BMC Gastroenterology

RESEARCH

Open Access

# Short- and long-term outcomes of neoadjuvant chemotherapy compared with neoadjuvant chemoradiotherapy for locally advanced rectal cancer: an updated meta-analysis

Yue Guo[1†], Zhifeng Guo[2†], Jiaojiao Zhang[3], Guowu Qian[4,5], Wangquan Ji[6], Linlin Song[2], Zhe Guo[2] and Zhuo Han[3*]

## Abstract

**Background and purpose** Neoadjuvant chemoradiotherapy (NACRT) is the standard treatment regimen for locally advanced rectal cancer (LARC) but has unavoidable radiation toxicity. With the advent of more optimized chemotherapy regimens, neoadjuvant chemotherapy (NAC) is sometimes offered as an alternative to NACRT. The purpose of this meta-analysis was to compare the short- and long-term outcomes of NAC and NACRT for LARC patients.

**Materials and methods** Eligible studies through June 15, 2023, were identified in the online databases. Short-term and long-term outcomes were synthesized. A total of 10 studies involving 14,807 patients (1714 vs. 13093) were included in this meta-analysis.

**Results** There were no significant differences between the two groups in terms of lymphovascular invasion, perineural invasion, R0 resection, local recurrence, overall survival, disease-free survival, or grade 3–4 adverse events. The NAC group had a lower rate of pathological complete response [OR (95% CI) = 0.61 (0.45, 0.82)] and tumor regression grade [OR (95% CI) = 0.42 (0.25, 0.70)] and a greater rate of sphincter preservation [OR (95% CI) = 1.57 (1.14, 2.16)] than did the NACRT group. In the prospective studies, no differences in pathological complete response [OR (95% CI) = 0.62 (0.35, 1.11)], tumor regression grade [OR (95% CI) = 0.72 (0.52, 1.00)], and rate of sphincter preservation [OR (95% CI) = 1.40 (0.94, 2.09)] have been found between the two groups.

**Conclusion** NAC was able to achieve similar short- and long-term outcomes as NACRT. It is worth noting that some prospective studies excluded patients with high-risk features. For those LARC patients with high-risk features, the efficacy of NAC versus NACRT needs to be further explored.

[†]Yue Guo and Zhifeng Guo are co-first authors of the article.

*Correspondence:
Zhuo Han
hanzhuodoc_2022@163.com

Full list of author information is available at the end of the article

**Keywords** Locally advanced rectal cancer, Neoadjuvant chemoradiotherapy, Neoadjuvant chemotherapy, Pathological complete response

## Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and affects men more severely than women [1, 2]. Approximately half of all CRC cases involve rectal cancer. Of these, locally advanced rectal cancer (LARC) accounts for a significant proportion of patients. Treatment of LARC has historically been considered a challenge due to the complexity of the pelvic anatomy [3]. Currently, the treatment standard for LARC patients integrates multidisciplinary methods, including neoadjuvant chemoradiotherapy (NACRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy [4, 5].

The goal of NACRT is to shrink tumors and control tumor growth before surgery to increase R0 resection rates and reduce the risk of postoperative recurrence. However, the efficacy of NACRT seems to be unsatisfactory. Previous reports have shown that (1) NACRT has no significant advantage in improving overall survival (OS) or disease-free survival (DFS) [6, 7]. (2) The rate of pathological complete response (pCR) after NACRT is unsatisfactory, ranging from approximately 9–27% [8–10]. (3) Although NACRT reduces local recurrence, the possibility of distant metastasis remains a challenge [11, 12]. (4) Patients with LARC subjected to preoperative radiotherapy are at risk of encountering radiotherapy-associated adverse reactions, notably intestinal, bladder, and femoral head toxicities, which may exert a deleterious influence on postoperative quality of life and physiological function [13, 14]. These factors may reduce the choice of NACRT as a preferred treatment option for physicians and patients.

Neoadjuvant chemotherapy (NAC) without radiotherapy has been shown to have efficacy similar to that of NACRT in patients with LARC and is often used as an alternative treatment option to NACRT due to its lack of radiation toxicity [15]. In a retrospective study by Han et al. [7], pCR was significantly greater in the NACRT group than in the NAC group (17.5% vs. 5.6%, $P = 0.047$), but there was no significant difference between the two groups in terms of 2-year OS or 2-year DFS. The results of the PROSPECT trial designed by Schrag et al. [6] showed that the NAC group achieved similar pCR, R0 resection, 5-year OS, and 5-year DFS rates as did the NACRT group. Preliminary results from the phase III trial conducted by Mei et al. [16] showed that patients who underwent NCA had similar pCR and R0 resection rates and lower rates of perioperative distant metastases than patients who underwent NACRT (0.7% vs. 3.1%, $P = 0.03$). Previously published studies differed in chemotherapy regimens, patient demographic characteristics, and experimental design, which may have led to inconsistent findings. Therefore, this study employs a meta-analysis to compare the short-term and long-term outcomes of NACRT and NAC for patients with LARC.

## Materials and methods

### Search strategy

The search terms used were as follows: (1) rectum cancer OR rectal neoplasms OR rectal cancer OR rectal tumors; (2) neoadjuvant OR (neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy) OR (with or without radiation); and (3) clinical trial OR study. A comprehensive search was conducted with specific keywords from the Pubmed, Embase, Web of Science, and Cochrane Library databases through June 15, 2023. Finally, duplicate studies were removed after the process of searching was complete. Moreover, the study was implemented according to the principles of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist.

### Inclusion and exclusion criteria

The studies were enrolled if they met the following criteria: (1) the type of disease included in the study was LARC; (2) the aim of the study was to determine whether not receiving neoadjuvant radiotherapy was beneficial for patients with LARC; and (3) the study design was retrospective case–control (neoadjuvant chemoradiotherapy vs. neoadjuvant chemotherapy) or prospective random clinical trial (RCT).

The reports were excluded if they met one of the following criteria: (1) the topic of study was not LARC; (2) the purpose of the study was not met; (3) the type of study was a conference paper, review or book; (4) no available data could be extracted from original articles; or (5) the study was written in another language instead of English.

### Data extraction and quality assessment

Two experienced individuals independently extracted the data from the original articles. The detailed term information was extracted from the included studies as follows: (a) first author; (b) year; (c) country; (d) interventions; (e) number of patients; (f) treatment plan; (g) type of surgery; (h) study period; i: study design; j: median or mean age; k: distance from the anal verge (cm); l: sphincter preservation, pCR, R0 resection, tumor regression grade (TRG), T downstage, N downstage, lymphovascular invasion, perineural invasion, local recurrence,

postoperative mortality, DFS, OS, and grade 3/4 adverse events.

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the studies included in this study. A study was considered to be of high quality if the NOS score exceeded six. The Cochrane Risk of Bias tool was used to assess the bias of prospective studies, and the bias levels were categorized into three, low bias, moderate bias, and high bias. The STROBE checklist was used to assess the reporting quality of the studies included in this study. Compliance with more than 80% of the criteria is considered high quality reporting. The primary indicator assessed was pCR. All assessments are independently completed by two experienced reviewers, and when there is a discrepancy in the evaluation results, a third reviewer will assist in resolving it.

### Statistical analysis

R (version 4.2.3) software was used to process the original data. Odds ratios (ORs) and hazard ratios (HRs) were utilized to assess the effect sizes of short-term and long-term outcome measures, respectively. All statistical analyses were conducted with the NACRT group as the reference group. Forest plots were drawn to show the results. The fixed or random effects model was applied to analyze the data. The $I^2$ test and $P$ value were used to check for heterogeneity in the pooled results. An $I^2 > 50\%$ or $P < 0.05$ was considered inevitable heterogeneity. Subsequently, subgroup analysis was carried out to control for heterogeneity to ensure the reliability of the results. The leave-one-out method was employed to conduct sensitivity analyses, assessing the impact of heterogeneity from individual studies on the overall results, thereby ensuring the robustness of the results. Egger's test was used to quantitatively evaluate publication bias. Studies with low quality data will be considered for exclusion. The test level was $\alpha = 0.05$.

