Dear reviewer,

We feel great thanks for your professional review work on our manuscript tiled "Tumour response following preoperative chemotherapy is affected by body mass index in patients with colorectal liver metastases" (Manuscript **No.89002**). As you are concerned, there are several problems that need to be addressed. Based on your valuable suggestions, we have made extensive corrections to our previous draft, the detailed corrections are listed below. (the revised/added contents were highlighted with yellow color in the revised manuscript).

1. **Abstract, Line 38:** Please rephrase sentence – a suggestion is: "a low BMI may be associated with better tumour response and longer PFS". Please avoid overstatement (note: no multivariable analysis was performed to investigate the relationship between BMI and PFS therefore BMI cannot be supported as independent predictor for longer PFS)

   The author's answer: Thank you for your professional opinion. The sentence in the revised manuscript has been rephrased according to your suggestion.

2. **Introduction**
   a. **Lines 51-53:** Please Add reference(s) used to support this statement, (note: However bear in mind that studies have shown that chemotherapy response is not a strong predictive factor to overall survival, EORTC 40983 trial Lancet Oncol, 14 (12) (2013), pp. 1208-1215)

   The author's answer: We have added references to support this statement.

3. **Material and Methods**
   a. **Lines 89-90**: Were underweight patients included in the study?

   The author's answer: Underweight patients were included in the study. A total of 5 out of 126 patients were underweight, of which 1(20%) patient had a complete tumour response after preoperative chemotherapy. The low BMI group included both underweight and normal weight patients.

   b. **Section 2.2:** A table in the supplementary material with all variables and their definitions (e.g age, tumour location, TNM stage, number of CLRM, size of mets etc) that were collected is advised to be included in this section. Was any weight loss recorded for the period between the initiation of neoadjuvant chemo and the time of surgery?

   The author's answer: We have created a new table **(Supplementary Table 1)** containing explanations or definitions of variables related to this study.

   In the newly revised manuscript, we have included data on weight changes from the initiation of neoadjuvant chemotherapy to the time of surgery and included it in the analysis, as detailed in **Tables 1 and 2.** A weight changes exceeding 5% were recorded as either weight gain or weight loss.

   c. **Section 2.4:** Did the authors record local and/or systematic recurrence during the follow up period?

   The author's answer: Yes, it was recorded. The recurrence of local and/or systemic was recorded as disease progression.

   d. **Section 2.5:** How did the authors decide on the sample size. Was a sample size calculation performed?

The author's answer: The rule of thumb for the required sample size is to ensure at least 10 events for each predictor parameter. During the study design stage, two predictors, BMI and bevacizumab, were mainly taken into consideration. Therefore, initially more than 20 events (those with complete tumor response) or 100 samples (the incidence of complete tumor response, TRG1-2, reported in previous literature was 20%) were considered sufficient. Actually, 27 events and four predictors were emerged in the multivariable model, which we consider acceptable for an exploratory study. Admittedly, the small sample size is one of the limitations in our study. And we will further expand the sample size in the future.

4. **Results**

   a. **Line 131:** The term synchronous liver metastases is preferred than simultaneous

   The author's answer: Thank you, it has been rectified.

   b. **Line 132:** How do the authors define "multiple" liver metastases. Additionally, the lobar metastatic distribution is advised to be included as a variable (bilobar vs unilobar)

   The author's answer: Multiple liver metastases were defined as colorectal liver metastases with more than one lesion. The lobar metastatic distribution was included as a variable in revised manuscript, as detailed in **Tables 1 and 2.**

   c. **Line 139**: What do the authors mean by simultaneous surgery?

   The author's answer: Simultaneous surgery refers to simultaneous resection of primary and metastatic liver tumour**.**

5. **Discussion**

   a. **Line 173:** Please improve sentence – highlight that obesity is an unfavourable prognostic factor in patients with colorectal cancer (not only for those who received chemotherapy) (Ref: Tech Coloproctol. 2016 Aug;20(8):517-35. doi: 10.1007/s10151-016-1498-3.)

   The author's answer: The sentence has been rephrased in the revised manuscript.

   b. **Line 177**: Please rephrase as univariable or multivariable analysis was not performed for PFS. A suggestion would be "… exhibited poorer response to chemotherapy and appeared to have shorter PFS compared to patients with low BMI".

   The author's answer: Corrected according to your suggestion.

   c. **The authors should add a paragraph where they discuss these findings in comparison with other studies**. For instance what did other studies show in terms of BMI and PFS, or tumour response?

   The author's answer: The revised manuscript now includes a new paragraph discussing relevant findings from previous literature.

   d. **Lines 228-239:** New results should be presented in the results section. This paragraph is advised to be moved in the relevant section as subgroup analysis. Please revise manuscript accordingly.

   The author's answer: Thank you for your reminder. We present the results of subgroup analysis in the **Results** section (last sentence of the "Relationship between BMI and tumour histological response" paragraph, highlighted in yellow). Considering

that this paragraph mainly discussed the role of bevacizumab in the relationship between BMI and tumor response, the authors feel that placing this paragraph in the **Discussion** section would still be appropriate.

e. **Lines 248-249:** The authors should expand on their limintation paragraph. The fact that genetic factors (e.g KRAS mutations) were not taken into account in the multivariable model should be mentioned as limitation. Please, expand on the selection bias – such as only patients with resectable disease were included. In addition, were variations on BMI pre and after neoadjuvant chemo considered? What did the authors do to overcome these limitations e.g multivariable model

The author's answer: We have expanded on the limintation paragraph in the revised manuscript.

f. A paragraph mentioning the implications of this study in clinical practice and what areas the authors suggest should be explored in the context of future research is recommended.

The author's answer: A paragraph was added that discussed the implications of this study in clinical practice and potential research perspectives.

6. **Conclusion**: Please rephrase line 252 " ···low BMI appears to be associated with better tumour response and longer PFS", to avoid overstatement.

   The author's answer: We have made correction based on your suggestion.

7. **Tables**

   a. **Table 1:** The histopathological characteristic of the primary tumour TNM is advised to be included. The median BMI of each group (low and high) should be included in this table. Please mention what statistical test was used – this could be mentioned below the table. Please define primary site colon (right vs left?) Please also see my comments for terminology above (synchronous liver mets).

   The author's answer: Thank you very much for your suggestion. The median BMI of the two groups has been included to this revised table. Referring to Fong's Clinical Risk Score (CRS), which is based on lymph node metastasis, simultaneous metastasis, number of metastases, diameter of largest metastases, and preoperative CEA level, we have included these five variables in this study. However, considering that there were already many variables included, we do not intend to include detailed TNM data for the primary tumor. Statistical test has been mentioned below **Table 1**. The localization of primary tumors was classified into two categories: rectum and colon. The term 'Primary site, colon' indicates that the primary tumor is located in the colon.

   b. **Supplementary table 2:** Please also include the statistical test that was used.

   The author's answer: Statistical test has been mentioned below **Supplementary table 2**.

8. **Other Comments:**

   a. Usually abbreviations are used alongside the full text on first appearance and thereafter the abbreviations can be used alone

   b. Please check the entire manuscript for typos.

The author's answer: Thank you, we have carefully checked the revised manuscript to avoid any mistakes.

Thank you very much for your attention and assistance. Look forward to hearing from you.

Best regards,
Authors of Manuscript No.89002
December 5th, 2023