Gastrointestinal Stromal Tumors: challenges in diagnosis and treatment

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ABSTRACT

Background: Gastrointestinal stromal tumors (GIST) are considered the most common mesenchymal neoplasms of the digestive system. They originate from the interstitial cells of Cajal and one of their major characteristics is the over expression of KIT protein Tyrosine Kinase, and they have both diagnostic and therapeutic dilemma. The aim of this study is to present the challenges encountered in the diagnosis and treatment of GIST cases in our facility, Saudi German hospital Riyadh Saudi Arabia during the past 10 years and compare the results obtained with that of other oncology centers.

Patients & Methods: This study is a retrospective study of cases with GIST that were diagnosed and treated in our center during the past 10 years. These studies include clinical characteristics, target therapy, imaging techniques, histopathology, immunohistochemistry, surgical techniques and prognosis of such cases. Results: thirty two patients were diagnosed as having GIST (24 males/8 females) with a mean age 62 years (31-83 years). Diagnosis was made preoperatively in 22 patients (69%) and intraoperatively with histopathological confirmation in ten patients (31%). The site of the tumor was detected in the stomach in twelve cases (37.5%), two in duodenum (6.25%), ten in small intestine (31.25%), two in mesentery (6.25%), four in colon (12.5%) and two rectal GIST (6.25%). The main presentation of the disease was anemia, GIT bleeding and abdominal mass. Twenty eight patients were considered resectable and they were operated upon (87.5%) and in four patients (12.5%) neoadjuvant therapy was started with favorable response in two cases and poor response in the other two with advanced GIST. All patients received Imatinib as adjuvant therapy. Mean follow up period was 33 months (4-54 months).

Conclusion: GIST is a challenging malignant tumor that requires a multidisciplinary approach in a highly specialized facility seeking the best management and prognosis.

Key words: Gastrointestinal Stromal Tumors; PET; Imatinib; C-KIT Treatment
Introduction

GIST is defined as a specific, KIT-expressing and KIT-signaling mesenchymal malignant tumor of the GIT [1] that accounts for less than 1% of digestive tract tumors [2]. GIST can develop in the gastrointestinal tract starting up from the esophagus down to the anal canal and it is stated that the stomach constitutes (60%) and the small intestine constitutes (30%) and they are the commonest sites for GIST and the remaining 10% of GISTs are found to be originating from the esophagus, omentum, mesentery, colon or rectum. It is found that up to 30% of GIST show malignant high risk behaviour such as invasion and metastases. [3]. The metastatic behaviour mostly is liver metastases [4]. GIST show over-expression of protein KIT which is a (Tyrosine Kinase) Receptor coded by the c-Kit proto-oncogene on chromosome 4, controlling apoptosis as well as cell proliferation[5]. That protein expression permits the differentiation and diagnosis of those tumors [6]. GIST show almost equal distribution between females and males[7].

In spite of the fact that most GISTs reported cases are sporadic cases there were several patients reported with familial mutations [7].

Diagnosis of GISTs based on histopathological and immunohistochemical studies , also the cornerstone diagnostic test of which is tyrosine kinase receptor KIT (CD117, c kit) expression [8].

Imaging techniques such as CT scan are used for localization of the lesion, and evaluate metastases at the time of diagnosis. Also it is used for evaluation of treatment response and assessment on follow up for detection of recurrence [6]. Endoscopic ultrasound (EUS) is used as an important tool in the GIST diagnosis and is also useful in extracting a tissue biopsy [6]. PET (Positron Emission Tomography) is useful in detecting small metastases which cannot be detected on CECT as it also helps to differentiate between an active lesion from inactive necrotic or scar tissues [9]. Surgery is considered as the standard primary treatment for resectable GIST tumors with no significant morbidity.

Imatinib mesylate ( GLIVEC ) is an effective and specific approved TKI inhibitor as target therapy for nonresectable or metastatic GIST cases with GIST as an adjuvant and neoadjuvant therapy [10].

Imatinib is very effective in increasing the possibility of negative margin without significant morbidity [11].

