (26.1–51.0)</td>
<td>44.4</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>25</td>
<td>26.3 (8.8–43.7)</td>
<td>32.6</td>
<td></td>
</tr>
</tbody>
</table>

* No median value calculated.

Figure 9  Mass at transverse colon and small intestine: (a) preoperative CT scan, (b) postoperative specimen showing part of small intestine and transverse colon.
Endoscopic examination usually describes GIST as submucosal changes, as protrusion or indentation. Endoscopic ultrasonography (EUS) plays an important role in the diagnostic work up of stromal tumors. As a rule, the EUS shows GIST as a hypoechoic mass originating usually from the muscularis propria and muscularis mucosa. However contrast-en-
hanced CT scan is currently the imaging modality of choice with a solid exophytic pattern of growth that displays contrast enhancement after its oral or intravenous administration, together with the absence of associated lymphadenopathy [14]. Although there is a role of endoscopic ultrasound guided biopsy, we believe that preoperative percutaneous, open or laparoscopic biopsy is discouraged as there is risk of hemorrhage, tumor rupture and peritoneal spillage. It is indicated only for clearly unresectable lesions or when treatment might be altered as in lymphoma or germ cell tumors [12,15]. Histological examination revealed spindle cell tumors in 66.1% of specimens, while 18% were epithelioid and 15.8% were mixed. This is comparable with the described incidence in other studies [17]. Surgical resection remains the treatment of choice for all resectable tumors since it is the only chance for cure [1,12]. In this study, patients who underwent complete resection had a 5 year survival of 53.4% which is comparable with other reports [12,28,29]. A 1–2 cm margin was advocated to achieve adequate resection [18]. However more recently, Dematteo et al. [19] demonstrated that tumor size (and not a wide negative microscopic margin) was more important in determining survival. In our study complete macroscopic resection was undertaken in 94/127 patients (74%). The goal of surgery is complete resection of gross disease avoiding tumor rupture and achieving negative margins. However, because the status of the microscopic margins does not appear to be important for survival – as proved in the current study – vital structures should not be sacrificed if gross tumor clearance has already been attained [19]. The shell-out procedure should be avoided except in difficult locations (cervical esophagus, rectum), provided the patient is informed for careful follow-up. Incomplete resection should be performed only for palliation of emergency symptoms e.g. bleeding, pain or mass effect [20]. Tumor rupture should be avoided as it is associated with intra-abdominal dissemination of tumor cells and subsequent high risk of local tumor recurrence [21]. We agree with De Matteo et al. and Blanke that GISTs rarely go to lymph nodes, so lymphadenectomy in the absence of gross involvement is not needed [12,22]. Treatment failures are known to affect almost half of GIST patients treated by surgery alone [17] and tend to be found in the liver in 65%, the peritoneal surface in 50% and in both in about 20% [12]. In agreement with these findings, we found tumor recurrence in 43 patients out of 94 patients who had complete surgical resection, 8 patients had liver metastases and 7 had pulmonary metastases while 23 patients had peritoneal deposits. Liver metastases of GIST are usually multiple, large in diameter, and localized in both lobes [23]. DFS of the 94 patients was 46.5%.

Re-do surgery was performed in 37 of these 43 patients. Aggressive surgical resection is justified in recurrent cases [24]; thus, patients should be followed up regularly starting from an early period after resection of the primary tumor, because early detection of metastasis could possibly enhance complete cytoreduction of the recurrent tumor burden. Furthermore, this complete cytoreduction followed by imatinib therapy might be able to improve the survival of patients with recurrent GISTs [20,23].

Different risk categories have been compiled by Fletcher et al. [11], based on primary tumor diameter and mitotic counts per 50 HPF which determine the risk of local recurrence and survival. In our study primary tumor presentation, gastric origin, tumor size and mitotic count had significant influence on DFS. This agrees with other studies [26,27]. Since the year 2000, there has been a shift in paradigm for the treatment of GIST, and Kit/PDGFRα tyrosine kinase inhibitors such as imatinib (Gleevec) have been applied in the treatment of unresectable or recurrent GISTs. This oral therapy has demonstrated good response in the majority of patients and has emerged as the gold standard treatment for patients with metastatic GISTs [20]. However, long-term success is limited due to the development of imatinib resistance via secondary mutations or clonal selection [30]. In this study, 4 patients with metastatic disease and 13 patients with recurrent disease received neoadjuvant Gleevec for 6 months.

Other inhibitors of Kit/PDGFRα receptors or downstream signaling molecules targets, such as protein kinase theta and tyrosine kinase inhibitors of VEGFRs, have been utilized in cases where imatinib has failed [31]. As this drug is very expensive it is not routinely used for outside clinical trials. Owing to the costliness of imatinib, not all patients with GIST in this study can afford imatinib adjuvant therapy. In addition, the patients treated with imatinib for advanced GIST will inevitably progress. Therefore, in the future we must evaluate the biological behavior of GIST accurately and carefully select the patients with a high risk for tumor recurrence and metastasis as candidates for imatinib adjuvant therapy in clinical trials.

### Table 6
Multivariate analysis of factors affecting disease free survival of the patients with GIST who underwent complete resection (n = 94).

<table>
<thead>
<tr>
<th>Factor</th>
<th>B</th>
<th>SE</th>
<th>p Value</th>
<th>OR</th>
<th>95.0% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>0.838</td>
<td>0.364</td>
<td>0.021</td>
<td>2.3</td>
<td>1.1–4.7</td>
</tr>
<tr>
<td>Mitosis (&lt;5)</td>
<td>0.209</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mitosis (5–10)</td>
<td>0.656</td>
<td>0.521</td>
<td>0.006</td>
<td>2.5</td>
<td>1.3–4.8</td>
</tr>
<tr>
<td>Mitosis (&gt;10)</td>
<td>0.329</td>
<td>0.178</td>
<td>0.006</td>
<td>2.5</td>
<td>1.3–4.8</td>
</tr>
<tr>
<td>Site</td>
<td>0.006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (&lt;5 cm)</td>
<td>0.058</td>
<td>0.058</td>
<td>0.002</td>
<td>6.2</td>
<td>1.9–20.0</td>
</tr>
<tr>
<td>Tumor size (5–10 cm)</td>
<td>0.596</td>
<td>0.002</td>
<td>0.958</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Tumor size (&gt;10 cm)</td>
<td>0.588</td>
<td>0.002</td>
<td>0.958</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

B: Regression coefficient, SE: standard error, OR: Odds Ratio, CI: confidence interval.
Mitosis ref. is < 5; tumor size ref. is < 5 cm.
Conclusion

Surgical resection is the mainstay of treatment of GIST. Tumor size, mitotic index, gastric origin and primary presentation are important predictors for disease specific survival in patients presenting with primary disease. It is still too early to come up with universal methods for the therapy of GIST patients. Considerable research efforts are required to explore the current thinking in the management of GIST, with particular emphasis on the impact of recent data regarding the management of GIST in the adjacent setting. The door is open wide on future studies until we settle on solid guidelines for the management of GIST.

References