Efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy for resectable esophageal cancer: a systematic review and meta-analysis

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Background: Esophageal cancer is often overlooked in its early stages, with approximately 70% of patients being diagnosed at a locally advanced or late stage. Surgical treatment and chemotherapy are the mainstays of esophageal cancer management. However, for locally advanced esophageal cancer, both surgery alone and chemotherapy alone have high rates of recurrence and metastasis. The objective of the research was to investigate the security and therapeutic efficacy of neoadjuvant immunochemotherapy (NICT) in the treatment of resectable, locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: We conducted a literature search on PubMed, Embase, Cochrane, Web of Science, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), China Biomedical Literature Database, and Wanfang for studies published before November 2023 that investigated on the clinical effectiveness and safety of neoadjuvant immunotherapy in resectable ESCC. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used for assessment, and Stata 17.0 was utilized for meta-analysis and sensitivity analysis.

Results: A total of 13 retrospective cohort studies involving 1,276 patients were included in this analysis. The NICT group showed a higher pathological complete response (pCR) rate [odds ratio (OR) =5.72; 95% confidence interval (CI), 3.40–9.63]. The major pathologic response (MPR) rate, objective response rate (ORR), R0 resection rate, and 1-year overall survival (OS) in the NICT group were better than those in the neoadjuvant chemotherapy (NCT) group (OR =3.70, 95% CI: 2.32–5.91; OR =2.22, 95% CI: 1.44–3.40; OR =2.63, 95% CI: 1.58–4.38; OR =10.08, 95% CI: 4.32–23.56). However, the NICT group also showed a drawback in terms of adverse reactions and postoperative complications. The incidence of rash (OR =4.69, 95% CI: 1.42–15.49) and pleural effusion (OR =3.99, 95% CI: 1.75–9.07) was significantly higher in the NCT group compared to the NICT group. The subgroup analysis indicates that the use of camrelizumab is associated with an increased incidence of rash. Additionally, performing a left thoracic esophagectomy and esophagogastric thoracic procedure significantly improved the R0 resection rate.

Conclusions: Neoadjuvant immunotherapy has shown promising efficacy in patients with locally advanced ESCC; however, it is linked to a higher occurrence of adverse events. Therefore, its use in clinical practice should be carefully considered.

Keywords: Esophageal cancer; neoadjuvant; immunotherapy

Introduction

Malignant esophageal cancer is one of the most common tumors, with a large number of new cases reported annually worldwide. This ranks as the sixth most common cause of cancer-related death (1). In Asia, the incidence of esophageal squamous cell carcinoma (ESCC) remains high, with over 90% of patients being pathologically classified as having this type of carcinoma (2,3). However, due to the lack of distinct early signs, many individuals are typically diagnosed when the disease is advanced, significantly impacting long-term survival prospects (4,5). These statistics underscore the significant threat that esophageal cancer poses to human health.

Based on the results of the CROSS study, preoperative neoadjuvant chemotherapy and radiation therapy have been accepted as the recommended treatment for individuals with advanced locally diagnosed ESCC (6). On the other hand, neoadjuvant chemotherapy may significantly increase toxic side effects and postoperative mortality, according to some research (7). A Japanese study, JCOG9907, demonstrated that radiotherapy did not significantly enhance the effectiveness of neoadjuvant chemotherapy (8), and neither

treatment approach significantly improved long-term patient survival (9,10). Hence, there is an urgent need to develop a new treatment plan that will enhance patient survival, decrease the occurrence of surgical complications, and improve safety.

Immunotherapy aims to boost the immune response against tumors by inhibiting the interaction between tumor cell surface ligands and T lymphocyte surface receptors. This approach has had a transformative effect on the treatment of several types of cancer, including ESCC. Based on the results of the KEYNOTE-590 trial, immunotherapies may be recommended as palliative treatment for patients with advanced esophageal cancer (11). Immune checkpoint inhibitors have been shown in preclinical trials to provide benefits as preoperative treatment. Immunotherapies may promote the development and growth of new antigen-specific T cells inside tumors, which might result in anti-tumor immune responses (12). Numerous studies have examined the effectiveness and side effects of neoadjuvant immunotherapy, including nivolumab (13), pembrolizumab (14), camrelizumab (15-17), sintilimab (18,19), and toripalimab (20-22). Overall, the utilization of neoadjuvant combined immunotherapy results in higher rates of major pathological response (MPR) and pathological complete response (pCR). However, neoadjuvant immunochemotherapy (NICT) represents a novel treatment approach. It is still unknown whether NICT treatment will complicate surgery, increase risk, or lead to post-surgery complications. In order to treat ESCC, this research aims to investigate the safety and therapeutic effectiveness of esophagectomy following NICT. The aim of this study was to investigate the efficacy and safety of NICT in the treatment of locally advanced resectable esophageal cancer. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-198/rc).

Highlight box

Key findings

- The neoadjuvant immunotherapy group demonstrated significant advantages in terms of pathological complete response, major pathologic response, objective response rate, R0 resection rate, and 1-year overall survival.
- The neoadjuvant immunotherapy group had a higher incidence of rash and pleural effusion.
- When it comes to selecting surgical methods, performing a left thoracic esophagectomy and esophagogastric thoracic procedure can significantly enhance the R0 resection rate.

What is known and what is new?

- Neoadjuvant chemotherapy can prolong the survival of patients with locally advanced esophageal cancer and improve their short-term efficacy.
- The combination of neoadjuvant immunotherapy and chemotherapy (NICT) has a more significant advantage in prolonging patient survival and improving short-term efficacy, but it also increases the probability of adverse events such as rash and pleural effusion.

What is the implication, and what should change now?

- The NICT has superior clinical efficacy, but it also increases the incidence of adverse events, and should be used with caution in clinical practice.

Methods

Under the ID CRD42023485797, the study protocol was uploaded to the International Prospective Register of Systematic Reviews database.

Search strategy and trial selection

We conducted a search for articles on the clinical effectiveness of immunotherapy for neoadjuvant treatment of resectable ESCC published before November 2023 in

China Biomedical Literature Database (CBM), Embase, Cochrane, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), PubMed, WanFang and Web of Science. The search keywords included "esophageal cancer", "neoadjuvant therapy", "immunotherapy", "PD-1", "PD-L1", and others.

Inclusion criteria: (I) pathological stage II–IVa; (II) experimental group: NICT; (III) control group: neoadjuvant chemotherapy; (IV) outcome: MPR, pCR, adverse reaction rate, short-term efficacy, R0 resection rate, surgical complications, 30-day, 90-day, and 1-year overall survival (OS).

Exclusion criteria: (I) serious information missing on outcome measures; (II) no more than 10 patients enrolled; (III) single-arm trials; and (IV) duplicate publications, case reports, reviews, expert opinions, and reviews.

Data collection

Using the aforementioned search method, two reviewers independently evaluated titles and abstracts to obtain the following data: (I) baseline data for each study; (II) endpoint data, including MPR, pCR, disease control rate (DCR), objective response rate (ORR), surgical complications, R0 resection rate, and Treatment Related Adverse Events (TRAE) incidence; and (III) study characteristics. To ensure that no data were missing or incorrectly classified, each research was examined more than once. A third researcher was consulted to resolve any disputes.

Assessing publication bias and study quality

The quality of the literature was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), which comprises eight items. The assessment encompasses aspects such as study population selection, comparability, and outcome evaluation. A total score of 9 is assigned, with articles scoring 6 or higher considered to be of high quality. In the event of disagreement during the assessment, a final decision will be reached through thorough discussion or by consulting a third investigator.

Outcome measures

Adverse events were assessed according to the standard Criteria Guidelines for Adverse Events, Version 4.0 (23), while tumor node metastasis classification (TNM) staging corresponded to the American Joint Committee on Cancer

(AJCC), Version 8 (24). After neoadjuvant treatment and surgical removal, pCR was defined as the absence of residual cancer cells in the completely excised cancer material, while MPR was characterized by the presence of fewer than 10% residual tumor cells.

Statistical analysis

Stata 17.0 was utilized for the meta-analysis, and the odds ratio (OR) was used as the pooled analysis measure for binary variables. A significant criterion of $P \leq 0.05$ was utilized to determine if there was a difference between the two groups. The I^2 statistic was employed to measure heterogeneity: If I^2 was less than 50%, we considered heterogeneity absent and used a fixed-effects model. If I^2 was 50% or greater, we considered heterogeneity present and used a random-effects model.

Results

Basic information included in literature

After an initial review, a full-text review, a review of the titles and abstracts, and a final review, a total of thirteen research findings were identified in the literature. Please refer to *Figure 1* for the search flow. *Table 1* presents details about the authors, publication dates, and the number of cases for the 13 studies included in the study characteristics table (25-37).

Literature quality evaluation

All 13 articles represent retrospective studies. The NOS scores of all 13 articles are ≥6, indicating a quality that is above average but below excellent. Please refer to *Table 1* for details.

Evaluation of efficacy outcomes

The study evaluated the efficacy of neoadjuvant immunotherapy by assessing pCR, MPR, DCR, ORR, and R0 resection rate.

