November 19th ,2013

World Journal of Gastroenterlogy

Article: "Evolving treatment strategies for rectal cancer: a critical review of current therapeutic options"
ESPS Number: 5854

Point-by-point response to the reviewers' comments

Dear Editor,

We would like to thank the Reviewers for careful review of our manuscript and for providing us with his comments and suggestion to improve the quality of our manuscript. The following responses have been prepared to address all the reviewers' comments in a point-by-point fashion.

Reviewer 1

 # Major comments
1. Comment: "The methodology used for selecting related studies for this revision should be provided."
Response: We have included a new section in the text ("Methods"), describing the methodology used for selecting studies for our article.

2. Comment: "In my opinion, a Figure showing the key anatomic concepts of rectal cancer should be provided. This illustration should include concepts such as peritoneal reflection, mesorectum, perirectal lymph nodes, Denonvilliers fascia, or hypogastric and parasympathetic pelvic nerves."
Response: As suggested, we provided a figure (Figure 1. Rectal anatomy) showing the main aspects of the rectal anatomy.

3. Comment: "I consider that the authors should present Tables showing information about the results from the referred trials mentioned in the sections "Neoadjuvant Treatment" and "The "Wait and See" Approach". Therefore, in the text of these sections the authors should comment only the most relevant findings from these studies. This could improve the comprehension for readers."

Response: Based on this comment we have modified our text, adding two new tables to the article: **"**Table 3 Major Neoadjuvant Therapy Trials" and **"**Table 4 Locoregional recurrence in patients with cCR who did not proceed to rectal resection". We also have modified the correspondent sections, only commenting in the text the most relevant findings of the main trials.

4. Comment "The section "Sphincter Preservation After Neoadjuvant Therapy" could be added to the prior section in the paper.

Response: As suggested, we have added the section "Sphincter Preservation After Neoadjuvant Therapy" to its prior section in the paper.

 # Minor comments

1. Comment: "The authors should use "*versus*" instead "versus" along the text."

Response: It was changed as requested by the reviewer.

2. Comment: "Use adequately the abbreviations at first place, for example: Endorectal ultrasound (EUS) or Magnetic resonance imaging (MRI)."

Response: All the abbreviations used in the text were revised and are now adequately used.

3. **Comment: "**Correct punctuation: for example "1,861" instead "1861", etc."

Response: All punctuation and numbers were corrected.

4. **Comment: "**There is a term missing at the end of the third paragraph in section "Neoadjuvant Treatment": "…within 6 to 12 ?? after completion…"
Response: The missing term was "weeks". However, with the inclusion of Table 3, this information was incorporated into that table.

5. **Comment: "**In the section "Minimal Invasive Surgery", data from Anderson C et al. about number of recovered lymph nodes are: (laparoscopy: 10, open=12) instead (laparoscopy: 10, open=11)."
Response: As requested, that data was corrected.

***Reviewer 2***

1. Comment: "The presentation of the material is quite clear, but in some cases could be enriched with tables"
Response: Based on this comment, we have modified our text, adding two new tables to the article: **"**Table 3 Major Neoadjuvant Therapy Trials" and **"**Table 4 Locoregional recurrence in patients with cCR who did not proceed to rectal resection".

2. Comment: "In the final part the summary should include the information about databases, which the authors used."
Response: We have added the following to the final part of the Abstract: "after an extensive search in PubMed and Embase databases, we critically review the current strategies and the most debatable matters in treatment of rectal cancer."

3. Comment: "Due to the fact that the article is of review character after the introduction it should include information on the method used, such as databases, data, material analysis period, the criteria for inclusion and exclusion."

Response: We have included a new section in the text ("Methods"), describing the methodology used for selecting studies for our article.

4. Comment: "The results are shown quite clearly, however, I would recommend to introduce changes in the individual chapters. In the chapter ?Pre treatment Evaluation and Staging"I would add the information that in case of rectal cancer which exclude a full colonoscopy, there is a possibility to carry out an examination by means of rectal infusion or intraoperative colonoscopy."

