Systematic Reviews

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Efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy for stage II–IVa esophageal cancer: a network meta-analysis

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Abstract

Objective The objective of this study was to evaluate the clinical efficacy and safety of neoadjuvant immunochemotherapy in the treatment of locally advanced, resectable esophageal cancer.

Methods Literature published before November 2023 on the clinical efficacy and safety of neoadjuvant immunotherapy in resectable esophageal squamous cell carcinoma was searched in CNKI, VIP, Wanfang, Chinese Biomedical Literature, PubMed, Embase, Cochrane, and the Web of Science. A meta-analysis was conducted using Stata 17.0.

Results The cumulative ranked probability results indicated that Camrelizumab + TN had the highest probability of achieving pCR, Camrelizumab + TP of achieving MPR, and Sintilimab + TP of achieving DCR and ORR. Camrelizumab + TP also had the highest probability of achieving an R0 resection rate. In terms of adverse events and postoperative complications, Pembrolizumab + TN had the highest likelihood of inducing myelosuppression and rash. Toripalimab + TP had the highest probability of inducing vomiting, while traditional chemotherapy alone had the highest likelihood of inducing postoperative cardiac adverse events.

Conclusion Neoadjuvant immunotherapy combined with chemotherapy has demonstrated superior clinical efficacy and safety compared to chemotherapy alone. The regimen of Camrelizumab + TP showed significant advantages in pCR, MPR, DCR, and R0 resection rates, particularly excelling in MPR and R0 resection rates. However, it was associated with a higher incidence of rash compared to chemotherapy alone and the Toripalimab + TP regimen. Neoadjuvant immunotherapy, when combined with chemotherapy, has been shown to reduce the occurrence of postoperative cardiac adverse events. Among the various treatment options, Sintilimab + TP exhibited the most favorable outcomes.

Systematic review registration PROSPERO Protocol Number: CRD42024623160.

Keywords Esophageal cancer, Neoadjuvant, Immunotherapy

Introduction

Esophageal cancer is a malignant tumor that poses a serious threat to human health, ranking 7th in incidence worldwide and 6th in mortality [1]. For patients with early-stage esophageal cancer, surgical resection is the preferred treatment method. However, up to 40 to 50% of esophageal cancer patients are initially diagnosed at

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a locally advanced stage, where surgery alone has poor outcomes, with a 5-year survival rate of only 15 to 34%. Therefore, the treatment of locally advanced esophageal cancer patients requires a multidisciplinary approach to improve their survival [2]. Neoadjuvant therapy refers to systemic treatment administered before the primary treatment modalities, such as surgery or radiotherapy, with the aim of reducing tumor size, downstaging the tumor, eliminating potential micrometastatic lesions, and thereby increasing the success and safety of surgical resection. The CROSS trial demonstrated that chemoradiotherapy prior to surgical resection can provide greater benefits for esophageal cancer patients [3]. Consequently, the National Comprehensive Cancer Network (NCCN) guidelines have adopted it as the standard of care [4]. Despite this, the treatment outcomes for esophageal cancer remain suboptimal, with a 5-year survival rate of only 20% [5, 6]. The Japanese study JCOG9907 indicated that adding radiotherapy to neoadjuvant therapy did not improve treatment effects and increased the probability of patients experiencing adverse reactions [7]. It is evident that using chemotherapy or radiotherapy alone in neoadjuvant therapy cannot significantly improve the long-term survival rates of patients [8, 9]. Therefore, there is an urgent need for new treatment methods to increase patient survival rates, reduce surgical complications, and enhance safety.

Tumor immunotherapy has developed rapidly over the past few decades, especially in the study of immune checkpoint inhibitors. Immune checkpoint inhibitors, such as programmed death-1 (PD-1) or its ligand (PD-L1) inhibitors and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies, can inhibit tumor progression by alleviating the immunosuppressive effects of immune checkpoint-related molecules and enhance the body's antitumor response, becoming a potential treatment for various solid tumors [10–12]. These drugs enhance antitumor immune responses by blocking immune checkpoint pathways, promoting T cell migration, proliferation, and the secretion of cytotoxic mediators [13]. Multiple immune checkpoint inhibitors have shown significant antitumor activity in esophageal squamous cell carcinoma. However, there is a lack of comparative effectiveness and safety data for different combinations of immune checkpoint inhibitors with chemotherapy regimens. In this study, we conducted a network meta-analysis of clinical trials investigating neoadjuvant immunotherapy combined with various chemotherapy regimens, statistically analyzing the efficacy differences of different immune checkpoint inhibitors combined with chemotherapy regimens across various outcome indicators, providing more evidence for clinicians to tailor treatment plans.

