Author's response to reviews

Title: Intermittent Versus Continuous Androgen Deprivation For Locally Advanced, Recurrent Or Metastatic Prostate Cancer: A Systematic Review And Meta-Analysis

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Author's response to reviews: see over
Dear Sir,

Thank you very much for your considerate comments on this paper!

We made all the requested adjusts, plus a thorough review of grammar mistakes and hope the paper is ready to advance now.

Best regards,

Tobias Engel

1. Is the question posed by the authors well defined? Yes, with the caveats outlined below in the Introduction and Methods
2. Are the methods appropriate and well described? Yes, with the caveats outlined below in the Methods
3. Are the data sound? Yes, the data is sound.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data? No, as discussed below, the Discussion is simply a reiterating of the results, and does not provide for enough analysis. The Conclusions, as also outlined below make statements, which are not supported by the data.
6. Are limitations of the work clearly stated? Yes, the authors do a good job of outlining the short-comings of the meta-analysis.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? They do tangentially discuss other references, but as stated about the discussion needs to be expanded, and the value of their meta-analysis needs to be placed within the context of how their results enhance previous studies.
8. Do the title and abstract accurately convey what has been found? Yes, the abstract is overall well-written.
9. Is the writing acceptable? There are some minor grammatical mistakes throughout the manuscript, as well as opportunities for revision to make the manuscript more readable.
10. Major Compulsory Revisions: The statistics are well performed, but the data needs to be further described and placed within a context in the discussion.
11. Minor Essential Revisions: Grammatical mistakes and general, although not critical readability issues.
12. Discretionary Revisions: None.

Abstract:

There are minor grammatical mistakes throughout Abstract. Corrected.

Paragraph 2: Would change to cancer-specific survival (CSS) instead of disease-specific survival. Would also carry this through in the reminder of the manuscript. Done.
Introduction:

There are minor grammatical mistakes throughout the Introduction. □ Paragraph 2: Unsure of the meaning or context of the "binomial ‘disease-treatment’". Corrected.

Paragraph 3: First sentence needs to be changed to clarify that references 5 and 6 were meta-analysis, and not original investigations with regards to IAD v CAD. Done.

Paragraph 4: This is a useful paragraph, as it provides the reason or support for further investigation into IAD v CAD (previous investigations are inconclusive). As it is written, it is too concise, and should be expanded to demonstrate the value of your investigation. Expanded.

Methods:

There are minor grammatical mistakes throughout the Methods. Corrected

Please specify the publication date range that was utilized a priori for your search (i.e. 10 years, 15 years, etc.). Done.

Please specify the outcomes that were utilized a priori for your search (i.e. OSS, CSS, side effect profile, QOL, etc). Done.

Please specify the language that was utilized a priori for your search (i.e. only English language). Done.

Overall, excellent description of the statistics utilized to perform the meta-analysis. This adds to the validity of the results.

Results:

Overall, excellent description of the outcomes measured, and the reasons for or against inclusion of certain trials.

It is necessary to outline all the side effects that were included in the analysis, as this is one of the biggest benefits of IAD, decreasing toxicity. It would be nice to also include, if available from the data, risk of cardiovascular equivalent outcomes (i.e. CAD, CVA, DM), as this is a reported risk with both IAD and CAD, and of significant influence. Done.

Discussion:

There are minor grammatical mistakes throughout the Discussion. Corrected.

Paragraph 9 & 10 & 11: All 3 paragraphs relate to TTP. The conclusion from these paragraphs and of TTP within this analysis is that it may be favorable with CAD, but that only 2 studies were available with data sufficient for inclusion, and therefore the
conclusion should be interpreted with caution. However, the majority of the text of these paragraphs relates to when hormones should be reintroduced for patients on IAD, which is not a focus of this investigation (only OS, CSS, and QOL was examined from the studies). Removed the paragraph and expanded the discussion.

Paragraph 13: Economic analysis was not part of this investigation, but it is an interesting concept with respect to IAD. This needs to be either omitted or further tied into your investigation. Expanded.

Overall, the discussion seems to reiterate results, but without adding to how it improves on the previously published literature (except in paragraph 3, where they state this analysis included “a greater number of studies”), or how this information can add to clinical practice. It does also not outline future directions for care of patients with prostate cancer with regards to IAD or CAD. Reviewed.

Conclusion:

The conclusion is supported by the data, except with regards to side effects. I would include only the side effects that had a reduction with IAD. It is not acceptable to “fewer symptoms”, but exactly what symptoms. Furthermore, your analysis did not include economic outcome, and therefore this should not be in your conclusion. Correct.