Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-24-169

Reviewer A

Comment 1: In this study, two courses of preoperative treatment were defined as the standard, but there were a certain number of cases in which three or more courses were performed, and the reasons for this should be described in detail. In addition, a comparison of the safety and efficacy between patients who received two courses and those who received three or more courses should be described.

Reply 1: Thank you! Safety and efficacy comparisons have been made between patients who received two courses and those who received three or more courses, but there was no difference in the results (Table S1). The reasons for patients receiving three or more courses of treatment have been stated, we have modified our text as advised (see Page 10-11, line 180-185; Page 12, line 206-208 and Table S1).

Changes in the text: Seventeen patients (17/106, 16.0%) who underwent more than two cycles of neoadjuvant therapy. These patients received more than two cycles of neoadjuvant therapy for the following reasons. Nine patients (9/17, 52.9%) did not show significant reduction in lymph nodes based on preoperative imaging assessment. Six patients (6/17, 35.3%) did not show significant reduction in tumor size based on preoperative imaging assessment. Two patients (2/17, 11.8%) received more than two cycles of neoadjuvant therapy due to personal reasons.
Therapeutic efficacy comparison had been made between patients who received two courses and those who received three or more courses, but there was no difference in the results (Table S1).

Comment 2: Adverse events of preoperative treatment need to be categorized and presented as irAE and chemotherapy adverse events. Additional analysis of the association between irAE and chemotherapy adverse events and postoperative complications is also needed.

Reply 2: Thanks for your sincere advice! We feel very sorry that it is difficult for us to conduct additional analysis of the association between chemotherapy adverse events, irAE and postoperative complications. Our study exists data bias due to the retrospective nature. Based on the data collection, we found that there were no patients with chemotherapy alone in this study. We were unable to divide the patients into chemotherapy alone and immunotherapy combination chemotherapy groups and therefore could not analyze the association between the groups. The irAEs and chemotherapy-related adverse events have been classified, we have modified our text as advised (see Page 14, line 253-263 and Page 30-31, Table 3).

Changes in the text: Neoadjuvant therapy-related adverse events in this study were divided into chemotherapy-related adverse events and immune-related adverse events, which are summarized in Table 3. The most common grade 1 or 2 chemotherapy-related adverse events were low hemoglobin (53/122, 43.4%), leukopenia (50/122, 40.9%), elevated aminotransferases (41/122, 33.6%), and thrombocytopenia (26/122, 21.3%). The most common grade 3 or 4 chemotherapy-related adverse events were leukopenia (13/122, 10.7%), low hemoglobin (10/122, 8.2%), neutropenia (7/122, 5.7%), and elevated aminotransferases (7/122, 5.7%). A total of 42 patients (42/122, 34.4%) had immune-related adverse events (irAEs), among which the most common grade 1 or 2 irAEs were skin rashes (15/122, 12.3%), cutaneous capillary proliferation (11/122, 9.0%), pneumonitis (8/122, 6.6%), diarrhea (6/122, 4.9%), hypothyroidism (5/122, 4.1%), and hyperthyroidism (2/122, 1.6%). The most common grade 3 or 4 irAEs were rash (2/122, 1.6%), pneumonia (2/122, 1.6%), and diarrhea (1/122, 0.8%).

Comment 3: Additional multivariate analysis is needed to analyze prognostic factors in Table 2.

Reply 3: Thanks for your advice! We have modified our text as advised (see Page 13-14, line 248-250 and Page 28-29, Table 2).

Changes in the text: Multivariate analyses did not produce meaningful results, possibly because this study was retrospective, the sample data may be biased, and larger sample sizes are needed to explore prognostic factors. (Table 2)

Comment 4: The authors have compared the safety and efficacy of preoperative ICI + chemotherapy primarily with preoperative CRT, but should be compared with previous reports on other preoperative chemotherapies. The safety and efficacy of preoperative DCF therapy for esophageal squamous cell carcinoma should be cited and compared with the present preoperative ICI plus chemotherapy.

Reply 4: Thanks for your advice! We have modified our text as advised (see Page 15-16, line 288-294).

Changes in the text: JCOG1109 compared the doublet and triplet of chemotherapy and chemoradiotherapy as neoadjuvant treatment. The results showed that the pCR rate in the DCF group (docetaxel + cisplatin + 5-FU) was significantly higher than that in the CF group (cisplatin + 5-FU) (2.1% vs 19.8%). The R0 resection rate in the DCF group was higher than that in the CF group (84.4% vs 85.6%). The study results indicated that both the CF group and the DCF group had lower pCR rates and R0 resection rates than those reported in this study (23).

Comment 5: NLR, which the authors focused on, has been reported many times before as a prognostic marker. In the present study, it is more interesting to examine

how NLR relates to the safety and efficacy of preoperative ICI + chemotherapy rather than prognosis. Data should be presented on how pre-treatment NLR and changes in NLR during preoperative treatment are associated with the safety and efficacy of preoperative ICI + chemotherapy.

Reply 5: Thanks! We have modified our text as advised (see Page 11-12, line 204-218; Page 33, Figure 2 and Table S1).

Changes in the text:
3.3 Correlation between neoadjuvant therapy cycle, NLR changes and therapeutic efficacy
According to the postoperative pathological remission, the patients were divided into MPR group and non-MPR group. Therapeutic efficacy comparison had been made between patients who received two courses and those who received three or more courses, but there was no difference in the results (Table S1). The NLR before neoadjuvant therapy and as well as before surgery were compared between the two groups. The results showed that there was no difference in NLR before neoadjuvant therapy between the MPR group and the non-MPR group (Table S1). However, patients in the MPR group had a lower last NLR before surgery compared with the non-MPR group (median 1.74 vs 2.47, P = 0.003) (Table S1). ΔNLR was defined as the ratio of the last NLR before surgery to t the NLR before neoadjuvant therapy. When ΔNLR <1, it indicates a decrease in NLR, and when ΔNLR ≥1, it indicates an increase or no change in NLR. Next, we analyzed the changes in NLR, and the results showed that a decrease in NLR was associated with a higher probability of achieving MPR compared to an increase in NLR (74.3% vs 31.3%, P=0.001) (Table S1). Figure 2 illustrates the distribution of ΔNLR in the MPR and non-MPR groups, revealing that patients with an increase in NLR were more concentrated in the non-MPR group.

