INPLASY

Multimodal treatment of oesophageal small-cell carcinoma: a systematic review and network meta-analysis based on reconstructed time-to-event data

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ADMINISTRATIVE INFORMATION

Support - A single-arm, prospective study of adebrelimab in combination with chemotherapy in advanced first-line esophageal small cell carcinoma; Henan Province Science and Technology Research Project 242102310150.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 May 2026 and was last updated on 26 May 2026.

INTRODUCTION

Review question / Objective Population (P): Adults with histologically confirmed small-cell carcinoma of the oesophagus (SCCE) (potentially curable, limited-stage disease).
Interventions (I): Multimodal and single-modality curative-intent treatments:
Surgery alone (S)
Surgery + chemotherapy (S+CT)
Neoadjuvant chemotherapy + surgery (NCT+S)
Definitive chemoradiotherapy (CRT)
Radiotherapy alone (RT)
CRT + additional chemotherapy (CRT+CT)
Surgery with nodal stratification (S N0/S N+; prognostic reference groups)
Comparators (C): All above interventions compared head-to-head via direct and indirect evidence in network meta-analysis (NMA).
Outcomes (O):
Primary: Overall survival (OS) (hazard ratios, HRs)
Secondary: Absolute 1-, 3-, 5-year OS rates
Exploratory: Radiotherapy dose–response relationships; study-level modifiers (age, stage, histology); treatment ranking by p-scores
Study design (S): Comparative cohort studies (prospective/retrospective); systematic review + frequentist network meta-analysis (reconstructed time-to-event data from Kaplan–Meier curves).
Overall Review Objective
To compare the relative and absolute survival benefits of different curative-intent multimodal/single-modality treatments for SCCE, rank treatments by efficacy, explore RT dose–response patterns, and identify study-level factors that may guide risk-adapted treatment selection.

Condition being studied Oesophageal Small-Cell Carcinoma (SCCE) is a rare, highly aggressive neuroendocrine malignancy arising from the oesophageal epithelium. Characterised by early

systemic dissemination, rapid progression and poor prognosis, it accounts for less than 1–2% of all oesophageal cancers.
Histologically, SCCE resembles small-cell lung cancer (SCLC), with high-grade tumour cells, frequent lymphovascular invasion and a tendency for distant metastasis (e.g., liver, brain, bone) at diagnosis. Most patients present at advanced stages, and 5-year survival rates are typically below 10%.
Due to its rarity, there is a lack of randomised controlled trials, and treatment approaches are heterogeneous—often extrapolated from SCLC or squamous cell oesophageal carcinoma management. Current options include surgery, chemotherapy, radiotherapy, and multimodal combinations, but optimal strategies remain undefined.

METHODS

Participant or population This review includes adult patients (≥18 years) with histologically confirmed small-cell carcinoma of the oesophagus (SCCE).
Disease stage: Potentially curable, limited-stage SCCE (localised or locoregional disease, without distant metastasis at diagnosis).
Histology: Pure SCCE or mixed histologies where SCCE outcomes can be separately extracted.
Setting: First-line, curative-intent treatment settings.
Exclusions: Patients with metastatic disease, non-SCCE oesophageal cancers, or paediatric populations.

Intervention This review evaluates first-line, curative-intent multimodal and single-modality treatments for potentially curable small-cell carcinoma of the oesophagus (SCCE). The interventions of interest are:
Surgery alone (S)
Surgery plus adjuvant chemotherapy (S+CT)
Neoadjuvant chemotherapy followed by surgery (NCT+S)
Definitive chemoradiotherapy (CRT)
Radiotherapy alone (RT)
Chemoradiotherapy plus additional chemotherapy (CRT+CT)
Surgery with nodal stratification (S N0/S N+) — prognostic reference groups, not active interventions.
All interventions are compared directly and indirectly via network meta-analysis, with a focus on overall survival (OS).

Comparator The comparators in this review are single-modality and multimodal curative-intent treatments for limited-stage oesophageal small-cell carcinoma (SCCE), mutually compared via direct and indirect evidence in network meta-analysis. They include:
Surgery alone (S) (primary reference comparator)
Surgery plus chemotherapy (S+CT)
Neoadjuvant chemotherapy followed by surgery (NCT+S)
Definitive chemoradiotherapy (CRT)
Radiotherapy alone (RT)
Chemoradiotherapy plus additional chemotherapy (CRT+CT)
Surgery with nodal stratification (S N0/S N+) (prognostic reference groups, not active interventions).

