

## Peer Review File

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### Reviewer A

**Comment 1:** The presentation of patient characteristics is too simple. The aim is to compare the effect of CRT in cN1,2, and 3. At least we need to know the comparison of these patients. Are there any differences among them, in addition to cN stage?

**Reply 1:** Thank you for pointing this out. We have added information on clinical T (cT) stage as well as median radiation dose in each group. Unfortunately, the database does not capture information pathologic T or N stage and details of chemotherapy regimens.

**Change in the text:** We have modified Table 1 to include cT stage and median radiation dose. We have also added cT stage in multivariable analysis in Table 3. The text in the Patient and Treatment Characteristics section has also been modified (page 7, lines 119-121, 124-125).

**Comment 2:** The conclusion is that the effect of CRT is less significant in cN3. But in these patients, the 5 yr OS rate was 0% in CRT alone group. It is hard to deny the importance of surgery based on this. Did author use any statistic method to evaluate "less significant"?

**Reply 2:** We agree completely. Surgery following CRT does offer a meaningful survival benefit to patients with cN3 disease.

**Change in the text:** The conclusion in the abstract (page 2, lines 41-43) and the conclusion at the end of the manuscript (pages 10-11, lines 202-206) are updated to reflect this.

**Comment 3:** What are the benefit and disadvantage of surgery? What about the complications and recur patterns of each treatment method?

**Reply 3:** We have included the disadvantages of surgery on page 8, lines 149-154: 'Esophagectomies can be associated with high mortality and morbidity. More than half of the patients experience compromised quality of life (QOL) from one or more therapy related long-term complications and it can take up to 9 months for the QOL to return to baseline postoperatively. The prolonged recovery from surgery and associated decline in performance status could preclude a subset of patients from receiving systemic therapy if they were to develop recurrent disease shortly after surgery'. The benefit is included in the context of OS results with each modality.

**Comment 4.** Based on your findings, what is the appropriate treatment for cN2 esophaguses adenocarcinoma?

**Reply 4:** Based on currently available data, the appropriate treatment for cN2 esophageal adenocarcinoma is trimodality therapy with CRT followed by surgical resection followed by immune checkpoint inhibitor therapy if there is pathologically residual disease in the surgical specimen.

**Reviewer B**

The author compares the result of the CRT alone and CRT followed by surgery for the patient of esophageal adenocarcinoma with NCD.

**Comment 1:** Author addressed their clinical question that surgery is beneficial for the patients cN3 patients or not. But the analysis was done as usual multivariate analysis and found the prognostic factor. The background of CRT alone group and CRT surgery group is obviously different. Moreover, due to a lack of information, it is hard to provide the solution to questions.

**Reply 1:** We agree with the reviewer that there is no simple answer to this question. Within the limitations of the current study as acknowledged in the manuscript (page 9, lines 179-193) and as outlined by the reviewer, we show that nearly 16% of patients with cN3 disease derive long term survival benefit from addition of surgery following concurrent CRT. Further prospective randomized studies with arms that are well-balanced with regards to clinically and molecularly relevant characteristics are warranted to define the subset of patients who are most likely to benefit from trimodality therapy.

**Comment 2:** Description of that surgery may not offer meaningful benefit to patients with N3 disease is too strong without any QOL data. The actual survival is more in the surgery group.

**Reply 2:** As noted in the response to reviewer 1, we completely agree. The conclusion in the abstract (page 2, lines 41-43) and the conclusion at the end of the manuscript (pages 10-11, lines 202-206) are updated to reflect this.

**Comment 3:** The author should discuss the peri-operative chemotherapy instead of neo-CRT. The author pointed out the poor post-operative condition after CRT, neo-chemo or peri-chemo will improve the post-operative condition of patients.

