

Total neoadjuvant therapy combined with immune checkpoint inhibitors for locally advanced rectal cancer: a systematic review and meta-analysis

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Abstract

Background: Total neoadjuvant therapy (TNT) has become the standard of care for locally advanced rectal cancer (LARC), achieving pathological complete response (pCR) rates of 15%–30%. Immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 antibodies, have shown remarkable efficacy in mismatch repair-deficient tumours. Whether adding ICIs to TNT can improve outcomes in proficient mismatch repair (pMMR)/microsatellite stable (MSS) LARC remains an area of active investigation. We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of TNT combined with ICIs compared with standard neoadjuvant therapy in LARC.

Methods: We searched PubMed/MEDLINE, EMBASE, Cochrane Library and Web of Science from inception through March 2026 for randomised controlled trials comparing neoadjuvant therapy with ICIs versus without ICIs in LARC. The primary outcome was the complete response (CR) rate, encompassing pCR and clinical complete response. Risk ratios (RRs) were pooled using a DerSimonian–Laird random-effects model. Heterogeneity was assessed with the I^2 statistic. Subgroup analyses were performed by radiotherapy type (short-course radiotherapy (SCRT) versus long-course radiotherapy (LCRT)). Risk of bias (RoB) was evaluated using the Cochrane RoB 2.0 tool, and certainty of evidence was graded according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. The review was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.

Results: Five randomised trials ($N = 1,070$; ICI arm = 429; control arm = 437) met inclusion criteria. Adding ICIs to neoadjuvant therapy significantly increased the CR rate (pooled RR 1.72, 95% confidence intervals (CI) 1.32–2.25; $p < 0.001$). Heterogeneity was moderate ($I^2 = 44.8\%$). Subgroup analysis revealed a greater benefit with SCRT-based regimens (RR 2.01, 95% CI 1.56–2.58; $I^2 = 0\%$) compared with LCRT-based regimens (RR 1.33, 95% CI 0.88–2.01; $I^2 = 39.5\%$). Leave-one-out sensitivity analyses confirmed the robustness of the pooled estimate. No significant publication bias was detected (Egger’s test $p = 0.84$). Additionally, eight single-arm TNT + ICI studies in pMMR/MSS LARC reported pCR rates of 37%–73%, consistently exceeding historical TNT benchmarks. The GRADE certainty of evidence was moderate, downgraded for indirectness.

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Conclusion: The addition of ICIs to neoadjuvant therapy significantly improves CR rates in LARC, with the greatest benefit observed when ICIs are combined with SCRT-based TNT. These findings support the integration of ICI into TNT as a strategy to enhance organ preservation opportunities. Long-term survival data from ongoing phase III trials are needed to confirm that these short-term benefits translate into durable oncologic outcomes.

Keywords: total neoadjuvant therapy, immune checkpoint inhibitors, locally advanced rectal cancer, pathological complete response, PD-1 inhibitors, organ preservation

Introduction

Colorectal cancer is the third most common malignancy globally and the second leading cause of cancer-related mortality, with rectal cancer accounting for approximately one-third of all colorectal malignancies [1, 2]. Locally advanced rectal cancer (LARC), defined as clinical stage T3–4 and/or node-positive disease, presents unique therapeutic challenges owing to its anatomic constraints and the need to balance oncologic radicality with quality-of-life preservation. The standard treatment paradigm has evolved from postoperative adjuvant therapy to neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME), which has significantly reduced local recurrence rates to below 10% [3, 4].

In recent years, total neoadjuvant therapy (TNT) – which consolidates all systemic chemotherapy before surgery, either as induction chemotherapy before chemoradiotherapy or as consolidation chemotherapy after short-course radiotherapy (SCRT) – has emerged as the new standard for high-risk LARC. Landmark phase III trials including RAPIDO, PRODIGE-23 and STELLAR demonstrated that TNT improves pathological complete response (pCR) rates to 25%–30%, enhances treatment compliance and reduces disease-related treatment failure compared with conventional nCRT [5–8]. Moreover, the OPRA trial established that TNT facilitates organ preservation through a watch-and-wait strategy in patients achieving clinical complete response (cCR) [9].

Despite these advances, pCR rates with TNT plateau at approximately 25%–30% in proficient mismatch repair/microsatellite stable (pMMR/MSS) tumours, leaving a substantial proportion of patients who do not achieve complete tumour regression. This represents a critical unmet need, particularly for patients seeking organ preservation. Concurrently, immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have demonstrated transformative efficacy in mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) rectal cancer, with single-agent dostarlimab achieving a 100% cCR rate in a landmark phase II trial [10]. However, dMMR/MSI-H tumours represent only 5%–15% of all rectal cancers, while the majority harbor pMMR/MSS phenotypes that are traditionally considered immunologically ‘cold’ and resistant to ICI monotherapy [11].

Radiotherapy has emerged as a potent immunomodulator capable of converting immunologically cold pMMR/MSS tumours into immune-responsive environments through several mechanisms: induction of immunogenic cell death, enhancement of antigen presentation, upregulation of PD-L1 expression and stimulation of the type I interferon pathway [12, 13]. Preclinical evidence suggests that hypofractionated SCRT may be particularly effective in this regard, as it produces a more pronounced abscopal effect and less lymphodepletion compared with conventionally fractionated long-course radiotherapy (LCRT) [14]. These observations have provided the biological rationale for combining ICIs with TNT in pMMR/MSS LARC.

Multiple phase II and phase III trials – including TORCH, UNION, STELLAR II, NRG-GI002, PRECAM and SPRING-01 – have recently reported results on integrating ICIs into neoadjuvant regimens for LARC, with varying degrees of success [15–22]. However, no prior systematic review has comprehensively pooled data across these trials to determine the magnitude of benefit from adding ICIs to TNT, nor has any prior meta-analysis specifically examined the differential effects by radiotherapy fractionation schedule (SCRT versus LCRT) or by mismatch repair status in the TNT setting.

