Author’s response to reviews

Title: Comparative Efficacy of Six Therapies for Hypopharyngeal and Laryngeal Neoplasms: a Network Meta-analysis

Authors:

Juan Che (zyyanzhenguo@126.com)

Yanlin Wang (zyysht0707@126.com)

Xiaolin Zhang (zyyyyyjm@126.com)

Jun Chen (zhry960034@bzmc.edu)

Version: 2 Date: 25 Jun 2018

Author’s response to reviews:

Editor Comments:

BMC Cancer operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Henry S. Park (Reviewer 2): Thank you for your thoughtful responses to the reviewers' comments, especially adding in Table S1 with the details of your primary outcomes data. I still have one major issue remaining that I do not believe have been adequately addressed. I understand the concept of clinical heterogeneity, but I do not believe that this is sufficiently accounted for when papers focusing completely on early-stage (stage I-II) glottic cancers (for whom the decision is surgery vs. RT) are lumped in with laryngeal/hypopharyngeal cancers of all stages (for locally advanced stages like larynx stage III-IV and hypopharynx stage II-IV, then surgery+RT vs. CCRT vs. ICRT tend to be the choices).

The concept of network meta-analysis is very interesting, but is not compelling enough to make the conclusions that RT alone is an inferior strategy in general (even though compared to TLM or surgery for early-stage glottic it may be just as good) and surgery+RT is a superior strategy in general (since this is not a recommended option for anyone with early-stage glottic cancer).
There are 7 papers included that appear to include only early-stage glottic cancers, and even more than include only locally advanced stages), so why not stratify by this factor and determine the optimal strategy for each of these subgroups? This change would make this paper clinically meaningful, whereas now the conclusions do not make any logical sense for an oncologist to help make clinical decisions.

Reply:

Dear reviewer, thank you very much for your comments. After carefully thinking about your suggestions, we all think that it is very necessary to conduct a subgroup analysis to reach a better comprehension of the efficacy of surgery, radiotherapy (RT), transoral laser microsurgery (TLM), radiotherapy combined with surgery (RT+S), induction chemotherapy radiotherapy (ICRT), and current chemotherapy radiotherapy (CCRT).

For early-stage (stage I-II) laryngeal/hypopharyngeal cancer patients, surgery alone, RT, and TLM are potential choices. While for patients in locally advanced stages like larynx stage III-IV and hypopharynx stage II-IV, surgery, RT, RT+S, ICRT and CCRT tend to be the choice. Among 28 included studies, 7 papers included only early-stage patients, 4 papers included both early-stage and locally advanced stages patients and 17 papers only included locally advanced stages patients (larynx stage III-IV and hypopharynx stage II-IV). For the treatments related to 7 papers included only early-stage patients were limited and the data were insufficient, we decided to add a subgroup analysis of 17 papers only included locally advanced stages patients (larynx stage III-IV and hypopharynx stage II-IV).

In the subgroup analysis, surgery, RT, RT+S, ICRT and CCRT were involved while TLM was not involved. The results of subgroup analysis were shown in Table S2 and Table S3. The network meta-analysis results were shown in Table S2 and SUCRA results were shown in Table S3. In term of 3-OS and 5-OS, RT+S showed a relatively lower HR and better performance when compared with others without statistically significance; in term of 3-DFS and 5-DFS, CCRT and surgery alone had similar performance. In term of 5-OSR, RT+S and surgery alone performed significantly better than RT (HR 0.39, 95% CrI 0.17-0.9; HR 0.31, 95% CrI 0.13-0.74). The SUCRA results shown in Table S3 that RT+S was the probably best treatments as for 3-OS and 5-OS (SUCRA = 0.8403, 0.8082). CCRT may be the best treatments in increasing 3-DFS (0.6947) while ICRT may be the best treatments in increasing 5-DFS (0.7707). Surgery alone ranked the highest in 5-OSR (0.3366). The subgroup analysis of 17 studies reported patients with larynx stage III-IV and hypopharynx stage II-IV showed similar results in term of 3-OS, 5-OS, 3-DFS, 5-DFS except that the results were all not statistically significant. More clinical researches will be required in the future.

We have added Table S2 and Table S3 and also revised the methods, results and discussion parts of manuscript accordingly. All revisions were shown in manuscript with track.
Reply:

Dear reviewer, thank you very much for your comments. The limitation of the sample set is a limitation of our study as we mentioned in discussion part. Sample sizes for some specific comparisons were not big enough. For instance, there were only 23 subjects treated by TLM in 3-DFS and 5-DFS. Therefore, more prospective trials will be required to better understand the efficacy of TLM in 3-DFS and 5-DFS. Sensitivity analysis results were shown in heat plot in Figure 3. The heat plot shows the influence of detaching a pair of direct comparison from the whole NMA analysis, which played a similar role in NMA as sensitivity analysis in pairwise meta-analysis. In consideration of the potential heterogeneity, we added a subgroup analysis of 17 papers only included locally advanced stages patients (larynx stage III-IV and hypopharynx stage II-IV) to reach a better conclusion. We have added Table S2 and Table S3 and also revised the methods, results and discussion parts of manuscript accordingly.