Materials and methods

Search strategy

Under the ID CRD42024623160, the study protocol was uploaded to the International Prospective Register of Systematic Reviews database. Search Strategy and Study Selection: PubMed, Embase, Cochrane, Web of Science, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), and Wanfang databases were searched for articles published before November 2023 evaluating the clinical efficacy and safety of neoadjuvant immunotherapy in resectable esophageal squamous cell carcinoma. Search keywords included "esophageal cancer," "neoadjuvant therapy," "immunotherapy," "PD-1," "PD-L1," and others. Inclusion criteria: (1) pathological stages II–IVa. (2) Experimental group: Neoadjuvant chemotherapy combined with immunotherapy, including PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors, along with combined chemotherapy. (3) Control group: Chemotherapy alone. (4) Outcomes: Major pathological response (MPR), pathological complete response (PCR), adverse reaction rate, short-term efficacy, R0 resection rate, and surgical complications. Exclusion Criteria: (1) Literature with missing outcome indicators (pCR, DCR, ORR, MPR, R0 resection rate) for three or more. (2) Studies enrolling no more than 10 patients. (3) Single-arm trials. (4) Duplicate publications, case reports, reviews, expert opinions, and editorials. Taking the PubMed search as an example, the search query is as follows:

((((((((((((((((Esophageal Neoplasms[MeSH Terms]) OR (Esophageal Neoplasm[Title/Abstract])) OR (Neoplasm, Esophageal[Title/Abstract])) OR (Esophagus Neoplasm[Title/Abstract])) OR (Esophagus Neoplasms[Title/Abstract])) OR (Neoplasm, Esophagus[Title/Abstract])) OR (Neoplasms, Esophagus[Title/Abstract])) OR (Neoplasms, Esophageal[Title/Abstract])) OR (Cancer of Esophagus[Title/Abstract])) OR (Cancer of the Esophagus[Title/Abstract])) OR (Esophagus Cancer[Title/Abstract])) OR (Cancer, Esophagus[Title/Abstract])) OR (Cancers, Esophagus[Title/Abstract])) OR (Esophagus Cancers[Title/Abstract])) OR (Esophageal Cancer[Title/Abstract])) OR (Cancer, Esophageal[Title/Abstract])) AND ((((((((((((((((Neoadjuvant Therapy[MeSH Terms]) OR (Neoadjuvant Therapies[Title/Abstract])) OR (Therapy, Neoadjuvant[Title/Abstract])) OR (Neoadjuvant Treatment[Title/Abstract])) OR (Treatment, Neoadjuvant[Title/Abstract])) OR (Neoadjuvant Chemoradiotherapy[Title/Abstract])) OR (Chemoradiotherapy, Neoadjuvant[Title/Abstract])) OR (Neoadjuvant Chemoradiotherapies[Title/Abstract])) OR

(Neoadjuvant Chemoradiation Therapy[Title/Abstract])) OR (Chemoradiation Therapy, Neoadjuvant[Title/Abstract])) OR (Neoadjuvant Chemoradiation Therapies[Title/Abstract])) OR (Therapy, Neoadjuvant Chemoradiation[Title/Abstract])) OR (Neoadjuvant Chemoradiation Treatment[Title/Abstract])) OR (Chemoradiation Treatment, Neoadjuvant[Title/Abstract])) OR (Neoadjuvant Chemoradiation Treatments[Title/Abstract])) OR (Neoadjuvant Chemoradiations[Title/Abstract])) OR (Neoadjuvant Radiotherapy[Title/Abstract])) OR (Neoadjuvant Systemic Therapy[Title/Abstract]))) AND ((Immunotherapy[MeSH Terms]) OR (Immunotherapies[Title/Abstract])).

Data collection

Two reviewers (Wang and Dong) independently screened titles and abstracts using the aforementioned search strategy and collected the following information: (1) study characteristics, including the first author, publication year, clinical trial number, study design, main inclusion criteria for patients, neoadjuvant therapy regimen, and sample size; (2) baseline data for each study; (3) endpoint data, including MPR, PCR, DCR, ORR, incidence of adverse reactions, R0 resection rate, and surgical complications. Each study was reviewed multiple times to ensure that the data was neither missing nor misflagged. Disagreements were resolved by consulting with a third researcher (Wu).

Publication bias and study quality assessment

An independent quality assessment was conducted by two investigators according to the Cochrane Handbook for Systematic Reviews of Interventions to ensure the objectivity and accuracy of the assessment results. In the event of a disagreement during the assessment, a final decision will be made through in-depth discussion or by consulting a third investigator.

The outcome measure

TNM staging was conducted according to the American Joint Committee on Cancer (AJCC) Staging System, Version 8 [14], and adverse events (AEs) were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 [15]. A pCR is defined as the absence of residual tumor cells in the tumor specimen following neoadjuvant therapy and surgical resection. A major pathological response (MPR) is defined as the presence of less than 10% residual tumor cells.

Statistical analysis

The risk of bias was assessed using the funnel plot created with Review Manager 5.3 for analysis. The network meta-analysis was conducted using the random-effects model within Stata software, under the framework of frequency analysis. The results for dichotomous variables were expressed as odds ratios (ORs), and for continuous variables as mean differences (MDs), along with their respective 95% confidence intervals (CIs). Since there is no closed loop in this study—meaning pairwise comparisons between interventions are made through indirect comparisons—no test for discordance is required. Statistical analysis can be performed directly using the consistency model. The "network" command can be utilized to generate evidence network plots, comparison-adjusted funnel plots, league tables, and cumulative ranking probability (SUCRA) plots. The results of the network meta-analysis were presented in a league table. In this table, the 95% CI of dichotomous variables did not cross 1, and the 95% CI for mean differences (MD) of continuous variables did not cross 0, indicating that the observed differences were statistically significant. The evidence network relationships were presented using an evidence network diagram. Publication bias and small sample size effects were depicted using a funnel plot. The best possible intervention measures were illustrated using a probability ranking diagram. The surface under the cumulative ranking was used to rank each intervention, with a larger surface area indicating a higher ranking and a better intervention. Comparison-adjusted funnel plots were drawn to detect potential publication bias in the results of both small and large studies.