The primary objective of this systematic review and meta-analysis was to evaluate the effect of adding ICIs to neoadjuvant therapy on complete response (CR) rates in patients with LARC. Secondary objectives included assessment of the differential efficacy of SCRT-based versus LCRT-based ICI-containing regimens, evaluation of safety profiles and appraisal of the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.

Methods

Study design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [23]. The protocol was developed a priori, and the eligibility criteria, search strategy and analysis plan were established before the literature search.

Eligibility criteria

Studies were eligible for inclusion if they met the following PICO criteria: (P) adult patients with histologically confirmed LARC (cT3–4 and/or N+ disease); (I) neoadjuvant therapy incorporating at least one ICI (PD-1 or PD-L1 antibody) combined with either TNT or nCRT; (C) neoadjuvant therapy without ICI (for randomised trials) or historical benchmarks (for single-arm studies); (O) (pCR, ypT0N0), cCR, composite (CR = pCR + cCR) or safety endpoints. Randomised controlled trials of any phase were included for the primary meta-analysis. Prospective single-arm studies reporting pCR rates of TNT + ICI were included for descriptive synthesis. Conference abstracts with sufficient quantitative data were eligible. Exclusion criteria included case reports, editorials, reviews without primary data, studies exclusively enrolling dMMR/MSI-H patients, duplicate publications and studies with fewer than ten participants.

Information sources and search strategy

We searched PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Web of Science from inception through 31 March 2026. The search strategy combined Medical Subject Headings and free-text terms for the following concepts: ('rectal neoplasms' OR 'rectal cancer' OR 'LARC') AND ('neoadjuvant therapy' OR 'TNT' OR 'chemoradiotherapy') AND ('immunotherapy' OR 'checkpoint inhibitor' OR 'PD-1' OR 'PD-L1' OR 'pembrolizumab' OR 'nivolumab' OR 'sintilimab' OR 'camrelizumab' OR 'toripalimab' OR 'envafolimab' OR 'tislelizumab' OR 'durvalumab'). The full search strategies are provided in [Supplementary Table S2](#) and [S3](#). Reference lists of included studies and relevant narrative reviews were hand-searched for additional eligible records.

Study selection and data extraction

Titles and abstracts of retrieved records were screened for relevance by two independent reviewers. Full-text articles of potentially eligible studies were assessed against the pre-specified inclusion and exclusion criteria. Disagreements were resolved by consensus. Data were extracted into a standardised form capturing: first author, year, trial name, country, study design, number of participants, clinical stage, mismatch repair status, radiotherapy type and dose, chemotherapy regimen, ICI agent and schedule, primary and secondary outcomes, adverse events and follow-up duration. For randomised trials, the number of events and total patients in each arm were extracted to compute risk ratios (RRs).

Risk of bias (RoB) assessment

RoB in individual randomised trials was assessed using the Cochrane RoB 2.0 tool across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result [24]. Each domain was rated as low risk, some concerns or high risk. Single-arm studies were assessed using the Methodological Index for Non-Randomised Studies criteria. The overall certainty of evidence for each outcome was evaluated using the GRADE framework [25].

Statistical analysis

The primary effect measure was the RR for CR (pCR or composite CR) in ICI-containing versus control neoadjuvant regimens. RRs with 95% confidence intervals (CIs) were calculated from event counts and pooled using a DerSimonian–Laird random-effects model, as clinical heterogeneity among trials was anticipated a priori [26]. Statistical heterogeneity was assessed using Cochran's Q statistic and the I^2 index. I^2

values of less than 25%, 25%–50% and greater than 50% were interpreted as low, moderate and substantial heterogeneity, respectively. A 95% prediction interval was calculated to characterise the distribution of true effects across settings.

Pre-specified subgroup analyses were conducted by radiotherapy type (SCRT-based versus LCRT-based regimens). Sensitivity analyses included leave-one-out analysis (sequentially excluding each study) and a fixed-effects model as a comparator. Publication bias was assessed using Egger's regression test when at least three studies were available. All analyses were performed using Python (scipy v1.17, numpy v2.4, pandas v3.0).

Results

Study selection

The systematic search identified 847 records from electronic databases and 124 from other sources (reference lists and conference abstracts). After removing 288 duplicates, 683 unique records were screened at the title and abstract level, of which 579 were excluded as irrelevant. The remaining 104 full-text articles were assessed for eligibility, and 91 were excluded for the following reasons: no TNT backbone ($n = 28$), no comparator arm and insufficient data for pooling ($n = 23$), duplicate patient cohorts ($n = 15$), insufficient outcome data ($n = 12$), exclusively dMMR/MSI-H populations ($n = 8$) and ongoing trials without results ($n = 5$). Ultimately, 13 studies were included in the systematic review, of which five randomised trials provided data for the meta-analysis. The PRISMA flow diagram is presented in [Figure 1](#).

