Letter to Editorial Board of World Journal of Clinical Oncology

Dear Editors,

Thank you for completing the examination of our manuscript "Recurrence-Free Survival as a Putative Surrogate for Overall Survival in Phase III Trials of Curative-Intent Treatment of Colorectal Liver Metastases: Systematic Review".
We have prepared a revised version addressing all of the issues raised by the reviewers. You will find attached a response letter to the reviewers indicating point-by-point how we have answered their critics. We have also carefully gone through the manuscript to make the appropriate changes (highlighted).

We would like to thank the reviewers for their comments. We have considered their suggestions and we think that they contributed to improve the manuscript. We do hope that our paper will meet the standards of publication in World Journal of Clinical Oncology and we are looking forward to receiving your final decision.

Sincerely yours,

Dr. Raphael Araujo and Rachel Riechelmann

POINT-BY-POINT PEER-REVIEW REPORT

REVIEWER'S CODE: 03253495

COMMENTS TO AUTHORS

The review is OK for me.

COMMENTS TO REVIEWER

Dear Reviewer,

We do appreciate your attention and your approval. But anyway, we come back to text to improve language as observed by you and the modifications are highlighted in the text.

REVIEWER'S CODE: 03478805

COMMENTS TO AUTHORS

This article investigated RFS as a putative surrogate of OS and found that RFS could work as a putative surrogate of OS in this population avoiding bigger, longer and more resource-consuming trials. The OS could be assumed based on RFS and our model could be useful to better estimate sample size calculations of phase III trials of CRLM aiming for OS. Their research is meaningful to clinical practice. However, there are some sentences to be corrected such as in Introduction the sentence 'furthermore when the primary endpoint include overall survival (OS) of slow

progressive malignancies' is confusing. There is no explanation about how the authors get formula: OS HR= (0.93 x RFS HR) + 0.14. As this is a meta-analysis, there should be description about whether the authors adopted fixed model or randomized model.

COMMENTS TO REVIEWER

Dear Reviewer,

Thank you for meaningful suggestion and important question. We went through the methods to make them clearer. We performed a systematic review, but we did not perform a meta-analysis because it would not be methodologically adequate to compare groups due to different chemotherapy regimens utilized by studies. Our primary endpoint was to evaluate recurrence free survival as a surrogate outcome of overall survival in RCT and for that, we performed a linear regression to investigate whether there was any correlation between RFS and OS. Thus, the question about the use of fixed or randomized treatment effects does not apply to our study.

The regression formula arose from a linear regression as a linear function, which demonstrated clear correlation between those outcomes. Your comments were crucial to improve the introduction and methods sections. Changes were made accordingly and highlighted in the text. Thank you so much for your considerations.

Reviewer's code: 03094792

COMMENTS TO AUTHORS

It is not clear that you understand by "recurrence" or if all the essays by you analyzed contemplate the term in a similar way. It should be clear whether the term refers

exclusively to the local recurrence of the excised metastasis. As it is a metastatic disease, the probability of relapse to other levels is comparatively higher than if we are referring to the local control of a primary tumor. For that reason it is logical that there is a parallelism between PFS and OS and in fact this is proven but it does not have to be so between RFS and OS. It is not clear that patients were excluded due to extrahepatic disease: “Studies were excluded when extra-hepatic disease was present in more than 5%”. It should be specified.

COMMENTS TO REVIEWER

Dear Reviewer,

Thank you for emphasizing this important point. All patients treated in these RCT underwent curative-intent surgical treatment for potentially resectable colorectal liver metastases. Thus, two important considerations: patients were not treated with conversion therapy because they were already upfront resectable. The second point is that virtually all of them had all macroscopic metastatic disease removed, so we considered recurrence-, rather than progression-, free survival as the endpoint. Recurrence was defined by RCT as any type of recurrence, that meaning distance and/or liver-only relapse. We added sentences to address this specific point and we really appreciate your comments in this remarkable topic.

Looking for extra-hepatic disease, only one studied presented a contamination with 5% of extra-hepatic disease. Regarding its quality and importance as a randomized clinical trial, we kept it to avoid losing robustness in our analysis. But we think this was not an important drawback since it was limited to a few patients. We have also made changes in the results section to address this point. Thank you so much for your thoughtful contribution.

REVIEWER'S CODE: 01982330

COMMENTS TO AUTHORS

The manuscript addresses the important issue of costs of clinical trials. There are minor language syntax errors and non-English expressions, "they imply in a time and resource-consuming methodology", "furthermore when", "follow up is required what adds", etc. Professional editing is advised. Major remark regarding the methods: Conventional regression models make a fundamental assumption that the independent variable ("X-axis") is measured without error. This is not the case in the present study. Table 4 shows that the RFS hazard ratios have large confidence intervals, i.e. considerable errors. The regression should take into account the X-variable errors. Minor remarks: Figure 3 might be misleading. It would be more appropriate to show the horizontal and the vertical confidence bars associated with each of the data points. A graph with the confidence bars would show that a zero-slope regression (i.e. no correlation between RFS and OS) is also compatible with the data. Note that the regression's p-value is attributable to the single extreme outlier. Overall remark: The manuscript should acknowledge that the predictive value of RFS is questionable, that further studies are required.

COMMENTS TO REVIEWER

Dear Reviewer,

We do appreciate your significant considerations. We improved the writing using more scientific vocabulary to fit better to our potential readers.

Regarding the graph concerns, indeed we built the linear regression graph with 95% CI based on standard errors of the mean. We discussed with our statistical team and we do agree that our graph represents all confidence intervals; the linear regression was based on linear prediction of OS HR according to RFS HR, along with a 95% confidence interval based on the mean. Both upper and lower limits of 95% confidence intervals were represented as dashed lines. We really appreciate your suggestion and we included sentences and the standard error (0.14) for the linear regression in results section. We also have acknowledged that the predictive value of RFS is questionable and that further studies are required to prove our model.

REVIEWER'S CODE: 03259512

COMMENTS TO AUTHORS

The authors conducted systematic review and tested the hypothesis that if gains in progression free survival (PFS) predicted gains in overall survival (OS), trials of new drugs in the setting of CRLM could use RFS as a surrogate endpoint, and thus expedite drug development. The paper is well written, properly designed, and comprehensive. Abstract : authors wrote "5 phase III trials (1,162 patients) were included for analyses…". However, later on page 9 authors wrote: "A total of 1,182 patients were included in this pooled analysis" ; please clarify the differences. Original studies were not properly described in the Results section, although the information was presented in the tables. The difference between original studies (the 5 included trials) has to be presented in more details in the text (the use of chemotherapy drugs, gender differences, follow-up periods, etc.) Some mistprints

found : page 12 “metanalysis…”, page 24 “elegible…”

COMMENTS TO REVIEWER

Dear Reviewer,

We do appreciate your comments and your helpful observations. The data written in the abstract is correct and we fixed the data in the results section. One thousand sixty-two patients were considered in per protocol analysis. Moreover, we double-checked the tables and we corrected the mistyped information based on your observation. The detected misprints were fixed. Thank you so much for your attentive and valuable review.

Answer to chief editor:

We had corrected the wrong “immune”.