Dear Editor,

I thank the reviewers for the valuable and instructive comments and would like to answer by a point-to-point response as follows.

Reviewer #1:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Summary of the manuscript. The manuscript really well summarized perioperative immunotherapy in patients with esophageal squamous cell carcinoma. As a reviewer there are some minor comments. 1. Page 4. Introduction. Concerning KEYNOTE-181 (ref. 28), the authors may state that Grade 3-5 adverse events less occurred in patients with pembrolizumab than in those with chemotherapy. In addition, the authors may also describe about adverse events in other studies (ref. 29 – 36).

Thank you for this great question.

It was reported that grade 3-5 trAEs occurred in 18.2% of patients with pembrolizumab versus 40.9% in those who underwent chemotherapy. The grade 3-5 trAEs occurred fewer in immunotherapy versus chemotherapy with 18.8% v 55.8% in “RATIONALE-302”, 18% vs 63% in “ATTRACTION-3”, and 19% vs 39% in “ESCORT”.

The occurrence rates of the grade 3-5 trAEs in these trials were more likely to be comparable.

I have added these words in the text in Page 5-6 in the revised manuscript.

2. Page 6. Neoadjuvant immunotherapy vs. conversion chemotherapy. Were there any conversion cases with immunotherapy in the cited reports?
Thanks for this comment.

This is a great question. I re-read the references and did not find any words about conversion cases. In table 1, it was summarized of reported clinical results of neoadjuvant immunotherapy for resectable ESCC, without those un-resectable cases which maybe benefitted from immunotherapy to be conversion cases. It should be explored in other trials which focus on those un-resectable cases to get a conversion therapy.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: I would like to congratulate all authors, for making efforts to take up this important subject, probing the current developments in the management of oesophageal squamous cell carcinoma. This review article addresses nicely the current developments of immunotherapy in managing oesophageal SCC. The article requires a lot of language polishing, and attending to grammatical errors would urge authors to utilise a standard review article template, rewrite the text with an introduction, purpose, objectives, and methodology, ending with a conclusion: Ring future and implications.

Thank you for the great comments.

Last week, the article has been proofread by Ms Joanne Gao, an expert in English language teaching who has been living in and working in ELICOS (English Language Intensive Courses for Overseas Students) sector in Australia for more than 15 years.

This review is written according to the review article template on the web of the BPG. I think the style of this review is acceptable for the journal.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: General Comments: In this manuscript, the author discusses the general treatment of esophageal cancer, followed by a specific discussion of immunotherapy. The article provides an overview of perioperative chemotherapy using immune checkpoint inhibitors, including the drugs used in immunotherapy, their mechanisms of action, and clinical trials conducted thus far. Reading this article can help readers understand the current state of perioperative immune checkpoint inhibitor therapy for esophageal cancer, which is useful. If the article were to provide more detailed information, readers would benefit even further.

Specific recommendations for revision-a) major:

1. In the introduction, the article notes that preoperative chemoradiotherapy (CRT) + surgery is the standard treatment in many countries. However, there are numerous clinical trials being conducted for preoperative chemotherapy + surgery, including the use of immune checkpoint inhibitors (ICI). The author is recommended to explain the reason for this.

Thank you for the comment.

In the section of “Introduction”, it has been told that “The five-year OS in patients undergoing nCRT and surgery is approximately 50%, and the incidence of local recurrence or distant metastasis remains high. Relapse after NCRT is common, and a major hurdle to overcome.” (Page 5)

And it was also told that “Neoadjuvant immunotherapy has been tried in a variety of other malignancies, including lung cancer, melanoma, bladder cancer, colon cancer and glioblastoma.” (Page 6) These two reasons made numerous of clinical trials being conducted for preoperative chemotherapy + surgery, including the use of immune checkpoint inhibitors (ICI).

I think these are the two reasons for the numerous clinical trials being conducted for those neoadjuvant therapy.

Furthermore, it is recommended to also discuss the issues associated with preoperative CRT. For example, late complications may have a negative impact on survival rates. By providing additional details on these issues, readers can gain a better understanding of the limitations and potential drawbacks of preoperative CRT, which may help to justify the need for alternative treatments like preoperative chemotherapy + surgery with ICI.

Thank you for this comment. I have added some details on the issues associated with preoperative CRT as below. The words were in Page 4 of the revised manuscript.

The utility of preoperative chemoradiotherapy has been confirmed in several subsequent meta-analyses showing improved overall survival when compared to all other treatment modalities including surgery alone, neoadjuvant chemotherapy and neoadjuvant radiotherapy, however at the cost of increased postoperative mortality. In a Japanese study, late complications were examined. Grade 2 anastomotic stricture was the most common event and was observed in 30% of the 33 patients. A total of 12 events of Grade 3 or worse complications were observed in 10 patients, including gastric tube ulcer, cardiac complications, and pulmonary complications. The 5-year incidence rate was 22%, and three patients died of the late complications. A clear advantage to neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy was not established.

2. In the last part of the introduction, the article discusses preoperative chemotherapy with ICI for other cancers. It would be desirable to provide information on the effectiveness, surgical outcomes, and long-term outcomes in other cancers where preoperative chemotherapy with ICI has been used.

Thank you for this comment. I have added some information on the issues associated with effectiveness, surgical outcomes, and long-term outcomes in other cancers where preoperative chemotherapy with ICI has been used. The words were in Page 5-6 of the revised manuscript.

