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Title: Overexpression of Nuclear β -catenin in Rectal Adenocarcinoma is Associated with Radioresistance

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Dear Editor

Thank you very much for your work! We read the reviewers' comments carefully. Here, we submit a list of responses to the comments.

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 reviewer

00068559

The authors studied the clinical significance of β -catenin overexpression and radioresistance in patients with rectal cancer. Now, preoperative radiotherapy was used especially for patients with locally advanced rectal cancer, aiming not only to improve overall and disease-free survival but also to downstage and reduce tumor volume, which may make sphincter-preserving surgery possible. In this study, all the 136

patients received preoperative radiotherapy and underwent Miles' operation. It would be better to provide the data of the distance from distal margin of rectal cancer to anal edge. And the discussion, the statement in the first paragraph, should make some modification.

Reponse: This is a good advice and the paper was rewritten according to the comment.

00073425

The paper presents the role of overexpression of nuclear β -catenin in rectal adenocarcinoma in radioresistance of tumor. This paper is very interesting and the problem is up to date. However, I have one comment. The examined material included 136 patients. I did not find any information concerning neoadjuvant chemoradiotherapy in these patients. It is a routine procedure in this kind of cancers. Does it mean that these patients were excluded from the study. It requires explanation.

Reponse: This is a good question. Yes, neoadjuvant chemoradiotherapy is a routine procedure of locally advanced rectal cancer. According to our knowledge, both preoperative chemoradiation and postoperative chemoradiotherapy are standard treatment of locally advanced rectal cancer in our schoolbook. In this study only those patients who accepted preoperative radiotherapy were included in order to study the prognostic value of nuclear β -catenin overexpression for radioresistance.

00503072

COMMENTS FOR THE AUTHOR: Overexpression of nuclear β -catenin in colonic and rectal adenocarcinoma have been well documented before. This study has focused on the association between nuclear β -catenin overexpression and preoperative radioresistance in patients with rectal adenocarcinoma. The authors found that an overexpression of β -catenin in nuclear maybe a useful predictor for preoperative radioresistance in postoperative resected specimens and biopsy. In general, this is a good attempt to study the clinical significance of β -catenin in patients with rectal cancer. But the concerns still remain. 1. The authors used postoperative resected specimens and biopsy to study the predicative significance of β -catenin in patients with rectal cancer received radio therapy. This is somewhat strange! The clinicians like to know the patients if they are sensitive to the radio therapy before operation, so most studies used preoperative colonoscopic biopsy to study it. Again, the expression and significance of β -catenin in preoperative colonoscopic biopsy and resected specimen obtained from same patient should be compared. 2. The authors claimed “this is the first study to investigate the prognostic value of nuclear β -catenin overexpression for radioresistance in rectal cancer”. This is not right. The predicative significance of overexpression of nuclear/membrane β -catenin in rectal cancer received radio therapy has been reported before and a similar manuscript has been published in International Journal of Colorectal diseases 2011,

26(9):1127-1134. 3. Of course there are some misspellings and small mistakes in the text, which should be corrected.

Reponse: 1.This is a good question. Yes in this study the expression of β -catenin in preoperative colonoscopic biopsy and resected specimen obtained from same patient were compared.

2. This is a good advice and the paper was rewritten according to the comment.

3. The English language was revised by a native English according to the comment.

00058361

This is a well written contribution free of scientific errors. I made some textual changes mainly typo's and spelling issues. See, PDF attached.

Reponse: Thank you very much. The English language was revised by a native English according to the comment.

00039316

I reviewed with interest the study entitled "Overexpression of Nuclear β -catenin in Rectal Adenocarcinoma Is Associated with Radioresistance"

The major issue that should be adressed by the authors is why the selected their population and they excluded patients on chemoradiotherapy which is the standard of neoadjuvant treatment for locally advanced rectal cancer. Therefore, the results of the study cannot be generalized to the majority of the patients and this is a significant

limitation of the study. Minor issues: State the retrospective design of the study in the methods. Add a paragraph in the discussion on the limitations of the study, including the design, patients selection, etc. Present the expression of b-catenin also in the surgically resected tumors and compare its expression to that on the biopsies before the radiation. Would this make any change to your results? Clarify what is the exact definition for b-catenin expression and keep it through out the paper. Is it $\geq 50\%$ staining or is it $\geq 50\%$ moderate to strong staining. Discuss the possibility of reaching to different conclusions if you used a different TRG system (there must be at least 4 of them). If your results are not reproducible with the other TRG systems, then it is also a strong limitation of your study. Since you identified 3 predictive factors for radioresistance in your multivariate analysis, you are encouraged to perform a discriminant analysis that will include all 3 factors to form a predictive model for radioresistance.

Response: This is a good question. Yes, neoadjuvant chemoradiotherapy is a routine procedure of locally advanced rectal cancer. According to our knowledge, both preoperative chemoradiation and postoperative chemoradiotherapy are standard treatment of locally advanced rectal cancer in our schoolbook. In this study only those patients who accepted preoperative radiotherapy were included in order to study the prognostic value of nuclear β -catenin overexpression for radioresistance.

The paper was revised according to the reviewer's comment of minor issues.

1. The retrospective design of the study is stated in the methods.
2. A paragraph on the limitations of the study was added in the discussion.
3. Present the expression of b-catenin also in the surgically resected tumors and compare its expression to that on the biopsies before the radiation. This would not make any change to our results. The aim of presenting the expression of b-catenin in the surgically resected tumors is to analyze the expression of b-catenin in tumor tissues after radiotherapy.
4. What is the exact definition for b-catenin expression is clarified.
5. We select a TRG system according to previous similar study based on reference.
6. This is a good advice and in the further study we will perform a discriminant analysis that will include all 3 factors to form a predictive model for radioresistance according to the comment.

3 References and typesetting were corrected