

Peer Review File

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Reviewer A

The authors reported short-term and pathological outcomes of patients who underwent esophagectomy after neoadjuvant chemotherapy with immune checkpoint inhibitors (ICI). They showed that esophagectomy after neoadjuvant chemotherapy with ICI could be performed safely and no tumor cells in the mucosal layer were relatively frequently found in patients with residual primary tumors.

The topic seems to be interesting, but there are some points to be revised.

Major

Comment 1. Is this retrospective study or prospective study? If this is a prospective phase II study as the authors described, they should show the number of the prospective trial.

Reply 1 :

This is a retrospective study. To avoid the confusion, we deleted “phase II trials” in the Highlight Box, and we also deleted “prospective phase II trials” in the second paragraph of Induction. We added “retrospective” in the second paragraph of Patients.

Changes in the text:

Highlight Box: “The use of immune checkpoint inhibitors....”

Second paragraph of Induction: “Published studies using immune checkpoint inhibitors as neoadjuvant regimen showed promising tumor response with objective response rate ranging from 22.2% to 55.6%”

Second paragraph of Patients: “Ultimately, 138 patients were included in this retrospective analysis.”

Comment 2. On page 8, line 184-185, the authors wrote that “preferential clearing of tumor cells in the mucosal layer is more common after immunotherapy”. The authors should show what study you compared with.

Reply 2 :

I am sorry for the confusion. Combined with Comment 9 of reviewer C, we modified this sentence as following.

Changes in the text:

First paragraph of Discussion: ““Notably, preferential clearing of tumor cells in the mucosal layer is common after neoadjuvant chemoimmunotherapy.”.”

Comment 3. On page 9, they compared their results with Cross study. In Cross study, more than 70% of the patients had cT3 tumors, whereas less than one-third of the patients had cT3 in this study. They should refer to this difference.

Reply 3:

Thanks for your careful review, 70% of the patients had cT3 tumors before chemoradiotherapy in Cross study. I am sorry that we only had the complete data of clinical staging after the treatment as this is a retrospective study. We make it clear in the part of Discussion and in the Table 1.

Changes in the text:

The fifth paragraph in Discussion: “In the CROSS study, 150 of 184 (84%) patients in the chemoradiotherapy arm had esophageal cancer of clinical T3 staging before treatment,”

Table 1 footnote: † clinical stage after treatment.

Reviewer B

This is very interesting manuscript and adds to the literature on this new approach. It is discouraging that the tumor clears from the mucosa/submucosa first making watch and wait in clinical complete response patients more worrisome.

Comment 1. In those that had residual disease, are you giving any adjuvant therapy? Any adjuvant immunotherapy?

Reply 1:

For those had residual disease, adjuvant immunotherapy was suggested. However, the decision was also made depending on the surgeon preference and patient physical status. As the aim of this study was to assess the pattern of tumor regression after neoadjuvant chemoimmunotherapy, postoperative treatment was not defined in this study.

Changes in the text:

none.

Comment 2. Did you compare the different immunotherapy sub-groups; any differences in therapy related toxicity or pathologic response?

Reply 2:

As shown in the fifth paragraph of Results “Pathological complete regression was observed in nine patients (18.8%) using pembrolizumab, 14 (21.5%) using camrelizumab, two (15.4%) using tislelizumab, and three (25.0%) using sintilimab, $P=0.919$ ”, we presume there is no difference among different immunotherapies. However, I am sorry we could not comment on the efficacy of different regimens due to small study number and retrospective nature.

Changes in the text:

none.

Comment 3. Given this is a safety paper, it would be nice to compare operative outcomes to patients that did not receive chemo/IO. Any difference in the ability to complete a minimally invasive approach? Any difference in intraoperative/postop blood transfusions? PNA/re-intubation? There was a single TEF, was this due to surgical technique or was the tumor more sticky to the airway due to immunotherapy?

Reply 3:

Thanks for your comment. I am sorry that open thoracic approach is more common in our hospital during the study period. As discussed in the third paragraph of Discussion: “Moreover, both the incidence of postoperative complications and length of hospital stay were consistent with our previous report in patients who underwent upfront esophagectomy”. Thus, we presume the preoperative use of immunotherapy is safe without increased surgical complications.