In the clinical trial, NCT02259621, neoadjuvant nivolumab was associated with few side effects, did not delay surgery, and induced a major pathological response (MPR) in 45% of resected tumors. In the trial of NADIM, patients received neoadjuvant treatment with paclitaxel and carboplatin plus nivolumab. In 51 patients for eligibility, of whom 46 patients received neoadjuvant treatment and surgery. At 24 months, progression-free survival (PFS) was 77.1%. 8 of 27 patients suffered from melanoma experienced a complete or MPR after a single dose of anti-PD-1, Pembrolizumab, all of whom remained disease free. In the single-arm phase 2 study, investigating two cycles of atezolizumab before cystectomy in 95 patients with muscle-invasive urothelial cancer (NCT02662309). The pathological complete response rate was 31%. In the exploratory NICHE study (NCT03026140), patients in early-stage colon cancers, with mismatch repair-deficient (dMMR) or MMR-proficient (pMMR) tumors, received a single dose of ipilimumab and two doses of nivolumab before surgery. Pathological response was observed in 20/20 dMMR tumors, with 19 MPRs and 12 pathological complete responses (pCRs). In MMR-proficient (pMMR) tumors, 4/15showed pathological responses, with 3 MPRs and 1 partial response. In the single-arm phase 2 clinical trial (NCT02550249)，a presurgical dose of nivolumab followed by postsurgical nivolumab until disease progression or unacceptable toxicity was tested in 30 patients. No obvious clinical benefit was substantiated following salvage surgery, two of the three patients treated with nivolumab before and after primary surgery remain alive 33 and 28 months later.

3. Although trAEs are explained in the main text, it is strongly recommended to further discuss the impact of trAEs that occur during preoperative treatment on surgery, based on previous reports and the author's own thoughts. For example, this may include the occurrence of trAEs that make surgery impossible, the extension of the time until surgery due to trAEs, and the impact of trAEs on surgical complications.

Thank you for this comment. I have further discussed the impact of trAEs that occur during preoperative treatment on surgery, based on previous reports and the author's own thoughts. These words, as shown below, were and could be read in Page 14-15.

Neoadjuvant immunotherapy is a double-edged sword, with the aim of enabling patients to receive better treatment in the future. Doctors need to use immunotherapy to kill tumor cells while reducing the damage to normal organs caused by immunotherapy. Impact of trAEs that occur during preoperative treatment on surgery should also be concerned. However, it is not uncommon for things to go against one's wishes. In the trial of “KEEP-G 03”, Grade 3-4 treatment-related adverse events (TRAEs) occurred in 36.7% (11/30) of patients. All TRAEs were hematological toxicities; none caused ≥30 days surgical

delay. However, in the multicenter, single- arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced ESCC, 34 patients (56.7%) had adverse events of grade 3 or worse, and one patient (1.7%) occurred a grade 5 adverse event and died due to pneumonia and acute respiratory failure. The risk of increased surgical complications after immunotherapy also exists. Therefore, before conducting neoadjuvant immunotherapy, it is best to form a multidisciplinary team related to trAEs in order to conduct comprehensive evaluation at any time during the immunotherapy, to detect and treat trAEs early, and minimize the impact of subsequent treatment and related complications caused trAEs. Evaluation or exploration of some biomarker related to trAEs should also be emphasized in the research field.

4. At the end of the ISSUES section, there is a statement that long-term results are awaited. I would like to know the author's thoughts on the expected long-term outcomes for esophageal cancer based on the effects seen in other cancer treatments.

Thank you for this comment. I have further discussed my thoughts on the expected long-term outcomes for esophageal cancer based on the effects seen in other cancer treatments. These words, as shown below, could be read in Page 17.

Neoadjuvant anti–PD-1 therapy has shown promise for resectable non–small cell lung cancer (NSCLC). A 5-year clinical outcome from the trial (NCT02259621), representing the longest follow-up data for neoadjuvant anti–PD-1 in any cancer type. With a median follow-up of 63 months, 5-year RFS and OS rates were 60% and 80%, respectively. Another study which aimed to evaluate the efficacy and feasibility of neoadjuvant anti–PD-1 treatment for localized mismatch repair–deficient (dMMR) colorectal cancer (CRC) had also reported a long-term follow-up data. Among patients undergoing surgery or achieving CR, the 2-year tumor-specific disease-free and overall survival rates were both 100%.

Specific recommendations for revision-b) minor:

1. I suggest providing more detailed information on the long-term outcomes, such as survival rates, while introducing CheckMate 577 as one of the most impactful clinical trials for checkpoint inhibitors in adjuvant chemotherapy for esophageal cancer.

Thank you for this comment. More detailed information on the long-term outcomes, such as survival rates, while introducing CheckMate-577 had been added in Page 13. The words are shown as below.

The CheckMate-577 trial is a global, randomized, double-blind, placebo-controlled phase 3 trial. In the trial, the disease-free survival benefit of Nivolumab for ESCC was observed (29.7 vs 11.0 mos).

2. The last sentence of the Introduction states that "an overview of the role of ICIs in this field, according to the stage of disease, alongside a discussion of the promising biomarkers and future perspectives." However, there is no mention of treatment according to disease stage in the main text. The article should be revised to include this information or additional details should be added to the main text. I hope these comments will be helpful.

Thank you for the great comment. I delete the words“according to the stage of disease,”and the sentence is more appropriate.