Author’s response to reviews

Title: Addition of platinum derivatives to neoadjuvant single-agent fluoropyrimidine chemoradiotherapy in patients with stage II/III rectal cancer - protocol for a systematic review and meta-analysis (PROSPERO CRD4201707306)

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Author’s response to reviews:

Dear editors,

Enclosed please find the re-submission of the manuscript entitled:

"Addition of platinum derivatives to neoadjuvant single-agent fluoropyrimidine chemoradiotherapy in patients with stage II/III rectal cancer – protocol for a systematic review and meta-analysis (PROSPERO CRD4201707306)".

We have found the reviewers’ comments very helpful and believe that these comments and our revisions have further improved the quality of the manuscript.
All comments of the reviewers are considered in this new version of the manuscript. Two versions of the revised manuscript were uploaded: one with tracked changes and a “clean” version.

All authors have read and approved the amended version of the manuscript. Thank you for your time and consideration of our revised manuscript.

Sincerely yours,

Markus K. Diener, MD
On behalf of all authors

Referee 1

1 Reviewer's comment This is a well written systematic review protocol. It appears that new information is now available since previous, similar reviews were carried out, therefore this is a valid update of previous reviews. I have the following comments. The review states it has been prepared according to the PRISMA-P statement and all aspects of the statement are covered here.

Our comment Thank you very much for the favorable appraisal of our work. Please find below the answers to your comments.

Alterations in manuscript None.
2 Reviewer's comment Methods

There has been no search for unpublished trials. This is important as extra information may be available and if not, it helps to put the amount of data available into context. The authors say they use search methods described by Cochrane, but the strategies included don't include the filter for RCTs, which is recommended.

Our comment We will search several trial registries for ongoing or unpublished trials. This was already stated in our manuscript but has been defined more precisely in our revision.

Regarding the Cochrane RCT search filter, a modified even more sensitive RCT filter will be used.


Alterations in manuscript Pg. 7 3rd paragraph: Clinical trial registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu, etc.) will be searched for ongoing or unpublished trials.

3 Reviewer's comment Statistical Analysis

There is no description how subgroups will be analysed. In this section the authors state 'Presumably, a statistical investigation of a potential publication bias based on a test of funnel plot asymmetry cannot be done because of too few trials in the meta-analyses'. It may be better to say that a test for asymmetry will be performed if there are an adequate number (e.g. >10) of RCTs. The discussion mentions a risk/benefit assessment of the different treatment strategies, but this is not mentioned in the Statistical Analysis section.

Our comment Subgroup analyses will be done in the same way as the primary analyses for the main endpoints. This has been defined more precisely.
The passage on publication bias assessment was changed according to the suggestion of the reviewer.

The risk/benefit assessment is not a statistical analysis, but rather the results of our meta-analyses regarding risks (e.g. toxicities) and benefits (e.g. survival) will be discussed in the light of their clinical implications and relevance. Therefore, the risk/benefit assessment is not mentioned in the Statistical Analysis section.

Alterations in manuscript Pg. 12 last paragraph: If possible, the following subgroup analyses will be done for the main endpoints to further investigate potential heterogeneity: Stage II vs. Stage III rectal cancer, adjuvant vs. no adjuvant treatment.

Pg. 12 last sentence, pg. 13 first sentence: Statistical investigation of a potential publication bias based on a test of funnel plot asymmetry will be done if there is a sufficient amount of RCTs (>10) available for analysis.

4 Reviewer's comment Other comments

A table of the trials already known about would be useful, even if the full searches have not been carried out yet. It would be nice to know which patient organisations were contacted and helped plan this review (Endpoints section)

Our comment We thank the reviewer for this relevant comment. A table about the trials already known has been added.

Furthermore, we added to the manuscript, which patient organisation has been involved.

Alterations in manuscript Pg 8 2nd paragraph: Table 2.
During the planning phase of the current systematic review, several representatives of patient organizations (German ILCO e.V., various local groups) have been contacted and responded that survival, quality of life and treatment toxicities would be of utmost importance from a patient’s perspective.

Referee 2

1 Reviewer's comment This interesting and relevant protocol plans to assess whether adding oxaliplatin to fluoropyrimidine-based neoadjuvant chemoradiotherapy can improve survival in patients with stage II-III rectal cancer. A previous review on this topic only assessed short-term outcomes, whereas this review plans to address more meaningful, long-term outcomes such as disease-free and overall survival, which have far greater potential to influence clinical policy/practice decisions. Assessment of toxicity and quality of life, may also play a key role in the making of decisions around treatment options. It is commendable that the authors have obtained patients' perspectives as to which outcomes are most important to them.