Regarding the case with TEF, our team presume its occurrence was the severe consequence of anastomotic leakage, as the fistula occurred on the 41st day after surgery as showed in the part

of Results. The occurrence of TEF could be early if it was due to surgical technique.

Changes in the text:

none.

Reviewer C

Li et al present an analysis of tumor regression patterns after neoadjuvant chemioimmunotherapy (CIO) in squamous cell carcinoma of the esophagus. The treatment landscape of esophageal cancer continues to evolve. There may be a trend away from neoadjuvant chemoradiation. Immunotherapy has become integral in the treatment of esophageal cancer. This analysis seeks to evaluate the effect of neoadjuvant CIO at the time of surgery.

Comment 1. Line 42, revise for grammar.

a. Consider: “131/138 (94.9%) had R0 resections” or “There were 131/138 (94.9%) who had R0 resections.”

Reply 1:

Thanks for your careful review. We revised accordingly.

Changes in the text:

“There were 131/138 (94.9%) who had R0 resections.”

Comment 2. Line 43, change “were” to was, median number is singular.

Reply 2:

Thanks for your careful review. We revised accordingly.

Changes in the text:

“the median number of resected lymph nodes was 28.”

Comment 3. Were the patients in this study part of larger clinical trial or was the choice of neoadjuvant therapy based on clinician preference?

Reply 3:

This was a retrospective study. As claimed in the third paragraph of Patients: “As there is still no consensus on the optimal neoadjuvant regimen, different types of immune checkpoint inhibitors were used based on surgeons’ experience and preference in China”, “Of the 138 patients in this study, there were 86 patients (62.3%) had immunotherapy in Shanghai Cancer Center, and 52 (37.7%) in their local hospitals.”

Changes in the text:

none.

4. Did the authors obtain IRB approval to waive informed consent due to the retrospective nature of this analysis?

Reply 4:

As shown in the part of “Ethical Statement”, the institutional review board of Fudan University Shanghai Cancer Center approved the esophageal carcinoma database used in the present study.

Changes in the text:

We also added it in the first paragraph of Patients.

5. Lines 60-62, these lines provide the rationale for this study. Consider including that adjuvant immunotherapy after neoadjuvant therapy and surgery is associated with better outcomes.

a. Consider adding this to the reference list: Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384(13):1191-203.

Reply 5:

Thanks for your comment, we revised accordingly.

Changes in the text:

We added it in the reference, updated the reference list.

Comment 6. Lines 79-80, states that chemoimmunotherapy was used for T1-4aN2 or T3-4aN1 total 138. Line 71, states that 251 patients received neoadjuvant therapy.

a. What were the clinical stages of the 113 patients that received neoadjuvant therapy that was not chemoimmunotherapy?

b. What therapy did they receive?

c. How did the authors decide to exclude this patient population from receiving chemoimmunotherapy?

Reply 6:

Thanks for your comment. I am sorry that there is still no consensus on the optimal neoadjuvant regimen for patients with advanced esophageal cancer in China, for the above questions:

a. Patients had similar clinical stages for those who did not receive chemoimmunotherapy in our hospital.

b. Most of them had chemotherapy.

c. The type of neoadjuvant therapy was decided by the surgeons' experience and preference.

As you know, many clinical trials are being performed around the world. In our hospital, the phase II trial using Pembrolizumab combined with chemotherapy is also being performed to evaluate the efficacy and safe, and to explore treatment resistance mechanisms (ClinicalTrials.gov ID: NCT05281003). We hope in the future we can know more about the value of neoadjuvant chemoimmunotherapy.

Changes in the text:

none

Comment 7. Lines 96-99, the text describes the choice of surgical procedures, Ivor Lewis for mid and lower third tumors, McKeown for upper thoracic tumors. Table 1 reports 49 upper tumors. Table 2 reports 64 McKeown esophagectomies.

a. This discrepancy is probably unimportant to the intent of the manuscript

b. The authors could consider revising lines 96-99 to reflect surgical planning.

c. McKeown is misspelled in table 2, (Mckewon)

Reply 7:

Thanks for your careful review.

a. It is the principle in our hospital that Ivor Lewis for mid and lower third tumors, McKeown for upper thoracic tumors. However, minimally invasive esophagectomy is being performed increasingly, McKeown procedure via minimally invasive approach is preferred, and some patients with mid and lower tumor could also had McKeown procedure.

