

Dear Editors and Reviewers:

Thank you for your letter and reviewer comments regarding our manuscript entitled, “IDO1/COX2 expression prediction for adverse prognosis in colorectal cancer” (ID: 38337). The reviewer comments are valuable and have greatly helped revise and improve our paper, as well as provide important guidance to enhance the significance of our research. We have reviewed the comments carefully and have made revisions, accordingly throughout the manuscript, which we hope will be met with approval. The changes are marked in red in the revised manuscript. The main corrections in the paper and our responses to the reviewer comments are as follows:

Responses to the reviewer comments:

Reviewer #1:

1. How was the sample size chosen?

**Response:** Our previous study was designed to detect the relationship between capecitabine-induced hand-foot syndrome (HFS) and celecoxib[1]. Based on Edward Lin’s study[2], the incidence of grade 1 HFS was 0.343 and 0.125, respectively, in the capecitabine group and the capecitabine combined with celecoxib group. We calculated that the sample size of this study should be 130 patients to detect hazard rates with 90% power ( $b = 0.01$ ) and a two-sided significance level of ( $\alpha = 0.05$ ). Based on our previous experience, we assumed that the follow-up rate of the study would be 15%, requiring the randomization of 150 patients. Finally, 139 patients enrolled in this study. After 6 years’ follow-up, 20 patients were lost follow-up, 24 patients did not have enough tissue sample for further analysis, and 95 patients were included in this analysis.

2. How were patients with rectal tumors managed? Didn't they receive neoadjuvant therapy?

**Response:** 49 patients in this study were rectal cancer. All the rectal cancer patients did not receive neoadjuvant chemoradiotherapy, since all rectal cancer patients were high

located rectal cancer (> 12cm from anal verge).

3. The TNM staging for colon and rectal tumors should not be aggregated. Results of rectal tumor staging should be provided.

**Response:** The TNM staging for colon and rectal cancer were provided in table 1 and 2

4. Were all 62 survivors tumor-free at their last visit?

**Response:** We did not find any progress for the survivors at the last follow-up.

5. What was the follow-up protocol?

**Response:** The follow-up protocol for stage II/III colorectal cancer patients were as follows. History and physical examination should be given every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years. A CEA test and abdominal and pelvic ultrasound test were recommended at baseline and every 3 to 6 months for 2 years, then every 6 months for a total of 5 years. Colonoscopy is recommended at approximately 1 year after resection. Repeat colonoscopy is typically recommended at 3 years, and every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma, in which case colonoscopy should be repeated in 1 year. Chest, abdominal, and the pelvic CT scan were recommended annually for up to 5 years. The follow-up protocol had been added in the manuscript.

6. How many patients were not included in this study because of either tissue or follow-up data were missing?

**Response:** 139 patients enrolled in the study. After 6 years' follow-up, 20 patients were lost follow-up, 24 patients did not have enough tissue sample for further analysis, and 95 patients were included in this analysis.

Reviewer #2:

1. Results of rectal tumor staging should be provided. And the TNM staging for colon

and rectal tumors should not be aggregated.

**Response:** The TNM staging for colon and rectal cancer were provided in table 1 and 2.

2. Some minor language polishing should be revised.

Response: The language had been polished.

Reviewer #3:

1. Very interesting study. After some minor language revision, it can be published.

Response: The language had been polished.

## **Reference**

1. Zhang R, Wu X, Wan D et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. *Annals of oncology* 2011; 23: 1348-1353.
2. Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Williston Park, NY)* 2002; 16: 31-37.