

Lian-Sheng Ma, Professor, President and Editor-in-Chief

World Journal of Gastroenterology

Jin-Lei Wang, Director,

Editorial Office, Baishideng Publishing Group Co., Limited

July 19, 2013

Dear Prof. Ma

Thank you for your kind letter concerning our manuscript entitled **“Better prognosis of AFP-producing gastric cancer without liver metastasis (ESPS Manuscript NO: 3558)”** by Hirajima et al. We have revised the manuscript according to referees’ comments using a red color font (highlighted revised version) and presented the outlining responses to your comments below.

We thank you for your valuable suggestions and comments for our manuscript. We have carefully revised it accordingly. Explanations have been provided point by point. We believe that our revised manuscript has been improved by these revisions and satisfy your concerns. We appreciate your work regarding our manuscript. We hope that the revised manuscript is now acceptable for publication in the **“World Journal of Gastroenterology”**.

Sincerely yours

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Referee #1

Comments to the Author

This is an interesting manuscript from a group that has done excellent work on gastric cancer. They evaluate the effect on AFP producing gastric carcinoma on survival. Their conclusion that AFP production is not an independent predictor of poor survival is in contradistinction to other reports. It appears from their data that it is not an independent predictor of poor prognosis. However patients with AFP producing gastric carcinomas are more likely to have a larger tumor, venous invasion, lymphatic invasion, lymphatic metastases, recurrence and liver metastases. All of these portend a worse prognosis. The fact that AFP was not an independent predictor of poor survival might be attributed to a type 2 error given the limited number of patients with AFP producing tumors in this series.

Response to Referee #1's comments

Thank you for your kind comments. We appreciate your contribution to the review of our manuscript and found your comments to be very helpful. We have revised our manuscript accordingly. We hope that our manuscript has been improved by these revisions and that we have adequately addressed your concerns.

Query

The sample size with AFP-producing gastric cancer is too small and is so different from control group with common gastric cancer in this study. The fact

that AFP was not an independent predictor of poor survival might be attributed to a type 2 error given the limited number of patients with AFP producing tumors in this series.

Reply

Thank you for your comment. As you indicated, we cannot deny a type 2 error because the sample size was comparatively small. However, the incidence of AFP-producing gastric cancer is extremely low and has been reported to be 1.3-15% in gastric cancer. If possible, we want to perform further analyses using a larger number of patients in the future. We revised the conclusions as follows.

Previous version:

Our results show that liver metastasis should be specifically targeted in an effort to improve the prognosis of AFP-producing GC.

In the present study, we demonstrated that liver metastasis was the only independent prognostic factor in AFP-producing GC. The fact that there are no standard or recommended treatments for liver metastasis of GC also means that there is no effective treatment strategy for AFP-producing GC.

Revised version:

Our results show that liver metastasis should be specifically targeted in an effort to improve the prognosis of AFP-producing GC. **However, our study included a small number of patients with AFP-producing GC. Therefore, a**

larger sample size is needed to confirm these clinical features of AFP-producing gastric cancer.

In the present study, we demonstrated that liver metastasis was the only independent prognostic factor in AFP-producing GC. The absence of standard or recommended treatments for liver metastasis of GC also means that there is no effective treatment strategy for AFP-producing GC.

Referee #2

Comments to the Author

This study evaluates the impact of AFP-producing tumors among patients submitted to gastric cancer resection. Although not statistically significant on the multivariate analysis, AFP-producing tumors were associated with a poorer prognosis when compared non-AFP-producing tumors. On the other hand, hepatic metastasis was associated with a poor prognosis in both groups (AFP-producing and/or non-AFP-producing tumors). In fact, hepatic metastasis was the only prognostic factor on the multivariate analysis. These results are very important and, theoretically, they could be used to approach patients with liver metastasis (main site of recurrence in AFP-producing group) in an individualized way. To my understanding, the conclusions of the study should include the following statements: AFP-producing tumor does not represent an independent risk factor for poor prognosis. The AFP-producing tumors are more frequently associated with the development of liver metastasis. Once present, hepatic metastasis will determine a very poor survival. Also, the

title of the manuscript suggests that among patients without liver metastasis the prognosis is better for AFP-producing tumors than for AFP-non-producing tumors. However, this was not demonstrated by the presented data. Thus it should be changed. Finally, I suggest that this paper is accepted after changes in the title and main text as suggested above. Thank you for the opportunity of reviewing such an interesting paper.