The protocol is generally clear and methodologically sound. Just a few minor comments:

Our comment Thank you very much for the favorable appraisal of our work. Please find below the answers to your comments.

Alterations in manuscript None.

2 Reviewer's comment Page 2; Para 1: The second sentence could benefit from additional context to explain why oxaliplatin may hold the potential for positively affecting survival e.g. positive results of in palliative/adjuvant setting (see general comments at end)

Our comment Oxaliplatin improved progression-free or disease-free survival respectively in the palliative/adjuvant setting. This was made more clear in the revised manuscript. Furthermore, the Background section was changed in response to the general comment at the end (please see our comment there), which will set this sentence into more context.
Alterations in manuscript Pg. 2 1st paragraph: The addition of oxaliplatin to fluoropyrimidine-based neoadjuvant chemoradiotherapy holds the potential of positively affecting survival in this context since it has been proven effective in the palliative and adjuvant setting of colorectal cancer.

Pg. 5 2nd paragraph: Oxaliplatin is one of these chemotherapeutic agents, which has proven to be effective in the palliative and adjuvant setting of colorectal cancer by improving progression-free or disease-free survival respectively.

3 Reviewer's comment Page 4; Para 1: …it is the third most common cause…. (remove the word "under")

Our comment We thank the reviewer for this comment and changed the sentence accordingly.

Alterations in manuscript Pg. 4 1st paragraph: Thus, it is one of the three most common causes of cancer deaths in adults of both sexes

4 Reviewer's comment Page 7; Systematic literature search: Is there a reason only MEDLINE was searched? Generally good practice to search at least two electronic databases e.g. MEDLINE and EMBASE. Will study authors be contacted to ascertain if they know of any other studies (unpublished/ongoing) that should be included in the systematic review? How will retrieved references (and duplicates) be managed e.g. with reference management software? Add detail. Also provide time parameters for searches e.g. MEDLINE 1966-2017.

Our comment We don’t know why the reviewer supposed that only MEDLINE will be searched. As stated already in the initial version of our manuscript three databases will be searched (MEDLINE; Web of Science; Cochrane CENTRAL). Please confer pg. 7 3rd paragraph.

To search for ongoing/unpublished trials, several trial registries will be searched. This has been specified more clearly in the manuscript.

The references will be managed with the reference management software Endnote™. This was added to the manuscript to clarify the review process.
No time restrictions will be applied. This was also clarified in the manuscript.

Alterations in manuscript Pg. 7 3rd paragraph: Clinical trial registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu, etc.) will be searched for ongoing or unpublished trials.

Pg. 8 3rd paragraph: Retrieved references will be stored in a file of the reference management software EndNote™. Duplicates will be removed and all other references will be put into specific folders (‘inclusion’, ‘exclusion with reason’, etc.) after screening.

Pg. 7 4th paragraph: The search strategies for other databases were constructed correspondingly. No language or other restrictions including date of publication will be applied.

5 Reviewer’s comment Page 7/8; Last para: I am not sure I understand what the last sentence means (“Eligibility will be assessed for the results?”) - consider revising/re-wording.

Our comment We thank the reviewer for his attentive review of our manuscript. This sentence slipped in at this place by accident. Therefore, we deleted the whole sentence.

Alterations in manuscript Pg. 8 1st paragraph last sentence was deleted.

6 Reviewer’s comment Page 9; Data extraction: Will authors of the individual studies be contacted to obtain any additional/missing data (or to check data if anything is unclear from the study report?) or to obtain summary data from any unpublished studies identified?

Our comment We thank the reviewer for this important comment. Authors of individual trials will be contacted in case of missing data. Equally, authors of unpublished trials will be contacted to obtain further information.

Alterations in manuscript Pg. 10 5th paragraph: In case of missing information or ambiguities in the publications of individual trials, the trial authors will be contacted to retrieve additional information.
7 Reviewer's comment Page 10; Para 2: Should this be extirpation?

Our comment The reviewer is right. The wording was changed accordingly.

Alterations in manuscript Pg. 10 3rd paragraph: abdominoperineal extirpation

8 Reviewer's comment Page 10; Endpoints: Would be useful to define outcomes e.g. time from randomisation to death (OS) etc. Are there likely to be differing definitions of disease-free survival across trials? If so, how will authors deal with this?

Our comment We cannot define the outcomes that are used in primary trials. However, usually overall survival and disease-free survival are defined similarly in clinical trials as time from start of treatment/randomization as suggested by the NCI dictionary (https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID=655245). If different definitions exist across trials, this will be stated and discussed in the final report.

