

Peer Review File

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First Round Peer Review

Reviewer A

Comment 1. This is a meta-analysis article in which most of the analyzed papers are cohorts without a control group which could be a bias, however, it does not detract from the importance of the work. As a suggestion it should be reinforced in the discussion.

Reply: Thank you very much for this important comment. A total of 9 literatures were included in this study, Table 1 listed the characteristics of the included studies. There are some limitations to this systematic review (Please see the revised manuscript at the page 9, line 185-189, revised portion are marked in red in the paper).

Comment 2. I would like to know if patients who undergone esophagectomy were submitted to radiotherapy or chemotherapy in any time of the treatment. If so, those patients were excluded from the analysis?

Reply: Thank you very much for this important comment. A total of 9 cohort studies are therapy for clinical T1a/T1b N0M0 esophageal cancer. Additional radical esophagectomy after endoscopic resection (ER), no postoperative adjuvant therapy was performed in selected patients undergoing esophageal surgery.

Comment 3. Almost all the studies were conducted in Asia. The population's physical characteristic is different from the European or American patient, which may impair the external validation of the work. Which reason the authors attribute the lack or non-inclusion of works from other continents?

Reply: We are appreciative of the reviewer's suggestion. Indeed, through a comprehensive and systematic literature search of the electronic database, randomized and retrospective cohort studies about early-stage esophageal cancer is relatively few in Europe and America or other continents.

Comment 4. Biological behavior of squamous Cell Cancer is different from adenocarcinoma. It is not clear in the methodology and conclusion whether the authors analyzed only squamous Cell Cancer or adenocarcinoma was included.

Reply: Thank you for your rigorous consideration, we totally understand yours concern. Current, for early-stage esophageal cancer, whether squamous cell carcinoma (SCC) or adenocarcinoma, most studies are retrospective, single-institution design, and small number of patients. Therefore, this study does not conduct further subgroup analysis on the pathology.

Comment 5. How the cancer staging was done before the decision to local resection or esophagectomy?

Reply: Thank you for pointing out this problem in the manuscript. All included patients had cT diagnosed with endoscopic resection (ER); cN0 diagnosed using endoscopic ultrasonography (EUS) and

computed tomography (CT) before ER. Clinical cancer stage was determined according to International Union Against Cancer.

Reviewer B

Comment 1. English editing is recommended, including the conclusions.

Reply: Thanks for your suggestions. We feel sorry for our poor writings. therefore, we accept the standard English language editing from the editorial office. And we hope the revised manuscript could be acceptable for you.

Comment 2. The authors do not provide the reader with any info about CRT toxicity and surgical morbidity. Without these data, I do not feel that the reader can clearly understand which is the best treatment option in these patients.

Reply: Thank you for pointing out this problem in the manuscript. A total of 9 cohort studies mainly focus on the long-term outcomes of additional treatment, such as OS、RFS; for short-term outcomes of CRT toxicity and surgical morbidity, A total of 9 cohort studies did not provide detailed data and descriptions. Even so, we fully agree with your comment. Thank you for your comments and suggestion concerning our manuscript again. We will continue to focus on a larger number of patients enrolled from multiple institutions studies in the future.

Reviewer C

Comment 1. Although methodologically weak (e.g. small number of patients for comparing DFS between the two groups) it is a well written article with great interest and worth to be published.

Reply: We thank the reviewer for reading our paper carefully and giving the above positive comments.

Reviewer D

Comment 1. We have already known that esophagesctomy for ESEC is superior to enoscopic resection plus CRT. In addition. Adenoca is the majority of this study, it is not appropriate comparison. The authors have to focus on SCC only.

Reply: We thank you for the critical comments and helpful suggestions. We have taken all these comments and suggestion into account, the 9 articles included in this study, 6 articles are from Japan, most are squamous cell carcinoma (SCC), relatively few in Europe and America. Thank you for your comments and suggestion concerning our manuscript again. We will continue to focus on a larger number of patients enrolled from multiple institutions studies in the future, especially against the SCC.

Second Round Peer Review

Comment 1. This study is the problematic methodology of this meta-analysis. In the terminology of clinical research, there are no “randomized or non-randomized cohort studies” or “randomized cohort studies”. The risk of bias is equivalent to quality assessment, but the authors wrongly regarded risk of bias as publication bias. The effect size measure in this meat-analysis, OR, is also problematic since in cohort studies, the effect size measure is HR.

