Author’s response to reviews

Title: The significance of preoperative serum carcinoembryonic antigen levels in the prediction of lymph node metastasis and prognosis in locally advanced gastric cancer: A retrospective analysis

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Author’s response to reviews:

Dear editor and reviewers

Thank you for reading our manuscript and reviewing it, which will help us improve it to a better scientific level. We revised our manuscript, and quite a lot of changes have taken place, so we have sent the revised manuscript, and a version containing all the changes to be visible.

At the following, the points mentioned by the editor and reviewers will be discussed:
Response to reviewers

To Reviewer 1:

1. In the first part of Results, the authors declared that the sensitivity and specificity of CEA for predicting LNM were 57% and 81.5%, respectively. From the perspective of tumor biological behaviors, the first step is the occurrence of gastric cancer, and the second step is the progression of gastric cancer with lymph node metastasis. Therefore, it seems that the authors should first test the sensitivity and specificity of CEA in predicting gastric cancer. If CEA is not so sensitive and specific in the diagnosis of gastric cancer, it is impossible to predict lymph node metastasis with such high sensitivity and specificity.

Response: Thank you for your kind suggestion, we also agree with your point of view. Therefore, we collected 172 patients with gastric benign lesion as a control to test the diagnostic value of CEA for gastric cancer, and the results showed that the levels of CEA in these two groups were different significantly. The median value of CEA in patients with gastric cancer was higher than that in patients with gastric benign lesion. Further ROC curve showed that the AUC of CEA in the diagnosis of gastric cancer is 0.727. When the clinical normal value of 3.4ng/ml is used as the cutoff value, the AUC is equal to 0.676. These data show that CEA has certain value for the diagnosis of gastric cancer, which is also the basis for us to discuss the predictive value of CEA on lymph node metastasis. We have added the associated content in the main text (Methods Section, Page 4, Line 29-33; Results Section, Page 6, line 16-42; and Discussion Section, Page 9, Line 44-54, Page 10, line 5-11).

2. The Normal reference values for CEA, CA199, and CA125 were assumed to be 3.4ng/ml, 37U/ml, and 35U/ml, respectively. CEA > 3.4 is abnormal, and conclusion showed that CEA > 3.21 may lead to lymph node metastasis. That is to say, some people with 3.21 < CEA < 3.4 need to consider lymph node metastasis even if CEA is normal. So what is the significance of setting the normal range of clinical setting? Should we consider changing the normal range in clinic? For example, CEA > 3.4 indicates a high degree of suspicion that the patient has cancer, while CEA < 3.4 need to consider lymph node metastasis even if CEA is normal. This is contradictory.
Response: These proposals are of great clinical values. The reason why we taken 3.2ng/ml as the cutoff value was simply because we obtained the value corresponding to CEA when the Youden index is the largest from the statistical point of view, and did ignore the clinical significance that this value actually represented. We have corrected this conclusion in the article. Next, we compared the predictive value of CEA and imaging examination for lymph node metastasis in the entire gastric cancer patients with a clinically recommended cutoff value (3.4 ng/ml). However, we noticed that 59% of patients with gastric cancer did not have CEA elevated, so we divided the patients into two groups, CEA greater than 3.4ng/ml and CEA less than 3.4ng/ml, and investigated the predictive value of CEA for lymph node metastasis. It was found that in CEA normal group, the AUC was only 0.523, and in CEA abnormal group, the AUC was 0.624. In final our conclusion is changed to that when the CEA do not increase in patients with gastric cancer, its ability to predict lymph node metastasis is also limited.

(Results Section, Page 7, line 14-53; and Discussion Section, Page 11, Line 44-54, Page 12, line 31-48).

3. The author's research ideas and research population should be adjusted. Firstly, the predictive value of CEA in the diagnosis of gastric cancer should be confirmed in the normal control population. Secondly, the cut-off point should be further analyzed in the abnormal population of CEA (>3.4), and its predictive value for lymph node metastasis should be analyzed.

Response: First, we have used patients with gastric benign lesion as a control to verify the diagnostic value of CEA for gastric cancer, as we answered in question one. Second. For patients with CEA greater than 3.4ng/ml, we further investigated the diagnostic value of CEA for lymph node metastasis. According to the highest Youden index, the optimal cut-off point for CEA is 7.12ng/ml, with the sensitivity is 0.588, specificity is 0.75, accuracy is 0.611, and the AUC is 0.623. The results are already summarized in Table 5. (Results Section, Page 7, line 51-53; and Discussion Section, Page 12, line 31-48).

To reviewer 2:

1. Authors investigated the utility of using serum CEA as a diagnostic and prognostic biomarker of locally advanced gastric cancer. the study is well designed and the statistical analysis is well illustrated and presented. there are a few typo and grammatical errors. I recommend the English language to be check by native professional.

Response: Thank you for your confirmation of our work. The article has been edited by professional English language editing company (AMERICAN JOURNAL EXPERTS; Certificate Verification Code: 0A18-4087-F40E-14A2-0078).
2. The values of sensitivity, specificity, negative predictive value, positive predictive value, the accuracy of CEA alone should be included in the body text and table. The discussion should be tailored to this area as well.

Response: Because we modified some of the contents, so the order of the tables was rearranged. But we have listed the content (sensitivity, specificity, negative predictive value, positive predictive value, the accuracy of CEA alone) you mentioned in detail in each table, and the above content was discussed in the discussion section. (Discussion Section, Page 12, line 12-22, 38-42).

Note: All lines and pages are in accordance with the PDF version generated by system.

Editorial Policies
Authors’ response: This manuscript is revised with strict adherence to all relevant BMC Editorial policies.

Yours sincerely

Zuoyi Jiao, MD
(on behalf of all authors).