

Dear editors and reviewers:

We are pleased to resubmit the revised version of 36846 "Predictive and prognostic value of serum AFP level and its dynamic changes for serum AFP elevated Advanced Gastric Cancer (AFPAGC)". We appreciated the constructive criticisms of the editors and the reviewers. We have modified the paper in response to the comments. The point to point responds to the reviewer's comments are listed as following:

Reviewer1

Comment1: (METERIALS AND METHODS, Patient selection, Page 5,) Q1:

What was the type of recurrence for patients relapsed after radical resection?

Q2: The authors should show total and median cycles of systemic chemotherapy. How was the second line chemotherapy?

Q3: Was the immunohistochemical staining not performed?

Response:

Thank you for you careful reading of our manuscript and thoughtful comments.

A1: The type of recurrence for patients relapsed after radical resection was generalized in one sentence in METERIALS AND METHODS(patient selection, Page 9), and was detailed in RESULTS(clinicopathological features of 105 AFPAGC, Page 10).

A2: Total and median cycles of systemic chemotherapy data was added in METERIALS AND METHODS(patient selection, Page 9). Second-line chemotherapy data was added in RESULTS(comparison of efficacy and toxicity of first-line chemotherapy regimens, Page 13).

A3: Also, immunohistochemical staining for AFP was only available in a few patients in this study. And we added them to RESULTS(clinicopathological features of 105 AFPAGC, Page 10-11). Because this is a retrospective study, we were not able to get all patients' IHC results and treatment details after first-line chemotherapy for further analyzing, we have to admit that this is one of shortcomings of this retrospective study.

Comment2: (RESULTS, Comparison of efficacy and toxicity of first-line

chemotherapy regimens, Page 7)

Q1: How did the authors decide the chemotherapy regimen for each patient?
The criteria and background of patients should be shown.

Q2: How often was the evaluation of chemotherapy (AFP measuring and CT imaging) performed?

Response:

Thank you for your valuable advice. I understand that background of patients may also have impact on patient's survival prognosis. We have revised our manuscript according to your thoughtful comments.

A1: In general treatment of inoperable locally advanced and/or metastatic (stage IV) GC, doublet combinations of platinum and fluoropyrimidines are generally used, there remains controversy regarding the utility of triplet regimens, especially in China and Japan. In our study, most of triplet regimens were given to those who had potential opportunity for surgery and good performance status (RESULTS (comparison of efficacy and toxicity of first-line chemotherapy regimens, Page 11)).

A2: According to your helpful suggestion, evaluation of chemotherapy was added in MATERIALS AND METHODS (evaluation and follow up, Page 9). Hopefully this will make our results clearer to readers.

Reviewer2:

Comment1: They should state the exact chemotherapy protocols. For example, taxane based: paclitaxel plus carboplatin? or which triplet regimens have been used? There are robust data confirming the poor prognosis for patients with AFP producing/expressing gastric cancer especially for resected disease. However, the beneficial effect of triplet regimens can be considered as a new finding. So, the regimens should be clarified.

Response:

Thank you for your instructive suggestions. We understand clarifying the exact chemotherapy regimens will offer more instructive significance to clinic practice. According to your helpful advice, we have revised our RESULTS (comparison of efficacy and toxicity of first-line chemotherapy regimens, Page 11-12).

Comment2: Did they administer anti-HER2 therapy?

Response:

The date of anti-HER2 therapy was also added in RESULTS(comparison of efficacy and toxicity of first-line chemotherapy regimens, Page 12).

Comment3: Can the presence of pretreatment liver metastases affect the AFP levels?

Response:

Thank you for your thoughtful idea. We revealed there's an association between serum AFP level and frequency of liver metastasis in this population (Page 34, Table 4). However, we cannot prove cause and effect between liver metastasis and elevation of serum AFP level by doing the present study. The definition of AFP-producing GC varies between studies owing to difficulty in setting the cut-off value, considering liver metastasis can be a factor for mild increase in AFP level, we chose $\text{AFP} \geq 20 \text{ ng/ml}$ as a cut-off value in our study. Anyway this is really interesting question and we are doing further research to investigate the specific carcinogenesis of AFP GC at the moment. Hopefully we could figure out this problem in the future.

We acknowledge all the reviewer's comments and suggestions very much, which are very valuable in improving the quality of our manuscript. Thank you very much for all your help and if you have any question about this paper, please don't hesitate to let me know.

Sincerely yours,

Lin Shen, MD, shenlin@bjmu.edu.cn