Author's response to reviews

Title: The Influence of the Treatment Response on the Impact of Resection Margin Status after Preoperative Chemoradiotherapy in Locally Advanced Rectal Cancer

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Author's response to reviews: see over
RE: submission of a revised manuscript entitled "The Influence of the Treatment Response on the Impact of Resection Margin Status after Preoperative Chemoradiotherapy in Locally Advanced Rectal Cancer" (MS: 1085503955100943)

Dear Editor:

Authors would like to thank editor and reviewers for the expert comments and interest on submitted work of ours. Manuscript was revised per comments and suggestions made by the reviewers. Point-by-point response to comments raised by the reviewers is provided below.

Thank you again for considering submitted manuscript of ours to be published in the BMC Cancer.

Regards,

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Point-by-point Responses to Reviewers’ Comments

Reviewer #1’s comments:

(1) The definition of good responder in the manuscript was "near total regression or downstaging of T stage", if the T stage was from T4 downstaged to T3, was it classified as good responder? Please specify the percentage of this group of patients.

Response: Authors would like to thank the reviewer for the detailed comment. Among eleven patients with cT4 disease, two were downstaged to ypT2 disease and nine were downstaged to ypT3 disease. All these patients were also classified as good responders. As treatment response including downstaging was not described in the manuscript, sentence describing the treatment response was added to the manuscript in the results section, as follows: “Downstaging from cT2 to ypTis was found in 1 patient (0.7%), from cT3 to ypTis, ypT1 and ypT2 in 2 (1.3%), 10 (6.6%) and 37 patients (24.5%), and from cT4 to ypT2, and ypT3 in 2 (1.3%), and 9 patients (6.0%), respectively.”

(2) There was no relationship of DRM with treatment outcome in the analysis. Which factor was the cut-off point of 7mm based on?

Response: Authors would like to thank the reviewer for the detailed comment. As briefly described in the method section of the manuscript, maximally selected rank analysis was used to define the cutting points. To clarify the studied endpoint, following sentence was added in the method section. Cutting points for RM as studied for all studied endpoints including, OS, DFS, LCR, and DMFS.

(3) In the part of ‘treatment’, page 7, the expression of “All patients underwent concurrent chemotherapy with radiation, consisting of a 5-fluorouracil (n=133) and capecitabine (n=18).”, here, the "and" should be “ or”.

Response: Authors would like to thank the reviewer for depicting typos. Correction was made accordingly. Thus, sentence was rephrased as "All patients underwent concurrent chemotherapy with radiation, consisting of a 5-fluorouracil (n=133) or capecitabine (n=18)."
Reviewer #2’s comments:

1. Major compulsory revisions:

(1) The authors said that few studies assessed the relation between resection margin and preoperative treatment. In fact, a positive CRM has been defined as tumor within 1-2mm from the transected margin in several guidelines such as NCCN guideline. The CRM has been shown to be a strong predictor of both LC and OS. It is an important consideration when postoperative treatment decisions are made. In a retrospective study of over 17,000 patients with rectal cancer reported by Nagtegaal, CRM was found to be a better predictor of LC for patients who had received preoperative therapy when these patients were compared with patients undergoing surgery as initial therapy. So many research conclusions reported by the authors in this article were confirmed by other researchers already. However, there is still some novel value in the article. For example, the current study used the microscopic measurements to evaluate the exact length in a tenth of a millimeter and analyzed RM as a continuous variable with the maximally selected rank statistics to avoid statistical bias. Furthermore, the study only included 151 patients with narrow margin to accrue more homogenous cohort.

Response: Authors would like to thank the reviewer for accepting the novelty of current study. Authors thoroughly agree with the comments that significance of RM has been thoroughly studied and authors believe it was expressed in the first paragraph of the background section by mentioning that “Resection margin (RM) of rectal cancer is a well-known and strong prognostic factor for survival as well as recurrence”. However, authors do agree that following paragraph might be misleading to the readers. To clarify the possible misunderstanding imposed by the inadequate words quoted in the background section, manuscript was revised as follows: “In addition, several studies evaluated the relation with other factors and treatment approaches for patients with positive CRM [4, 5] whereas many previous studies suggested only the prognostic effects of CRM [1, 6-10].”

