Reviewer's report

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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In this article the authors reported conventionally fractionated preoperative CRT followed by total mesorectal excision for 151 cases with locally advanced rectal cancer and found that CRM of 1.5mm was significantly related with worse clinical outcomes, but the impact was different for treatment response to preoperative CRT. So the authors suggested that postoperative treatment strategy might be individualized based on this finding. However, there are some issues and deficiencies in the article.

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.

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 caudal 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.

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 fluouracil-leucovorin (n=111), capecitabine
(n=21), and FOLFOX (n=10)." The authors should give us the detail of their therapeutic regimen like NCCN guideline.

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'.

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.

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).

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

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.

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
references given in this sentence.

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.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.