Patients and Methods

This retrospective study was performed on thirty two patients in Saudi German Hospital, Riyadh, Saudi Arabia, from the period from June 2005 to December 2015 reviewing data of the patients, after scientific and ethical approval. Diagnosis included use of upper and lower GIT endoscopy, CT scan , endoscopic ultrasound (EUS), large core needle biopsy (LCNB), fine needle aspiration biopsy ( FNAB) and also PET scan. Tu-
mors were evaluated for resectability and complete excision of the neoplasm.

Imatinib mesylate is used for both adjuvant and neoadjuvant patients. Histological parameters were assessed by pathologists for histopathological confirmation of GIST diagnosis and assessment of the immunohistochemical characteristics as well as the mitotic rate and actin, Vimentin and S-100 protein.

The tumors classification was done according to Fletcher’s classification matching with guidelines of the American NCI as high , intermediate , low and very low risk [6]. Follow up for the patients was done at 1, 3, and 6 months postoperatively with CT scan then using PET scan every year which was used for evaluation of the occurrence or exclusion of recurrence or metastases.

Results

32 cases had GIST tumors; 24 male patients and 8 females. 22 cases were diagnosed to have GIST in the preoperative setting by radiological, histopathological and immunohistochemistry examination. 10 cases also had been confirmed postoperatively through histopathological studies held on the surgical specimens; these cases were 2 gastric GISTS, 2 Duodenal GISTS, 2 mesenteric GISTS and 4 intestinal GISTs. Tumor locations were as follows: 12 in stomach, 2 in duodenum, 10 in small intestines, 2 in the mesentery, 4 in the colon and 2 in the rectum.

All patient presentations had variable manifestations such as anemia in 28 cases, gastrointestinal bleeding in 10 cases, abdominal pain in 8 cases, palpable mass in 10 cases, nausea, vomiting in 6 cases, constipation in 4 cases and loss of weight in 12 cases.

Out of the 32 patients in our study 28 underwent surgery and the other 4 non-operable patients at presentation received 400 mg/day glivec as neoadjuvant therapy for 6 months, with convenient response in 2 patients with large GIST detected by PET scan which became operable. On the other hand the other 2 patients had metastases with poor response to the neoadjuvant imatinib therapy and were maintained on the imatinib treatment.

Regarding the surgery type : there were 8 partial gastrectomies, and 4 patients underwent distal gastrectomies and 2 duodenopancreatectomy (Whipple’s operation) ; also 2 excisions of the mesentery with intestinal resection, 10 intestinal resections, 2 transverse colectomies, and 2 anterior resections for GIST of the rectum with all patients having negative resection margins (Table 1 - page 28).

Classification according to Fletcher prognostic scale showed 10 tumors with low risk, 6 tumors at moderate risk and 16 tumors with high risk (Table 2). According to the cell type 20 tumors were fusiform , 8 tumors epithelioid cell and 4 tumors were found to be mixed types. The tumor weight ranged from 205 mg to 12 kg.
Table 1: Operative procedures performed in 30 GIST Tumors out of 32 Tumors

<table>
<thead>
<tr>
<th>Origin of GIST</th>
<th>Type of Resection</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>stomach</td>
<td>partial gastrectomy</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>distal gastrectomy</td>
<td>4</td>
</tr>
<tr>
<td>mesentery</td>
<td>mesenteric excision</td>
<td>2</td>
</tr>
<tr>
<td>intestines</td>
<td>intestinal resection</td>
<td>10</td>
</tr>
<tr>
<td>colon</td>
<td>transverse colectomy</td>
<td>2</td>
</tr>
<tr>
<td>rectum</td>
<td>anterior resection</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Fletcher Prognostic Classification of 16 GIST Tumors

<table>
<thead>
<tr>
<th>RISK</th>
<th>NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
</tr>
<tr>
<td>Medium</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 3: Classification of the Patients According to the Immunohistochemistry

<table>
<thead>
<tr>
<th>IMMUNOHISTOCHEMISTRY TEST</th>
<th>NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive CD117, CD 34</td>
<td>28</td>
</tr>
<tr>
<td>Positive Vimentin</td>
<td>10</td>
</tr>
<tr>
<td>Positive S-100 Protein</td>
<td>8</td>
</tr>
</tbody>
</table>

Immunohistochemistry of 28 neoplasms was $+$ ve for CD 117 and CD 34, 10 patients were $+$ ve for vimentin and actin and 8 patients were $+$ ve for S-100 protein (Table 3). No mortality was encountered in this study but there were 6 morbidities (2 had wound infection, 2 patients with lung affection had medical treatment and 2 patients with incisional hernia had surgical repair done for them.)

