

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5489-meta-analysis.doc).

**Title:** The combination of chemotherapy and DC-CIK immunotherapy on colon cancer patients in China: a meta-analysis

**Author:** Zheng-Xu Wang, Jun-Xia Cao, Zhi-Ping Liu, Yu-Xin Cui, Chun-Yun Li, Duo Li, Xiao-Yan Zhang, Jin-Long Liu and Jun-Li Li

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5489

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) The first reviewer:

Several comments regarding to the manuscript entitled “The combination of chemotherapy and DC-CIK immunotherapy on colon cancer: a meta-analysis” are listed below:

1. Although the authors claim that this is the first study to evaluate the survival and the effect of the treatment by the extraction and meta-analysis of the pooled data in colon cancer, the summarized data from these trials are all from China. Since different race may contribute to the differential responses in cancer treatment, the authors should modify the article title to reflect the geological area of their statistical summary.

**Answer:** Yes, you are right and we have discussed this point in the part of the limitations of the study (p14-p15). And we also have corrected the title of the paper according to your advice (p1, line 2). Thanks for your useful suggestion. .

2. The conclusion from this manuscript is based on the summaries of other published studies. As the studies with “positive association” normally tend to be published easier than the other ones, analysis of the published results from other studies may contribute the bias to the summary.

**Answer:** We have tried to include all the valid studies in the searchable sources. Therefore, we did not exclude the negative results. However, as you pointed out, most of the published studies showed the positive results. And getting access to unpublished research data is not as easy as saying. Hence we drew our conclusion based on these studies. We discussed the potential bias as part of the limitation of this study in p15 (line 14). Thank you for your concern.

3. Randomization is one of the critical point in statistical analysis. Although those published studies should be the randomized trials, selection process for the

suitable trials to be included for statistical analysis in this manuscript may not be randomized.

**Answer:** We have addressed this point on table 1 and four randomized studies included in our statistical analysis and in addition we selected all the trials provided the sufficient data but not only the suitable trials. And as considering the data extraction process, which was independently conducted by two authors (Jun-Xia Cao and Chun-Yun Li) and disagreement was adjudicated by a third author (Duo Li) after referring back to the original publications that have been described in paper (p6, line 4-13). Thank you.

4. The authors stated in the manuscript (p.8) that some of the clinical information from the trials, such as tumor diameter, performance status, and age were not analyzed due to insufficient data. However, the tumor status, tumor size and patient age are important factors involving in patient survival. Without adjusting these parameters, the conclusion drawn from this manuscript may not be adequate. Also, the authors did not state in the abstract nor in the conclusion that these parameters, such as tumor status, tumor size and patient age, were not adjusted in the statistical summaries they made.

**Answer:** We have amended our description about the patients' information in the second paragraph (p8, line 14-18) and we would like to point out that the information of the tumor diameter and performance status were not adequate, but the stage and the patients age were extracted from every selected paper and listed in table 1. In addition, although some of them are not provided, we actually analyzed the known data by  $\chi^2$  test. We found that the patients' age would impact on the efficacy of DC-CIK cell therapy (data not shown)(p8, line 14-18).

5. Although 7 trials were narrowed down for statistical analysis, the summarized results present in this manuscript for disease-free survival were only from 2 trials. Due to the small population size (94-163 patients), the conclusion the authors made may not be adequate.

**Answer:** Indeed, the analysis for disease free survival was only included in two trials, that is the problem we concerned as well. We therefore discussed it in the second paragraph of the discussion (p13, line 25-26) and the first paragraph of the limitations of the study (p15, line 1-10). Thank you very much.

6. There are several grammatical errors and typos (ex. P.9 "chemontherapy" should be "chemotherapy"; "showsed" should be "showed"; "sumarrized" should be "summarized", "andequite" should be "adequate", Fig.1 "36 vitro experiment" should be "36 in vitro experiments",.....) throughout this manuscript, and some sentences need to be rewritten. The authors should be more careful on the language editing, and English editing is needed for this manuscript.

**Answer:** Thanks indeed. We have corrected the grammatical errors and types (p9, p11 and Figure 1) according to your advice. And we also carefully checked the paper throughout to polish the language and grammar.

(2) The second reviewer:

1.Introduction: you mentioned recognize CSCs in colon cancer, but you not specify which markers are used to identify them.

**Answer: Yes, we have added this content in the part of the introduction (p4, line 20-24). Colon cancer stem-like cells (CSCs) or tumor-initiating cells (TICs) highly expressed the stem cell marker Sox2, POU5F1, LGR5 and ALDH1A1. Thank you.**

2.You based the study in seven trials, and only are comparable the six where they used both DC and CIK.

**Answer: Only six of seven trials were used both DC and CIK, and the other one was used just CIK. We mainly want to compare the combination of chemotherapy and DC-CIK immunotherapy, so although this trial only used the CIK, which combined with chemotherapy, that why we included it and thank you very much.**

(3)The third reviewer:

1.In this manuscript the authors investigated whether autologous DC-CIK therapy is able to improve the therapeutic efficacy of chemotherapy in colon cancer. The authors conducted a systematic review of published papers from several different sources. They found that the combination of the DC-CIK immunotherapy and chemotherapy demonstrates a superiority in prolonging the survival time and enhancing immunological responses. In recent years there has been great interest in cancer immunotherapy, which has the potential of controlling metastatic disease, prolonging time to recurrence, and ultimately serving as a preventive measure. The study is well performed and the manuscript is clear and convincing.

**Answer: Thanks for your kindness.**


2.Minor point: The introduction could be shortened and/or moved to the Discussion section.

**Answer: We have modified and shortened our introduction and discussion according to all advices from the three reviewers. Thank you very much.**

3 References and typesetting were corrected

**Answer: We have corrected our references and typesetting one by one according to the journal format of the World Journal of Gastroenterology.**

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

A handwritten signature in black ink, appearing to read 'Wang Zhongjun', is written on a light blue background. The signature is fluid and cursive, with a horizontal line underneath it.

Best regards,  
Sincerely yours,  
Zheng-Xu Wang, MD, PhD  
Prof. of Biotherapy Center