Reply: Thank you very much for this important comment. As you said, there is no random or non-random way to express cohort studies, which we have corrected in the article. Recommendations and decisions that rely on systematic reviews and meta-analysis may be particularly influenced by selective dissemination results, as recommendations will be based on biased research samples. This study is no exception. Conclusions obtained from meta-analysis are easily affected by publication bias. Therefore, Funnel plots tests and Egger's and Begg's tests were used to measure publication risk. As for odds ratio (OR), it is mainly used in retrospective case-control studies. The correlation between event results and a certain factor can be established by acquiring the data of case group and control group, so as to study the correlation between the two. We also compared the effects of post-ER CRT versus esophagectomy on esophageal cancer recurrence and metastasis, which was assessed using an OR value. Hazard Ratio (HR) was used to evaluate the effects of CRT and esophagectomy on overall survival and disease-free survival of patients with esophageal cancer after ER. The reason for your trouble is that we did not describe it clearly in the manuscript, so we further modified the manuscript. We hope that our explanations and changes can dispel your doubts. (Please see the revised manuscript at the page 5, line 101-107; and page 5-6, line 109-111, revised portion are marked in red in the paper).

Comment 2.

2.1 the abstract needs substantial revisions. In the background, the authors did not present the controversy regarding the long-term outcomes when comparing CRT with esophagectomy.

Reply: Thank you very much for this important comment. We have reviewed the literature and made additional supplement. (Please see the revised manuscript at the page 3, line 56-58, revised portion are marked in red in the paper).

2.2 In the methods, the inclusion criteria should be briefly constructed based on the PICOS principle and please describe the data extraction for effect sizes or outcomes.

Reply: We are appreciative of the reviewer's suggestion. According to the PICOS principle, we have made further improvements to the inclusion criteria; made a supplementary description for data extraction (Please see the revised manuscript at the page 4, line 75-79; and page 5, line 92-95, revised portion are marked in red in the paper).

2.3 The risk of bias assessments for RCTs and retrospective cohort studies should be described separately. In the results, please report the risk of bias of included studies and indicated whether the OR values were adjusted. The conclusion needs comments for the clinical implications of the findings.

Reply: Thank you very much for this important comment. We have made a supplementary description for quality Assessment and Sensitivity analysis and evaluation of publication bias. (Please see the revised manuscript at the page 5, line 96-98; and page 7, line 139-144, revised portion are marked in red in the paper).

Comment 3. the introduction of the main text is poor, the authors need to describe the controversy regarding the comparative long-term outcomes between CRT and esophagectomy, analyze the potential reasons, and clearly explain why a meta-analysis can solve this

controversy. The definition of long-term survival should be provided and explain why this outcome is important clinically.

Reply: We are appreciative of the reviewer's suggestion. We have made a supplementary description for introduction and definition of long-term survival. (Please see the revised manuscript at the page 3, line 56-65; and page 4-5, line 88-90, revised portion are marked in red in the paper).

As for the long-term survival, which usually used to evaluate the long-term efficacy of tumor treatment in clinical practice, which has its certain scientific nature, mainly because most tumors after comprehensive treatment, some patients will relapse and metastasis or drug resistance progression or even death. If there is no recurrence and metastasis 5 years after treatment, the risk and probability of recurrence is very low, which can be considered as clinical cure (but does not mean that there is no recurrence risk at all). Therefore, long-term survival rate is commonly used to evaluate the efficacy of tumor treatment, and it is also convenient to compare the differences in treatment efficacy between different countries and regions.

Comment 4.

4.1 in the methodology of the main text, please describe the inclusion criteria strictly according to the PICOS principle, in particular the clinical research design of studies to be included. Please also clearly describe the data extraction for survival outcomes and effect size measures, in particular the definition of long-term outcomes and whether the effect size measures were adjusted.

Reply: We are appreciative of the reviewer's suggestion. According to the PICOS principle, we have made further improvements to the inclusion criteria; made a supplementary description for data extraction (Please see the revised manuscript at the page 4, line 75-79; and page 5, line 92-95, revised portion are marked in red in the paper).

4.2The risk of bias assessment tools for RCTs and retrospective cohort studies should be described separately and in detail.

Reply: Thank you very much for this important comment. We have made a supplementary description for quality Assessment and Sensitivity analysis and evaluation of publication bias. (Please see the revised manuscript at the page 5, line 96-98; and page 7, line 139-144, revised portion are marked in red in the paper).

4.3 In statistics, please explain the pooling of OR and HR values, which cannot be pooled together. Please describe the test of sources of heterogeneity such as subgroup analysis. Please describe the P value for statistical significance.

Reply: Thank you for your rigorous consideration, we totally understand yours concern. We have made a supplementary description for Statistical Analysis. (Please see the revised manuscript at the page 5-6, line 108-114, revised portion are marked in red in the paper).

Thank you again for your positive comments on our manuscript. JTD is an influential journal which aims to improve our understanding of cancer prevention and treatment. from all the papers published in your journal, readers have been learning a lot. Hopefully, we could have our article been considered of publication in your journal.