Author's response to reviews

Title: Chemotherapy for advanced pancreatic cancer: A systematic review and network meta-analysis

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Author's response to reviews: see over
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Dear Editors and Reviewers of BMC Cancer,

Thank you for reviewing our paper and providing us with the opportunity to submit a REVISED manuscript. Please find our detailed responses to the reviewers’ comments below with the corresponding changes made to the manuscript highlighted.

Should you have any further concerns, we would be more than happy to address them. We look forward to having our work appear in your journal.

-Gillian Gresham

Responses to Reviewer 1:

The paper provides important information on treatment of metastatic pancreatic cancer by a sound methodology

1. Minor essential revision

a) Although methodology is well described, we suggest a deeper discussion of the inconsistency risk in MTC.

Response: We thank the reviewer for this suggestion and have addressed this in the discussion section of the manuscript (Page 16, lines 1-10). We agree that factors such as inconsistency are amongst the top methodological challenges of multi treatment comparisons and recognize that this can effect the validity of our effect estimates in the indirect comparisons. Several additional references have been added to the discussion of inconsistency in MTC (References 51-53) Our network meta-analysis presents a slightly different scenario, because the majority of our comparisons are represented by only one trial (the geometry of this network does not contain any “closed stars”).

APA

b) Some recently published meta-analysis should be referenced and discussed for an overall scenarion depiction

RESPONSE: Published meta-analyses have been referenced (References 41-51) and discussed in the Discussion section on page 15 (Lines 1-20). Two more recent systematic reviews and a Cochrane protocol have been added to the list of referenced systematic reviews (References 59-51). Similarities and differences between the recent published meta-analyses and our own results have been summarized while highlighting the limitation of comparing with these published reports, as they pre-date some of the treatments that were included in our own analysis (FOLFIRINOX, Gemcitabine+NAB-Paclitaxel) and do not include indirect comparisons. However, when comparing our results from the pairwise comparisons to the findings of the other published systematic reviews, we found similar results, described in further detail in lines 7-12 (highlighted).

Responses to Reviewer 2:

This is a network meta-analysis about the efficacy of different chemotherapeutic agents in metastatic pancreatic cancer. The network meta-analysis is nicely done
1. Minor Revisions:
1.1 Minor revisions in the methods

a) The algorithm needs some parentheses to be correct

Response: We thank the reviewer for bringing this concern to our attention. The algorithm has been corrected and verified. It has been changed and highlighted in the Methods section on Page 4 and line 3 of “Identification of Randomized Studies.”

b) Why did the authors exclude randomized phase II trials? Please clarify

Response: We appreciate your query and have attempted to further elaborate our reasoning for excluding randomized phase II trials in the methods section (Page 4, Line 7). This was an a priori decision that we made, after discussion between the other collaborators on the project. The reason for excluding randomized phase II trials involves the risk of introducing further heterogeneity and inconsistency to our analysis as the primary endpoints and populations are often different in phase II studies compared to Phase III. Because we were assessing risk of bias in our studies, we also found that the majority of the Phase II studies did not meet the inclusion criteria as they are often unmasked and represent small study populations of a generally healthier population. Therefore, to reduce bias and heterogeneity in the indirect comparisons we did not include Phase II studies for this analysis. Furthermore, phase II studies might by nature of their small size be conducted in single centers with unique referral patterns, and might be less representative of a more general population with pancreatic as would be found in a large multicenter study. The smaller sample size in a phase II study would also caused these results to have less proportional impact within a NMA. Therefore, we wanted to limit the scope of the review. However, a separate analysis of Phase II trials could be conducted in future projects.

1.2 Minor revisions in the discussion

a) Write your results in the first paragraph of the discussion.

Response: Thank you for this suggestion. We have re-arranged and edited the discussion to address your recommendation. The main findings from our analysis are now presented in the first paragraph of the discussion on page 13 (Lines 1-14 of Discussion).

b) A prior meta-analysis found that patients with performance status 0-1 had benefit from combination whereas patients with worse performance status did not have any benefit. A discussion of this factor (performance status) in the decision is important.


Response: We thank the reviewer for identifying and highlighting important results from the meta-analysis published by Heinemann et al (Reference 41). We agree that this is an important finding that should be further discussed and have added this to our discussion on page 14, Line 22.

This finding supports the large effect estimates that were observed in our NMA including all trials in comparison to our subgroup analysis that had excluded trials with >85% population with
an ECOG of 0-1. These finding reflect the introduction of confounding by performance status (where healthier patients are generally given more aggressive combination treatments and do better than those with worse performance status) and the threat to external validity this problem poses, especially with regards to the PEFG and FOLFIRINOX regimens that included such a high proportion of patients with good performance status (ECOG 0-1).

c) “Another limitation included the fact that the WinBUGS code does not account for correlation in multi-arm trials, however this was not applicable for this particular analysis as no 3-arm trials were included in the study”. There is no need to write a limitation of statistical package if it is not applicable for this study. The authors can remove this sentence.

Response: Thank you for the suggestion. We have removed this sentence from the discussion section.

2.0 Major revisions

2.1 Major revisions of the results section

a) The meta-analysis has generated many results but the authors should choose the most important results, figures, and tables. There are too many figures and tables and it is difficult for the reader to concentrate on the important results.

Some suggestions:
- Table 3 as supplement
- Figure 3, 4, 6 as supplement
- Try to re-write the results more concise.

Response: We apologize for presenting so many results and lacking concise and clear presentation of our findings. This task was difficult, as we did not want our manuscript to focus on only one or two “favorite” regimens. Instead, we aimed to stay as objective and unbiased as possible in presenting the results. For this reason, we had originally decided to present the results form all significant findings related to our third figure (the effect estimates from the network meta-analysis).

Realizing that this may create confusion and an overwhelming amount of information that may not be immediately useful to the readers, we have attempted to re-write and format the results in a way that still meets our expectation of objectivity in results, while removing any redundancy and overwhelming results. The results have been presented following the significant findings from Figure 3, moving from left to right of the figure and starting with gemcitabine.

The subgroup analyses have been shortened to present the most important findings, while our results from the analysis of safety have also been reduced. Changes have been made throughout and are tracked in the document.

Following your suggestions, Table 3 has been changed to a supplementary table (it is now supplementary Table 1) and Figures 4 and 6 have also been changed to supplementary figures. We have discussed and agreed to keep Figure 3 as a main figure in our analysis, as this was central to the presentation of most of our results and discussion. Although there is a lot of information presented in this figure, it is a common method of presenting results from network meta-analysis, thus readers may be familiar with this figure, and detailed instructions on how to read and interpret the findings are provided as a footnote.