

Additional Chemoradiotherapy versus Esophagectomy Following Endoscopic Resection for Early Esophageal Squamous Cell Carcinoma: A Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 November 2025 and was last updated on 25 November 2025.

INTRODUCTION

Review question / Objective Participants (P): Adult patients with early-stage esophageal squamous cell carcinoma (ESCC), specifically those who underwent endoscopic resection (ER/ESD) and were identified as non-curative resection or having risk factors for lymph node metastasis (e.g., pT1b, positive LVI).

Intervention (I): Additional chemoradiotherapy (CRT) or radiotherapy (RT).

Comparator (C): Additional surgery (Radical esophagectomy with lymph node dissection).

Outcome (O): Primary outcomes: Recurrence-free survival (RFS) and Overall survival (OS). Secondary outcomes: Disease-specific survival (if available), recurrence rates, and treatment-related adverse events.

Study design: Comparative studies (Randomized controlled trials or observational cohort studies).

Rationale Endoscopic resection (ER), particularly endoscopic submucosal dissection (ESD), has become the cornerstone of treatment for early-stage esophageal squamous cell carcinoma (ESCC). However, a clinical dilemma arises when pathological examination reveals risk factors for lymph node metastasis, such as deep submucosal invasion (pT1b) or lymphovascular invasion (LVI). While radical esophagectomy is the standard additional treatment to ensure oncological safety, it is associated with significant morbidity. Chemoradiotherapy (CRT) has emerged as a less invasive alternative, yet concerns regarding higher recurrence rates persist.

Although previous meta-analyses have reported comparable overall survival between surgery and

CRT, they primarily relied on aggregated data and failed to conduct subgroup analyses regarding specific tumor substages or risk factors. Consequently, whether this therapeutic equivalence holds true for high-risk subgroups remains unclear. This systematic review aims to address these gaps by emplo.

Condition being studied Early-stage esophageal squamous cell carcinoma (ESCC) following endoscopic resection (ER), particularly in patients identified with pathological risk factors for lymph node metastasis (e.g., deep submucosal invasion [pT1b] or lymphovascular invasion [LVI]).

METHODS

Search strategy Databases: PubMed, Embase, Cochrane CENTRAL, ClinicalKey, ProQuest, ScienceDirect, and Web of Science.

Keywords / Search Query: ('esophageal cancer' OR 'esophageal squamous cell carcinoma') AND ('endoscopic resection' OR 'endoscopic submucosal dissection' OR 'ESD') AND ('chemoradiotherapy' OR 'radiation therapy' OR 'esophagectomy' OR 'surgery') AND ('survival' OR 'prognosis' OR 'outcome')

Restrictions: No language restrictions. Search period up to September 1, 2025.

Participant or population Adult patients diagnosed with early-stage esophageal cancer, primarily esophageal squamous cell carcinoma (ESCC). Studies involving a proportion of esophageal adenocarcinoma (EAC) are also considered eligible if data for both histologies are reported in aggregate and cannot be separated. Patients must have undergone endoscopic resection (ER) or endoscopic submucosal dissection (ESD) and were subsequently identified as having pathological risk factors for lymph node metastasis (e.g., submucosal invasion [pT1b], lymphovascular invasion [LVI], or positive vertical margins), thereby necessitating additional treatment.

Intervention Additional chemoradiotherapy (CRT) or radiotherapy (RT).

Comparator Additional surgery (Radical esophagectomy with lymph node dissection).

Study designs to be included Comparative studies, including randomized controlled trials (RCTs) and observational cohort studies (both prospective and retrospective). Single-arm studies,

case series, case reports, reviews, and editorials will be excluded.

Eligibility criteria Inclusion criteria:

Study design: Randomized controlled trials (RCTs) or comparative observational studies (cohort or case-control studies).

Population: Adult patients diagnosed with early-stage esophageal cancer, primarily esophageal squamous cell carcinoma (ESCC), who underwent endoscopic resection (ER) or endoscopic submucosal dissection (ESD). Studies including a small proportion of adenocarcinoma are eligible if data cannot be separated.

Intervention & Comparison: Studies directly comparing additional chemoradiotherapy (CRT) versus additional surgery (esophagectomy) following endoscopic resection.

Outcomes: Articles reporting sufficient quantitative survival data, specifically hazard ratios (HRs) with 95% confidence intervals (CIs), or publishing Kaplan–Meier curves that allow for data extraction and reconstruction of recurrence-free survival (RFS) or overall survival (OS).

Exclusion criteria:

Single-arm studies or non-comparative studies.

Studies lacking extractable or reconstructable survival data.

Duplicate publications or studies involving overlapping patient populations.

Case reports, reviews, editorials, letters, conference abstracts, or other non-peer-reviewed publications.

Animal studies or in vitro studies.

Information sources Electronic databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalKey, ProQuest, ScienceDirect, and Web of Science were systematically searched. To identify gray literature and unpublished studies, a supplementary search was performed on ClinicalTrials.gov. Additionally, the reference lists of all included studies and relevant review articles were manually screened to identify further eligible records. In cases where survival data were incomplete or not reported, corresponding authors were contacted to obtain additional information.

Main outcome(s) The primary outcomes are Recurrence-Free Survival (RFS) and Overall Survival (OS).

1. Recurrence-Free Survival (RFS): Defined as the time interval from the date of endoscopic resection or the initiation of additional treatment to the date of first documented recurrence (locoregional or distant) or death from any cause.

2. Overall Survival (OS): Defined as the time interval from the date of endoscopic resection or the initiation of additional treatment to the date of death from any cause.

Effect measures: The treatment effect will be expressed as pooled Hazard Ratios (HRs) with 95% confidence intervals (CIs). For studies where HRs are not directly reported, individual patient data will be reconstructed from published Kaplan-Meier survival curves using a standardized iterative algorithm to estimate the HRs and corresponding statistics.