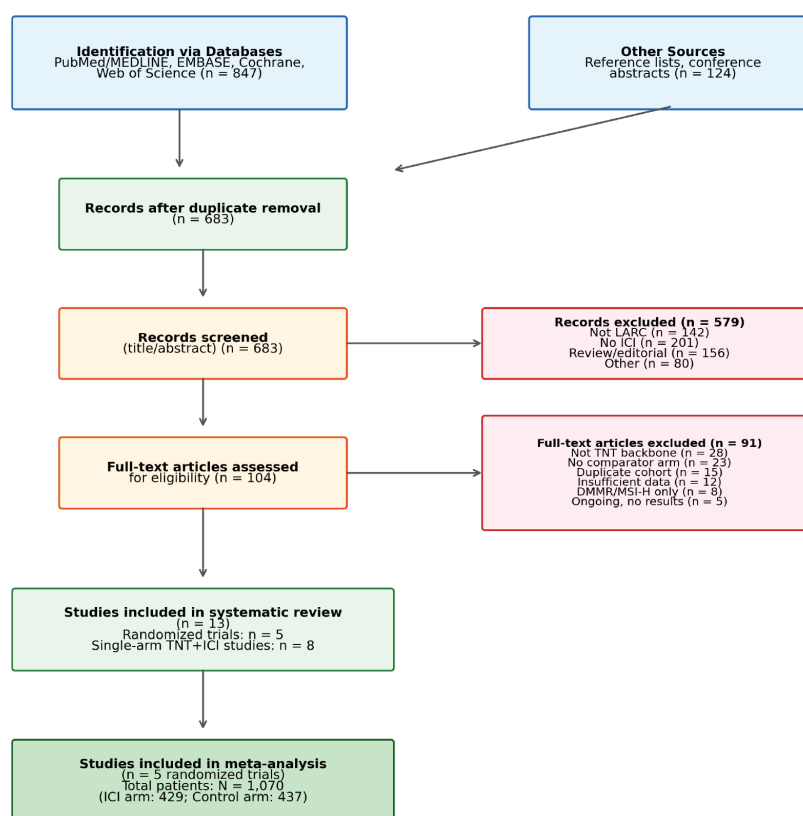


Figure 1. PRISMA 2020 flow diagram.

Characteristics of included studies

The five randomised trials included in the meta-analysis enrolled a total of 1,070 patients (ICI arm: 429; control arm: 437). Four trials were conducted in China and one in the United States. The ICI agents evaluated included sintilimab (three trials), camrelizumab (one trial) and pembrolizumab (one trial). Radiotherapy regimens comprised SCRT (25 Gy in 5 fractions; three trials) and LCRT (50–50.4 Gy in 25–28 fractions; two trials). Chemotherapy backbones included CAPOX, mFOLFOX and FOLFOX. The characteristics of included studies are summarised in Table 1.

Among the eight additional single-arm prospective studies included in the qualitative synthesis, pCR rates ranged from 36.7% to 72.7%, consistently exceeding the historical TNT benchmark of approximately 25%–30%. Notable single-arm results included the TORCH trial [15] reporting a CR rate of 56.5% with SCRT-based TNT plus toripalimab in pMMR/MSS patients, and the PRECAM study [30] reporting a pCR rate of 62.5% with SCRT plus envafolimab in MSS patients.

Risk of bias

RoB assessments using the RoB 2.0 tool are summarised in Supplementary Table S2. Three of the five randomised trials were rated as having some concerns overall, primarily due to the open-label design inherent in immunotherapy trials, which introduced potential for performance bias. The UNION trial [16] was rated as high RoB in the domain of deviations from intended interventions because the control arm used LCRT-based chemotherapy rather than an equivalent SCRT-based TNT comparator, confounding the effect of ICI with the effect of radiotherapy fractionation. The NRG-GI002 trial [18] was rated as low RoB given its rigorous multi-institutional randomisation and blinded outcome assessment.

Primary outcome: CR rate

Five randomised trials provided data on CR rates. The pooled RR for CR with ICI-containing neoadjuvant therapy versus control was 1.72 (95% CI: 1.32–2.25; $z = 3.96$; $p < 0.001$), indicating a statistically significant 72% relative increase in CR rates with the addition of ICIs (Figure 2). Heterogeneity was moderate ($I^2 = 44.8\%$; $Q = 7.25$; $p = 0.12$). The 95% prediction interval ranged from 0.65 to 4.57, indicating that while the pooled effect favours ICI addition, the magnitude of benefit may vary across future settings. CR rates in the ICI arms ranged from 32.2% (NRG-GI002) to 59.2% (SPRING-01), compared with 15.3%–32.7% in the control arms.

Table 1. Characteristics of included randomised trials.

Trial	Phase	Country	N (ICI/Ctrl)	RT type	ICI Agent	CR ICI	CR Ctrl
[18] (NRG-GI002)	II	USA	90/95	LCRT + FOLFOX	Pembrolizumab	32.2%	29.5%
[21] (Sun Yat-sen)	II	China	67/67	LCRT + CapeOx	Sintilimab	44.8%	26.9%
[16] (UNION)	III	China	113/118	SCRT + CAPOX	Camrelizumab	39.8%	15.3%
[17] (STELLAR II)	II/III	China	110/108	SCRT + CAPOX	Sintilimab	45.5%	24.7%*
[20] (SPRING-01)	II	China	49/49	SCRT + CAPOX	Sintilimab	59.2%	32.7%

CR, complete response (pCR + cCR where applicable); ICI, immune checkpoint inhibitor; LCRT, long-course chemoradiotherapy; SCRT, short-course radiotherapy. *CR rate (composite pCR+cCR). UNION control arm used LCRT+CAPOX (not SCRT-based TNT)

