



Comparison of the efficacy of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy in locally advanced rectal cancer patients: meta-analysis of randomized controlled trials

De-xin Zeng, MM^a, Ruo-Nan Liu, MM^a, Xian-Kun Ren, MM^b, Peng Zhang, MM^a, Ling-Han Tang, MM^a, Ling Tan, MM^c, Rehman Zia Ur, MM^a, Mao-Ru Zhao, PhD^a, Peng Guo, MM^a, Pan Zhang, MM^a, Jun Du, MM^a, Xian Qin, MM^a, Shi-Yan Wan, MM^a, Lu-Qian Deng, MM^a, Ya-Jun Luo, MD^d, Zi-Lin Liu, MM^e, Jiang-Wei Xiao, MD, PhD^{a,*}

Background: Preoperative neoadjuvant chemoradiotherapy (nCRT) is considered to be the standard treatment strategy for locally advanced rectal cancer (LARC); however, the risk of adverse events and postoperative recurrence remains significant. This study aimed to evaluate the non-inferiority of neoadjuvant chemotherapy (nCT) compared with nCRT in patients with LARC and to assess the possibility of eliminating radiotherapy on the basis of guaranteed efficacy.

Materials and methods: We searched the PubMed, Embase, and Cochrane Library databases to identify randomized controlled trials (RCTs) comparing the efficacy of nCRT and nCT for LARC. The study protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO).

Results: A total of 2706 patients from seven studies were included in the meta-analysis. There was no significant difference in overall survival (OS) or disease-free survival (DFS) between the nCT and nCRT groups. This study demonstrated a lower rate of infection (OR = 0.53, 95% CI = 0.34–0.82; $P = 0.005$), anastomotic leak (OR = 0.55, 95% CI = 0.34–0.87; $P = 0.01$), tumor regression grade (TRG) 0–1 (OR = 0.50, 95% CI = 0.36–0.69; $P < 0.0001$), preventive diverting ileostomy (OR = 0.41, 95% CI = 0.17–1.02; $P = 0.05$), and leukopenia (OR = 0.50, 95% CI = 0.25–1.01; $P = 0.05$) in the nCT group. However, there was no significant difference in the other toxic events, such as intestinal obstruction, urinary complications, diarrhea, and surgical or pathological outcomes, such as clinical fistula, sphincter preservation, postoperative mortality (≤ 60 d), R0 resection, ypStage 0–I, positive circumferential resection margin (CRM+), or pathological complete response (pCR) between the two groups.

Conclusion: This study indicated that OS and DFS were not lower in the nCT group than in the nCRT group. In addition, the nCT group had fewer complications. Preoperative nCT is expected to become a standard treatment option for most patients with stage II–III LARC. It is worth noting that radiotherapy cannot be ignored for some patients who need to ensure the conversion effect of neoadjuvant therapy and strongly request to preserve organ function.

Keywords: locally advanced rectal cancer, meta-analysis, neoadjuvant chemoradiotherapy, neoadjuvant chemotherapy, randomized controlled trials

Introduction

Colorectal cancer (CRC) was the third most common malignant neoplasm and was the second leading cause of cancer death worldwide, after lung cancer, in 2020^[1]. Its burden is estimated to increase by 60%, exceeding 2.2 million new cases and 1.1 million cancer deaths by 2030^[2]. The rectal lymphatic drainage area was distributed along the medial space of the obturator foramen of the

internal iliac artery, and if metastasis occurred, lymphatic drainage would be transferred upwards, laterally, and downwards, which can lead to a high risk of recurrence.

Total mesorectal excision (TME) combined with autonomous nerve protection technology is clearly insufficient to cope with local recurrence (LR) of LARC^[3], resulting in LR rates as high as approximately 15–45%^[4,5]. Consequently, multimodality

^aDepartment of Gastrointestinal Surgery, Clinical Medical College and The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan Province, China,

^bDepartment of Gastrointestinal Surgery, Medical Center Hospital of Qionglai City, Qionglai, China, ^cDepartment of Urology, People's Hospital Affiliated to Chongqing Three Gorges Medical College, Chongqing, China, ^dDepartment of Gastrointestinal Surgery, Sichuan Cancer Hospital, University of Electronic Science and Technology of China, Chengdu, China and ^eDepartment of Gastrointestinal Surgery, West China TianFu Hospital, Sichuan University, Sichuan, China

De-xin Zeng, Ruo-nan Liu, and Xian-kun Ren are co-first author.

