Author's response to reviews

Title: Optimal schedule of Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer: A meta-analysis of comparative studies

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Author's response to reviews: see over
Dear Dr. Claire Barnard,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Optimal schedule of Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer: A meta-analysis of comparative studies”. (MS: 1484451648545559).

We have studied editor’s and reviewer’s comments carefully. We have made revision which marked in red in a marked-version and refresh this manuscript in cleaned-version. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

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List of Responses

Responses to editorial comments

1. PRISMA guidelines: Please ensure the manuscript fully adheres to the PRISMA reporting guidelines (http://www.prisma-statement.org/2.1.2-%20-%20PRISMA%202009%20Checklist.pdf)

   We are sure that this manuscript mainly adheres to the PRISMA reporting guidelines. We also cited it at the 9th reference. To make the legibility of this paper, we made some modifications on the guideline. For example, we describe the search process in form of rules other than unusual table. However, the text words and databases used for searching were not influenced.

2. Authors' contributions: Please include this section at the end of your manuscript. More information can be found at http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle#formatting-contributions

   We are very sorry for our negligence of authors’ contributions. This section has been added at the end of our manuscript.
3. Acknowledgements: Please also include this section at the end of your manuscript. More information can be found at http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle#formatting-acknowledgements

   We are very sorry for our negligence of acknowledgements. This section has been also added at the end of our manuscript.

4. Please rename the "disclosure" section to "Competing interests". More information on competing interests can be see at http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle#formatting-competing

   We are very sorry for our unapt writing. This section has been corrected.

5. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

   Done.

Dear Reviewers:

Thank you for your comments concerning our manuscript entitled “Optimal schedule of Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer: A meta-analysis of comparative studies” (MS: 148445164854559). 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. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Reviewer # 1 (Dr Ashish Kamat)

Abstract:
1. “However, additional interferon #-2b might be useful for patients with BCG refractory cases.” No data presented in the results section supports this sentence.
   
   As Reviewer suggested that no data supports this view. This kind of sentence can be only appeared in discussion. We have deleted it from abstract.

Methods and statistics were appropriate.
The data was presented in an unbiased manner.

   Thank you for your approval on the sections of Methods and Results.

Discussion:
1. Why was reference 45 not used in the meta-analysis regarding BCG and IFN? Was it excluded and why? Are there other studies to support the use of INF in BCG
refractory patients?

In the reference 45, Joudi et al did reveal that BCG plus IFN-alpha can be effectively applied to patients having BCG failure. And the same conclusion was shown by many other papers. So we summarized “additional interferon-2b might be useful for patients with BCG refractory cases” in the section of abstract-results. However, no comparative data was available in these studies for meta-analysis.

2. Add further discussion of publication bias in high-risk NMIBC subgroup analysis. How does this impact the interpretation of the results?

The publication bias has been present at the table and discussion, and the bias can only be solved by including more studies. So the suggestion of promoting more large-volume, well-designed, RCTs with extensive follow-up was post in the end of Conclusions. At the last, we don’t think the significant conclusions can be overturned by the potential bias.

Figure numbers (1-11) do not match legend (1A/B-5A/B, 6).

We are very sorry for the confusing figure numbers. To remaining the quality of picture, we didn’t joint the divisive figure 1-5. Figure 1-2 matched with legend 1; Figure 3-4 matched with legend 2; Figure 5-6 matched with legend 3; Figure 7-8 matched with legend 4; Figure 9-10 matched with legend 5; Figure 11 matched with legend 6.

The manuscript would benefit from scientific review to correct grammatical errors.

We have invited a native-English speaker to perform a general careful review on our revised manuscript. We hope the revision would satisfy the need of the readers.

Reviewer # 2 (Dr Claire Vale)

Major Compulsory Revisions

1. I am unclear why the authors have chosen to combine RCTs with other study designs in this meta-analysis. There are good, methodological reasons why pooling RCTs with non-randomised study results may be inappropriate, yet the authors have not provided a clear rationale for so doing in this review. My concern is that the inclusion of the non-randomised trials may be inappropriately inflating the power of the analyses and thus overplaying the reliability of the results. Furthermore, in a number of the meta-analyses presented, the estimate of effect associated with the non-randomised studies is greater than that of the RCTs therefore exaggerating treatment effect sizes. They do present results based only on the RCT in the sensitivity analysis section however, my preference would have been for these to be the main findings. Whilst this may lead to an inevitable reduction in power and precision in the meta-analysis, I think the findings would be more readily interpretable and less prone to bias.
To avoid potential publication bias, we try to include all available studies whatever design of the trails. After that, sensitivity analyses based on only RCTs were addressed. Fortunately, the conclusions of sensitivity analyses mainly complied with main findings. It may indicate that the observational studies effectively contained the most important inherent nature of included RCTs in genetic structure and that largely improved the predictability and reliability of this meta-analysis.

It is really true as Reviewer suggested that numbers of meta-analyses estimated of effect from non-randomized studies greatly exaggerated the treatment effects. However, the exaggerations were mainly caused by the low qualities of included studies other than meta-analysis itself. In our review, the included non-RCTs were all assessed by The Newcastle-Ottawa Scale (NOS), and all of them were with high quality. In spite of this, a warning-like notice was posted following the sensitivity analysis: ‘Inclusion of the non-randomized trials might inappropriately inflate the power of the analyses, thus the findings on PFS in this analysis should be interpreted with caution.’

