Author's response to reviews

Title: A Meta-analysis of the Randomized Controlled Trials on Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer

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Version: 3 Date: 28 August 2012

Author's response to reviews: see over
Author's covering letter for initial submission

Title: Benefits of Hyperthermic Intraperitoneal Chemotherapy for Patients with Serosal Invasion in Gastric Cancer: A Meta-Analysis of the Randomized Controlled Trials

Authors:

Version: 1 Date: 28 August 2012

Comments: see over
Dear Sir,

Thank you very much for your comments and suggestions on improving our manuscript “A Meta-analysis of the Randomized Controlled Trials on Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer”. 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 corrections which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’s comments are as follows:

Following reviewer 1’s comments and suggestions:

1. Following Reviewer1, “The selection criteria is RCT studies focusing on advanced gastric cancer patients consisted of macroscopic serosal invasion and without distant metastasis or peritoneal carcinomatosis. Whether the surgery is R0 or R1 resection needs to be addressed in the dataset. For patients with R0 resection but high probability of peritoneal recurrence, HIPC may play an
important role. There is the point for this meta-analysis, but no data is available.” This is a fairly good suggestion. According to your suggestions, we extracted the data of radical surgery plans and peritoneal recurrence, and redressed the table with the additional data cautiously (Table 1). Then we did meta-analysis of the peritoneal dissemination group, and patients in the two trials of this group were all received R0 radical surgery. The result RR value was 0.45 (95%CI 0.28-0.72; P=0.001; fixed-effect model) and showed in Fig 4. This may reveal that for gastric cancer patients (serosal invasion) with R0 radical resection but high probability of peritoneal recurrence, HIPC may play an important role.

Table 1 Basic characteristics of trials included in the present study
2. Follow Reviewer 1, “The limitation of meta-analysis is its dependence on the quality of RCT studies. However, even with the Jadad scoring system, the quality of RCT studies can not be fully accessed. Therefore, it should be noted in the discussion. We
appreciate this kind suggestion very much. According to your suggestions, we studied the evaluation criterion of RCTs again carefully. The Jadad-scale system had some drawbacks not obvious such like the relationship between the score and the degree to which a study was free from bias. However, the modified Jadad-scale with 7 scores used in the study was intuitive and sententious. In the discussion part we added “In spite of all articles included in the studies were RCT and the Jadad-scale was used to assess the investigations, the quality of RCT studies cannot be fully accessed. The bias caused by quality of included articles may be a factor which may influence the result of the study. Although the Jadad-scale is visualized and pellucid, a consummate and exhaustive appraisal procedure is still awaited.”

3. Following Review 1, “The title of the paper may be modified to expose your points clearly.” Thank you for your excellent suggestions. According to your suggestions, we changed the title as “Benefits of Hyperthermic Intraperitoneal Chemotherapy for Patients with Serosal Invasion in Gastric Cancer: A Meta-Analysis of the Randomized Controlled Trials” to expose our points clearly.

Following reviewer 2’s comments and suggestions:
1. Following Reviewer 2, “In the methodology, authors included only randomized controlled trials, and therefore Risk Ratios (RRs) should be the proper effect size rather than Odds Ratios (ORs). Recalculation of RRs is advised.” Thank you for your excellent suggestions. According to your suggestions, we recalculated the RRs. The new results still suggested that HIPC may improve the overall survival rate of patients with gastric cancer. Then we changed some data and words in the abstract, methods, result parts of the manuscript. The changes we made as “Thus, we created two subgroups for analysis: MMC subgroup and 5-FU subgroup. As a result, significant survival improvements were found in the HIPC group compared to the control group, as well as in the MMC subgroup ($RR=0.75$, 95%CI 0.65-0.86; $P<0.00001$; fixed-effect model), and in the 5-FU group ($RR=0.69$, 95%CI 0.52-0.90; $P<0.00001$; fixed-effect model). There was no obvious statistical heterogeneity in the trials. All trials analysis provided similar results ($RR=0.73$, 95%CI 0.64-0.83; $P<0.00001$; fixed-effect model) without statistical heterogeneity ($I^2=0\%$). Four trials [19, 22, 24, 25] utilized systemic chemotherapy after surgery for both the HIPC and control groups. We used additional analysis to obtain results that were identical in the group without systemic chemotherapy ($RR=0.71$, 95%CI 0.59-0.87; $P<0.00001$; fixed-effect model) and the group with systemic chemotherapy ($RR=0.75$, 95%CI
0.63-0.89; \( P < 0.00001 \); fixed-effect model) (Figure 3). Sensitivity analysis was performed without the low quality trials and the results were the same (\( RR = 0.74, 95\% CI \ 0.64-0.86; \ P < 0.00001 \)).” The regulative forest plots were showed as Fig 2 and Fig 3.

**Figure 2** Risk ratios for overall survival rates of all 10 randomized controlled trials.

**Figure 3** Risk ratios for overall survival rate of trials with or without systemic chemotherapy.
2. Following Reviewer 2, “Needs some language corrections before being published.” We appreciate this kind suggestion very much. According to your suggestions, we checked the spelling and grammar of the paper carefully. Then, all corrections were highlighted in blue font.

Thank you for your kind comments and suggestions again.

Please let us know if more explanations will be needed.

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