

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-420>

### Reviewer A

In this review, Ke et al. try to summary the surgical intervention after neoadjuvant therapy in EC. The critical view of the research area in some sections is poor. In detail, please find the following concerns:

1. In many sections, the author only summary the reported findings, lack of depth in depicting their own findings or opinions.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 19, line 295-301 and Page 11, line 348-351 and Page 13, line 431-433 and Page 15, line 494-497).

2. The author should highlight the differences between ESCC and EAC during the summary.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, In the conclusion, we have modified our text as advised (see Page 16, line 524-525).

3. The references should be updated.

**Reply:** we have modified our text as advised (see Page 18, line 584-585 and Page 20, line 656-658)

4. The author should include a 'Future Expectations/Perspectives' part to present their own opinions.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, In the Future Expectations, we have modified our text as advised (see Page 16-17, line 533-538).

### Reviewer B

This paper presents a narrative review of the comprehensive content of esophageal cancer treatment. The authors review preoperative treatment of esophageal cancer, surgical timing after preoperative treatment, outcomes by procedure, and management of postoperative complications. Key findings show the recommendation of chemoradiation for preoperative treatment and total gastrectomy for esophagogastric junction adenocarcinoma with Siewert type II. This manuscript requires major revision as listed below.

Major comments:

1. There is a lack of review articles comparing outcomes between preoperative chemotherapy plus surgery and preoperative chemoradiotherapy plus surgery, and none of the randomized controlled trials from the US or Europe showed a significant difference in 5-year survival rates [1-3]. In addition, severe adverse events are significantly more common with preoperative chemoradiotherapy [4]. Moreover, in a three-arm study (JCOG1109 NExT study) of locally advanced esophageal squamous cell carcinomas at stages II and III, preoperative DCF significantly prolonged overall survival compared with preoperative CF. On the other hand,

preoperative CF-RT did not improve overall survival compared with preoperative CF, indicating that preoperative DCF is the new standard of preoperative treatment for this patient population [5]. The review article needs to be revised to include the above information.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, In Neoadjuvant chemoradiotherapy, we have modified our text as advised (see Page 6, line 178-183). In complications, we have modified our text as advised (see Page 15, line 484-486). In Neoadjuvant chemotherapy, we have modified our text as advised (see Page 5, line 149-152).

References:

- 1) Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, Barbour AP, Gotley DC, Smithers BM. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer*. 2011 Feb;47(3):354-60. doi: 10.1016/j.ejca.2010.09.009. PMID: 21084184.
- 2) von Döbeln GA, Klevebro F, Jacobsen AB, Johannessen HO, Nielsen NH, Johnsen G, Hatlevoll I, Glenjen NI, Friesland S, Lundell L, Yu J, Nilsson M. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. *Dis Esophagus*. 2019 Feb 1;32(2). doi: 10.1093/dote/doy078. PMID: 30137281.
- 3) Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, Wilke H, Budach W. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. *Eur J Cancer*. 2017 Aug;81:183-190. doi: 10.1016/j.ejca.2017.04.027. PMID: 28628843.
- 4) Klevebro F, Johnsen G, Johnson E, Viste A, Myrnäs T, Szabo E, Jacobsen AB, Friesland S, Tsai JA, Persson S, Lindblad M, Lundell L, Nilsson M. Morbidity and mortality after surgery for cancer of the oesophagus and gastro-oesophageal junction: A randomized clinical trial of neoadjuvant chemotherapy vs. neoadjuvant chemoradiation. *Eur J Surg Oncol*. 2015 Jul;41(7):920-6. doi: 10.1016/j.ejso.2015.03.226. Epub 2015 Apr 8. PMID: 25908010.
- 5) Kato K, et al: A randomized controlled phase III trial comparing two chemotherapy regimens and chemoradiotherapy regimens as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study. *J Clin Oncol*. 2022;40(4\_suppl):238.

2. Two articles from China were reviewed regarding the indicated procedure for Siewert type II adenocarcinoma of the esophagogastric junction, with the key findings stating that total gastrectomy is the most useful. However, both articles were small reports from a single institution, and the level of evidence was considered very low. Although no conclusion was reached regarding the necessity of mediastinal dissection according to the length of esophageal invasion, it is necessary to review the frequency of mediastinal lymph node metastasis according to the length of esophageal invasion and to discuss the right thoracic approach [6].

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 12, line 386-391).

Reference:

- 6) Kurokawa Y, Takeuchi H, Doki Y, Mine S, Terashima M, Yasuda T, Yoshida K, Daiko H, Sakuramoto S, Yoshikawa T, Kunisaki C, Seto Y, Tamura S, Shimokawa T, Sano T, Kitagawa

Y. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. *Ann Surg.* 2021 Jul 1;274(1):120-127. doi: 10.1097/SLA.0000000000003499. PMID: 31404008.

In conclusion, while the manuscript presents an interesting and potentially valuable review of esophageal cancer treatment, it requires substantial revisions to address the concerns raised above. We believe that by incorporating the suggested changes and providing more robust evidence, this manuscript could make a significant contribution to the field. We look forward to receiving a revised version of the manuscript for further consideration.