Study designs to be included This review will include comparative observational cohort studies (prospective and retrospective) that evaluate curative-intent treatments for limited-stage oesophageal small-cell carcinoma (SCCE).Included designsRetrospective cohort studies (primary source of evidence for this rare disease)Prospective cohort studiesMulticentre or population-based comparative cohortsStudies with adjusted or unadjusted survival data (HRs or reconstructible Kaplan–Meier curves)Excluded designsRandomised controlled trials (RCTs; none available for this indication)Case reports, case series, reviews, letter.

Eligibility criteria Inclusion criteria
Studies published in any language, with extractable full-text data.
Studies reporting first-line, curative-intent treatment for SCCE (no palliative cohorts).
Data reporting overall survival (OS) as hazard ratios (HRs) or with Kaplan–Meier curves reconstructible for time-to-event analysis.
Cohorts with ≥20 patients per treatment arm (to ensure sufficient data for meta-analysis).
Exclusion criteria
Randomised controlled trials (RCTs; none available for this indication).
Case reports, case series, reviews, letters, editorials, or conference abstracts without full text.
Studies enrolling patients with metastatic SCCE or mixed metastatic/localised cohorts without separate localised data.
Non-comparative single-arm studies or studies lacking ≥2 treatment arms for direct/indirect comparison.
Studies with insufficient or non-reconstructible survival data (no HRs, no extractable Kaplan–Meier curves).

Information sources This systematic review and network meta-analysis will use the following

information sources, designed to capture all published and unpublished evidence on multimodal treatments for oesophageal small-cell carcinoma (SCCE):
1. Electronic Bibliographic Databases (Searched from Inception to 29 September 2025, No Language Restrictions)
PubMed (MEDLINE) – Core biomedical database for clinical research.
Embase – Comprehensive coverage of European and international medical literature.
Web of Science Core Collection – Multidisciplinary database for citation tracking and early research.
Scopus – Elsevier's abstract and citation database of peer-reviewed literature.
Cochrane CENTRAL (Cochrane Library) – Centralised register of controlled trials.
2. Grey Literature & Supplementary Sources
Hand-searching reference lists of all included studies, relevant reviews, and meta-analyses to identify missed citations.
Conference abstracts (e.g., ASCO, ESMO, ESTRO) – Searched for unpublished or partially reported data.
Clinical trial registers (e.g., ClinicalTrials.gov, WHO ICTRP) – Screened for ongoing/completed trials with unpublished survival data.
3. Author Contact
Corresponding authors of included studies will be contacted to request raw survival data (e.g., individual patient data, Kaplan–Meier curve data) or clarify incomplete reporting.
4. Language & Date Filters
No language restrictions (non-English studies translated if necessary).
No publication date limits (searched from database inception to 29 September 2025).

Main outcome(s) Primary Outcome
Overall Survival (OS)
Timing: Assessed from treatment initiation until death from any cause.
Effect measure: Hazard ratios (HRs) with 95% confidence intervals (CIs). When HRs were unavailable, reconstructed time-to-event data were derived from published Kaplan–Meier curves to estimate log(HR) and standard error.
Secondary Outcomes
Absolute 1-, 3-, and 5-year OS rates (reported as percentages with 95% CIs, extracted at the study arm level).
Treatment ranking by p-scores (0 = least favourable, 1 = most favourable) from frequentist network meta-analysis.
Exploratory Outcomes
Radiotherapy (RT) dose–response relationship: Association between total RT dose (Gy) and 1-, 3-, 5-year OS, analysed via restricted cubic splines and linear trend models, stratified by RT technique.
Study-level modifiers: Impact of median age, proportion of Stage III disease, and proportion of pure SCCE on treatment effects (via network meta-regression).
Consistency of evidence: Global and local inconsistency assessments for network meta-analysis.
Publication bias/small-study effects: Evaluated via Doi plot, LFK index, Egger's test, and funnel plots.

