INPLASY PROTOCOL

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Support: **No.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Evaluation of Neoadjuvant Immune Combined Therapy and Traditional Neoadjuvant Therapy for Resectable Esophageal Cancer: A Systematic Review and Single-arm and Network Meta-analysis

Wang, HS[1]; Song, CY[2]; Zhao, XH[3]; Deng, WZ[4]; Shen, WB[5].

Review question / Objective: **Population: Patients with histologically-confirmed resectable esophageal carcinoma; Intervention: Neoadjuvant immunotherapy combined with chemotherapy or neoadjuvant immunotherapy combined with chemoradiotherapy followed by surgery; Control: Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery; Outcomes: Treatment related adverse events, r0 resection rate, pathological complete response, major pathological response, objective response rate, disease control rate, postoperative complications, postoperative mortality, 1/2/3/5year overall survival, 1/2/3/5year disease free survival; Study Design: All prospective and restrospective studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2022 and was last updated on 15 December 2022 (registration number INPLASY2022120060).

INTRODUCTION

Review question / Objective: **Population: Patients with histologically-confirmed resectable esophageal carcinoma; Intervention: Neoadjuvant immunotherapy combined with chemotherapy or neoadjuvant immunotherapy combined with chemoradiotherapy followed by surgery; Control: Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery;**

Outcomes: Treatment related adverse events, r0 resection rate, pathological complete response, major pathological response, objective response rate, disease control rate, postoperative complications, postoperative mortality, 1/2/3/5year overall survival, 1/2/3/5year disease free survival; **Study Design:** All prospective and restrospective studies.

Rationale: CROSS trials have set the neoadjuvant chemoradiotherapy as the standard treatment for locally advanced esophageal cancer. We want to evaluate the efficacy and safety outcomes of neoadjuvant immunotherapy combined with chemotherapy or chemoradiotherapy and neoadjuvant chemotherapy or chemoradiotherapy for patients with locally esophageal cancer.

Condition being studied: Esophageal cancer is one of the most prevalent types of cancer, characterized by high mortality rate worldwide. In addition, EC is the 7th leading cause of cancer-related death in men. The current overall 5- year survival rate is approximately 20%. Surgery remains the mainstay for early-stage esophageal cancer. And neoadjuvant chemoradiotherapy was the standard treatment for locally advanced cases. Neoadjuvant immunotherapy for patients with locally advanced esophageal cancer has developed rapidly in recent years. However, whether neoadjuvant immunotherapy combined with chemotherapy or chemoradiotherapy has an advantage over traditional neoadjuvant therapy is still inconclusive.

METHODS

Search strategy: Pubmed: ((((((((((((((((((((((((immunotherapy[Title/Abstract]) OR ("immune checkpoint inhibitors"[Title/Abstract])) OR ("programmed cell death 1 receptor"[Title/Abstract])) OR ("programmed cell death ligand 1"[Title/Abstract])) OR ("cytotoxic T lymphocyte-associated antigen-4 antigen"[Title/Abstract])) OR ("CTLA-4 antigen"[Title/Abstract])) OR (anti-CTLA-4[Title/Abstract])) OR (CTLA-4[Title/Abstract])) OR (anti-PD-1[Title/Abstract])) OR (anti-PD-L1[Title/Abstract])) OR (PD-1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (Durvalumab[Title/Abstract])) OR (Atezolizumab[Title/Abstract])) OR (avelumab[Title/Abstract])) OR (Pembrolizumab[Title/Abstract])) OR (Nivolumab[Title/Abstract])) OR (Toripalimab[Title/Abstract])) OR (Tislelizumab[Title/Abstract])) OR (Camrelizumab[Title/Abstract])) OR (Sintilimab[Title/Abstract])) OR (Tremelimumab[Title/Abstract])) OR (Ipilimumab[Title/Abstract])) OR (Lambrolizumab[Title/Abstract])) OR (cemiplimab[Title/Abstract])) OR (PDCD1[Title/Abstract])) OR (CD274[Title/Abstract])) AND ((((Neoadjuvant[Title/Abstract]) OR (Preoperative[Title/Abstract])) OR (Perioperative[Title/Abstract])) OR (before[Title/Abstract]))) AND ((((((((((((((((((("Esophageal Neoplasms"[MeSH Terms]) OR ("Cancer of Esophagus"[Title/Abstract])) OR ("Cancer of the Esophagus"[Title/Abstract])) OR ("Esophageal Cancer"[Title/Abstract])) OR ("Esophagus Cancer"[Title/Abstract])) OR ("esophageal neoplasm"[Title/Abstract])) OR ("Esophagus Neoplasm"[Title/Abstract])) OR ("carcinoma of esophagus"[Title/Abstract])) OR ("Esophageal squamous cell carcinoma"[Title/Abstract])) OR ("Esophageal squamous carcinoma"[Title/Abstract])) OR ("Esophageal squamous cell cancer"[Title/Abstract])) OR ("Esophageal carcinoma"[Title/Abstract])) OR ("esophageal adenocarcinoma"[Title/Abstract])) OR ("esophageal malignancy"[Title/Abstract])) OR (ESCC[Title/Abstract])) OR (Esophagus[Title/Abstract])) OR (Esophageal[Title/Abstract])) OR (oesophagus[Title/Abstract])) OR (oesophageal[Title/Abstract]))