## Results

### Basic characteristics of the included studies

Based on a predesigned search strategy, two independent evaluators initially identified a total of 11,317 studies and subsequently excluded 11,307 studies. Ultimately, 10 studies were included in this meta-analysis (Fig. 1).

A total of 14,807 patients were included in this meta-analysis; 13,093 (88.42%) were in the NACRT group, and 1,714 (11.58%) were in the NAC group. These ten studies included three RCTs with patients from China [16, 17], Canada, Switzerland, and the United States [6]. Half of the studies were from China [7, 16–19], and three studies were from Japan [20–22]. One study [23] had an NOS score of 5, and the remaining studies had NOS scores of 6 or above (Table S1). All prospective studies were assessed as low bias (Figure S1), and the reporting quality of all studies was assessed as high (Table S2). Table 1 and Table S3 document the patient characteristics and treatment protocols of these studies.

### Tumor response to neoadjuvant treatment

Evaluation of pCR in the ten included studies revealed significant heterogeneity among the included prospective studies ($I^2 = 77\%$, $P = 0.01$); therefore, a random effects model was used. The results showed that the pCR rate in the NAC group was lower than that in the NACRT group [OR (95% CI) = 0.61 (0.45,0.82), $Z$ = -3.28, $P < 0.01$]. Subgroup analyses of the retrospective studies revealed that the pCR rate was lower in the NAC group than in the NACRT group [OR (95% CI) = 0.62 (0.46, 0.83), $Z$ = -3.19, $P < 0.01$], and that there was no significant difference in the pCR rate between the NAC and NACRT groups in the prospective studies [OR (95% CI) = 0.62 (0.35, 1.11), $Z$ = -1.62, $P = 0.11$] (Fig. 2A). Evaluation of the TRG in the six included studies revealed heterogeneity ($I^2 = 76\%$, $P < 0.01$); therefore, a random effects model was used. The results showed that the TRG rate was lower in the NAC group than in the NACRT group [OR (95% CI) = 0.42 (0.25, 0.70), $Z$ = -3.37, $P < 0.01$]. Subgroup analyses of the retrospective studies revealed that the TRG rate was lower in the NAC group than in the NACRT group [OR (95% CI) = 0.26 (0.14, 0.47), $Z$ = -4.40, $P < 0.01$], and that there was no significant difference in the pCR rate between the NAC and NACRT groups in the prospective studies [OR (95% CI) = 0.72 (0.52, 1.00), $Z$ = -1.94, $P = 0.05$] (Fig. 2B).

### R0 resection and sphincter preservation

Evaluation of R0 resection in the six included studies revealed no significant heterogeneity among the included studies ($I^2 = 0\%$, $P = 0.61$), with no significant difference in R0 resection rates between the NAC group and the NACRT group [OR (95% CI) = 1.42 (0.94, 2.14), $Z = 1.66$, $P = 0.10$]. Subgroup analyses revealed no significant difference in R0 resection rates between the NAC and NACRT groups in either retrospective or prospective studies [retrospective: OR (95% CI) = 1.21 (0.76, 1.91), $Z = 0.80$, $P = 0.42$; prospective: OR (95% CI) = 1.21 (0.76, 1.91), $Z = 0.80$, $P = 0.42$] (Fig. 2C). Evaluation of sphincter preservation in the six included studies revealed no significant heterogeneity ($I^2 = 25\%$, $P = 0.25$), and the percentage of patients with sphincter preservation in the NAC group was greater than that in the NACRT group [OR (95% CI) = 1.57 (1.14, 2.16), $Z = 2.73$, $P < 0.01$]. Subgroup analyses of the retrospective studies showed that the rate of sphincter preservation was greater in the NAC group than in the NACRT group [OR (95% CI) = 1.94 (1.12, 3.37), $Z = 2.35$, $P = 0.02$], and there was no significant difference in the rate of sphincter preservation between the NAC and NACRT groups in the prospective

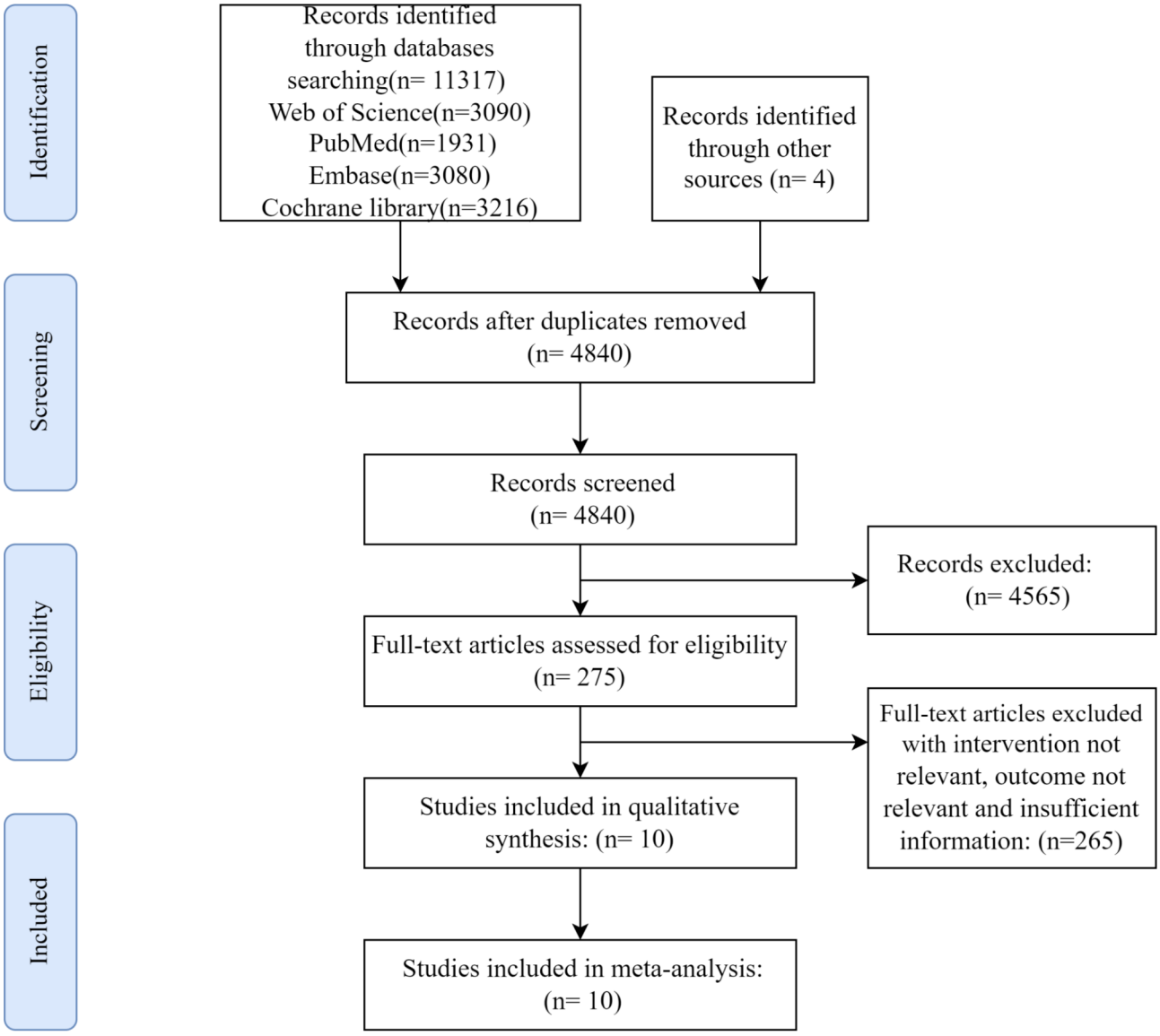


**Fig. 1** PRISMA flow diagram showing the selection of articles for meta-analysis

studies [OR (95% CI) = 1.40 (0.94, 2.09), $Z = 1.66$, $P = 0.10$] (Fig. 2D).