(2) Page 7: “The secondary PTV for reduced field (PTV-RF) included the mesorectum of gross lesion plus 1cm margin.” But in the RTOG consensus guidelines the group did recommend that any boost clinical target volumes extend to entire mesorectum and presacral region at involved levels, including ~2 cm cephalad and caudad in the mesorectum and ~2 cm on gross tumor within the anorectum. Maybe the volume of the authors’ “secondary PTV” was somewhat small in this article.

Response: Authors would like to thank the reviewer for the detailed comment. Intention of the
depicted paragraph was to define the margin used for PTV from the CTV and not to define CTV.
CTV definition used for studied patients accrued to the study is not much different from the
definition of the CTV provided by the RTOG consensus guideline as mentioned by the reviewer.
In order to provide the appropriate expansion margin from CTV to PTV, 1 cm was used, as
institutional one standard deviation of set-up error and organ motion for pelvis prone set-up
used for rectal cancer treatment was 0.5 cm. To clarify possible misunderstanding, paragraph
was rephrased as follows: “Initial clinical target volume (CTV) covered GTV and mesorectal
tissues with craniocaudal extension and regional lymphatics including the perirectal, presacral,
and the both internal iliac nodes. The initial planning target volume for large field (PTV-LF)
included the initial CTV plus a 1cm margin. Reduced CTV included primary lesion harboring
mesorectal tissues with craniocaudal extension and grossly enlarged lateral pelvic lymph node.
The secondary PTV for reduced field (PTV-RF) was also expanded for 1 cm from the reduced
CTV.”

(3) Page 7: “All patients underwent concurrent chemotherapy with radiation, consisting of a 5-
fluorouracil (n=133) and capecitabine (n=18).” “The regimens of postoperative chemotherapy
were fluorouracil-leucovorin (n=111), capecitabine (n=21), and FOLFOX (n=10).” The authors
should give us the detail of their therapeutic regimen like NCCN guideline.

Response: First, there were several typos in the submitted manuscript. Depicted sentences
should have been “All patients underwent concurrent chemotherapy with radiation, consisting
of a 5-fluorouracil (n=133) or capecitabine (n=18).” and “The regimens of postoperative
chemotherapy were fluorouracil-leucovorin (n=111), capecitabine (n=21), or FOLFOX (n=10).”
Following reviewer’s suggestion, manuscript was further revised to include the more detailed
chemotherapy regimen employed in the current study as follows: “All patients underwent
concurrent chemotherapy with radiation, consisting of a 5-fluorouracil (n=133) or capecitabine
(n=18). Most patients (n=133) underwent a 5-fluorouracil 500 mg/m² intravenous (IV) bolus
injection for 3 days during week 1 and 5 of CRT, and 18 patients received capecitabine 1,650
mg/m² daily on days with radiotherapy.” and “The regimens of postoperative chemotherapy
were fluorouracil-leucovorin (n=111), capecitabine (n=21), or FOLFOX (n=10). Fluorouracil-
leucovorin regimen was 6 cycles of 5-fluorouracil 400 mg/m² IV bolus and leucovorin 20 mg/m²
IV bolus for 5 days every 4 weeks. Capecitabine was given 1250 mg/m² twice daily without drug
holiday for 2 weeks followed by one week rest repeated every 3 weeks upto 8 cycles for 6
months. FOLFOX regimen was either FOLFOX-4 or modified FOLFOX-6. Each cycle of
FOLFOX-4 consisted of oxaliplatin (85 mg/m²) on day 1 and folinic acid (200 mg/m²) and a
bolus of 5-FU (400 mg/m²) followed by a 22-hr infusion of 5-FU (600 mg/m²) on days 1 and 2, which was repeated every 2 weeks. Modified FOLFOX-6 consisted of oxaliplatin (85 mg/m²), folinic acid (400 mg/m²) and a bolus of 5-FU (400 mg/m²) followed by a 46-hr infusion of 5-FU (2400 mg/m²) repeated every 2 weeks.”

