

## Peer Review File

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### Reviewer A

Thank you for allowing me to review this well written commentary. The points you highlight are relevant and a good message about interpretation with caution.

Response – Thank you for reviewing our article.

### Reviewer B

The authors submit a commentary on Yang Y, Liu J, Liu Z, et al. Two-year outcomes of clinical N2-3 esophageal squamous cell carcinoma after neoadjuvant chemotherapy and immunotherapy from the phase 2 NICE study. J Thorac Cardiovasc Surg. 2024 Mar;167(3):838-847.e1. The NICE study is another trial evaluating chemoimmunotherapy to chemoradiation followed by surgery.

1. Lines 46-53, the authors discuss the issues of locoregional recurrence and its effect on patient satisfaction, quality of life and willingness to pursue a particular treatment strategy.
  - a. Yang et al reported 10% LRR, NEOCRTEC5010 reported 12.2% LRR and CROSS reported 5.9%.
  - b. This LRR is comparable to other studies and may not be a specific weakness of chemoIO.
  - c. Local recurrences can be morbid but nodal recurrences can be treated by surgery or radiation and have better outcomes than distant recurrences.

Response – Thank you, and we agree that distant recurrences do have a worse survival than local/regional recurrences, the point we were trying to make is that local recurrences can have more symptomatic impact for esophageal cancer than in some other cancers and that should be considered in the treatment algorithm.

2. Line 64, change “studies” to “study’s”

Response – Thank you, and this change has been made.

3. It makes sense that CRT would have a higher major pathologic response rate because of the local effect of radiation. As mentioned by Yang and by many other authors, pCR is a not a particularly accurate surrogate for overall survival. Tang et al studied CRT vs chemo alone and did not find a survival difference but a difference in pathologic complete response.

- a. Tang H, Wang H, Fang Y, Zhu JY, Yin J, Shen YX, et al. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy for locally advanced esophageal squamous cell carcinoma: a prospective multicenter randomized clinical trial. Ann Oncol. 2023;34(2):163-72.

Response – We agree that path CR is not a perfect assessment for future overall survival, but along with major pathologic response are the only current indicators that we have in order to predict future risk for recurrent disease and mortality.

4. The authors could consider highlighting the impressive difference within the study population of those who had MPR versus those who did not. The OS survival was almost double at 2 years (91.4 vs 47.7%). Yang et al, reference Z. Liu, J. Liu and Z. Li Signal Transduct Target Ther 2022 Vol. 7 Issue 1 Pages 233. As a treating physician, tailoring the therapy to a particular patient and tumor biology would be critical. If a prediction could be made on pathologic response such as PDL-1 status then chemoIO versus NCRT could be planned.

Response – Yes, we agree, and we have included this impressive outcome in the editorial to bring attention to the impact that the major pathologic response has on outcome in this population.