Alterations in manuscript Pg. 11 2nd paragraph: If differing definitions of the endpoints stated above are used in individual trials, this will be reported and potential implications for the results will be discussed.

9 Reviewer's comment Page 11; Qualitative analysis: Perhaps a better heading would be "Qualitative assessment of included trials"? Also, how many assessors will there be and how will judgments be made / disagreements be resolved? If there is not enough information to make an assessment, will the study authors be contacted? Also, the last para on page 11 seems a bit disjointed - perhaps better to include this information as part of the previous paragraph about using the risk of bias tool.

Our comment We thank the reviewer for these important comments on the qualitative analysis section. The heading was adopted according to the reviewer suggestion.

Equally to the study selection and data extraction process, two reviewers performed the qualitative assessment independently and ambiguities were resolved by discussion with a third reviewer.
The last paragraph has been removed completely, since all of it is already mentioned in the study selection or qualitative assessment section respectively and we wanted to avoid redundancy.

Alterations in manuscript Pg. 11 heading: Qualitative assessment of included trials

Pg. 11 4th paragraph: Two reviewers will independently assess risk of bias of each trial. Disagreements will be resolved by discussion or by consulting a third reviewer.

Pg. 12 2nd paragraph: deleted.

10 Reviewer's comment Page 12; Line 23: "…mean difference((S)MD) with its 95% confidence interval will be used"

Our comment Thanks, this was changed as suggested.

Alterations in manuscript Pg. 12 2nd paragraph: for the ordinal outcome QoL, the (standardized) mean difference ((S)MD) with its 95% confidence interval will be used

11 Reviewer's comment Page 12; Line 38: Consider changing sentence to state that meta-analysis will be performed if identified trials are sufficiently similar in design/comparison and if heterogeneity in the results is observed, this will be further explored via subgroup/sensitivity analyses.

Our comment We thank the reviewer for this suggestion. However, we did not change our manuscript regarding this point, since it is our belief that it makes no sense conducting meta-analysis in cases of substantial heterogeneity or variation. This belief is also supported by the recommendations of the Cochrane Handbook (http://handbook-5-1.cochrane.org).

Alterations in manuscript None.
12 Reviewer’s comment Page 14; Line 30: Better to use the words "allow for better" rather than "guarantee" generalisability of results?

Our comment Thank you for this comment. We changed the wording accordingly.

Alterations in manuscript Pg. 14 1st paragraph: The wide patient selection criteria of all patients with locally advanced rectal cancer (UICC stage II or III disease) will allow for better generalizability and representativeness of the results.

13 Reviewer's comment Page 16; Author contributions: Who is the guarantor for this work?

Our comment The persons holding responsibility for the manuscript have been added.

Alterations in manuscript Pg. 16 1st paragraph: FJH, PP and MKD hold final responsibility for this publication.

14 Reviewer's comment General comments:

Authors switch between using (chemo-)radiation, chemoradiotherapy and radiochemotherapy throughout. It would be better to keep this descriptor consistent.

Our comment We thank the reviewer for this comment and changed the wording throughout the manuscript.

Alterations in manuscript We changed the wording throughout the manuscript to “chemoradiotherapy”.

15 Reviewer's comment There is quite a bit of overlap between the Background section and the first paragraph of the Discussion section. Consider amalgamating these two sections into the Background section and then leading the discussion from the second paragraph.
Our comment The reviewer is right. To avoid redundancy we changed the manuscript as suggested by the reviewer by moving the first paragraph from the discussion (in part) to the background section and starting the discussion with the second paragraph.

Alterations in manuscript Pg. 4 2nd paragraph: Multimodal treatment strategies including neoadjuvant chemoradiotherapy have contributed to reduce rates of local recurrence in cases of nodal-positive disease or an advanced T-stage. However, neither neoadjuvant radiation nor neoadjuvant chemoradiotherapy were able to improve overall survival, which is the ultimate goal of any cancer-directed therapy [8-10]. This led to different approaches in the recent use of neoadjuvant chemoradiotherapy. While some clinicians favoured a more selective indication for neoadjuvant chemoradiotherapy e.g. based on preoperative radiologic assessment of the circumferential resection margin [11-13], others started to exert and investigate more effective chemotherapeutic agents in the setting of preoperative chemoradiotherapy [14, 15]. This second approach aims at reducing not only rates of local recurrence but also distant recurrence, which remain at a high level of up to 30% after curative resection of advanced rectal cancer.

Oxaliplatin is one of these chemotherapeutic agents, which has proven to be effective in the palliative and adjuvant setting of colorectal cancer by improving progression-free or disease-free survival respectively [16, 17]

Discussion section: 1st paragraph removed.