Author's response to reviews

Title: Prognostic Value of alpha-Fetoprotein and Des-gamma-Carboxy Prothrombin Responses in Patients with Hepatocellular Carcinoma treated with Transarterial Chemoembolization

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Reply to reviewers’ comments:

MS: 1654988464706614; Prognostic Value of alpha-Fetoprotein and Des-gamma -Carboxy Prothrombin Responses in Patients with Hepatocellular Carcinoma treated with Transarterial Chemoembolization. Yong Kang Lee, Seung Up Kim, Do Young Kim, Sang Hoon Ahn, Do Yun Lee, Kwang-Hyub Han, Chae Yoon Chon and Jun Yong Park

Dear reviewer

First of all, thank you for the critique about our manuscript. As reviewer’s suggestion, we desperately tried to revise this article is consistent with not only ours but also reviewer’s intention. Finally, many parts of this manuscript have corrected and improved. However, we are sorry that we still were not able to reflect all of reviewer’s comments. Indeed, the subject of our study still highly selective as has been pointed out. Recognizing that it will limit the value of the study, we could not include more patients with an elevated AFP and normal DCP nor with elevated DCP with normal AFP in our statistical analysis. We revised our conclusion as ‘….who showed pretreatment elevation of both AFP and DCP’, so that readers should not be confused. Even with the revisions, there are still some limitations. We believe it could be a good lesson in publishing more polished articles in future. We hope for your generous consideration.

Sincerely,

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Reviewer’s report

The revised version of the article by Lee et al. was reviewed. I have still several concerns on this article that should be clarified.

1. With regard to the response by the authors to my comment #1 for original version, they explained that the study population in their study is different from patients included in the previous study by Kang et al. (Eur J Gastroenterol Hepatol 2012; 24: 849-856) from the same institution. However, this previous study included 350 patients with pretreatment elevation of both AFP and DCP who underwent TACE, termed as “palliative therapy”, between 2003 and 2007 (please see Table 1 of this article). The study period of the present study is between 2003 and 2005. How is the difference between these patient population? If the study patients between these two groups are different as the authors mentioned, how did they divided these patients (i.e., patients with pretreatment elevation of AFP and DCP who underwent TACE) into two groups, one of the previous study and the other for the present study? This reviewer still cannot trust the response. Please explain this point. I believe that it can be O.K. if study patients of the two studies overlap, because the focuses of the two studies are clearly different (prognostic value of baseline AFP and DCP in the previous study vs. the value of responses of AFP and DCP by TACE in the present study). I recommend that the authors rather emphasize this difference.

Ans) In the previous study by Kang et al. (Eur J Gastroenterol Hepatol 2012;24:849-856), 350 patients with pretreatment elevated both AFP and DCP were treated with palliative therapy such as TACE, concurrent chemo-radiation therapy, only radiotherapy, systemic chemotherapy and hepatic arterial infusion chemotherapy etc. This population is very complex and heterogenous. So, we just selected the patients with both AFP > 20 ng/mL and DCP > 20 mAU/mL who underwent TACE as an initial treatment modality in this study. However, we added and revised this issue in the patients section as follows; Some study subjects were also included in article published recently and analyzed about prognostic value of AFP and DCP by the same institute. However, the aim of this study is clearly different from previous one focusing on the prognostic value of baseline AFP and DCP in all patients with treatment-naïve HCC. In the present study, we focused on the prognostic value of the responses of AFP and DCP by TACE.

2. With regard to the response to my comment #2 for original version, the authors described that they did univariate and multivariate analyses for PFS and OS including antiviral therapies (nucleoside analogue intake or interferon) and viral factors (HBeAg atatus and HBV DNA levels) as factors. They described that these factors did not show independent association with PFS and OS. However, they showed no data on these re-analyses in the revised version. In revised Table 3, only the size and the
number of tumors were added as factors. Therefore, it would be questionable whether they really re-analyzed including viral factors. Please re-make Table 3 including factors of antiviral therapy and viral status for uni- and multivariate analyses for both PFS and OS.

**Ans** We have revised these issues as suggested by this reviewer.

3. With regard to the response to my comment #3 for original version, they stand their selection of patients (select only patients with both elevated pretreatment AFP and DCP). Nonetheless, it will make a strong selection bias and will importantly decline the value of the study, because the results can be true only on the very limited population of patients with HCC that does not represent the entire patients with HCC. Especially because the authors concluded that baseline DCP elevation is the factor that affects OS, this conclusion should be based on all HCC patients treated by TACE including those without DCP elevation. (One cannot conclude that base line DCP elevation is a predictive factor for OS when they only analyzed patients with elevated baseline DCP.) At least, they should included all HCC patients treated by TACE when evaluating baseline elevation of AFP and DCP.

**Ans** We definitely agree to the reviewer’s comment. However, because we simply investigated the prognostic values of AFP and DCP responses simultaneously, we inevitably selected only patients with elevated AFP and DCP in spite of a potential selection bias.

4. With regard to the response to my minor comment #1 for original version, the authors described that AFP usually return to normal range within 25-35 days after tumor removal. Please provide the literature for this.

**Ans** In fact, the half life of AFP is 5~7 days & DCP is 2~3 days. Previous study showed that two and three weeks after TACE, both the time course of AFP and PIVKA-II showed significant correlations with the tumor necrosis[1]. Furthermore AFP should return to normal within 25~35 days of tumor removal, which produce AFP[2]. Our study group rechecked AFP & DCP at 1 month (4weeks) interval with imaging modalities during TACE treatment.


5. Page 5, lines 3-4 of the revised version, conclusion of the abstract: This sentence should be corrected. This sentence can lead misunderstanding that the findings can be applicable for all HCC patients receiving TACE. This study can lead the conclusion that AFP response and higher baseline DCP level are significant predictors of OS in treatment-naïve patients with HCC receiving TACE, only when “patients showed pretreatment elevation of both AFP and DCP”, i.e., very limited subpopulation of HCC patients receiving TACE.

\textit{Ans)} We revised as suggested.

6. Page 9, lines 11-12 of the revised version: “at the time of best radiologic response” How did the authors determine the “best radiologic response”?

\textit{Ans)} As we describe in this article, patients had a CT or MRI scan after TACE regularly. Considering that we retrospectively investigated our subject, we could collect every image series taken after TACE with different time intervals as 1~3 months. We easily know that compacted lipiodolization is a best radiologic response after TACE. However, subjects who did not showed CR, we compared every consecutive dual image taken after TACE, one by one. Then we could find out the image indicating disease progression estimated by mRECIST. The image took just prior to that image indicated disease progression determined as the best radiologic response.

7. Page 12, lines 3-6 of the revised version: Here, they should described all factors included univariate analysis and the condition for that the factors are included to further multivariate analysis (usually $p<0.05$ by univariate analysis).

8. Page 21, line 8 of the revised version: “old age and poor general condition as cachexia” Please provide their criteria to avoid surgical resection.

\textit{Ans)} We have revised these (revision numbered 7, 8) as suggested.