#### Lymphovascular invasion and perineural invasion

Evaluation of lymphovascular invasion in the three included studies revealed significant heterogeneity ($I^2 = 63\%$, $P = 0.07$); therefore, a random effects model was used. The results revealed no significant difference in lymphovascular invasion rates between the NAC group and the NACRT group [OR (95% CI) = 2.71 (0.80, 9.13), $Z = 1.61$, $P = 0.11$] (Fig. 3A). Evaluation of perineural invasion in the three included studies revealed no significant heterogeneity between the included studies ($I^2 = 0\%$, $P = 0.39$), with no significant difference in perineural invasion rates between the NAC group and the NACRT group [OR (95% CI) = 1.45 (0.78, 2.69), $Z = 1.17$, $P = 0.24$] (Fig. 3B).

#### Local recurrence, DFS and OS

Evaluation of local recurrence in the three included studies revealed no significant heterogeneity among the included studies ($I^2 = 45\%$, $P = 0.16$), with no significant difference in local recurrence rates between the NAC group and the NACRT group [HR (95% CI) = 1.40 (0.82, 2.39), $Z = 1.24$, $P = 0.21$]. Subgroup analysis of the prospective studies showed no significant difference in local recurrence rates between the NAC group and the NACRT group [HR (95% CI) = 1.04 (0.56, 1.92), $Z = 0.11$, $P = 0.91$] (Fig. 4A). Evaluation of DFS in the three included studies revealed no significant heterogeneity among the included studies ($I^2 = 38\%$, $P = 0.20$),

**Table 1** Characteristics and treatments of the included studies

| Study | Countries | Duration | Type | Follow-up (months) | Group | *N* | Treatment regimens | Surgery type | Age | cT2/cT3/cT4 | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sakuyama, 2016 | Japan | 2001–2014 | Retrospective | NA | NAC | 44 | FOLFOX: 6 cycles | ISR (34), other (10) | 57.4 | 0/38/6 | ABEF |
| | | | | | NACRT | 44 | 5FU + RT (45 Gy/25 F) | ISR (44) | 56 | 9/35/0 | |
| Sada, 2018 | US | 2006–2012 | Retrospective | NA | NAC | 410 | NA | NA | NA | NA | A |
| | | | | | NACRT | 11,614 | NA | NA | NA | NA | |
| Okuyama, 2018 | Japan | 2010–2016 | Retrospective | 45.4 | NAC | 27 | SOX + CET, SOX + mFOLFOX6 | LAR (19), APR (8) | 66 | 0/24/3 | ACDEG |
| | | | | | NACRT | 28 | 5FU + RT (45 Gy/25F) | LAR (8), APR (20) | 68 | 0/22/5 | |
| Sato, 2019 | Japan | 2002–2016 | Retrospective | NA | NAC | 16 | SOX: 3 cycles | NA | 67.5 | NA | AD |
| | | | | | NACRT | 10 | 5FU + RT (40–45 Gy) | NA | 66 | NA | |
| Deng, 2019 | China | 2010–2015 | Prospective | 45.2 | NAC | 165 | mFOLFOX6 | NA | 54.1 | 1/114/50 | ACDGHIJ |
| | | | | | NACRT | 330 | LV + FU/mFOLFOX6 + RT (46.0–50.4 Gy/23–25 F) | NA | 54/52.2 | 11/206/113 | |
| Zhao, 2022 | China | 2016–2021 | Retrospective | 34.5 | NAC | 92 | mFOLFOX6/CAPEOX | NA | 61.23 | 3/48/41 | ABCGHIJ |
| | | | | | NACRT | 92 | mFOLFOX6/CAPEOX + RT (50 Gy/25F) | NA | 60.6 | 3/38/49 | |
| Yin, 2023 | China | 2015–2018 | Retrospective | 24.5 | NAC | 21 | 5FU + LV + CPT-11: 9–13 cycles + TT | LAR (9) | 58 | 1/13/7 | ABCDEFJ |
| | | | | | NACRT | 42 | 5FU + LV + CPT-11: 9–16 cycles + TT + RT (46–50.4 Gy/25–30 F) | LAR (24), ISR (4), APR (2) | 62 | 1/26/15 | |
| Han, 2023 | China | 2016–2021 | Retrospective | 30 | NAC | 54 | CAPEOX/FOLFOX: 3–8 cycles | NA | 60 | 0/35/19 | ABDFGJ |
| | | | | | NACRT | 101 | CAPEOX/FOLFOX: 1–8 cycles + CAP + RT (50 Gy/25F) | NA | 68 | 0/40/61 | |
| Mei, 2023 | China | 2014–2020 | Prospective | 60 | NAC | 300 | CAPEOX | LAR (251), APR (14), ISR (6), Other (1) | 60 | 16/201/83 | ABCDJ |
| | | | | | NACRT | 289 | CAP + RT (50 Gy/25F) | LAR (234), APR (15), ISR (8), Other (4) | 60 | 11/202/76 | |
| Schrag, 2023 | CAN, CH and US | 2012–2018 | Prospective | 58 | NAC | 585 | FOLFOX6 | APR (13), LAR (522) | 57 | 63/521/0 | ABCGHIJ |
| | | | | | NACRT | 543 | FU/CAP + RT (50.4 Gy/28F) | APR (10), LAR (500) | 57 | 38/505/0 | |

Note: CAN: Canada; CH: Switzerland; US: United States; N: Number of patients; Age: Median or mean age; cT: Clinical T category; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; RT: radiotherapy; FOLFOX: fluorouracil, leucovorin, and oxaliplatin; 5FU: 5-fluorauracil; SOX: tegafurgimeracil-oteracil potassium and oxaliplatin; CET: cetuximab; mFOLFOX6: modified infusional fluorouracil, leucovorin, and oxaliplatin; FU: fluorouracil; CAPEOX: capecitabine and oxaliplatin; LV: leucovorin; CPT-11: irinotecan; TT: targeted therapy; CAP: capecitabine; ISR: intersphincteric resection; LAR: low anterior resection; APR: abdominoperineal resection; NA: not available. A: pathological complete response; B: tumor regression grade; C: R0 resection; D: sphincter preservation; E: lymphovascular invasion; F: perineural invasion; G: local recurrence; H: overall survival; I: disease-free survival; J: grade 3–4 adverse events; NA: not available