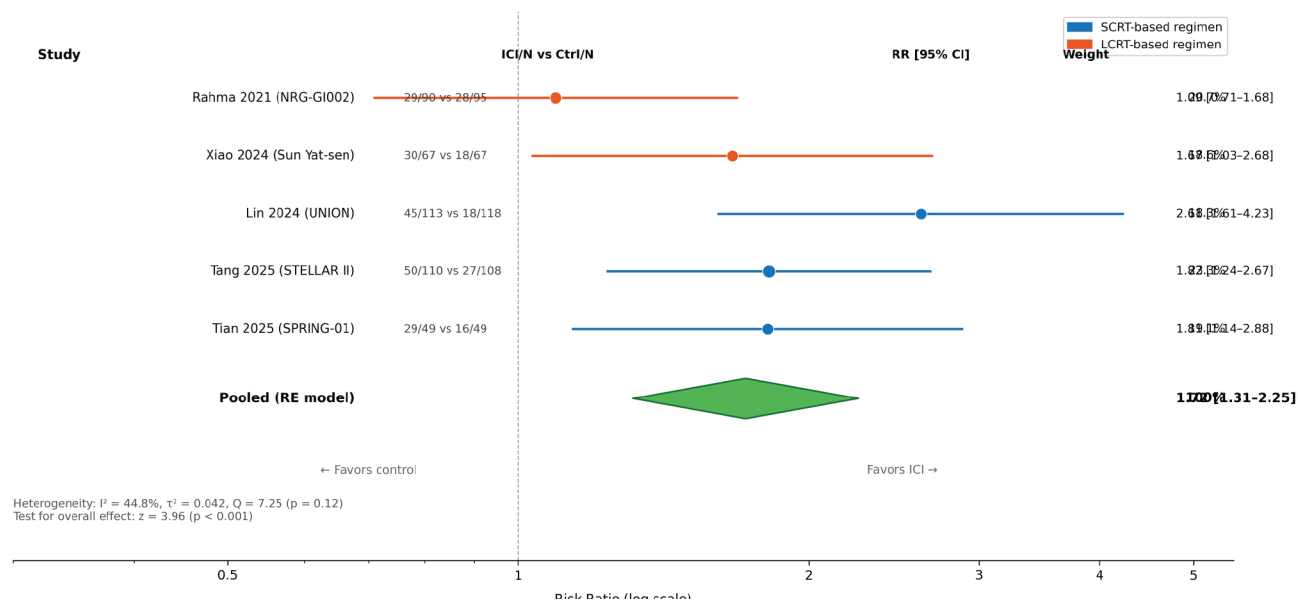


Figure 2. Forest plot. Forest plot showing the RR for CR with ICI-containing neoadjuvant therapy versus control. Squares represent individual study estimates, with size proportional to study weight. The diamond represents the pooled estimate from the random-effects model.

Subgroup analysis by radiotherapy type

Pre-specified subgroup analysis by radiotherapy type revealed a striking differential effect (Figure 3). In SCRT-based regimens (three trials: UNION, STELLAR II, SPRING-01), the pooled RR was 2.01 (95% CI: 1.56–2.58; $I^2 = 0\%$), demonstrating a twofold increase in CR rates with ICI addition and no heterogeneity among studies. In LCRT-based regimens (two trials: NRG-GI002 [21]), the pooled RR was 1.33 (95% CI: 0.88–2.01; $I^2 = 39.5\%$), suggesting a more modest and non-statistically significant benefit. The test for subgroup differences was statistically significant ($Q = 4.18$; $p = 0.041$), supporting a differential effect by radiotherapy fractionation schedule.

Sensitivity analyses

Leave-one-out sensitivity analyses confirmed the robustness of the primary result (Supplementary Table S3). Excluding any single study yielded pooled RRs ranging from 1.57 to 1.93, all remaining statistically significant. The most notable change occurred when the NRG-GI002 trial was excluded (RR increased from 1.72 to 1.93), reflecting the null result of this trial. The fixed-effects model produced a virtually identical pooled estimate (RR 1.71, 95% CI: 1.40–2.08), suggesting that the random-effects model was appropriate and the between-study variance was modest.

Publication bias

Visual inspection of the funnel plot (Figure 4) did not reveal marked asymmetry. Egger's regression test yielded a non-significant result (intercept = 4.08; $p = 0.84$), providing no evidence of small-study effects or publication bias. However, given the limited number of studies ($k = 5$), the power to detect publication bias was inherently low and these results should be interpreted cautiously.

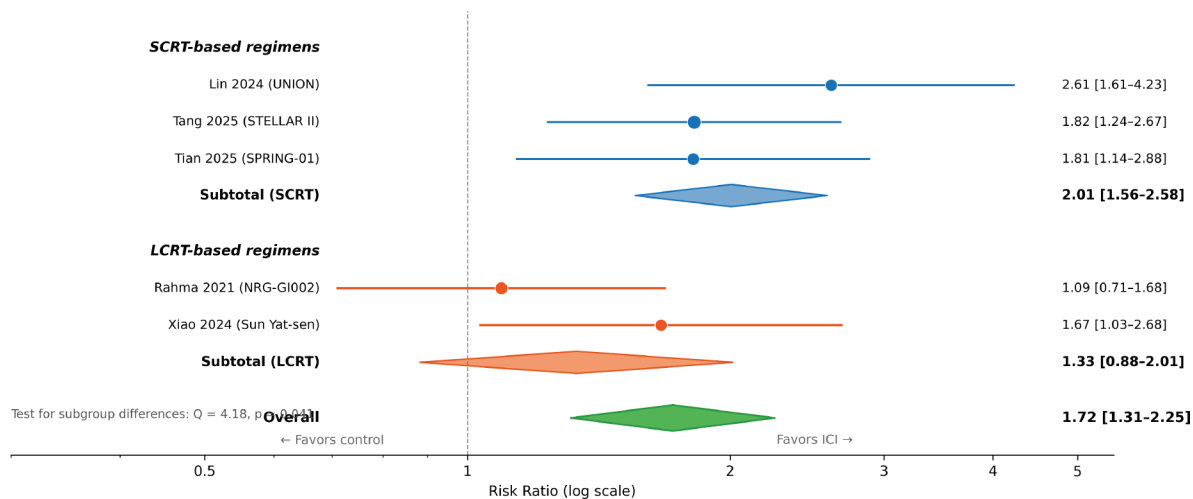


Figure 3. Subgroup analysis by RT type. Subgroup forest plot comparing SCRT-based and LCRT-based regimens. SCRT-based regimens showed a significantly greater benefit from ICI addition (RR 2.01; $I^2 = 0\%$) compared with LCRT-based regimens (RR 1.33; $I^2 = 39.5\%$). Test for subgroup difference: $p = 0.041$.

