Research Article

Current Status on Gastric Stromal Tumor

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**ABSTRACT**

**Background:** Gastrointestinal Stromal Tumor (GIST) is the most common mesenchymal neoplasms of the gastrointestinal (GI) tract, occupying 0.2% of all digestive tract cancer cases. The main affected site is the stomach (50% cases). The vast majority (95%) have a mutation in the Kit gene. Surgery is the treatment of choice, with complete tumor resection with free margins, and no need for lymphadenectomy. Minimal invasive surgery may be an option, mainly for small tumors and patients with localized disease. The emergence of molecular targeted therapy has brought great advances in the treatment of unresectable metastatic tumors, and in cases of recurrence after surgical treatment.

**KEYWORDS:** GIST, imatinib, gastrectomy, laparoscopic resection, stomach neoplasm, c-Kit

**INTRODUCTION**

Gastrointestinal Stromal Tumor (GIST) is the most common mesenchymal neoplasms of the gastrointestinal (GI) tract, occupying 0.2% of all digestive tract cancer cases. It has an estimated incidence of 14.5 inhabitants / million / year and prevalence of 129 / million inhabitants / year. In the US the annual incidence is 5-6 thousand cases / year with a 3-year survival rate of 73% [1].

The mean age is 58 years, with no gender preference. The main affected site is the stomach (50% cases), followed by small intestine (25%), colon (10%), and other locations such as the rectum, esophagus, mesenteric and retroperitoneal (15%) [2]. Of 2,583 cases of malignancies of the stomach treated at Hospital das Clínicas – University of São Paulo School of Medicine (HCFMUSP) from 1971 and 2006, the GIST accounted for only 2% and adenocarcinoma accounts for 93% of cases [4].

It is believed that these tumors are originated in the interstitial cells of Cajal (1893). These cells, which are present in all gastrointestinal tract, work as true pacemakers integrating the smooth muscles of the digestive tract with the autonomic nervous system in its peristaltic activity [5].

The term gastrointestinal stromal tumor was introduced by Mazur and Clark in 1983 as a reference to the main group of mesenchymal tumors of the gastrointestinal tract, which could not be distinguished from smooth muscle or neurogenic origin [6]. To date, it is now known that GIST is a distinct cancer and it is estimated that 72% of these tumors diagnosed today were wrongly classified in the past as leiomyomas, leiomyosarcomas or tumors of neural origin between schwannomas or neuromiomas [7]. This differentiation has been possible only due to the emergence of immunohistochemical staining techniques (1980) that are essential for diagnosis.

**HISTOLOGY AND IMMUNOHISTOCHEMICAL ASPECTS**

This distinct group of mesenchymal neoplasms are consisted of spindle cell, i.e., elongated nuclei present in 70% of cases, epitheloid cells with rounded nuclei and abundant cytoplasm (20%) or mixed (10%) and has mutation in the tirosinikinase (TK) receiver [8].

The vast majority (95%) have a mutation in the Kit gene. This gene encodes a transmembrane receptor with tyrosine kinase activity immunologically recognized as CD-117 (c-kit) [9,10]. The human proto-oncogene c-kit has been described by Yarden et al. in 1987, however was Hirota et al. in 1998 that, although interestingly did not mention Yarden’s work, proposed to be the origin of GIST the interstitial cells of Cajal and that Kit mutation leads to the development of this neoplasia [11,12]. Kit is a TK transmembrane receptor and is responsible for various cell functions, among which proliferation, adhesion, apoptosis, and cell differentiation. The mutation that occurs in the Kit gene leads to a constitutive activation in Kit protein causing unopposed cell proliferation stimulus. This entails the development of tumor [13]. Most of positive c-KIT GIST also express positivity for other receptor, the CD-34 (70% of cases), which are more common in the esophagus and rectum. S-100 protein and Desmin are rarely positive. Nonetheless, Vimentin and Smooth Muscle Actin (1A 4) marker may be positive in 15-60% of cases. A small percentage shows no mutation in c-Kit, but in the growth factor receptor alpha derived from platelets (PDGFRα) [14].

A calcium-regulated chloride channel protein was identified from transcriptional gene expression profiling studies on GIST [15,16]. This protein is known as DOG1 (discovered on GIST-1) and has high specificity and sensitivity for GIST and is expressed strongly on their cell surface. The polyclonal antibodies against this protein have been found to label GIST independently of c-KIT/PDGFRα mutational status [17, 18].