Response: the following sentence was added to section Pretreatment Evaluation and Staging: "In cases in which a full colonoscopy cannot be performed, a preoperative double-contrast barium enema or a CT colonography may be used. Alternatively, for patients with incomplete preoperative colonoscopy, intraoperative colonoscopy may be used as an effective method to detect synchronous lesions."(page 4, paragraph 2)

5. Comment: "In the chapter "Neoadjuvant Treatment"the abbreviatiom of SCRT is not explained"

Response: We have included the words "short-course radiotherapy" in the text (section: Neoadjuvant Tretament) to explain the abbreviation "SCRT". (page 7, paragraph 1, line 1)

6. Comment: "In the sentence "Radical surgery should be performed within 6 to 12 after completion of the neoadjuvant treatment" the word "weeks" is missing.

Response: This information was corrected and incorporated into Table 3.

7. Comment: "In the chapter "Radical Surgical Approach" there is no information on protective ileostomy in case of ultra-low colorectal anastomosis or in patients with high risk of the leakage (after neoadjuvant therapy or performed by a less experienced surgeon). The information on when protective ileostomy should be removed should also be included."

Response: Following this comment, we have added a new paragraph (third paragraph) to the section "Radical Surgical Approach", discussing indications for diverting ostmies in rectal cancer surgery. We also included information on when an ileostomy should be reversed.

8. **Comment: "**The authors should; mention the manometirc examination of rectal sphincter which result may have an influence on the decision concerning the type of procedure (either LAR or APR)."

Response: In the section "Sphincter Preservation in Ultra-low Rectal Tumors" we have added the following information "Thus, ISR must be considered for patients with adequate sphincteric function, as demonstrated by manometric evaluation of anal sphincters, and for those that can accept that functional results may be suboptimum."

9. **Comment:** In the chapter "Sphincter Preservation in Ultra-low Rectal Tumors" in type I of Rullier classification the word "less than 1 cm" should probably be replaced with the word "more".

Response: As correctly suggested, we have changed "less than 1 cm" to "more than 1 cm".

 # Reviewer 3

1. Comment: "I have no major comments but the chapter on the robotic approach should mention also the disadvantages of this technique like the complete losso of the sensory sensation, the time needed to set up the robot."

Response: Based on this comment, we have added the following paragraph to the text "Several technical issues of the robotic surgery, however, should be carefully taken into account. There is a loss of tactile sensation with the robotic approach, which results in lack of tensile feedback to the surgeon. It can cause excessive traction of tissues and damage to anatomic structures, particularly

during the initial experiences with the technique. Operative time is usually longer using the robotic system as compared with the laparoscopic approach, particularly because docking and separation of the robotic instruments from patient is a time consuming procedure. The patient's surgical position cannot be modified without undoking the robotic instruments, which may result in prolonged operative time and potential delay in conversion to open surgery if it is eventually necessary." (page 17, paragraph 3)

 # Reviewer 4

1. Comment: "The TNM staging system is well known, therefore, I think you don't need to notice table 1 and 2."

Response: We thank the reviewer for this suggestion. However, as stated by a another reviewer, "The presented manuscript contains numerous valuable information in the field of oncology and surgical treatment of rectal cancer. It can be read primarily for the gastroenterologist, but also for novice surgeons working in Colorectal Units." Therefore we believe that Tables 1 and 2 can be useful to facilitate reading of our article, particularly for novice surgeons and medical students.

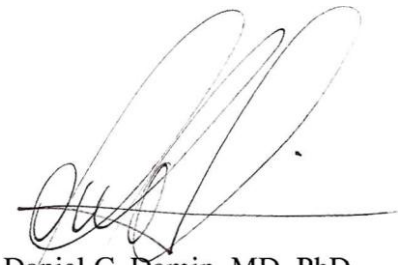
2. **Comment: "**I think you would be better to describe "the sphincter preservation" integrating the distal margin, after neoadjuvant chemoradiotherapy, and in ultralow rectal tumors."

Response: As suggested, the section "Sphincter Preservation after Neoadjuvant Therapy" was described right at the end of the section "Neoadjuvant Treatment".

3. Comment: "Would you write the results of reviewed articles without precise explanation about the technique?"

Response: We do believe this a truly valuable comment. In order to make our article more precise and clear, we have included a new section in the text ("Methods"), describing in detail the methodology used for selecting studies for our article.

Sincerely yours,



Daniel C. Damin, MD, PhD

Department of Surgery

Federal University of Rio Grande do Sul, Brazil