**Peer Review File**

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## Review comments

### Reviewer A

*This retrospective study is interesting because:*
*1. this neoadjuvant chemotherapy (DCF) is not popular outside Japan. This study showed and divided the outcomes to 4 groups.*
*2. this study showed that prognosis of ypT+N0 was equivalent to ypT0N0.*
*3. this study confirmed that prognosis of ypT0N+ was poorer than ypT+N0 which might lead to study of adjuvant nivolumab or others in the future.*

*Although, the group of ypT0N+ (n=5) is likely too small of sample size. This article is a good preliminary study for further study.*

Response:
We thank the reviewer for the careful review of our manuscript and your helpful comments. We acknowledge that small sample size is a limitation of this study, especially regarding the ypT0N+ group. We look forward to conducting future studies.

### Reviewer B

*The study by Chinen et al is a retrospective study of 101 patients with esophageal squamous cell carcinoma who underwent neoadjuvant DCF chemotherapy. The author's primary endpoint is difference in overall survival based on the degree of pathologic response. They found that the primary driver of survival was ypN0 status.*

*Comment 1: My primary question is why the authors did the analysis in the manner they did - creating four groups and then doing pairwise comparisons. Why not look at the various factors - path CR, ypT status, ypN status in multivariable analysis, to see if N0 status was independent predictor of prognosis?*
Response:
Prior studies have shown that the N factor is a more effective prognostic factor than the T factor. Due to the small number of cases and the risk of overfitting, we limited the explanatory variables to only the N factor and the T factor. Pathological CR refers to ypT0 and ypN0, and it is included in the categories of ypT and ypN. We have included additional sentences in the Introduction section and Methods sections (page 6, lines 72-73, and page 10, lines 146-147).

Ref: 17. Shen J, Kong M, Yang H, et al. Pathological complete response after neoadjuvant treatment determines survival in esophageal squamous cell carcinoma patients (NEOCRTEC5010). Ann Transl Med. 2021;9:1516.

*Specific comments*

*Comment 2: Introduction - the authors discuss the checkmate trial that led to the approval of nivolumab for patients without a pCR after CRT and Esophagectomy as a means to frame the current study and ultimately raise the question of whether the checkmate data applies to patients who get DCF rather than chemoRT. The authors fail to note that in the Checkmate 577 trial, subgroup analysis continues to show a benefit for yN0 patients who received adjuvant Nivo. This should be acknowledged and further discussed.*

Response:

We thank the reviewer for this comment. In Their study, Lin (2023) reported the following:

> 'In the CheckMate 577 trial, patients with ypN0 (HR = 0.74, 95%CI: 0.51-1.06) did not derive discernible benefits from nivolumab adjuvant therapy. On the other hand, patients with ypN+ (HR =0.67, 95% CI: 0.53-0.86) who received nivolumab demonstrated improved disease-free survival.' (p. 05)

Ref 18. Lin Y, Liang HW, Liu Y, Pan XB. Nivolumab adjuvant therapy for esophageal cancer: a review based on subgroup analysis of CheckMate 577 trial. Front Immunol. 2023;14:1264912.

We added related sentences in the Introduction section (page 6, lines 71-75).

*Comment 3: Methods:*

*Line 94- methods state that patients with DCF or just CF were included, however later on the authors state that patients who did not receive DCF were excluded. Furthermore, the introduction focused on DCF, so this confusing and needs clarity.*

Response:

In this study, we excluded patients receiving CF regimen. We added the relevant sentences in the Methods section (page 8, lines 105-106).

*Comment 4: Line 104 - why were patients with intraabdominal esopahgeal cancer excluded? This would include distal esophagus and GEJ junction siewert 1, who are clearly treated as esophageal cancers (and not gastric).*

Response:

Patients with cervical and intraabdominal esophageal cancer were excluded according to the JCOG1109 study, which was used as a basis for NAC-DCF in the previous study.

To emphasize that the subject of this study was squamous cell carcinoma of the thoracic esophagus, we added relevant sentences in the Highlight Box, Introduction, Discussions and Conclusions section (page 6, line 65, page 7, line 79, page 11, line 183 and page 13, line 220).

Ref 22. Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). Jpn J Clin Oncol 2013;43:752-5.

*Comment 5: Line 139-143 is not clearly written and was confusing.*

Response:

The text regarding frequency and proportion was moved to the Exposures and Outcomes section, and the results are presented in Table 2. We added relevant sentences in the Methods

and Results sections (page 9, lines 125-127; page 11, lines 166-167; and Table 2).

*Comment 6: Results:*
*163-166 - regarding pairwise comparisons, I am a bit confused by the findings. This is the heart of the paper, and the authors highlight that ypT+n0 had significant differences in survival compared to ypTanyN+ along with no difference between ypT0N0 and ypT+N0. However Path CR also showed no statistically significant difference between ypTanyN+ (p values 0.56 and 0.09). This suggests significant underpowering of the study, since it does not pass face validity that ypT0N0 would not be better than ypTanyN+, but ypT+N0 would be. If this was not the finding, then table 2 is confusing as constructed and needs clarity*
Response:
Multiple comparisons of nonparametric tests in survival time analysis are not yet well established. The items regarding pairwise comparisons were deleted because the indications for pairwise comparisons differ in this context. Instead, we added relevant sentences in the Abstract and Results sections (page 3, lines 39-40 and page 11, lines 169-170).

*Comment 7: 167-171 - awkwardly written. The corresponding figure and table help, but the syntax and grammar of the paragraph are hard to read. This corresponds with a confusing methods section that describes these results. Please revise.*
Response:
We revised relevant sentences in the Results section accordingly (page 11, lines 172-174).

*Comment 8: 172- why even include patients that received palliative chemo and adjuvant nivolumab. The numbers may be small, but with the overall numbers being small, that can significantly impact results and make it hard to interpret whether N status after NAC is the driving factor, or whether that is confounded by adjuvant treatment.*
Response:
In this study, nivolumab was used as palliative care, reather than adjuvant therapy. We revised the relevant sentences in the Results section accordingly (page 11, lines 177-178).

*Comment 9: The strengths and limitations section could use language revision. It is somewhat confusing. Specific areas 186-189 - I do not understand what the authors are trying to say. Are they claiming that because some patients did not receive DCF this could be a confounder, but because we are looking at path response, regardless of regimen, it really isn't confounding. First off -I thought patients who did not receive DCF were excluded (see my earlier comment. Second, if the neoajduvant regimen doesn't matter, and only the pathologic response matters with respect to prognosis, then why should we expect a difference NAC vs ChemoRT matter with respect to path CR and indication for adjuvant nivo (which is a central theme of the paper)?*
Response:
As mentioned above, we excluded patients who underwent the CF regimen as NAC with DCF was the subject of the analysis.

*Comment 10: 190-194 - I do not understand what the authors are referring to.*
Response:

We revised the relevant sentences in the Discussion section (page 12, lines 190-197).

*Comment 11: Line 203 needs grammatical revision.*
Response:
We revised the relevant sentences in the Discussion section (page 12, lines 203-204).