

Format for ANSWERING REVIEWERS



April 28, 2015

Dr. Jing Yu,

Science Editor, Editorial Office

World Journal of Gastroenterology

Dear Dr Yu,

Thank you for your kind mail of April 27, 2015 regarding our manuscript.

We appreciate the reviewer's comments regarding our paper.

The reviewer's comments helped us to improve our paper.

We hereby send the revised manuscript and the summary of the responses to the reviewer's suggestions.

Your kind consideration would be appreciated.

We look forward to receiving your reply.

Sincerely yours,

Kiyoshi Maeda MD

Department of Surgical Oncology

Osaka City University Graduate School of Medicine

Title: Inflammation-based factors and prognosis in patients with colorectal cancer

Author: Kiyoshi Maeda, Masatusne Shibutani, Hiroshi Otani, Hisashi Nagahara, Tetsuro Ikeya,

Yasuhito Iseki, Hiroaki Tanaka, Kazuya Muguruma, Kosei Hirakawa

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16381

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

Response to Reviewer 1

Thank you for your appropriate comments. We agreed with your suggestions and revised the manuscript accordingly.

1. As you suggested the title was changed as follows.
“Inflammation-based factors and prognosis in patients with advanced colorectal cancer” →
“Inflammation-based factors and prognosis in patients with colorectal cancer”

2. Thank you for your appropriate suggestion.

We added the contents about CRP, GPS, NLR and combination of clinicopathological factors and inflammation-based factors.

- 1) Page 4, line 17 - line 23

Nozoe et al.^[19] reported that the preoperative elevation of CRP was related to recurrence after curative resection for CRC. Toiyama et al.^[20] reported a correlation between elevated CRP and recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. We investigated the correlation between serum CRP levels and the prognosis of patients with stage IV CRC who underwent the palliative resection of their primary tumor^[20]. We found that a high preoperative serum CRP level was a convenient marker for identifying the stage IV CRC patients with a poor prognosis.

- 2) Page 5, line 6 - line 13

Sugimoto et al.^[22] examined patients with stage II CRC who underwent a curative resection and reported that the cancer specific survival was significantly worse in the patients with a GPS of 2 than in those with a GPS of 1 or 0. Proctor et al.^[35] also reported that a raised GPS was associated with reduced overall survival and cancer specific survival in CRC patients, independent of age, gender and Dukes' stage. Moreover, GPS of 2 has been reported to be an independent significant prognostic factor, even in patients with unresectable stage IV CRC^[23, 24]. Ishizuka et al.^[24] reported a correlation between GPS and chemotherapy tolerance and noted that it would be useful for deciding the indications for palliative surgery or preoperative chemotherapy.

- 3) Page 5, line 25 – Page 6, line 15

NLR can therefore be considered as a balance between the pro-tumor inflammation status and the anti-tumor immune status. Although the cut-off values varied between 2.5 to 5 in the previous reports^[25-27], emerging evidence shows that an elevated NLR is significantly associated with poor prognosis in patients with CRC. We analyzed 674 CRC patients who underwent surgery and used a receiver operating characteristic curve to determine an appropriate cut-off value^[25]. As a result, an $NLR > 2.5$ was a significant independent predictive factor for cancer-specific survival. With respect to patients with unresectable stage IV CRC, Chua et al.^[26] examined 349 patients with unresectable CRC who received first-line palliative chemotherapy and reported that the prognosis of patients with an NLR

of > 5 was significantly worse than the prognosis of the patients with an NLR of < 5 . They also reported that a high NLR resulted in a reduced response to chemotherapy and that the reduction of NLR after one cycle of chemotherapy in a subset of patients resulted in improved survival. Li et al. ^[27] performed a meta-analysis of CRC patients and concluded that the NLR is an inexpensive, widely available and reproducible index that is closely associated with survival. Because a peripheral blood cell count is a quick and easy assay to perform, NLR is a useful marker for identifying patients with a poor prognosis and allows for the planning of more frequent surveillance and intensive therapy in patients with unresectable stage IV CRC.

4) Page 10, line 3-line14

We classified the patients, using a combination of four prognostic factors, into three risk groups: patients without any prognostic factors (the low-risk group), patients with one or two prognostic factors (the intermediate-risk group) and patients with three or four prognostic factors (the high-risk group). There were significant ($p < 0.0001$) differences in the postoperative cancer specific survival rates among the three groups. The median survival time (MST) was only five months in the high-risk group, compared to 21.5 months in the intermediate-risk group and 37 months in the low-risk group. The MST of the high-risk group was five months, which was very short and similar to that reported for patients with stage IV CRC who received the best supportive care without surgery or chemotherapy. Therefore, there may be no survival benefit associated with palliative resection in the high-risk group. On the other hand, relatively better survival is expected in the low-risk group. This risk classification is simple and easy to use and may be helpful for determining the optimal treatment for patients with stage IV CRC.

3. Thank you for your appropriate suggestion.

Native check has been performed.

Response to Reviewer 2

Thank you for your appreciate comments. We agreed with your suggestions and change “unresectable metastatic disease” to “unresectable stage IV CRC”.