Results

Literature search results

A total of 518 relevant articles were identified. Eleven studies were selected based on the inclusion and exclusion criteria [16–26]. See Fig. 1 for an illustration of the literature screening process. The publication years ranged from 2009 to 2023. All selected studies were two-arm trials involving seven different treatment regimens, which included Pembrolizumab + TN, Camrelizumab + TN, Camrelizumab + TP, Pembrolizumab + PC, Pembrolizumab + TP, Camrelizumab + TP, Sintilimab + TP, and Toripalimab + TP.

Essential characteristics included in the study

Refer to Table 1 for details on the authors, publication dates, and number of cases across the 11 studies included in the study characteristics table.

Literature quality evaluation

The overall quality of the 11 included literatures was fair; see Fig. 2 for details.

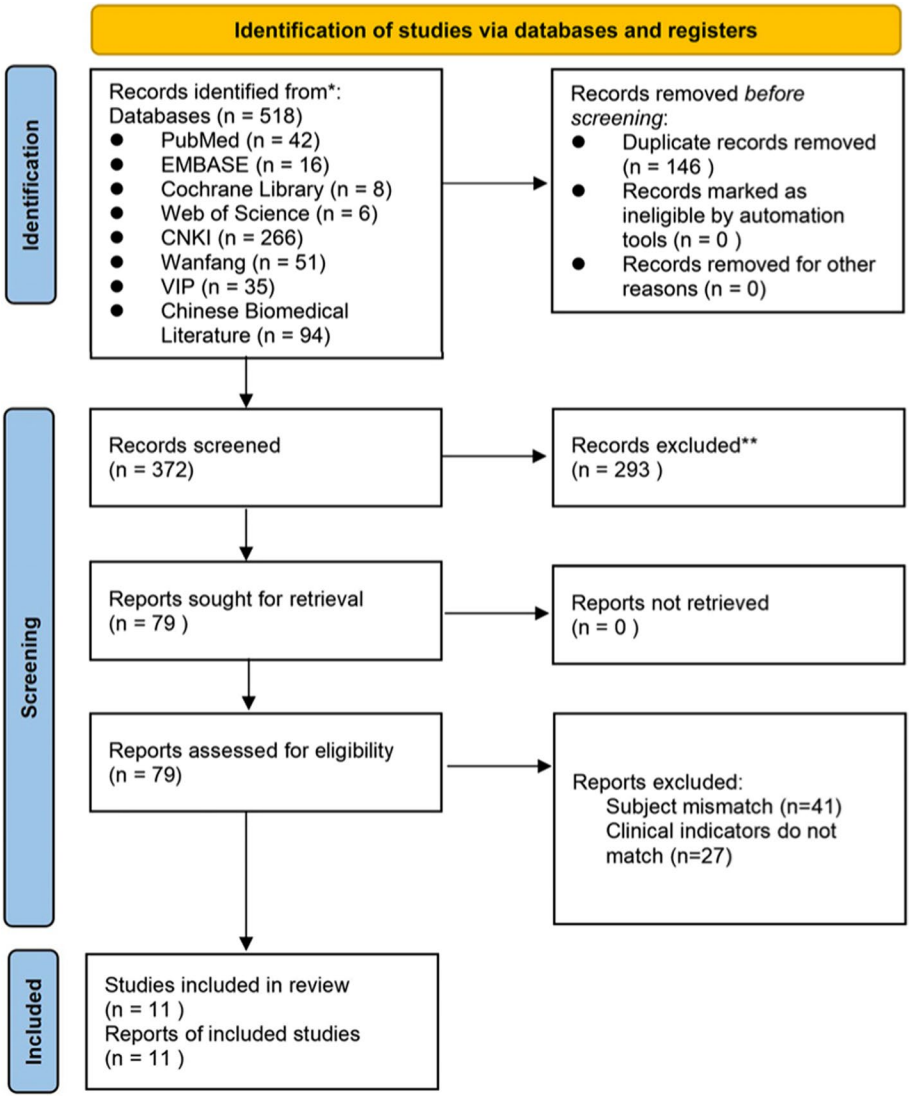

Fig. 1 Literature search flow chart

Results of network meta-analysis

Network graph

The network diagram presented in Fig. 3 depicts the relationships among PCR, MPR, DCR, ORR, R0 resection rate, adverse reaction rate, and surgical complications.

Pairwise comparison

For pCR, the regimens of Camrelizumab + TN [OR = 13.93, 95% CI (1.49, 129.78)], Camrelizumab + TP [OR = 6.50, 95% CI (3.47, 12.17)], and Sintilimab + TP [OR = 7.02, 95% CI (1.44, 34.25)] were superior to chemotherapy alone. No significant differences were observed among the remaining treatment groups. In terms of MPR, Camrelizumab + TP [OR = 4.62, 95% CI (2.74, 7.77)] demonstrated superiority over chemotherapy alone. Similarly, Camrelizumab + TP [OR = 3.61, 95% CI (1.34, 9.74)] was superior in ORR. Pembrolizumab + PC [OR = 2.37, 95% CI (1.37, 4.11)], Pembrolizumab + TP [OR = 3.93, 95% CI (1.58, 9.74)], and Sintilimab + TP [OR = 4.56, 95% CI (1.60, 13.06)] were superior to chemotherapy alone in achieving R0 resection rates. Camrelizumab + TP [OR = 5.79, 95% CI (1.07, 31.16)], Pembrolizumab + PC [OR = 2.93, 95% CI (1.40, 6.15)], and Sintilimab + TP [OR = 5.25, 95% CI (1.27, 21.66)] also showed superiority over chemotherapy alone. However, no significant differences were observed between the groups in terms of myelosuppression, vomiting, and postoperative cardiac complications. Camrelizumab + TP [OR = 10.15, 95% CI (2.70, 38.15)] was significantly more likely

