INPLASY

Comparative Efficacy and Safety of Neoadjuvant Immunochemotherapy Versus Neoadjuvant Chemoradiotherapy in Locally Advanced Resectable Esophageal Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis

INPLASY202670021
doi: 10.37766/inplasy2026.7.0021
Received: 9 July 2026
Published: 9 July 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670021

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 July 2026 and was last updated on 9 July 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review and meta-analysis is to compare the efficacy and safety of neoadjuvant immunochemotherapy versus neoadjuvant chemoradiotherapy in patients with locally advanced resectable esophageal squamous cell carcinoma.

The research question is defined according to the PICOS framework as follows:

• Population (P): Patients with histologically confirmed locally advanced, resectable esophageal squamous cell carcinoma.

• Intervention (I): Neoadjuvant immunotherapy combined with chemotherapy (immunochemotherapy).

• Comparison (C): Neoadjuvant chemoradiotherapy.

• Outcomes (O): At least one of the following primary or secondary clinical outcomes must be reported: pathological complete response (pCR) rate, major pathological response (MPR) rate, R0 resection rate, incidence of grade ≥3 treatment-related serious adverse events (tr-SAE), and surgical complication rate.

• Study Design (S): Both randomized controlled trials (RCTs) and observational studies (cohort studies) that provide extractable outcome data will be included. We will strictly exclude case reports, systematic reviews or meta-analyses, cell culture or animal studies, conference abstracts, and studies reporting invalid or insufficient data on efficacy and safety. Furthermore, studies involving patients who previously received immunotherapy or radiotherapy, as well as those evaluating neoadjuvant immunochemoradiotherapy (triple-modality therapy), will be excluded to ensure a clear head-to-head comparison between the two specified neoadjuvant strategies.

Condition being studied Esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype of esophageal cancer, accounting for approximately 85% of all esophageal cancer cases worldwide. In 2020, there were an estimated 604,100 new cases of esophageal cancer and 544,100 related deaths

globally, making it the seventh most common cancer and the sixth leading cause of cancer-related mortality worldwide. The global burden is projected to increase by more than 50% from 2020 to 2040, reaching nearly 1 million new cases per year. ESCC demonstrates marked geographic variation, with the highest incidence rates observed in Eastern Asia, Southern Africa, and Eastern Africa. Asia accounts for approximately 80% of global ESCC cases, with China alone contributing to 54% of this burden. Major risk factors include tobacco smoking and heavy alcohol consumption, which together may account for roughly 90% of ESCC cases in Western countries.

Locally advanced ESCC is defined as disease that has spread from its primary site to adjacent tissues or regional lymph nodes without distant metastasis. More than one-third of patients present with locally advanced disease at diagnosis. The prognosis for these patients remains poor, with a global 5-year overall survival (OS) rate of approximately 15–25%. For patients treated with surgery alone, 5-year survival rates are approximately 25%. Even after radical surgery, recurrence occurs in 38% of patients, with 75% of recurrences occurring within the first 2 years. Although neoadjuvant or definitive chemoradiotherapy (CRT) has been the standard treatment for locally advanced ESCC, patient outcomes remain unsatisfactory, with recurrence rates as high as 30–50%. Current guidelines endorse neoadjuvant chemoradiotherapy followed by surgery as the standard of care for operable locally advanced ESCC. However, given the substantial treatment-related morbidity and the persistent poor prognosis, there is a pressing need for more effective and less toxic therapeutic strategies. The emergence of immune checkpoint inhibitors has opened new avenues for treatment, and neoadjuvant immunochemotherapy is being increasingly investigated as a potential alternative to neoadjuvant chemoradiotherapy in this patient population.Patients with locally advanced esophageal squamous cell carcinoma.

METHODS

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Participant or population Patients with locally advanced esophageal squamous cell carcinoma.

Intervention Receiving neoadjuvant immunochemotherapy (immunotherapy combined with chemotherapy）.

Comparator Receiving neoadjuvant chemoradiotherapy.

Study designs to be included Both randomized controlled trials (RCTs) and observational studies (cohort studies) that provide extractable outcome data will be included.

