

2018/10/22

Professor Fang-Fang Ji,
Science Editor, Editorial Office

***World Journal of Gastrointestinal Oncology*, Baishideng Publishing Group Inc**

Dear Professor Fang-Fang Ji,

Manuscript ID: NO: 42215

Title: **The Impact of Time from Diagnosis to Chemotherapy in Advanced Gastric Cancer: A Propensity Score Matching Study to Balance Prognostic Factors**

Thank you very much for your careful and thoughtful review of our manuscript, titled **"The Impact of Time from Diagnosis to Chemotherapy in Advanced Gastric Cancer: A Propensity Score Matching Study to Balance Prognostic Factors"**. We have revised our manuscript, with the changes highlighted using track changes in Microsoft Word (version 15.26), and have answered all questions in a point-by-point manner.

The manuscript has been revised by an language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors.

We sincerely hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***. We believe that our manuscript is now much improved and that we have resolved several issues that were raised. Our research should be useful to many readers of ***World Journal of Gastrointestinal Oncology***.

Thank you in advance for considering our manuscript for publication.

Sincerely,

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Responses to Reviewer #1's comments (Reviewer's code: 02540650)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. We asked a language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors in the revised manuscript.

Our responses to your comments are as follows:

Reviewer 1's comments

Comments: In this meta analysis, the authors discussed a frequently published topic, although well written, designed and analyzed however it lacks the following points:

Comments #1: In methodology; waiting time is very short and were not categorized, how can we judge insignificant result with this short waiting time (2 weeks)?

Response to comment #1: Thank you for your comment. As we explained in the "Discussion" section in the original manuscript, the median WT from diagnosis to the initiation of chemotherapy was 17 days. Generally, we see patients weekly because our consultation days are fixed on the same day of the week for each physician. In addition, we used the Kaplan-Meier method to preliminarily evaluate 3 groups with the following WTs: less than 2 weeks, 2-4 weeks, and more than 4 weeks. These results indicated that the survival curves of those with WTs of 2-4 weeks and more than 4 weeks nearly overlapped (*Supplementary Figure*).

Therefore, we set the cutoff time was 2 weeks and have shown the categorized data in a supplementary figure.

Comments #2: Why you exclude patients had underwent gastric resection and only those received chemotherapy were enrolled.

Response to comment #2: We excluded only patients with indications for curative treatment; we included patients who had recurrence after surgery, as most studies of unresectable gastric cancer include recurrent cases after surgery. Therefore, we have added this information to Tables 1 and 4 as disease status (unresectable or recurrent).

Comments #3: The sample size is very low in comparison to others i.e (Brenkman et al., 2017)

Response to comment #3: Brenkman et al targeted patients undergoing perioperative chemotherapy and gastrectomy for gastric cancer but not patients intended for chemotherapy due to unresectable advanced gastric cancer. Strictly speaking, their patients were different from ours. As we discussed in the original manuscript, there were some papers addressing resectable solid cancer with larger sample sizes, but there have been few reports on whether a delay in the initiation of chemotherapy for unresectable solid cancer will lead to adverse outcomes among patients. Therefore, in this sense, we think that this paper is novel.

Comments #4: Statistical sensitivity analysis is not included in your study for different degrees of tumor differentiation

Response to comment #4: We analyzed the data, including different degrees of tumor differentiation as histology type: intestinal or not. In this study, there were no significantly different cases with histology types between early WT and elective WT. Therefore, we did not perform an overall survival analysis using different degrees of tumor differentiation.

Comments #5: Discussion needs to be more descriptive and to be cited with more disagreed conclusions.

Response to comment #5: Thank you for your comment. In the extent of our search, we did not find any more papers with discordant conclusions. However, recently, Elimova E et al reported that asymptomatic patients with delayed therapy (≥ 4 weeks) had a good OS compared with patients with early therapy (< 4 weeks), but the difference was not significant (*Oncology* 2015; 89(4): 215-220). They concluded that asymptomatic patients with delayed therapy had no detrimental effect on OS, suggesting that the timing of therapy can be based on patient selection. Therefore, we added the following sentences in the limitations section of the Discussion on page 16 in the revised manuscript.

However, Elimova E et al also reported that asymptomatic patients with delayed therapy (≥ 4 weeks) had a good OS compared with patients with early therapy (< 4 weeks), but the difference was not significant ^[17]. They concluded that asymptomatic patients with delayed therapy had no detrimental effect on OS, suggesting that the timing of therapy can be based on patient selection.

Comments #6: Many spelling mistakes are needed to be corrected with language editing.

