

## Peer Review File

**Article information:** <https://dx.doi.org/10.21037/gist-21-2>

**Reviewer 1**

**Comments to the authors:**

**1. In page 2-3, the authors introduced some reports on the incidental diagnosis of small GIST in surgical specimens. Although these are important findings, the manuscript did not show their significance in the role of surgery for the diagnosis of GIST in this section.**

**Reply 1:** we add new lines text as advised

Changes in the text: Despite this, surgery remains one of the important diagnostic and therapeutic methods for small tumors accidentally excised during operation for another reason and its significance is supported by international guidelines (2).. ( see page 2, line 91-93)

**2. In page 4, the authors described preoperative treatment with imatinib for some GISTs. Some papers may be missed e.g. Br J Cancer. 117(1):25-32, 2017 by Kurokawa et al. Please recheck the references corresponding to these sentences.**

**Reply 2:** We add article to reference

Changes in the text: see page 5 Line 141.

**3. In page 6, the authors mentioned that the most common gastric GIST procedure is a wedge or a segmental resection in the case of favorable tumor localization, and that in difficult cases e.g. tumors near the GE junction, the open method should be considered. Although these are classical concepts of surgery for gastric GIST, local**

**resection may be more commonly performed using new surgical techniques such as laparoscopic and endoscopic cooperative surgery (LECS) even for tumors closely located to the cardia. Please describe the current status, or otherwise show the references for the sentences in the present manuscript.**

Reply 3: We agree that currently with developing new techniques, minimally invasive surgery is more and more common even in the case of unfavorable localization. But still open surgery should be considered in difficult locations and the most important is oncological outcomes.

Changes in the text: See page 6-7 line 183-185 we add: With the development of minimally invasive techniques, operations in unfavorable/difficult anatomically locations are more often performed laparoscopically and/or endoscopically and are now the standard method of treatment in experienced centers.

**4. The authors used the term “limited resection (LR)” in the “Duodenum” and “Small intestine” sections. More details of LR should be described in each section. Does it mean local resection or other surgical procedures?**

Reply 4: We define precisely each procedure.

Changes in the text: see page 7 line 199 “and limited resection defined as segmental duodenal resection.”

See page 8 line 224 “Limited resection defined as segmental resection of small intestine with GISTs is usually recommended”

**5. In page 7, the authors described that the patients in the LR group had less late complications than in the PD group and no postoperative newly developed diabetes mellitus, and that the minimally invasive LR (MILR) group had a shorter duration of surgery and shorter length of postoperative hospital stay. Please show the references corresponding to these sentences.**

Reply 5: Thank you for this remark we have added appropriate references and changed the text – line 221.

**6. In the “Colorectum” section in page 8, the authors described that for low- or low-grade tumors, local tumor resection (LTR) or sphincter preservation may be performed. What is the “low- or low-grade tumors”?**

Reply 6: It should be very low-risk, low-risk, it has been changed accordingly.

Changes in the text: see page 8 line 237 we change for “very low-risk, low-risk”

**7. In page 9, the “New techniques of GIST treatment” section may be deleted.**

Reply 7: New techniques of GIST treatment section is for laparoscopic and robotic methods described below. We agree that the laparoscopic approach is standard but we also write about new techniques as robotic surgery, endoscopic GIST treatment, and connecting these methods what is still news and not widely available. See page 11, so we believe that it may be interesting for the readers, we would like to not delete this section. We have added new references there.

**8. In the “Surgical treatment of residual lesions after systemic treatment of primary unresectable / disseminated cases of GIST” section in page 12, the resection of residual GIST lesions after systemic treatment was discussed. I wonder why only unresectable or disseminated GIST, but not metastatic GIST, was focused.**

Reply 8: In term disseminated cases of GIST we included metastatic.

Changes in the text: see page 12 line 337 In patients with unresectable or disseminated GIST(including metastatic)

**9. In Figure 1, only CT findings were shown. Laparoscopic image should also be shown.**

Reply 9: We have added laparoscopic image.

**10. Please recheck all the references throughout the manuscript. Some references did not relate to the sentences in the main document e.g. ref no.43 for the sentences about LECS.**

Reply 10: Thank you for this remark, we have changed it

**11. Abbreviations should be defined at first mention, e.g. PD for pancreatoduodenectomy. Then, use abbreviations without full-spelling throughout the manuscript.**

Reply 11: We have corrected it as required in the full manuscript.

