Peer Review File
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First Round Peer Review

Reviewer A

Comment 1: Lines 36-37, definitive chemoradiation has become the standard of care for cervical esophageal cancer but has not always been the standard.

Reply 1: Definitive chemoradiation therapy (dCRT) was recommended for cervical esophageal squamous cell cancer by National Comprehensive Cancer Network (NCCN). Accordingly, we have adopted a more rigorous expression.

Changes in the text: We have modified the expression as advised (see Page 2, line 24-26).

Comment 2: Line 39, it is not clear what the term, "the best surgical time" means. a. Does it mean a window for primary or salvage esophagectomy?

Reply 2: In real world, local control rates of dCRT remain poor. The best surgical time" means a window for primary esophagectomy. In order not to cause ambiguity, we modify the literal expression.

Changes in the text: To avoid causing ambiguities, we have modified the way of expression as advised (see Page 2, line 27-27).

Comment 3: The manuscript would benefit from English language editing

Reply 3: Based on the reviewers' comments, we have performed language editing in professional English. Modified sections were shown in Page 2-3, line 36-47 and Page 10-11, lines 219-226.

Changes in the text: Modified sections were Page 2-3, line 36-47 and Page 10-11, lines 219-226.

Comment 4: Lines 75-76, Reference 7 (Kelly et al) described the use of adjuvant

Nivolumab in resected esophageal and GEJ cancers after induction chemoradiation. It is not clear that this reference would support the statement that surgical resection is better than definitive chemoradiation. Additionally, the New England Journal study did not include cervical esophageal cancers.

Reply 4: Allow us to thank the reviewer for pointing out inappropriate literature citation here. Kelly et al described the use of adjuvant Nivolumab in resected esophageal and GEJ cancers after induction chemoradiation. We mean here was that surgery-based multimodal therapy could increase the survival rate of patients with CEC. We have modified the reference（PMID: 27859977 and PMID: 34329601）.

Changes in the text: Modified literatures were shown in Page 16, line 344-348.

Comment 5: Reference 9 should include the authors and the published citation, even if it remains in abstract form. This reviewer found it difficult to find the abstract on the ASCO meeting site.

Reply 5: We have recently published this study in J Immunother Cancer (2022 Mar) and updated it in Ref.

Changes in the text: Page 16, line 351-353, the reference was modified to Liu J, Yang Y, Liu Z, et al. Multicenter, single-arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma. J Immunother Cancer 2022;10.

Comment 6: Line 63, the trial registration is reported as SCINIC trial, while line 100 states the trial name as SCENIC, please rectify the discrepancy.

Reply 6: The trial registration is reported as SCENIC trial. We have rectified the discrepancy

Changes in the text: line 63: We have rectified the discrepancy (see Page 3, line 56).

Comment 7: Lines 45-57, the abstract lists 36 patients enrolled and describes the endpoint of the study. While further in the body of the manuscript (lines 98-100) the

text describes the time period of the study as April 2022 through April 2025. a. This is confusing to the reader; from the abstract it appears that this manuscript is reporting on the results of a study of 36 patients that has been completed. b. The abstract should be revised to clarify that the study population has already been enrolled and initiated therapy.

Reply 7: We plan to recruit patients for initial treatment in April 2022, but no patients have yet been recruited into this study due to the sudden worse of the Covid-19 in Shanghai. We have already revised abstract.

Changes in the text: We have modified the part of the abstract as advised (see Page 2-3, line 36-49).

Comment 8: Line 170, please define SAE, it appears to mean serious adverse events.

Reply 8: In our study, adverse events (AEs) were assessed throughout the study and up to 30 days after the last dose of study drug or initiation of a new anticancer therapy, whichever occurred first, according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. An SAE is any untoward medical occurrence that, at any dose. SAEs include results in death/disability/incapacity/life-threatening/hospitalization/ prolongation of existing hospitalization

Changes in the text: we added some data about SAE definition (see Page 9, line 179-188)

Comment 9: The manuscript switches between past and future tense. This manuscript is a description of a study in progress, the section on data analysis (lines 197-204) should probably be written in future tense since the analysis will take place in the future.