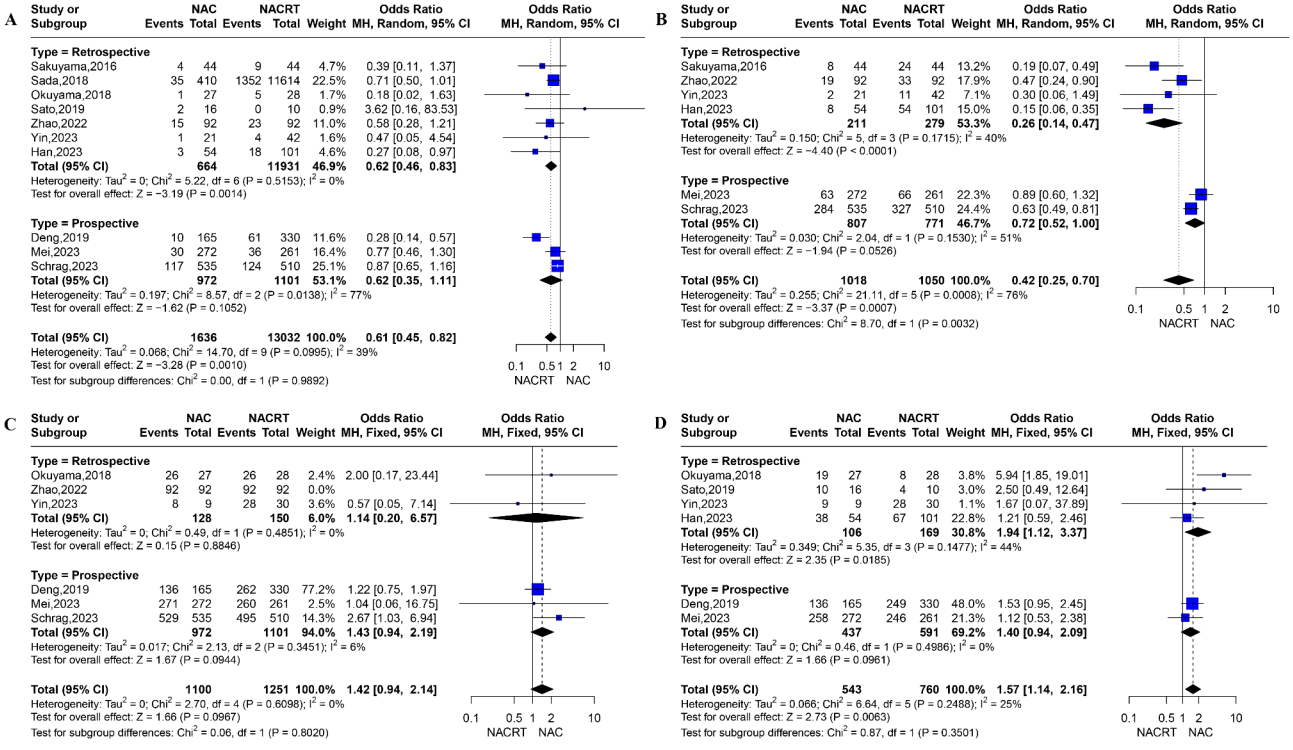


**Fig. 2** Forest plot of pathological complete response (**A**), tumor regression grade (**B**), R0 resection (**C**), and sphincter preservation (**D**) between the NAC and NACRT groups. Note: NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy

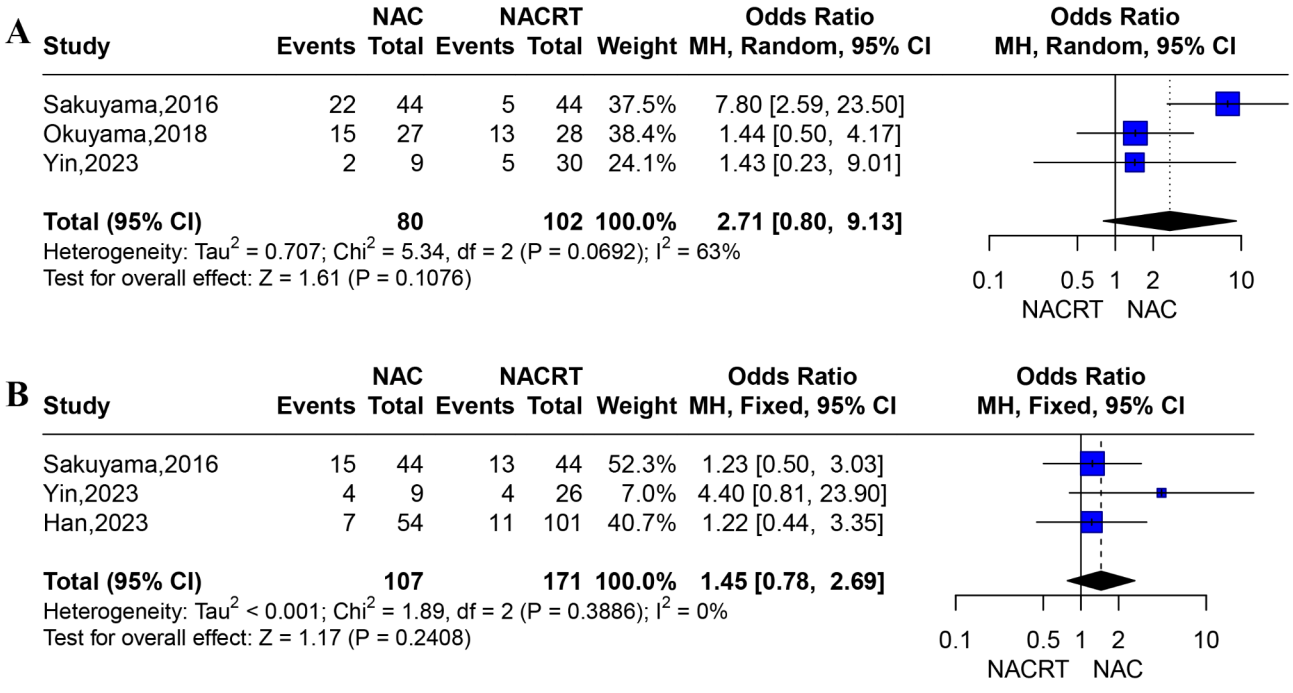


**Fig. 3** Forest plot of lymphovascular invasion (**A**) and perineural invasion (**B**) between the NAC and NACRT groups. Note: NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy

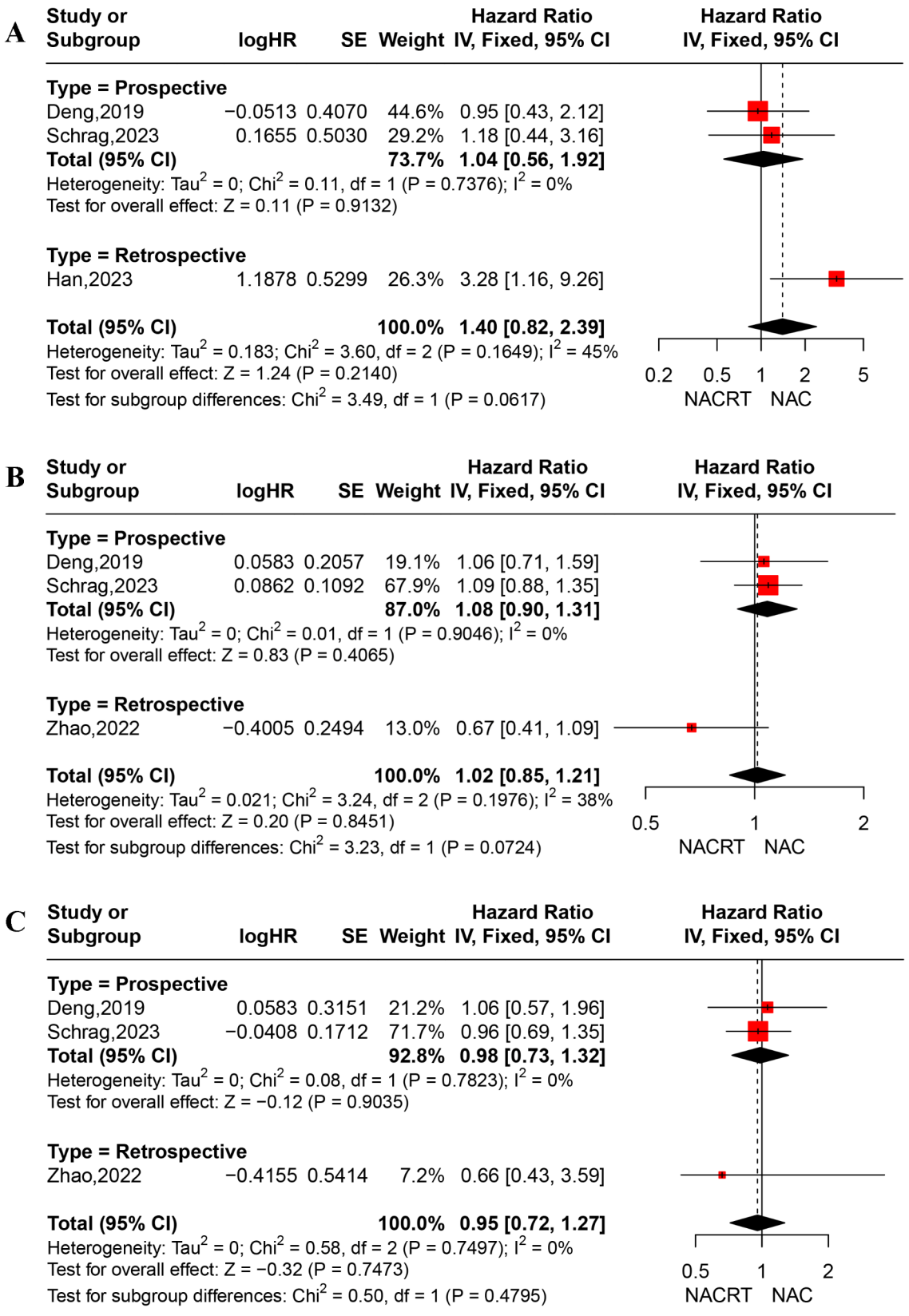


**Fig. 4** Forest plot of local recurrence (**A**), disease-free survival (**B**) and overall survival (**C**) between the NAC and NACRT groups. Note: NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy

with no significant difference in DFS rates between the NAC group and the NACRT group [HR (95% CI) = 1.02 (0.85, 1.21), $Z = 0.20$, $P = 0.85$]. Subgroup analysis of the prospective studies showed no significant difference in DFS rates between the NAC group and the NACRT group [HR (95% CI) = 1.08 (0.90, 1.31), Z = 0.83, $P = 0.41$] (Fig. 4B). Evaluation of OS in the three included studies revealed no significant heterogeneity among the included studies ($I^2 = 0\%$, $P = 0.75$), with no significant difference in OS rates between the NAC group and the NACRT group [HR (95% CI) = 0.95 (0.72, 1.27), $Z$ = -0.32, $P = 0.75$]. Subgroup analysis of the prospective studies showed no significant difference in OS rates between the NAC group and the NACRT group [HR (95% CI) = 0.98 (0.73, 1.32), -Z = 0.12, $P = 0.90$] (Fig. 4C).

### Grade 3–4 adverse events

Evaluation of Grade 3–4 adverse events and toxicities in the six included studies revealed significant heterogeneity ($I^2 = 96\%$, $P < 0.01$); therefore, a random effects model was used. The results showed no significant difference in the incidence of Grade 3–4 adverse events between the NAC and NACRT groups [OR (95% CI) = 0.72 (0.23, 2.23), $Z$ = -0.57, $P = 0.57$]. Subgroup analyses revealed no significant differences in the incidence of Grade 3–4 adverse events or toxicities between the NAC group and the NACRT group in either the retrospective or prospective studies [retrospective: OR (95% CI) = 0.62 (0.32, 1.22), $Z$ = -1.39, $P = 0.16$; prospective: OR (95% CI) = 0.87 (0.15, 5.16), $Z$ = -0.15, $P = 0.88$] (Figure S2). Table S4 details the grade 3–4 adverse events included in the study.

### Subgroup analysis for Asia and Euro-America

The main results were categorized into two subgroups based on region (Asia and Europe-America). All the subtotal results for each subgroup were consistent with the overall results (Figure S3). Thus, there is reason to believe that effect sizes will stabilize and 95% confidence intervals will narrow as more studies from both regions are included.

### Sensitivity analysis

The results of the sensitivity analysis using the leave-one-out test showed that eliminating any one study did not affect the pooled results, indicating that the results are robust and reliable (Figure S4). The results of the sensitivity analysis of the pCR rate of the prospective studies using the leave-one-out test showed that eliminating any one prospective study did not affect the pooled results, indicating that the results of the prospective studies are robust and reliable (Figure S5).

### Publication bias

No publication bias was detected in this study. Egger's test revealed $P$ values exceeding 0.05 (pCR: 0.118; TRG: 0.109; R0 resection: 0.910; sphincter preservation: 0.414; lymphovascular invasion: 0.817; perineural invasion: 0.136; local recurrence: 0.411; OS: 0.612; DFS: 0.434; grade 3–4 adverse events: 0.393).

## Discussion

Preoperative NACRT is the standard treatment for LARC according to the National Comprehensive Cancer Network guidelines [24]; however, some studies indicates that NAC can achieve similar rates of pCR, R0 resection, and OS as NACRT, while avoiding radiation toxicity [6, 16, 17]. Therefore, NAC is considered an attractive alternative to NACRT. To further explore the short- and long-term efficacy of NAC versus NACRT, we conducted a meta-analysis of studies published up to June 15, 2023. Compared with a similar previous meta-analysis by Lin et al. [25], this meta-analysis excluded one study [26] whose treatment regimen did not meet the inclusion criteria and added five new studies [6, 7, 16, 18, 19], as well as meta-analyses for TRG, lymphovascular invasion, perineural invasion, OS, DFS, and grade 3/4 adverse events. This is the first meta-analysis that comprehensively compares the short- and long-term outcomes of NAC and NACRT in patients with LARC and was designed to explore the possibility of NAC replacing NACRT as the preferred option for the clinical treatment of LARC. Ten studies including 14,807 (NAC:1714 vs. NACRT:13093) patients were identified as eligible for this meta-analysis. The results showed that NAC was inferior to NACRT in terms of pCR and TRG and was noninferior to NACRT in terms of lymphovascular invasion, perineural invasion, R0 resection, local recurrence, OS, DFS, and grade 3–4 adverse events but was superior to NACRT in terms of sphincter preservation. Notably, recently published prospective studies have shown that NAC is not inferior to NACRT in terms of pCR or TRG [6, 16, 17].

The pCR rate is an important indicator for evaluating the effect of neoadjuvant therapy, and in general, chemoradiotherapy tends to yield a higher pCR rate than chemotherapy or radiotherapy alone [27]. The present meta-analysis also obtained similar results, i.e., the pCR rate in the NAC group was lower than that in the NACRT group [OR (95% CI) = 0.61 (0.45, 0.82), $P < 0.01$]. However, in the prospective studies, there was no significant difference in the pCR rate between the NAC and NACRT groups [OR (95% CI) = 0.62 (0.35, 1.11), $P = 0.11$]. By comparison, we can easily find that the prospective group was more refined in patient selection. Mei et al. [16] recruited only LARC patients with imaging suggestive of clinical cT2N + or cT3-4aNany disease; Schrag et al. [6] recruited only LARC patients with clinical stage

T2 lymph node-positive, T3 lymph node-negative, or T3 lymph node-positive disease. This finding suggested that for LARC patients with T2/T3 stage disease, NAC not only achieved similar pCR results to those of NACRT but also potentially reduced the possibility of overmedication. The TRG reflects the extent of pathological changes in tumors after neoadjuvant therapy and is often evaluated along with the pCR to assess the effectiveness of neoadjuvant therapy. The present meta-analysis revealed that the TRG rate was lower in the NAC group than in the NACRT group [OR (95% CI) = 0.42 (0.25, 0.70), $P < 0.01$]; however, in the prospective study, this difference was no longer significant [OR (95% CI) = 0.72 (0.52, 1.00), $P = 0.05$], which was consistent with the pCR results. Therefore, we recommend that patients with T3/T4 stage disease and willingness to undergo surgery be considered for NAC and that patients with T4 stage disease and unwillingness to undergo surgery be considered for NACRT.

