Hospital Universitario "La Fe"
Hospital Universitario y Politecnico La Fe, Avda de Fernando Abril Martorell, n.106, piso 5, torre G
46026 Valencia,
Spain
Tel 0034-961244000, Fax 0034-963868864

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Dear Editor

**Re: Submission of a Revised Invited Original Contribution to World Journal of Gastroenterology**

we would be grateful for the consideration of our revised manuscript "**Pelvic exenterations for primary rectal cancer: analysis from a 10-year National prospective database",** by G.Pellino, S Biondo, A Codina Cazador, JM Enríquez-Navascues, E Espín, JV Roig, E García-Granero on behalf of the Rectal Cancer Project for publication in *World Journal of Gastroenterology*.

All authors have read and complied with author guidelines, and they all have seen and approved this manuscript for publication. None of the authors had conflict of interest to disclose in relation to this manuscript.

We are grateful to the reviewers for their precious contributions and comments. We have revised the text accordingly and we hope that you will now find it suitable for publication in *World Journal of Gastroenterology.*
The revised manuscript was prepared on the file revised by the Editor, according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision for the manuscript type: 'Retrospective Cohort Study' available on wjgnet. All changes are highlighted along the manuscript.
We have requested professional English revision of the text and added further analyses as per reviewers' comments.
Below please find a point-by-point reply to the reviewers.

Thank you.

We look forward to receiving your decision in due time.

Yours Faithfully,

Gianluca Pellino, MD, EBSQ-c, FASCRS and

Eduardo García-Granero MD,PhD, EBSQ-c

Corresponding Author

On behalf of the co-authors

**Reply to Reviewers**

We would like to thank the Reviewers for their kind opinions and precious comments that have enhanced the clarity of our manuscript. We revised the text accordingly, and hope that all queries were addressed satisfactorily.

**Reviewer #1**

*Comments to the Author*
*The authors present a study about pelvic exenteration in patients with locally advanced primary rectal cancer. The data originate from a prospective national register which was retrospectively analysed. There were 82 patients included in the study of whom 64 who underwent pelvic exenteration before 2013 and had therefore a long-term follow up. The article is well written and present a descriptive overview over this important area in colorectal surgery.*

*Few minor issues are listed below:*

*Q1. Introduction: The first paragraph presents some information about ColoRectal cancer incidence and survival rates. I would suggest to limit this paragraph to rectal cancer only which is the subject of the study. The incidence, survival and management of locally advanced rectal cancer then should be stated.*

**A1: We have revised the introduction as recommended (pag 6-7).**

*Q2. Method: Well-designed study*

**A2: Thank you.**

*Q3. Results: R+ resections increased local recurrence (HR 5.58 95% CI 1.04-30.07 p=0.04) this is very wide confidence of interval, I wonder if the HR is still significant? Please, comment on this. In page 11 the authors mention "Quality of mesorectum according was classified as "good" in 74% of patients" what classification the authors are referring to?*

**A3: As suggested by the reviewer, the CI is quite wide, but significance is maintained as the "0" value is not included in the interval. However, we have added a statement to interpret findings cautiously (pag. 15).**
**We have clarified assessment of the specimen in the method section (pag. 9)**

*Q4 Discussion As the authors stated, pelvic exenteration is a complex procedure with a high rate of postoperative complications. A few lines about quality of life after pelvic exenteration would be useful so the reader can understand the delicate balance of surgical decision making in patients with locally advanced primary rectal cancer. The section about limitations of the study is very good and the authors recommendations to interpret results with caution, is well placed.*
*."*
**A4: We have further stressed the importance of quality of life as a research priority in these patients (pag 17). Thank you.**

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**Reviewer #2**

*I think this is an interesting topic becoming of most interest in the field of ultraradical primary surgery in rectal cancer. The study stresses the dificulties odf balancing risks and benefits in term of survival well. The series is short and probably heterogeneous as data camefrom numerous Hospitals even though those Institutions were recruiting patients under the requirements of the Spanish Viking project study.*

*Comments to the Authors:*

*Q1. Inclusion and Exclusion Criteria*
*What about surgical technique description? at least a reference*
*Bowel preparation, DVT and antibiotics prophylaxis, postoperative care (Fast track, traditional)?*

**A1: Since the analysis included many centers, there could have been variability in some details of perioperative management. A reference standard of care was suggested by the beyond-TME initiative, which has been now mentioned in the method section (pag 9). Data on antibiotic prophylaxis was not available. Bowel preparation is usually recommended, whereas strict enhanced recovery pathways have not been applied.**
**The problem of standardizing the management of pelvic exenteration has not yet been solved, as suggested by the beyond TME collaborative [ref 19]; this has been highlighted in the discussion (pag. 17).**

