



January 17^h, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6871-review.doc).

Title: Bevacizumab in the pre-operative treatment of locally advanced rectal cancer: a systematic review

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewers.

(1) REVIEWER 00159314: *"Dear authors, Your article is well written and accurate. Anyway, I have some suggestions. You must provide in the article the criteria for advanced rectal cancer and the staging according to American Joint Committee Cancer. It is important to know if the patients have only local advanced disease or they have distant metastasis. I recommend to realize a link between the presented studies. It seems to be like a sequence of studies, more than a review. I recommend to provide a systematic arrangement of the studies: total number of patients, stages of the diseases, treatment regimen, complications, etc. Thus, a clear conclusion could be obtain easier. I consider that the conclusion should be shorter with a clear take home message. Perhaps a chapter of discussions should be inserted."*

Authors' reply: We really thank the Referee for these positive comments. According to the Referee's comments, we have implemented the manuscript. In particular: 1) we have added more information about the criteria for defining "locally advanced" rectal cancer (please see page 4, lines 7-10): all the studies discussed cT3 or more, cN0 or more, cM0 patients (i.e. non metastatic disease amenable to radical surgery). There are only 2 studies which enrolled also stage IV patients (ref. 19 and 20), but the number of metastatic cases was extremely low: therefore, conclusions can be derived only for stage II and III LARC patients; 2) we tried to realize a link among the discussed studies by grouping them according to the "global treatment strategy" evaluated in each trial (e.g. neoadjuvant CT-RT, induction CT followed by neoadjuvant CT-RT, etc.). We modified the text to make the general architecture of the review clearer to the readers (please see page 4, lines 10-20); 3) we have added Tables 1 to 4 (please see pages 24-27) to provide a more systematic arrangement of the studies without overloading the text with excessive information; 3) we have renamed and improved the Conclusion section (now entitled Discussion) and added a new (shorter) paragraph of Conclusions (please see chapters 4 and 5, pages 13-15; please see also reply to Reviewer 01093440).

(2) REVIEWER 00058525: *"This is a comprehensive review of the literature on the current status of Bevacizumab in the management of rectal cancer. The paper is on the whole written and appropriately referenced. There are some minor typos. My only major comment to the editors is that it reads a bit like the introduction to a thesis submission."*

Authors' reply: We really thank the Referee for appreciating the comprehensiveness of our paper. We apologized for minor typing mistakes (the article has been thoroughly amended). We agree with the comment that no definitive conclusions can be made about the role of bevacizumab in the pre-operative management of locally advanced rectal cancer (please see also reply to Reviewer 01093440), as we have only preliminary phase I-II studies available and results are conflicting. However, this justifies in our opinion the need for a comprehensive evaluation of this drug in this setting: instead of immediately moving to larger phase III studies (as happened in the adjuvant setting for colon and breast cancer), a rethinking of the antiangiogenetic approach is essential to design more informative trials on selected patient populations. In order to make this point clearer to the readers, we have modified the Introduction section (please see page 4, lines 10-20).

(3) REVIEWER 01093440: *"This paper is just a description of trials available without any critical evaluation and a tentative to indicate new ideas for future trials. The paper may be resubmitted when there will be more data and it will be possible to make a meta-analysis."*

Authors' reply: We can understand the criticisms raised by the Referee. However, as also pointed out by Reviewers 00159314 and 00058525 and our replies, a thorough evaluation of the available data is the only way to design really conclusive and informative trials in the future: therefore, we do believe that it is not necessary to wait for additional data, as suggested by the Referee, but rather better understand the available data to develop better treatment strategies to be tested (please see revised chapter 4, Discussion). Moreover, as member of the Italian collaborative GONO (Gruppo Oncologico Nord Ovest) group we are currently testing an innovative approach in the pre-operative treatment of LARC: in the TRUST trial (please see ref. 28), FOLFOXIRI (which has been never tested in the adjuvant setting in colorectal cancer before) plus bevacizumab is integrated in the induction phase and followed by bevacizumab plus fluoropyrimidine CT-RT among high-risk patients as defined by magnetic resonance criteria.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Lorenzo Fornaro', written in a cursive style.

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