Peer Review File

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Reviewer A

This manuscript reports on metanalysis at investigating the effects of immunotherapy and chemotherapy (NICT) in management of esophageal Squamous cell carcinomas (ESCC).

The manuscript is well written. The research methods are sound and appropriately defined. The results clearly demonstrate the superiority of NICT over chemotherapy alone in terms of response rates and survival outcomes.

Few minor points -

Comment 1: Page 2 - lines 54 - 59 - the terms neoadjuvant chemoradiotherapy and NICT have been used interchangeably which needs appropriate correction and modification.
Reply 1: Dear Reviewer Expert, we greatly appreciate your affirmation and suggestions. we have modified our text as advised.
Changes in the text: we have modified our text as advised (see Page 2, line 61-65).

Comment 2: page 2 Line 54 - the abbreviation MPR has been used without corresponding explanation. in addition, there are several other abbreviations used in the manuscript with no corresponding explanation of the abbreviation.
Reply 2: I have completed defining terms such as MPR and PCR in accordance with the requirements. (MPR: major pathological response, PCR: pathological complete response)
Changes in the text: we have modified our text as advised (see Page 2, line 59-60).

Reviewer B

The authors present a meta-analysis including 13 heterogeneous studies of neoadjuvant regimes for esophageal squamous cell carcinoma and report improved pCR, MCR, R0 resections and 1-year overall survival in those who received chemotherapy+ immunotherapy compared to (allegedly) chemotherapy alone. Also, the authors also report increased postoperative complications (rash and effusion) in the induction IO group.
I have the following comments:

Comment 1:-The study has many gaps in methodology, and data weaknesses. For example, the Forest plot data (such as I2) does not visually match the estimates. Another

example is Figure 2, where the authors evaluated 11/13 studies as high-quality in terms of random sequence generation. This is inaccurate considering the retrospective design of the included studies. I would recommend reviewing the statistical analysis of this study to ensure accuracy.

Reply 1: Dear Reviewer, we extend our sincerest gratitude for your suggestions. Herein, I provide an explanation of the relevant recommendations.

-In the context of forest plots, when assessing heterogeneity visually, we typically consider the range of the 95% confidence intervals across different studies and their degree of overlap, as well as the range of the pooled diamond plot. Although many studies in the article show a wide range of confidence intervals, there is often overlap. Furthermore, the heterogeneity of the forest plot ultimately needs to be assessed using I^2, along with specific P-values. Furthermore, there are limited publications on subgroup analysis; hence, specific heterogeneity analyses for each subgroup are not presented. The figures originally showcase representative heterogeneity. To enhance the clarity of the information presented in the figures, I have revised all forest plots to display the results of the heterogeneity analyses for each subgroup.

- In response to the selection of quality assessment methods, I have given thorough consideration to your suggestions and have engaged in in-depth study and adjustments. All 13 articles included in this study are retrospective in nature, as detailed in Figure 2(The content has been revised.). To ensure the accuracy of the statistical results, we have revised our literature quality assessment system to the Newcastle-Ottawa Scale (NOS Scale), with the specific scoring indicated in Figure 2. Overall, the quality of the 13 publications is above average, with a good level of credibility.

Changes in the text: In response to the heterogeneity I^2 issue raised by the reviewing experts, I have replaced all images throughout the manuscript, displaying the I^2 for each subgroup. (see Page 4, line 122-124, Figure 2/ see Page 5, line 140-142, Figure 3/ see Page 5, line 147-149, Figure 4/ see Page 5, line 157-161, Figure 5 and 6/ see Page 6, line 170-174, Figure 7 and 8/ see Page 7, line 189-195, Figure 9, 10 and 11/ see Page 8, line 195-204, Figure 12 and 13)

-The specific method for evaluating the quality of literature, we have modified our text as advised (see Page 2, line 94-97). We have provided supplementary information on the specific scoring results for each article, as illustrated in Figure 2(see Page 4, line 122-124, Figure 2).

Comment 2:-The authors fail to specify the type of studies that were included and the type of induction regimes compared. It seems like they include retrospective series comparing induction chemo-immunotherapy with a variety of different approaches (including chemotherapy and /or radiation). Still, this is never addressed in the manuscript. Given the lack of insight on the specific types of regimes that are compared

in this meta-analysis, it is really challenging to interpret the findings and think about generalizability.

Reply 2: The 13 articles examined are all retrospective cohort studies. The majority of these studies compare neoadjuvant immunotherapy combined with chemotherapy to neoadjuvant chemotherapy alone. A few studies, such as the one by Zhang B[30], include neoadjuvant radiotherapy. However, we have selected only those studies that compare neoadjuvant immunotherapy combined with chemotherapy to neoadjuvant chemotherapy alone. Detailed supplementary information on the specific chemotherapy regimens and choices of immunomodulatory drugs is provided in Figure 2.

Changes in the text: we added some data (see Page 4, line 122-124, Figure 2), we have modified our text as advised (see Page 4, line 128-129). The details are shown in the figure below.

