Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-27

Reviewer A

Comment 1: I commend the authors on a well-written review article. It provides a review of the existing literature in perioperative treatment modalities and summarises these well with landmark and recently published studies.

Reply 1: Thank you.

Changes in the text: Please see below.

Few amendments:

Comment 2: 1) Inclusion of Countries who are involved in trials, particularly in table 5.

Reply 2: We have added the countries involved to improve the quality of the tables. To this end, a new column titled "Study Sites" was added to Tables 1-5.

Changes in the text: Please see the revised Tables 1-5 document with a new column titled "Study Sites" added to Tables 1-5.

Comment 3: 2) Inclusion of Surgical approach, although this strictly not within the context of the title of this study, I feel a short paragraph on minimally invasive surgery and impact on postoperative outcomes is important to mention.

Reply 3: We have added a new section titled "Surgical Approach" and a short paragraph reviewing minimally invasive surgery.

Changes in the text: Please see page 17, lines 393-407 with track changes

Comment 4: Very similar articles already in the literature therefore question further this article would add much more.

Reply 4: We appreciate your concern regarding the potential redundancy of this article. While we do agree that other articles reviewing peri-operative approaches in esophageal cancer exist, we believe our article is unique such that it not only takes a deep dive into historic trials supporting our current standard of care but also provides readers recent data presented as recently as January 2023 at GI ASCO 2023. Our paper also includes a discussion on forward-thinking approaches, such as the use of ctDNA, which is emerging as an important tool in gastrointestinal cancers and is not as often referenced in other reviews. We also hope our tables, which include neoadjuvant chemotherapy, peri-operative chemotherapy, neoadjuvant/definitive chemoradiation, and adjuvant trials, can serve as quick reference guides for medical oncologists, radiation oncologists and surgeons in understanding the trial populations and high-level

outcomes results. Our table of ongoing immunotherapy trials with estimated trial completion dates will also help readers understand where the clinical research is today and when we can expect the results of some eagerly anticipated trial data. We added some recent updates in the discussion that were not included in the first draft, including a recent 2022 meta-analysis of neoadjuvant immunotherapy, new data from a phase 2 trial using immunotherapy in MSI-H GEJ/gastric cancers (INFINITY) presented at GI ASCO 2023 in January 2023, and updated results from the Neo-Aegis also reported at GI ASCO 2023.

Changes in the text: Please see page 11, lines 219-221, page 15, lines 333-336, and 346-348.

Reviewer B

Comment 1: This is a well-written, comprehensive review of the literature addressing all of the potential therapeutic approaches for resectable esophageal cancer. The authors nicely summarize the data, provide some analysis, and identify new directions, including the emerging data on ctDNA. I have no additional comments.

Reply 1: Thank you.

Changes in the text: None.

Reviewer C

Comment 1: Thank you to the authors for a thorough literature review on a very complex disease process. The changing data over the last few decades calls for an organized summary such as this. The authors use various headings to organize the data: preop chemo, periop chemo, neoadjuvant CRT, neoadjuvant CRT vs neoadjuvant or periop chemo, definitive chemo and salvage esophagectomy, sequential preop chemo and CRT, PET-directed therapy, adjuvant approaches after neoadjuvant CRT, adjuvant approaches in periop therapy, adjuvant approaches without neoadjuvant therapy, ctDNA, and periop targeted therapy. Some suggested revisions are outlined but overall this manuscript will be a worthy contribution to the literature.

Reply 1: Thank you for your expertise and for reviewing our manuscript so carefully. We have addressed each of your concerns and recommendations with care.

Changes in the text: Please see below.

Comment 2: Preoperative and neoadjuvant are used interchangeableably throughout the paper. With the number of abbreviations involved in the text, consider using uniform language.

Reply 2: We have changed the term “preoperative” when used to “neoadjuvant” throughout the text. We ensured neoadjuvant chemotherapy was abbreviated as “nCTX” at the first instance and used consistently in the text. We also ensured neoadjuvant chemoradiation was abbreviated as “nCRT” and used consistently in the text. While abbreviations were made in the body text,

we did not abbreviate these in the subsection titles. We modified some sentences to improve brevity and avoid redundancy in using “neoadjuvant” and “preoperative.”

