Author's response to reviews

Title: Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma: a prospective evaluation

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*BMC cancer* Editorial Office

Re: MS: 2096622635375850

Dear Editor.

We thank the editors and reviewers of the *BMC cancer* for giving us positive answers about our revision article entitled: “Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma: a prospective evaluation”. We have made some corrections in the manuscript using a professional language editing service by a native-English speaker.

The changes are specified in enclosed summary of changes. The changes within the revised manuscript were highlighted (in blue).

We hope the revised manuscript will better meet the requirements of the *BMC cancer* for publication. We thank again for the constructive comments and by the editors and reviewers.

Sincerely yours,

Thank you very much for your attention.

Sincerely yours,

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SUMMARY OF CHANGES

Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma: a prospective evaluation

1. We have changed the sentence in the Background of the ABSTRACT in revised manuscript on page 2, line 3 as following:

Clinicians often experience extrahepatic metastases associated with hepatocellular carcinoma (HCC), even if there is no evidence of intrahepatic recurrence after treatment ➔ even if no evidence of intrahepatic recurrence after treatment is observed.

2. We have changed the sentence in the “Introduction” of revised manuscript on page 3, lines 12–15 as following:

Actually, it was reported that intrahepatic metastases and multicentric occurrence after initial treatment of small hepatocellular carcinomas less than 2 cm in diameter was 23.7% at 1 year, 64.5% at 3rd year, and 76.1% at 5th year [8]. ➔ It was reported that the percentages of intrahepatic metastases and multicentric occurrences found after initial treatment of small hepatocellular carcinomas less than 2 cm in diameter was 23.7% after 1 year, 64.5% after 3 years, and 76.1% after 5 years [8].
3. We have changed the sentence in the “Introduction” in revised manuscript on page 3, lines 17–19 as following:

In addition, extrahepatic metastases may occur after a long-term remission after locoregional therapies for early stage HCC. In addition, extrahepatic metastases may occur after locoregional therapies for early stage HCC and a long-term remission.

4. We have changed the sentence in the “Patients” of the METHODS in revised manuscript on page 4, lines 19–23 as following:

Among these patients, 64 in whom serum levels of PIVKA-II and AFP at the time of diagnosis were not available, 43 who had metastases at the time of diagnosis, and 15 who were untreated were excluded. We also excluded the patients with taking warfarin, which was no one. Patients whose serum levels of PIVKA-II and AFP at the time of diagnosis were not available (64 patients), those who had metastases at the time of diagnosis (43), those who were untreated (15), were excluded. Any patients who may have been taking warfarin would have also been excluded, though none of the patients in this study were treated with it.

5. According to editor’s comment, we now added that statement in the “Patients” of the METHODS in revised manuscript on page 5, lines 1–2, as following

We obtained written informed consents from all patients enrolled.
6. We have changed the sentence in the “Baseline characteristics” of section of the results in revised manuscript on page 7, lines 11–13 as following:

The seropositivity for hepatitis B virus surface antigen and anti-hepatitis C virus antibody were 95.2% and 3.7%, respectively. ➔ The percentages of patients who were seropositive for hepatitis B virus surface antigen and anti-hepatitis C virus antibody were 95.2% and 3.7%, respectively.

7. We have changed the sentence in the “subgroup analysis according to treatment modality” section of the results in revised manuscript on page 11, lines 13–16 as following:

Patients with PIVKA-II ≥300 mAU/mL had a 6.4-fold (95% confidence interval [CI], 3.255-12.711, P < 0.001) increased risk and those with platelet count > 130K a 1.8-fold (95% confidence interval [CI], 1.084-3.154, P = 0.024) increased risk in the TACE group. ➔ Patients with PIVKA-II ≥ 300 mAU/mL had a 6.4-fold increased risk (95% confidence interval [CI], 3.255-12.711, P < 0.001), and those with platelet count > 130K had a 1.8-fold increased risk (95% confidence interval [CI], 1.084-3.154, P = 0.024) in the TACE group.

8. We have changed the sentence in the Discussion of revised manuscript on page 14, lines 9-11 as following:

Together, these findings suggest that the PIVKA-II levels are independently related to extrahepatic metastases regardless of serum AFP level and tumor staging; additionally, they showed a strong association with early stages with low AFP. ➔ Together, these findings suggest that the PIVKA-II levels
are independently related to extrahepatic metastases regardless the serum level of AFP and tumor staging and showed a strong association with in early stage with low AFP.

9. We have changed the sentence in the “Discussion” of revised manuscript on page 15, line 19 as following:

Our overall results may be explained by the different source of blood supply to tumor between intra- and extra-hepatic HCCs.