(4) Page 7-8: “The pathologic responses were categorized into 4 tiers as reported previously. No regression was defined as no evidence of radiation-related changes (fibrosis, necrosis, vascular change). Minimal regression was defined as dominant tumor mass with obvious radiation-related change. Moderate regression was defined as dominant radiation-related change with residual tumor. Near total regression was defined as microscopic residual tumor in fibrotic tissue.” In fact now there are several criteria used to evaluate the pathologic tumor regression in patients with rectal carcinoma who underwent preoperative CRT followed by total mesorectal excision. This is still a controversy. For example, in many other reports the authors used Dvorak’s tumor regression grading (TRG) as the criterion to evaluate the pathologic tumor regression. According to the references in this article, the authors used their own criterion to evaluate the pathologic tumor regression. What is the merit of their criterion? The authors should explain this question in the article because many research findings in this article is on the basis of their own criterion and other researchers could compare their study outcomes with the authors’

Response: Criterion employed in current study was the one proposed and recommended to be used by the Korean Society of Pathologists. Therefore, our institution as well as many centers in Korea adapted this standardized reporting system. For scientific truthfulness, we intended to report the results as same as the pathologic reports described in medical records. However, the contents and individual definition of the grade used in current manuscript is not quite different from the Dvorak’s system. Tumor mass, fibrotic changes, irradiation vasculopathy and peri-tumorous inflammatory reaction were semiquantitatively graded into 5 tiers in Dvorak’s system as well as the system of the Korean Society of Pathologists. Therefore, grade 0, 1, 2, 3, 4 in Dvorak’s system can be converted as no regression, minimal regression, moderate regression, near total regression, and total regression, respectively. In order to clarify possible misunderstanding and confusion, in addition to detailed description for the criteria used, corresponding grade in more frequently used Dvorak’s system was added in the manuscript as follows: “This grading system evaluates tumor regression grade on the basis of proportion between radiation change and residual tumor burden similar to that of Dvorak’s system [12]. Thus, no regression, minimal regression, moderate regression, and
near total regression correspond to grade 0, 1, 2, and 3 of Dworak’s system, respectively."

5. Page 8: “To evaluate the relation between the effect of CRM and treatment response to preoperative CRT, patients were divided into two subgroups, good responders and poor responders. Good responders were patients showing near total regression or down-staging of T stage and poor responders were the other patients showing none of the two features.” Where is the source of the definition “good responders” and “poor responders”? Is this definition created arbitrarily by the authors of this article or other researchers who mentioned it in other article? The authors must give us the clear explanation.

Response: As mentioned in the manuscript, authors hypothesized that significance of positive RM could be determined by tumor biology of residual tumor cells. Although the concept of either downstage or pathologic response has frequently been adopted in numerous studies, clinical impact was limited for both criteria. By combining these already well-known criteria into one, clinical significance was much more prominent. Authors are not aware of any other studies which have adopted this concept. Thus, definition of response was, authors believe, novel to current study. To clarify possible misunderstanding, paragraph was rephrased as follows: “To evaluate the relationship between the effect of CRM and treatment response to preoperative CRT, patients were arbitrarily divided into two subgroups: good responders and poor responders. Good responder was defined as patients showing near total regression or down-staging of T stage, whereas poor responder was defined as patients showing none of two features.”

2. Minor Essential Revisions:

(1) spelling mistakes: comprisedof (Page 4, paragraph 1); preoperativeCRT (Page 6, paragraph 1); secondaryPTV (Page 7, paragraph 1); andtransfer (Page 7, paragraph 2); mentionedvarious (Page 11, paragraph 1); guidelineshave (Page 12, paragraph 1); mmfor (Page 12, paragraph 2); onthe (Page 13, paragraph 2); tothe (Page 13, paragraph 2); respondersmayexpect (Page 13, paragraph 2); correlatedwith (Page 14, paragraph 2); nor survival (Page 14, paragraph 2).

Response: Authors would like to apologize for many typos throughout the manuscript. These are mainly spacing errors and authors believe such typos may have occurred during the file conversion process. As a corresponding author of the manuscript, I do acknowledge that it was solely my responsibility to carefully re-review the manuscript prior to submission. All depicted
typos were corrected as necessary and revised manuscript was thoroughly reviewed repeatedly before submission. Followings are corrected version of phrases with depicted typos.

Page 4 in introduction section

However, recent strategies of preoperative treatment comprised of various modalities influence the significance of RM.

Page 6 in methods section

(1) histologically confirmed primary rectal cancer, (2) cT3-4 or N+ without clinical evidence of distant metastasis, (3) total mesorectal excision followed by preoperative CRT, (4) close resection margin less than 0.5 cm for CRM or less than 1.0 cm for DRM. There were 151 cases meeting the inclusion criteria.