**Reply 3:** Thank you for the thoughtful comment. While perioperative chemotherapy is an option, studies have shown that neoadjuvant CRT leads to higher pathologic response rates and a lower risk of locoregional disease progression with similar survival outcomes (Goense et al., J Surg Oncol. 2017 Jun;115(7):812-820. doi: 10.1002/jso.24596.). Another recent phase III trial showed that oncologic and operative outcomes were comparable between the two modalities (Reynolds et al., DOI: 10.1200/JCO.2021.39.15\_suppl.4004 Journal of Clinical Oncology 39, no. 15\_suppl (May 20, 2021) 4004-4004). Furthermore, neoadjuvant CRT is the most commonly used modality for the treatment of esophageal adenocarcinoma in the US. Therefore, we have focused our analysis on neoadjuvant CRT.

**Comment 4:** In Table 1, you should describe the percent of each column as the proportion of the person within the group, CRT alone or CRT followed by surgery. The denominator is wrong.

**Reply 4:** Thank you for the careful review and the comment. We have corrected the percentages and updated the table.

**Change in the text:** Table 1 is updated.

#### **Reviewer C**

**Comment 1:** cN3 patients (>6 positive LNs) is a very heterogenous group of patients, many of them are even considered as "unresectable" case due to the burden of the metastatic lymph nodes. Thus, the "selection bias" of whether the patients are fit for surgery greatly affect, if not the sole reason for, the results of this analysis. Additional data such as cT-category of the primary tumor, ycT-category, ycN-category, and number of positive lymph nodes before and after neoadjuvant CRT should be presented and added into the analysis in order to make the result be considered meaningful. Besides, a multivariable analysis should be performed for the cN3 subgroup independently.

**Reply 1:** We completely agree with the reviewer that one of the weaknesses of the study is possibility of selection bias as highlighted in the discussion (Pages 9-10, line 183-184). We have added information on cT stage. Unfortunately, information on ycT and ycN stage as well as the number of positive lymph nodes before and after neoadjuvant CRT are not captured in the NCDB.

**Change in the text:** Table 1 and 3 are updated to include cT stage information. We have also updated the text on page 10, lines 188-193.

**Comment 2:** in Table 1, for the location of the primary tumor and cN-category, the total sum of percentage of each component is >100%. Is it an input error?

**Reply 2:** Thank you for the careful review and the comment. We have corrected the percentages.

**Change in the text:** We have updated Table 1.

#### **Reviewer D**

General comment:

The authors tried to reveal whether neoadjuvant chemoradiotherapy plus planned surgery is beneficial compared to definitive chemoradiotherapy using National Cancer Database. Their research question is important for general readers; researchers, clinicians and patients. The answer to their question might change clinical practice or be a rationale for future trial; however I have a major concern about study design, and statistical analysis in the current study.

Specific comment

Participants

Major comments

**Comment#1** Exclusion criteria is not clear. Please describe the range of dose of radiotherapy or chemotherapy which the current study considered as a curative or palliative therapy, rather than the following description “the lower doses of radiation or chemotherapy for symptomatic management (page 6, line 95-96)”.

**Reply 1:** Thank you for pointing this out. Patients who received curative intent radiation (dose > 4000cGy) were included in the analysis.

**Change in the text:** We have updated median radiation dose in each group in Table 1 and updated the information in Materials and Methods section (page 6, lines 92-97).

**Comment#2** Irradiation dose of radiotherapy modifies the effect of radiotherapy. The information of irradiation dose of included patients in two groups is necessary.

**Reply 2:** Please refer to the response and change in the text noted above.

Minor point

**Comment #1** Please confirm the described percentage about location of the primary, clinical N stage.

**Reply 1:** Thank you for pointing this out. The percentages are updated in Table 1.

**Change in the text:** Please refer to the updated Table 1.

Methods

Major comments

**Comment #1** Table 1 showed that age, gender, race, location of primary tumor, clinical N stage and treatment center are probably confounding factors for overall survival in the included patients. If you tried to compare the overall survival of neoadjuvant CRT plus surgery vs. CRT, the statistical analysis which adjusted the effect from those confounding factors is indispensable.