R0 resection is critical for patients with LARC because it improves patient prognosis, reduces the risk of recurrence, and improves the outcome of surgical treatment. Patients with LARC who undergo either preoperative NAC or NACRT can achieve satisfactory R0 resection rates [28–30]. In this meta-analysis, the NAC and NACRT groups were found to have similar R0 resection rates [OR (95% CI) = 1.42 (0.94, 2.14), $P = 0.10$]. This demonstrates that the preoperative choice of NAC or NACRT is unlikely to result in a change in the R0 resection outcome. Sphincter preservation is closely related to patient quality of life and is one of the therapeutic goals for both patients and physicians. However, NACRT, especially radiotherapy and sphincter-saving operations, tends to cause a series of functional gastrointestinal diseases, such as a high frequency of bowel movements, urgency, and fecal incontinence [31–34], which leads to deterioration of quality of life [35, 36]. The results of this meta-analysis showed that the sphincter preservation rate was greater in the NAC group than in the NACRT group [OR (95% CI) = 1.57 (1.14, 2.16), $P < 0.01$]. In the prospective studies, we found no significant difference in sphincter preservation between the NAC group and the NACRT group. In retrospective studies, patients with tumors closer to the anus were more likely to choose NACRT, whereas in prospective RCT studies, patients were randomized to their treatment regimen. Therefore, this study suggests that the main factor affecting SPR may be the location of the tumor, and further studies are needed to confirm whether NAC improves SPR relative to NACRT.

Lymphovascular invasion refers to the invasion of tumor cells into small lymphatic vessels or blood vessels [37]. Perineural invasion is a pathological process in which a tumor invades a neural structure and spreads through the nerve sheath [38]. Lymphovascular invasion and perineural invasion are important biomarkers for the prognosis of rectal cancer [39], and positive lymphovascular invasion or perineural invasion is usually associated with tumor recurrence as well as poorer OS and DFS [40, 41]. Thus, lymphovascular invasion and perineural invasion can reflect the effectiveness of preoperative neoadjuvant therapy. The results of the present meta-analysis showed that there was no significant difference in lymphovascular invasion or perineural invasion positivity between the NAC group and the NACRT group [lymphovascular invasion: OR (95% CI) = 2.71 (0.80, 9.13), $P = 0.11$; perineural invasion: OR (95% CI) = 1.14 (0.78, 2.69), $P = 0.24$]. These findings suggested that patients in the NAC and NACRT groups may have similar risks of tumor recurrence and survival.

Monitoring recurrence and survival in LARC patients with or without neoadjuvant therapy is critical for evaluating treatment efficacy. Okamura et al. [42] found that more than 80% of local recurrences or distant metastases occurred within 2.2 years and 98.7% within 5 years of surgery. Ruppert et al. [43] found that, in high-risk patients (involved in the mesorectal fascia and/or cT4 stage) who underwent NACRT, the 5-year survival rates were 5.9% (95% CI, 3.0-8.8) for local recurrence and 34.5% (95% CI, 28.6-40.4) for distant metastasis, with the worst DFS and OS. Matsuda et al. [44] found that LARC patients treated with capecitabine in combination with oxaliplatin and irinotecan had a 3-year local recurrence rate of 3.9%, a 3-year DFS rate of 77.3%, and a 3-year OS rate of 96.0%. Furthermore, the type of surgery can markedly affect both functional outcomes and oncologic results in patients with rectal cancer. In particular, for low rectal cancer, more extensive surgery is often required to achieve radical tumor resection, which can pose challenges to sphincter preservation and may lead to postoperative bowel function alterations [34]. It is important to note that patients with low rectal cancer might have a higher risk of postoperative recurrence and potentially face lower postoperative survival rates, although these outcomes are influenced by a multitude of factors beyond the type of surgery [39, 45]. Reducing recurrence and improving survival in patients with LARC remain major challenges. The results of this meta-analysis showed that there was no significant difference in local recurrence [HR (95% CI) = 1.40 (0.82, 2.39), $P = 0.21$]; OS [HR (95% CI) = 0.95 (0.72, 1.27), $P = 0.75$]; or DFS [HR (95% CI) = 1.02 (0.85, 1.21), $P = 0.85$] between the NAC and NACRT groups. Some studies have shown that patients who achieve pCR tend to have better long-term outcomes [46, 47]. In this study, the meta-analysis of long-term outcomes was mainly derived from prospective studies. We compared the meta-analysis of prospective studies and found that the NAC group had consistent results with the NACRT group in terms of pCR and long-term outcomes.

The safety of treatment regimens has received extensive attention from physicians and patients. Radiation toxicity is one of the limitations of NACRT and is difficult to avoid. No significant difference in the incidence of grade 3/4 adverse events between the NAC and NACRT groups was found in this meta-analysis [OR (95% CI) = 0.72 (0.23, 2.23), $P = 0.57$]. Radiotherapy is not the cause of all adverse effects and mainly causes localized adverse effects at the site of irradiation, such as anastomotic leakage, radiation enteritis, and sexual dysfunction [48–50]. The occurrence of adverse events is influenced by a variety of factors, such as the radiation dose and the genetic and pathologic characteristics of the patient [51–53]. Therefore, clinicians need to choose safer treatment options based on the individual characteristics of different patients.

The following limitations of this study must be recognized. First, seven retrospective studies and three prospective studies were included in this study, and the occurrence of recall bias and selection bias is inevitable in retrospective studies. Second, NAC treatment regimens are gradually improving [54], and the NAC treatment regimens used in each study were not identical and not always optimal. In addition, due to the different follow-up periods in each study, the long-term efficacy of NAC and NACRT needs to be further evaluated in future clinical studies. Finally, in some prospective studies, patients with high-risk features such as CRM invasion were excluded [6, 16, 55], thus further studies are needed to determine the efficacy of NAC and NACRT in these patients.

## Conclusions

NAC was able to achieve similar short- and long-term outcomes as NACRT. It is worth noting that some prospective studies excluded patients with high-risk features. For those LARC patients with high-risk features, the efficacy of NAC versus NACRT needs to be further explored.

### Abbreviations

| | |
|---|---|
| CRC | Colorectal cancer |
| LARC | Locally advanced rectal cancer |
| NACRT | Neoadjuvant chemoradiotherapy |
| TME | Total mesorectal excision |
| OS | Overall survival |
| DFS | Disease-free survival |
| pCR | Pathological complete response |
| NAC | Neoadjuvant chemotherapy |
| RCT | Randomized clinical trial |
| PRISMA | Preferred Reporting Items for Systematic Review and Meta-analysis |
| TRG | Tumor regression grade |
| NOS | Newcastle–Ottawa Scale |
| OR | Odds ratio |
| HR | Hazard ratio |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03667-8.

Supplementary Material 1

### Acknowledgements

The authors gratefully acknowledge the financial support from Technology Department of Henan Province and Nanyang City Science and Technology Bureau.

### Author contributions

YG, ZFG and GWQ wrote the manuscript. JJZ and ZH assisted in the statistical analyses and data visualization. WQJ, ZG and LLS read the manuscript and revised it. ZH supervised the study as the corresponding author. All authors approved the final manuscript.

### Funding

This study was funded by the Henan Provincial Key Research and Development Special Program of Science and Technology Department of Henan Province (231111310900) and the Science and Technology Research Project Foundation of Nanyang City Science and Technology Bureau (KJGG095).

