Author’s response to reviews

Title: Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: a systematic review and meta-analysis

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Authors’ response to reviews:

Dear Prof. Zargar,

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal. Additionally, the revised manuscript has been edited and proofread by American Journal Experts.

I look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Li-jin Zhang

Corresponding author
Replies to Reviewer

Point by point responses comments

Replies to Rodrick Ven Den Bergh (Reviewer 1)

This is a thoroughly performed review according to the accepted standards for systematic review.

- A 2013 review by Cozzi et al may be referred to.

Response: We deeply appreciate the reviewer’s positive evaluation of our work. After reading the Cozzi’s article, we have intuitive understanding of the format for systematic reviews.

- Perineural invasion is based on biopsy results in the radiotherapy group, while on prostatectomy specimen in the RP group?

Response: Thanks for your careful review and professional comment. In the revised version of the manuscript, some sentences have been added to address this issue. (Inclusion and exclusion criteria, line 2, page 2)

How difficult is it to report PNI in biopsy cores only? ('Third, the pathological diagnosis of PCa and the detection method of PNI varied throughout the eligible studies.')

Response: As the greatest density of nerves is posterior, the presence of PNI in each case was different. The number of cores obtained and the number of sections taken at different levels through the tissue influence the surface area of prostatic tissue and, therefore, the potential number of nerves available for examination may not be sampled if only one histological section is taken.

- Readers may not be familiar with the Begg test.

Response: One of the great problems with systematic review is that not all studies carried out are published. Although the main graphical method for identifying publication bias is the use of funnel plots, the variance of the effect estimate is not the same for all points. As a commonly used method of sensitivity analysis in meta-analysis, the Begg test is to divide each estimate by its standard error, which makes it a bit more complicated. The effect is to give us estimates which have the same variance.
'... others argue that PNI is not an independent predictor of BCR.' Are only studies presenting multivariable analysis included in the meta-analysis, or are univariate analyses also included?

Response: In RT group, 5 studies presenting multivariable analysis, 1 presenting univariate analysis. In RP group, 11 studies presenting both univariate and multivariable analysis, 2 studies presenting multivariable analysis. As we have already mentioned in our original manuscript: When the study provided the results of both the multivariate and univariate outcomes, we chose the multivariate model. (Data extraction and Study Quality, line 5-6, page 3)

- NOS please write in full.

Response: We apologize for the language problems in the original manuscript, and corrections have been made in the revised version. (Data extraction and Study Quality, line 7, page 3)

- 'Therefore, we suggested that some patients with PCa and PNI may benefit from systemic therapy.' Since PNI seems to be mainly related to local (ECE) tumor extension, and not to metastasis, it would sound more logical to advise adjuvant local therapy instead of systemic treatment when PNI is present? Please provide further explanation in the discussion.

Response: Thank you for your thoughtful suggestion. Cozzi et al found that PNI at needle biopsy shows a statistically significant higher incidence of local tumor extension in patients of PCa. Therefore, the author suggests that patients with PNI in needle biopsy should provide adjuvant local therapy. In the present study, our central conclusion from our data is that the presence of PNI is associated with higher risk of BCR in both RP and RT group. Patients with BCR have a much worse prognosis and often develop metastasis and can die of PCa disease [1]. Combined with your professional suggestion, we made some changes in the revised manuscript. (Discussion, line 1-2, page 6)

- One of the main clinical implications of this may be that pathologists are encouraged to report this factor.

Response: We deeply appreciate the reviewer’s positive evaluation of our work.
Is there any rationale for advising to perform surgery versus radiotherapy in patients with PNI?

Response: Thank you for raising this critical issue. Unfortunately, there is no study to compare the clinical efficacy between RP and RT in PCa patients with PNI by now. Therefore, based on the current literature evidence, we can’t make the appropriate advice. However, we think this may be a good point that can prompt us to conduct an in-depth study on this issue.

Tobias Gross (Reviewer 2)

1) Overall only 222 articles were retrieved from the search with only 149 non-duplicates. This very low count demonstrates that the search strategy was not appropriate. This is supported by other published systematic reviews with similar topic.

Response: Thank you for raising this critical issue, and we acknowledged that there was a certain limitations in our search strategy. Compared with other systematic reviews, only retrieved 222 related articles were retrieved in our study. However, we manually searched the reference lists of relevant literature to find additional publications of interest. In addition, a strictly inclusion and exclusion criteria was taken in our study, which could increase the feasibility of our findings. The search strategies used in Pubmed and EMBASE lists as follows:


EMBASE: 'perineural invasion':ab,ti AND 'prostate cancer':ab,ti AND 'radical prostatectomy':ab,ti AND 'biochemical recurrence':ab,ti 74 articles

EMBASE: 'perineural invasion':ab,ti AND 'prostate cancer':ab,ti AND 'radiotherapy':ab,ti AND 'biochemical recurrence':ab,ti 18 articles

2) Performing a Meta-analysis in a systematic review including only non-RCT’s is not appropriate.

Response: We are greatly appreciate with the expert's professional opinion. However, no relevant RCTs were founded during the search of relevant literature. As a limitation in this study, we have already explained in the original manuscript (Discussion, line 22-23, page 5), thus, we hope that there will more relevant RCTs to prove our conclusions in the future. (Discussion, line 2-3, page 6)
3) The conclusion that patients with PNI might benefit from systemic treatment is not justifiable, as this systematic review does not assess the impact of PNI on overall survival/cancer specific survival. There is still a lack of data that even biochemical recurrence per se has an impact on these factors.

Response: Biochemical recurrence defined as a detectable PSA level following RP in the absence of clinical progression, is the most common pattern of disease relapse. Patients with biochemical recurrence have a much worse prognosis and often develop metastasis and can die of the PCa. Since biochemical recurrence has been reported to lead to distant metastasis and cancer death[2], it is necessary for men with biochemical recurrence to undergo salvage radiation or hormonal therapy[3]. Therefore, to identify a modifiable factors that affect the progression of BCR may help physicians in the selection of patients who are more likely to benefit from adjuvant multimodal therapy. To making our conclusion more appropriate, we made some changes in the revised manuscript. (Discussion, line 1-2, page 6)

