Peer Review File

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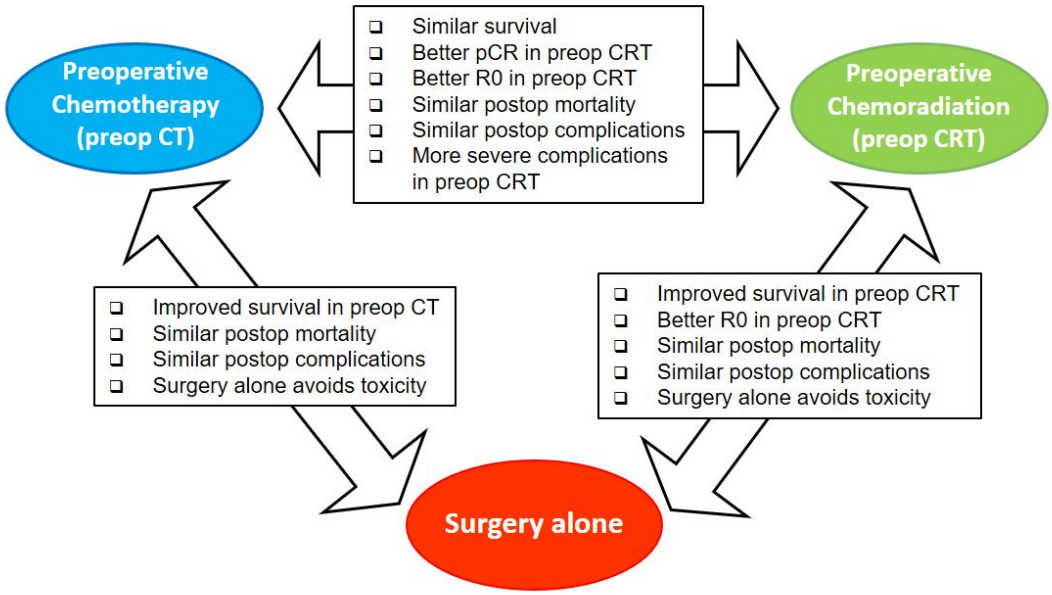
Reviewer A

The presented work is a well-crafted and comprehensive manuscript which effectively aggregates the available evidence on perioperative treatment strategies for gastroesophageal junction cancer. It stands out as it focuses on clinical evidence derived from randomized prospective trials and hence avoids the pitfalls and biases associated with data arising from retrospective studies. The authors pursue a well-designed approach in analyzing 5 modality-informed groups (A-E) to provide the reader with both aggregated and granular study outcomes. The manuscript leverages an innovative approach to impute missing data to encompass a broad range of RCTs which the authors transparently present to the reader. There are a few points the authors should include to improve on the quality of the review.

A.1 Reviewer comment: I would suggest to add a conceptual figure which outlines the different perioperative treatment approaches (CT vs. CRT vs. surgery alone) including potential advantages and challenges and including some key references for each approach



Reply A.1: Thank you for your comment. We have created a figure that shows the comparison of the three treatment approaches (preoperative CT, preoperative CRT, and surgery alone).

Change in the text A.1: We have made the above Figure 2, which will be submitted as a separate figure file. We have added the figure 2 title "Summary of preoperative chemotherapy, preoperative chemoradiation, and surgery alone" in the "JGO submission draft" file in the "FIGURE LEGEND/TITLE" section. We have also added "Finally, Figure 2 conceptually summarizes the advantages and challenges of preoperative CT, preoperative CRT, and surgery alone based on results presented here." in the text (page 12, line 270-272). Additionally, below is the list of the key references we used in this figure 2 to summarize each approach. These are

all from the references we included in our systematic review.

1. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715-21.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074-84.
4. von Döbeln GA, Klevebro F, Jacobsen AB, et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. Dis Esophagus. 2019;32(2).
5. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851-6.

A.2 Reviewer comment: I would suggest including a section in the introduction on some of the potential molecular reasons for chemo- and/or radiosensitivity as well as some reference to recent work on trying to classify GEJ tumors using genomic, transcriptomic and epigenetic approaches (DOI: 10.18632/oncotarget.22216 and DOI: 10.3390/cancers12051208) and which implications this might have for treatment selection

Reply A.2: Thank you for your suggestion to add some molecular background on GEJ tumors. We would like to incorporate those suggestions in our manuscript.

Change in the text A.2: We have added some comments in the introduction about DNA methylation signatures, mRNA and microRNA and its future use as follows (see page 5, line 104-106 of "JGO submission draft" file): Recently, there has been also better molecular and genetic characterization of GEJ tumors over traditional anatomical classification, namely unique DNA methylation signatures, mRNA and microRNA expression patterns..