### Data availability

The data for this study can be found on Pubmed, Embase, Web of Science, and Cochrane Library databases.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Author details

[1]Department of Anorectal Branch, Nanyang Central Hospital, Nanyang 473005, China
[2]Nanyang Maternal and Child Health Care Hospital, Nanyang Central Hospital, Nanyang 473005, China
[3]Tangdu Hospital, Air Force Medical University, Xi'an 710038, China
[4]Gastrointestinal Surgery Ward II, Department of General Surgery, Nanyang Central Hospital, Nanyang 473005, China
[5]Henan Province Colorectal Tumor Minimally Invasive Engineering and Technology Research Center, Nanyang 473005, China
[6]Department of Epidemiology, College of Public Health, Zhengzhou University, Zhengzhou 450001, China

Received: 18 April 2024 / Accepted: 3 February 2025
Published online: 17 February 2025

### References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91. https://doi.org/10.1136/gutjnl-2015-310912.
2. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin. 2022;72(5):409–36. https://doi.org/10.3322/caac.21731.
3. Quezada-Diaz FF, Smith JJ. Neoadjuvant therapy for rectal Cancer. Surg Oncol Clin N Am. 2022;31(2):279–91. https://doi.org/10.1016/j.soc.2021.11.008.
4. Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice guidelines in

Oncology. J Natl Compr Canc Netw. 2018;16(7):874–901. https://doi.org/10.6004/jnccn.2018.0061.
5. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv263. https://doi.org/10.1093/annonc/mdy161.
6. Schrag D, Shi Q, Weiser MR, Gollub MJ, Saltz LB, Musher BL, et al. Preoperative treatment of locally advanced rectal Cancer. N Engl J Med. 2023;389(4):322–34. https://doi.org/10.1056/NEJMoa2303269.
7. Han YM, Qi WX, Wang SB, Cao WG, Chen JY, Cai G. Identification of patients with locally advanced rectal cancer eligible for neoadjuvant chemotherapy alone: results of a retrospective study. Cancer Med. 2023;12(12):13309–18. https://doi.org/10.1002/cam4.6029.
8. He F, Ju HQ, Ding Y, Jiang Z, Li Z, Huang B, et al. Association between adjuvant chemotherapy and survival in patients with rectal cancer and pathological complete response after neoadjuvant chemoradiotherapy and resection. Br J Cancer. 2020;123(8):1244–52. https://doi.org/10.1038/s41416-020-0989-1.
9. Oh CR, Kim JE, Lee JS, Kim SY, Kim TW, Choi J, et al. Preoperative Chemoradiotherapy with Capecitabine with or without Temozolomide in patients with locally advanced rectal Cancer: a prospective, randomised phase II study stratified by O(6)-Methylguanine DNA methyltransferase status: KCSG-CO17-02. Clin Oncol (R Coll Radiol). 2023;35(2):e143–52. https://doi.org/10.1016/j.clon.2022.10.016.
10. Yamazaki T, Gunderson AJ, Gilchrist M, Whiteford M, Kiely MX, Hayman A, et al. Galunisertib plus neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: a single-arm, phase 2 trial. Lancet Oncol. 2022;23(9):1189–200. https://doi.org/10.1016/S1470-2045(22)00446-6.
11. Akgun E, Caliskan C, Bozbiyik O, Yoldas T, Doganavsargil B, Ozkok S, et al. Effect of interval between neoadjuvant chemoradiotherapy and surgery on disease recurrence and survival in rectal cancer: long-term results of a randomized clinical trial. BJS Open. 2022;6(5). https://doi.org/10.1093/bjsopen/zrac107.
12. De Felice F, Musio D, Magnante AL, Bulzonetti N, Benevento I, Caiazzo R, et al. Disease Control, Survival, and toxicity outcome after intensified Neoadjuvant Chemoradiotherapy for locally advanced rectal Cancer: a single-Institution experience. Clin Colorectal Cancer. 2016;15(2):e17–22. https://doi.org/10.1016/j.clcc.2016.02.006.
13. Downing A, Glaser AW, Finan PJ, Wright P, Thomas JD, Gilbert A, et al. Functional outcomes and Health-Related Quality of Life after curative treatment for rectal Cancer: a Population-Level Study in England. Int J Radiat Oncol Biol Phys. 2019;103(5):1132–42. https://doi.org/10.1016/j.ijrobp.2018.12.005.
14. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. JAMA. 2005;294(20):2587–93. https://doi.org/10.1001/jama.294.20.2587.
15. Brouquet A, Bachet JB, Huguet F, Karoui M, Artru P, Sabbagh C, et al. NORAD01-GRECCAR16 multicenter phase III non-inferiority randomized trial comparing preoperative modified FOLFIRINOX without irradiation to radiochemotherapy for resectable locally advanced rectal cancer (intergroup FRENCH-GRECCAR- PRODIGE trial). BMC Cancer. 2020;20(1):485. https://doi.org/10.1186/s12885-020-06968-1.
16. Mei WJ, Wang XZ, Li YF, Sun YM, Yang CK, Lin JZ, et al. Neoadjuvant Chemotherapy with CAPOX Versus Chemoradiation for locally advanced rectal Cancer with Uninvolved Mesorectal Fascia (CONVERT): initial results of a phase III trial. Ann Surg. 2023;277(4):557–64. https://doi.org/10.1097/SLA.0000000000005780.
17. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Neoadjuvant Modified FOLFOX6 with or without Radiation Versus Fluorouracil Plus Radiation for locally advanced rectal Cancer: final results of the Chinese FOWARC trial. J Clin Oncol. 2019;37(34):3223–33. https://doi.org/10.1200/JCO.18.02309.
18. Zhao X, Han P, Zhang L, Ma J, Dong F, Zang L, et al. Prolonged neoadjuvant chemotherapy without radiation versus total neoadjuvant therapy for locally advanced rectal cancer: a propensity score matched study. Front Oncol. 2022;12:953790. https://doi.org/10.3389/fonc.2022.953790.
19. Yin TC, Chen PJ, Yeh YS, Li CC, Chen YC, Su WC, et al. Efficacy of concurrent radiotherapy in patients with locally advanced rectal cancer and synchronous metastasis receiving systemic therapy. Front Oncol. 2023;13:1099168. https://doi.org/10.3389/fonc.2023.1099168.
20. Sakuyama N, Kojima M, Kawano S, Akimoto T, Saito N, Ito M, et al. Histological differences between preoperative chemoradiotherapy and chemotherapy for rectal cancer: a clinicopathological study. Pathol Int. 2016;66(5):273–80. https://doi.org/10.1111/pin.12409.
21. Okuyama T, Sameshima S, Takeshita E, Yoshioka R, Yamagata Y, Ono Y, et al. Therapeutic effects of oxaliplatin-based neoadjuvant chemotherapy and chemoradiotherapy in patients with locally advanced rectal cancer: a single-center, retrospective cohort study. World J Surg Oncol. 2018;16(1):105. https://doi.org/10.1186/s12957-018-1403-9.
22. Sato K, Miura T, Morohashi S, Sakamoto Y, Morohashi H, Yoshida T, et al. Comparable regional therapeutic effects between neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy for locally advanced lower rectal cancer in terms of histopathological analysis. Mol Clin Oncol. 2019;10(6):619–24. https://doi.org/10.3892/mco.2019.1835.
23. Sada YH, Tran Cao HS, Chang GJ, Artinyan A, Musher BL, Smaglo BG, et al. Prognostic value of neoadjuvant treatment response in locally advanced rectal cancer. J Surg Res. 2018;226:15–23. https://doi.org/10.1016/j.jss.2018.01.025.
24. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen Y-J, Ciombor KK, et al. NCCN guidelines insights: rectal Cancer, Version 6.2020. J Natl Compr Canc Netw. 2020;18(7):806–15. https://doi.org/10.6004/jnccn.2020.0032.
25. Lin H, Wang L, Zhong X, Zhang X, Shao L, Wu J. Meta-analysis of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for locally advanced rectal cancer. World J Surg Oncol. 2021;19(1):141. https://doi.org/10.1186/s12957-021-02251-0.
26. Matsumoto T, Hasegawa S, Zaima M, Inoue N, Sakai Y. Outcomes of Neoadjuvant Chemotherapy without Radiation for rectal Cancer. Dig Surg. 2015;32(4):275–83. https://doi.org/10.1159/000430469.
27. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Modified FOLFOX6 with or without Radiation Versus Fluorouracil and Leucovorin with Radiation in Neoadjuvant Treatment of locally advanced rectal Cancer: initial results of the Chinese FOWARC multicenter, Open-Label, Randomized three-arm phase III trial. J Clin Oncol. 2016;34(27):3300–7. https://doi.org/10.1200/JCO.2016.66.6198.
28. Zhang W, Zhou H, Jiang J, Zhu Y, Zou S, Jiang L, et al. Neoadjuvant chemotherapy with modified FOLFOXIRI for locally advanced rectal cancer to transform effectively EMVI and MRF from positive to negative: results of a long-term single center phase 2 clinical trial. BMC Cancer. 2023;23(1):592. https://doi.org/10.1186/s12885-023-11103-x.
29. Jo H, Kim ST, Lee J, Park SH, Park JO, Park YS, et al. A phase II study of Preoperative Chemoradiotherapy with Capecitabine Plus Simvastatin in patients with locally advanced rectal Cancer. Cancer Res Treat. 2023;55(1):189–95. https://doi.org/10.4143/crt.2021.1527.
30. Nassoiy S, Christopher W, Marcus R, Keller J, Weiss J, Chang SC, et al. Treatment utilization and outcomes for locally advanced rectal Cancer in older patients. JAMA Surg. 2022;157(11):e224456. https://doi.org/10.1001/jamasurg.2022.4456.
31. Sipaviciute A, Sileika E, Burneckis A, Dulskas A. Late gastrointestinal toxicity after radiotherapy for rectal cancer: a systematic review. Int J Colorectal Dis. 2020;35(6):977–83. https://doi.org/10.1007/s00384-020-03595-x.
32. Bryant CL, Lunniss PJ, Knowles CH, Thaha MA, Chan CL. Anterior resection syndrome. Lancet Oncol. 2012;13(9):e403–8. https://doi.org/10.1016/S1470-2045(12)70236-X.
33. Dulskas A, Kavaliauskas P, Pilipavicius L, Jodinskas M, Mikalonis M, Samalavicius NE. Long-term bowel dysfunction following low anterior resection. Sci Rep. 2020;10(1):11882. https://doi.org/10.1038/s41598-020-68900-8.
34. McKenna NP, Bews KA, Yost KJ, Cima RR, Habermann EB. Bowel dysfunction after low anterior resection for Colorectal Cancer: a frequent late effect of surgery infrequently treated. J Am Coll Surg. 2022;234(4):529–37. https://doi.org/10.1097/XCS.0000000000000085.
35. Celerier B, Denost Q, Van Geluwe B, Pontallier A, Rullier E. The risk of definitive stoma formation at 10 years after low and ultralow anterior resection for rectal cancer. Colorectal Dis. 2016;18(1):59–66. https://doi.org/10.1111/codi.13124.
36. Bascoul-Mollevi C, Gourgou S, Borg C, Etienne PL, Rio E, Rullier E, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER PRODIGE 23): Health-related quality of life longitudinal analysis. Eur J Cancer. 2023;186:151–65. https://doi.org/10.1016/j.ejca.2023.03.021.
37. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000;124(7):979–94. https://doi.org/10.5858/2000-124-0979-PFICC.
38. Batsakis JG. Nerves and neurotropic carcinomas. Ann Otol Rhinol Laryngol. 1985;94(4 Pt 1):426–7.