Among the six studies (25-28,30,36) with available pCR data, patients in the NICT group had a significantly higher rate of pCR compared to the chemotherapy group [OR =5.72, 95% confidence interval (CI): 3.40–9.63]. Subgroup analysis by immunotherapy group and surgical method revealed that the McKeown procedure led to a higher pCR

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Wang et al. Meta-analysis of neoadjuvant chemo-immunotherapy in ESCC
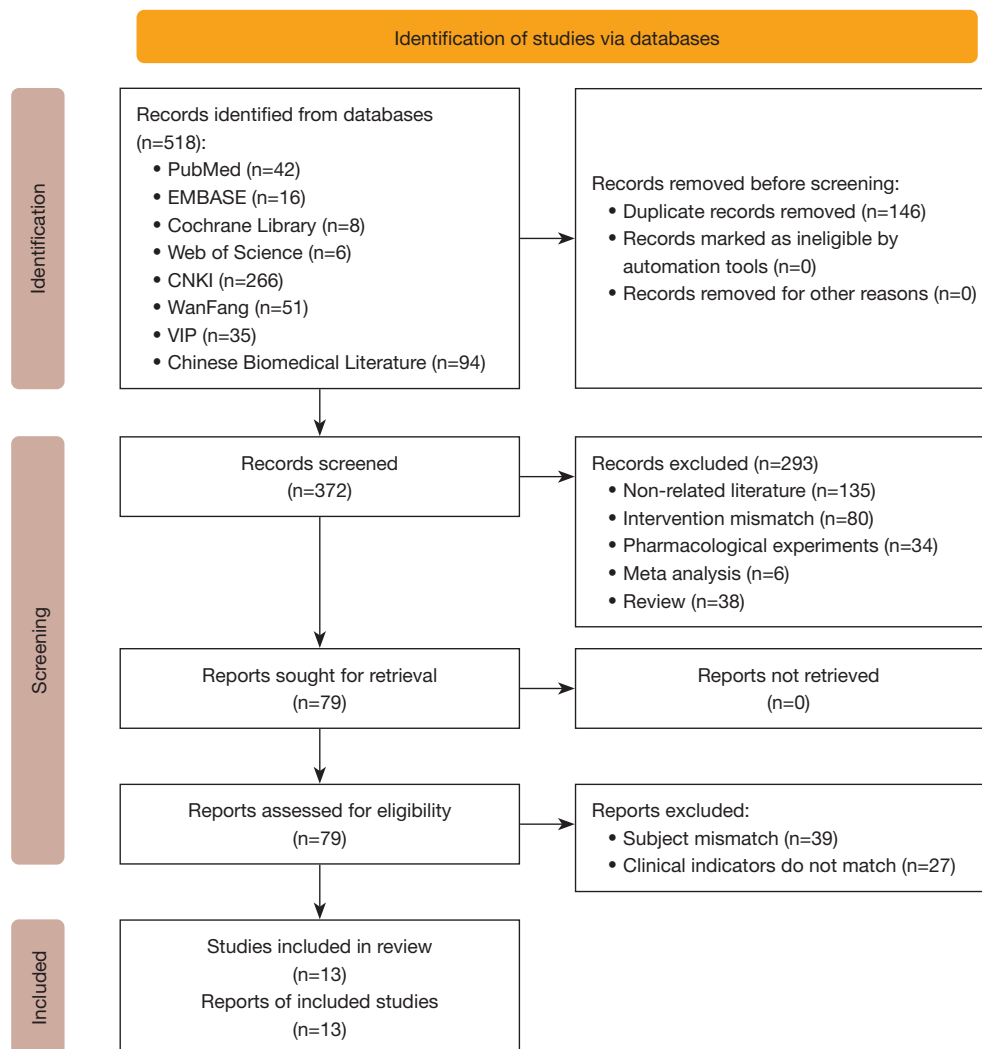
Figure 1 Literature screening flowchart.

rate compared to other surgical procedures. Furthermore, carrelizumab showed a significant advantage over other immunotherapy drugs (OR =6.68; 95% CI: 3.37–13.24), as depicted in *Figures 2,3*.

Among the three studies (27,29,30) with available MPR data, individuals in the combination group exhibited better response rates than those in the chemotherapy group (OR =3.70, 95% CI: 2.32–5.91) when it came to severe diseases. Subgroup analyses of the immunotherapy revealed significant differences between the carrelizumab study arms (OR =4.60, 95% CI: 2.73–7.75). As seen in *Figure 4*.

Patients in the immunotherapy group exhibited a higher rate of ORR compared to those in the control group (OR =2.22; 95% CI: 1.44–3.40, P<0.001), as reported in

seven studies (26,31-36) that documented ORR, as shown in *Figure 5*, the subgroup analysis of immunotherapy revealed statistically significant differences between the pembrolizumab trial groups. In all seven of these studies (26,31-36), there was no significant difference in the DCR between the NCT and NICT groups. The subgroup analysis is illustrated in *Figure 6*, showing a significant difference between the carrelizumab trial groups.

R0 resection rates were reported in all seven trials (26-28,31,32,35,36). Patients who received NICT had higher R0 resection rates compared to those who underwent NCT alone, as indicated by a review. The groups that received immunotherapy with pembrolizumab (OR =2.77, 95% CI: 1.40–5.48, P=0.003) and sintilimab (OR =5.25,

Table 1 Basic information on the literature included

Author, reference	Age[†] (male/female), years		Gender (male/female)		Tumor grade	NICT/ NCT	Chemotherapy regimen		Surgery	Study type	NOS
	NICT	NCT	NICT	NCT			NCT	NICT			
Hong et al., 2022 (25)	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 et al., 2022 (26)	NA	NA	30/17	33/14	II–III	47/47	Platinum + paclitaxel/ platinum + fluorouracil	Sintilimab/pembrolizumab/ camrelizumab/toripalimab	McKeown	Retrospective	9
Huang et al., 2021 (27)	59.2±7.3	58.9±6.4	21/2	30/1	II–IVA	23/31	Docetaxel + nedaplatin	Pembrolizumab	Mediastinoscopy + laparoscopic partial esophagectomy + cervical esophagogastric anastomosis (transabdominal + cervical surgery)	Retrospective	7
Zhou et al., 2023 (28)	65.89±6.06	64.50±4.54	17/2	31/9	II–IVA	19/40	Docetaxel + nedaplatin	Camrelizumab	McKeown	Retrospective	7
Zhang et al., 2023 (29)	60.68±7.44	60.08±7.78	31/3	94/3	II–IVA	34/97	Platinum + paclitaxel	Camrelizumab	NA	Retrospective	9
Qiao et al., 2022 (30)	64.15±7.29	64.15±7.29	38/10	147/59	I–IV	48/206	Platinum + paclitaxel	Camrelizumab	McKeown	Retrospective	7
Wang et al., 2023 (31)	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 et al., 2021 (32)	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 et al., 2022 (33)	57.91±8.06	56.70±7.95	30/16	29/17	II–III	46/46	Nedaplatin + paclitaxel	Pembrolizumab	NA	Retrospective	7
Wang et al., 2023 (34)	60.06±3.01	60.03±2.98	17/13	16/14	II–IVA	30/30	Carboplatin + paclitaxel	Camrelizumab	NA	Retrospective	7
Wang et al., 2022 (35)	64.21±3.27	63.73±3.32	18/2	20/3	II–IVA	20/23	Cisplatin + paclitaxel	Camrelizumab	NA	Retrospective	6
Yao et al., 2023 (36)	58.89±7.29	61.28±7.91	32/6	25/4	II–IVA	38/29	Nedaplatin + paclitaxel	Sintilimab	Thoracoscopic three incision esophagectomy for esophageal cancer	Retrospective	7
Liu et al., 2023 (37)	56.26±5.11	57.98±5.75	20/23	18/25	IIB–IVA	43/43	Nedaplatin + paclitaxel	Toripalimab	McKeown	Retrospective	7

[†], data are presented as mean ± standard deviation. "NICT"- the neoadjuvant immunochemotherapy group, NCT- the neoadjuvant chemotherapy group, "NA" represents that the information has not been clearly described, "NOS"-Newcastle-Ottawa Quality Assessment Scale.
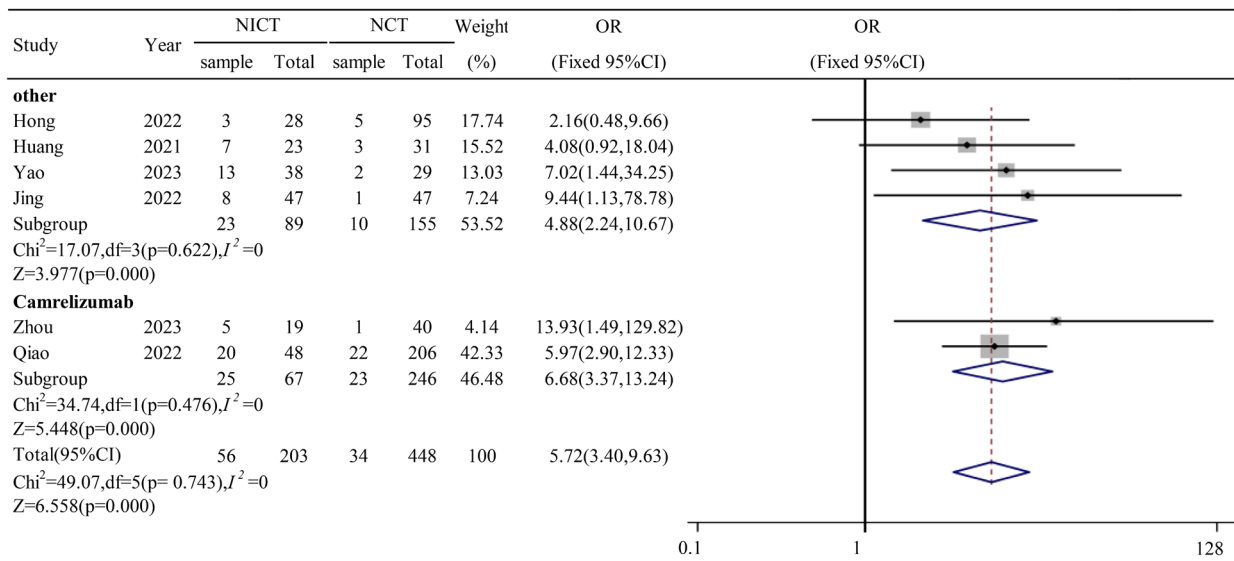
| Study | Year | NICT | | NCT | | Weight | OR | OR |
		sample	Total	sample	Total	(%)	(Fixed 95%CI)	(Fixed 95%CI)
other								
Hong	2022	3	28	5	95	17.74	2.16(0.48,9.66)	
Huang	2021	7	23	3	31	15.52	4.08(0.92,18.04)	
Yao	2023	13	38	2	29	13.03	7.02(1.44,34.25)	
Jing	2022	8	47	1	47	7.24	9.44(1.13,78.78)	
Subgroup		23	89	10	155	53.52	4.88(2.24,10.67)	
Chi^2=17.07,df=3(p=0.622),I^2=0								
Z=3.977(p=0.000)								
Camrelizumab								
Zhou	2023	5	19	1	40	4.14	13.93(1.49,129.82)	
Qiao	2022	20	48	22	206	42.33	5.97(2.90,12.33)	
Subgroup		25	67	23	246	46.48	6.68(3.37,13.24)	
Chi^2=34.74,df=1(p=0.476),I^2=0								
Z=5.448(p=0.000)								
Total(95%CI)		56	203	34	448	100	5.72(3.40,9.63)	
Chi^2=49.07,df=5(p= 0.743),I^2=0								
Z=6.558(p=0.000)								