Response to comment #6: As we commented, we asked a language editing company (American Journal Experts; <http://www.aje.com/jp/>) to correct the syntax errors in the revised manuscript.

We hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

Responses to Reviewer #2's comments (Reviewer's code: 02941552)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. We asked a language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors in the revised manuscript.

Our responses to your comments are as follows:

Reviewer 2's comments

Comments: This study analyzed the prognosis of stage IV gastric cancer according to waiting time from diagnosis to chemotherapy. This is a well designed study and provide useful information.

Response to comment: Thank you for your encouraging comment.

We believe that our revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

Responses to Reviewer #3's comments (Reviewer's code: 02545023)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. We asked a language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors in the revised manuscript.

Our responses to your comments are as follows:

Reviewer 3's comments

Comments: In this study, the authors have evaluated the effect of treatment delay on clinical outcomes in patients with advanced gastric cancer. The result could be helpful for designing of the chemotherapy regimen. There are some points that need to be improved.

Comment #1. There are several grammatical errors need to be corrected.

Response to comment #1: We asked a language editing company (American Journal Experts; <http://www.aje.com/jp/>) to correct the syntax errors in the revised manuscript.

Comment #2. Another group has also published a similar study in 2015, this should be discussed. (Early Versus Delayed Therapy of Advanced Gastric Cancer Patients – Does it make a difference? *Oncology*. 2015;89(4):215-220. doi:10.1159/000434647.)

Response to comment #2: Thank you for your advice. We have cited the paper and added the following sentences in the limitations section in the Discussion on page 16 in the revised manuscript.

However, Elimova E et al also reported that asymptomatic patients with delayed therapy (≥ 4 weeks) had a good OS compared with patients with early therapy (< 4 weeks), but the difference was not significant ^[17]. They concluded that asymptomatic patients with delayed therapy had no detrimental effect on OS, suggesting that the timing of therapy can be based on patient selection.

Thank you very much. We believe that our revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

Responses to Reviewer #4's comments (Reviewer's code: 03713770)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. We asked a language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors in the revised manuscript.

Our responses to your comments are as follows:

Reviewer 4's comments

Comments: ESPS Manuscript NO: 03713770 Title: The Impact of Time from Diagnosis to Chemotherapy in Advanced Gastric Cancer: A propensity score matching study The manuscript is well designed and had appropriate methodology. Also, it was considered relevant to a current problem in advanced gastric cancer treatment. The text is easy to follow as well as readable and presentable but there are no new ideas. Also, abstract section has to be improved. Overall, this is a very interesting study but it needs some revisions.

Response to comment: Thank you for your comment. As you pointed out, one paper has been published on the same topic: Early Versus Delayed Therapy of Advanced Gastric Cancer Patients – Does it make a difference? Oncology. 2015;89(4):215-220. They also reported that asymptomatic patients with delayed therapy (≥ 4 weeks) had a good OS compared with patients with early therapy (< 4 weeks), but the difference was not significant. They concluded that asymptomatic patients with delayed therapy had no detrimental effect on OS, suggesting that timing of therapy can be based on patient selection. In the present study, to minimize the impact of potential selective bias, we analyzed propensity score matching. As result, we can conclude that a longer WT in patients with A-GC does not appear to be associated with worse prognosis. We think this point is a new idea.

In addition, we revised the Abstract section.

Thank you very much. We believe that our revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

Responses to Reviewer #5's comments (Reviewer's code: 03270609)

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that the revised manuscript is significantly improved because of your comments. We asked a language editing company (**American Journal Experts; <http://www.aje.com/jp/>**) to correct the syntax errors in the revised manuscript.

Our responses to your comments are as follows:

Reviewer 5's comments

Comments: The study is relevant and the obtained results are of practical interest. This problem continues to be discussed in the scientific circles and is far from final conclusions. Therefore, each new study allows us to advance in understanding this problem. Although the authors found no correlations between the time to initiation of treatment and the long-term outcome of treatment for patients receiving chemotherapy due to the inoperable gastric cancer, they noted a number of other important factors affecting to the survival of these patients. These data are important, since they allow us to outline the approaches to correcting the treatment, in order to improve the results. However, the manuscript contains a number of significant shortcomings, which are, to a greater extent, technical in nature. After correcting the indicated shortcomings, the manuscript can be accepted for publication.

Comment #1. The title of the manuscript. The authors found a relationship between the CRP levels, Alb levels and monotherapy with long-term results of advanced gastric cancer treatment, but the title of the manuscript emphasizes only the time from diagnosis to chemotherapy.