Embase: (immunotherapy:ti,ab,kw OR 'immune checkpoint inhibitors':ti,ab,kw OR 'programmed cell death 1 receptor':ti,ab,kw OR 'programmed cell death ligand 1':ti,ab,kw OR 'cytotoxic t lymphocyte-associated antigen-4 antigen':ti,ab,kw OR 'ctla-4 antigen':ti,ab,kw OR 'anti ctla 4':ti,ab,kw OR 'ctla 4':ti,ab,kw OR 'anti pd 1':ti,ab,kw

OR 'anti pd l1':ti,ab,kw OR 'pd 1':ti,ab,kw OR 'pd l1':ti,ab,kw OR durvalumab:ti,ab,kw OR atezolizumab:ti,ab,kw OR avelumab:ti,ab,kw OR pembrolizumab:ti,ab,kw OR nivolumab:ti,ab,kw OR toripalimab:ti,ab,kw OR tislelizumab:ti,ab,kw OR camrelizumab:ti,ab,kw OR sintilimab:ti,ab,kw OR tremelimumab:ti,ab,kw OR ipilimumab:ti,ab,kw OR lambrolizumab:ti,ab,kw OR cemiplimab:ti,ab,kw OR pdcd1:ti,ab,kw OR cd274:ti,ab,kw) AND (neoadjuvant:ti,ab,kw OR preoperative:ti,ab,kw OR perioperative:ti,ab,kw OR before:ti,ab,kw) AND ('esophageal neoplasms':ti,ab,kw OR 'cancer of esophagus':ti,ab,kw OR 'cancer of the esophagus':ti,ab,kw OR 'esophageal cancer':ti,ab,kw OR 'esophagus cancer':ti,ab,kw OR 'esophageal neoplasm':ti,ab,kw OR 'esophagus neoplasm':ti,ab,kw OR 'carcinoma of esophagus':ti,ab,kw OR 'esophageal squamous cell carcinoma':ti,ab,kw OR 'esophageal squamous carcinoma':ti,ab,kw OR 'esophageal squamous cell cancer':ti,ab,kw OR 'esophageal carcinoma':ti,ab,kw OR 'esophageal adenocarcinoma':ti,ab,kw OR 'esophageal malignancy':ti,ab,kw OR escc:ti,ab,kw OR esophagus:ti,ab,kw OR esophageal:ti,ab,kw OR oesophagus:ti,ab,kw OR oesophageal:ti,ab,kw)

WOS:

(((((((((((((((((((((((TS=(immunotherapy)) OR TS=("immune checkpoint inhibitors")) OR TS=("programmed cell death 1 receptor")) OR TS=("programmed cell death ligand 1")) OR TS=("cytotoxic T lymphocyte-associated antigen-4 antigen")) OR TS=("CTLA-4 antigen")) OR TS=(anti-CTLA-4)) OR TS=(CTLA-4)) OR TS=(anti-PD-1)) OR TS=(anti-PD-L1)) OR TS=(PD-1)) OR TS=(PD-L1)) OR TS=(Durvalumab)) OR TS=(Atezolizumab)) OR TS=(avelumab)) OR TS=(Pembrolizumab)) OR TS=(Nivolumab)) OR TS=(Toripalimab)) OR TS=(Tislelizumab)) OR TS=(Camrelizumab)) OR TS=(Sintilimab)) OR TS=(Tremelimumab)) OR TS=(Ipilimumab)) OR TS=(Lambrolizumab)) OR TS=(cemiplimab)) OR TS=(PDCD1)) OR TS=(CD274)) AND ((((TS=(Neoadjuvant)) OR TS=(Preoperative)) OR TS=(Perioperative)) OR TS=(before)) AND ((((((((((((((((((TS=("Esophageal Neoplasms")) OR TS=("Cancer of Esophagus")) OR TS=("Cancer of the Esophagus")) OR TS=("Esophageal Cancer")) OR TS=("Esophagus Cancer")) OR TS=("esophageal neoplasm")) OR TS=("Esophagus Neoplasm")) OR TS=("carcinoma of esophagus")) OR TS=("Esophageal squamous cell carcinoma")) OR TS=("Esophageal squamous carcinoma")) OR TS=("Esophageal squamous cell cancer")) OR TS=("Esophageal carcinoma")) OR TS=("esophageal adenocarcinoma")) OR TS=("esophageal malignancy")) OR TS=(ESCC)) OR TS=(Esophagus)) OR TS=(Esophageal)) OR TS=(oesophagus)) OR TS=(oesophageal))

Cochrane Library:

((immunotherapy):ti,ab,kw OR ("immune checkpoint inhibitors"):ti,ab,kw OR ("programmed cell death 1 receptor"):ti,ab,kw OR ("programmed cell death ligand 1"):ti,ab,kw OR ("cytotoxic T lymphocyte-associated antigen-4 antigen"):ti,ab,kw OR ("CTLA-4 antigen"):ti,ab,kw OR (anti-CTLA-4):ti,ab,kw OR (CTLA-4):ti,ab,kw OR (anti-PD-1):ti,ab,kw OR (anti-PD-L1):ti,ab,kw OR (PD-1):ti,ab,kw OR (PD-L1):ti,ab,kw OR (Durvalumab):ti,ab,kw OR (Atezolizumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (Pembrolizumab):ti,ab,kw OR (Nivolumab):ti,ab,kw OR (Toripalimab):ti,ab,kw OR (Tislelizumab):ti,ab,kw OR (Camrelizumab):ti,ab,kw OR (Sintilimab):ti,ab,kw OR (Tremelimumab):ti,ab,kw OR (Ipilimumab):ti,ab,kw OR (Lambrolizumab):ti,ab,kw OR (cemiplimab):ti,ab,kw OR (PDCD1):ti,ab,kw OR (CD274):ti,ab,kw) AND ((Neoadjuvant):ti,ab,kw OR (Preoperative):ti,ab,kw OR (Perioperative):ti,ab,kw OR (before):ti,ab,kw) AND (("Esophageal Neoplasms"):ti,ab,kw OR ("Cancer of Esophagus"):ti,ab,kw OR ("Cancer of the Esophagus"):ti,ab,kw OR ("Esophageal

Cancer"):ti,ab,kw OR ("Esophagus Cancer"):ti,ab,kw OR ("esophageal neoplasm"):ti,ab,kw OR ("Esophagus Neoplasm"):ti,ab,kw OR ("carcinoma of esophagus"):ti,ab,kw OR ("Esophageal squamous cell carcinoma"):ti,ab,kw OR ("Esophageal squamous carcinoma"):ti,ab,kw OR ("Esophageal squamous cell cancer"):ti,ab,kw OR ("Esophageal carcinoma"):ti,ab,kw OR ("esophageal adenocarcinoma"):ti,ab,kw OR ("esophageal malignancy"):ti,ab,kw OR (ESCC):ti,ab,kw OR (Esophagus):ti,ab,kw OR (Esophageal):ti,ab,kw OR (oesophagus):ti,ab,kw OR (oesophageal):ti,ab,kw).

Participant or population: Patients with histologically-confirmed resectable esophagealcarcinoma.

Intervention: Neoadjuvant immunotherapy combined with chemotherapy or neoadjuvant immunotherapy combined with chemoradiotherapy followed by surgery.