For histological and immunohistochemistry GIST diagnosis is recommended by the National Institute of Health (NIH) studying CD-117, CD-34, 1A 4, Desmin and Ki-67 (cell proliferation antigen), which does not help in the diagnosis but has strong influence on prognosis [19].

**DIAGNOSIS AND TREATMENT APPROACH**

Most patients with GIST are diagnosed due to symptoms caused by the tumor size, leading to abdominal pain and hemorrhage (50% of cases) [20]. One third of patients has already liver and peritoneum metastasis at the diagnosis [21]. The diagnostic evaluation is based on imaging methods, with significant role of endoscopy and endoscopic ultrasound (EUS). These methods provide the location, consistency and tumor size, as well the aspect of the submucosal and mucosal integrity. Biopsies have low sensitivity because they can not reach the submucosal layer. But the biopsy with fine-needle aspiration by EUS is useful for the differential diagnosis [22,23]. Ultrasonography can be helpful, but CT scan is necessary for the location and assessment of tumor, usually showing solid mass with calcification area, central necrosis, and to identify possible metastasis sites [24]. Magnetic resonance imaging can provide insight on specific cases, but usually is not required.

Surgery is the treatment of choice, with complete tumor resection with free margins. There is no need for lymphadenectomy, because these tumors very rarely lead to lymphatic spread. DeMatteo et al.
(2000) published a review of 200 cases of GIST, which 94 of them already had metastasis at diagnosis. There were only 6% of lymph node involvement in patients with metastatic disease [25]. Miettinen et al. (2005) reported another review of 1,765 cases of gastric GIST with long follow up and stated “... the fact of GIST does not develop lymph node metastasis should avoid lymph node dissection [26]. Exceptionally neoplastic lymph node invasion may occur, however, in general, is due to invasion by contiguity. Enucleation should be avoided and, if necessary, adjacent organs must be removed with the tumor, in order to reach R0 resection. Incisional biopsies (pre or intraoperative) should also be avoided because it can lead to neoplastic cells dissemination.

The type of surgery and the type of approach will depend on the tumor’s size, characteristics and location. For small tumors located on the greater curvature the first option is the laparoscopic wedge resection. For smaller tumors located in gastric antrum, laparoscopic or conventional distal gastrectomy should be preferred. For tumors located in the lesser curvature an option would be to conduct endogastric surgery or hybrid procedures (laparoscopic and endoscopic) [27]. Tumors between 2 and 5 cm can be removed by wedge resection or through partial or total gastrectomy depending on the location, giving preference to the minimal invasive access. Lesions smaller than 2 cm, due to its low degree of aggressiveness can be followed up every 6/12 months, as long as they are asymptomatic. The tumor’s perforation often outweighs the benefits of minimally invasive surgery. One option would be to perform video-assisted surgery. For tumors located in the lesser curvature an option would be to perform video-assisted surgery. For small tumors located in gastric antrum, laparoscopic or conventional distal gastrectomy should be preferred. For tumors located in the greater curvature the first option is the laparoscopy approach for small tumors and localized disease. The laparoscopic approach for small tumors and localized disease is feasible and should be performed whenever possible. The long-term survival rates, quick and accurate diagnosis is essential. In order to provide better outcomes and long-term survival rates, quick and accurate diagnosis is essential. The laparoscopic approach for small tumors and localized disease is feasible and should be performed whenever possible. The emergence of molecular targeted therapy has brought great advances in the treatment of unresectable metastatic tumors, and in cases of recurrence after surgical treatment.

**Table 1: Proposed Approach for Defining Risk of Aggressive Behavior in GISTs**

<table>
<thead>
<tr>
<th>Size (largest dimension)</th>
<th>Mitotic Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>very low risk</td>
<td>&lt;2 cm</td>
</tr>
<tr>
<td>low risk</td>
<td>&lt;5 cm</td>
</tr>
<tr>
<td>intermediate risk</td>
<td>&lt;5 cm</td>
</tr>
<tr>
<td>high risk</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
</tr>
</tbody>
</table>

Adapted from Fletcher et al. (2002) [31]

HPP: high-power fields

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**References**