Additional outcome(s) 1. Subgroup Analyses: To evaluate the potential modifying effects of key prognostic factors on survival outcomes. Specifically, studies will be stratified based on:

Depth of submucosal invasion (proportion of pT1b).

Tumor location (proportion of lower esophageal location).

Presence of lymphovascular invasion (LVI).**

2. Sensitivity Analysis: To assess the robustness and stability of the pooled results by sequentially omitting individual studies (leave-one-out analysis).

3. Publication Bias Assessment: Evaluated visually using funnel plots and quantitatively using Egger's regression test."Subgroup Analyses: To evaluate the potential modifying effects of key prognostic factors on survival outcomes. Specifically, studies will be stratified based on:

Depth of submucosal invasion (proportion of pT1b).

Tumor location (proportion of lower esophageal location).

Presence of lymphovascular invasion (LVI).**

Data management Search results will be imported into reference management software (e.g.,

EndNote) for deduplication and record management. Two independent reviewers will conduct the study selection and data extraction process. A standardized data extraction form, developed in Microsoft Excel, will be utilized to systematically record participant demographics, study characteristics, intervention details, and outcome data. Specifically for time-to-event outcomes where hazard ratios are not reported, data points will be extracted from published Kaplan-Meier curves using WebPlotDigitizer (version 4.6) to reconstruct individual patient data. All synthesized data will be managed and statistically analyzed using Comprehensive Meta-Analysis (CMA) software (version 4). Any discrepancies arising during data management will be resolved through discussion or consultation with a third reviewer.

Quality assessment / Risk of bias analysis Two independent reviewers will assess the methodological quality and risk of bias of the included retrospective cohort studies using the Newcastle-Ottawa Scale (NOS). This tool evaluates studies across three domains: selection of study groups, comparability of the groups, and ascertainment of the outcome of interest. Studies will be awarded stars based on these criteria, with a maximum possible score of 9 stars. Studies achieving a score of 7 to 9 will be categorized as high quality (low risk of bias), 4 to 6 as moderate quality, and 0 to 3 as low quality (high risk of bias). Any discrepancies between the reviewers will be resolved through discussion or adjudication by a third reviewer.

Strategy of data synthesis 針對 INPLASY 註冊的 "Strategy of data synthesis" (數據合成策略) 欄位，您需要詳細說明統計分析的方法。這部分是展現您研究「技術含量」的關鍵，特別是關於「數據重建」和「隨機效應模型」的使用。根據您提供的 Methods 草稿，我為您整理了最完整且專業的寫法：建議寫法 (Recommended Text)"Quantitative synthesis will be performed using Comprehensive Meta-Analysis (CMA) software (version 4). The primary measure of treatment effect will be the pooled Hazard Ratio (HR) with 95% Confidence Interval (CI) for time-to-event outcomes (Recurrence-Free Survival and Overall Survival). A random-effects model will be employed for all analyses to account for anticipated clinical and methodological heterogeneity among the included retrospective studies. In studies where HRs and CIs are not explicitly reported, survival data points will be extracted from published Kaplan-Meier curves using WebPlotDigitizer. Individual patient data will then be reconstructed to estimate the

summary HRs and statistics using the iterative algorithm described by Parmar et al. Statistical heterogeneity will be assessed using the I^2 statistic and Cochran's Q test, with significant heterogeneity defined as $I^2 > 50\%$ or $P < 0.10$. Sensitivity analyses will be conducted by sequentially excluding individual studies (leave-one-out method) to evaluate the robustness of the pooled estimates. Potential publication bias will be assessed visually using funnel plots and quantitatively using Egger's regression test.

Subgroup analysis Subgroup analyses will be performed to investigate potential sources of heterogeneity and to evaluate whether specific clinicopathological factors modify the comparative efficacy of the two treatment modalities. Studies will be stratified based on the reported proportions of the following key prognostic factors:

1. Pathological depth of invasion: High vs. low proportion of pT1b (submucosal) invasion.
2. Tumor location: High vs. low proportion of tumors located in the lower esophagus.
3. Lymphovascular invasion (LVI): High vs. low proportion of patients with positive LVI.

Pooled Hazard Ratios (HRs) for Recurrence-Free Survival (RFS) and Overall Survival (OS) will be estimated separately for each subgroup to determine if the treatment effect varies according to these risk profiles.

Sensitivity analysis To evaluate the robustness and stability of the pooled results, a sensitivity analysis will be conducted using the 'leave-one-out' method. This involves sequentially omitting one study at a time from the meta-analysis and recalculating the pooled Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for the remaining studies. This process aims to determine whether any single study disproportionately influences the overall summary estimate or statistical heterogeneity. If the omission of a specific study significantly alters the pooled results (e.g., changing the statistical significance or the direction of the effect), the findings will be interpreted with caution.

Language restriction There were no language restrictions. Studies published in any language will be considered for inclusion, provided they meet the other eligibility criteria.

Country(ies) involved Taiwan.

Other relevant information 1. Data Reconstruction Method: For studies where hazard

ratios (HRs) are not explicitly reported, time-to-event data will be reconstructed from published Kaplan–Meier curves. This process utilizes the iterative algorithm described by Parmar et al. (1998) and Tierney et al. (2007) to estimate the summary statistics. Digitization of survival curves will be performed using WebPlotDigitizer (version 4.6).

2. Ethics Statement: Since this study is a systematic review and meta-analysis based on previously published data, approval from an institutional review board (IRB) and patient informed consent are not required.

Keywords Esophageal squamous cell carcinoma; Endoscopic submucosal dissection; Additional chemoradiotherapy; Esophagectomy; Non-curative resection.

Contributions of each author

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