### **Reviewer C**

1. There is an error in the subtitle. Page 10, Line 328-329.

**Reply:** we have modified our text as advised (see Page 11, line 356-357).

2. The significance of this paper is not expound sufficiently. The authors need to highlight this paper's innovative contributions.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 16-17, line 533-538).

### **Reviewer D**

The authors reviewed the neoadjuvant therapy and timing of surgical intervention for esophageal cancer, which is close to the clinical practice and hot spots. The content of the review has certain reference value for clinical practice. However, it is inevitable that the content is not exact or accurate. Please revise and then can be consider publication thereafter.

1. Line 31-33: Compared with chemotherapy, chemoradiotherapy can improve overall survival (OS) and pathologic complete response (PCR) and reduce the incidence of adverse events. However, there were several important clinical trials indicate the OS benefit on Neoadjuvant chemotherapy.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 1-2, line 33-34).

2. Line 37-38: Chemoinmunotherapy is a new mode of treatment, in addition, the best surgical method for Siewert type II adenocarcinoma is transabdominal total gastrectomy. This statement is clearly false, and neither international guidelines, consensus nor Chinese consensus have confirmed the conclusion of the lack of clinical evidence as much as the authors' team

**Reply:** we have modified our text as advised(see Page 2, line38-39).

3. It is not difficult to see from the methodology and conclusion of the abstract that the authors ignored the option of "neoadjuvant chemotherapy" in the search term. The conclusions given

at the same time also do not take into account the affirmation of the role of systemic chemotherapy in the Neo-AEGIS study and the JOCG1109 study.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 2, line 56-57) , And these two studies were added(see Page 5, line 142-143 and line 149-152).

4. Keywords did not contain any information about the timing of surgery.

**Reply:** we have modified our text as advised (see Page 3, line83-84).

5. Line 88-90: The authors describe global data, whereas the references cite Chinese data.

**Reply:** we have modified our text as advised (see Page 17-18, line569-571).

6. Line 99-100: I do not know how the authors obtained the postoperative mortality rate, which is both inaccurate and subversive. In addition, the authors cited a review (6) that described surgical survival in detail in the full text of the review, but the authors cited incorrect data.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 3-4, line100-101), meanwhile, we also have modified surgical survival(see Page 4, line105 )

7. Line 101: please add the reference.

**Reply:** we have modified our text as advised (see Page 25, line827-828).

8. Line 105: did the mention of "traditional chemoradiotherapy" was definitive CRT?

**Reply:** Thank you for the reviewers' comments concerning our manuscript. The conventional chemoradiotherapy we refer to here is definitive chemoradiotherapy.

9. Why is the methodology in the main text quite different from that mentioned in the abstract?

**Reply:** Thank you for the reviewers' comments concerning our manuscript. We found that the keywords used in the two parts were different, in order to find more meaningful articles.

10. Although the authors mentioned immunotherapy several times, it is not "mainly" treatment, and no guideline considers it as evidence-based medicine at this stage.

**Reply:** Thank you for the reviewers' comments concerning our manuscript. Although chemoradiotherapy is still the standard treatment for esophageal cancer at present, more patients will benefit from immunotherapy in the future as more clinical trials are conducted safely. We hope this article can provide some reference basis.

11. In the introduction of EC neoadjuvant chemotherapy, the authors listed some studies, including meta-analysis. Unfortunately, many important studies were missed.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 5, line142-143 and line 149-152).

12. CAOSS trial was probably a clerical error.

**Reply:** we have modified our text as advised (see Page 6, line 169).

13. The retrospective study by Han et al. (22). This is not a retrospective study, but a meta-analysis.

**Reply:** we have modified our text as advised (see Page 6, line 183).

14. Immune-related therapy has risen to first-line rather than second-line treatment.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 7, line 207-208 and Page 20, line 656-658).

15. The authors "Summary: Neoadjuvant therapy includes NCT, NCRT, immunotherapy, and targeted therapy", however, we did not see any phase 3 trials evidence for the use of targeted agents in neoadjuvant therapy, especially in ESCC.

**Reply:** Thank you for the reviewers' comments concerning our manuscript. We believe that as a new treatment, the reliability of neoadjuvant targeting needs to be verified. The current study is still in phase II clinical trials due to many factors. We believe that with the deepening of research and scientific progress, more trials will be carried out.

16. In any case, the content of neoadjuvant and multimodality therapy is too cumbersome and deviated from the topic.

**Reply:** Thank you for the reviewers' comments concerning our manuscript. Our aim is to review the key published studies and conclude that neoadjuvant multimodal therapy is the future direction of treatment.

17. If Sweet's procedure is to be introduced, I think the transcervical and mediastinal approach should also be mentioned. In addition, it is also necessary to clarify the concept of minimally invasive surgery including robot-assisted surgery, which is not a parallel concept.

**Reply:** Thank you for the reviewers' comments concerning our manuscript, we have modified our text as advised (see Page 12, line 391-394 and Page 13 line 413-414 ).

The language in the text still leaves room for refinement.