INPLASY

Comparative Efficacy of Short-Course versus Long-Course Radiotherapy with or without Immunotherapy for Neoadjuvant Treatment of Rectal Cancer: A Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None reported.

Review Stage at time of this submission - The review has not yet started.

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 22 October 2025 and was last updated on 22 October 2025.

INTRODUCTION

Review question / Objective To compare the efficacy and safety of neoadjuvant short-course radiotherapy (SCRT) versus long-course chemoradiotherapy (LCRT), each with or without immune checkpoint inhibitors (ICIs), in non-metastatic rectal adenocarcinoma.

Rationale However, a critical and unresolved clinical question emerges: for patients with pMMR LARC, what constitutes the optimal radiotherapeutic backbone when combined with immunotherapy? Direct comparative evidence between the two intensified strategies—SCRT plus immunotherapy(SCRT+ICIs) versus LCRT plus immunotherapy (LCRT+ICIs)—is lacking, as no head-to-head trials exist. Conventional pairwise meta-analyses are unable to address this key question.

Condition being studied The optimal radiotherapeutic backbone for combining with immunotherapy in proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC) remains uncertain without direct comparative trials. Randomized controlled trials (RCTs) comparing neoadjuvant radiotherapy (SCRT/LCRT) plus ICIs versus radiotherapy alone were eligible.

METHODS

Search strategy A systematic literature search was performed across electronic databases, including PubMed, Embase, Cochrane Library, and Medline databases, from their inception until September 20, 2025. Furthermore, proceedings of major international oncology conferences (e.g., ASCO, ESMO, ASTRO) from the past three years were screened for eligible studies. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to the core concepts: ("rectal cancer") AND ("neoadjuvant therapy" OR "immunotherapy" OR "radiotherapy") AND ("randomized controlled trial"). No language restrictions were applied. The

search strategy was first developed for PubMed/MEDLINE and then appropriately adapted for the syntax and subject headings of each of the other electronic databases. No language or date restrictions were applied.

Participant or population Patients with newly diagnosed, non-metastatic rectal adenocarcinoma, including those with early-stage (e.g., cT1-2N0) but ultra-low tumors requiring radical surgery, as well as locally advanced disease (cT3-4 or N+).

Intervention RCTs comparing neoadjuvant radiotherapy (SCRT or LCRT) combined with anti-PD-1/PD-L1/CTLA-4 immunotherapy versus neoadjuvant radiotherapy alone (SCRT or LCRT).

Comparator RCTs comparing neoadjuvant radiotherapy (SCRT or LCRT) combined with anti-PD-1/PD-L1/CTLA-4 immunotherapy versus neoadjuvant radiotherapy alone (SCRT or LCRT).

Study designs to be included Only phase II or III RCTs were included.

Eligibility criteria Studies were included based on the following PICOS Citeria:
A.Population: Patients with newly diagnosed, non-metastatic rectal adenocarcinoma, including those with early-stage (e.g., cT1-2N0) but ultra-low tumors requiring radical surgery, as well as locally advanced disease (cT3-4 or N+).
B.Interventions and Comparators: RCTs comparing neoadjuvant radiotherapy (SCRT or LCRT) combined with anti-PD-1/PD-L1/CTLA-4 immunotherapy versus neoadjuvant radiotherapy alone (SCRT or LCRT).
C.Outcomes: The primary outcome was the proportion of patients achieving a pathological complete response (pCR), defined as ypT0N0. Secondary outcomes included rates of grade ≥3 treatment-related adverse events (TRAEs).
D.Study Design: Only phase II or III RCTs were included.
Exclusion citeria were: non-randomized studies, studies using other experimental agents (e.g., EGFR inhibitors), studies without a standard-of-care control arm, and studies with unavailable outcome data.

Information sources A systematic literature search was performed across electronic databases, including PubMed, Embase, Cochrane Library, and Medline databases, from their inception until September 20, 2025. Furthermore, proceedings of major international oncology conferences (e.g., ASCO, ESMO, ASTRO) from the past three years were screened for eligible studies.

Main outcome(s) The primary outcome, pCR, was defined uniformly across all studies as ypT0N0.