Response to Referee #2's comments

Thank you for your helpful comments. We appreciate your contribution to the review of our manuscript and found your comments to be very helpful. We have revised our manuscript accordingly. We hope that our manuscript has been improved by these revisions and that we have adequately addressed your concerns.

Query

The title of the manuscript suggests that among patients without liver metastasis the prognosis is better for AFP-producing tumors than for AFP-non-producing tumors. However, this was not demonstrated by the presented data. Thus it should be changed.

Reply

Thank you for your comment. In this study, we could only conclude that the prognosis of AFP-producing gastric cancer without liver metastasis was similar to that of common gastric cancer without it. As you indicated, this manuscript

title is confusing; therefore, we corrected it as follows.

Previous versions:

Title: Better prognosis of AFP-producing gastric cancer without liver metastasis

Revised versions:

Title: Liver metastasis is the only independent prognostic factor in AFP-producing gastric cancer

Referee #3

Comments to the Author

In the study of Hirajima et al. the authors examined the tumor associated antigen AFP in resected specimens from patients with gastric carcinoma (GC), by immunohistochemistry. They conclude that the AFP is not an independent prognostic factor, whereas the only independent significant marker is represented by the presence of liver metastases. a) Nevertheless there are several doubts about the aim and originality of the study: the correlation between alpha-fetoprotein producing gastric cancer and high incidence of liver metastasis is known and the poorer prognosis of patients with liver metastasis is known too. In fact patients with liver metastases are already currently monitored and treated, as related to poor prognosis. b) Moreover, the authors should also clarify the sentence on the manuscript title, that results confusing: in particular which are the patients with a better prognosis? The sample size is too small (n=23) and not adequate for a title so pretentious. Doubts exist also

about the choice of the statistical method used to compare samples so different in size. c) Recurrence term is incorrect: it is better if the authors refer to metastasis. d) The legends of the figures need to be clarified. In particular, a brief description is needed to explain the panels A and B in the figures. In conclusion this manuscript need to extensive revision to meet the criteria of scientific quality for publication.

Response to Referee #3's comments

Thank you for your helpful comments. We appreciate your contribution to the review of our manuscript and found your comments to be very helpful. We have revised our manuscript accordingly. We hope that our manuscript has been improved by these revisions and that we have adequately addressed your concerns.

1.

Query

There are several doubts about the aim and originality of the study: the correlation between alpha-fetoprotein producing gastric cancer and high incidence of liver metastasis is known and the poorer prognosis of patients with liver metastasis is known too. In fact patients with liver metastases are already currently monitored and treated, as related to poor prognosis.

Reply

Thank you for your comment. In the "Introduction" section, we described

differences between our study and previous studies on AFP-producing gastric cancer as follows. Most previous studies exhibited a poor prognosis with a high incidence of lymphatic invasion, venous invasion, and synchronous and metachronous liver metastasis. Therefore, AFP-producing GC has been associated with a poorer prognosis than AFP-non producing GC. However, most of these studies were restricted to the overall prognosis, and few studies conducted subgroup analyses with special reference to the presence or absence of liver metastasis. In present study, we re-evaluated the clinicopathological characteristics and clinical outcomes of consecutive patients with AFP-producing GC. The results obtained clearly demonstrated that clinical behaviors were different between patients with and without AFP-producing GC. However, the prognosis according to the presence or absence of liver metastasis was similar between patients with and without AFP-producing GC. It is very important to note that the prognosis of AFP-producing gastric cancer among patients without liver metastasis is not worse than AFP-non producing gastric cancer. Moreover, this study demonstrated that the poorer overall prognosis of AFP-producing GC is not related to difficulties in treating it, but from the lack of effective and recommended treatments for liver metastasis of common GC. Our results show that liver metastasis should be specifically targeted in an effort to improve the prognosis of AFP-producing GC

2.