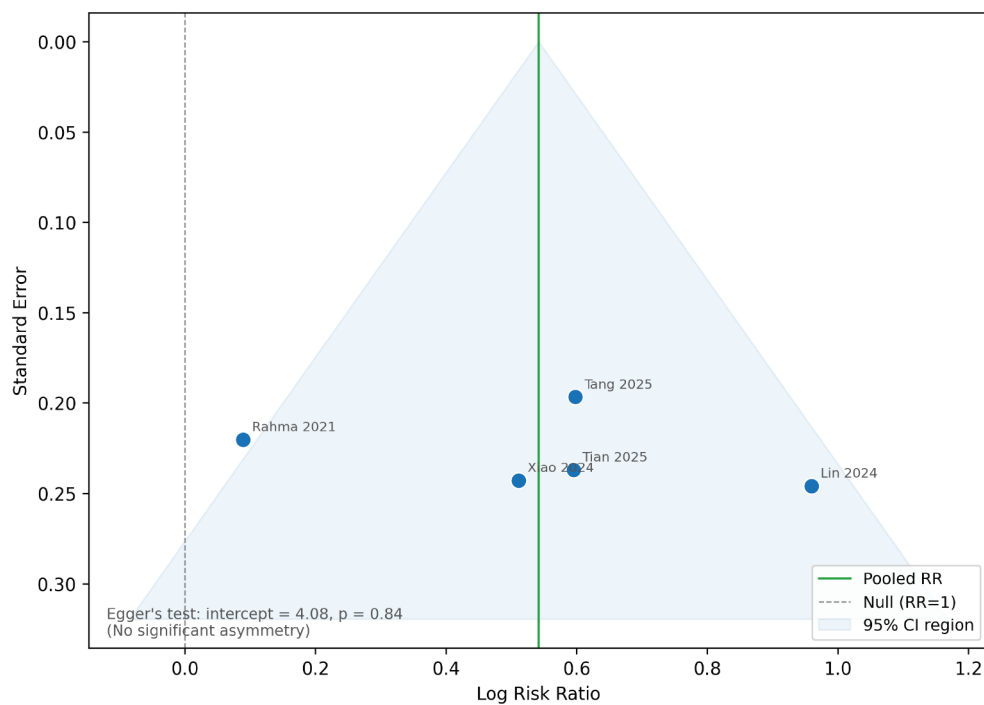


Figure 4. Funnel plot. Funnel plot for assessment of publication bias. The vertical green line indicates the pooled effect estimate. The dashed line indicates the null effect (RR = 1). The shaded region represents the 95% CI.

Safety profile

Across the five randomised trials, the addition of ICIs to neoadjuvant therapy was associated with a modest increase in grade 3–4 adverse events. The STELLAR II trial reported grade 3–5 toxicity rates of 33.3% in the iTNT group versus 20.5% in the TNT group, with thrombocytopenia being the most common event. The NRG-GI002 trial observed grade 3–4 adverse events in 48.2% of the pembrolizumab arm versus 37.3% of the control arm during chemoradiotherapy. Immune-related adverse events were generally infrequent and manageable; the STELLAR II trial reported immune-related adverse events in 13.5% of patients, with only 3 grade 3 cases. Surgical complication rates were similar between ICI and control arms across all reporting trials.

GRADE assessment

The certainty of evidence for the primary outcome (CR rate) was rated as moderate using the GRADE framework (Table 3). The evidence was based on randomised trials (starting at high certainty) but was downgraded by one level for indirectness, as the UNION trial used a non-standard comparator (LCRT-based chemotherapy versus SCRT-based ICI-containing TNT), making it difficult to isolate the ICI contribution from the radiotherapy fractionation effect. No downgrading was warranted for RoB (most trials had low or some concerns), inconsistency ($I^2 = 44.8\%$, considered moderate), imprecision (the CI excluded 1.0) or publication bias (Egger's test non-significant).

Discussion

This systematic review and meta-analysis, encompassing five randomised trials and 1,070 patients, demonstrates that the addition of ICIs to neoadjuvant therapy significantly improves CR rates in LARC, with a pooled RR of 1.72 (95% CI: 1.32–2.25; $p < 0.001$). To the best of our knowledge, this is the first meta-analysis to specifically examine the effect of ICI addition in the context of TNT-based regimens and to perform a pre-specified subgroup analysis by radiotherapy fractionation schedule.

The most striking finding was the differential efficacy of ICI addition by radiotherapy type. SCRT-based regimens combined with ICIs demonstrated a twofold increase in CR rates (RR 2.01; $I^2 = 0\%$), whereas LCRT-based regimens showed a more modest, non-significant benefit (RR 1.33). This differential effect has important biological plausibility. Hypofractionated SCRT delivers higher doses per fraction (5 Gy), which induces more potent immunogenic cell death, greater release of tumour-associated antigens and stronger activation of the cGAS-STING pathway compared with the conventional 1.8–2.0 Gy per fraction used in LCRT [12–14]. Furthermore, SCRT is associated with less lymphodepletion than LCRT, preserving circulating lymphocytes that are essential for mounting an effective anti-tumour immune response in conjunction with ICI [27]. These findings align with preclinical data showing superior synergy between hypofractionated radiotherapy and PD-1/PD-L1 blockade. It must be acknowledged, however, that this subgroup analysis is susceptible to confounding: the three SCRT-based and two LCRT-based trials differed not only in radiotherapy fractionation schedule but also in ICI agent, chemotherapy backbone, trial phase and geographic setting. These co-varying factors preclude definitive attribution of the differential benefit to radiotherapy fractionation alone, and the subgroup findings should be regarded as hypothesis-generating rather than confirmatory.