2. There is significant heterogeneity associated with the estimates of treatment effect that the authors should pay more consideration to both in the text of the results sections and in the discussion.

Four analyses for BCG plus MMC vs. BCG were addressed; significant heterogeneities were observed in all of them. The added description can be found in page 9-paragraph 2-the last sentence (Resluts) and page 14-paragraph 2-line 8-11 (Discussion).

3. The authors have excluded 19 studies on the basis of their reports being in languages other than English. Whilst it is unclear whether all 19 would have been eligible for inclusion, this needs some consideration. It would seem unreasonable to exclude so many eligible studies for language only reasons. Whilst there is little evidence of publication bias reported (using the Egger test) then I believe this test is of limited use where there are relatively small numbers of trials. It is important to include all eligible studies once identified.

Considering the Reviewer’s suggestion, we reconsidered all non-english papers with assistance from translater. No additional study was identified.

4. There are some paragraphs in the introduction and discussion in particular where the messages of the authors are unclear. These need to be addressed prior to publication.

We have invited a native-English speaker to perform a general careful review on our revised manuscript. We hope the revision would satisfy the need of the readers.

5. It would be useful to see the full search strategies used to identify studies from the major bibliographic databases - perhaps as appendices in the supplementary section. It is unclear whether sensitive evidence based strategies for identifying RCT study
designs (or other study designs) such as those developed by the Cochrane Collaboration have been used.

We conducted the search and study selection according to PRISMA (reference 9). We present the full electronic search strategy (page 4-paragraph 2), so that it could be repeated. Then the process for selecting studies (i.e., screening, eligibility, included in systematic review and meta-analysis) was stated (Fig. S1).

We didn’t care study design when we made searching; and the design was assessed by two authors, respectively, after all available studies were identified. Because non-RCTs are our targets, too.

**Minor essential revisions**

1. It would be useful to see Tables of study characteristics would be better presented as part of the main manuscript rather than as supplementary materials.

   We have made correction according to the Reviewer’s comments.

2. The results section and figure legends refer to figures 1A and B, 2A and B etc whereas the figures are labelled 1,2,3,4 etc

   We are very sorry for the confusing figure numbers. To remaining the quality of picture, we didn’t joint the divisive figure 1-5. Figure 1-2 matched with legend 1; Figure 3-4 matched with legend 2; Figure 5-6 matched with legend 3; Figure 7-8 matched with legend 4; Figure 9-10 matched with legend 5; Figure 11 matched with legend 6.

**Reviewer # 3 (Dr Salvatore siracusano)**

a) at the time is not confirmed Clearly That maintenance BCG is superior as reported by Malmstrom PU Eur Urol 56: 247, 2009.

   In the study, Malmstrom et al showed that BCG maintenance reduced 32% risk of recurrence on BCG compared to MMC (p<0.0001), while there was a 28% risk increase (p=0.006) for BCG in the trials without maintenance. Indirectly, they revealed that BCG maintenance is superior to non-maintenance. However, Badalament RA et al (J Clin Oncol, 5(3):441-449) and Koga et al (Int J Urol 2010, 17(9):759-766) failed to report a significant superiority of BCG maintenance therapy. Of cause, all conclusions cannot ensure eternity. After all, no direct evidence with LOE 1a is available until now. Our meta-analysis provided direct evidence for the superiority of BCG maintenance therapy. We don’t think that our study is better than that by Malmstrom et al. Nevertheless, we promise to keep impartiality when analyzing our data.

b) the problem of the dose should be analyzed according to the recent work appeared in Eur Urol in 2013 by Oddens J and Co-workers with special reference to toxicity and the cost/benefits that the treatment entails.

   Our meta-analysis was addressed earlier than publication of the paper by
Oddens J et al. So, the available data from their study were not included in primary version of our meta-analysis. In the revised version, we identified them.

As Reviewer suggested, Oddens J et al investigated the dosing problem of BCG usage in patients with NMIBC. They compared full dose (FD) with 1/3 dose (1/3D) in terms of recurrence, disease-free rate, progression, presence of CIS, distant metastases and survival status. Their work is well done. We believe that their conclusions can benefit patients and doctors. However, some limitations are also present in this study. Firstly, the methods used for randomization and blinding were not shown, which may decrease the strength. Secondly, when comparing the patient outcomes, the authors didn’t think about the actual duration of BCG.

The results of our meta-analyses weren’t altered after included the data from Oddens J et al. This may suggested the reliability of our study. Of course, large-volume, well-designed RCTs with extensive follow-up are still needed to confirm and update our findings.

We agree with the reviewer that dose should be analyzed with special reference to toxicity and the cost/benefits that the treatment entails. However, it’s still difficult to balance the toxicity and benefits, though many studies (i.e., study by Oddens J et al) have tried to solve the problem. Look from the current evidences, we suggested that all patients with superficial BCa should be encouraged to tolerate BCG maintenance with standard-dose if well tolerated, because patients can benefit from reducing recurrence. As a high-cost illness, the containing costs can be essentially lessened after the number of recurrences reduced.

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’ and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.