0.1   1   128

Figure 2 The forest plot of pCR (drug type). NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio; pCR, pathological complete response.

| Study | Year | NICT | | NCT | | Weight | OR | OR |
		sample	Total	sample	Total	(%)	(Fixed 95%CI)	(Fixed 95%CI)
McKeown								
Hong	2022	3	28	5	95	17.74	2.16(0.48,9.66)	
Zhou	2023	5	19	1	40	4.14	13.93(1.49,129.82)	
Qiao	2022	20	48	22	206	42.33	5.97(2.90,12.33)	
Jing	2022	8	47	1	47	7.24	9.44(1.13,78.78)	
Subgroup		36	142	29	388	71.46	5.84(3.24,10.53)	
Chi^2=39.35,df=3(p=0.480),I^2=0								
Z=5.863(p<0.01)								
other								
Huang	2021	7	23	3	31	15.52	4.08(0.92,18.04)	
Yao	2023	13	38	2	29	13.03	7.02(1.44,34.25)	
Subgroup		20	61	5	60	28.54	5.42(1.85,15.91)	
Chi^2=10.61,df=1(p=0.623),I^2=0								
Z=3.079(p=0.002)								
Total(95%CI)		56	203	34	448	100	5.72(3.40,9.63)	
Chi^2=49.07,df=5(p= 0.743),I^2=0								
Z=6.558(p<0.01)								

0.3   1   150

Figure 3 The forest plot of pCR (surgical methods). NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio; pCR, pathological complete response.

95% CI: 1.27–21.66, P=0.02) demonstrated significantly higher R0 resection rates than the control group. Based on the surgical technique, the R0 resection rate was significantly increased by left thoracoesophageal resection and esophagogastric (or colon or jejunal) chest/neck anastomosis, or thoracoscopic three incision esophagectomy for esophageal cancer, as demonstrated in *Figures 7,8*.

Adverse reactions and postoperative complications

Eleven trials (26,27,29-37) reporting the incidence of myelosuppression did not find a significant difference between the NICT and NCT groups. The five studies (25-28,36) that reported the incidence of pneumonia did not show any differences between the two groups. Statistically
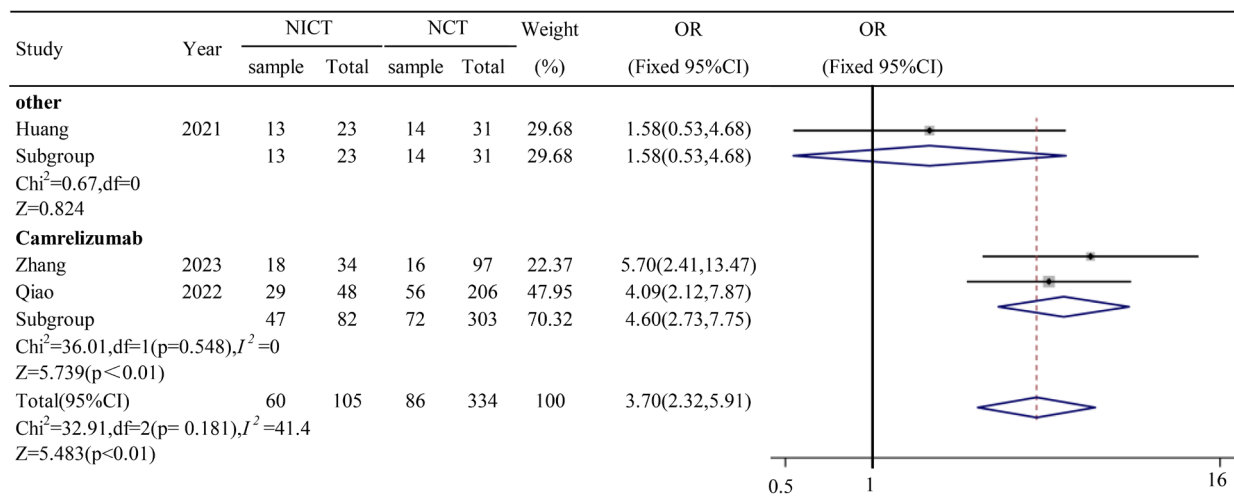
Figure 4 The forest plot of MPR. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio; MPR, major pathologic response.
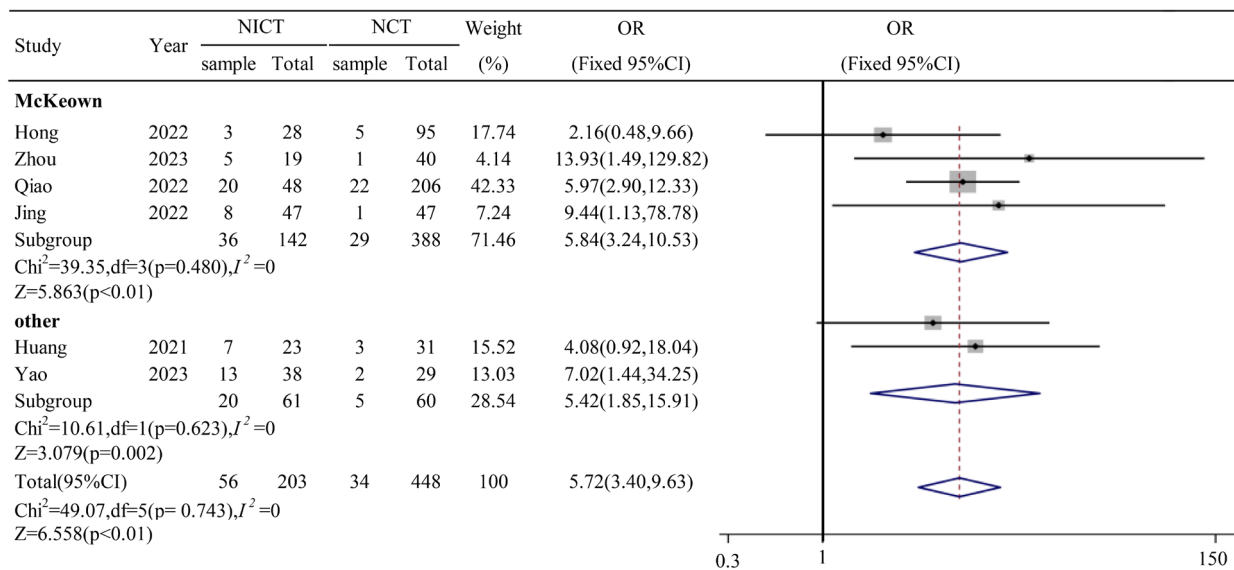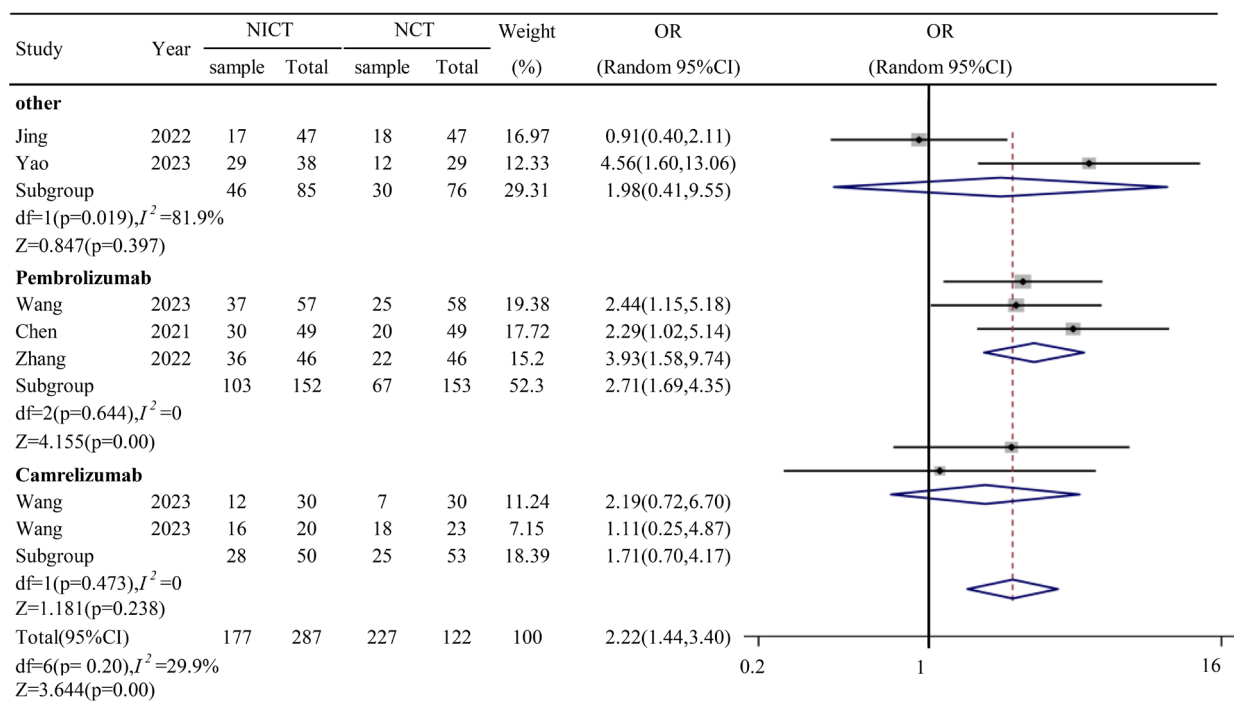

Figure 5 The forest plot of ORR. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio; ORR, objective response rate.

significant differences were found between the carrelizumab study arms (OR =10.15, 95% CI: 2.70–38.15, P=0.001) in seven studies (26,27,29,30,35-37) that investigated the incidence of rash following NCT. The findings revealed that the immunotherapy group had a higher incidence of

rash compared to the NCT group (OR =4.69, 95% CI: 1.42–15.49) (*Figure 9*). Ten studies (25,27,29-32,34-37) reported the incidence of vomiting after neoadjuvant chemotherapy, and there was no statistically significant difference between NICT and NCT (*Figure 10*). Five studies