Table 1 Basic information included in literature

Author, reference	Age (male/female)		Gender (male/female)		Tumor grade	NICT/NCT	NCT	NICT	Operation
	NICT	NCI	NICT	NCI					
Huang B 2021 [16]	59.2 ± 7.3	58.9 ± 6.4	21/2	30/1	II–IVA	23/31	TN	Pembrolizumab + TN	Mediastinoscopy + laparoscopic partial esophagectomy + cervical esophagogastric anastomosis
Zhou RQ 2023 [17]	65.89 ± 6.06	64.50 ± 4.54	17/2	31/9	II–IVA	19/40	TN	Camrelizumab + TN	McKeown
Zhang BH 2023 [18]	60.68 ± 7.44	60.08 ± 7.78	31/3	94/3	II–IVA	34/97	TP	Camrelizumab + TP	NA
Qiao YJ 2022 [19]	64.15 ± 7.29	64.15 ± 7.29	38/10	147/59	I–IV	48/206	TP	Camrelizumab + TP	McKeown
Wang XZ 2023 [20]	57.13 ± 9.11	58.80 ± 9.21	33/24	36/22	IIA–III	57/58	PC	Pembrolizumab + PC	Left thoracoesophageal resection and esophagogastric (or colon or jejunal) chest/neck anastomosis
Chen J 2021 [21]	56.37 ± 5.81	54.86 ± 7.05	31/18	35/14	II–III	49/49	PC	Pembrolizumab + PC	Left thoracoesophageal resection and esophagogastric (or colon or jejunal) chest/neck anastomosis
Zhang XW 2022 [22]	57.91 ± 8.06	56.70 ± 7.95	30/16	29/17	II–III	46/46	TP	Pembrolizumab + TP	NA
Wang JP 2023 [23]	60.06 ± 3.01	60.03 ± 2.98	17/13	16/14	II–IVA	30/30	TP	Camrelizumab + TP	NA
Wang XL 2022 [24]	64.21 ± 3.27	63.73 ± 3.32	18/2	20/3	II–IVA	20/23	TP	Camrelizumab + TP	NA
Yao P 2023 [25]	58.89 ± 7.29	61.28 ± 7.91	32/6	25/4	II–IVA	38/29	TP	Sintilimab + TP	Thoracoscopic three incision esophagectomy for esophageal cancer
Liu F 2023 [26]	56.26 ± 5.11	57.98 ± 5.75	20/23	18/25	IIB–IVA	43/43	TP	Toripalimab + TP	McKeown

NICT, the neoadjuvant immunochemotherapy group; *NCT*, the neoadjuvant chemotherapy group; *NA*, the information has not been clearly described; *TN*, docetaxel + nedaplatin; *PC*, pemetrexed + cisplatin; *TP*, paclitaxel + nedaplatin

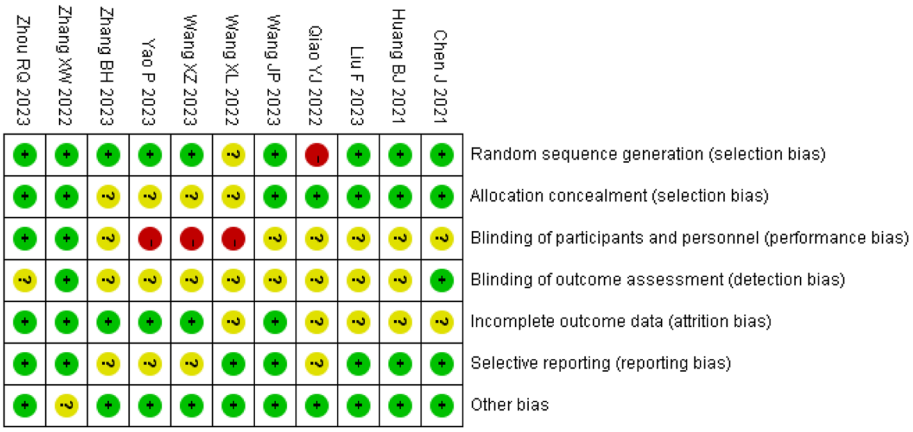

Fig. 2 Risk bias evaluation

than chemotherapy alone to cause a rash after neoadjuvant therapy. Additionally, the combination of Camrelizumab + TP [OR = 13.82, 95% CI (2.48, 76.94)] was found to be significantly more effective than Toripalimab + TP. See Tables 2, 3, 4, 5, 6, 7, 8, 9, and 10 for detailed comparisons.

