Professor **Godefridus Peters, PhD**
Editor-in-Chief,
World Journal of Clinical Oncology
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Dear Professor,

Subject: Submission of revised manuscript 34035

We thank reviewers for careful reading our manuscript and for giving useful comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below.

We hope the revised version is now suitable for publication and look forward to hearing from you.

Yours sincerely,

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Response letter to the Reviewers:

Thank you for your review of our paper. We have answered each of your points below, and described in the revised manuscript (yellow highlighted).

Reviewer #2 (Comments to the Author (Required)):

1. The abstract should specify why these patients have been classified as stage IV. It is clarified in the text but not in the abstract. It is necessary for the exclusive readers of the abstract to grasp the essence of the article. Also in the 7th AJCC, M1a (Stage IV) is considered the presence of lymphadenopathy in the common iliac chain and in the external iliac.

- Thank you for your important comments. In the abstract, we added the sentence that explains why patients have been classified as stage IV (**Page 4, Line 72 - 73**).

2. L64-L66 – "Clinical LPLN metastasis was defined as LN with a maximum diameter of 10 mm or more on preoperative pelvic computed tomography scan". Usually considered positive if: Lymphadenopathies > 5 mm (short axis) seen, with irregular border and heterogeneous signal intensity.

- We understand your comments. However, there is no consensus regarding this issue. In this study, we defined the lymph node metastasis as the lymphadenopathy more than 10 mm maximum diameter.

3. L113-114 – "In Western countries, LPLN metastasis is generally considered as a metastatic disease". Only if involvement of the external iliac chain or common iliac (primitive).

- We understand your comments. We know that internal iliac LN is the regional LN in the AJCC 7th. However, LPLN metastasis including internal iliac LN has been regarded as distant metastasis in general (*Ann Surg*. 2012; **255**: 1129-34).

4. L115 – L116 – " ... and preoperative chemoradiation and total mesorectal excision (TME) is the standard treatment" This means that the lateral lymph nodes of the pelvis are treated prophylactically. But this treatment is done with radiotherapy instead of with surgery. Modern radiotherapy has minimal toxicity and presents less morbidity than LPLN. (JCOG0212)

- In JCOG 0212 there was no significant difference in postoperative complication rate between ME group and LPLND group. We think that LPLND can be safely administered.

5. L157-L159 – "Neoadjuvant chemoradiotherapy (NACRT) was not administered at the participating institutions because it is uncertain whether this approach improves" Neoadjuvant chemoradiotherapy has shown benefit in survival. Although not in the reference included by you in paragraph.

- As you stated, Swedish trial showed the benefit of OS in NACRT group. However, in general, there is no evidence of Neoadjuvant chemoradiotherapy which improve the survival for Stage IV low rectal cancer. We added the reference to the revise manuscript.
- Huh JW, Kim HC, Park HC, Choi DH, Park JO, Park YS, Park YA, Cho YB, Yun SH, Lee WY, Chun HK. Is Chemoradiotherapy Beneficial for Stage IV Rectal Cancer? *Oncology*. 2015;89(1):14-22. doi: 10.1159/000371390. Epub 2015 Mar 11. PubMed PMID: 25765183.
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6. L199-L200 – "classified as "R0", and the other patients in whom R0 resection could not be achieved were classified as "R2". This grouping is losing much information. R2 is not the same because of local or metastatic disease. The information should be unbundled.

- In this study, there were no patients with R2 in local disease, i.e., all the patients had negative circumferential resection margin. We added in the revised manuscript (**Page 9, Line 160 - 161**).

7. Table 2 represents the variables associated with the 2 groups compared. Indeed they show that they are statistically similar. But clinically it has not been proven. There are missing key parameters to be able to say it. For example resectability criteria? Comorbidity? Response to chemotherapy? Etc. They can be different groups. Survival in this clinical situation marks more the metastatic disease than the local tumor. And the diversity of metastatic situations is great. At that level, the groups may not be balanced in terms of metastatic loading and location.

- As the reviewer said, we could not examined parameters such as resectability criteria, comorbidity and response to chemotherapy. So, this is the limitation of this study. We added the description in the revised manuscripts (**Page 17, Line 344 - 346**).

8. L303-L304 "To date, the clinical significance of NACRT for stage IV low rectal cancer remains still unclear" There is no top-level evidence and probably never will be. There is consensus and results from series with long survivals.

- We agree with the reviewer.

9. L310 – L312 "because systemic sites were overwhelmingly more common than pelvic recurrences after primary tumor resection" This happened before. With the new drugs, survival has increased considerably: There is a need to achieve local control, either radical or at least to avoid the great morbidity caused by the primary tumor in these patients.

- LPLND was not effective for local control in this study. As the reviewer said, NACRT may be useful for local control.

10. L 327 The main limitation: It is not known if the groups were well-balanced for the survival variables: resectability, chemotherapy and response. It is not known which patients were given chemotherapy. What kind, how many cycles? And its repercussion on survival. They should put it.

- We could not present the detailed survival variables of individual patients. We added the description in the revised manuscript (**Page 17, Line 344 - 346**).