A.3 Reviewer comment: I would encourage the authors to reference some of the ongoing head-to-head RCTs which aim to specifically address preoperative CT vs. CRT like our randomized RACE trial DOI: 10.1186/s12885-020-07388-x (NCT04375605)

Reply A.3: Thank you for your suggestion. We would like to incorporate this ongoing trial to our manuscript. Besides the RACE trial, the following ongoing trials have been included in the main text from before (page 14, line 318-321): NCT03604991, NCT04592913, NCT02509286.

Change in the text A.3: We have added some comments about the RACE trial as follows (see page 15, line 335-338 of "JGO submission draft"): Another ongoing RCT is the RACE trial (NCT04375605) which compares the preoperative FLOT (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) to the preoperative FLOT followed by radiochemotherapy (5-fluorouracil/oxaliplatin and radiation).

Reviewer B

The authors have performed a very thorough and methodologically sound meta analysis on one of the main research subjects in esophagi gastric cancer treatment. The methodology is described well. I do have some comments on the chosen inclusion period of papers.

B.1 Reviewer comment: the authors describe they have reviewed journals from 1946. It is

probably not very relevant to include older papers into this analysis as so much has changed in diagnostic and treatment modalities, as well as toxicity and complications of treatment. Please include relevant studies from for example 2000 only.

Reply B.1: We greatly appreciate review B's comment about a potential limitation of our review. We conducted our literature search to include articles published from 1946 so that we can identify as many relevant articles as possible. As a result, we found and included two articles published before 2000 in this systematic review (Walsh 1996 and Zhang 1998), and our dataset includes patients no earlier than 1978, with most patients represented from 1990s to 2000s. After discussing with other authors, we felt they should still be included because their neoadjuvant treatments are still comparable to the recent studies (Walsh 1996 performed cisplatin, 5-FU and radiation, and Zhang 1998 performed radiation for neoadjuvant treatment respectively). However, we recognize your concerns and have added the surgical advancements over time as a potential limitation in our review and have added a statement about this in the discussion section.

In our re-examination of these smaller studies, we noticed minor numerical errors which we have corrected. They do not change the statistical analysis presented.

Change in the text B.1: We have added the following statement in the limitation paragraph (page 16, line 358-363): Lastly, we have performed a comprehensive review by including studies for the past three decades from the 1990s. As there has been advancement in surgical intervention and supportive care for chemotherapy and radiation treatment over time, the datasets between the older and newer trials may be heterogeneous. We encourage other interested researchers to repeat similar analyses, especially with the results release of several upcoming randomized controlled trials.

B.2 Reviewer comment: in addition to this the inclusion ends in 2000 and is to this date 1,5 year old. Please also include relevant recent papers. Some are discussed in the discussion section but could be included in the analysis.

Reply B.2: Besides the RACE trial that was mentioned by the review A, we have identified two other studies relevant to our systematic review.

The Neo-AEGIS trial (NCT01726452) released only preliminary results May 2021. This study conducted neoadjuvant CROSS versus MAGIC (or FLOT) regimen in GEJ tumors. Some of the outcomes were reported at the ASCO Annual meeting as an abstract, which is the reason we did not include as one of the study for systematic review but we included its preliminary result in the discussion section due to clinical importance (see page 15, line 324-333).

The other study is PMID: 34858829. This study conducted by Tian et al. reports the result of neoadjuvant CRT versus surgery alone in GEJ tumors patients. The pCR was superior in the neoadjuvant CRT 97.0% compared to 87.7% in the surgery only group. The OS times was 39 months and better in the noadjuvant CRT compared to 30 months in the surgery only group. This study would meet our inclusion criteria for our systematic review, though we did not include it given that it was just published recently in November 2021, outside our pre-specified window.

We agree these trials could be added to a future systematic review once the final results are

publicly available, but we do not believe they would change our findings here. We would be more than happy to conduct such updated systematic review at a later time. We thought because they were recently available, that at least a discussion was important. We have noted in our limitation section as well.

Change in the text B.2: we have added the following statement in the discussion section (page15, line 335-343): Another ongoing RCT is the RACE trial (NCT04375605) which compares the preoperative FLOT (5-fluorouracil/folinic acid/oxaliplatin/docetaxel) to the preoperative FLOT followed by radiochemotherapy (5-fluorouracil/oxaliplatin and radiation). Additionally, Tian et al. recently published a study that compared neoadjuvant CRT versus surgery alone for GEJ tumors. The pCR was 97.0% vs. 87.7% ($p<0.05$) and the OS times was 39 months vs. 30 months ($p=0.01$) in the neoadjuvant CRT vs. surgery only, which is consistent with our result. Once the final results of the ongoing trials are available, an updated analysis including all of the relevant studies is warranted.