

## **Response to specific comments:**

### **Reviewer #1:**

1. The manuscript has been revised extensively. The font and references have been formatted.
2. The main timepoints in the evolution of the GIST concept have been clearly pointed out: ex diagnosis issues (HE, electron microscopy, IHC: CD34, CD117, subsequent antibodies)/ex note years for the beginning of use of CD34, CD117 for the diagnosis of GIST and the same for treatment types has been done.
3. Brief information on extra-digestive GIST and on composite tumors with a GIST component have been added.
4. The evolution of classification system including table, reference and year has been presented.

### **Reviewer # 2:**

1. The paper has been seen and corrected by a person proficient in medical English.
2. Page 4, line 25, tyrosine kinase inhibitor (TKA) imatinib. should be corrected as ...(TKI) imatinib mesylate: done.
3. Page 5, line 15: pulomanry--◇ pulmonary: done.
4. Page 6, line 11: epitheloid should be corrected as: epithelioid: done.
5. Page 7, line 6; small bowel bleed, should be corrected as small bowel bleeding: done.
6. Page 7, line 24: anintramural introphytic, should be corrected as: an intramural endophytic: done.

7. Page 15, line 19: diagnosi and mutational should be corrected as: diagnosis and mutational: done.
8. Page 3, Epidemiology. In this section the author should mention that the real incidence is not known because a lot of tumors have not been tested for the KIT or the PDGFRA gene mutations: done.
9. Page 5, last paragraph: GISTs are well circumscribed tumors...This paragraph should be under the section/title Histology: done.
10. Page 6, Clinical aspects. The author should mention that occasionally tumor rupture into the peritoneal cavity may also cause intraabdominal bleeding and peritoneal seeding of tumor cells (Machairas A, et al. Dig Dis Sci 2010; 55: 3315-3327): done.
11. Page 7, Diagnosis. The author may add that: The main drawback of CT is inability to differentiate between inflammatory adhesions and involvement of contiguous organs. In case of large gastric GISTs it is often difficult to decide if the tumor arises from the stomach, pancreas, liver or colon. (Machairas et al. Dig Dis Sci 2010; 55: 3315-3327): done.
12. Page 14, Endoscopic resection. Indeed endoscopic treatment is efficacious for the treatment of GISTs of the upper GI tract, for patients with no recurrence or metastases (Marcella C, et al. Clin Endosc 2020; 2019). The author should specify that this treatment is used mainly for the upper GI tract: done.
13. Page 18, first paragraph. Since there are no specific recommendations, follow up in these patients is based on the clinician's opinion taking into account the tumor site,

size and mitotic index (PDQ Adult Treatment Editorial Board. National cancer Institute (US): 2002-2019): done.

14. The author should add a paragraph for the follow up and survival in these patients, and shorten the Summary section (page 20): done.

15. Page 18, 2nd paragraph. Treatment of unresectable, metastatic or recurrent GISTs. The author has described the current treatment for advanced disease briefly without having reported any results from literature. One recent paper is the one of Wang J et al. *Medicine* 2020; 99(9): e19275, in which series significant tumor shrinkage was observed in almost 30% of cases, by using preoperative imatinib: done.

16. New title "Recent advances in the management of GISTs" has been given.