Author’s response to reviews

Title: Comparison of Survival Benefits of Nephron-Sparing Intervention or Active Surveillance for Patients with Localized Renal Masses: A Systematic Review and Meta-Analysis

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Author’s response to reviews:

Dear editor and reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled "Comparison of Survival Benefits of Nephron-Sparing Intervention or Active Surveillance for Patients with Localized Renal Masses: A Systematic Review and Meta-Analysis" (BURO-D-19-00109). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are highlighted in yellow in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: This paper as a meta-analysis has limitations which should be considered in conclusion: It is based 6 or 7 papers. Just two of the studies are prospective. Just English and Chinese literature are included.

Response: As mentioned by the reviewer, only two studies are prospective cohort studies and all the studies are English literature, which are limitations to be noted. We have also mentioned these limitations when we drew conclusions in the part of discussion (part of Discussion in Text, line 17, page 8).
2. Response to comment: Data on cardiovascular survival is just based on two papers. The conclusion from these two papers, is that AS has more cardiovascular consequences than surgery! Which just shows very different populations in these two groups (sicker patient in AS group), and this can induce less overall survival of this group, which simply is based on their underlying condition, not the treatment method.

I think the best conclusion from the reviewed papers, is that: we need better prospective cohort studies with matched groups based on comorbidities and age, to be able to make any definitive statement about these different treatment methods.

Response: We are very appreciated with the reviewer's comments. In the part of discussion, we have also mentioned that the selection bias might contribute to this result. The AS group represents an extreme condition where patients did not experience intervention (especially surgery) for some reasons, but the most likely are age, comorbidities, tumor characteristics, and patient preference. The surgeon and the patient would omit intervention and choose AS among elderly patients, which aims to reduce potential overtreatment without conceding oncologic outcomes and may result in worse cardiovascular survival in the AS group. Therefore, patients at high cardiovascular risk are very reasonable candidates for AS. Therefore, we made changes in the conclusions according to the suggestion from the reviewer (part of Conclusions in Abstract, line 15, page 2, and part of Conclusions in Text, line 3, page 9).

Special thanks to you for your good comments.

Reviewer #2:

1. Response to comment: In the abstract they use the acronym TA without defined it before.

Response: According to the suggestion, we reviewed and made corrections in the abstract (Page 2, part of Methods, line 3).

2. Response to comment: In the Materials and Methods section, in the strategy research they should selected only articles written in English. But in the flow-cart of study selection the excluded 7 articles because not in English or Chinese.

Response: Actually, we selected papers written in English, thus we made correction in the flowchart (Figure 1).

3. Response to comment: Moreover, they stated in the eligibility criteria the exclusion of reviews but in table 1 they included six retrospective reviews.
Response: We are very sorry for the ambiguous expression of "retrospective reviews", in fact, these studies were retrospective studies using a single center or multicenter data, or even national database, and they were original articles, not the type of reviews. To make it clear, we made corrections in the Table 1, and changed "retrospective reviews" to "retrospective".

4. Response to comment: They selected 8 papers for systematic review and 7 for meta-analysis. In the discussion they mentioned 9 papers.

Response: After excluding one study focused on CKD upstaging free survival, only seven papers were included for meta-analysis, which have relative high quality (> 6 stars). We corrected the number of studies (7 not 9) in the part of discussion (part of Discussion in Text, line 20, page 8).

5. Response to comment: Only 3 up to 7 selected papers studied TA patients and the meta-regression analysis did not find significant differences between PN and TA. This result cannot translate in the conclusion that "TA (Thermal Ablation) may be an attractive option for those patients deciding against AS.

Response: We are very appreciated with this important suggestion and agree with it. Therefore, we removed the statement that "TA (Thermal Ablation) may be an attractive option for those patients deciding against AS". Further larger prospective cohort studies with matched groups based on comorbidities and age are needed to compare partial nephrectomy and thermal ablation for those deciding against AS.

6. Response to comment: Of course, benign renal masses have different survival rates compared to malignancies. In the revision they included every kind of masses without a previous diagnosis before treatment. This selection bias may impact on the meta-analysis results nevertheless meta-regression did not find differences between T1a and others (but this stratification is not clear).

Response: As we mentioned in the limitations, studies of TA and AS may include patients with benign tumors and may overestimate the efficacy of these management options, which may have an impact on the meta-analysis results. And this could be quite difficult to resolve due to lack of pathology data in the clinical practice and in the previous studies. However, we believed that improved diagnostics and judicious use of renal mass biopsy may improve the understanding of tumor biology in future studies.

7. Response to comment: They did not stress all limitations of the paper.
Response: We have addressed six limitations in the part of discussion. (1) lack of unpublished studies or studies written in other language; (2) only two studies are prospective studies, the nature of other retrospective studies might render the results less trustworthy; (3) failed to compare survival between matched groups; (4) only two studies focused on CVSS, and the risk of random error might increase since patients in AS group might be sicker, and further studies are needed; (5) lack of pathology data in TA or AS group; (6) influence from the quality of selected studies and the reporting bias.

Special thanks to you for your good comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. If you have any queries, please don't hesitate to contact me at the address below.

Thank you and best regards.

Yours sincerely,

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