

22nd March 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6967- definitive.doc).

Title: Locally advanced rectal cancer: the importance of a multidisciplinary approach

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6967

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

- 1 Format has been updated
- 2 Revision has been made according to the suggestions of the reviewer

Reviewer 69015:

- 1: A new section concerning trials investigating the use of neo-adjuvant treatment in locally advanced rectal cancer has been added.
- 2: In the review clinical data regarding the different impact of treatment performed by a multidisciplinary team versus standard treatment have been reported (Enríquez-Navascués JM, Borda N, Lizerazu A, Placer C, Elosegui JL, Ciria JP, Lacasta A, Bujanda L. Patterns of local recurrence in rectal cancer after a multidisciplinary approach. *World J Gastroenterol* 2011 Apr 7;17(13):1674-84).
- 3: Even if cetuximab and bevacizumab have been widely investigated in neo-adjuvant treatment of LARC, results are conflicting and these drugs are not approved for clinical use.

Reviewer 70056:

The manuscript has been revised by a native English speaker.

Reviewer 69774:

- 1-2: A new section concerning trials investigating the use of neo-adjuvant treatment in locally advanced rectal cancer has been added, comprising a comparison of data between the trials on neo-adjuvant treatment.
 - 3: One of the identical passages has been deleted.
 - 4: A paragraph explaining "Wait-and-see policy" has been added.
 - 5: In the manuscript the results of the EXPERT-C for cetuximab and ECOG 3204 for bevacizumab in the peroperative setting have been added.
- Moreover, the studies of Grimminger et al. and Erben et al. have been cited.

Reviewer 68868:

- 1: The definition of LARC has been added in the text (page 4).

2: The role of each professional figure involved in LARC treatment is explained in table 1

3: Recommended modality of treatment for LARC have been summarized in table 2

Reviewer 70920:

1: Definitions of TNM and AJCC have been provided

2: CRT has been defined (page 4)

3: The reference of De Bari et al. has been added

4: The reference of Musio et al. has been added in the paragraph discussing "Wait-and-see policy"

5: The reference of Dedemadi G has been added to the text in the paragraph discussing "Wait-and-see policy"

6: We do agree that ubiquitin-proteasome system represents an important pathway that plays a complex role in the carcinogenesis. Nevertheless, although proteasome inhibition may have a role in sensitizing cancer to chemotherapy and radiotherapy, it still represents a subject of study and it has not been introduced in the clinical practice, yet. Since the review is conceived as a clinical revision of the literature, we believe that including this topic might be misleading for the reader. Nevertheless, we will add a paragraph if it is considered necessary.

7: The reference of Genovesi has been added in the text

Reviewer 68897:

1-2: The manuscript has been revised as suggested

3: The definition of AJCC has been added in the text

4: a paragraph regarding the evidences of neo-adjuvant treatment in LARC has been added, comprising the Dutch trial

5: The text has been modified accordingly

6: EXPERT-C trial has been added and the section regarding new drugs and targeted therapies has been expanded

Safety concerns of bevacizumab has been added.

Imaging tools such as MRI and FDG-PET have been discussed in the text

Reviewer 2397907:

1-2: The references by Bosset et al and Aklilu et al. have been added

3: Table 2 has been deleted and the section about targeted therapies and new drugs has been enriched

Minor corrections have been performed.

References and typesetting were corrected.

We hope that our manuscript can now be considered for publication in *World Journal of Gastroenterology*.

Yours Sincerely,

Rossana Berardi, MD

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