INPLASY PROTOCOL

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Neoadjuvant immune checkpoint inhibitor in combination with chemotherapy or chemoradiotherapy in resectable esophageal cancer: A systematic review and meta-analysis

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Review question / Objective: **It remains unclear whether addition of immune checkpoint inhibitor (ICI) to neoadjuvant chemoradiotherapy (nCRT) or neoadjuvant chemotherapy (nCT) can increase antitumor efficacy in resectable esophageal cancer (EC). we performed the systematic review and meta-analysis to assess antitumor efficacy and safety of nICRT and nICT, and made a comparison with nCRT and nICT. We used pathological complete response (pCR) as the primary outcomes of interest.**
Condition being studied: **Initial findings from a number of phase 1 or 2 trials have supported the tolerability and/or antitumor efficacy of ICI plus nICRT (nICRT) and nICT (nICT). However, the superiority of this combination strategy remains uncertain due to lack of randomized control trials (RCTs) with long-term outcomes. Moreover, there are still outstanding questions such as the selection of nICRT or nICT, the ideal predictive biomarkers, and timing of surgical resection.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 June 2022 and was last updated on 12 June 2022 (registration number INPLASY202260052).

INTRODUCTION

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METHODS

Search strategy: We searched PubMed, Embase, Cochrane Library and Web of Science for relevant publications from January 1, 2000 until December 31, 2021, using the search terms "esophageal cancer", "neoadjuvant", "preoperative", "immune checkpoint inhibitors", "PD-1/PD-L1", and "chemoradiotherapy". The search strategy in details is presented in Supplementary File: Table S. Abstracts of recent important meetings were also inspected, including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and American Society for Radiation Oncology (ASTRO). References of of relevant studies were reviewed for additional articles.

Participant or population: Patients with resectable esophageal cancer.

Intervention: Neoadjuvant immune checkpoint inhibitors with radiotherapy and/or chemotherapy.

Comparator: Neoadjuvant chemotherapy and chemoradiotherapy.

Study designs to be included: Literature search, inclusion and exclusion criteria, data extraction and quality assessment, statistical analysis, data analysis and interpretation, manuscript writing, and final approval of manuscript.

Eligibility criteria: (1) single-arm or multi-arm trials examining nICRT or nICT in resectable EC; (2) reported at least one of the following outcomes: pCR (defined as no viable tumor cells in the resected specimen), grade ≥3 treatment-related adverse events (TRAEs), surgical resection rate (the ratio of patients who underwent surgical resection to those who were planned to), R0 resection rate (the ratio of patients achieving a R0 resection to all patients undergoing surgical resection), and the incidence of surgical mortality rate; and (3) published in English.

Information sources: PubMed, Embase, Cochrane Library and Web of Science.

Main outcome(s): The primary outcome of interest were pCR. The second outcome of interest was safety, including surgical resection rate, R0 resection rate, surgical delay rate, surgical mortality rate, and grade ≥3 TRAEs. The inverse variance method was used to calculate pooled estimates of the outcomes and their 95% CIs.

Quality assessment / Risk of bias analysis: Risk of bias of individual trials was independently assessed by two authors. The Cochrane Risk of Bias Tool was used to assess risk of bias of RCTs. The trials were finally classified as low (all domains indicated as low risk), high (one or more domains indicated as high risk), and unclear risk of bias (more than three domains indicated as unclear risk).

Strategy of data synthesis: The random effect model was used for statistical analysis, using the software R (version 4.1.1, R Foundation for Statistical Computing) via the meta package. The inverse variance method was used to calculate pooled estimates of the outcomes and their 95% CIs. the Chi-square (χ2) and I-square (I2) test were performed to detect the presence of heterogeneity, and significant heterogeneity was considered present if P value of less than 0.10 or I2 greater than 50%.

Subgroup analysis: Subgroup analyses in patients receiving nICRT or nICT were performed according to histological type and PD-L1 expression.

Sensitivity analysis: Sensitivity analysis was performed to verify the stability of the pooled results by removing the data of an individual study each time.

Country(ies) involved: China.

Keywords: neoadjuvant; immune checkpoint inhibitor; chemotherapy; radiotherapy; esophageal cancer ; meta-analysis.

Contributions of each author:

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