The included patients were large. I think the simple methods (stratification and matching including multiple confounding factors), or advanced methods (propensity score matching or inverse probability weighting) are probably feasible.

**Reply 1:** We agree with the reviewer. We have performed multivariable analysis with Cox proportional hazards model and the significant findings are shown in Table 3.

Minor comments

**Comment #1** Please describe what factors were used to identify predictors of utilization of surgery (page 6, line 104).

**Reply 1:** Thank you for raising the question. In keeping with the overall objective of the analysis and avoid further confounding factors, we have not included the predictors of utilization of surgery in the analysis.

**Change in the Text:** We have deleted lines 110-111 on page 6 in the tracked version.

Results

Major comments

**Comment #1** Simple comparison of overall survival between two groups is not appropriate for the current study. Please check major comment #1 in the Methods.

**Reply 1:** We agree with the reviewer. We have included information from Kaplan Meier analysis and Cox proportional hazards which was used to generate the survival curves.

**Change in the text:** We have updated the Materials and Methods section (page 6, lines 103-112).

**Comment #2** Table 2 included most of the information of Figure 1,2 3. Please revise Figures and Table

**Reply 2:** Thank you for the suggestion. We have replaced Figure 1, 2, 3 with a new figure (now Figure 1) showing OS difference between CRT + surgery group and CRT group alone. Table 2 describes median OS and 5-year OS based on cN stage in each group.

**Change in the manuscript:** Please refer to the new Figure 1.

Interpretation and conclusions

Major comments

**Comment #1** Please make structured Discussion. For example, the key finding is described in the first paragraph. The description of the first paragraph in the current Discussion section is already described in the current Introduction section.

**Reply 1:** We appreciate the reviewer's suggestion. We have updated the discussion and streamlined it. We have deleted most of the content of the first paragraph.

**Change in the text:** Please refer to the updated discussion section (pages 8-10)

**Reviewer E**

The authors attempt to approach an interesting and relevant question with the NCDB. The

question of role of surgery in patients with N3 disease. This question is relevant despite the fact that NCNN does not consider that question an issue, as the recommendations are for CRT followed by surgery in all N+ fit patients regardless of number of nodes. This paper is valuable as in the community practitioners may encounter N2-3 patients that would be considered clinical stage IVa and do not offer curative approaches for these patients. I have a few comments:

**Comment 1.** Including upper thoracic esophageal cancers to the analysis may be difficult to interpret as some of these patients will have anatomic features that preclude their surgery. Moreover, in those N3 disease may correspond to disease that could be considered metastatic so it would be important to comment on that.

**Reply 1:** Thank you for the excellent comment. We agree with it completely.

**Change in the text:** We have modified the discussion section to acknowledge this (page 10, lines 188-190).

**Comment 2.** The authors should be more clear in explaining to the readers a limitation given by the fact that some of the N3 disease could be non-regional LN and therefore better categorized as stage IV, not infrequently patients with LN-driven M1 disease (i.e. retroperitoneal) receive CRT as therapy when they should have been considered candidates for chemotherapy alone and those clearly could be the case for the non-surgical patients.

**Reply 2:** We agree with the reviewer's comment. Unfortunately, the information on the specific site of lymph node involvement is not captured in the NCDB which makes the analysis somewhat challenging.

**Change in the text:** We have modified the discussion section to include this (page 11, lines 191-193).

**Comment 3.** The authors should streamline the discussion.

**Reply 3:** We appreciate the reviewer's suggestion.

**Change in the text:** Please refer to the updated discussion section (pages 8-10).

**Comment 4.** The authors should acknowledge in the introduction the changes in AJCC8 regarding clinical staging, especially stage IVa.

**Reply 4:** Thank you for the suggestion.

**Change in the text:** We have acknowledged in the introduction section that patients with clinical T1-4aN2M0, TanyN3M0, and T4bN0-2M0 disease are now classified as stage IVa disease in the AJCC 8<sup>th</sup> staging system (page 5, lines 70-72).