

24th November 2019

Dear Dr Yan,

Reference:

Name of Journal- World Journal of Gastrointestinal Surgery

Manuscript NO- 51472

Manuscript Type- Retrospective Cohort Study

Article title- RETROSPECTIVE COHORT STUDY OF STATIN THERAPY EFFECT ON RESECTED COLORECTAL LIVER METASTASES

Below is a point-by-point response to the editor's comments:

1. Article highlights (Page 17)- Now included
2. Reference list (Page 18)- Now modified accordingly
3. Abbreviation (Tables 1 and 2)- All tables replaced to remove abbreviations
4. Superscript letter (Tables 1-3) - All tables replaced to remove superscripts

All the requested changes to the manuscript, including reviewer's comments, are highlighted in red font. I look forward to hearing from you.

Yours sincerely
Edward Alabraba

Reviewer #1

(1) "The results are well-organized according to the author's research, but there is one issue with statistical analysis. In presenting the results of each table, there is no indication of statistical significance between groups. It should be supplemented for that issue."

Response: The tables include superscripts that indicate the p-value for univariate and multivariate analysis of each variable. We have adjusted the tables to include columns containing the actual values.

Reviewer #2

(1) "The manuscript analyses the impact of statins on resected colorectal liver metastases. This is an interesting approach, but some major aspects should be checked/explained: - In this type of work, usually there are some inclusion and exclusion criteria, how was this process done?"

Response: In the first 4 lines of the 'Patients' sub-section of the 'Methods' section, we indicate that subjects were identified from a prospectively maintained database of patients who underwent primary hepatic resection for CRLM. We also indicate that we excluded the patients who did not actually undergo hepatic resection. We have altered the text to clarify this further.

(2) "Please, explain. - Please, analyze in details the weakness of the work."

Response: In the last paragraph of the discussion, we indicate the perceived weaknesses of the work. We discuss the limitation that it is a single tertiary centre retrospective study and may not represent the experience of other centres. We also mention that we excluded CRLM patients who did not undergo resection, so results may only apply to those patients with CRLM treated with liver resection and not to all patients with CRLM.

(3) "Please, analyze the impact of time under medication as well as type of statin on the final result; in this line, while refining data maybe some conclusion could be determined."

Response: We were unable to obtain accurate data on the length of time patients had been on statin therapy but this will certainly be an important refinement that can be assessed by future studies prospectively following up patients who have colorectal cancer diagnosis and are taking statins while in surveillance for colorectal cancer metastases. We have added this point to the limitations of the study

(4) "The authors mention that they have not taken into account the individual statins because there are no reports on this topic, but this is the novelty of the work."

Response: We agree this is an interesting area that could improve our understanding of statin action in CRLM. The difficulty in this regard is that some patients have switched statin type during the study period, usually due to intolerance of drugs. We were thus unable to analyse the effect of specific statins but feel this can be addressed in future prospective studies.

Reviewer #3

(1) The organization and analysis of results need improvement. The results are not well defined and need improvement, and methods introduction should be moved to the Methods section.

Response: We have removed the superscripts and more clearly stated the p values in the results tables to better define the results. We moved the methods introduction statement "The primary aim of this study was to evaluate the impact of statin therapy on the survival of patients undergoing liver resection for CRLM. The secondary aim was to determine whether statin therapy influenced histopathological features of CRLM." from the end of the 'Background' section to a new sub-section titled 'Aims' at the start of the 'Methods' section.

(2) The authors indicate that "The IMD did not have a significant relationship with the use of statins ($p=0.253$)". The authors should discuss this point in more detail (Statistical analysis).

Response: We analysed the relationship between these categorical variables using Chi-squared test and showed there was no significant relationship. We felt this was an important topic to investigate as it addresses the question of whether any perceived effect of statins on CRLM is due to variation in statin usage according to patients' socioeconomic status. As we did not see any effect of IMD on outcome of CRLM, we can thus conclude that IMD neither affects statin usage nor outcome of CRLM. We have clarified the quoted results section and included further explanatory detail on IMD in the methods and also in the discussion.

(3) In Statistical analysis and Table 3, the statistical significance between each group should be explained in more detail, and if possible, add some statistical parameters (P value, e.g.).

Response: We have removed the superscripts and more clearly stated the p values in the results tables to better define the results.

(4) The different types and different doses of statins should be explained in more detail in the Methods and Results section. Can you further explain the comparison of results?

Response: We certainly appreciate that this study is an opportunity to define a novel and unique effect of different types of statins and different doses on CRLM. Statins vary in type, each of which has different dose ranges which are used by the general practitioners depending on patient preference and tolerance. Individual patients in our study switched statin type and doses used varied over the study period. The heterogeneity in statin usage made it difficult to collect accurate data on statin type used, dose used, and length of time specific statins were used at specific doses. We feel this can be addressed in well-designed future prospective studies. We have added this point to the limitations of the study.