- b. We revised it as “The McKeown procedure with cervical anastomosis and Ivor-Lewis procedure with thoracic anastomosis, via open or minimally invasive approach, were performed depending on the surgeon’s preference”
- c. Thanks again, and we corrected it.

Changes in the text:

We delete the “The McKeown procedure with cervical anastomosis is usually performed for tumors in the upper thoracic esophagus, while the Ivor-Lewis procedure with thoracic anastomosis is always performed for those with tumors located in the middle or lower thoracic esophagus.”

Comment 8. Lines 177-180, this paragraph is difficult to interpret. It requires an understanding of the terms such as regression toward the invasive front. This requires an in-depth familiarity of the report by Shaprio. The authors should define these terms for the reader and consider providing a graphical explanation in a supplemental figure.

Reply 8:

Thanks for your comment, we added explanation for readers.

Changes in the text :

“Of the 102 patients who had residual tumors in the esophageal wall (mucosa, submucosa, muscularis propria, and adventitia, as showed in Figure 2), 30 (29.4%) showed regression toward the lumen (more regression in the muscularis propria and the adventitia), eight (7.8%) had regression toward the invasive front (more regression in the mucosa and the submucosa), 27 (26.5%) had concentric regression (more regression in the mucosa and the adventitia), and 37 (36.2%) had random regression (comparable extent of regression in all layers) .”

Comment 9. Lines 184-185, the authors have demonstrated that clearing of the mucosal layer is common after chemoimmunotherapy. The authors do not provide any comparison to conclude that mucosal clearing is more common after chemoimmunotherapy than after chemoradiation.

- a. Consider: “Notably, preferential clearing of tumor cells in the mucosal layer is common after neoadjuvant chemoimmunotherapy.”

Reply 9 :

Thanks for your suggestion. We revised accordingly.

Changes in the text :

“Notably, preferential clearing of tumor cells in the mucosal layer is common after neoadjuvant chemoimmunotherapy.”

Comment 10. Lines 221-223, the phrase, “In the published study” is confusing. A reader may conclude the authors are referring to the CROSS trial. Also this sentence has two references. Consider: “Previous studies have reported absent residual tumor in the mucosa in 28-29% of patients undergoing neoadjuvant chemoradiation,12, 18”

Reply 10:

Thanks for your suggestion. We revised accordingly.

Changes in the text:

“Previous studies have reported absent residual tumors in the mucosa layers were observed in

approximately 28–29% of patients with residual tumors after chemoradiotherapy (12, 19)”

11. Lines 196-206: The stated aim of the study is to assess the pattern of tumor regression after neoadjuvant chemoimmunotherapy. This paragraph discusses the surgical outcomes. The authors do provide their surgical outcomes in the results. If this is one of intended aims is to demonstrate the safety of surgery after induction chemoummunotherapy this should be stated at the end of the introduction

a. Additionally, the authors should address the limitations in making these conclusions. This is a non-randomized study which is subject to considerable selection bias.

Reply 11:

Thanks for your suggestion. We revised accordingly.

Changes in the text 11:

We added “The safety of esophagectomy after neoadjuvant chemoimmunotherapy was also evaluated in this study.” at the end of the introduction.

We added “in this retrospective study” in the part of abstract conclusion and manuscript conclusion.

Comment 12. There has been a longstanding controversy over the benefit of surgery after chemoradiation compared to chemoradiation alone in squamous cell carcinoma. The trend toward eliminating the radiation is predicated on proceeding to surgery. Few would argue that aggressive systemic therapy without local therapy is an acceptable treatment strategy. The authors’ warning that a lack of detectable tumor in the mucosa or submucosa after chemoimmunotherapy is not reassuring is noteworthy

Reply 12:

Thanks for your comments.

Changes in the text:

None.