Query

The authors should also clarify the sentence on the manuscript title, that results

confusing: in particular which are the patients with a better prognosis?

Reply

Thank you for your comment. We did not conclude that the prognosis of AFP-producing tumors is better among patients without liver metastasis than those with AFP-non-producing tumors, but did demonstrate that the prognosis of AFP-producing gastric cancer without liver metastasis is similar to that of common gastric cancer without it. As you indicated, this manuscript title is confusing; therefore, we corrected it as follows.

Previous versions:

Title: Better prognosis of AFP-producing gastric cancer without liver metastasis

Revised versions:

Title: Liver metastasis is the only independent prognostic factor in AFP-producing gastric cancer

3.

Query

The sample size is too small (n=23) and not adequate for a title so pretentious. Doubts exist also about the choice of the statistical method used to compare samples so different in size.

Reply

Thank you for your comments. As you indicated, the sample size of AFP-producing gastric cancer was too small, may have limited the analysis of differences in clinicopathological features between patients with and without AFP-producing gastric cancer. However, as you already know, previous studies regarding AFP-gastric cancer also consisted of comparatively small numbers of patients because the incidence of AFP-producing gastric cancer is extremely low and has been reported to be 1.3-15% in gastric cancer. If possible, we want to perform further analyses with a larger number of patients including other cohorts of our related hospitals in the future. We revised the conclusions as follows.

Previous versions:

Our results show that liver metastasis should be specifically targeted in an effort to improve the prognosis of AFP-producing GC.

In the present study, we demonstrated that liver metastasis was the only independent prognostic factor in AFP-producing GC. The fact that there are no standard or recommended treatments for liver metastasis of GC also means that there is no effective treatment strategy for AFP-producing GC.

Revised versions:

Our results show that liver metastasis should be specifically targeted in an effort to improve the prognosis of AFP-producing GC. **However, our study included a small number of patients with AFP-producing GC. Therefore, a larger sample size is needed to confirm these clinical features of AFP-producing**

gastric cancer.

In the present study, we demonstrated that liver metastasis was the only independent prognostic factor in AFP-producing GC. The absence of standard or recommended treatments for liver metastasis of GC also means that there is no effective treatment strategy for AFP-producing GC.

4.

Query

The legends of the figures need to be clarified. In particular, a brief description is needed to explain the panels A and B in the figures.

Reply

Thank you for your comment. We corrected the figure title to clarify the two panels in **Figure 2** as follows.

Previous versions:

Figure 2 Survival curves between patients with and without AFP-producing GC according to the presence or absence of liver metastasis

The prognosis of AFP-producing GC was similar to that of AFP-non producing GC according to the presence ($P = 0.3778$) or absence ($P = 0.5024$) of liver metastasis

Revised versions:

Figure 2 Survival curves between patients with and without AFP-producing GC

according to the presence (Figure 2A) or absence (Figure 2B) of liver metastasis
The prognosis of AFP-producing GC was similar to that of AFP-non producing
GC according to the presence (Figure 2A, $P = 0.3778$) or absence (Figure 2B, $P =$
 0.5024) of liver metastasis

Again, if you have any further comments on the re-submitted manuscript, we
are willing to revise it accordingly. We found your comments to be very
valuable and appreciate your concerns and contributions for the review of our
manuscript. Thank you.

Title: Liver metastasis is the only independent prognostic factor in AFP-producing gastric cancer

Author: Shoji Hirajima, Shuhei Komatsu, Daisuke Ichikawa, Takeshi Kubota, Kazuma Okamoto, Atsushi Shiozaki, Hitoshi Fujiwara, Hirotaka Konishi, Eigo Otsuji

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 3558