Cumulative sort probability results

In terms of clinical efficacy, the SUCRA curve results indicated the following probability order for achieving pCR: Camrelizumab + TN (0.809), Sintilimab + TP (0.631), Camrelizumab + TP (0.609), Pembrolizumab + TN (0.437), and Chemotherapy (0.014). These results suggest that Camrelizumab + TN had the highest

Fig. 3 Network graph

Table 2 pCR

Chemotherapy	4.08 (0.92,18.04)	13.93 (1.49,129.78)	6.50 (3.47,12.17)	7.02 (1.44,34.25)
	PembrolizumabTN	3.41 (0.23,49.78)	1.59 (0.32,7.98)	1.72 (0.20,15.08)
		CamrelizumabTN	0.47 (0.05,4.74)	0.50 (0.03,7.79)
			CamrelizumabTP	1.08 (0.20,5.94)
				SintilimabTP

Table 3 MPR

Chemotherapy	1.58 (0.53,4.68)	4.62 (2.74,7.77)
	PembrolizumabTN	2.92 (0.88,9.76)
		CamrelizumabTP

Table 4 DCR

Chemotherapy	3.61 (1.34,9.74)	1.33 (0.55,3.18)	4.63 (0.93,23.15)	7.71 (0.85,70.08)
	CamrelizumabTP	0.37 (0.10,1.38)	1.28 (0.19,8.51)	2.14 (0.19,24.05)
		PembrolizumabPC	3.49 (0.56,21.78)	5.81 (0.54,62.39)
			PembrolizumabTP	1.66 (0.11,25.56)
				SintilimabTP

Table 5 ORR

Chemotherapy	1.71 (0.70,4.17)	2.37 (1.37,4.11)	3.93 (1.58,9.74)	4.56 (1.60,13.06)
	CamrelizumabTP	1.39 (0.49,3.95)	2.30 (0.64,8.20)	2.67 (0.67,10.59)
		PembrolizumabPC	1.66 (0.57,4.80)	1.93 (0.59,6.31)
			PembrolizumabTP	1.16 (0.29,4.66)
				SintilimabTP

Table 6 R0 resection rates

Chemotherapy	2.02 (0.36,11.48)	1.48 (0.06,38.04)	5.79 (1.07,31.16)	2.93 (1.40,6.15)	5.25 (1.27,21.66)
	PembrolizumabTN	0.73 (0.02,29.11)	2.86 (0.25,32.19)	1.45 (0.22,9.59)	2.60 (0.28,24.47)
		CamrelizumabTN	3.91 (0.10,151.27)	1.98 (0.07,55.24)	3.54 (0.10,122.38)
			CamrelizumabTP	0.51 (0.08,3.19)	0.91 (0.10,8.20)
				PembrolizumabPC	1.79 (0.36,8.87)
					SintilimabTP

Table 7 Myelosuppression

Chemotherapy	3.00 (0.69,13.10)	0.83 (0.44,1.55)	0.78 (0.33,1.88)	0.66 (0.21,2.06)	1.45 (0.42,5.00)	1.90 (0.43,8.37)
	PembrolizumabTN	0.28 (0.06,1.37)	0.26 (0.05,1.45)	0.22 (0.03,1.42)	0.48 (0.07,3.31)	0.63 (0.08,5.12)
		CamrelizumabTP	0.95 (0.32,2.79)	0.80 (0.22,2.93)	1.75 (0.44,7.02)	2.29 (0.46,11.49)
			PembrolizumabPC	0.84 (0.20,3.54)	1.85 (0.41,8.41)	2.42 (0.43,13.54)
				PembrolizumabTP	2.19 (0.41,11.75)	2.86 (0.44,18.58)
					SintilimabTP	1.31 (0.19,9.04)
						ToripalimabTP

Table 8 Vomiting

Chemotherapy	1.35 (0.44,4.16)	0.95 (0.50,1.78)	0.92 (0.50,1.69)	1.38 (0.51,3.76)	1.38 (0.55,3.46)
	PembrolizumabTN	0.70 (0.19,2.55)	0.68 (0.19,2.44)	1.02 (0.23,4.62)	1.03 (0.24,4.37)
		CamrelizumabTP	0.97 (0.40,2.33)	1.46 (0.45,4.76)	1.46 (0.48,4.44)
			PembrolizumabPC	1.51 (0.47,4.87)	1.51 (0.50,4.54)
				SintilimabTP	1.00 (0.26,3.89)
					ToripalimabTP

Table 9 Rash

Chemotherapy	18.70 (0.98,357.25)	10.15 (2.70,38.15)	5.25 (0.60,46.30)	0.73 (0.25,2.19)
	PembrolizumabTN	0.54 (0.02,13.76)	0.28 (0.01,10.97)	0.04 (0.00,0.91)
		CamrelizumabTP	0.52 (0.04,6.61)	0.07 (0.01,0.40)
			SintilimabTP	0.14 (0.01,1.60)
				ToripalimabTP

Table 10 Cardiac events

Chemotherapy	0.82 (0.01,103.16)	0.98 (0.02,39.42)	0.36 (0.00,61.92)
	CamrelizumabTN	1.18 (0.00,519.10)	0.44 (0.00,509.95)
		CamrelizumabTP	0.37 (0.00,209.56)
			SintilimabTP

efficacy in improving the rate of pCR. In the MPR study, Camrelizumab + TP (0.976) showed greater efficacy than Pembrolizumab + TN (0.423) and Chemotherapy (0.101), indicating the highest efficacy of Camrelizumab + TP in improving the rate of MPR. For DCR, the efficacy of different treatments was ranked as Sintilimab + TP (0.817) > Pembrolizumab + TP (0.707) > Camrelizumab + TP (0.647) > Pembrolizumab + PC (0.245) > Chemotherapy (0.084), indicating that Sintilimab + TP had the highest efficacy in improving the DCR. In the ORR analysis, Sintilimab + TP (0.841) had a higher efficacy compared to Pembrolizumab + TP (0.784), Pembrolizumab + PC (0.509), Camrelizumab + TP (0.336), and Chemotherapy (0.03), suggesting that Sintilimab + TP had the highest efficacy in improving the ORR. Regarding the R0 resection rate, the order from highest to lowest was Camrelizumab + TP (0.771), Sintilimab + TP (0.754), Pembrolizumab + PC (0.558), Pembrolizumab + TN (0.416), Camrelizumab + TN (0.368), and Chemotherapy (0.132), suggesting that Camrelizumab + TP has the greatest advantage in improving the R0 resection rate.