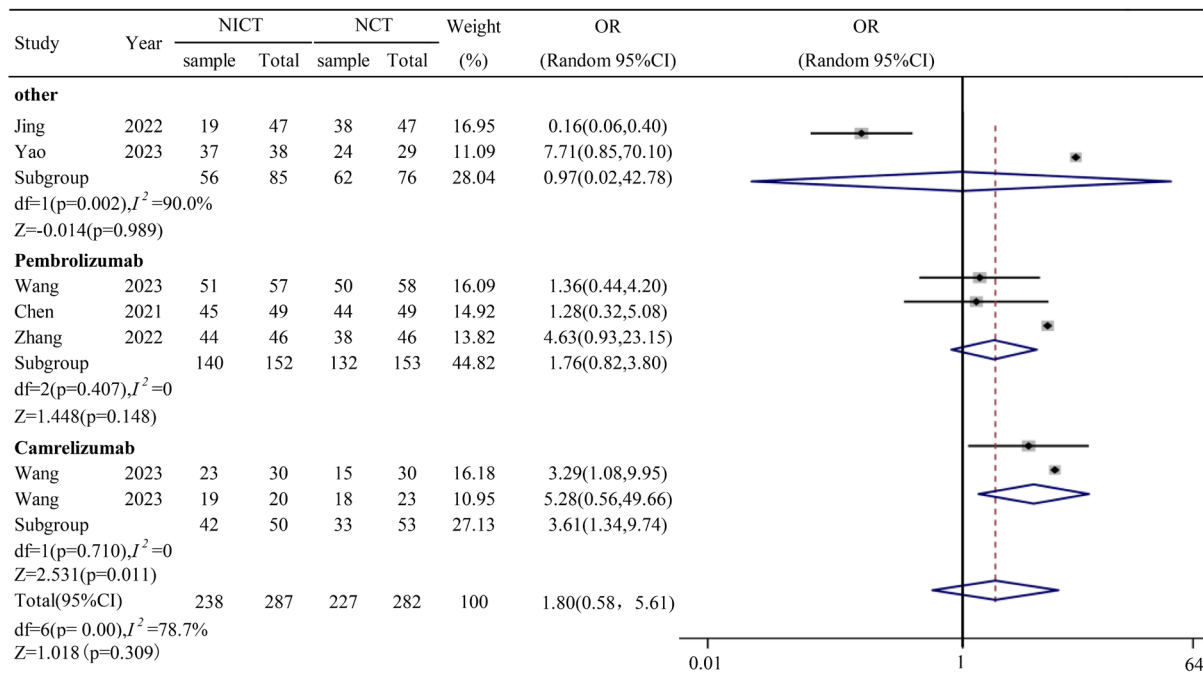| Study	Year	NICT		NCT		Weight	OR	OR
		sample	Total	sample	Total	(%)	(Random 95%CI)	(Random 95%CI)
other								
Jing	2022	19	47	38	47	16.95	0.16(0.06,0.40)	
Yao	2023	37	38	24	29	11.09	7.71(0.85,70.10)	
Subgroup		56	85	62	76	28.04	0.97(0.02,42.78)	
df=1(p=0.002),I^2=90.0%								
Z=-0.014(p=0.989)								
Pembrolizumab								
Wang	2023	51	57	50	58	16.09	1.36(0.44,4.20)	
Chen	2021	45	49	44	49	14.92	1.28(0.32,5.08)	
Zhang	2022	44	46	38	46	13.82	4.63(0.93,23.15)	
Subgroup		140	152	132	153	44.82	1.76(0.82,3.80)	
df=2(p=0.407),I^2=0								
Z=1.448(p=0.148)								
Camrelizumab								
Wang	2023	23	30	15	30	16.18	3.29(1.08,9.95)	
Wang	2023	19	20	18	23	10.95	5.28(0.56,49.66)	
Subgroup		42	50	33	53	27.13	3.61(1.34,9.74)	
df=1(p=0.710),I^2=0								
Z=2.531(p=0.011)								
Total(95%CI)		238	287	227	282	100	1.80(0.58, 5.61)	
df=6(p= 0.00),I^2=78.7%								
Z=1.018 (p=0.309)							0.01 1 64	

Figure 6 The forest plot of DCR. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio; DCR, disease control rate.
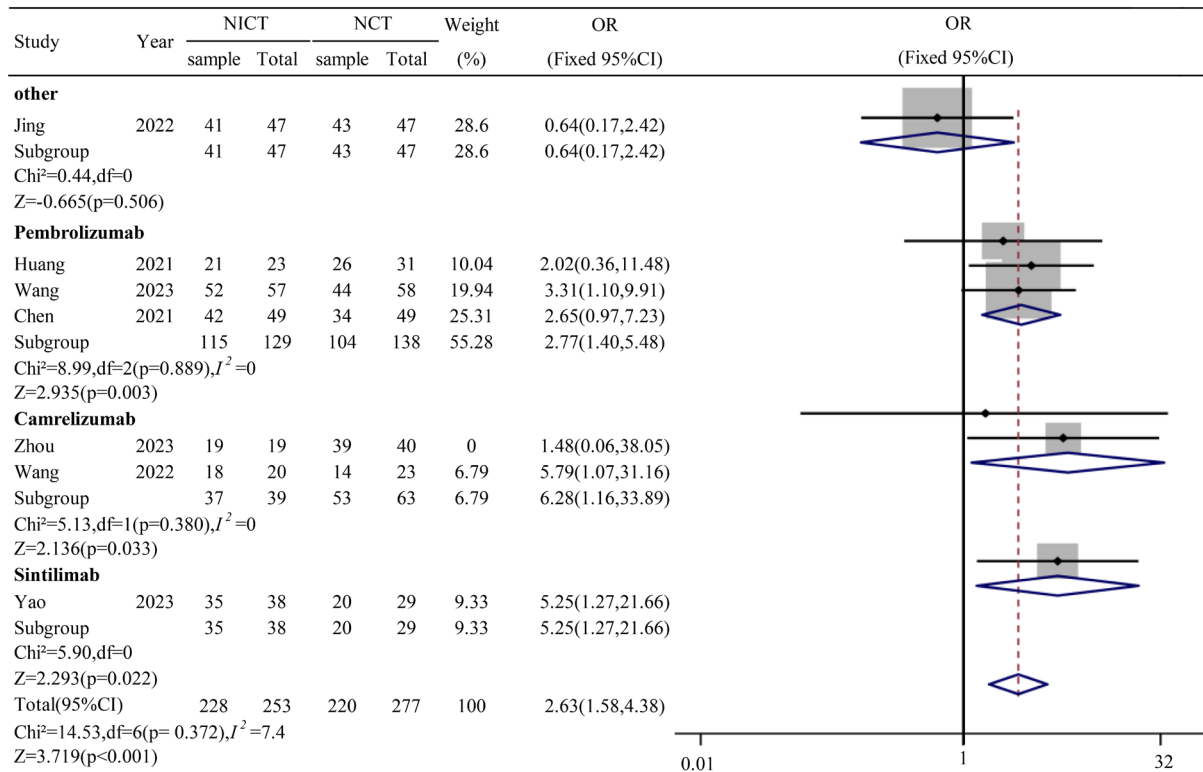
Study	Year	NICT		NCT		Weight	OR	OR
		sample	Total	sample	Total	(%)	(Fixed 95%CI)	(Fixed 95%CI)
other								
Jing	2022	41	47	43	47	28.6	0.64(0.17,2.42)	
Subgroup		41	47	43	47	28.6	0.64(0.17,2.42)	
Chi²=0.44,df=0								
Z=-0.665(p=0.506)								
Pembrolizumab								
Huang	2021	21	23	26	31	10.04	2.02(0.36,11.48)	
Wang	2023	52	57	44	58	19.94	3.31(1.10,9.91)	
Chen	2021	42	49	34	49	25.31	2.65(0.97,7.23)	
Subgroup		115	129	104	138	55.28	2.77(1.40,5.48)	
Chi²=8.99,df=2(p=0.889),I^2=0								
Z=2.935(p=0.003)								
Camrelizumab								
Zhou	2023	19	19	39	40	0	1.48(0.06,38.05)	
Wang	2022	18	20	14	23	6.79	5.79(1.07,31.16)	
Subgroup		37	39	53	63	6.79	6.28(1.16,33.89)	
Chi²=5.13,df=1(p=0.380),I^2=0								
Z=2.136(p=0.033)								
Sintilimab								
Yao	2023	35	38	20	29	9.33	5.25(1.27,21.66)	
Subgroup		35	38	20	29	9.33	5.25(1.27,21.66)	
Chi²=5.90,df=0								
Z=2.293(p=0.022)								
Total(95%CI)		228	253	220	277	100	2.63(1.58,4.38)	
Chi²=14.53,df=6(p= 0.372),I^2=7.4								
Z=3.719(p<0.001)							0.01 1 32	

