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Peer Review File

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Reviewer A

Perhaps I am missing something but I find the distinct train of thought on this topic somewhat blurred. The very important NEOCRET trial should be central to the discussion and summarised and briefly critiqued. The reasons why you consider that this in addition to CROSS do not establish a definite standard of care in the must be clearer, as most of the world would disagree.

Reply1:
Despite the widespread enthusiasm for multimodality therapy for esophageal cancer, currently
available data are not truly defifinitive. Such trials should standardize all treatment arms, including the surgical procedure. The problem of surgical variability is heightened in randomized
controlled trials (RCTs) where the quality of surgery could influence
the final outcome and might compromise the generalizability of
results.

The comments on pCR rates and R0 rates are not strongly made.

Reply2:
The comments on pCR rates and R0 rates have been stated in the second paragraphof the comment.

With this title the readers would expect some expert comment on watch and wait (SINO) as well, and of course on dCRT.

Reply3:
Sorry, due to space constraints, we can't discuss the topic of esophageal preservation too much.

The new trials in China are of interest but not necessarily tightly connected with the title and purpose of the article, conversely it is very important to comment and reference Checkmate 577.

Reply4:
Sorry, The main purpose of this article is to discuss neoadjuvant therapy. Checkmate 577 confirmed the value of postoperative adjuvant therapy in prolonging DFS. But

there was no analysis of the quality of surgery in the enrolled patients.

Reviewer B

In this comment on the response by Ceppa et al on the results of the NEOCRTEC5010 trial, the authors call into question the efficacy of the 3 field surgical approach and systemic regimen employed prior to adopting the practice changing findings put forward by this trial.

First, the authors call into question the validity of the comment reporting the extent of nodal dissection as a reason for improved outcomes. In fact, the trial mandated supracarinal dissection along both RLN in all patients. This is beyond what is practiced in a standard 2 field lymphadenectomy on a routine basis in North America. In this regard, I would tend to agree with Ceppa. Along these lines, the authors comment on a potentially spurious R0 resection ate owing to lack of reporting on circumferential margins. The utility of circumferential margins after en bloc esophagectomy in predicting recurrence have been called into question in multiple studies and in fact, data borne from numerous sources have failed to show any impact of a positive circumferential margin from a clinical standpoint. This does not thus negate the impressive findings put forward in this randomized study.
Finally, pointing out an excellent pCR of 30-50% regardless of construct (randomized trial versus real life setting) cannot be used to diminish the importance of the results put forth in this trail. Nor does it negate the need for meticulous surgical technique. Finally, although the chemotherapeutic regimen employed may not be standard in all settings, they do not again negate the importance of meticulous surgical technique that was mandated in this trail
Accordingly, I do not believe the response to Ceppa's comments are valid in this setting and I cannot recommend its publication.

Reply:
In China, squamous cell carcinoma is predominated. Extented or total 2 field lymphadenectomy is recommended by the guideline in China .Cervical lymph node dissection is considered an additional procedure. The effect of circumferential margins on prognosis is indeed uncertain. But if the problem is not highlighted, some doctors will mistakenly think the quality of Chinese surgery is better. Data from the authors' institution showed that the promising pCR rates of patients receiving NEOCRTEC5010 or CROSS regimen could not be repeated in the real-world setting.

Reviewer C

The authors reviewed that trimodality treatment for resectable locally advanced esophageal squamous cell carcinoma. This review may have considerable implication. However, there are several limitations that considerably reduce the significance of this study.

1. Considering the remarkable development of immune checkpoint inhibitor in recent years, the authors should explain on the position of ICI in multidisciplinary treatment.

Reply1:

Based on our preliminary experience, esophagectomy is safe and feasible following combined neoadjuvant immunotherapy with chemotherapy for locally advanced esophageal cancer.But large-scale prospective randomized controlled studies are needed.

2. Details of surgical methods should be mention (e.g., robotic surgery, thoracoscopic surgery, and mediastinal surgery).

Reply2:

The problem of surgical variability is heightened in randomized controlled trials (RCTs) where the quality of surgery could influence the final outcome and might compromise the generalizability of results.