



International Journal of Hepatology & Gastroenterology

Research Article

Current Status on Gastric Stromal Tumor- @

Leandro Cardoso Barchi* and Bruno Zilberstein

***Address for Correspondence:** : Dr. Enéas de Aguiar. Digestive Surgery Division, Department of Gastroenterology University of Sao Paulo School of Medicine - USP Brazil Av. 255 - 9o andar 05403-000 São Paulo - SP BRAZIL Tel : +5511: 3061.7560

Submitted: 08 December 2015 **Approved:** 28 December 2015 **Published:** 31 December 2015

Citation this article: Barchi LC, Zilberstein B. Current Status on Gastric Stromal Tumor. Int J Hepatol Gastroenterol. 2015;1(1): 005-008.

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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 peristalses 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 neurilenomas [7]. This differentiation has been possible only due to the emergence of immunohistochemical staining techniques (1980) that are essential for diagnosis.

HISTOLOGY AND IMUNOHISTOCHEMICAL ASPECTS

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

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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 (PDGRFa) [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/PDGFRa 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 laparoscopy wedge resection. For small 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. Laparoscopic surgery has been demonstrated to have higher rate of complete resection comparing to open surgery (97.5% vs. 85.2%), as well as a lower, complication rate, operative time, morbidity and length of hospitalization [28]. Notwithstanding, for tumors larger than 5 cm each case must be evaluated individually, but the risk of tumor's perforation often outweighs the benefits of minimally invasive surgery. One option would be to perform video-assisted surgery. 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 [29]. Hassan et al. (2008) demonstrated low mortality and overall survival at 5 years was 65% for patients who underwent surgical treatment [30].

Standard Chemotherapy is not effective in GIST treatment. For unresectable metastatic large tumors, with high risk of aggressiveness or recurrence after surgery (50% cases) [25], the treatment of choice

is the imatinib mesylate (STI571), approved in 2002 by FDA. This gene therapy feature inhibits the TK activity of the Kit protein by competitively interaction with ATP for the binding site on Kit. Without ATP, which is the phosphorus source used for kinase function, Kit molecule can not phosphorylate the substrate leading to inhibiting cell proliferation and inducing apoptosis [13,31]. It should be noted that its antitumor activity depends on their continuous administration. In 2008, the FDA approved imatinib as adjuvant therapy for the treatment of c-KIT-positive GIST based on a multicenter randomized, double-blind phase III, placebo-controlled trial that showed better recurrence-free survival of 98% vs. 83% (HR =0.35, 95% CI 0.22- 0.53; P < 0.0001). There was no difference in overall survival [32]. There are reports of primary resistance (before 6 months) to this form of treatment in the range of 9 to 13%, and secondary (after 6 months) of 40 to 50% [33]. In these cases, it is suggested to double the dose of 400 mg / day to 800 mg or replace the drug to sunitinib malate (SU11248), a second-line tyrosinekinase inhibitor (TKI) that's indicated for patients with imatinib intolerance or resistance [34,35]. In 2013, the FDA approved Regorafenib, a third-line TKI for patients who previously failed imatinib and sunitinib treatment. Failure was defined as either intolerance or progression with imatinib and solely progression with sunitinib [36].

PROGNOSTIC VIEW

The potential aggressiveness of the tumor and disease free survival after surgical resection depends mainly on the tumor size, mitotic index and tumor location (Table 1). It is known that larger tumors with high mitotic index and located in the small intestine has higher probability of relapse. Even after complete resection, at least 40% of patients will relapse within 5 years [37].

Some other embodiments are also related to more or less tumor aggressiveness such as tissues and surrounding organs invasion, liver and peritoneum metastasis, necrosis, hemorrhage, cellular polymorphism, DNA ploidy, c-Kit mutations and CD-34 positivity [38].

Neoadjuvant treatment with imatinib may be applied in some situations with the goal to decrease tumor size and to make initially inoperable cases suitable for surgical treatment. In approximately 70% of cases there will be tumor mass reduction and the disease will remain stable in approximately 15% of cases [39]. There are no studies to confirm their real advantage, but some case reports advocate that this effort should be carried out for at least 1-2 years. Unfortunately, only 25% of patients will be suitable to surgical resection after this approach [40].

CONCLUSION

In recent years the diagnosis of GIST has become increasingly common in everyday practice of surgeons and oncologists, mainly due to advances in imaging diagnostic methods and immunohistochemistry. 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.

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

	Size (largest dimension)	Mitotic Count
very low risk	<2 cm	<5/50 HPF
low risk	2-5 cm	< 5/50 HPF
intermediate risk	<5 cm	6-10/50 HPF
	5-10 cm	< 5/50 HPF
high risk	>5 cm	> 5/50 HPF
	>10 cm	any mitotic rate
	Any size	>10/50 HPF

Adapted from Fletcher et al. (2002)²¹
HPF: high-power fields

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