The null result from the NRG-GI002 trial deserves careful consideration. Several factors may explain the discordant findings. First, pembrolizumab was administered during and after chemoradiotherapy (LCRT-based) rather than with SCRT, potentially limiting the immunomodulatory synergy. Second, the NRG-GI002 used NAR score rather than pCR as the primary endpoint, and the trial may have been underpowered to detect a meaningful difference in pCR. Third, the induction FOLFOX preceding chemoradiotherapy may have induced lymphodepletion that attenuated the subsequent ICI effect. Notably, long-term follow-up data from NRG-GI002 showed a trend toward improved 3-year overall survival with pembrolizumab (95% versus 84%), suggesting that pCR may not capture the full benefit of ICI integration [28].

In contrast, the Chinese trials (UNION, STELLAR II, TORCH, SPRING-01) predominantly employed SCRT-based TNT backbones with anti-PD-1 agents (camrelizumab, sintilimab, toripalimab) and consistently demonstrated CR rates exceeding 40%. The UNION trial, the only phase III study in this analysis, reported a pCR rate of 39.8% with SCRT plus camrelizumab and CAPOX versus 15.3% with LCRT plus CAPOX. However, as noted in the RoB assessment, the UNION trial's design confounds the effect of ICI with the effect of radiotherapy fractionation,

since the comparator arm used LCRT rather than SCRT. This design limitation has been highlighted by editorialists and represents a critical caveat when interpreting the trial's results [29].

The single-arm TNT + ICI studies further support the potential of this approach. The PRECAM study achieved a remarkable pCR rate of 62.5% with SCRT plus envafoimab (a subcutaneously administered PD-L1 antibody) in MSS patients, and the TORCH trial reported CR rates exceeding 50% with SCRT plus toripalimab. These rates substantially surpass the historical TNT benchmark of 25%–30% established by RAPIDO and PRODIGE-23, and approach levels that could make organ preservation a realistic goal for the majority of LARC patients (Figure 5).

This review has several strengths. First, we adhered to PRISMA 2020 guidelines and employed a comprehensive search strategy across multiple databases. Second, we restricted the primary meta-analysis to randomised trials, providing the highest level of evidence for comparative effectiveness. Third, we performed pre-specified subgroup analyses that yielded clinically meaningful insights into the differential efficacy by radiotherapy type. Fourth, we applied rigorous RoB assessment and GRADE evaluation, providing a transparent appraisal of evidence certainty. Finally, the inclusion of single-arm studies for descriptive synthesis provides a comprehensive landscape of TNT+ICI outcomes.

Several limitations warrant acknowledgment. First, the number of randomised trials was limited ($k = 5$), constraining the power of subgroup analyses and publication bias assessment. Second, heterogeneity in trial designs – including different ICI agents, radiotherapy types, chemotherapy backbones and outcome definitions (pCR versus composite CR) – introduces clinical heterogeneity that cannot be fully captured by statistical measures. Third, the UNION trial's confounded design (SCRT + ICI versus LCRT alone) inflates the apparent benefit of ICI addition, as the control arm used a non-standard comparator. Fourth, most trials (4 of 5) were conducted in China, potentially limiting generalisability to Western populations with different genetic backgrounds, tumour biology and healthcare systems. Prospective studies enrolling ethnically diverse populations – including European, North American, Latin American and Middle Eastern cohorts – are urgently needed to confirm whether the efficacy signals observed in Chinese patients are reproducible across different ethnic groups. Differences in immune microenvironment composition, gut microbiome and tumour mutational landscape between Asian and non-Asian populations may modulate the magnitude of ICI benefit. Fifth, individual patient data were not available, precluding analyses stratified by PD-L1 expression, tumour mutational burden (TMB) or other potential predictive biomarkers. Sixth, follow-up durations were short in most trials and long-term survival outcomes (DFS, OS) were not mature. Whether improved pCR rates translate into improved survival remains unproven in the TNT + ICI setting. Finally, the exclusive reliance on published data introduces the risk of reporting bias.

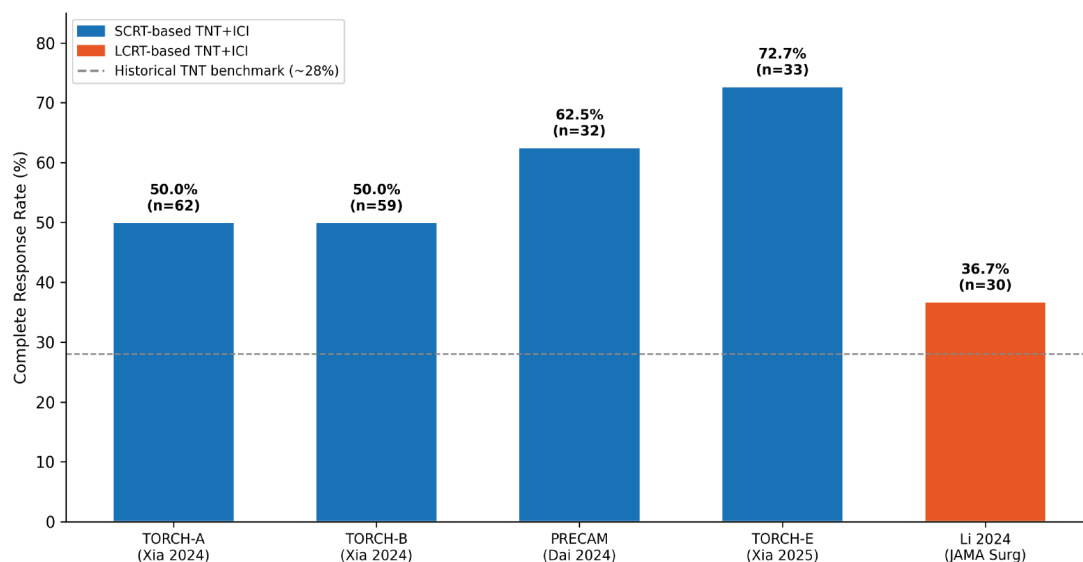


Figure 5. Single-arm TNT + ICI studies. Bar chart showing CR rates in single-arm studies of TNT combined with ICIs in pMMR/MSS LARC. The dashed line indicates the historical TNT benchmark (~28%). All studies exceeded the benchmark.