The SUCRA curves also displayed the associated probabilities of adverse reactions and postoperative complications. For myelosuppression, the ranking from highest to lowest possibility was Pembrolizumab + TN (0.861), Toripalimab + TP (0.721), Sintilimab + TP (0.621), Chemotherapy (0.459), Camrelizumab + TP (0.311), Pembrolizumab + PC (0.298), and Pembrolizumab + TP (0.228), indicating that Pembrolizumab + TN has the highest likelihood of causing myelosuppression, while Pembrolizumab + TP has the lowest likelihood. For rash initiation, the order from highest to lowest probability was Pembrolizumab + TN (0.835), Camrelizumab + TP (0.761), Sintilimab + TP (0.61), Chemotherapy (0.204), and Toripalimab + TP (0.09), suggesting that Pembrolizumab + TN has the highest probability of rash initiation, while Toripalimab + TP has the lowest probability. For

emesis, the order of probability from highest to lowest was Toripalimab + TP (0.655), Sintilimab + TP (0.644), Pembrolizumab + TN (0.626), Chemotherapy (0.395), Camrelizumab + TP (0.355), and Pembrolizumab + PC (0.326), indicating that Toripalimab + TP has the highest probability of emesis, while Pembrolizumab + PC has the lowest probability. For the incidence of postoperative cardiac events, the order from highest to lowest probability was Chemotherapy (0.565), Camrelizumab + TP (0.545), Camrelizumab + TN (0.509), and Sintilimab + TP (0.381), suggesting that traditional chemotherapy alone has the highest likelihood of causing postoperative cardiac adverse events. See Fig. 4 for details.

Inconsistency test

No consistency test was conducted, as none of the nine outcome measures in this study formed closed loops.

Publication bias test

We assessed publication bias across outcome measures using correction-comparison funnel plots. The plots demonstrated good symmetry, with no significant asymmetries or abnormal distributions observed. This suggested that our findings possess high statistical reliability and were not significantly affected by publication bias. Refer to Fig. 5 for visual representation.

Discussion

Esophageal cancer is a highly prevalent malignant tumor worldwide. Due to its nonspecific early symptoms, patients often present at an advanced stage, missing the opportunity for minimally invasive surgery [27, 28]. Although a combination of surgery and adjuvant chemotherapy and radiotherapy is widely used, the cure rate for esophageal cancer remains unsatisfactory, with its mortality rate ranking among the highest in the world [29]. The goal of neoadjuvant therapy is to provide preoperative treatment for patients with resectable tumors, with the expectation of reducing tumor size and grade before surgery, thereby achieving complete tumor resection and improving prognosis [30, 31]. In recent years, immunotherapy, represented by the programmed death receptor 1 (PD-1), has shown significant efficacy in the treatment of esophageal squamous cell carcinoma [32, 33]. Phase III clinical trials KEYNOTE-590 and Checkmate 649 further demonstrated that patients with advanced esophageal cancer can benefit from first-line treatment with pembrolizumab or nivolumab combined with chemotherapy