Reply 9: The section on data analysis has been written in future tense.

Changes in the text: We have modified our text in data analysis section as advised (see Page 9-10, line 219-226).

Comment 10: Lines 242-244, the NEOCRTEC 5010 and CROSS studies showed

improved outcomes for induction chemoradiation followed by surgery compared to surgery alone. The context of this portion of the discussion seems to imply that these studies showed improved outcomes with surgery after induction therapy compared to definitive chemo-radiation. a. The authors should clarify the wording.b. CROSS included 75% adenocarcinomac. Two studies of thoracic squamous cell carcinoma surgery after induction chemoradiation compared to definitive chemoradiation did not show a clear survival advantage in the surgical group (FFCD 9102. J Clin Oncol. 2007;25(10):1160-1168 and Stahl et al J Clin Oncol. 2005;23(10):2310-2317.)

Reply 10: In cross study, median overall survival was 49.4 months in the chemoradiotherapy–surgery group versus 24.0 months in the surgery group. Although only 84 (23%) had squamous cell carcinoma. Patients with squamous cell carcinoma and patients with adenocarcinoma both benefited from neoadjuvant chemoradiotherapy. In NEOCRTEC5010 study, all included cases were esophageal squamous cell carcinoma. The pathologic complete response rate was 43.2% in group neoadjuvant chemoradiotherapy(CRT). Compared with group surgery alone, group CRT had a higher R0 resection rate (98.4% v 91.2%; P = 0.002), a better median overall survival (100.1 months v 66.5 months; hazard ratio, 0.71; 95% CI, 0.53 to 0.96; P =0.025), and a prolonged disease-free survival (100.1 months v 41.7 months; hazard ratio, 0.58; 95% CI, 0.43 to 0.78; P=0.001). Above content, we have supplemented in the manuscript. In summary, we aim to improve the long-term survival of cervical esophageal cancer by neoadjuvant therapy.

FFCD9902 study suggested that patients with locally advanced thoracic esophageal cancers, especially epidermoid, who respond to chemoradiation, there is no benefit for the addition of surgery after chemoradiation compared with the continuation of additional chemoradiation. About our SCENIC study， we want to screen patients sensitive to treatment by immunization plus chemotherapy who will receive additional immunization plus chemoradiation, while patients insensitive to treatment were treated with surgery. We expect to improve the overall survival of this population with cervical esophageal squamous cell carcinoma.

In Stahl's study, adding surgery to chemoradiotherapy does not increase survival but improves local tumor control of patients with locally advanced esophageal squamous cell carcinoma. Poor local control rate of cervical esophageal cancer resulted in the poor quality of life due to dysphagia, stenosis, and bleeding. If additional surgery can improve the local control rate, it may improve the quality of life to some extent.
Changes in the text: We added some data about NEOCRTEC 5010 and CROSS study into discussion section (see Page 13, line 270-281).

Comment 11: Line 256-257, Although well tolerated and potentially effective, it seems an overstatement that tislezumab, carboplatin and pacitaxel would be considered harmless.a. Consider revising this statement, such as: "In order to use a chemoselection strategy to stratify patients, the screen therapy must be effective and well tolerated."
Reply 11: The reviewer has made a very good point here. We have modified this statement.
Changes in the text: We have revised this statement as advised (see Page 14, line 295-296)

Comment 12: Do the authors plan to collect and report specific mutations or PDL-1 status of the tumors at the time of diagnosis. It would an interesting adjunct to the main study to assess tumor response and outcomes based on common mutations and PDL-1 status.
Reply 12: Allow us to thank the reviewer for their enlightening suggestion. We plan to carry out ctDNA expression level and PD-L1 status detection. Then, we want to assess tumor response and outcomes based on ctDNA expression and PDL-1 status and analyze their value in tumor diagnosis and relationship with prognosis.
Changes in the text: No changes in the text.

