Point-by-point responses

Manuscript ID: **55160**

Invited Manuscript ID: **03475120**

Name of Journal: **World Journal of Gastrointestinal Pharmacology and Therapeutics**

Manuscript Type: **Retrospective study**

Title: **Do liver metastases from gastric cancer contraindicate aggressive surgical resection? A 14-year single-center experience**

Corresponding author: **Tomohide Hori, PhD., MD., FACS.**, Editorial Board member of World Journal of Gastrointestinal Oncology (Number ID: 03475120)

Thank you for your valuable suggestions.

According to reviewers' comments, we revised our initial manuscript.

Please review our revised manuscript.

We prepared **Marked revised manuscript** and **Clear version**. In the marked version, additional mentions are in Red, and deleted sentences are shown in Red with strikethrough.

Also, this summary of responses (**Point-by-point responses**) was separately made.

English language: Manuscript (Main body, table and figures) has been already checked by English consultant (edanz editing, ordering ID: J2002-139237-Hori). I attached a Certificate for English language, with this letter.

If you have any questions, please do not hesitate to contact me by e-mail.

Sincerely yours,

Tomohide Hori, PhD., MD., FACS.

Number ID: 03475120, Editorial Board member of World Journal of Gastrointestinal Oncology

To Reviewer #1

'This manuscript is well organized and meet the requirements of ethics, it has certain value of clinical application. However, there still some limitations due to a small sample size. Authors can eliminate this limitation by seeking collaboration to expand the samples.'

Thank you for your valuable suggestion.

At first, we clearly mentioned this point as 'This was a retrospective study performed in a single institution and therefore has inherent limitations due to bias and a small sample size. (page 13 line 25-27, in the Marked revised manuscript)'.

As shown in Table 5, sample sizes of each paper were small.

According to your suggestions, we added a mention in the revised manuscript as 'As shown in Table 5, only 14 papers have been previously documented, and almost all of these important papers were written based on retrospective design and/or single-center experience. Sample size were shown in **Table 5**. (page 13 line 23-25, in the Marked revised manuscript)'.

To Reviewer #2

'Interesting article looking at single institution outcomes associated with liver resection in metastatic gastric cancer in s small case series over 14 years. There

are a number of issues with this paper.'

Thank you for your positive evaluation.

According to your valuable suggestions, we revised our initial manuscript as below.

1. Image modalities

'The authors do not categorise how they stage these patients for assessment of their metastatic disease. Is it by CT only, do they have PET scans, laparoscopy, bone scans etc. How can we assure that there is no other evidence of disease.'

In all cases, thoracoabdominal enhanced CT were routinely performed for checking extrahepatic diseases. Positron emission tomography/computed tomography was also used. If any bone metastases were suspected, bone scintigraphy were performed. Routine laparoscopy was not employed in our institution.

According to your suggestions, we added a mention in the revised manuscript as 'In all cases, thoracoabdominal enhanced computed tomography were routinely performed for checking extrahepatic diseases. Positron emission tomography/computed tomography was also used. (page 7 line 23-25, in the Marked revised manuscript)'.

2. Neoadjuvant therapy

'The authors need to discuss in detail why neoadjuvant therapy as a

therapeutic trial was not used in all of these patients. This is particularly true on patients with synchronous disease and as a separate group metachronous disease should also be discussed to exclude other sites or at least assess response. to merely use it as a bridge to resection in inoperable patients makes little logical sense Failure to include or discuss these issues greatly limits the applicability of this study to western cohorts where neoadjuvent therapy is a routine for advanced gastric cancer as defined in this paper.'

Thank you for your positive evaluation.

We agree that perioperative chemotherapy (including neoadjuvant and adjuvant chemotherapies) is so important for Stage IV GC patients, and also thought that surgical curability (*i.e.*, graphical and surgical R0) is also important for these patients.

At first, we described this point as 'The curability of LR is important for patients with LMGC. In the present study, the initial LR was curative in 29 patients. Adjuvant chemotherapy after curative surgery (*i.e.*, graphical and surgical R0) is strongly recommended in patients with stage IV GC[28-32], and perioperative chemotherapy was introduced in 23 patients.' (Page 13 line 20-23, in the Marked revised manuscript).

Next, GC patient with synchronous LMGC is categorized as Stage IV, and neoadjuvant and/or adjuvant chemotherapy will be introduced for synchronous LMGC as possible. Although neoadjuvant and/or adjuvant therapies were introduced in all of 13 patients with synchronous LMGC, 6 of 17 patients with metachronous LMGC did not receive perioperative chemotherapy.

In these 6 patients with metachronous LMGC, the surgical curability (*i.e.*, graphical and surgical R0) of LR was accomplished in each. Though introduction of perioperative chemotherapy may involve a difficulty due to some reasons (*e.g.*, underlying disorder and performance status), and LR with surgical curability may be beneficial for metachronous LMGC patients who had some difficulty of perioperative chemotherapy.

