INPLASY PROTOCOL

To cite: Wu et al. Efficacy and Safety of Immune Checkpoint Inhibitors as Preoperative Neoadjuvant Therapy for Resectable Locally Advanced Esophageal Carcinoma: A Single-Arm Meta-Analysis. Inplasy protocol 202270079. doi: 10.37766/inplasy2022.7.0079

Received: 17 July 2022

Published: 17 July 2022

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Support: **NSFC(No.82074315).**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Efficacy and Safety of Immune Checkpoint Inhibitors as Preoperative Neoadjuvant Therapy for Resectable Locally Advanced Esophageal Carcinoma: A Single-Arm Meta-Analysis

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Review question / Objective: **(1)studies involving patients with pathologically confirmed ESCC or EAC, and were evaluated rlaESCC/rlaEAC with clinical stages II-IV(T1-4aNxM0); (2)studies involving patients treated with preoperative neoadjuvant ICIs plus chemotherapy or chemo-radiotherapy(CRT); (3)studies reporting either efficacy and safety, including complete resection rate(R0 resection), objective response rate(ORR), pathological complete response(pCR), major pathological response(MPR), pathological downstaging(Pds), main preoperative adverse events (AEs), PD-L1 combined positive score(CPS) and median survival(DFS, disease-free survival; PFS, progression-free survival; OS, overall survival); (4) Studies that included prospective clinical trials and retrospective studies, both randomized controlled trials(RCTs) and single-arm trials.**
Condition being studied: **Efficacy and safety of immune checkpoint inhibitors as preoperative neoadjuvant therapy for resectable locally advanced esophageal carcinoma.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2022 and was last updated on 17 July 2022 (registration number INPLASY202270079).

INTRODUCTION

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major pathological response(MPR), pathological downstaging(Pds), main preoperative adverse events (AEs), PD-L1 combined positive score(CPS) and median survival(DFS, disease-free survival; PFS, progression-free survival; OS, overall survival); (4) Studies that included prospective clinical trials and retrospective studies, both randomized controlled trials(RCTs) and single-arm trials.

Condition being studied: Efficacy and safety of immune checkpoint inhibitors as preoperative neoadjuvant therapy for resectable locally advanced esophageal carcinoma.

METHODS

Participant or population: Patients with pathologically confirmed esophageal squamous cell carcinoma(ESCC) or adenocarcinoma(EAC), and were evaluated resectable locally advanced ESCC or EAC with clinical stages II-IV(T1-4aNxM0).

Intervention: Preoperative neoadjuvant ICIs plus chemotherapy or chemoradiotherapy.

Comparator: Preoperative chemotherapy, chemoradiotherapy or single-arm trials without control groups.

Study designs to be included: Studies that included prospective clinical trials and retrospective studies, both randomized controlled trials(RCTs) and single-arm trials.

Eligibility criteria: The inclusion criteria were as follows: (1)studies involving patients with pathologically confirmed ESCC or EAC, and were evaluated rlaESCC/rlaEAC with clinical stages II-IV(T1-4aNxM0); (2)studies involving patients treated with preoperative neoadjuvant ICIs plus chemotherapy or chemoradiotherapy (CRT); (3)studies reporting either efficacy and safety, including complete resection rate(R0 resection), objective response rate(ORR), pathological complete response (pCR), major pathological response(MPR), pathological downstaging(Pds), main preoperative adverse events (AEs), PD-L1 combined positive score(CPS) and median survival(DFS, disease-free survival; PFS, progression-free survival; OS, overall survival); (4) Studies that included prospective clinical trials and retrospective studies, both randomized controlled trials(RCTs) and single-arm trials. The exclusion criteria were as follows: (1)studies on animal testing or basic research; (2) reviews, comments, conference abstract or case report; (3) results data were missing or incomplete reportings; (4)studies were published repeatedly; (5)studies did not include the outcome indicators required for this meta-analysis.

Information sources: The PubMed, Cochrane Library, Embase and ClinicalTrials.gov were searched for related studies, from inception until July 1, 2022.

Main outcome(s): R0 resection, ORR, pCR, MPR, Pds, AEs, PD-L1 CPS and median survival.

Quality assessment / Risk of bias analysis: The Cochrane Handbook (Higgins et al., 2011) was utilized to assess the quality of all included RCTs. And included single-arm studies were evaluated by methodological index for non-randomized studies (MINORS): 0 score, it was not reported in the article evaluated; 1 score, it was reported but inadequately; 2 score, it was reported adequately (Slim K et al., 2003).

Strategy of data synthesis: The Stata version 14.0 software was used to carry out the statistical analysis. The 95 % confidence intervals (CI) were calculated for all pooled effect sizes. Cochran,s Q and $\chi 2$ test statistics were used to examine the heterogeneity across studies and test level was set as $\alpha = 0.1$. The fixed-effects model was adopted if heterogeneity was low of the results ($P > 0.1$, $I2 < 50\%$), if heterogeneity was high(($P \leq 0.1$, $I2 \geq 50\%$), the random-effects model was chosen. The sensitivity analysis, subgroup analysis and univariate meta-regression analysis were employed to deal with the pooled results with high heterogeneity. Moreover, Egger's test, Begg's test, Funnel-plot-based trim

and fill method were performed to objectively evaluate the potential publication bias of included studies. The online Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (https://gdt.gradepro.org/app/) was used to evaluate the quality of evidence as follows: risk of bias, inconsistency, indirectness, imprecision and other considerations. The quality of evidence was--high, moderate, low, or very low.

Subgroup analysis: Subgroup analysis will be performed where possible,including publication year, region, disease status, clinical stage ,ECOG median age and proportion of male etc.

Sensitivity analysis: Sensitivity analysis will be conducted to evalate the stability of the results by excluding the studies one by one, and then reanalysis the remining studies by STATA 14.0 software.

Country(ies) involved: China.

Keywords: Immune Checkpoint Inhibitors; Preoperative Neoadjuvant Therapy; Resectable Locally Advanced Esophageal Carcinoma; Single-Arm Meta-Analysis; Efficacy and Safety.

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