Comment 13: Immunotherapy has been a paradigm shift in the treatment of many malignancies. Recent studies such as Kelly et al have cause a change to NCCN

treatment recommendations. Clearly the outcomes for CEC leave room for improvement. The use of chemo-immunotherapy to select for responders may allow for more tailored treatment strategies based on the biologic behavior of the individual cancers.

Reply 13: We strongly agree with the reviewer's opinion that immunotherapy has been a paradigm shift in the treatment of many malignancies, but most studies have targeted thoracic esophageal squamous cell carcinoma, while there is still a large room for the treatment of CEC. The use of chemo-immunotherapy to select for responders may allow for more tailored treatment strategies based on the biologic behavior of the individual cancers.

Changes in the text: No changes in the text.

Reviewer B

Comment 1: The evidence of the neoadjuvant regimen remains obscure. Although the authors cited reference #10, the regimen used in the study was tislelizumab plus cisplatin and 5-fluorouracil. Were there any studies that used tislelizumab plus nab-paclitaxel and carboplatin?

Reply 1: TD-NICE was carried out by Yan et al for locally advanced thoracic esophageal squamous cell carcinoma. The treatment regimen was tislelizumab plus nab-paclitaxel and carboplatin. The results have been reported in 2021 ESMO IO. Abstract 144P.

Changes in the text: No changes in the text.

Comment 2: Page 5, Line 150: The authors used the Japanese lymph node classification in this study, but no reference was cited. Please insert the appropriate reference here.

Reply 2: Thanks to the reviewer's comment. We have inserted the appropriate reference here (Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. Esophagus. 2017;14(1):1-36).

Changes in the text: We have inserted the appropriate reference (see Page 16, line 360)

Second Round Peer Review

Comment 1: Tense of the text of manuscript is awkward. The manuscript needs additional language editing. For example, in the abstract

a) Lines 24-28, consider: "Definitive chemoradiation is the preferred treatment for Cervical esophageal carcinoma (CEC), per the National Comprehensive Cancer Network (NCCN) guidelines. However, in treatment failures, salvage surgery poses significant technical challenges. If non-responders could be identified, prior to chemoradiation, these patients may benefit from primary esophagectomy."

b) Lines 28-31, consider: "PD-1 inhibitor is widely used and recognized as an effective treatment method in various cancers including esophageal cancer, and our previous study indicated that 45.4% of esophageal cancer patients treated with PD-1 monoclonal antibody before surgery could obtain a pathologic complete remission."

c) Lines 31-35, consider: "Therefore, we propose to screen for treatment response to neoadjuvant immunotherapy plus chemotherapy to select patients who are radiosensitive and potential candidates for laryngeal preservation. While non-responders are likely to be insensitive to chemoradiation would be offered radical esophagectomy."

d) Line 41, change "will be received" to "will receive"

e) Line 47 change "endpoint" to "endpoints."

Reply 1: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: a） Lines 24-28, we have modified to "Definitive chemoradiation is the preferred treatment for Cervical esophageal carcinoma (CEC), per the National Comprehensive Cancer Network (NCCN) guidelines. However, in treatment failures, salvage surgery poses significant technical challenges. If non-responders could be identified, prior to chemoradiation, these patients may benefit from primary esophagectomy."

b) Lines 28-31, we have modified to “PD-1 inhibitor is widely used and recognized as an effective treatment method in various cancers including esophageal cancer, and our previous study indicated that 45.4% of esophageal cancer patients treated with PD-1 monoclonal antibody before surgery could obtain a pathologic complete remission.”

c) Lines 31-35, we have modified to “Therefore, we propose to screen for treatment response to neoadjuvant immunotherapy plus chemotherapy to select patients who are radiosensitive and potential candidates for laryngeal preservation. While non-responders are likely to be insensitive to chemoradiation would be offered radical esophagectomy.”

d) Line 41, we have changed “will be received” to “will receive”

e) Line 47, we have changed “endpoint” to “endpoints.”