*Corresponding author. Address: Department of Gastrointestinal Surgery, Clinical Medical College and The First Affiliated Hospital of Chengdu Medical College, Chengdu 610500, Sichuan Province, China. E-mail: xiaojiangwei2018@163.com (J.-W. Xiao).

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treatment is considered a standard treatment for patients with stage II-III LARC and consists of preoperative fluoropyrimidine combined with simultaneous radiotherapy followed by TME surgery and adjuvant chemotherapy^[6–8], which results in a significant reduction in the incidence of LR to 5–10%^[9]. However, adverse events can continuously occur. In terms of nCRT, adding radiotherapy on the basis of the TME did not significantly improve the OS of patients^[10,11], and the related toxic events increased^[12–14]. In addition, peritoneal fibrosis caused by radiotherapy increases surgical difficulty, which also affects the resection rate of tumors and lymph nodes. Regarding adjuvant radiotherapy, a non-negligible proportion of patients have poor compliance with this strategy and are unable to complete the planned dose of adjuvant chemotherapy after undergoing destructive TME surgery as well as experiencing toxicities of chemotherapy drugs themselves^[15].

With the advancements in TME technology and the emphasis on tumor-free methods, the clearance of tumor micrometastases and lymph nodes has been ensured^[16]. TME surgery and preoperative radiotherapy seemed to have overlapping effects on LR. Thus, radiotherapy has been questioned because of its higher rate of toxicity and minimal improvement in survival indicators^[17,18].

nCT seems to be a promising treatment option because it is likely to reduce the above adverse events. The FOWARC study demonstrated less toxicity and a lower rate of pCR in the nCT group and a similar tumor downstaging rate in the two groups^[9]. Moreover, Schrag *et al* confirmed a better DFS outcome in the nCT group and similar OS and LR outcomes between the two groups^[19]. However, several studies have shown that aggressive nCT based on radiotherapy increases toxicity^[20–22]. The efficacy was still controversial between the two groups.

This study aimed to evaluate the non-inferiority of nCT compared with nCRT in patients with LARC and to assess the possibility of eliminating radiotherapy on the basis of guaranteed efficacy. During preoperative neoadjuvant therapy, we performed a meta-analysis of seven RCTs to evaluate toxicity, pathological outcomes, and survival indicators. This study could help guide the preoperative treatment of LARC patients.

Materials and methods

Literature search

The meta-analysis conformed to the PRISMA standards and was fully compliant with the PRISMA 2020 statement^[23]. We conducted each quality assessment based on AMSTAR 2^[24], which is highly descriptive and consistent. The program was registered on the International Prospective Register of Systematic Reviews prior to conducting this systematic review.

Data sources and search strategy

We systematically searched PubMed, Embase, and the Cochrane Library and obtained relevant studies from inception to 22 July 2023. The search terms included were related to LARC, drug therapy, nCT, nCRT, and RCT. The search strategies are shown in Supplemental Table 1, <http://links.lww.com/JS9/D816> and Supplemental Digital Content 3, <http://links.lww.com/JS9/D816>, using PubMed as an example.

Eligibility criteria

The inclusion criteria were relevant RCTs assessing the association between nCT and nCRT in patients with LARC. The specific details were as follows: patients with locally advanced rectal cancer received nCT or nCRT followed by standard TME surgery. The outcome measures reported at least one of the following outcomes: complications, pathological outcomes, OS, and DFS. The study design was limited to RCTs. Studies were excluded if they were (1) nonhuman studies; (2) non-comparative studies; (3) non-original studies (case reports, letters, reviews, editorials, and conference articles); and (4) no outcome measures of interest were reported.

Data extraction and outcome measures

With a predesigned table, two researchers independently screened all the included studies and extracted the relevant data. Disagreements were resolved by another senior researcher. The demographic and outcome data were extracted. The demographic information of the included studies included the reference and year, country, sample size, nCT and nCRT method, and operation method. The following outcomes were compared: (1) complications: infection, anastomotic leak, intestinal obstruction, urinary complications, and diarrhea; (2) pathological outcomes: CRM, R0 resection, and pCR; and (3) survival outcomes: OS and DFS.