According to your suggestion, we added the mention as 'GC patient with synchronous LMGC is categorized as Stage IV, and neoadjuvant and/or adjuvant chemotherapy will be introduced for synchronous LMGC as possible. Although neoadjuvant and/or adjuvant therapies were introduced in all of 13 patients with synchronous LMGC, 6 of 17 patients with metachronous LMGC did not receive perioperative chemotherapy (**Figure 2**). In these 6 patients with metachronous LMGC, the surgical curability (*i.e.*, graphical and surgical R0) of LR was accomplished in each. Though introduction of perioperative chemotherapy may involve a difficulty due to some reasons (*e.g.*, underlying disorder and performance status), and LR with surgical curability may be beneficial for metachronous LMGC patients who had some difficulty of perioperative chemotherapy.' (Page 13 line 23-page 14 line 4, in the Marked revised manuscript).

3. Localized dissemination (evaluated as P1) and peritonectomy

'The authors when talking of the primary tumpours note that 2 patients has peritoneal dissemination. What exactly does this mean. Was this simply a T4B tumour or was this distant dissemination. In which case what primary

treatment was employed. was a "peritonectomy " performed or other therapy. Where did these patients have recurrence. IF distant peritoneal disease these patients really should be excluded.'

Thank you for your positive evaluation.

In our two patients with peritoneal dissemination, there were no distant disseminations. Their disseminations were localized nearly at the primary GC, , and were evaluated as P1 according to Japanese classification[2]. Graphical and surgical R0 was accomplished by peritonectomy in each patient.

According to your suggestion, we added the mention as 'In our two patients with peritoneal dissemination, there were no distant disseminations. Their disseminations were localized nearly at the primary GC (*i.e.*, P1[2]), and graphical and surgical R0 was accomplished by peritonectomy in each patient.' (Page 12 line 28-page 13 line 2, in the Marked revised manuscript).

4. Importance of additional surgeries for recurrences after the initial LR

'The addition of discussing further resections for recurrences after resection is outside of the scope of this paper. Again the treatment of these is superficial with no information about the staging or selection processces for these patients and a comparison of survival between these and patients who did not receive resection without far more detail regarding selection is superficial and adds nothing to the paper.'

Thank you for your positive evaluation.

We believe the combined strategy of aggressive curative surgeries and chemotherapy during the perioperative period of LR comes first for patients with

LMGC. However, introduction of perioperative chemotherapy may involve a difficulty due to some reasons (e.g., underlying disorder and performance status), and LR with surgical curability may be beneficial for metachronous LMGC patients who had some difficulty of perioperative chemotherapy. If surgical curability additional surgery will be obtained in carefully-selected patients, additional surgery becomes a beneficial therapeutic option even after the initial LR. This point should be mentioned.

According to your suggestion, we discussed this point and added the mention as 'Three of 6 patients with metachronous LMGC who did not receive perioperative chemotherapy were undergone additional surgeries for recurrence after the initial LR, and two of these 6 patients were still alive. Surgical curability is important for LR and additional surgery. LR and additional surgery may be beneficial for these metachronous LMGC patients if surgical curability is obtained, though we believe the combined strategy of aggressive curative surgeries and chemotherapy during the perioperative period of LR comes first for patients with LMGC.' (Page 14 line 9-15, in the Marked revised manuscript), and 'Though introduction of perioperative chemotherapy may involve a difficulty due to some reasons (*e.g.*, underlying disorder and performance status), and LR with surgical curability may be beneficial for metachronous LMGC patients who had some difficulty of perioperative chemotherapy.' (Page 14 line 1-4, in the Marked revised manuscript).

To Science Editor

'Recommend for potential acceptance. 1 Scientific quality: B,D. This article is about liver metastases from gastric cancer contraindicate aggressive surgical resection, within the scope of WJG. Summary of peer-review report: Interesting article looking at single institution outcomes associated with liver resection in metastatic gastric cancer in s small case series over 14 years. This manuscript is well organized and meet the requirements of ethics, it has certain value of clinical application. However, there still some limitations due to a small sample size. 5 tables and 4 figures. 34 references were cited, including 8 latest references from 2017-2020. 2 self-citation articles. 2 Language quality: 2A. Edited by Edanz language editing services. 3 Academic norms and rules: Retrospective Study. Copyright license agreement, signed informed consent, IRB and BRC files are complete and qualified. Conflict-of-Interest statement file is not qualified. Bing search and CrossCheck are eligible. 4 Others: Without financial support. Corresponding author has published 3 articles in BPG. Invited manuscript.'

Thank you for your positive evaluation as 'Recommend for potential acceptance.'.

<u>To Editorial Office Director</u>

'Recommend for rejection. I have checked the comments written by the science editor, but I don't agree with the science editor. The sample size is small, the design of the study has a problem.'

At first, we clearly mentioned this point as 'This was a retrospective study performed in a single institution and therefore has inherent limitations due to bias and a small sample size. Thus, the conclusions must be interpreted with extreme caution. (page 14 line 18-20, in the Marked revised manuscript)'.

As shown in Table 5, sample sizes of each paper were small.

According to your suggestions, we added a mention in the revised manuscript as 'As shown in Table 5, only 14 papers have been previously documented, and almost all of these important papers were written based on retrospective design and/or single-center experience. Sample size were shown in **Table 5**. (page 14 line 16-18, in the Marked revised manuscript)'.

To Company Editor-in-Chief

'I recommend the manuscript to be published in the World Journal of Gastrointestinal Pharmacology and Therapeutics.'

According to your suggestion, we switch the target journal to 'World Journal of Gastrointestinal Pharmacology and Therapeutics'.