39. Saadoun JE, Meillat H, Zemmour C, Brunelle S, Lapeyre A, de Chaisemartin C, et al. Nomogram to predict disease recurrence in patients with locally advanced rectal cancer undergoing rectal surgery after neoadjuvant therapy: retrospective cohort study. BJS Open. 2022;6(6). https://doi.org/10.1093/bjsopen/zrac138.
40. Kim YI, Kim CW, Kim JH, Kim J, Ro JS, Lee JL, et al. Clinical implication of Perineural and Lymphovascular Invasion in rectal Cancer patients who underwent surgery after preoperative chemoradiotherapy. Dis Colon Rectum. 2022;65(11):1325–34. https://doi.org/10.1097/DCR.0000000000002219.
41. Sun Q, Liu T, Liu P, Luo J, Zhang N, Lu K, et al. Perineural and lymphovascular invasion predicts for poor prognosis in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery. J Cancer. 2019;10(10):2243–9. https://doi.org/10.7150/jca.31473.
42. Okamura R, Itatani Y, Fujita Y, Hoshino N, Okumura S, Nishiyama K, et al. Postoperative recurrence in locally advanced rectal cancer: how does neoadjuvant treatment affect recurrence pattern? World J Surg Oncol. 2023;21(1):247. https://doi.org/10.1186/s12957-023-03136-0.
43. Ruppert R, Junginger T, Kube R, Strassburg J, Lewin A, Baral J, et al. Risk-adapted neoadjuvant chemoradiotherapy in rectal Cancer: final report of the OCUM Study. J Clin Oncol. 2023;41(24):4025–34. https://doi.org/10.1200/JCO.22.02166.
44. Matsuda C, Kudo T, Morimoto Y, Kagawa Y, Tei M, Ide Y, et al. A phase II study of neoadjuvant capecitabine, oxaliplatin, and irinotecan (XELOXIRI) in patients with locally advanced rectal cancer. Ann Gastroenterol Surg. 2023;7(1):81–90. https://doi.org/10.1002/ags3.12600.
45. Nacion AJD, Park YY, Yang SY, Kim NK. Critical and challenging issues in the Surgical Management of low-lying rectal Cancer. Yonsei Med J. 2018;59(6):703–16. https://doi.org/10.3349/ymj.2018.59.6.703.
46. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835–44. https://doi.org/10.1016/S1470-2045(10)70172-8.
47. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg. 2012;99(7):918–28. https://doi.org/10.1002/bjs.8702.
48. Jiang W, Wang H, Zheng J, Zhao Y, Xu S, Zhuo S, et al. Post-operative anastomotic leakage and collagen changes in patients with rectal cancer undergoing neoadjuvant chemotherapy vs chemoradiotherapy. Gastroenterol Rep (Oxf). 2022;10:goac058. https://doi.org/10.1093/gastro/goac058.
49. Baxter NN, Hartman LK, Tepper JE, Ricciardi R, Durham SB, Virnig BA. Postoperative irradiation for rectal cancer increases the risk of small bowel obstruction after surgery. Ann Surg. 2007;245(4):553–9. https://doi.org/10.1097/01.sla.0000250432.35369.65.
50. Custers PA, van der Sande ME, Grotenhuis BA, Peters FP, van Kuijk SMJ, Beets GL, et al. Long-term quality of life and functional outcome of patients with rectal Cancer following a Watch-and-wait Approach. JAMA Surg. 2023;158(5):e230146. https://doi.org/10.1001/jamasurg.2023.0146.
51. Xu Y, Zou H, Shao Z, Zhang X, Ren X, He H, et al. Efficacy and safety of different radiotherapy doses in neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: a retrospective study. Front Oncol. 2023;13:1119323. https://doi.org/10.3389/fonc.2023.1119323.
52. Smith JJ, Wasserman I, Milgrom SA, Chow OS, Chen CT, Patil S, et al. Single nucleotide polymorphism TGFbeta1 R25P correlates with Acute Toxicity during Neoadjuvant Chemoradiotherapy in rectal Cancer patients. Int J Radiat Oncol Biol Phys. 2017;97(5):924–30. https://doi.org/10.1016/j.ijrobp.2016.12.015.
53. Gordeyev S, Ivanov V, Fedianin M, Chernikh M, Kozlov N, Petrov L, et al. Neoadjuvant chemoradiotherapy for locally advanced rectal cancer with peritumoral abscesses and fistulas. Strahlenther Onkol. 2022;198(2):201–8. https://doi.org/10.1007/s00066-021-01878-y.
54. Rouanet P, Castan F, Mazard T, Lemanski C, Nougaret S, Deshayes E, et al. GRECCAR 14 - a multicentric, randomized, phase II-III study evaluating the tailored management of locally advanced rectal carcinoma after a favourable response to induction chemotherapy: study protocol. Colorectal Dis. 2023;25(10):2078–86. https://doi.org/10.1111/codi.16740.
55. O'Cathail SM, Adams R, Hawkins MA, Sebag-Montefiore D, Marijnen CAM, Fokas E. Patient-reported outcomes in PROSPECT trial (Alliance N1048) - FOLFOX is not a panacea. Clin Transl Radiat Oncol. 2023;43:100672. https://doi.org/10.1016/j.ctro.2023.100672.


## Publisher's note