Study quality assessment

The 7-point Cochrane scale^[25] was used to assess the quality of the identified studies and included seven assessment items: random sequence generation (1 point), allocation concealment (1 point), blinding of participants and personnel (1 point), blinding of outcome assessment (1 point), incomplete outcome data (1 point), selective reporting (1 point), and other bias (1 point). A score of 0 to 7 was assigned, and higher scores indicated higher quality. Any study with a score of at least 4 was considered to have high methodological quality, and disagreements between the two researchers were resolved by a third researcher who made the final decision. We used Review Manager 5.4 to evaluate the results of the quality assessment.

Statistical analysis

The hazard ratio (HR) with a 95% confidence interval (CI) was used to estimate OS and DFS, while the odds ratio (OR) with a 95% CI was used to evaluate complications and pathological outcomes. A *P*-value of 0.05 was used as the critical value for determining statistical significance. χ^2 and I^2 statistics were used to assess heterogeneity in our studies. A fixed-effect model was applied only if the *P*-value on the *Q* test was greater than 0.05 and I^2 was less than 50%, while a random-effects model was applied because of significant heterogeneity. The sensitivity analysis was conducted for more than two outcome indicators. Each study was sequentially removed in the sensitivity analysis, and the meta-analysis of the remnant studies was conducted and compared with the results before the previous elimination was performed. Publication biases were determined using funnel plot analysis. The analysis was performed with Review Manager (version 5.4.).