The findings of this meta-analysis have several implications. For clinical practice, the data support the preferential use of SCRT-based TNT as the backbone for ICI integration in LARC, consistent with the biological rationale for hypofractionated radiotherapy as an immunomodulator. For patients with pMMR/MSS LARC who seek organ preservation, the addition of an anti-PD-1 agent to SCRT-based TNT may nearly double the likelihood of achieving a CR, thereby expanding eligibility for watch-and-wait strategies. From a clinical implementation perspective, SCRT (25 Gy in 5 fractions) is logistically simpler and less resource-intensive than LCRT, making SCRT-based TNT a more feasible backbone for ICI integration in resource-constrained settings. However, anti-PD-1 agents add considerable cost and require dedicated infusion infrastructure; agents such as sintilimab are substantially less expensive than pembrolizumab in high-income countries, and this disparity may restrict broad adoption in low- and middle-income health systems. Until long-term survival benefit is firmly established, clinicians and health authorities should weigh the incremental CR gain against cost and toxicity burden. Prospective cost-effectiveness analyses will be essential to guide equitable integration of ICIs into routine LARC management globally.

Several priorities emerge. First, ongoing phase III trials with standardised comparators – such as SCRT-based TNT with versus without ICI – are needed to definitively establish the benefit of ICI addition. The phase III portions of STELLAR II and the design of UNICORN will address this need. Second, predictive and prognostic biomarkers must be systematically validated to identify patients most likely to benefit from ICI addition and to minimise unnecessary toxicity and cost in non-responders. Circulating tumour DNA (ctDNA) represents a particularly promising non-invasive tool: early ctDNA clearance during neoadjuvant therapy correlates with pCR in rectal cancer, and longitudinal ctDNA dynamics during TNT + ICI may provide real-time surrogates for treatment response and minimal residual disease. Tissue-based biomarkers – including PD-L1 expression by combined positive score, Immunoscore, TMB and multiplex immunofluorescence profiling of the tumour immune microenvironment – should be incorporated as co-primary or secondary endpoints in future prospective trial designs to enable biomarker-driven patient stratification. Third, longer follow-up is essential to determine whether pCR improvements translate into superior DFS and OS. Fourth, the optimal sequencing of ICI relative to radiotherapy (concurrent, consolidation or induction) remains to be defined. The TORCH trial's finding that consolidation iTNT (SCRT first, then ICI + chemo) yielded a higher cCR rate and lower thrombocytopenia than induction iTNT provides initial guidance [15].

Conclusion

This systematic review and meta-analysis demonstrates that the addition of ICIs to neoadjuvant therapy significantly improves CR rates in LARC, with a pooled RR of 1.72 (95% CI: 1.32–2.25). The benefit is most pronounced when ICIs are combined with SCRT-based TNT (RR 2.01), with no heterogeneity among SCRT-based trials. The greater synergy observed with SCRT-based regimens is consistent with the superior immunomodulatory profile of hypofractionated radiotherapy and underscores radiotherapy fractionation as a key determinant of ICI efficacy in this setting. These findings support the emerging paradigm of integrating immunotherapy into TNT as a strategy to enhance tumour regression and expand organ preservation opportunities in LARC. Confirmation from mature phase III survival data and biomarker-guided patient selection remain critical next steps.

Conflicts of interest

The authors declare no conflicts of interest.

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This research received no external funding.

Author contributions

All authors contributed equally to this article.

Data availability

The data supporting the conclusions of this article are available within the article and its supplementary materials.

Use of artificial intelligence

As all authors are non English native speaker, AI has been used for language edits and proofreading namely paperpal®. Tables were professionally formatted with Claude®. The content of the article is purely human with no use of generative AI.

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Supplementary materials

Supplementary Table S1. Eligibility criteria.

Category	Criteria
Inclusion criteria	1. Adult patients (≥ 18 years). 2. Histologically confirmed rectal adenocarcinoma. 3. Locally advanced disease (cT3–4 and/or N+). 4. Neoadjuvant regimen including at least one ICI (PD-1 or PD-L1 antibody) combined with radiotherapy and/or chemotherapy. 5. Study design: randomized controlled trial (for meta-analysis) or prospective single-arm study (for descriptive synthesis). 6. Reported pCR, cCR, or composite CR rate. 7. Full-text article or conference abstract providing sufficient quantitative data. 8. Published in English.
Exclusion criteria	1. Case reports, editorials, or narrative reviews lacking primary data. 2. Studies exclusively enrolling dMMR/MSI-H patients. 3. Duplicate publications (only the most complete dataset retained). 4. Studies with fewer than ten participants. 5. Absence of an ICI in the neoadjuvant regimen. 6. No reported surgical outcomes or response assessment metrics. 7. Retrospective studies (for meta-analysis component).

Supplementary Table 2. RoB assessment (Cochrane RoB 2.0).

Panel A. Summary RoB matrix.

Study	D1 randomization	D2 deviations	D3 missing data	D4 outcome measurement	D5 reported result	Overall
Rahma <i>et al</i> [18] (NRG-GI002)	+ Low	? Some concerns	+ Low	+ Low	+ Low	? Some concerns
Xiao <i>et al</i> [21] (Sun Yat-sen)	+ Low	? Some concerns	+ Low	+ Low	+ Low	? Some concerns
Lin <i>et al</i> [16] (UNION)	+ Low	– High	? Some concerns	+ Low	+ Low	– High
Tang <i>et al</i> [17] (STELLAR II)	+ Low	? Some concerns	? Some concerns	+ Low	+ Low	? Some concerns
Tian <i>et al</i> [20] (SPRING-01)	? Some concerns	? Some concerns	+ Low	+ Low	+ Low	? Some concerns

Legend:

+ Low RoB

? Some concerns

– High RoB

D1 = Randomization process; D2 = Deviations from intended interventions; D3 = Missing outcome data; D4 = Measurement of the outcome; D5 = Selection of the reported result

Panel B. Detailed domain-by-domain justifications.