**12. GIST is an abbreviation of gastrointestinal stromal tumor, therefore, the term ‘GIST tumor’ duplicates tumor.**

Reply 12: Thank you for this remark, we have changed it

Changes in the text: see page 9 line 244

**13. There are some other grammatical and syntax errors throughout the paper.**

Reply 13: The entire text was checked again in terms of linguistic corrections

**Reviewer 2**

**Comments to the authors:**

**This manuscript, entitled “Surgical management of gastrointestinal stromal tumors”, is a comprehensive review regarding surgery in treatment of GIST. Authors are ambitious to cover different aspects regarding GIST management, including resection of primary tumor, neoadjuvant treatment, and role of surgery after TKI use. In addition, special consideration to different part of GI system has also been mentioned.**

Thank you for this general remarks.

**I have several opinions.**

**(1) For the citations, I would like to suggest authors to put the citation just after a phrase of statement rather than at the end of a paragraph or a section. In addition, some statement should be supported with reference. For example, in line 80 and 81 “The recommended approach is R0 resection with margins of about 1–2 cm” and line 108, 109, and 110 “Lymphadenectomy is not necessary as lymphatic invasion has not usually been reported, it should be reserved only for clinically positive nodes as it may be reported in pediatric GIST”, please give the reference.**

Reply 1: Thank you for this remark, we have changed it also we have included footnotes after each section for better clarity of the text.

Changes in the text: see page 4 line 100 and page 5 line 126

**(2) I do not totally agree with the opinions which authors provided in the section of “En bloc GIST resection of primary GIST”. For the patients with massive bleeding and high-grade obstruction of GI tract, the first priority is to stop bleeding or restore GI patency. The surgical procedure should be as simple as possible. After patient recovery, systemic treatment with TKI should be started. It is a little bit like the concept of neoadjuvant therapy. Complicated procedures should not be the choice of endangered patients.**

Reply 2: we agree that patients in hemorrhagic or septic shock should undergo the simplest possible operation and after that we think about completely tumor resection. In this paragraph, we were talking about patients who are bleeding or have an obstruction but are fit to survive extensive surgery and it has been added to the text (line 151: if the patient is enough fit for such surgery).

**(3) English editing is necessary for this article.**

Reply 3: The linguistic corrections have been made in the text.

**(4) I have an interesting finding that I cannot found any single reference from Raut CP in this review article. While Raut is one of the dominant figures in this field and has published several important relevant studies, I cannot imagine that none of his work has been included in the reference list. This implicated that this narrative review may be biased.**

Reply 4: We cite Raut CP reference 25 Colombo C, Ronellenfitsch U, Yuxin Z, Rutkowski P, Miceli R, Bylina E, Hohenberger P, Raut CP, Gronchi A. Clinical, pathological and surgical characteristics of duodenal gastrointestinal stromal tumor and their influence on survival: a multi-center study. Ann Surg Oncol. 2012 Oct;19(11):3361-7. doi: 10.1245/s10434-012-2559-0. Epub 2012 Jul 28. PMID: 22843188. However we have added two more references from Raut CP as the first author - Changes in the text: Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol. 2006 May 20;24(15):2325-31. doi: 10.1200/JCO.2005.05.3439. PMID: 16710031. Line 343 Fairweather M, Balachandran VP, Li GZ, Bertagnolli MM, Antonescu C, Tap W, Singer S, DeMatteo RP, Raut CP. Cytoreductive Surgery for Metastatic Gastrointestinal Stromal Tumors Treated With Tyrosine Kinase Inhibitors: A 2-institutional Analysis. Ann Surg. 2018

Aug;268(2):296-302. doi: 10.1097/SLA.0000000000002281. PMID: 28448384; PMCID: PMC6203295. Line 343

(5) I suggested authors to provide more relevant knowledge regarding impact of TKI on surgical outcome. The effect of TKI on surgery is also an important issue and it should be mentioned more.

Reply 5: Thank you for this remark. We have added this issue line 377-382.

Changes in the text: Currently, after resection of primary GIST at significant risk of relapse, systemic adjuvant therapy with imatinib is the standard of care as it is associated with relapse-free survival and overall survival benefits. The surgical strategy in locally advanced/marginally resectable GIST with sensitive mutations is also affected by possibility of preoperative use of imatinib to facilitate resection with microscopically clear margins as well as to decrease extent and morbidity of the surgical procedure.