Comparator: Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy followed by surgery.

Study designs to be included: All prospective and restrospective studies.

Eligibility criteria: Inclusion criteria included:(1)patients with resectable esophageal cancer confirmed histopathologically, (2) studies that included patients who received neoadjuvant Immunotherapy combined with chemotherapy or chemoradiotherapy, (3) patients reveived radical surgery after neoadjuvant immune combined therapy, (4) studies were published in any languages.Exclusion criteria included: (1)unpublished data, (2) case reports, meta-analysis, academic papers, editorials, letters, review papers, comments, and basic science articles, (3) no correlation results, (4) studies that included other types of treatment, (5) sample size was less than 10.

Information sources: Pubmed, Embase, WOS, Cochrane Library database. ASCO, ESMO, AACR coference abstracts. contact with authors. trial registers. Search manually relevant literature and grey literature.

Main outcome(s): R0 resection rate, pathological complete response, major pathological response, 1/2/3/5year overall survival, 1/2/3/5year disease free survival.

Additional outcome(s): Treatment related adverse events, objective response rate, disease control rate, postoperative complications, postoperative mortality.

Data management: Endnote 20 software will be used to manage the articles obtained by searching the relevant databases. In the first step, two reviewers will independently filter duplicate articles through Endnote and exclude them, then exclude articles that do not meet the inclusion criteria by investigating the title and abstract, and finally screen the full text of remaining articles to finalize the eligible articles. If there are disagreements between the two reviewers, a discussion with the third reviewer will be conducted as a way to resolve the disagreements.

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias of each article included. The Cochrane Handbook for Systematic Reviews of Interventions will be used for the RCT studies. We will assess the risk of bias according to the following ranges: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain will be assessed as high, low or uncertain risk of bias. The risk of bias graph will be reported to demonstrate the results and details of assessment. The Methodological Index for Nonrandomized Studies will be used for the nonrandomized single-group series. The Newcastle-Ottawa Scale will be used for the nonrandomized dual-group series.
We will evaluate all the strength of the body of evidence according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE)

guideline. The quality of evidence will be classified into 4 levels: high, moderate, low, and very low.
We will use funnel plots and Egger test to assess publication bias when more than 10 eligible articles are included. If publication bias is suspected in a study, we will consult the corresponding author for more information. If publication bias does exist, we will analyze publication bias in the studies.

Strategy of data synthesis: All statistical analyses were performed using STATA software version 14 (STATA, College Station, TX). The combined RR and 95% confidence interval (CI) were converted to incidence rate to assess the efficacy and safety of neoadjuvant therapy. $P < 0.05$ for the Q test or $I 2 > 50\%$ for the I2 test were considered to indicate a significant heterogeneity in the literature, and the random-effects model was adopted; otherwise, the fixed-effects model was used.

Subgroup analysis: When significant heterogeneity exists and sufficient data are available, we will conduct subgroup analysis to further explore the sources of heterogeneity. We will conduct subgroup analysis of each parameter (such as article type, type of pathology, the immunotherapy drug, PD-L1/PD-1 expression levels, chemotherapy drug, radiation dose, and so on), when the extracted data are sufficient.

Sensitivity analysis: Sensitivity analyses will be carried out by sequentially removing individual studies to evaluate the robustness of the pooled results of these studies.

Language restriction: All languages.

Country(ies) involved: China (Department of Radiation Oncology, Fourth Hospital of Hebei Medical University, 12 Jiankang Road, Shijiazhuang 050011, Hebei Province, People's Republic of China).

Keywords: esophageal cancer, neoadjuvant, immunotherapy, meta-analysis, systematic review.

Dissemination plans: We will publish it in an academic journal after the study.

Contributions of each author:
Author 1 - hesong wang - Author 1 conducted a statistical analysis of the study and completed the manuscript.
Email: wanghesongmz@163.com
Author 2 - chunyang song - Author 2 conducted literature screening, data extraction, and quality evaluation.
Author 3 - wenzhao deng - Author 3 conducted literature screening, data extraction, and quality evaluation.
Author 4 - xiaohan zhao - Author 4 will participate in the discussion when the opinions of Author 2 and author 3 appear differently.
Author 5 - wenbin shen - Author 5 will revise and contribute the manuscript.