Comment 6: The following statement on page 5, line 69, lacks a connection to the previous context: is it an error for chemoradiotherapy rather than chemotherapy? “The findings imply that the combination of neoadjuvant immunotherapy and chemotherapy 70 is more effective than neoadjuvant chemotherapy alone."

Reply 6: Thanks! There is nothing wrong with that, and I modified some things to make the logic more accurate (see Page 6, line 74-76).

Changes in the text: Compared to simple chemotherapy, it demonstrated unprecedented rates of R0 resection and pathologic complete response (pCR).

Comment 7: The neutrophil-to-lymphocyte ratio on page 5, line 76 should be NLR since it is the second entry.

Reply 7: Thanks! We have modified our text as advised (see Page 6, line 92).

Changes in the text: In a retrospective study carried out by Shota et al, it was observed that NLR during relapse could serve as a prognostic biomarker for ESCC (13).

Comment 8: The data of serum markers such as CA125, CYFRA21-1, AFP, SCC, etc. in Figures 5 and 6 should be clearly indicated at which timing.

Reply 8: Thanks! We have modified our text as advised (see Page 35, line 525-526 and Page 36, line 534-535).

Changes in the text: Tumor markers are all indicators of patients before neoadjuvant therapy.

Reviewer B

Comment 1: There is no information about neoadjuvant chemotherapy. Please provide the regimens of the neoadjuvant chemotherapy other than immunotherapy in Method section and table.

Reply 1: Thank you! We have modified our text as advised (see Page 8, line 129-131 and Page 27, Table 1).

Changes in the text: The chemotherapy regimen consisted of paclitaxel plus platinum-based agents, specifically: paclitaxel (135-175mg/m^2, q3w) + cisplatin (75-100mg/m^2, q3w) / nedaplatin (80-100mg/m^2, q3w) / carboplatin (AUC=5, q3w).

Comment 2: I considered the incidence of vocal cord paralysis was quite low. Please add the type of esophagectomy and the range of lymph node dissection in Method section and table. Did the authors perform recurrent nerve lymph node dissection?

Reply 2: Thank you! All surgical patients underwent Two-field lymph node dissection and Three-field lymph node dissection, and most of them underwent lymph node dissection of the recurrent laryngeal nerve. We have modified our text as advised (see Page 8, line 132-136; Page 14, line 266 and Page 27, Table 1).

Changes in the text:
In this study, 106 patients who underwent surgery experienced postoperative complications including pneumonitis in 27 cases (25.5%), vocal cord paralysis in 23 cases (21.7%), pleural effusion in 16 cases (15.1%), gastrointestinal reactions in nine cases (8.5%), esophageal anastomotic stenosis in eight cases (7.5%), anastomotic leakage in five cases (4.7%), and bleeding in three cases (2.8%).
Esophagectomy includes right thorax-epigastric two-incision esophagectomy (Ivor-Lewis method) and left cervical-right thorax-epigastric midline three-incision

esophagectomy (McKeown method). Lymph node dissection includes two-field lymph node dissection (thoracoabdominal + superior mediastinum) and three-field lymph node dissection (bilateral lower neck and supraclavicular + thoracoabdominal + superior mediastinum).

Comment 3: A total of 11 patients underwent postoperative radiation therapy. Please provide the indication of postoperative radiation therapy.

Reply 3: Thank you! We have modified our text as advised (see Page 11, line 185-188).

Changes in the text: Eleven patients (11/122, 9.0%) received postoperative radiotherapy, with six (6/11, 54.5%) undergoing lymph node radiotherapy due to lymph node recurrence metastasis, three (3/11, 27.3%) receiving brain radiotherapy due to brain metastasis, and two (2/11, 27.3%) receiving bone radiotherapy due to bone metastasis.

Comment 4: The authors described neoadjuvant immunotherapy was feasible and effective for resettable ESCC patients. However, the patients underwent also chemotherapy in addition to immunotherapy. Therefore, the authors should modify abstract and conclusions to avoid misleading. (For example, neoadjuvant immunotherapy→neoadjuvant immunotherapy combined with chemotherapy)

Reply 4: Thank you! We have modified our text as advised (see Page 3, line 27; Page 3, line 30-31 and Page 3, line 41).

Changes in the text: The objective of this research was to investigate the effectiveness and safety of neoadjuvant immunotherapy combined with chemotherapy in treating surgically removable esophageal squamous cell carcinoma (ESCC).
From January 1, 2016 to April 1, 2023, we conducted a retrospective analysis of patients diagnosed with resectable esophageal cancer who underwent neoadjuvant immunotherapy combined with chemotherapy.
Neoadjuvant immunotherapy combined with chemotherapy demonstrates satisfactory efficacy in the treatment of locally advanced ESCC, with manageable treatment-related adverse events and postoperative complications.

Comment 5: In line 118 of page 7, the primary pathologic response (MPR) was incorrect. Please change to the major pathologic response (MPR).

Reply 5: Thank you! We have modified our text as advised (see Page 9, line 146).

Changes in the text: The major pathologic response (MPR) was defined as less than 10% residual tumor cells, and pCR was defined as the absence of evidence of residual tumor cells (18).