Author, reference	Age (male/female) 》		Gender (male/female)		Tumor grade	NICT/ NCT	NCT	NICT	Sugery	Study type	NOS
	NICT	NCT	NICT	NCT			Chemotherapy regimen				
Hong ZN 2022	58.5±7.4	61.0±6.4	22/6	42/53	II-IVA	28/95	Platinum + paclitaxel / Platinum + Fluorouracil	Sintilimab/Pembrolizumab/ Camrelizumab	McKeown	retrospective	8
Jing SW 2022	NA	NA	30/17	33/14	II-III	47/47	Platinum + paclitaxel / Platinum + Fluorouracil	Sintilimab/Pembrolizumab/ Camrelizumab/Toripalimab	McKeown	retrospective	9
Huang BJ 2021	59.2±7.3	58.9±6.4	21/2	30/1	II-IVA	23/31	Docetaxel + Nidaptin	Pembrolizumab	Mediastinoscopy+laparoscopic partial esophagectomy+cervical esophagogastric anastomosis (transabdominal+cervical surgery)	retrospective	7
Zhou RQ 2023	65.89±6.06	64.50±4.54	17/2	31/9	II-IVA	19/40	Docetaxel + Nidaptin	Camrelizumab	McKeown	retrospective	7
Zhang BH 2023	60.68±7.44	60.08±7.78	31/3	94/3	II-IVA	34/97	Platinum + Paclitaxel	Camrelizumab	NA	retrospective	9
Qiao YJ 2022	64.15±7.29	64.15±7.29	38/10	147/59	I-IV	48/206	Platinum + Paclitaxel	Camrelizumab	McKeown	retrospective	7
Wang XZ 2023	57.13±9.11	58.80 ± 9.21	33/24	36/22	IIA-III	57/58	Pemetrexed + Cisplatin	Pembrolizumab	Left thoracoesophageal resection and esophagogastric (or colon or jejunal) chest/neck anastomosis	retrospective	7
Chen J 2021	56.37±5.81	54.86±7.05	31/18	35/14	II-III	49/49	Pemetrexed + Cisplatin	Pembrolizumab	Left thoracoesophageal resection and esophagogastric (or colon or jejunal) chest/neck anastomosis	retrospective	6
Zhang XW 2022	57.91±8.06	56.70±7.95	30/16	29/17	II-III	46/46	Nidaptin + Paclitaxel	Pembrolizumab	NA	retrospective	7
Wang JP 2023	60.06±3.01	60.03±2.98	17/13	16/14	II-IVA	30/30	Carboplatin + Paclitaxel	Camrelizumab	NA	retrospective	7
Wang XL 2022	64.21±3.27	63.73±3.32	18/2	20/3	II-IVA	20/23	Cisplatin + Paclitaxel	Camrelizumab	NA	retrospective	6
Yao P 2023	58.89±7.29	61.28±7.91	32/6	25/4	II-IVA	38/29	Nidaptin + Paclitaxel	Sintilimab	Thoracoscopic three incision esophagectomy for esophageal cancer	retrospective	7
Liu F 2023	56.26±5.11	57.98±5.75	20/23	18/25	IIB-IVA	43/43	Nidaptin + Paclitaxel	Toripalimab	McKeown	retrospective	7

Other comments:

Abstract:
-Provide definitions for all abbreviations at first mention.
Reply: Thank you for your detailed corrections. I have carefully reviewed the abstract section and have provided the full names of CNKI, VIP, MPR, ORR, and NCT at their first appearance.
Changes in the text: Abstract: We have modified our text as advised (see Page 1, line 9, 18-20).

-Need to mention what type of studies were included in this meta-analysis in the abstract and title.
Reply: This study has included a total of 13 retrospective cohort studies, encompassing 1276 patients, which have been fully detailed in the abstract.
Changes in the text: We have modified our text as advised (see Page 1, line 15).

-The authors mention the agent carrelizumab “led to an increase incidence of rash”. Establishing causality in a meta-analysis of heterogeneous studies is complicated, especially during a subgroup analysis. I suggest referring to this as an “association”.

Reply: I strongly endorse the recommendations of the review experts and have revised the statement to read: "Subgroup analysis indicates that the use of carfilzomib is associated with an increased incidence of rash."
Changes in the text: We have modified our text as advised (see Page 1, line 24-25).

-The conclusion states that this study demonstrates favorable efficiency and safety profiles with NICT. Still, the authors, report increased perioperative complications in the Results section before. As it stands, the conclusions are not supported by the results reported in the abstract. This needs to be modified.
Reply: The conclusions have been revised as required: “the new adjuvant immunotherapy demonstrates favorable efficacy in patients with locally advanced esophageal squamous cell carcinoma (ESCC), while also increasing the incidence of adverse events. Therefore, in clinical treatment, the selection should be based on the patient's physical condition and the degree of response to medication.”
Changes in the text: We have modified our text as advised (see Page 1, line 28-30).

Introduction:
-It is unclear if NICT represents neoadjuvant immunotherapy combined with immunotherapy (line 55) or neoadjuvant chemoradiotherapy (line 56).
Reply: Introduction:
Thank you for your correction. We have made the amendment, and the experimental group (NICT) represents neoadjuvant immunotherapy combined with chemotherapy.
Changes in the text: Introduction:
-We have modified our text as advised (see Page 2, line 61-65).

Methodology:
-Clarifying the aim of this study is crucial. For this, please look at prior comment.
Reply: In accordance with the aforementioned commentary, I have expanded upon the objectives of this study in Methodology 1.1.
Changes in the text: We have modified our text as advised (see Page 2, line 70-72).

-Line 127 –“Among the three studies with Medication Possession Ratio data”. Please clarify what this means. Did you mean “Major pathologic response”?
Reply: Yes, there was a mistake in the original version, which has now been corrected. The text refers to the "Major pathological response."
Changes in the text: We have modified our text as advised (see Page 5, line 143).