Figure 7 The forest plot of R0 resection rates (drug type). NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.
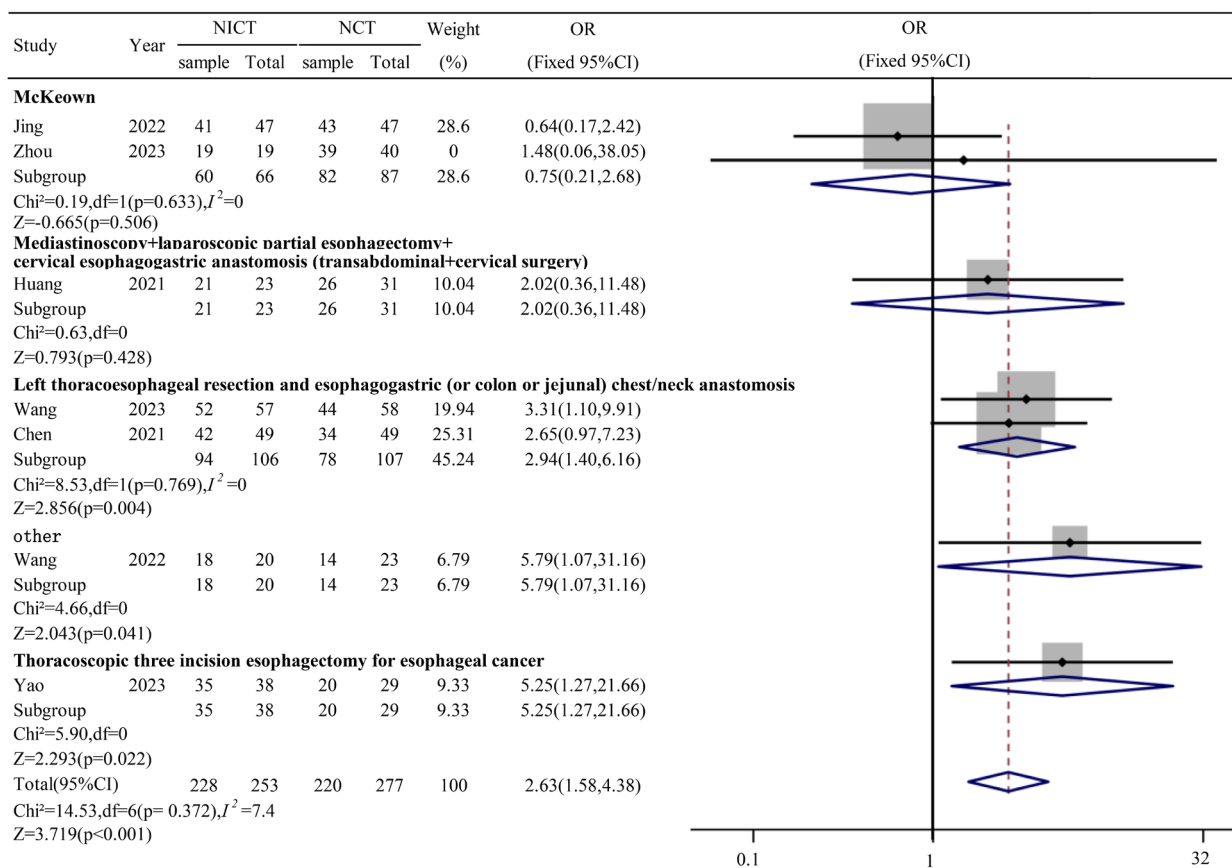
Figure 8 The forest plot of R0 resection rates (surgical methods). NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.

(25,28-30,36) reported rates of cardiac events, and a meta-analysis showed no difference between the two groups (*Figure 11*). Two studies (25,28) reported the incidence of postoperative pleural effusion, and a meta-analysis revealed a higher occurrence in patients undergoing NICT. According to *Figure 12*, individuals with NCT had a 3.99-fold higher risk of experiencing this event compared to those who received combined immunizations.

Survival

In three studies (25,28,29), there was no difference in 30-day survival between the two groups. According to two studies (28,29), there was no statistically significant difference in the 90-day survival rates in either of the groups. Two studies (26,29) also showed that the immunotherapy group outlived the chemotherapy group by 1 year (OR =10.08, 95% CI: 4.32–23.56, P<0.001) (*Figure 13*).

Assessment of publication bias

The ORR, R0 resection rate, and bone marrow suppression were selected as criteria for evaluation. The funnel plot was generated using STATA 17.0 software for analysis. As shown in *Figure 14*, the funnel plot displayed a generally uniform distribution overall but was slightly asymmetric, indicating the potential presence of publication bias in the included articles. This bias may be associated with an inadequate sample size or low article quality (*Figure 14*).

Sensitivity analysis

Sensitivity analysis was conducted on the pCR of six studies (25-28,30,36). The reliability of the analysis's conclusions was demonstrated by the lack of any significant differences between the findings before and after conducting a sensitivity analysis (*Figure 15*).
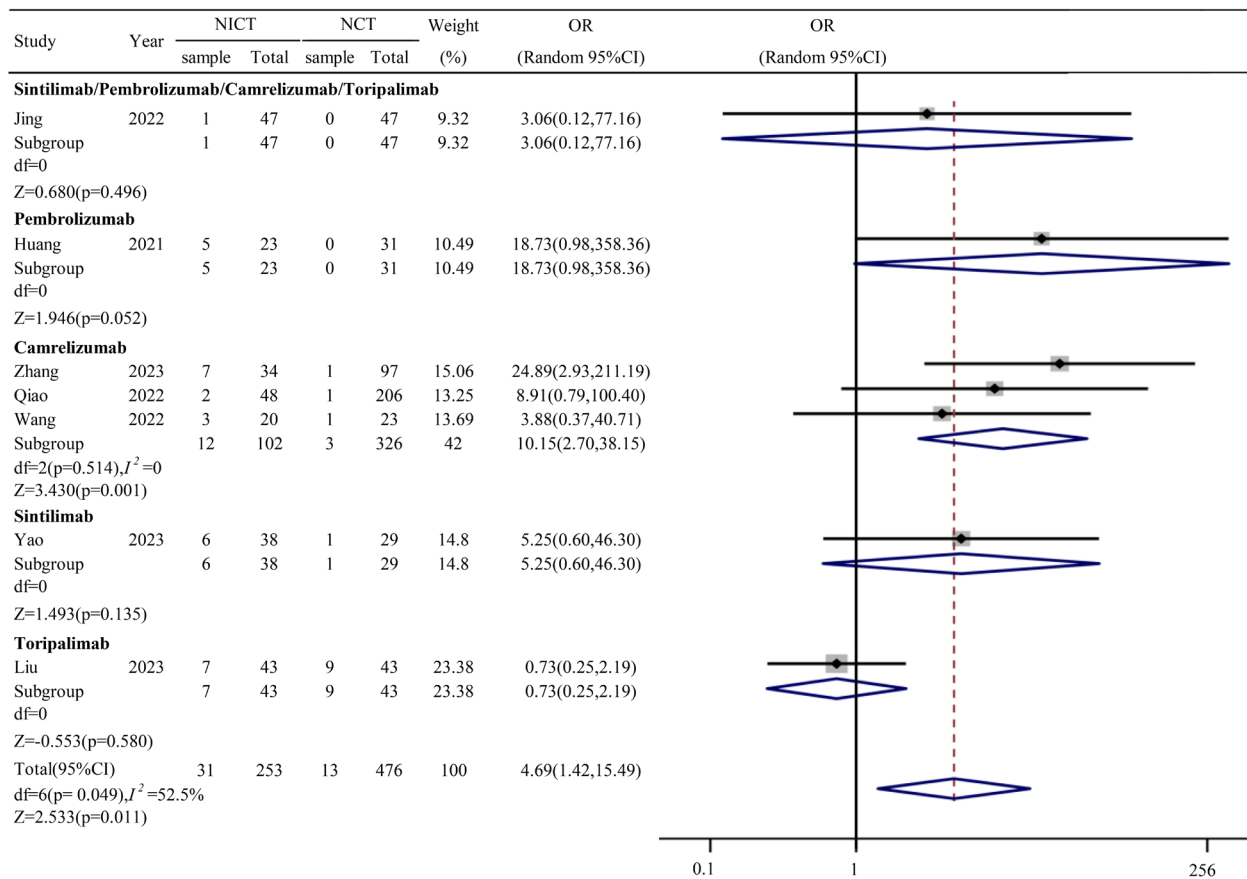
| Study | Year | NICT | | NCT | | Weight | OR | OR |
		sample	Total	sample	Total	(%)	(Random 95%CI)	(Random 95%CI)
Sintilimab/Pembrolizumab/Camrelizumab/Toripalimab								
Jing	2022	1	47	0	47	9.32	3.06(0.12,77.16)	
Subgroup		1	47	0	47	9.32	3.06(0.12,77.16)	
df=0								
Z=0.680(p=0.496)								
Pembrolizumab								
Huang	2021	5	23	0	31	10.49	18.73(0.98,358.36)	
Subgroup		5	23	0	31	10.49	18.73(0.98,358.36)	
df=0								
Z=1.946(p=0.052)								
Camrelizumab								
Zhang	2023	7	34	1	97	15.06	24.89(2.93,211.19)	
Qiao	2022	2	48	1	206	13.25	8.91(0.79,100.40)	
Wang	2022	3	20	1	23	13.69	3.88(0.37,40.71)	
Subgroup		12	102	3	326	42	10.15(2.70,38.15)	
df=2(p=0.514),I^2=0								
Z=3.430(p=0.001)								
Sintilimab								
Yao	2023	6	38	1	29	14.8	5.25(0.60,46.30)	
Subgroup		6	38	1	29	14.8	5.25(0.60,46.30)	
df=0								
Z=1.493(p=0.135)								
Toripalimab								
Liu	2023	7	43	9	43	23.38	0.73(0.25,2.19)	
Subgroup		7	43	9	43	23.38	0.73(0.25,2.19)	
df=0								
Z=-0.553(p=0.580)								
Total(95%CI)		31	253	13	476	100	4.69(1.42,15.49)	
df=6(p= 0.049),I^2=52.5%								
Z=2.533(p=0.011)								

0.1   1   256

Figure 9 The forest plot of Rash. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.

Discussion

Immunotherapy has advanced rapidly in recent years for patients with ESCC. With studies such as ESCORT, ATTRACTION-3, and KEYNOTE-181, immunotherapy was established as a second-line treatment option in 2019 (38-40). Furthermore, in the same year, the Food and Drug Administration (FDA) approved pembrolizumab for the treatment of programmed death-ligand 1 (PD-L1)-positive (Combined Positive Score ≥10) ESCC that had relapsed, progressed locally, or metastasized (41). Furthermore, as evidenced by the latest phase III research studies KEYNOTE-590 and Checkmate 649 (11,42), individuals with advanced esophageal cancer may benefit from initial treatment with pembrolizumab or nivolumab alongside chemotherapy. These investigations demonstrate the efficacy of immunosuppressants. The National Cancer Center of Japan initiated the JCOG 1804E phase 1 study (clinical trial number NCT03914443) in 2019 to evaluate

the effectiveness of preoperative nivolumab in combination with chemotherapy for the treatment of advanced localized esophageal cancer. These clinical trials are advancing immunotherapy research in the field of neoadjuvant therapy for ESCC. At the 2020 ESMO conference, Liu *et al.* (43) presented the NICE investigation of neoadjuvant camrelizumab in combination with chemotherapy for advanced locally advanced ESCC. All 11 patients in the NICT trial underwent successful operations and achieved R0 resection. Additionally, the pCR rates were 45.4%, a rate comparable to the results of the CROSS study (44).