Response to comment # 1: Thank you for your comment. As you suggested, we revised the title as follows: The Impact of Time from Diagnosis to Chemotherapy in Advanced Gastric Cancer: A Propensity Score Matching Study to Balance Prognostic Factors

Comment #2. Materials and methods. The following characteristics of patients are not reflected in the manuscript: - The patients were unresectable due to the primary tumor or in the connection with the distant metastases? - The nature of metastatic lesions (liver, peritoneal dissemination, lung, solitary or multiple metastases). These data also could influence to the results of therapy.

Response to comment # 2: Thank you for your comment. In the present study, we did not evaluate the nature of metastatic lesions (liver, peritoneal dissemination, lung, solitary, or multiple metastases) because this was a small sample size study.

Instead, we evaluated the number of metastatic lesions, but we did not find that this factor influenced the results of therapy.

Comment #3. Results: The comparison of treatment results in primary patients with advanced gastric cancer and in patients with relapse of gastric cancer was not reflected in manuscript. There is a discrepancy between the data in the text of the manuscript and in Table 2.

Response to comment # 3: Thank you for your comment. In the present study, there were only 7 cases (6.3%) with relapse of gastric cancer. Therefore, we did not divide them due to the study's small sample size. As you indicated, this information is important; therefore, we added the disease status (unresectable or recurrent) to Tables 1 and 4 in the revised manuscript.

Comment #4. There are unsuccessful subheadings, for example, "A-GC patients in the early and elective WT groups" The first paragraph in this section would be logical to place in the "Patient characteristics" section, especially since the data in it are related to the Table 1.

Response to comment # 4: Thank you for your comment. As you indicated, we have moved the first paragraph of "A-GC patients in the early and elective WT groups" to the "Patient characteristics" section. In addition, we have revised the subheading, "A-GC patients in the early and elective WT groups" to "Univariate and multiple logistic regression analyses of prognosis in A-GC patients *in the early and elective WT groups*".

Comment #5. As reflected by the survival curves, the authors give data on the median survival, and not on the overall survival, that is traditionally given in the percentages relative to a certain time interval (Figure 3, 4, Supplementary Figure).

Response to comment # 5: We have revised this information.

Comment #6: Regression analysis does not include data on the impact of targeted therapy to the patient survival.

Response to comment # 6: In the present study, there was no impact of targeted therapy on patient survival due to the study's small sample size. In addition, there were no difference between early WT and delayed WT. Therefore, we did not analyze targeted therapy.

Comment # 7: Discussion. There are no references to the publications: "There are, however, few reports on whether delay in the initiation of chemotherapy for unresectable solid cancer."

Response to comment # 7: We have cited a related reference (Ref #17) and revised the following sentence.

"There have been, however, few reports on~" → "However, there have been few reports on~".

Comment # 8: There are stylistic shortcomings in the language, for example: "Therefore, patients with A-GC will have patients with lung cancer who will not be able to receive them." "We assessed these individuals to assess the impact of WT on overall survival ..." Unsuccessful expressions: "advanced cancer without surgical indication" is inoperable cancer.

Response to comment # 8: We asked a language editing company (American Journal Experts; <http://www.aje.com/jp/>) to correct stylistic shortcomings in the language in the revised manuscript.

Comment # 9: Tables. The authors only quote percentages, not giving absolute number of cases. In the calculations there are obvious errors. For example, in Table 1-2 there is a discrepancy between the frequency of cases in the «Total group» and the groups «Early WT» and «Elective WT». When I tried to calculate the number of patients in the groups, the result was a fractional number

Response to comment # 9: We have corrected the number of cases.

Comment # 10: In the title of Table 3, "Multiple logistic regression analysis of prognosis in A-GC patients" is indicated only to multivariate analysis, although the table presents data on univariate analysis and multivariate analysis.

Response to comment # 10: We have revised the title of Table 3.

Thank you very much. We believe that our revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

2018/11/21

Professor Fang-Fang Ji,
Science Editor, Editorial Office

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Responses to the editor

Thank you very much for your comments regarding our manuscript.

Our responses to your comments are as follows:

Comment 1 About the informed consent, please provide your consent format of your institute.

Response to comment #1: We submit our consent format for systemic chemotherapy of our institute.

Comment 2 Please provide the web site for ref 1 and 2.

Response to comment #2: We have added the web site information for ref 1 and 2.

We sincerely hope that the revised manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

Thank you in advance for considering our manuscript for publication.

Sincerely,

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