Study	Domain-by-domain justification
Rahma <i>et al</i> [18] (NRG-GI002)	D1 (Low): Multi-institutional stratified block randomization by T stage and N stage. D2 (Some concerns): Open-label design; however, both arms received identical TNT backbone (FOLFOX → CRT), and awareness of ICI assignment was unlikely to influence surgical technique or pathological assessment. D3 (Low): 137/185 (74%) evaluable for primary endpoint (NAR score); attrition balanced between arms. D4 (Low): pCR assessed by pathologist on resected specimen; objective endpoint unlikely affected by open-label design. D5 (Low): Pre-specified primary (NAR score) and secondary endpoints (pCR, cCR) reported as planned.
Xiao <i>et al</i> [21] (Sun Yat-sen)	D1 (Low): Single-center randomized 1:1 with computer-generated sequence. D2 (Some concerns): Open-label; however, identical NACRT backbone in both arms. The addition of sintilimab was the only difference, and outcomes were objectively assessed. D3 (Low): All 134 randomized patients included in ITT analysis. D4 (Low): CR assessed by standardized pathological and imaging criteria. D5 (Low): Pre-registered on ClinicalTrials.gov (NCT04304209); primary endpoint reported as planned.
Lin <i>et al</i> [16] (UNION)	D1 (Low): Multicenter randomized 1:1 with stratification by cT stage ($\leq T3$ versus $T4$) and cN stage ($N0$ versus $N+$). D2 (High): Critical concern — the experimental arm (SCRT + camrelizumab + CAPOX) and control arm (LCRT + CAPOX) differ by BOTH immunotherapy AND radiotherapy fractionation. This confounded design makes it impossible to isolate the ICI contribution from the RT fractionation effect. The control arm does not represent an equivalent TNT backbone. D3 (Some concerns): Surgery rates differed between arms (92.0% versus 83.9%), potentially affecting pCR denominators. D4 (Low): pCR assessed by a blinded independent review committee. D5 (Low): Pre-specified hierarchical testing of pCR, EFS, and OS.
Tang <i>et al</i> [17] (STELLAR II)	D1 (Low): Multicenter randomized 1:1 across 10 hospitals. D2 (Some concerns): Open-label; both arms received the same SCRT-based TNT backbone, with sintilimab the only additional agent. Seven patients in the iTNT group did not receive immunotherapy, but the analysis was ITT-based. D3 (Some concerns): Composite CR endpoint combines pCR (in surgical patients) with cCR (in W&W patients), and the proportions opting for W&W differed between arms, which may introduce outcome measurement variability. D4 (Low): Pathological assessment on surgical specimens is objective. D5 (Low): Phase 2 primary endpoint (CR rate) and planned phase 3 endpoint (3-year DFS) reported as designed.
Tian <i>et al</i> [20] (SPRING-01)	D1 (Some concerns): Single-center, open-label randomization; randomization method not fully detailed in available reports. D2 (Some concerns): Open-label design; SCRT + CAPOX backbone identical in both arms; awareness of sintilimab assignment unlikely to affect pathological assessment. D3 (Low): All randomized patients included in ITT analysis. D4 (Low): pCR assessed by pathological evaluation of resected specimen. D5 (Low): Primary endpoint (pCR) reported as pre-specified in protocol.

Note: All five trials were open-label, which is standard for immunotherapy trials where blinding is impractical due to immune-related adverse event monitoring requirements. The primary outcome (pCR) is an objective pathological endpoint unlikely to be influenced by lack of blinding. The UNION trial received a High overall rating due to the critical confound in D2: the comparison of SCRT-based ICI-containing TNT versus LCRT-based chemotherapy alone introduces two simultaneous treatment differences (radiotherapy fractionation AND immunotherapy), precluding isolation of the ICI effect

Supplementary S2. Database search strategies

PubMed/MEDLINE Search: (("rectal neoplasms"[MeSH] OR "rectal cancer" OR "rectal adenocarcinoma" OR "locally advanced rectal") AND ("neoadjuvant therapy"[MeSH] OR "total neoadjuvant" OR "TNT" OR "chemoradiotherapy" OR " SCRT") AND ("immunotherapy"[MeSH] OR "checkpoint inhibitor" OR "PD-1" OR "PD-L1" OR "pembrolizumab" OR "nivolumab" OR "sintilimab" OR "camrelizumab" OR "toripalimab" OR "envafolimab" OR "tislelizumab" OR "durvalumab" OR "avelumab"))

Filters: Humans; English language. Date range: inception to March 31, 2026.

Similar strategies were adapted for EMBASE (using Emtree terms), CENTRAL, and Web of Science.

Supplementary Table S3. Leave-one-out sensitivity analysis.

Study excluded	Pooled RR	95% CI	I ² (%)	Interpretation
Rahma <i>et al</i> [18] (NRG-GI002)	1.926	1.541–2.408	0.0	Significant
Xiao <i>et al</i> [21] (Sun Yat-sen)	1.736	1.234–2.441	58.5	Significant
Lin <i>et al</i> [16] (UNION)	1.567	1.230–1.995	18.5	Significant
Tang <i>et al</i> [17] (STELLAR II)	1.697	1.209–2.395	58.2	Significant
Tian <i>et al</i> [20] (SPRING-01)	1.702	1.209–2.395	58.2	Significant
None (Overall)	1.719	1.315–2.249	44.8	Significant

RR, risk ratio; CI, confidence interval. The pooled estimate remains statistically significant regardless of which study is excluded, confirming the robustness of the primary finding