ANSWERING REVIEWERS

June 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11147-edited.doc).

Title: Impression of Prognosis regarding Pathologic Stage after Preoperative Chemoradiotherapy in Rectal Cancer

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11147

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 reviewers comment

Reviewer 42065; This is a retrospective study to ascertain whether pathologic stage can be used as a prognostic indicator for cancer patients receiving preoperative chemoradiotherapy, using recurrence free survival as the primary end point. The authors have minimized potential confounders factors by multivariate regression. This study provides evidence that the pathological staging is a good prognostic indicator for cancer patients receiving preoperative chemoradiotherapy to predict survival. I suggest acceptance of the study for publication after minor revision. It is better if the authors can provide criteria of how they selection patients for preoperative chemoradiotherapy for clinical stage II or III disease.

(Answer) Thank you for your nice comment. For selection criteria for preoperative

chemoraiotherapy, we agree with your comment and add in the method section. We recommended upfront resection for patients with obstructive lesion. For patients with cT3-4 and/or N+, we checked whether tumor involve mesorecal fascia using MRI or CT. When we decide to get clear mesorectal margin by upfront surgery, we explained the current disease status, possible advantage of PCRT, and expected response rate to patient, and let patient involve in selection of treatment plan. If mesorectal fascia involvement was suspected, we recommend PCRT primarily.

Reviewer 0050445; In the present study of Park et al., the authors presented Impression of Prognosis regarding Pathologic Stage after Preoperative Chemoradiotherapy in Rectal Cancer. The paper is well written and the themes of this review are unique. I think this paper has some major problems. 1. Authors performed a unique perioperative chemotherapy. Please show the evidence about this therapy. 2: How did physicians decide PCRT group or no-PCRT group? Please describe the criteria for the decision. 3. The response rate of PCRT should be written. 4. Various regimens of PCRT should be discussed compared to the regimen used in this study. 5. Authors performed a unique adjuvant therapy. Please show the evidence about this therapy. I think the length of the adjuvant therapy was short. 6. The frequency of oxaliplatin for adjuvant chemotherapy should be written especially in the patients with stage III. Because it is related with the patients' overall survival. 7. There are no description about side effects. Please show these data about PCRT and adjuvant therapy.

(Answer) 2. Thank you for comment. It is very core aspect and drawback of this study at the same time. Now, preoperative chemoradiotherapy (PCRT) was primarily recommended to patents with cT3-4 and/or N+ mid and low rectal cancer which located within 10cm from anal verge. Diversion using stoma formation before PCRT was usually performed. During the study period in this manucsirpt, we selectively give PCRT for mid and low rectal cancer patients. As we mentioned in answer for former reviewers comment, we recommended upfront resection for patients with obstructive lesion. For patients with cT3-4 and/or N+, we checked whether tumor involve mesorecal fascia using MRI or CT. When we decide to get clear mesorectal margin by upfront surgery, we explained the current disease status, possible advantage of PCRT, and expected response rate to patient, and let patient involve in selection of treatment plan. If mesorectal fascia involvement was suspected, we recommend PCRT primarily.

6. We mentioned frequency of oxaliplatin-based chemotherapy and its effect on recurrence-free survival in result section **.**

1, 3, 4, 5, 7. We delivered mean dose of 50.4 Gy over 28 fractions. Combined chemotherapy was 5-FU or capecitabine. It is generally used protocol of long-course preoperative chemoraiotherapy in many countries and we evaluate the efficacy of these regimens in the preoperative chemoradiotherapy setting *[Park JH, et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer, 2011; 117(16):3703-12]* Adjuvant chemotherapy was recommended for all paitents who received PCRT regardless of pathologic stage according to NCCN guideline. For No-PCRT patients, radiation therapy was recommended for stage III and II with high-risk patients for NCCN guidelines. Regimens fro adjuvant chemotherapy was decided based on NCCN guideline and national public insurance strategies. We tried to evaluate the role of pathologic stage for prognostification of pathologic stage after PCRT and to show the overview of prognosis by reporting pathologic stage of patients who did not receive PCRT. Because the prognosis based on pathologic stage was impressed well. The effectiveness or hazards of PCRT or response of PCRT was not a purpose of this study. In addition we are working on comparison of prognostic implication of tumor response to PCRT with pathologic stage. Although we are very thankful and agree with reviewer`s comment on PCRT regimen and tumor response, we did not include those issues in this manuscript.

Reviewer 7745; This is a retrospective study investigating the prognosis of rectal cancer patients who underwent PCRT. Authors indicated that pathologic stage could predict prognosis in PCRT patients. However, the issue has already been reported by many previous papers, and the presentation of the results was not adequate for the purpose of the study. 1) For the main purpose of this study, the comparison between subjects with and without PCRT is not necessary. The Table 1, which shows the comparison, confuses and misleads readers. Figures are also confusing, because Kaplan-Meier curves shows the comparison too. Authors intended to show that pathological stage could be used in PCRT subjects. So, they should describe a Kaplan-Meier curve of each pathologic stage of PCRT subjects alone in one graph. In this paper, the reference to non-PCRT subjects is not only unnecessary but only a hamper. 2) I cannot see the sentences in the text referring to the Table 2.

(Answer) Thank you for reviewers comment.

1) The purpose of this study was not show only to show prognostic implication of pathologic stage in PCRT patients. I intended to show "overview of prognosis" of rectal cancer patients who treated with PCRT. I just want to show pathologic stage of No-PCRT patients together with PCRT patients and don`t intend compare prognosis between two groups. Because we usually have "impression" for prognosis in patients who did not treated with PCRT. We already got used to remind prognosis using pathologic stage in no-PCRT patents. However, we do not have impression of prognosis for patients who did not respond to PCRT although the good prognosis of well-responded patient was well-known. We only have vague and inaccurate insight that poor responder might have aggressive behavior and poor prognosis. How the prognosis was much worse in poor-responder was not well-known. I want to show these impressions using showing well-perceived prognosis model. Therefore the prognosis of no-PCRT patients was necessary for purpose of this study. It is lamentable it looks like comparison to show pathologic stage of PCRT and no-PCRT together, however, it is necessary for this study.

2) I mentioned contents in result section and reference in text.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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