The study results showed that the immunotherapy group had higher rates of pCR, MPR, ORR, and R0 resection compared to the chemotherapy group. Subgroup analysis of the pCR rate revealed differences among the study groups based on different surgical methods and immune drugs, with the carrelizumab study group showing superior efficacy. The McKeown surgical technique may enhance effectiveness and
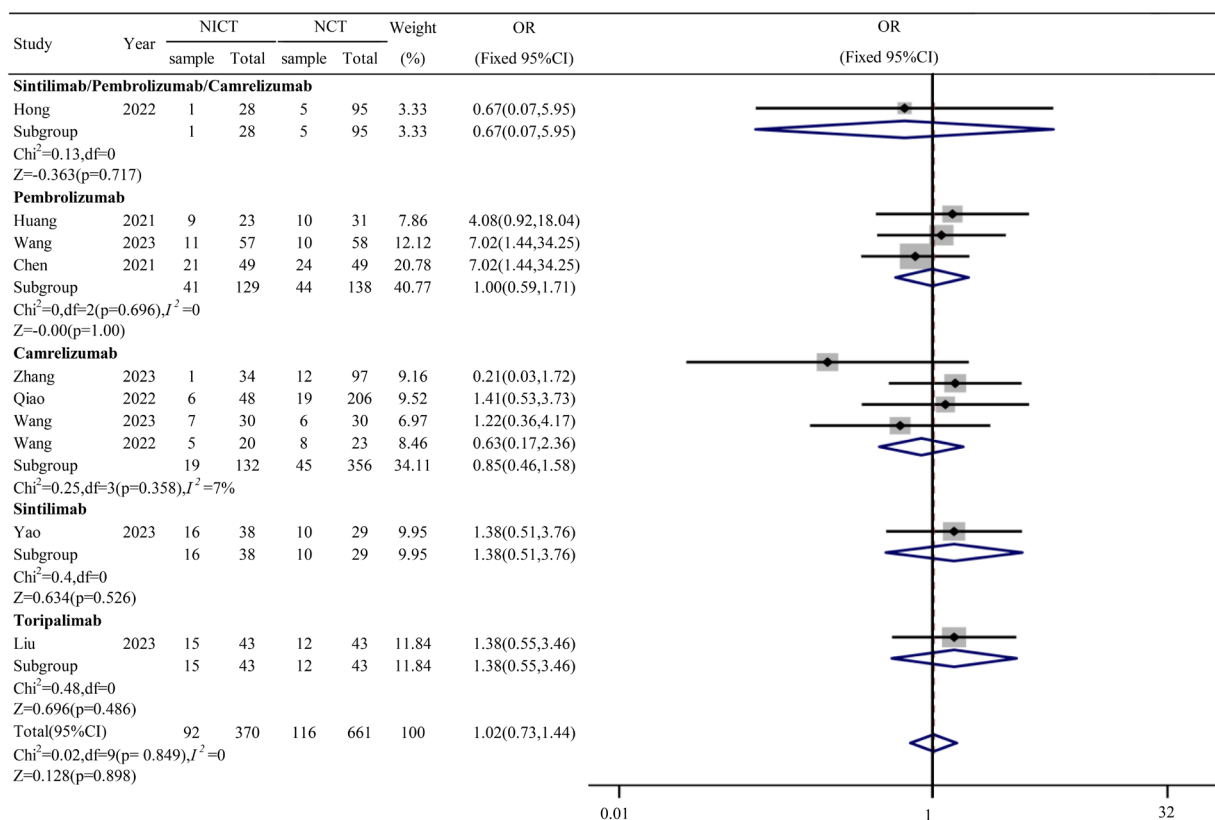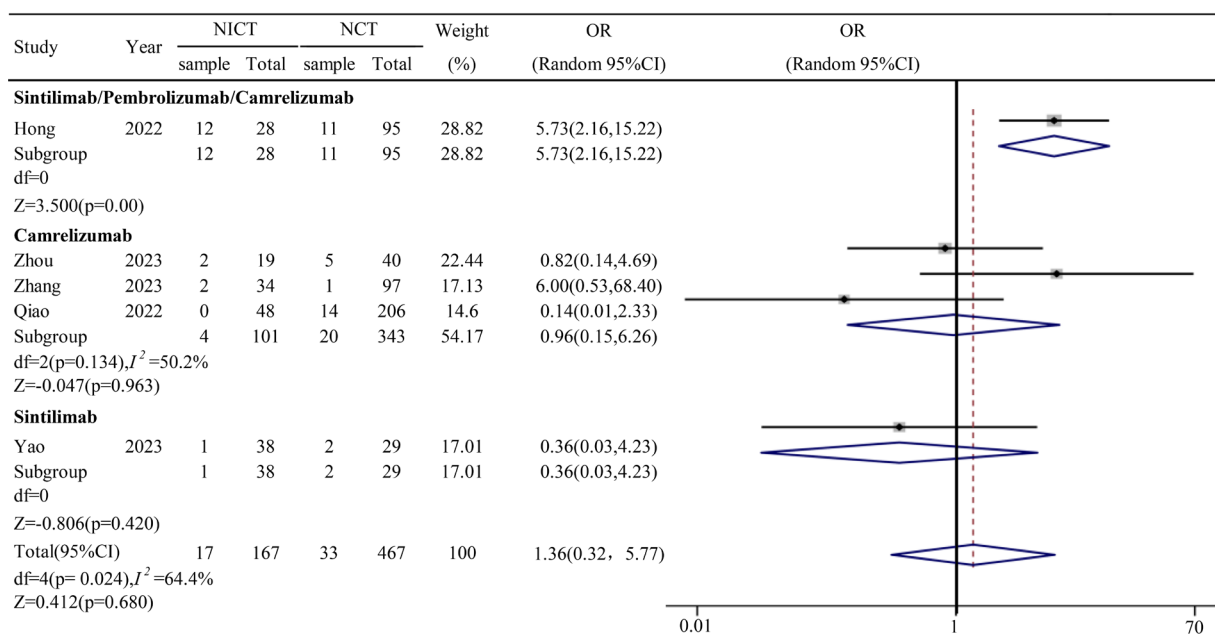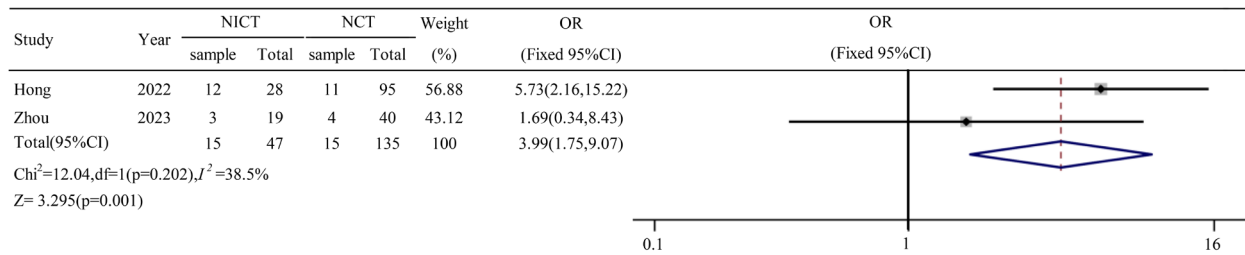
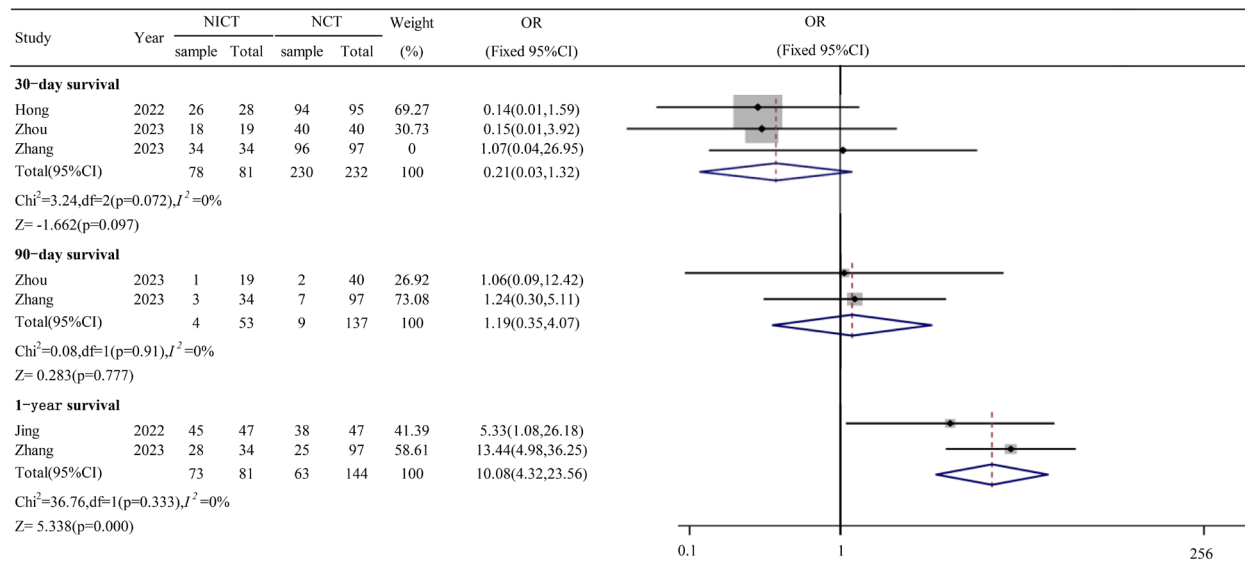| Study	Year	NICT sample	NICT Total	NCT sample	NCT Total	Weight (%)	OR (Fixed 95%CI)	OR (Fixed 95%CI)
Sintilimab/Pembrolizumab/Camrelizumab								
Hong	2022	1	28	5	95	3.33	0.67(0.07,5.95)	
Subgroup		1	28	5	95	3.33	0.67(0.07,5.95)	
Chi^2=0.13,df=0								
Z=-0.363(p=0.717)								
Pembrolizumab								
Huang	2021	9	23	10	31	7.86	4.08(0.92,18.04)	
Wang	2023	11	57	10	58	12.12	7.02(1.44,34.25)	
Chen	2021	21	49	24	49	20.78	7.02(1.44,34.25)	
Subgroup		41	129	44	138	40.77	1.00(0.59,1.71)	
Chi^2=0,df=2(p=0.696),I^2=0								
Z=-0.00(p=1.00)								
Camrelizumab								
Zhang	2023	1	34	12	97	9.16	0.21(0.03,1.72)	
Qiao	2022	6	48	19	206	9.52	1.41(0.53,3.73)	
Wang	2023	7	30	6	30	6.97	1.22(0.36,4.17)	
Wang	2022	5	20	8	23	8.46	0.63(0.17,2.36)	
Subgroup		19	132	45	356	34.11	0.85(0.46,1.58)	
Chi^2=0.25,df=3(p=0.358),I^2=7%								
Sintilimab								
Yao	2023	16	38	10	29	9.95	1.38(0.51,3.76)	
Subgroup		16	38	10	29	9.95	1.38(0.51,3.76)	
Chi^2=0.4,df=0								
Z=0.634(p=0.526)								
Toripalimab								
Liu	2023	15	43	12	43	11.84	1.38(0.55,3.46)	
Subgroup		15	43	12	43	11.84	1.38(0.55,3.46)	
Chi^2=0.48,df=0								
Z=0.696(p=0.486)								
Total(95%CI)		92	370	116	661	100	1.02(0.73,1.44)	
Chi^2=0.02,df=9(p=0.849),I^2=0								
Z=0.128(p=0.898)								

0.01   1   32

Figure 10 The forest plot of vomit. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.