Comment 2: Lines 80-82: consider: “The ideal treatment would improve long-term survival, preserve organ function and good quality of life.”

Reply 2: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: Lines 80-82: We have modified to “The ideal treatment would improve long-term survival, preserve organ function and good quality of life.”

Comment 3: Line 86, eliminate “part of.”

Reply 3: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: We have eliminated “part of.”

Comment 4: Lines 112-114, this study intends to identify patients who should undergo surgical resection (non-responders) and those who should undergo definitive chemoradiation (responders to induction therapy). The wording in the text states that all patients are planned to undergo neoadjuvant therapy and resection.

a) Consider: Potentially curative CEC patients who are candidates for neoadjuvant immunochemotherapy followed by resection or definitive chemoradiation will be

recruited for this study."

Reply 4: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: We have modified to "Potentially curative CEC patients who are candidates for neoadjuvant immunochemotherapy followed by resection or definitive chemoradiation will be recruited for this study."

Comment 5: Lines 170-172. Imaging every 4 weeks seems to be excessive. Could the authors clarify why monthly imaging would be performed?

Reply 5: Our initial idea was that early local recurrence or metastasis can be detected more easily with a high frequency of follow-up. However, after investigator discussion, we agree with the reviewers that imaging assessment every 4 weeks is indeed excessive, so we have revised to imaging assessment every 3 months.

Comment 6: Line 235, consider changing: "Another research" to "Nakata et al reported a 5-year survival of CEC patients after dCRT of over 50%. In the chemoradiotherapy group, 15 patients failed to acquire local control and 11 of then underwent salvage surgery, and the 5-year OS of the salvage surgery group was 64.8% which was significantly higher than that in conservative treatment group (44%) (15).

Reply 6: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: Line 235-240, We have modified to "Another research" to "Nakata et al reported a 5-year survival of CEC patients after dCRT of over 50%. In the chemoradiotherapy group, 15 patients failed to acquire local control and 11 of then underwent salvage surgery, and the 5-year OS of the salvage surgery group was 64.8% which was significantly higher than that in conservative treatment group (44%) (15)."

Comment 7: Lines 270-281, the authors summarize the NEOCRTEC 5010 and CROSS trials however it is not clear that these trials support the argument that the authors are proposing. Both trials establish that induction chemoradiation followed by surgery is

superior to surgery alone for thoracic and EG junction cancers. The authors are proposing screening for potential response to definitive chemoradiation with induction chemoimmunotherapy. Then offering surgery for non-responders or definitive chemoradiation for responders. Consider eliminating or modifying this portion of the discussion. It could be argued that CEC represents a different disease process than more distal cancers. Certainly, the challenges of resection after chemoradiation are different in these two disease processes.

Reply 7: The reviewer has made a very good point here. We agree with the reviewer's opinion.

Changes in the text: We have eliminated this portion of the discussion.

Comment 8: Line 296, change, "screen" to "screening"

Reply 8: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: Line 296: we have changed "screen" to "screening"

Comment 9: Lines 262-269,

a) Lines 262-263, consider modifying the wording to a less forceful statement such as: "…with the acculumated evidence of clinical trials, the NCCN guidelines for CEC might be updated for the following reasons…"

b) consider including the references for point 1 (lines263-265)

Reply 9: Many thanks to the reviewers for pointing out our manuscript language problems and giving very good comments.

Changes in the text: Lines 262-263: we have changed "with the accumulation of evidence from clinical trials, the NCCN guidelines for CEC need to be updated for the following reasons" to "with the acculumated evidence of clinical trials, the NCCN guidelines for CEC might be updated for the following reasons"

Comment 10: This study holds great promise and may mark the beginning of a paradigm shift in the treatment strategy of CEC. I look forward to the results of this

trial.

Reply 10: Thanks to the reviewers for their recognition of our work, we equally expect to improve the treatment outcome of cervical esophageal squamous cell carcinoma through this study.