Eligibility criteria Inclusion Criteria
1. Population: Patients with locally advanced esophageal squamous cell carcinoma.
2. Intervention: Receiving neoadjuvant immunochemotherapy (immunotherapy combined with chemotherapy).
3. Comparison: Receiving neoadjuvant chemoradiotherapy.
4. Outcomes: Enrolled patient data and at least one primary or secondary clinical outcome reported, such as pathological complete response (pCR) rate, major pathological response (MPR) rate, objective response rate (ORR), incidence of grade ≥3 treatment related serious adverse events (tr SAE), R0 resection rate, and surgical complication rate, etc.
5. Study Design: Prospective trials or cohort studies.
6. Language: Articles published in English.

Exclusion Criteria
1. Studies reporting patients with unresectable or metastatic disease.
2. Studies in which patients had previously received immunotherapy or radiotherapy, or those evaluating neoadjuvant immunochemoradiotherapy (triple modality therapy).
3. Studies reporting invalid or insufficient data on the efficacy and safety of neoadjuvant immunotherapy.
4. Studies that violate any of the above inclusion criteria. In addition, reviewers will further exclude case reports, conference abstracts, comments, letters, systematic reviews or meta analyses; cell culture or animal studies; and studies that do not provide results for the specified outcome measures.

Information sources The main databases to be searched are PubMed、Embase、Cochrane Library and Web of Science.

Main outcome(s) pCR、MPR、R0 resection、Incidence of TRAEs、≥Grade3 TRAEs、Total postoperative complications.

Quality assessment / Risk of bias analysis For the randomized controlled trial (RCT): The revised

Cochrane risk-of-bias tool for randomized trials (RoB 2.0) will be employed. This tool evaluates bias across five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain, as well as the overall risk of bias, will be judged as "low risk," "some concerns," or "high risk."

For retrospective cohort studies: The Newcastle-Ottawa Scale (NOS) will be utilized to assess methodological quality. The NOS evaluates studies across three domains: selection (4 items, maximum 4 stars), comparability (1 item, maximum 2 stars), and outcome (3 items, maximum 3 stars), with a total score ranging from 0 to 9 stars. Studies with a NOS score of ≥7 stars will be considered high quality; 5–6 stars will be considered moderate quality; and ≤4 stars will be considered low quality.

For assessment of the overall certainty of evidence: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be applied to rate the overall quality of evidence for each outcome. The certainty of evidence will be categorized as "high," "moderate," "low," or "very low." Given that the body of evidence consists predominantly of retrospective cohort studies, the overall certainty of evidence is expected to be downgraded accordingly.

Sensitivity analysis: To assess the robustness of the pooled results, a sensitivity analysis will be performed by excluding the single RCT to evaluate whether the inclusion of this study significantly influences the overall effect estimates.

The results of the quality assessment will be presented in summary tables. Funnel plots and Egger's test will be used to visually and statistically assess the potential for publication bias when at least 10 studies are included.

Strategy of data synthesis The meta-analysis used Review Manager, version 5.4 (RevMan), a proprietary software provided by the Cochrane Collaboration[26], and and Stata statistical software (version 18.0). The primary observational endpoints were described previously. To compare the safety and efficacy of neoadjuvant ICIs combined with chemotherapy versus routine neoadjuvant therapy, risk ratios (RRs) and 95% CIs were utilized as efficacy indicators. Heterogeneity was assessed using the $\chi 2$ test and I^2 statistic. In the presence of significant heterogeneity (I^2>50%), the random-effects model was employed; otherwise, the fixed-effects model was used. Sensitivity analysis were conducted to identify potential sources of heterogeneity. The potential for publication bias was evaluated by visually inspecting funnel plots and conducting Egger's test. All P values were two-sided, and a significance level of 0.05 was considered statistically significant.

Subgroup analysis Not applicable.

Sensitivity analysis Sensitivity analysis were conducted to identify potential sources of heterogeneity.

Language restriction English.

Country(ies) involved China.

Keywords Esophageal Squamous Cell Carcinoma; Neoadjuvant Immunotherapy; Neoadjuvant Chemoradiotherapy.

Contributions of each author

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