Study	Year	NICT sample	NICT Total	NCT sample	NCT Total	Weight (%)	OR (Random 95%CI)	OR (Random 95%CI)
Sintilimab/Pembrolizumab/Camrelizumab								
Hong	2022	12	28	11	95	28.82	5.73(2.16,15.22)	
Subgroup		12	28	11	95	28.82	5.73(2.16,15.22)	
df=0								
Z=3.500(p=0.00)								
Camrelizumab								
Zhou	2023	2	19	5	40	22.44	0.82(0.14,4.69)	
Zhang	2023	2	34	1	97	17.13	6.00(0.53,68.40)	
Qiao	2022	0	48	14	206	14.6	0.14(0.01,2.33)	
Subgroup		4	101	20	343	54.17	0.96(0.15,6.26)	
df=2(p=0.134),I^2=50.2%								
Z=-0.047(p=0.963)								
Sintilimab								
Yao	2023	1	38	2	29	17.01	0.36(0.03,4.23)	
Subgroup		1	38	2	29	17.01	0.36(0.03,4.23)	
df=0								
Z=-0.806(p=0.420)								
Total(95%CI)		17	167	33	467	100	1.36(0.32, 5.77)	
df=4(p=0.024),I^2=64.4%								
Z=0.412(p=0.680)								

0.01   1   70

Figure 11 The forest plot of cardiac events. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.

| Study | Year | NICT | | NCT | | Weight | OR | OR |
		sample	Total	sample	Total	(%)	(Fixed 95%CI)	(Fixed 95%CI)
Hong	2022	12	28	11	95	56.88	5.73(2.16,15.22)	
Zhou	2023	3	19	4	40	43.12	1.69(0.34,8.43)	
Total(95%CI)		15	47	15	135	100	3.99(1.75,9.07)	

Chi²=12.04,df=1(p=0.202),I^2=38.5%

Z= 3.295(p=0.001)

Figure 12 The forest plot of postoperative pleural effusion. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.

| Study | Year | NICT | | NCT | | Weight | OR | OR |
		sample	Total	sample	Total	(%)	(Fixed 95%CI)	(Fixed 95%CI)
30-day survival								
Hong	2022	26	28	94	95	69.27	0.14(0.01,1.59)	
Zhou	2023	18	19	40	40	30.73	0.15(0.01,3.92)	
Zhang	2023	34	34	96	97	0	1.07(0.04,26.95)	
Total(95%CI)		78	81	230	232	100	0.21(0.03,1.32)	
90-day survival								
Zhou	2023	1	19	2	40	26.92	1.06(0.09,12.42)	
Zhang	2023	3	34	7	97	73.08	1.24(0.30,5.11)	
Total(95%CI)		4	53	9	137	100	1.19(0.35,4.07)	
1-year survival								
Jing	2022	45	47	38	47	41.39	5.33(1.08,26.18)	
Zhang	2023	28	34	25	97	58.61	13.44(4.98,36.25)	
Total(95%CI)		73	81	63	144	100	10.08(4.32,23.56)	

Chi²=3.24,df=2(p=0.072),I^2=0%   Z= -1.662(p=0.097)

Chi²=0.08,df=1(p=0.91),I^2=0%   Z= 0.283(p=0.777)

Chi²=36.76,df=1(p=0.333),I^2=0%   Z= 5.338(p=0.000)

Figure 13 The forest plot of survival rate. NICT, neoadjuvant immunochemotherapy; NCT, neoadjuvant chemotherapy; CI, confidence interval; OR, odds ratio.
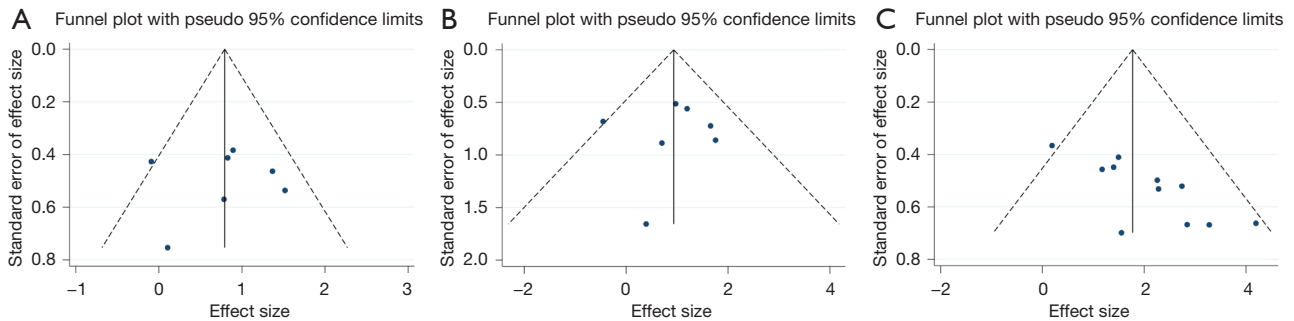
Figure 14 The funnel plot of ORR, R0 resection rate, and bone marrow suppression: assessment of publication bias. ORR, objective response rate.
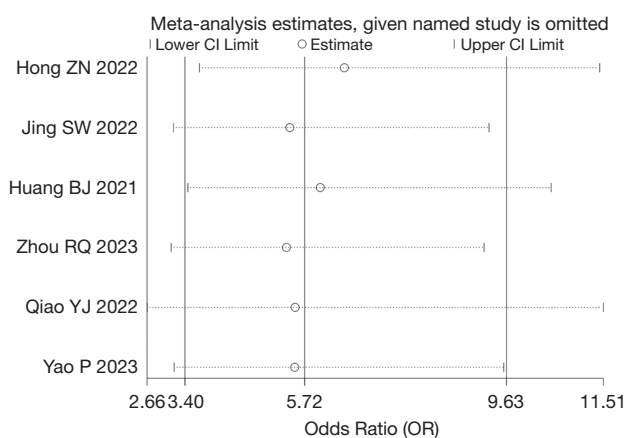
Figure 15 Sensitivity analysis based on pCR. pCR, pathological complete response; CI, confidence interval.

reduce the incidence of postoperative complications, according to a previous study (45). As a result, it was believed that the types of immunotherapies and surgical techniques had an impact on the pCR rate after neoadjuvant immunotherapy. The analysis of MPR by the immunopharmaceuticals subgroup for the primary pathological response rate revealed statistical differences in MPR between the carrelizumab study groups, further emphasizing the clinical efficacy of immunotherapy. The results of the subgroup analysis of DCR and ORR revealed statistical differences between the pembrolizumab and carrelizumab study groups, respectively. This indicates that there is still a disparity in short-term efficacy among different immune drugs, which may be associated with the programmed cell death protein 1 (PD-1)/PD-L1 levels of patients (46). Subgroup analysis of the R0 resection rate revealed that patients in the pembrolizumab arm who received neoadjuvant immunotherapy were superior to those who received neoadjuvant chemotherapy, indicating a significant improvement in the R0 resection rate with pembrolizumab. It was also found that performing a left thoracic esophagectomy and creating an esophagogastric, esophagocolonic, or esophagojejunal thoracic/collateral anastomosis could result in a higher R0 resection rate, indicating that different surgical methods have a certain influence. The aforementioned factors influence the impact of neoadjuvant immunotherapy on the rates of surgical resection.

In terms of adverse reactions and postoperative complications following neoadjuvant immunotherapy, patients in the NICT group did not experience an increased incidence of bone marrow suppression, pneumonia, vomiting, or cardiac adverse events, indicating a favorable safety profile. However,

compared to the control group, the NICT group experienced a significantly higher occurrence of rash. Subgroup analysis revealed statistical differences between the carrelizumab study arms (OR =10.15, 95% CI: 2.70–38.15, P=0.001). This finding suggests that increased use of immunotherapy during neoadjuvant therapy may elevate the likelihood of skin-related adverse events. The examples documented by Shu *et al.* (47) are consistent with the findings of this study. As a result, when immunotherapy is used in clinical practice, it is necessary to be vigilant for the occurrence of skin adverse events. The study also found that neoadjuvant immunotherapy increased the occurrence of postoperative pleural effusion, which may be associated with the surgical approach.

The survival analysis indicated that there was no difference in the survival rates at 30 and 90 days between the two groups. On the other hand, the group that received neoadjuvant immunotherapy exhibited a significantly higher 1-year survival rate (OR =10.08, 95% CI: 4.32–23.56, P<0.001) compared to the group that received neoadjuvant chemotherapy. This suggests that receiving neoadjuvant therapy in combination with immunization may enhance the long-term survival rate of individuals with advanced locally diagnosed ESCC.

