Author's response to reviews

Title: Adjuvant Therapy in the Treatment of Gallbladder Cancer: A Meta-Analysis

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Version: 3
Date: 20 May 2015

Author's response to reviews: see over
Dear editor:

We would like to submit the enclosed manuscript entitled "Adjuvant Therapy in the Treatment of Gallbladder Cancer: A Meta-Analysis", which we wish to be considered for publication in your magazine.

Gallbladder cancer (GBC) is an uncommon cancer but represents the most aggressive type among the biliary tree cancers (BTCs). Complete surgical resection offers the only chance for cure so far. In United States, GBC accounts for approximately 9,760 new cases and 3,370 new deaths per year. Only 10% of patients of GBC present with early-stage disease are considered surgical candidates.

Regarding adjuvant therapy (AT) for GBC, only one phase III multicenter prospective randomized controlled trial (RCT) indicated that patients with gallbladder carcinoma who undergo R1 but not R0 resections may derive some benefit from systemic chemotherapy. However, other trials that had examined the values of AT, including chemotherapy (CT), radiotherapy (RT), and chemoradiotherapy (CRT), were limited by their small numbers of patients or their retrospective and non-randomized study design.

But the benefit of adjuvant therapy for gallbladder cancer (GBC) is unclear as evidenced by conflicting results from various nonrandomized studies while only one phase III multicenter prospective randomized controlled trial (RCT) up to now. There is still no meta-analysis of adjuvant treatments based on the study of retrospective and non-randomized studies except of RCT.

The aim of this study was to conduct a meta-analysis to identify whether AT, i.e. RT, CT, or CRT, could improve OS compared with surgery alone for the entire group or subgroups (node status, margins status, American Joint Committee on Cancer [AJCC] staging, and countries vary) of GBC on the basis of those retrospective and non-randomized data.

We used data from PubMed and Embase published between October 1967 and October 2014. Studies that evaluated AT compared with curative-intent surgery alone for resected GBC were included. Subgroup analyses of benefit based on node status, margins status, and American Joint Committee on Cancer (AJCC) staging were prespecified. Data were weighted and pooled using random-effect modeling. At last, ten retrospective studies involving 3,191 patients were analyzed. There was a nonsignificant improvement in OS with AT compared with surgery alone (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.56–1.03). A significant improvement was observed in OS with chemotherapy (CT) compared with surgery alone (HR, 0.42; 95% CI, 0.22–0.80) by sensitivity analysis. The greatest benefit for AT was also observed in those with R1 disease (HR, 0.33; 95% CI, 0.19–0.59), LN-positive disease (HR, 0.71; 95% CI, 0.63–0.81), and AJCC staging meeting or exceeding tumor Stage II (HR, 0.45; 95% CI, 0.26–0.79), but not in those with LN-negative or R0 disease.

Our results strongly support the use of CT as an AT in GBC. Moreover, patients with node positivity, margin positivity, or non–stage I disease are more likely to benefit from AT. We believe that the results of our meta-analysis will contribute to the use of CT as an AT in patients with GBC, especially those with the high risk factors described above.

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work; there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

What’s more, we have revised my manuscript to include line and page numbers according to the editor’s request and thanks very much.

With thanks for your consideration, I am Bin Wang. My E-mail: qcwangb@163.com.

Sincerely yours,

Bin Wang
Point-by-point description of the changes

Revised our manuscript according to the editors.

1. “Adherence to PRISMA and a completed checklist as an additional file. PRISMA guidelines: In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/about/editorialpolicies#StandardsofReporting), could you please ensure your manuscript reporting adheres to PRISMA guidelines (http://www.prisma-statement.org/) for reporting systematic reviews. This is so your methodology can be fully evaluated and utilised. Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript. We would also ask that you include a completed copy of the PRISMA flowchart for your study as a figure in your manuscript.”
   
   Our study is observational studies and not RCT. So this Meta-analysis of the observational studies was written according to the MOOSE group but not PRISMA statement. So I have included a completed MOOSE checklist as an additional file and also included a completed copy of the PRISMA flowchart for your study as a figure in our manuscript. Thanks very much.

2. “Conclusions section according to instructions for authors”.
   I have revised the conclusions section in light according to instructions for authors. Thanks very much.

3. “Statement in Author’s Contribution confirming that all Authors read and approved the final version”.
   Yes, I have revised authors’ contributions in light according to your advice.

4. “Figure legends for all figures”
   I have listed all the figure legends for all figures. Thanks very much.

5. “Move the table to the end of the main manuscript file.”
   I have moved the table to the end of the main manuscript file. Thanks very much.

Point-by-point response to the concerns of reviewer Robert E Roses:

1. “The manuscript should make the study design, inclusion and exclusion criteria of the evaluated studies explicit in written and table form.”
   I have talked about it in the part “Materials and Methods” of our manuscript. I have also reconfirmed it in “MOOSE checklist”. Thanks very much.

2. “The specifics of treatment when evaluable (type and duration of chemo, radiation dosing) should be provided”.
   I have added these content on table 1 according to your advice. Thanks very much.

3. “The matching of cohorts in the individual studies should be revisited and demographic data pooled to the extent possible to allow for at least a rough assessment of potential confounding. Optimally some effort should be made to address the selection bias inherent in all of the included studies or- at the very least- this should be explicitly discussed as a limitation of the study.”
   In our Meta analysis, the quality of the studies included was various and the observational studies we included had much heterogeneity. Selection bias could distort the relationship between adjuvant therapy and overall survival. Therefore, we
used random-effects modeling, made OS as the only end point and used sensitivity analyses (RT, CT, CRT, node status, margins status, AJCC stage, and multiple country analysis) to address this. I have discussed this as a limitation in our study. Thanks very much.

4. “Reference is made to an estimation of hazard ratio based on figures in individual studies- this sounds methodologically dubious- and should be avoided or clarified.”

Thank you for your beneficial comments. I must clarify that in the all included 10 studies, Kaplan-Meier curve was used to obtain HR and its standard error only to verify the results calculated from the parameters mentioned in our Meta analysis. I have clarified this kind of method and added these content in the part of method and discussion. Thanks very much.

Response to the concerns of reviewer Clancy Jake Clark:

5. “The authors indicated that meta-analyses can be performed using such data but I would argue that retrospective and non-RCTs in a meta-analysis introduce bias (known and unknown). It is difficult for me to overcome this methodologic barrier while reading the manuscript.”

Thank you for your beneficial comments.
GBC is an uncommon cancer and lack of randomized data. It is well known that meta-analysis is mainly based on RCT, but if there were insufficient RCT, non-RCT or retrospective studies may play a complementary role under these circumstances according to the Cochrane systematic review (http://www.cochrane.org/) [11].
Yes, our study do has some limitations. The quality of the studies included was various and the observational studies we included had much heterogeneity. Therefore, we used random-effects modeling, made OS as the only end point and used sensitivity analyses (RT, CT, CRT, node status, margins status, AJCC stage, and multiple country analysis) to address this according to the Cochrane systematic review.
Thanks a lot again.