Changes in the text: We have modified the text as described. Please note the pages and lines here reflect the page number and lines of the most recent revision, where the order of certain sections was changed based on Reviewer C Comment 3 (next). Please see the changes on:

-page 6, lines 97, 98, 101

-page 7, line 135

-page 8, lines 150, 162

-page 12, line 262

-page 13, line 279

-page 15, line 344

-page 17, lines 391

-page 18, lines 412, 415

Comment 3: The current headings can seem unclear and disordered to the flow of the text. Consider organizing the body within the topics of neoadjuvant tx, perioperative tx, adjuvant tx, and definitive tx, and others; and discuss the use of chemo, rads, and targeted therapies within the specified time frame.

Reply 3: Thank you for this comment, and we appreciate your suggestion to better organize this paper. Under MAIN BODY, we have reorganized the discussion order and headings under the following Major Headings and Subheadings:

- NEOADJUVANT TREATMENT
    - Neoadjuvant Chemotherapy
    - Neoadjuvant Plus Adjuvant Chemotherapy
    - Neoadjuvant Chemoradiation
    - Chemoradiation versus Chemotherapy
    - Sequential Chemotherapy and Chemoradiation
    - PET-Guided Neoadjuvant Therapy
    - Role of Targeted Therapies
- DEFINITIVE CHEMORADIATION
- SURGICAL APPROACH
- ADJUVANT THERAPY
    - Following Neoadjuvant Chemoradiation

    - Following Neoadjuvant Chemotherapy
    - Following Upfront Surgery
- POTENTIAL ROLE OF CTDNA
- SUMMARY

We felt this was the best way to organize the trials reviewed under the Neoadjuvant and Adjuvant Settings based on your suggestion and the overarching trial designs. The studies evaluating adjuvant therapy were often based on specific populations after specified neoadjuvant therapies (or lack of), and the FDA approvals for some adjuvant therapy (for example, Checkmate 577) are contingent on what neoadjuvant therapy the patient received. In general, we felt the discussion of adjuvant therapy largely relies on the neoadjuvant approach, and this is how the treatment options are also presented in the NCCN guidelines. As such, the adjuvant discussion was organized this way. For neoadjuvant approaches, we renamed some of the headings and reordered the renamed sub-sections; for instance, we moved up the targeted therapy discussion. We also separated Definitive Chemoradiation as a separate major heading, as suggested.

Changes in text: Subsections/headings reworded and re-ordered as above starting on page 6 under MAIN BODY.

Comment 4: 3. The sentence in line 264 requires references.

Reply 4: We have cited and updated the references in this paragraph. Kelsen D, JO 2007; Ott K, JCO 2006, and Lordick, Lancet Oncol 2007 were moved from after the 2nd sentence to after the first sentence starting with "Studies suggest that…" accordingly. The data from these 3 trials address the statements in the first 2 sentences in this section.

Changes in text: See page 12, lines 261-262

Comment 5: 4. In the targeted therapies discussion, there should be mention of the recent focus on neoadjuvant immunotherapy. Consider this reference:

Ge F, Huo Z, Cai X, Hu Q, Chen W, Lin G, Zhong R, You Z, Wang R, Lu Y, Wang R, Huang Q, Zhang H, Song A, Li C, Wen Y, Jiang Y, Liang H, He J, Liang W, Liu J. Evaluation of Clinical and Safety Outcomes of Neoadjuvant Immunotherapy Combined With Chemotherapy for Patients With Resectable Esophageal Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022 Nov 1;5(11):e2239778. doi: 10.1001/jamanetworkopen.2022.39778. PMID: 36322089; PMCID: PMC9631099.

Reply 5: We agree the focus of immunotherapy in the neoadjuvant setting is critical to discuss. To this end, we feel we did include a discussion first outlining what immunotherapies have been studied (immune checkpoint inhibitors), the definition/mechanism of action of these drugs, a few phase 2 trials, some single-arm trials studying immunotherapy in the neoadjuvant setting, and the promising role of immune checkpoint inhibitors in the MSI-H/dMMR subgroup. We also included a table referenced in the text, which reviews ongoing trials with immunotherapy

in the neoadjuvant setting. We cited the reference you suggested as it includes an analysis with a larger number of patients. To this end, we included a sentence summarizing the paper's findings with a reference on page 15, line 333.

Changes in text: Please see the sentence with reference added on page 15, lines 333-336.

Comment 6: 5. The summary should describe the current best level evidence for AC vs. SCC because, as the authors mentioned in the introduction, the problem with interpreting these published landmark studies is that the majority of them included both histologies even though we now know that they have very different pathophysiologies.

Reply 6: We agree with your comment and have added 2 summary statements (trying to keep within the word limit) for the management of SCC and AC separately and included the informative trials.

Changes in text: Please see page 23, lines 544-548.