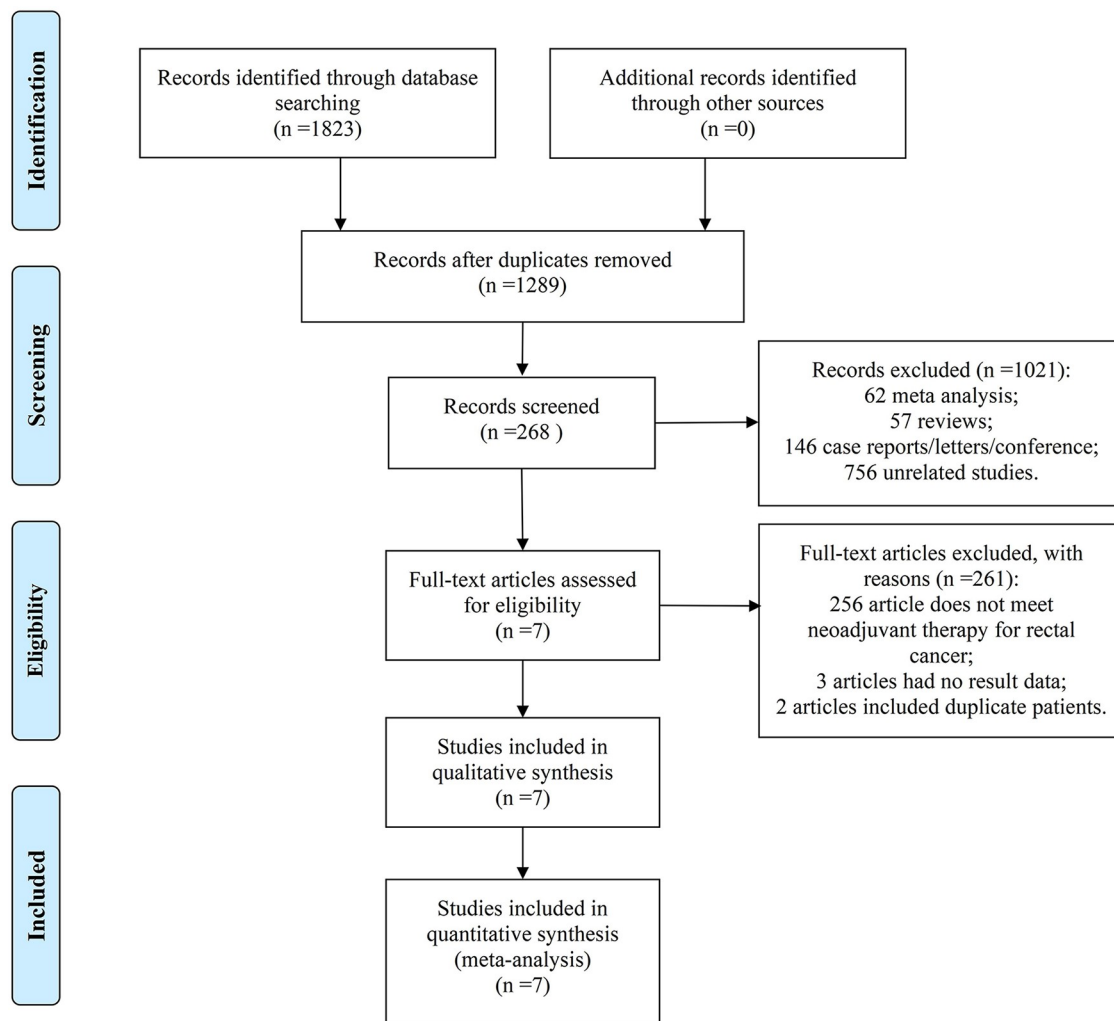


Figure 1. Flowchart showed the selection of potentially relevant studies for the present study.

Results

Literature selection and quality assessment

The procedure for the literature search is shown in Figure 1. A total of 1823 studies were identified in the initial search. After excluding duplicate articles, we subsequently reviewed the titles, abstracts, and full texts. Ultimately, seven RCTs^[9,19,26–30] with 2706 patients were included in this study, and the baseline information is shown in Table 1. The results of the quality assessment are shown in Figure 2. Generally, the risk of bias in the included studies was moderate to low, and the quality of the studies was high.

Complications and toxicities

The results are summarized in Figure 3 and Figure 3a. Low statistical heterogeneity existed between the studies, and the fixed-effects model was applied. The results showed a significantly lower rate of infection (OR: 0.53, 95% CI: 0.34–0.82, $I^2 = 0\%$, $P = 0.005$) and anastomotic leak (OR = 0.55, 95% CI = 0.34–0.87; $I^2 = 74\%$, $P = 0.01$) in the nCT group. There were no significant differences in the rates of intestinal

obstruction (OR: 1.11, 95% CI: 0.48–2.57, $I^2 = 0\%$, $P = 0.80$), urinary complications (OR: 0.81, 95% CI: 0.33–1.98, $I^2 = 0\%$, $P = 0.64$), or diarrhea (OR: 0.67, 95% CI: 0.42–1.09, $I^2 = 0\%$, $P = 0.10$) between the two groups. In addition, we used the random-effects model due to obvious statistical heterogeneity in clinical fistula (OR: 0.79, 95% CI: 0.11–5.75, $I^2 = 74\%$, $P = 0.82$), leukopenia (OR: 0.50, 95% CI: 0.25–1.01, $I^2 = 68\%$, $P = 0.05$), and nausea/vomiting (OR: 1.34, 95% CI: 0.32–5.55, $I^2 = 83\%$, $P = 0.69$).

Survival analysis

The results are shown in Figure 4. Low statistical heterogeneity existed between the studies, and the fixed-effects model was applied. Overall, there were no significant differences in OS (HR: 1.04, 95% CI: 0.78–1.41, $I^2 = 0\%$, $P = 0.78$) or DFS (HR: 0.92, 95% CI: 0.76–1.12, $I^2 = 0\%$, $P = 0.43$) between the two groups.

Pathological findings and surgical outcomes

The results are presented in Figure 5 and Figure 5a. Low statistical heterogeneity existed between the studies, and the fixed-

Table 1
Clinical characteristics of LARC patients undergoing neoadjuvant therapy from 10 included studies

References and year	Country	Sample size		Neoadjuvant therapy		Operation method	
		nCT	nCRT	nCT	nCRT	nCT	nCRT
Deng.2016/2019 ^[9,26]	China	152	290	mFOLFOX6† × 4–6 cycles	mFOLFOX6† × 4–6 cycles/de Gramont × 5 cycles; 46.0–50.4 Gy 23–28 fractions/5–6 weeks	TME	TME
Mei.2023 ^[27]	China	272	261	CAPOX × 4 cycles	capecitabine†; 50 Gy 25 fractions/5 weeks	TME	TME
Rouanet.2017 ^[28]	France	10	120	FOLFIRINOX × 4 cycles	capecitabine††; 44 Gy 25 fractions/5 weeks	TME	TME
Schrag.2023 ^[19]	America	585	543	mFOLFOX6 × 6 cycles	5-FU/capecitabine†††	APR, LAR	APR, LAR
Sun.2019 ^[29]	China	88	132	mFOLFOX6	mFOLFOX6 × 4–6 cycles/5-FU† × 5 cycles; 46.0–50.4 Gy 23–28 fractions/5–6 weeks	TME	TME
Xie.2021 ^[30]	China	94	159	mFOLFOX6 × 4–6 cycles	mFOLFOX6/5-FU†; 46.0–50.4 Gy 23–28 fractions/5–6 weeks	TME	TME

