Response Letter

Dear editor and reviewers,

Thanks for your kindly help in our previous manuscripts(Prognostic value of circulating tumor cells in esophageal cancer:A meta-analysis, NO.31994).We have revised the manuscript,and would like to re-submit it for your consideration.We have addressed the comments raised by the reviewers,and the amendments are highlighted in red in the revised manuscript.Point by point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal. If you have any queries, please don't hesitate to contact me at the address below.

With best wishes,

Yours sincerely,

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Replies to Editor and Reviewers

First of all, we thank both reviewers and editor for their positive and constructive comments and suggestions.

Reviewer's code: 01982330

Comment 1: ABSTRACT:Results:"aggressive disease progression": undefined. Specify the measurement criteria. I2: undefined. Either specify in Methods, or remove from the abstract. Contradiction: "significantly associated... $P=0.09$... T stage ... $P=0.83$". Not significant P's.Throughout the RESULTS from page 5 to page 7, the significance of tests and the reported P-values cause confusion. For example the result "RR=1.47, 95%CI: 1.09-1.98, I2=36%, $P=0.16$" is confusing.

This reader is more interested in the P-value of RR=1.47, which is not reported. Instead, the heterogeneity's P is reported, which is barely relevant.

Response: Thank you very much for the suggestion.We have omited the aggressive,I^2,and heterogeneity's P from the Abstract,and added *P*-values in the Results.

Comment 2: Conclusion:"High-quality randomized controlled trials are warranted.": randomized what against what? "high-quality": how? Either be more specific, or shorten to "Prospective trials".

Response: Thank you very much for the suggestion.We have shortened the High-quality randomized controlled trials to Prospective trials in Conclusion.

Comment 3: MAIN TEXT: page 7: "CTCs-positive patients had a higher risk for OS in these subgroups". OS is not a risk. Sentence missing an adjective. Did the authors meant higher risk for poor/shorter/decreased... OS?

Response: Thank you very much for the suggestion.We meant CTCs-positive patients had a higher risk for poor OS in these subgroups.

Comment 4: I suggest to omit the heterogeneity's P from the RESULTS, mention that they are available in Table 3. I also suggest to report the RR's and HR's P-values in the RESULTS and the tables.

Response: Thank you very much for the suggestion.We have omited the aggressive,I^2,and heterogeneity's P from the Abstract,and added *P*-values in the Results and the Table 3.

Reviewer's code: 03259512

Comment 1: Page 7: please correct missing data in this sentence "Pooled analysis showed that CTCs-positivity in stage III and IV was greater than that in I and II (RR=1.48, 95%CI: 1.07-2.06, I2=47%, P=0.09)…"

Response: Thank you very much for the suggestion.We have added *P*-values in the Results.

Comment 2: Page 9: you pointed at the limitations of your analysis "… limitations. First, potential biases such as gender, age, and race could not be

avoided or controlled…". You have to explain further the character of these specific limitations and shortly mention that females are less susceptive to this type of cancer etc; white man in certain countries are more susceptible, in Asia (specifically in China) the squamous esophageal cancer is detected more often than esophageal adenocarcinoma etc…

Response: Thank you very much for the suggestion.We have shortly mentioned females,white man,ect in the manuscript.

Comment 3: Tables and Figures: please add Figure Legends-they all are missing! Only Figure titles are provided. It is not enough.

Response:Thank you very much for the suggestion.We have added Figure Legends in the manuscript.

Comment 4: I suggest to use abbreviation EsC instead of EC for esophageal cancer (as EC is more often used (nearly 52000 articles) as abbreviation for endothelial cells on PubMed and Medline.Please make it clear in the tables what EC means- is it esophageal adenocarcinoma?

Response: Thank you very much for the suggestion.In the paragraph,we had indicated that EC means Esophageal cancer and ESCC means Esophageal Squamous Cell carcinoma.

Reviewer's code: 03092223

Comment 1: I suggest only additional analysis, as evaluate the correlation between CTC-negative patients (since most methods use EPCAM-positive cells and exclude EPCAM-negative CTC) and disease progression.

Response: Thank you very much for the suggestion.In our meta analysis,overall analyses revealed that CTCs-positivity predicted disease progression.The HRs for disease progression were available in 6 studies,when the Reeh 2015 study(used Cellsearch) was removed, no influence of the results in the five remaining studies(used EPCAM-positive cells) was observed.Therefor,EPCAM-positive patients also had poor disease progression.

Comment 2: Is posssible to have meta-analysis in CTC-free patients vs EPCAM-negative CTC patients?

Response: To the the best of our knowledge,there is no meta-analysis in CTC-free patients vs EPCAM-negative CTC patients.