Page 7 in methods section

The secondary PTV for reduced field (PTV-RF) was also expanded for 1 cm from the reduced CTV.

Page 7 in methods section

patient refusal in 2 patients, comorbidities or old age in 4 patients, wound problem in 1 patient, and transfer to the other hospital in 2 patients.

Page 12 in results section

In contrast, age, sex, performance score, clinical stage, CEA, distance of tumor from anal verge, pathologic type, and pathologic response lacked statistical significance on above mentioned various clinical end-points.

Page 13 in discussion section

Since the initial proposal by Quirke et al., which favored distance of 1mm over 0mm as cut off point[8], several large prospective studies and guidelines have adopted criteria of ≤ 1 mm as CRM involvement[5, 14, 15].

Page 13 in discussion section

All studied end-points were segregated with maximal difference at CRM of 1.5 mm in current study.
In subgroup analysis based on the response to preoperative CRT, the impact of positive CRM was not significant in the good responders to preoperative CRT in contrast to the poor responders.

Page 14 in discussion section

Accordingly, 1 cm DRM has been recommended [15]. However, in the systemic review of Bujko et al., length of DRM was not correlated with recurrence rates or survival. So, it was concluded that <1 cm DRM did not jeopardize oncologic safety [17].

(2) What does “ tiersas” mean (Page 7, paragraph 3)?

Response: Identical spacing error as mentioned above. It should have been “ tiers as”.

Page 8 in method section, sentence was rephrased as follows: The pathologic responses were categorized into 4 tiers as reported previously.

(3) Page 11: “In the subgroup of good responders, CRM of 1.5mm did not have any prognostic effect on all studied end-points. In contrast, the poor responders demonstrated a significant difference in the clinical results according to the CRM status. Figure 1 shows the OS curves according to CRM status in good and poor responders.” But in Figure 1 some important data such as P value were missed so that we cannot ensure if the authors’ conclusion is right.

Response: Authors would like to thank the reviewer for the detailed comment. To provide thorough information in a given figure, p-values are added to the respective figures. In order to provide detailed results, table 4 with subgroup analysis was also added to the manuscript.

(4) Page 12: “On the contrary, Natagaal et al. reported that CRM of #2 mm was associated with high risk of local recurrence in the series of 656 rectal cancer patients without preoperative treatment and proposed CRM of 2mm as the adequate limit. However, this study was criticized for the treatment heterogeneity of patients included for analysis despite large sample size.” There is no relevant reference given in this sentence.

Response: Authors would like to thank the reviewer for detailed comment. Corresponding reference was added.

Page 12 in discussion section
On the contrary, Natagaal et al. reported that CRM of \( \leq 2 \) mm was associated with high risk for local recurrence in the series of 656 rectal cancer patients without preoperative treatment and proposed CRM of 2 mm as the adequate limit [8].

Discretionary Revisions:

Page 8: “The median follow-up time for surviving patients was 43.1 months. Five-year OS, DFS, LRC, and DMFS were 84.5\%, 72.8\%, 86.3\%, and 74.2\%, respectively.” Page 11: “The distribution of significant factors in multivariate analysis were compared between patients with CRM\#1.5mm and CRM>1.5mm in good responders. The distribution of ypT, ypN, lymphatic invasion and perineural invasion was not significantly different according to CRM status.” I recommend that some figures should be used to illustrate them visually and detailedly.

Response: Thank you for the comment. Figure with OS and DFS was added (Figure 1). Also, comparative figures according to CRM for good responders and poor responders were added following the suggestion (Figure 2).

Editor’s comments:

(1) After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

We advise you to seek the assistance of a fluent English speaking colleague, or to have a professional editing service correct your language. Please ensure that particular attention is paid to the abstract.

Response: As already mentioned above, there were numerous typos, which were mainly spacing errors. Manuscript was thoroughly reviewed by fluent English speaking co-authors prior to corrected version submission, giving more attention to the abstract.

(2) Please update your ethics statement to include the name of the ethics committee that approved your study.

Response: Statement was updated to include the name of the involved ethics committee.
After the approval of the institutional review board of Seoul National University Hospital, medical records of 403 patients with rectal cancer who underwent preoperative CRT followed by total mesorectal excision between January 2004 and December 2010 were retrospectively reviewed.