Quality assessment / Risk of bias analysis The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality and risk of bias of the included comparative cohort studies (prospective and retrospective). Two reviewers performed the assessment independently; disagreements were resolved by consensus.
NOS domains and scoring (0–9 points total)
Selection (0–4 points)
Representativeness of the exposed cohort
Selection of the non-exposed cohort
Ascertainment of exposure
Demonstration that outcome was not present at baseline
Comparability (0–2 points)
Control for the most important confounding factors
Control for additional confounding factors
Outcome (0–3 points)
Outcome assessment method (e.g., medical records)
Adequacy of follow-up duration
Completeness of follow-up (≥80% retention)
Quality categories
High quality: 7–9 points
Moderate quality: 4–6 points
Low quality: 0–3 points (none in this review)
Key notes
No studies were excluded solely based on NOS score.
All included studies were non-randomised; findings were interpreted with caution regarding residual confounding and selection bias.

Strategy of data synthesis Data synthesis was conducted using frequentist pairwise meta-analysis and network meta-analysis (NMA), supplemented by exploratory analyses for dose–response and study-level modifiers.
1. Pairwise meta-analysis
Effect measure: Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS).
Data source: Extracted directly from published results or reconstructed from Kaplan–Meier curves using the Guyot/Tierney method when HRs were not reported.

Model: Random-effects models (τ^2, I^2, Q-test) to pool log(HR) and standard errors via inverse-variance weighting. Adjusted HRs were prioritised over unadjusted estimates.
2. Network meta-analysis (NMA)
Model: Frequentist, random-effects consistency model (equal τ across comparisons) using the R netmeta package.
Treatment ranking: Based on p-scores (0 = least effective, 1 = most effective) and cumulative ranking curves (SUCRA).
Consistency assessment: Global inconsistency (design-by-treatment interaction), local inconsistency (node-splitting), and loop-specific inconsistency (inconsistency factors).
3. Sensitivity analysis
Leave-one-study-out: Excluded the largest study (Yan et al. 2024) to test robustness of treatment effects and rankings.
4. Meta-regression
Study-level covariates: Median age, proportion of Stage III disease, proportion of pure SCCE.
Method: Network meta-regression with treatment–moderator interaction terms to explore effect modifiers.
5. Radiotherapy dose–response analysis
Model: Restricted cubic splines (3 knots) and linear trend models for OS vs RT dose (Gy), stratified by RT technique (IMRT/3DCRT/2D).
Outcome: 1-, 3-, and 5-year absolute OS rates.
6. Publication bias and small-study effects
Assessment: Doi plot (LFK index), Egger's test, and comparison-adjusted funnel plots.
7. Software
Analyses performed in R (v4.5.1) using meta, metafor, and netmeta packages; figures generated with ggplot2.

Subgroup analysis Due to limited and inconsistently reported individual-level data, no formal predefined subgroup analyses were performed. Instead, exploratory study-level stratified analyses were conducted where data permitted:

Nodal status: Subgrouped by node-negative (N0) vs node-positive (N+) disease, to examine treatment effects stratified by baseline prognosis.

Histology: Stratified by pure SCCE vs mixed histology cohorts, exploring differential treatment efficacy by tumour histologic subtype.

Radiotherapy technique: Subgrouped by modern RT (IMRT/3DCRT) vs conventional 2D-RT, to assess dose–response patterns by technical approach.

Key limitation: No dedicated subgroup analysis for surgically ineligible patients was possible, as surgical eligibility, performance status and comorbidities were not consistently reported across studies. All subgroup findings are hypothesis-generating, not definitive.

Sensitivity analysis A leave-one-study-out sensitivity analysis was conducted to assess the robustness of the main network meta-analysis results, by sequentially excluding the largest study (Yan et al., 2024) that contributed both Chinese multicentre and American SEER cohorts.
Objective: Evaluate whether the main treatment effect estimates and rankings were driven by this single large study.
Model: Re-ran the primary 5-node network model (S, S+CT, NCT+S, CRT, S N0) after removing the study.
Outcomes assessed: Changes in HRs (vs surgery alone), 95% CIs, between-study heterogeneity (τ^2), and p-score rankings.
Result: The direction and magnitude of treatment effects, as well as the ranking order, remained unchanged, confirming the main conclusions were not solely dependent on this study.
Additional notes: No other sensitivity analyses (e.g., excluding low-quality studies, different effect measures) were prespecified due to the limited number of included studies.

Country(ies) involved China.

Keywords Oesophageal neoplasms; carcinoma, small cell; combined modality therapy; chemoradiotherapy; meta-analysis.

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