Peer Review File

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Reviewer A

First, the title needs to indicate the comparison between PTX and PF.
Comment 1: indicate the comparison
Reply 1: We have modified the title as advised.
Changes in the text: Page 1, line 3-5.

Second, the abstract needs some revisions. The background did not present the clinical controversy regarding the efficacy and toxicity of PTX vs. PF and did not indicate why meta-analysis is appropriate to address this issue. The methods did not describe the inclusion criteria according to the PICOS principles, the risk of bias assessment tool of included studies, and main statistical methods for the meta-analysis. The results did not report the sample sizes in the PTX and PF groups, respectively, and the risk of bias of include studies. It is also necessary to report the pooled HR values in addition to P values.

Comment 2: abstract needs some revisions
Reply 2: We have supplemented the inclusion criteria, the risk of bias assessment tool and main statistical methods for the meta-analysis in the abstract as advised.
Changes in the text: see Page 1, line 26-34, Page 2, line 1-20.

Third, the introduction of the main text did not review the clinical controversy regarding the efficacy and toxicity of PTX vs. PF, did not analyze the potential reasons for the controversy, and did not indicate why meta-analysis is appropriate to address this issue. Importantly, meta-analysis is used to address controversy.

Comment 3: introduction needs some revisions
Reply 3: We have supplemented the relevant contents in the introduction as advised.
Changes in the text: see Page 3, line 31-33, Page 4, line 1.

Fourth, in the methodology of the main text, the literature search in PubMed, CNKI, and Google Scholar is far inadequate, which would result in selection bias. In the quality assessment, JADAD has been outdated, which is not commonly used in the methodology of the meta-analysis of RCTs in recent decade. The authors need to use Cochrane RoB 2.0 and describe this instrument in detail. In statistics, please specify the effect size measures in this meta-analysis of the efficacy and toxicity outcomes, describe the funnel plots to observe the publication bias, analyze the influence of the risk of bias on the pooled results, and ensure $P<0.05$ is two-sided.

Comment 4: methodology needs some revisions
Reply 4: Cochrane RoB 2.0 has been used in this meta-analysis and the relevant contents has been supplemented as advised.
Changes in the text: see Page 5, line 23-27.

Finally, please consider to cite the below related papers: 1. Lin W, Huang Y, Zhu L, Li W, Zhao L, Pan X, Lin J, Guo T. Pembrolizumab combined with paclitaxel and platinum as induction therapy for locally advanced esophageal squamous cell carcinoma: a retrospective, single-center, three-arm study. J Gastrointest Oncol 2022;13(6):2758-2768. doi: 10.21037/jgo-22-1196. 2. Liu Y, Yang L, Zhang S, Lin B. The efficacy and safety of concurrent chemoradiotherapy with induction chemotherapy vs. concurrent chemoradiotherapy alone for locally advanced nasopharyngeal carcinoma: a systematic-review and meta-analysis. Transl Cancer Res 2022;11(5):1207-1218. doi: 10.21037/tcr-22-604.

Comment 5: suggested references
Reply 5: The two related papers have been cited in this article.
Changes in the text: see Page 12, line 22-27.

Reviewer B

The question, study sought to resolve some practical issues. But,
Comment 1: the authors searched three data bases, PubMed, CNKI and google scholar. But missed two main data bases such as Cochrane Central and Embase.
Reply1: According to the previous round of your review, we have supplemented the 2022 literature and expanded the data base, and Embase has been covered in our search scope. However, because we do not have an Cochrane Central account, the scope of the search literature does not include this data base.
Changes in the text: Page 4 Line 14-15.

Comment 2: The authors used the MeSH terms such as "esophageal neoplasm" “Chemoradiotherapies”, “Paclitaxel”, and “Docetaxel”. Are the mesh terms sufficient ?. The main comparative chemotherapeutic agents such as platinum and 5 FU are not included in search strategy. This might have affected results of the search.
Reply2: After searching for "Paclitaxel" and "Docetaxel" with MeSH terms, in order to avoid deleting important articles due to the restriction of search terms, two clinicians will read the title and abstract of the articles independently, manually screening, and finally determined the included articles.
Changes in the text: Page 4 Line 17-20.

Comment 3: There are contradictory statements in the results part. In the abstract, it was mentioned that, only 2-year OS is different, but in results section, it is mentioned 1, 2 and 3 year OS are significantly different. The Forest plots are showing only 2 year OS are statistically different

Reply3: Due to the inclusion of new literature during the last round of revisions, some changes have occurred in the results. We forgot to modify the results section, and we are very sorry.
Changes in the text: Page 9 Line 12-15.

Reviewer C

Well written meta-analysis with appropriate inclusion of RCTs. Very interesting topic, and very applicable. I like the contrast between the West and China regarding chemo backbones.

-Any reason why all the studies are all in China, there were no other RCTs outside of China?
Reply 1: We consider that the reason why fluorouracil combined with cisplatin (PF) is preferred for chemotherapy of esophageal cancer in western countries：(1) RTOG8501 and 9405 are the main trials of evidence-based medicine (1A), since these two trials, the PF regimen has been considered as the standard drug regimen for definitive concurrent chemoradiotherapy for esophageal cancer. Although the CROSS study used the paclitaxel carboplatin regimen, however, no head-to-head prospective studies confirmed that paclitaxel combined with platinum (PTX) regimen are superior to previous PF regimen；(2) In Asian countries, esophageal squamous cell carcinoma is more common (>90%), and most oncologists prefer to use taxanes in clinical treatment and trial design. In the CROSS study, the pCR rate of neoadjuvant concurrent chemoradiotherapy for squamous cell carcinoma reached 49%. Therefore, comparing the efficacy of TPX regimen in patients with squamous cell carcinoma is our main research objective.

