

The authors would like to thank for review and for valuable comments and suggestions, which were involved in the manuscript. All changes are highlighted in red. The language has been improved, and the manuscript corrected by English language specialist American Manuscript Editors attaching language certificate letter.

A detailed description of the Reviewer's comments:

**Reviewer's code:** 03648477

This is well prepared and well designed labor-intensive review that can contribute to the current literature. It is worth publishing after minor spelling correction in manuscript file (especially in abstract section). Thanks for all Authors.

First, thank you for your encouraging words. Manuscript language has been reviewed, improved and corrected by English language specialists American Manuscript Editors®. We attach language certificate letter.

**Reviewer's code:** 03253691

The authors summarized the management of GISTs. This is well written paper and I believe readers will learn some key points of GISTs.

However, I believe readers request more.

1. Figures are the keys for this kind of reviews, if the authors aim to be remembered. As a reader, I want to see endoscopic view of GISTs, endosonographic details of GISTs, any CT images, especially for small bowel GISTs, liver met etc.

We have added several images of GISTs image test. Legends:

**Figure 1:** Figure 1A and 1B show respectively a gastric tumor and a duodenal tumor of exophytic growth with well-defined borders. Appreciate in figure 1C the different densities inside the tumor due to due to necrosis, haemorrhage, or degenerative components. Figure 1D shows a Jejunal GIST in left iliac fossa.

**Figure 2:** In figure 2b it is appreciated a large hepatic metastasis in segment IV. Figure 2b shows the CT of a patient with disseminated peritoneal disease "GISTosis".

**Figure 3:** Rectal GIST on the posterior wall of the rectum.

**Figure 4:** Characteristic endoscopic image of gastric GIST.

**Figure 5:** In Endoscopic Ultrasonography (EUS) GISTs are typically hypoechoic submucosal mass with well-defined margins.

**Figure 6:** Figure 6A giant gastric GIST on a patient with Neurofibromatosis type 1; 6B: Gastric GIST with a unique liver metastasis. Appreciate the elevated metabolism of glucose in these lesions.

**Figure 7: Histological sections of Ileal GIST. Figure 7A Hematoxylin eosin staining; 7B Immunohistochemistry with C-KIT.**

2. I'm not sure the title is appropriate, because main topic is not tyrosine kinase inhibitors.

Title has been changed to: **“Gastrointestinal Stromal Tumors (GISTs): a multidisciplinary challenge”**

3. I want to hear more about Cajal Cells. What are they...? With the knowledge of pathophysiology of GISTs, readers can move forward beyond the treatment.

In order to clarify the origin and function of Cajal Cells, the following paragraph has been introduced:

“Interstitial cells of Cajal (ICCs) are recognized as the precursor cells of GISTs being implicated in the regulation of gut peristalsis. They are considered the pacemaker cells of the gastrointestinal tract and are immunostained by antibodies against CD117 (KIT) like GISTs<sup>[6, 7]</sup>. ICCs are located between the layers of the muscularis propria in the interface between the autonomic innervation of the gastrointestinal wall and the smooth muscle, having immunophenotypic and ultrastructural features of smooth muscle and neuronal differentiation.<sup>[8]</sup>”

4. As a reader, I want to see more details in algorithm figure (fig 1). Roles of various modalities (physicians) should be implemented into the figure.

We have reviewed the algorithm and we have introduced proposed improvements. See Figure 8 in page 54.

5. How about the term "tumor perforation"? I do not mean the free intraperitoneal perforation, I mean serosal perforation of the tumour. I believe, pathology reports should include this item, because its relationship with prognosis has been showed.

In Page 25 Line 21, it was added:

“The depth of tumor infiltration, including serosal penetration has been proposed as a prognostic factor for patients with GISTs with significantly poorer prognosis compared to its absence.<sup>[120, 121]</sup>”

Finally, following editor recommendation, authors have added a section of conclusion. See Page 26.

## **“CONCLUSION**

The diagnosis of GIST has increased in recent years thanks to new imaging techniques which have increased the interest in the management of this type of tumors.

The clinical diagnosis is based on the CT, EDA and/or endoscopic ultrasound and staging diagnosis is obtained by CT and FDG-PET. The histological diagnosis is based on ultrasound (US)-guided biopsy or percutaneous biopsy prior to surgery; In case of high suspicion in the imaging tests, surgical resection without previous biopsy would be justified.

The biological behavior of the GIST is explained according to the mitotic index, Ki67, anatomical location, size and mutational status.

Surgical resection with free margins of tumor disease R0 is the only potentially curative therapeutic option.

Therapies with Tyrosine Kinase Inhibitors (Imatinib, Sunitinib and Regorafenib) have let a noteworthy improvement in the rates of disease-free survival and overall survival, even in recurrent or unresectable metastatic GISTs.

GISTs are the paradigm of a Cancer with molecular targeted therapy and its management requires a multidisciplinary approach.”

Yours sincerely,