

May 22, 2021

Somchai Amornyotin

Kusum K Kharbanda

Tdutomu Nishida

Editors-in-Chief

World Journal of Gastrointestinal Pathophysiology

Dear Editors:

On behalf of all co-authors, I would like to submit our revised manuscript 65503 titled “**Current treatment strategies and future perspectives for gastrointestinal stromal tumors**” for publication in the *World Journal of Gastrointestinal Pathophysiology*.

This manuscript had been previously submitted to the *World Journal of Gastrointestinal Oncology* and the previous journal has asked me for the manuscript to be transferred to the present journal.

We sincerely appreciate the careful review of our manuscript and the helpful suggestions provided, which have contributed considerably to its improvement. The manuscript has been revised as suggested, and detailed responses to the individual comments have been enclosed. For ease of review, the comments have been indicated by bold font; our responses are in standard font.

We sincerely hope that the manuscript is now suitable for publication in this journal, and would be pleased to respond to any further queries regarding this submission.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Yoichi Sugiyama, M.D.

Department of Surgery

JA Hiroshima General Hospital, Hiroshima, Japan

Address: 1-3-3, Jigozen, Hatsukaichi-city, Hiroshima 738-8503, JAPAN

Telephone: +81-829-36-3111 Fax: +81-829-36-5573

E-mail: sugiyama0113@gmail.com

Responses to reviewers' comments

Comment from reviewer 1

Reviewer #1: Although the manuscript contains much important information on the issue of gastrointestinal stromal tumor treatment, in my opinion, unfortunately, it does not meet for comprehensive review. The text is too general, it includes issues of surgery, neoadjuvant treatment, adjuvant treatment and palliative therapy. This is the reason why it does not go into too much detail of the discussed topics. The text seems to me more like a chapter in a textbook. Therefore I have to recommend to the authors to divide the text into two or more parts (e.g. surgery and systemic therapy) and elaborate the information into greater details. I have less important comment on the term "neoadjuvant chemotherapy" which is used in the text and even in the abstract. Imatinib is a targeted therapy, therefore I do not recommend to use a term chemotherapy for imatinib. GIST is considered to be chemoresistant and chemotherapy is usually used for the treatment of GIST. My recommendations for the editorial board is to accept the article for publication but after for major editing of the text.

Response

We sincerely appreciate the careful review of our manuscript. As suggested, we have divided the text into three parts: SURGERY, RISK ASSESSMENT AND ADJUVANT THERAPY, and SYSTEMIC THERAPY. In the SURGERY section, we have reported on laparoscopic surgery, especially LECS. Various LECS techniques have been devised, but there are no clear suggestions on which technique to select; these have therefore been summarized in this section. The possibility of surgical intervention for GIST with metastases has also been discussed.

In the RISK ASSESSMENT AND ADJUVANT THERAPY section, we mentioned basic research in addition to general risk assessment; regarding adjuvant therapy, we discussed various aspects of imatinib administration, and particularly the duration of administration, based on data from various clinical trials.

Finally, in the SYSTEMIC THERAPY section, we included the latest findings on each exon mutation, the clinical impact of each mutation, the expected findings

of liquid biopsy in the future, and expected results from research on TKIs other than imatinib and immune checkpoint inhibitors.

As correctly observed, imatinib is a TKI and not chemotherapy; the term “neoadjuvant chemotherapy” has therefore been replaced by “neoadjuvant therapy.” We appreciate your observations, and apologize for the error.

Comment from reviewer 2

The manuscript discussed treatment strategies for current GIST and promising treatments based on clinical trial. In addition, the application of more surgical techniques in the field of GIST is described. 2.The language quality in the manuscript is good. 3.The evidence on diagnosis, treatment, and prognosis is overwhelming.

Response

We sincerely appreciate your careful appraisal of our manuscript.

Comment from reviewer 3

This article pointed out three different GISTs corresponded to various management. Overall I found the article to read as a laundry list of abstracts of GISTs related studies rather than an in depth review of the findings and scientific value behind all of the studies. It is suggested that readers would appreciate a more synthesized overview of not only what research has been done, but which aligned (suggesting there may be something valuable to their findings) versus discordant and why they are discordant. Here are some other major issues:

Thank you very much for taking the time to review our manuscript, which has now been revised based on your observations.

We have re-read and re-examined the cited papers based on our findings. The data included in the manuscript has mainly been discussed from a clinical perspective. In addition, we have revised the manuscript based on the major issues indicated. Our point-by-point responses have been provided below:

- 1. The introduction is of redundancy and complications and needed to be simplify. The purpose of this review in introduction section should be**

consistent with the core tip section.

As suggested, we have reviewed the introduction and have revised it to ensure consistency with the core tip section.

- 2. First part in the main text, "images" is recommended to be revised as "imaging". The main idea of the whole article is not about submucosal tumor, and it is suggested to omit the irrelevant content about submucosal tumor. Rather, the focus is on depicting things of GISTs.**

As correctly observed, the term "image" was incorrect. In addition, the parts on imaging and the submucosal tumors were removed because the manuscript has been revised to ensure that the focus is mainly on the treatment of GIST.

- 3. Third part of "UNRESECTABLE, RECURRENT OR METASTATIC GIST" is clunky and unclear, not as logic as the first part with subheadings. The table 4 at the end seems to do a better job than the text of the paper. Additionally, in terms of table 4, the advantage is the refinement treatment choices for specific exon mutations, but KIT gene also included exon 8,14,18, which lacks explanation in the article. And table 4 summaries are not complete and full, for example, wild type GISTs with BRAF mutation is sensitive to Dabrafenib based on pervious literature.**

The manuscript has been revised to improve logic and clarity, and the mentioned text has been included in the "SYSTEMIC THERAPY" section. We have also added the findings pertaining to exons 8, 14, and 18, as suggested. In addition, we have read the papers pertaining to the BRAF gene and dabrafenib again, and have added new findings.

- 4. There are word choice and grammatical errors throughout the manuscript whose correction would improve readability. Additionally, the use of subheadings is not standardized and confusing.**

The entire manuscript has been re-edited to ensure that all grammar and readability issues have been addressed. In addition, the headings have been standardized and the text has been divided under three major headings: SURGERY, RISK ASSESSMENT AND ADJUVANT THERAPY, and SYSTEMIC THERAPY; the subheadings have also been revised to prevent any confusion.

- 5. Every table should be marked a detailed and separate abbreviation for comprehension.**

We have described the abbreviations in each table for clarity.

- 6. The full text should be marked with a total abbreviation list.**

As suggested, we have added a list of abbreviations before the introduction section.