Additional outcome(s) Grade ≥3 Treatment-Related Adverse Events (TRAEs) Assessment

Data management
1 Direct Meta-Analysis of RCTs
To provide a foundational assessment of the comparative efficacy and safety between key interventions for which direct evidence was available from RCTs, we first performed conventional pairwise meta-analyses. Direct comparisons were conducted for the following key contrasts: (1) SCRT plus ICIs vs. SCRT alone; (2) LCRT plus ICIs vs. LCRT alone. For each direct comparison, pooled odd ratios (ORs) with 95% confidence intervals (CIs) were calculated.
To facilitate a descriptive comparison with the single-arm studies, the pooled event rates (pCR and grade≥3 TRAEs) for each strategy (SCRT+ICIs and LCRT+ICIs) were also calculated from the RCTs included in the direct comparisons. The pooled pCR and grade≥3 TRAEs rates for each strategy (SCRT+ICIs and LCRT+ICIs) were calculated separately using a random-effects generic inverse-variance model based on the Freeman-Tukey double arcsine transformation. A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled pCR and grade≥3 TRAEs rates by sequentially removing each individual study and recalculating the pooled estimate. We assessed statistical heterogeneity using the I^2 statistic. Based on this assessment, a fixed-effect model was chosen for I^2 values ≤ 50%, and a random-effects model was chosen for I^2 values > 50%. All direct meta-analyses were performed using the meta package in R software.

2 Network Meta-Analysis of RCTs
Data Synthesis: Data synthesis was performed using a frequentist approach to network meta-analysis (NMA). All analyses were conducted using the netmeta package (version 4.0.0) in R software (version 4.2.0).
Model Specification: For the dichotomous outcome pCR and grade≥3 TRAEs, we used a generalised linear model (GLM) framework with a logit link function. Both fixed-effect and random-effects models were fitted.
Model Selection and Heterogeneity: The choice between fixed-effect and random-effects models was guided by a combination of statistical metrics and clinical considerations. The magnitude of statistical heterogeneity was estimated using the between-study standard deviation (τ). The I^2 statistic was used to quantify the percentage of total variability attributable to heterogeneity rather

than chance. Due to anticipated clinical and methodological diversity between studies, the random-effects model was preferred a priori and is presented as the primary analysis.
Assessment of Inconsistency: The assumption of consistency (agreement between direct and indirect evidence) was assessed globally and locally. Global inconsistency was evaluated using a design-by-treatment interaction model and quantified using the Q statistic. Local inconsistency was evaluated by separating direct from indirect evidence for specific comparisons where possible.
Output Presentation: Results are presented as risk ratio (RR) with 95% confidence intervals (CIs) for all pairwise comparisons for each outcome. The surface under the cumulative ranking curve (SUCRA) and mean ranks were calculated to estimate the probability and hierarchy of each intervention being the best for achieving pCR and being the safest for achieving grade≥3 TRAEs. Separate rankings were generated for efficacy (pCR) and safety (grade≥3 TRAEs). The networks of evidence for each outcome were illustrated graphically, where the size of the nodes is weighted by the number of patients, and the thickness of the edges is weighted by the number of studies informing each direct comparison.

3 Supplemental Meta Analysis of Single-Arm Studies
Eligibility CIteria and Search Strategy: The search strategy used for RCT identification was adapted and expanded to include non-randomized, single-arm prospective studies. For the supplementary analysis of single-arm studies, the PICOS criteria were adapted from the primary RCT-based analysis. The population, intervention, and outcome (pCR and grade≥3 TRAEs) definitions remained identical. The key adaptation was the inclusion of single-arm phase II or III studies (removing the requirement for a comparator arm). Retrospective studies, case series, and studies with overlapping populations were excluded.
Data Synthesis and Statistical Analysis: Data extraction and the approach for calculating pooled effect estimates were consistent with those described previously for the analysis of RCTs (Section 2.8).

Quality assessment / Risk of bias analysis The methodological quality of each included RCT was independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2.0), evaluating biases arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Strategy of data synthesis Data synthesis was performed using a frequentist approach to network meta-analysis (NMA). All analyses were conducted using the netmeta package (version 4.0.0) in R software (version 4.2.0).

Subgroup analysis None.

Sensitivity analysis A leave-one-out sensitivity analysis was performed to assess the robustness of the pooled pCR and grade≥3 TRAEs rates by sequentially removing each individual study and recalculating the pooled estimate.

Language restriction None.

Country(ies) involved No restriction.

Other relevant information None.

Keywords Rectal Neoplasms; Neoadjuvant Therapy; Short-Course Radiotherapy; Immunotherapy; Immune Checkpoint Inhibitors; Network Meta-Analysis; Pathologic Complete Response; Proficient Mismatch Repair

Dissemination plans Publication in Peer-Reviewed Journal.

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