

To: Lian-Sheng Ma, Editorial Office Director, Company Editor-in-Chief, Editorial Office

Dear Prof. Lian-Sheng Ma:

Thank you for your kind comments on manuscript NO.: 74675, a retrospective cohort study, entitled **“Efficacy of neoadjuvant chemotherapy for initially resectable colorectal liver metastases: A retrospective cohort study.”** We have revised the manuscript per your comments and look forward to your favorable response.

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** The submitted paper analyzes the effect of neoadjuvant chemotherapy for initially resectable colorectal liver metastases in a Japanese retrospective cohort; this issue is quite complex, also due to the characteristics and classification criteria used in various publications. Here the authors compare patients who underwent liver resection with individuals that received neoadjuvant chemotherapy prior to surgery. The authors were able to extract, from the entire cohort, two groups with similar characteristics (50 subjects each) and undergoing the two different therapeutic options, that were followed for up to 10 years. Within these groups, patients were also classified as low or high risk according to the presence of preoperative CEA levels,

primary histological type and primary lymph node metastases. The authors detected a significantly better survival at 5 years in patients with neoadjuvant therapy. Although the data are interesting, there are some points that need to be clarified: Patients' characteristics before the propensity score matching should be reported in a table The number of the patients still present in the various groups in the Kaplan-Meier curve Although the numbers are quite small, did the authors observe any difference among the various treatments?

**Response:**

- 1) We have added the "Patient characteristics before the propensity score matching" to Table 1.
- 2) Regarding treatments other than hepatectomy, adjuvant chemotherapy after primary resection and after hepatectomy were examined and described in Tables 1 and 3. There was no difference in these treatments between the high- and low-risk groups. We added the following text to the revised manuscript:

The background characteristics were comparable when stratified by high- and low-risk, respectively (Page 13, lines 22-24).

Furthermore, we have added the following text to the revised manuscript:

No patient received preoperative chemotherapy before resection of the primary lesion. (Page 7, lines 12-13.).

Reviewer #2:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The manuscript is well-written and describes a therapeutic benefit for the patients from NAC. A flow chart could add an extra strength and clarity for the reader

**Response:**

1) We have added a “Study flow diagram” submitted as Figure 1 to depict the patient selection process.

2) We have fixed the following text to the revised manuscript:

Among them, 297 resectable cases were included in this study. Among these cases, patients with synchronous liver metastases who received liver-first surgery or simultaneous resection of CRLM and the primary lesion were excluded (Page 7, lines 7–10).

Reviewer #3:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** This is a study with a clear objective. The work is well written; however, I suggest that the authors present the inclusion and exclusion criteria more clearly.

**Response:**

1) We have added a “Study flow diagram” submitted as Figure 1 to depict the patient selection process.

2) In the text, it was difficult to understand the original indication for NAC and the background of patients that received NAC in resectable CRLM. Therefore, we have revised the text as follows:

Originally, NAC was administered to those with marginally resectable CRLMs who did not satisfy either of these criteria<sup>[12]</sup>. However, there were patients who underwent upfront

hepatectomy (at their own request) although they met the criteria for NAC initially. Conversely, there were patients who received NAC although they met the criteria for resectable CRLM initially. Therefore, patients who met the criteria for resectable CRLM included those who underwent upfront hepatectomy or received NAC (Page 8, lines 20–27).

Reviewer #4:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** It is a work that explains the experience of his working group in colorectal cancer metastases. It is very well structured, explained and written. The results and conclusion are in agreement with current data that the most unfavorable patients benefit from neoadjuvant chemotherapy treatment. But it raises some questions: - Inclusion criteria for the analysis. It goes from 644 to 297, but only 61 are excluded. A flowchart could help. - The work refers to colorectal cancer. But then only the primary is cited as right and left. - The strategy for the treatment of synchronous tumors is not explained: liver first, primary primary, simultaneous ... - No case of preconditioning is mentioned and whether this has been an exclusion criterion.

**Response:**

1) We have added a “Study flow diagram” submitted as Figure 1 to depict the patient selection process.

2) We have added the following text to the revised manuscript:

In addition, left-sided tumors included carcinomas in the descending colon, sigmoid colon, and rectum, and right-sided tumors included carcinomas in the cecum, ascending colon, and transverse

colon (Page 8, lines 3–6).

3) We have added the following text to the revised manuscript:

Among them, 297 resectable cases were included in this study. Among these cases, patients with synchronous liver metastases who received liver-first surgery or simultaneous resection of CRLM and the primary lesion were excluded (Page 7, lines 7–10).

Sincerely yours,

Kazuhisa Takeda

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