-Consider discussing whether you would recommend using cisplatin vs. carboplatin and docetaxel vs. paclitaxel, perhaps in the discussion
Reply 2: The chemotherapy of esophageal cancer has always been platinum-based combination, among which cisplatin is the most effective and has the most sufficient evidence. It is used for neoadjuvant chemotherapy, adjuvant chemotherapy, combined concurrent radiotherapy and rescue chemotherapy in advanced cases. Carboplatin did not show any more advantage in the treatment of oesophageal cancer as compared to cisplatin. However, its nephrotoxicity, gastrointestinal reaction, ototoxicity were lower than cisplatin, therefore, carboplatin can be selected as an alternative treatment for clinical cisplatin intolerance.
Paclitaxel is an anti-microtubuler drug and a broad-spectrum anti-tumor drug. It is widely used in the chemotherapy of esophageal cancer. Its toxicity mainly includes allergic reactions, peripheral neurotoxicity, cardiovascular toxicity, hematological toxicity, and gastrointestinal toxicity. Docetaxel is a new type of anti-microtubuler drug following paclitaxel, with a stronger pharmacological effect and an anti-tumor activity 1.3-12 times that of paclitaxel. Its cardiovascular toxicity is lower than that of paclitaxel.

However, its application evidence in esophageal cancer is not as sufficient as paclitaxel and is generally recommended as a second-line therapy.
Changes in the text: Page 13 Line 11-23.

-Consider drawing parallel between squamous esophageal and squamous lung, where the platinum/taxane is also the standard of care chemo-radiation
-Maybe some discussion about immunotherapy checkpoint inhibitor and how we should consider alternate chemo backbones in other chemo-RT trials, as currently most of the studies use 5FU/platinum rather than taxane/platinum.
Reply 3: We have added content related to immunotherapy in the discussion section. In the drug treatment of esophageal cancer, based on the results of KEYNOTE-590 et al., chemotherapy combined with immunotherapy has become a standard recommendation for advanced patients. However, for locally advanced esophageal cancer, the optimal mode and efficacy data of the combination of chemoradotherapy and immunotherapy have not been published yet, and definitive chemoradiotherapy is still the standard treatment，several ongoing Phase III RCTs include KEYNOTE-975, RATIONALE 311 and ESCORT-CRT. The drug regimen chosen by KEYNOTE-975 was PF regimen combined with PD-1 inhibitors, and the other two trials were the study of paclitaxel+carboplatin combined with PD-1 inhibitors. Which regimen has higher synergistic efficacy and lower toxic response when combined with immunotherapy is our focus.
Changes in the text: Page 14 Line 11-22.

Reviewer D
1. Please revise your Title to “a systematic review and meta-analysis”.
Reply 1: We have revised the title as advised.
Changes in the text: Page 1, line 4.

2. Please check all abbreviations in the abstract and main text, such as below in the abstract. All abbreviated terms should be full when they first appear.

28 controversial. This study aimed to systematically evaluate the efficacy and toxicity of
29 PTX and PF in the CCRT of unresectable esophageal cancer.

Reply 2: We have checked all abbreviations in the abstract and main text, and have added full terms as advised in abstract.
Changes in the text: Page 1, line 33-34.

3. Please add citation of references for your previous study.

27 Our previous study found insufficient evidence to confirm the superiority or inferiority
28 of either of these two schemes, especially for esophageal squamous cell carcinoma.

Reply 3: We have added the citation of reference.
Changes in the text: Page 3, line 31.

4. The below two sentences have the same meaning. Please check and revise.

> and two studies (13,16) reported the 5-year OS rate. There was no significant difference between the two regimens in terms of the 1-, 2- and 3-year PTX program (RR =1.17, 95% CI: 0.98–1.38, P=0.075; RR =1.27, 95% CI: 0.97–1.67, P=0.082; RR =1.18, 95% CI: 0.58–2.39, P=0.656, respectively). The combined meta-analysis results also showed that there was no significant statistical difference in 1-, 3-, and 5-year survival rates between the two CCRT regimens. In terms of disease PFS, the combined meta-analysis results showed that the 1-, 2-, and 3-year PFS of two the regimens were not significantly different (P=0.075, 0.082, 0.656, respectively), as shown in Figure 5A-5C.

Reply 4: We have checked and revised the sentences.
Changes in the text: Page 9, line 10-18.

5. Table 1:
Please add citation of references for each study in your Table 1.
Reply 5: We have added the citation of references for each study.
Changes in the text: Page 19, Table 1.

6. Table 2:
1) Please indicate how the data is presented in below variable. For example, range.

Table 2 Meta-analysis results of the short-term therapeutic effects of the PTX and PF regimens in CCRT

Index	Effect model	Test value	Short-term therapeutic effect (%)	
			PTX	PF
Complete remission	Fixed effects model	I^2=0%, P=0.676	14.71–33.33	5.71–32.14

2) The below variable is wrong.

Dose control rate	Fixed effects model

PTX, toxicity of paclitaxel combined with platinum; P

Reply 6: We obtained data from the original text, and the short-term therapeutic effect (%) was the number of people reaching Complete remission / Partial remission / Objective response rate / Disease control rate divided by the total number of samples, so as to obtain the short-term therapeutic effect range of the different studies of the two regimens.
Changes in the text: Page 21, Table 2.