*Q2. Endpoints and definitions*
*DFS includes even LR*

**A2: Any attempt was made not to include LR among DFS.**

*Q3.*
*http://www.aecirujanos.es/images/stories/recursos/secciones/coloproctologia/2015/proyecto_vikingo/documentos/definiciones_proyecto_vikingo.pdf*
*This link leads to information only in Spanish, so details definitions can not be understood*

**A3: We have added English references, and we apologize for the inconvenience (pag. 9).**

*Q4. "The number of procedures per hospital of 2.5 ± 3.1", is per year?*

**A4: It is the crude, overall value. It has been specified (pag. 11).**

*Q5. Baseline patients characteristics and surgical details*
*"65.9% were male", and number of women?*
*"Most patients were staged as rmcT4 and had extensive nodal involvement". Define this or refers to a publication where definitions can be found.*
*"Neoadjuvant treatment was offered to 72% of patients and included radiotherapy in 93% of them. Fifty-four(65.9%) patients received postoperative chemotherapy, which was associated with radiotherapy in 6(11.1%)". Time to/from surgery with neoadjuvant or adjuvant therapy.*
*"An anastomosis was attempted in 15 patients". What clinical features do they have: previous RT, post-surgery RT.*

**A5: The number of women has been added to the text (page 11).**
**We have made the meaning of "mrcT4" clearer in the text, we apologize for the confusion. (page 11)**
**Unfortunately data on the start/end of neoadjuvant or adjuvant treatment were not collected on the database; we have disclosed it (page 11).**
**We have described this in the text (page 11).**

*Q6. Primary aim: short-term outcomes and pathology*
*"anastomotic leak in four patients, accounting for a relative rate of 26.7%". In which group of patients this complication happened? and how long after surgery. Morbidity time recorded is no apparent in the text.*

*"The mean number of isolated nodes was well higher than 12". As the site of these metastasis is the Mesorectum it should be described.*

*"Nineteen patients (23.2%) received R+ve resection, one of them with both circumferential and distal margin affected". What was the pathologic definition for positive margin?*

*"Twenty percent of patients did not have any response to preoperative neoadjuvant treatment, one patient had complete pathological response (1.7%) and the remaining had a different spectrum of response". Please define describe or refers to Table.*

**A6: Thirty-day morbidity was recorded in the database, and patients were followed thereafter according to the local policies. We thank the reviewer for this important observation. The data of diagnosis of the complication was not recorded; since leaks might occur well after 30 days, we have removed statements on this complication. Oncologic outcome was updated yearly by the responsible collaborator at each center. Information added to the method section (pag. 9)**

**The number of nodes isolated is reported in Table 3. We have added the percentage of patients who had nodal cancer involvement in the text (page 12).**

**Negative/positive margin definition has now been clarified in the Method section (page 9)**

**We have added reference to Table 3 to avoid repeating the information, thank you (page 12).**

*Q7.Primary aim: recurrence and survival*

*"For the purpose of long-term outcomes, we excluded 18 patients who received PE after 2013, thereby analyzing 64 patients." Why were they excluded? explain.*

*"and partially good or bad quality mesorectum". Definitions?*

*Any data about pattern of recurrence and its relationship with pathologic prognostic factors?*

*Definition of time to any 1st site of recurrence ; from surgery or from the end of treatment if it also has adjuvant?*

**A7: We excluded patients who did not complete 5-year follow-up, therefore we did not include those operated on earlier than 5 years from the analysis. This has been specified in the Inclusion/Exclusion Criteria, (page 8)**

**A reference to definition of quality of the mesorectum used for the registry has been added in the method section (page 9).**

**Recurrence has been related with the date of surgery, as date of end/start of adjuvant treatment was not available.**

*Q8. DISCUSSION*

*"The number of lymph node harvested in specimen from patients who underwent neoadjuvant treatment in the vast majority of case is matter of debate, and the PelvEx collaborative found it to be significantly associated with survival [13]". Have you study +LN influence in survival? Overall and recurrence? This should be studied.*

**A8: Thank you for raising a very important issue. We have compared the oncologic outcome of patients with +ve vs -ve nodes, and found no statistically significant difference in terms of LR, DFS, and OS; however, all tended to be worse if nodes were positive. We have added this to the results (pag. 12) and discussion (pag. 15) sections.**

**LR 52 months vs 47 months LogRank 0.39**
**DFS 51 months vs 43 months LogRank 0.20**
**OS 46 months vs 39 months LogRank 0.29**