This study has limitations. Firstly, several of the clinical studies included in this meta-analysis are still awaiting completion of their objectives. Analyzing the impact of neoadjuvant treatment on survival parameters such as OS and PFS was not feasible; additional data are required to obtain reliable findings. Furthermore, bias may have resulted from the limited number of included studies, insufficient sample size, absence of randomized controlled trials (RCTs), and reliance on single study types, despite a comprehensive search of previous research. Therefore, to further confirm the findings of this study, additional high-quality research and subsequent network meta-analyses are necessary. Furthermore, there is still uncertainty about the therapeutic effectiveness of different immunotherapy drugs when combined with various surgical techniques. The present study's limitations also underscore the obstacles that need to be addressed before the implementation of neoadjuvant immunotherapy. Future research will be able to improve control over adverse responses and surgical complications, as well as enhancing patient outcomes and quality of life, by elucidating the underlying causes of each issue.

Conclusions

Neoadjuvant immunotherapy has shown promising efficacy

in patients with locally advanced ESCC; however, it is linked to a higher occurrence of adverse events. Therefore, its use in clinical practice should be carefully considered.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-198/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-198/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-198/coif). All authors report that this study was supported by Scientific Research Project of Higher Education Department of Anhui Province (No. 2023AH050834). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rodriguez GM, DePuy D, Aljehani M, et al. Trends in Epidemiology of Esophageal Cancer in the US, 1975-2018. JAMA Netw Open 2023;6:e2329497.
2. Zheng R, Zhang S, Zeng H, et al. Cancer incidence and mortality in China, 2016. J Natl Cancer Center 2022;2:1-9.
3. Jazieh K, Yoon H, Zhu M. Advances in Immunotherapy in Esophagogastric Cancer. Hematol Oncol Clin North Am 2024;38:599-616.
4. Kaderi ASA, Sabita J, Tiwari VK, et al. Treatment Response to Neoadjuvant Therapy in Squamous Esophageal Cancer-Correlation Between Metabolic Response and Histopathology. J Gastrointest Cancer 2024. [Epub ahead of print]. doi: 10.1007/s12029-024-01013-x.
5. Zhang W, Zhu M, Xiang Y, et al. Current and future perspectives in unresectable locally advanced esophageal squamous cell cancer (Review). Oncol Rep 2024;51:65.
6. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
7. Gaber CE, Sarker J, Abdelaziz AI, et al. Pathologic complete response in patients with esophageal cancer receiving neoadjuvant chemotherapy or chemoradiation: A systematic review and meta-analysis. Cancer Med 2024;13:e7076.
8. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.
9. Pasquali S, Yim G, Vohra RS, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Ann Surg 2017;265:481-91.
10. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-8.
11. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
12. Gao Y, Zhang H, Qiu Y, et al. Effect of Neoadjuvant Immunotherapy Combined with Chemotherapy on Pulmonary Function and Postoperative Pulmonary Complications in Esophageal Cancer: A Retrospective Study. Curr Cancer Drug Targets 2024. [Epub ahead of print]. doi: 10.2174/0115680096280761231229055929.
13. Kelly RJ, Landon BV, Zaidi AH, et al. Neoadjuvant

nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. Nat Med 2024;30:1023-34.

14. Li B, Wang Y, Yu H, et al. Pattern of tumor regression after neoadjuvant chemoimmunotherapy for esophageal squamous cell carcinoma. J Thorac Dis 2023;15:5517-24.

15. Chao L, Liu J, Chen Y, et al. Benefits of camrelizumab plus carboplatin and albumin paclitaxel as induction therapy for locally advanced borderline resectable or unresectable esophageal squamous cell carcinoma. Thorac Cancer 2024;15:622-9.

16. Kang NN, Zheng H, Hu JX, et al. Camrelizumab in combination with neoadjuvant chemotherapy in resectable locally advanced esophageal squamous carcinoma cancer: Results from a retrospective study. Kaohsiung J Med Sci 2024;40:291-5.

17. Chen M, Huang Y, Zhang S, et al. Camrelizumab in combination with chemotherapy versus concurrent chemoradiotherapy for the conversion of locally advanced unresectable oesophageal squamous carcinoma: protocol for a two-arm, open-label phase II trial. BMJ Open 2024;14:e075421.

18. Li C, Yu P, Li H, et al. Study on the efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy regimen for III-IVA esophageal squamous cell carcinoma post-surgery. J Cardiothorac Surg 2024;19:26.

19. Sun HB, Xing WQ, Liu XB, et al. A multicenter randomized, controlled clinical trial of adjuvant sintilimab for esophageal squamous cell carcinoma. Future Oncol 2023;19:1777-84.

20. Xu X, Sun Z, Liu Q, et al. Neoadjuvant chemoradiotherapy combined with sequential perioperative toripalimab in locally advanced esophageal squamous cell cancer. J Immunother Cancer 2024;12:e008631.

21. He W, Leng X, Mao T, et al. Toripalimab Plus Paclitaxel and Carboplatin as Neoadjuvant Therapy in Locally Advanced Resectable Esophageal Squamous Cell Carcinoma. Oncologist 2022;27:e18-28.

22. Li M, Sun H, Yang W, et al. A Phase 1b Clinical Trial of Neoadjuvant Radio-immunotherapy for Esophageal Squamous Cell Cancer. Int J Radiat Oncol Biol Phys 2024;S0360-3016(23)08304-9.

23. Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed) 2021;112:90-2.

24. Inada M, Nishimura Y, Ishikawa K, et al. Comparing the 7th and 8th editions of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system for esophageal squamous cell carcinoma treated by definitive radiotherapy. Esophagus 2019;16:371-6.

25. Hong ZN, Zhang Z, Chen Z, et al. Safety and feasibility of esophagectomy following combined neoadjuvant immunotherapy and chemotherapy for locally advanced esophageal cancer: a propensity score matching. Esophagus 2022;19:224-32.

26. Jing SW, Zhai C, Zhang W, et al. Comparison of neoadjuvant immunotherapy plus chemotherapy versus chemotherapy alone for patients with locally advanced esophageal squamous cell carcinoma: A propensity score matching. Front Immunol 2022;13:970534.

27. Huang B, Shi H, Gong X, et al. Comparison of efficacy and safety between pembrolizumab combined with chemotherapy and simple chemotherapy in neoadjuvant therapy for esophageal squamous cell carcinoma. J Gastrointest Oncol 2021;12:2013-21.

28. Zhou RQ, Luo J, Li LJ, et al. Neoadjuvant camrelizumab plus chemotherapy in locally advanced oesophageal squamous cell carcinoma: a retrospective cohort study. BMC Surg 2023;23:114.

29. Zhang B, Zhao H, Wu X, et al. Perioperative outcomes of neoadjuvant chemotherapy plus camrelizumab compared with chemotherapy alone and chemoradiotherapy for locally advanced esophageal squamous cell cancer. Front Immunol 2023;14:1066527.

30. Qiao Y, Zhao C, Li X, et al. Efficacy and safety of camrelizumab in combination with neoadjuvant chemotherapy for ESCC and its impact on esophagectomy. Front Immunol 2022;13:953229.

31. Wang XZ, Liu ZG, Du YL, et al. Clinical trial of pembrolizumab injection combined with PC regimen in the treatment of patients with esophageal squamous cell carcinoma. The Chinese Journal of Clinical Pharmacology 2023;39:936-40.

32. Chen J, Gao YH, Ma DD, et al. Effectiveness of Pembrolizumab Combined with Pemetrexed and Cisplatin in Preoperative Neoadjuvant Chemotherapy of Esophageal Squamous Cell Carcinoma and Its Effects on SCCA, CEA, and PD-1/PD-L1. Medical & Pharmaceutical Journal of Chinese People's Liberation Army 2021;33:23-7.

33. Zhang XW, Wang RJ, Zhang X, et al. Clinical efficacy of pembrolizumab combined with neoadjuvant chemotherapy in treatment of stage II and II esophageal cancer. Shaanxi

Medical Journal 2022;51:870-3.

34. Wang JP, Ma ZK, Xue HC, et al. Camrelizumab combined with chemotherapy in neoadjuvant therapy for resectable/potentially resectable locally advanced esophageal squamous cell carcinoma-a prospective study. Heilongjiang Medicine and Pharmacy 2023;46:39-41.

35. Wang XL, Xiu JW, Li X, et al. Clinical study of carrelizumab combined with albumin-bound paclitaxel and cisplatin in preoperative neoadjuvant therapy for locally advanced esophageal cancer. Clinical Journal of Medical Officers 2022;50:806-9.

36. Yao P, Bie J, Li JF, et al. Clinical Observation of Sintilimab Combined with Albumin-Bound Paclitaxel and Nedaplatin in Preoperative Neoadjuvant Therapy for Locally Advanced Esophageal Cancer. Sichuan Medical Journal 2023;44:579-84.

37. Liu F, Dong HY, Wang YL, et al. Effects of Toripali combined with neoadjuvant chemotherapy on PD-1,PD-L1 levels and postoperative survival in patients with locally advanced esophageal cancer. Chinese Journal of Health Laboratory Technology 2023;33:520-3.

38. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:1506-17. Erratum in: Lancet Oncol 2019;20:e613.

39. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832-42.

40. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin

Oncol 2020;38:4138-48.

41. Leng XF, Daiko H, Han YT, et al. Optimal preoperative neoadjuvant therapy for resectable locally advanced esophageal squamous cell carcinoma. Ann N Y Acad Sci 2020;1482:213-24.

42. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.

43. Liu J, Li Z, Fu X, et al. 127P A prospective phase II clinical trial exploring neoadjuvant immunotherapy combined with chemotherapy in resectable thoracic esophageal squamous cell cancer (TESCC) with multi-station lymph node metastases (NICE study): Preliminary results. Ann Oncol 2020;31:S1292.

44. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 2014;32:385-91.

45. Luo RJ, Li ZJ, He ZF, et al. The efficacy and feasibility of neoadjuvant immunotherapy plus chemotherapy followed by McKeown minimally invasive oesophagectomy for locally advanced oesophageal squamous cell carcinoma. J Minim Access Surg 2023. [Epub ahead of print]. doi: 10.4103/jmas.jmas_65_23.

46. Chen XF, Guo QS. Effect of camrelizumab combined with albumin-binding paclitaxel + cisplatin chemotherapy on preoperative treatment of locally advanced esophageal cancer and its influence on PD-1 and PD-L1 levels. Chinese Journal of Modern Drug Application 2023;17:1-5.

47. Shu LL, Liao XY. Severe rash with pruritus due to carrelizumab during maintenance hemodialysis in patients with malignant tumors:a report of two cases. Journal of Clinical Nephrology 2022;22:86-8.