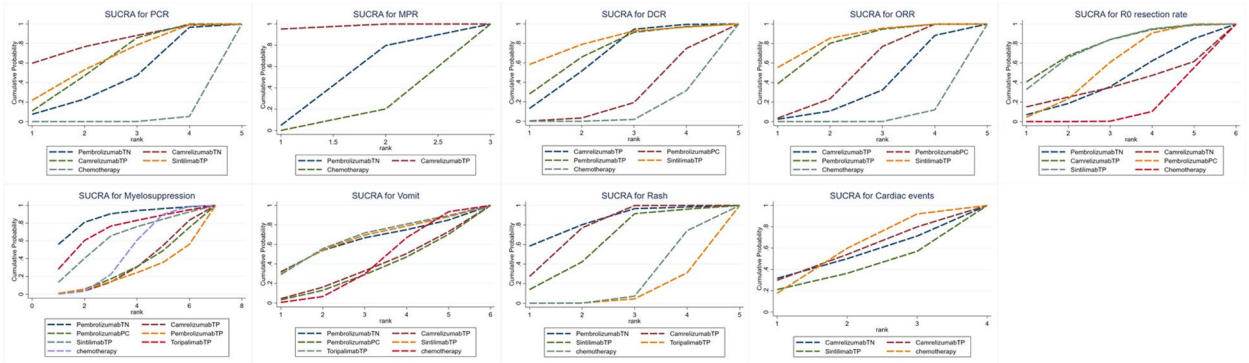

Fig. 4 Cumulative sort probability results

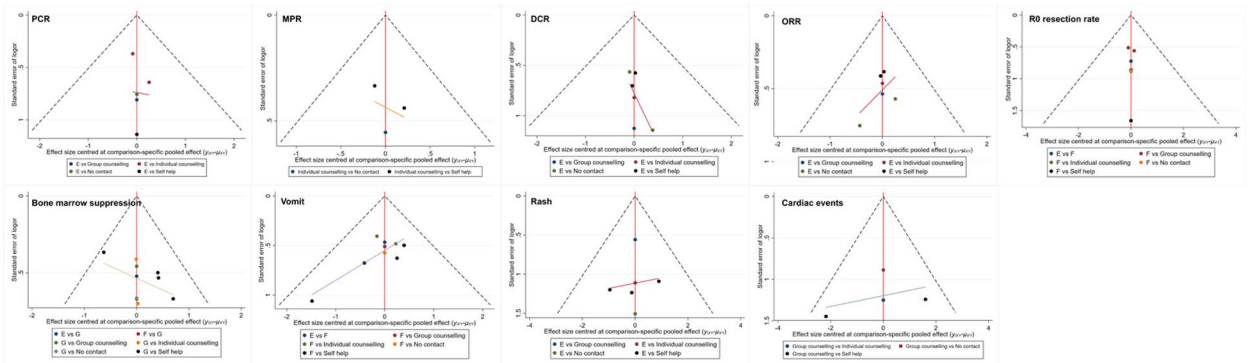

Fig. 5 Funnel plot

[34, 35]. In a meta-analysis of 27 clinical trials involving 815 patients conducted by Ge Fei and colleagues, the overall pCR rate for neoadjuvant immunotherapy was 31.4% [36]. The latest data from clinical trials show that the drug retention rate for chemotherapy alone is 33.3% [37], while the highest drug retention rate for neoadjuvant immunotherapy combined with chemotherapy is 72.4% [38]. These studies have demonstrated the effectiveness of immune checkpoint inhibitors and provided substantial evidence for the feasibility of neoadjuvant immunotherapy. However, some patients experience varying degrees of tumor regression or progression when receiving neoadjuvant immunotherapy combined with chemotherapy [39], and there is a significant difference in treatment sensitivity to neoadjuvant immunotherapy combined with chemotherapy among different patients, which poses certain challenges for clinical treatment decisions. This article aims to compare and analyze the clinical efficacy and safety of neoadjuvant immunotherapy regimens for esophageal cancer, providing a basis for determining the best indications for immunotherapy in esophageal cancer.

In this meta-analysis, we assessed the efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy for locally advanced esophageal cancer. Our study demonstrated that Camrelizumab combined with chemotherapy is superior to chemotherapy alone in terms of pCR. This finding is consistent with the results of a multicenter, randomized, parallel-controlled phase III study (ESCORT-NEO/NCCES01) organized by Qin et al., where the Camrelizumab + TP group showed a significantly higher pCR rate of 15.4% compared to 4.7% in the TP group (Camrelizumab + TP vs TP: difference 10.9%, 95% CI 3.7–18.1, $P = 0.0034$) [40]. Liu et al. also observed in a multicenter, single-arm, phase II trial that Camrelizumab combined with chemotherapy achieved a pCR of 39.2% in patients with locally advanced esophageal cancer, further confirming the outstanding efficacy of immunotherapy combined with chemotherapy in terms of pCR [41]. In terms of MPR, Camrelizumab + TP was superior to chemotherapy alone, echoing the results of the ESCORT-NEO/NCCES01 study, whose prospective multicenter randomized clinical trial found significant differences in the rates of MPR between the Camrelizumab + TP and TP groups, at 36.2% and 20.9%, respectively, and the R0 resection rate in the Camrelizumab + TP group reached 95.7% [40]. In a phase II trial of squamous cell carcinoma of the head and neck conducted by Wu et al., patients treated with Camrelizumab combined with paclitaxel and cisplatin as neoadjuvant therapy achieved an MPR rate of 63% and an even more encouraging pCR rate of 55.6% [42]. Additionally, this study found that Sintilimab combined with chemotherapy is superior to chemotherapy alone in terms of ORR, which is consistent with the ORIENT-15 study results, where 616 patients receiving Sintilimab combined with chemotherapy achieved an objective response rate of 65%, compared to only 45% in the chemotherapy group. The study also found that the survival curves of patients with PD-1 CPS ≥ 10 separated from those with negative patients in the early stages, but both were statistically significant [43]. In KEYNOTE-590, 749 patients received Pembrolizumab + Chemotherapy, and among patients with esophageal squamous cell carcinoma with PD-L1 CPS ≥ 10, the median survival of patients in the Pembrolizumab + Chemotherapy group reached 13.9 months, significantly better than the control group's 8.8 months. The combination group also showed a significant advantage in terms of progression-free survival (6.3 months vs 5.8 months) [34]. This study, through network meta-analysis, found that Camrelizumab combined with chemotherapy can significantly increase pCR, DCR, and R0 resection rates. However, it also observed a higher incidence of rash in the Camrelizumab + TP group compared to chemotherapy alone and the Toripalimab + TP regimen. This corresponds to the adverse effect guidelines for immune checkpoint inhibitors published by the Chinese Society of Clinical Oncology. It is noteworthy that, compared with other control groups combined with Camrelizumab and chemotherapy, there were no significant differences in terms of bone marrow suppression, vomiting, and postoperative cardiac complications, also indicating the acceptable nature of its adverse reactions.

