Author's response to reviews

Title: Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer.

Authors:

Kyung A Kwon (kkinga78@naver.com)
Sung Hyun Kim (kshmoon@dau.ac.kr)
Sung Yong Oh (drosy@dau.ac.kr)
Suee Lee (suee97@hanmail.net)
Jin-Yeong Han (jyhan@dau.ac.kr)
Kyeong Hee Kim (progreen@dau.ac.kr)
Ri Young Goh (gogi3506@hanmail.net)
Hong Jo Choi (hjchoi@dau.ac.kr)
Ki Jae Park (gspark@dau.ac.kr)
Mee Sook Roh (msroh@dau.ac.kr)
Hyo-Jin Kim (kimhj@dau.ac.kr)
Hyuk-Chan Kwon (hckwon@dau.ac.kr)
Jong Hoon Lee (jh2002@dau.ac.kr)

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Author's response to reviews: see over
Dear editor and reviewer

I am so glad to receive your decision and revision letter.

We, all of authors, discussed and revised our paper as below.

We will wait your review and answer.

Thanks your comment and concern our paper again…

Sincerely yours

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Correspondence: Hyuk-Chan Kwon & 1st Author Kyunga Kwon

Department of Internal Medicine, Dong-A University College of Medicine,
3-1 Dongdaeshin-dong, Seo-gu, Busan, 602-715, Korea.
(Tel) 82-51-240-5044
(Fax) 82-51-246-5044
(E-mail) hckwon@dau.ac.kr
Dear Dr Gennaro Galizia

I am very honored that you were a reviewer of our paper. And I appreciate your reading it and making clear comments. Depending on your point, we corrected a few things.

# Major comments

1. Thank you for your comments. We agreed with your comments. Serum values of VEGF, IL-6, and CRP levels do not follow normal distribution with a broad range. Therefore I used the median as the cutoff value. According your comments, we individuated continuous variables for the ROC curve (VEGF 825 pg/mL, IL-6 11.69 pg/mL, and CRP 0.185 mg/dL). And the statistical analysis was checked and corrected.

   VEGF, IL-6, and CRP cut-off values for survival analysis were determined by ROC curve; 825 pg/mL, 11.68 pg/mL, and 0.185 mg/dL, respectively.

2. I appreciate your point regarding the lack of data concerning post operative serum levels. I thought that the lack of postoperative serum VEGF, IL-6, CRP levels was an important a limitation of this study, I totally agree with your comments. I added to this content on the discussion section of the manuscript.

   The most important limitation of this study is the lack of post operative VEGF, IL-6 and CRP levels. De Vita et al. suggested preoperative VEGF and CEA levels as good prognostic indicators for curative and noncurative surgery, and VEGF levels dropped significantly after surgery, with a further downward trend until the 30th postoperative day. However if we had determined postoperative serum levels of VEGF, IL-6, and CRP, we would have been able to obtain more information with regard to prognosis. For examples, normalization of postoperative serum levels could suggest radical surgery; serum level decrement would show secretion of the marker by the tumor, and patients undergoing potentially curative surgery who does not show serum level normalization of the marker should undergo treatment with chemotherapy regardless of the TNM stage, and increased serum levels during the follow-up period could be prediction of recurrence.

# Minor comments

1. Thank you for your comments. For stage II and III colorectal cancer patients, NCCN guidelines recommend annual, chest, abdomen and pelvic CT scans are recommended annually for the first 3 to 5 years. However in our country, the insurance allows patient to be followed by CT scan every 3 months for the first 2 years, and then every 6 months for a total of 5 years.
2. Thank you for your comments. Informations on the control group regarding sex, and age were added to the results section.

The control group consisted of 50 persons who underwent health check-ups (25 men and 25 women; median age, 41.5 years; range, 18 to 68 years) absence of neoplastic disease was established in these patients through laboratory testing including serum VEGF, IL-6 and CRP levels.

3. Thanks for your careful reviews. I have modified the table format and related parts.

   The normal value of CEA in my institution is 0-5 ng/mL : therefore, I determined a cut-off value for CEA of 5. We presented research on the prognostic significance of metastatic lymph node ratio in node-positive colon cancer [Ann Surg Oncol. 2007;14:1712-17]. According to findings from this study, ratio-based staging, which reflects the number of LNs examined and the quality of LN dissection, is a potent modality for prognostic stratification in patients with LN positive colon cancer. On the basis of Kaplan-Meier plots, cutoff points for quartiles of the LNR which is considered the best indicator for separation of patients with regards to 5-year DFS, were between quartiles 1 and 2, and between 3 and 4. And the cutoff level based on the classification was divided into 3 groups. (pN1 0.01-0.11; pN2 0.12-0.24; pN3 0.25-0.92).

4. Thank you for your comments. Overlapping part of Table 3 has been modified.
Dear. Dr Moritz Koch

I am very honored that you were a reviewer of our paper. And I appreciate your reading it and making clear comments. Depending on your point, we corrected a few things.

# Major comments
1. The authors should state and explain why they switched in the results part between mean values for examining differences between control and cancer patients and median values for survival analysis.

A: Thank you for your comments. For a comparison of the value of VEGF, IL-6 and CRP between the control and the patients group, I added the median values as well as the averages values in Table 2.

2. There is no detailed information regarding histopathological reports of the resection margins of the patients included in this study. Although the authors claim that they only examined patients with curative resection it should be further shown if they had patients with R1 resection and how many patients were excluded due to not curative resection.

A: Thank you for your comments. We agreed with your comments. You pointed out that the data regarding resection margin was missing. To review the data, most patient underwent surgery with R0 resection; however 11 of them underwent surgery with R1. We decided to exclude patients who underwent surgery with R1 resection.

A total of 143 patients who underwent surgery for colorectal cancer at Dong-A University Hospital between December 2005 and December 2008 were enrolled in this study. All patients had histologically confirmed adenocarcinoma of the colon or rectum, and a 132 of the 143 had undergone a potentially curative resection. A 11 of the 143 patients showed microscopic evidence of residual disease; therefore, they were excluded.
3. The statistical analysis needs to be checked by a statistician. It is not clear to me why the authors did not perform a multivariate analysis to show the true prognostic effect of VEGF. As VEGF was significantly associated with tumor size and CEA levels it might not be an independent prognostic factor. UICC stage as a known prognostic factor should also be included in survival analysis to underline the quality of the study and patient cohort.

A: Thanks for your careful reviews. We checked the statistical analysis and corrected some parts of statistics.

4. Clinical informations regarding follow-up time and number of patients with subsequent metastases and disease recurrence are completely missing and should be included to enhance the clinical and prognostic value of this paper.

A: Thank you for your comments. We added clinical informations regarding follow-up time.

A total of 11 colorectal cancer patients died of malignancy and 6 patients were lost during the observation period. The median follow-up period was 18.53 months (range 0.73-43.17).

Minor comments
1. The lines in Table 1 are shifted and, therefore, Table 1 is unclear.

A: Thank you for your comments. Table 1 has been re-created with modifications.

2. The manuscript needs to be revised by a native speaker as there are some spelling and grammatical errors.

A: Thanks for your careful reviews. I corrected English grammar.