

Dr. Monjur Ahmed

Editor-in-Chief of World Journal of Gastrointestinal Oncology:

Nov 19th, 2019

Dear Dr. Monjur Ahmed

Thank you very much for having considered our manuscript, "**Impact of preoperative chemoradiotherapy using concurrent S-1 and CPT-11 on long-term clinical outcomes in locally advanced rectal cancer**" (Manuscript Number: 51571), for possible publication in *World Journal of Gastrointestinal Oncology*. We were very pleased to see the favorable comments of the two reviewers. We fundamentally agree with all these comments and have incorporated the suggestions from the comments into the revised manuscript. Here, we are submitting the revised manuscript for reconsideration for publication. We have made all the suggested changes in the manuscript using red-colored text. We have provided our point-by-point responses to each of the comments by the reviewers as below.

We believe that the comments have greatly improved our manuscript and hope that you find our revised manuscript suitable for publication in *World Journal of*

Gastrointestinal Oncology. We look forward to hearing from you at your earliest convenience.

Sincerely,

Kei Kimura

Reviewer #1: This study investigated the clinical outcomes of patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy using tegafur/gimeracil/oteracil (S-1) plus irinotecan (CPT-11), and result demonstrated that good compliance, favorable tumor regression and feasible oncologic outcomes were confirmed on preoperative chemoradiotherapy using S-1 plus CPT-11. Research has certain clinical guiding significance, but the authors did not report MMR expressions and MSI results in the study cases. because Lynch syndrome may be ineffective for a 5-Fu-based chemotherapy regimen. so please supplement the MMR expression or MSI status data of the study case.

→ We appreciate the very helpful comment and suggestion. Lynch syndrome may be ineffective for a 5-Fu-based chemotherapy regimen. However, in September 2018, in Japan, “MSI test kit (FALCO)” was approved as a companion diagnostic for pembrolizumab. Prior to that, MSI was not measured in the clinical setting and has not been investigated in this study. In the future, MSI testing will be performed for the appropriate patients at appropriate timing.

Reviewer #2: This study is a single center retrospective study on the preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer. The authors investigated the efficacy and safety for a new CRT pattern with S-1 (80 mg/m²/day), CPT-11 (60 mg/m²/day), and radiation (total 45 Gy). The results revealed good compliance and favorable tumor regression after treating by preoperative S-1 and CPT-11. The study is of great interest to oncologists generally, and particularly to researchers working on colorectal cancer. However, there are several critical flaws. 1. It was well known that the quality of surgery had the impact of local recurrence of rectal cancer. How can we know that the qualities of surgery? Can you present the data on the TME qualities of the resected specimens? 2. Additional variable such as EMVI should be included prognostic analysis for RFS and LFS to identify patients who benefit from preoperative CRT. 3. Did the author performed the preoperative tumor evaluation after CRT with CT or ultrasound enteroscopy? The tumor stage after CRT is an important parameter for evaluating the efficacy of CRT regimen.

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1. Thank you for your comment. Our institute focuses on CRM negative rather than TME qualities. In order to ensure CRM, extended TME surgery is performed. Two surgeons (more than 20 years of experience in rectal cancer surgery) performed surgery in this study.
2. We (with a single radiologist with over 20 years of experience in radiologic diagnosis) measured EMVI status, and which was added as a variable. We reviewed the significant prognostic factors for RFS and LFS. Multivariate analysis showed that no risk factors for LFS were detected. However, MFI and EMVI were associated with poor RFS for locally advanced rectal cancer.

3. We have performed the preoperative evaluation after CRT with MRI rather than ultrasound endoscopy. However, the agreement between MRI tumor regression and pathological tumor regression is low and MRI tumor regression cannot be used as a surrogate of pathological tumor regression. Further studies are warranted to assess the preoperative tumor status for risk stratification after surgery.

We believe that incorporating your advice has greatly improved our revised document. Thank you once again.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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