With the continuous development of immune checkpoint inhibitors, the neoadjuvant approaches for esophageal cancer treatment that combine chemotherapy and immunotherapy are becoming increasingly diverse. Immune checkpoint inhibitors represented by Camrelizumab, Sintilimab, Pembrolizumab, and others have all shown outstanding efficacy. However, there are still differences in the clinical efficacy and adverse reaction levels of different combination regimens, which can make it difficult for clinicians to choose. The probability ranking results of this study show that Camrelizumab + TP has the best advantage in terms of MPR and R0 resection rates, while Camrelizumab + TN shows the best advantage in pCR. It is inferred that Camrelizumab combined with chemotherapy can show good efficacy in local tumor reduction, which corresponds with the results of the ESCORT-NEO/NCCES01 trial. SUCRA analysis also shows that Sintilimab + TP has the best advantage in DCR and ORR, consistent with the study by Huang et al., which observed ORR and DCR of 71.42% and 85.71%, respectively, after treating 7 patients with malignant tumors for 8 courses with Sintilimab [44].

The adverse reactions induced by immune checkpoint inhibitors are an issue that cannot be ignored in immunotherapy. Toshihiko Doizai observed in clinical practice that the incidence of rash induced by Pembrolizumab is as high as 9%, which deserves attention. This is consistent with the results of this study, where among all combination regimens, Pembrolizumab has the highest probability of inducing rash [45]. The detailed instructions for Toripalimab mention that the incidence of all adverse reactions is 97.7%, with rash, skin depigmentation, and itching being the adverse reactions with an incidence of ≥ 10%. The incidence of grade 3 and above adverse reactions is 28.9%, without specifically mentioning the incidence of vomiting. However, this study found that the probability of vomiting induced by Toripalimab + TP is the highest, and it is less likely to induce rash, which deserves attention. In addition, this study found that the incidence of postoperative cardiac events in patients receiving chemotherapy alone is the highest, suggesting that the combination of neoadjuvant immunotherapy and chemotherapy can reduce the incidence of postoperative cardiac adverse events.

Overall, the combination of neoadjuvant immunotherapy and chemotherapy has shown excellent results in terms of efficacy and safety. The outcomes of numerous clinical trials indicate that immunotherapy, whether used alone or in combination with chemotherapy, does not significantly increase the risk of adverse events [46–48]. Researchers such as Ge Fei mentioned in their report that the total incidence of adverse events with neoadjuvant immunotherapy combined with chemotherapy is 26.9% [36]. They also emphasized that no treatment-related deaths were observed, further confirming the good tolerability of the treatment regimen, which aligns with the findings of our study. In future research, it would be beneficial to focus on comparing the efficacy differences between various immune checkpoint inhibitors, as well as on how to effectively reduce the incidence of adverse reactions such as rash, in order to optimize treatment plans.

Limitations

Firstly, since most of the included clinical trials did not provide long-term follow-up results and complete survival data, we are unable to determine the benefits of neoadjuvant immunotherapy on prolonged survival. More high-quality studies are needed in the future to provide progression-free survival (PFS) and overall survival (OS) data, which will help determine the long-term survival benefits of neoadjuvant immunotherapy. Secondly, most of the studies included in this analysis did not report the status of PD-L1 expression. Some studies have shown that the level of PD-L1 in primary tumors is correlated with an increased tumor mutational burden. This increased mutational burden is directly related to the effectiveness of immunosuppressants. Subgroup analysis could not be performed in this study, making it difficult to provide more direct evidence for clinical use. Thirdly, some literature did not include pCR, MPR, and other prognostic indicators of neoadjuvant therapy, which may bias the results. Fourthly, due to the limited number of clinical studies available, this paper includes some retrospective studies. Although the articles use propensity score matching, the results may still be biased.

Conclusion

The combination of neoadjuvant immunotherapy and chemotherapy has demonstrated advantages in terms of clinical efficacy and safety compared to chemotherapy alone. The Camrelizumab + TP regimen showed several advantages in terms of pCR, MPR, DCR, and R0 resection rate, particularly excelling in MPR and R0 resection rate. However, it is worth noting that the incidence of rash was higher in the Camrelizumab + TP group compared to chemotherapy alone and the Toripalimab + TP regimen. Neoadjuvant immunotherapy combined with chemotherapy can reduce the incidence of postoperative cardiac adverse events, with Sintilimab + TP being the most effective option. Limited by the number and quality of included studies, the above conclusions need to be verified by additional high-quality studies.

Abbreviations

pCR	Pathological complete response
DCR	Disease control rate
ORR	Overall response rate
MPR	Major pathological response
NCCN	National Comprehensive Cancer Network
PD-1	Programmed death receptor-1
PD-L1	Programmed death-ligand 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CBM	Chinese Biomedical Literature Database
CNKI	China National Knowledge Infrastructure
VIP	China Science and Technology Journal Database
AJCC	American Joint Committee on Cancer
AEs	Adverse events
CTCAE	Common Terminology Criteria for Adverse Events
ORs	Odds ratios
MDs	Mean differences
CIs	Confidence intervals
SUCRA	Cumulative ranking probability
NICT	The neoadjuvant immunochemotherapy group
NCT	The neoadjuvant chemotherapy group
NA	The information has not been clearly described
TN	Docetaxel + Nedaplatin
PC	Pemetrexed + Cisplatin
TP	Paclitaxel + Nedaplatin

Authors' contributions

MX Wang: conception and design, provision of study materials or patients. WH Dong: conception and design, administrative support, provision of study materials or patients. QM Sun: administrative support. AX Liu: collection and assembly of data. BR Zhang: collection and assembly of data. T Lai: data

analysis and interpretation. All authors: manuscript writing, final approval of manuscript.

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Declarations

Ethics approval and consent to participate
Since this study is a meta-analysis, informed consent and publication consent are not required.

Competing interests
The authors declare no competing interests.

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