Neoadjuvant imatinib was given for 10 patients while adjuvant imatinib was given for 22 patients.

Mean follow up period was 66 months (8-108 months) and during that time 4 patients developed liver metastases. 2 patients who had resection anastomosis for treatment of GIST of the colon presented with liver metastases; also surgical metastasectomy was performed, the other 2 patients had large liver metastases less than one year after surgical resection of intestinal GIST and these 2 patients were put under glivec therapy with poor response, but the course was stationary.
Figures 1, 2 and 3: Active rectal mass

**Figure 1**

![Image of an abdominal CT scan]

**Figure 2**

![Image of a PET scan]
Figure 3

Figure 4: Multiple liver metastasis
Discussion

GIST is the most common malignant mesenchymal tumor and originates in the GIT [12]. It is known that these malignant tumors originate from intestinal cells of Cajal [13]. GISTs presented with a variety of clinical manifestations that included abdominal pain, bleeding, intestinal obstruction and (or) perforation [14]. Most common site of GIST is stomach then the small intestine, then colorectal then esophagus followed by the peritoneum, omentum and mesentery [15]. Our study demonstrates a higher incidence in stomach (37.5%) followed by small intestines (31.25%) and then the colon (12.5%) which is matching with what has been stated in the literature.

The most common sign is anaemia [16] and this matches our study as anemia represented 87.5% of the cases.

Bleeding is the most common symptom (30-40%) of cases. The manifestations reported in our study matched those reported in the literature [17].

CT scan is the standard method of choice for diagnosis however Endoscopic biopsy in most cases does not support sufficient proper evidence for establishing GIST diagnosis due to their submucosal nature [18]. This was also encountered in this study as endoscopic biopsy confirmed the diagnosis of GIST in 4 out of 8 cases [19].

PET-FDG provides information about the tumor activity and showed high sensitivity in evaluating early-and long-term response to glivec in CD 117 positive GIST cases [20].

Choi et al’s study showed that CT scan is a specific and sensitive tool to evaluate metastatic GIST response to Imatinib, if response is considered as decreased size more than 15% or tumor decrease more than 20% at 3 months after the start of treatment with a 100% specificity and 97% sensitivity in comparison to the PET response [21]. The consensus of the Lugano conference concluded that PET scan is to be used in cases of early evaluation of response prior to surgical intervention or if metastases are suspected. In our study, only 10 patients had been diagnosed and followed up using PET scan before neoadjuvant Imatinib therapy [22].

As there are multiple differential diagnoses to GIST in GIST histology, this tumor is confirmed through molecular biological and immunohistochemical methods with c-KIT overexpression (CD117) considered the marker of choice. Approximately more than 80% of GIST tumors are c-KIT+ve to CD117, 65-70% are +ve to CD 34, 35-40% +ve to Actin and Vimentin, 4% +ve to S-100 protein and 2% +ve to desmin and or Keratin [23]. In our study 87.5% of cases were found to be positive for CD117 and CD34, 31, 25% for Vementin and actin and 25% positive for S-protein which is matching with other literature. Surgery is the state of the art in the treatment of GIST [24]. In our study, surgery was done for 30 patients (93.75%) with complete surgical excision, while 8 had partial gastrectomy, 4 had distal gastrectomy, 2 had excision of the mesentery with nearby intesti-
tine, 10 had intestinal resection, 2 had transverse colectomy, 2 had anterior resection and 2 had pancreaticoduodenectomy for duodenal GIST.

Imatinib Mesylate (glivec) plays a very important rule in the management of GISTs and its mechanism is inhibition of c-KIT, which has a major effect in the c-KIT positive GIST [25]. Many studies showed the great consensus that indicates Imatinib mesylate (glivec) treatment increases the overall survival in c-kit+ve patients [26].

Conclusion

Gastro-intestinal stromal tumor (GIST) is considered as a challenging disease in need of a professional multidisciplinary management representing multiple integrated specialties.

References