de Gramont, leucovorin 400 mg/m² intravenously followed by fluorouracil 400 mg/m² intravenously and fluorouracil 2.4 g/m² by 48 hours continuous intravenous infusion; mFOLFOX6†, de Gramont × 5 cycles plus oxaliplatin 85 mg/m² intravenously on day 1 of each chemotherapy cycle; CAPOX, oxaliplatin 130 mg/m² IV day 1 and capecitabine 1000 mg/m² twice daily for 14 d; capecitabine†, 825 mg/m² twice daily administered orally and concurrently with radiation; 5-FU, 225 mg/m² of body surface area per day; 5-FU†, 400 mg/m² IV bolus followed by a 46 hours continuous infusion; FOLFOX, 2 hours oxaliplatin infusion at a dose of 85 mg/m² with concurrent IV infusion of leucovorin 400 mg/m² followed by 5-FU given, as described above (5-FU†), every 2 weeks; FOLFIRINOX, 180 mg/m² irinotecan, 85 mg/m² oxaliplatin, 200 mg/m² elvorin, and 5-fluorouracil (400 mg/m² bolus followed by 2400 mg/m² continuous infusion for 46 hours) delivered over 8 weeks (day 1 = day 15); capecitabine††, 1600 mg/m² daily in two identical doses taken during the radiotherapy days; capecitabine†††, 825 mg/m² twice daily, 5 days per week on days of radiation therapy.

effects model was applied. Our results revealed no significant differences in R0 resection (OR: 1.31, 95% CI: 0.79–2.17, $I^2 = 12\%$, $P = 0.29$), sphincter preservation (OR: 1.15, 95% CI: 0.76–1.72, $I^2 = 0\%$, $P = 0.51$), CRM (+) (OR: 2.08, 95% CI: 0.37–11.54, $I^2 = 0\%$, $P = 0.40$), or postoperative mortality (≤ 60 d) (OR: 0.44, 95% CI: 0.05–4.28, $I^2 = 0\%$, $P = 0.48$) between the two groups. Additionally, the random-effects model was used because of measurable statistical heterogeneity in pCR (OR: 0.59, 95% CI: 0.33–1.04, $I^2 = 70\%$, $P = 0.07$), TRG 0–1 (OR: 0.50, 95% CI: 0.36–0.69, $I^2 = 53\%$, $P < 0.0001$), preventive diverting ileostomy (OR: 0.41, 95% CI: 0.17–1.02, $I^2 = 83\%$, $P = 0.05$), and ypStage 0–I (OR: 0.84, 95% CI: 0.62–1.15, $I^2 = 54\%$, $P = 0.28$). Overall, a lower rate of TRG 0–1 and preventive diverting ileostomy occurred in the nCT group, and for clinical fistula and pCR, no measurable differences were detected between the two groups.

Publication bias and sensitivity analysis

We estimated publication bias by observing the symmetry of the funnel plots in Supplemental Figure 1. The funnel plot showed that most points were basically symmetrical, which indicated that the included studies were relatively stable and credible with little possibility of publication bias. Our sensitivity analysis revealed slight heterogeneity except for clinical fistula, pCR, TRG 0–1, preventive diverting ileostomy, leukopenia, nausea/vomiting, and ypStage 0–I ($I^2 = 74\%$, $I^2 = 70\%$, $I^2 = 67\%$, $I^2 = 83\%$, $I^2 = 68\%$, $I^2 = 83\%$, $I^2 = 54\%$, respectively). In terms of clinical fistula, we found significant heterogeneity among the studies from Rouanet *et al*^[28]. The heterogeneity was reduced after the exclusion of this study ($I^2 = 2\%$). There was marked heterogeneity in pCR due to the study of Deng *et al*^[9], and this heterogeneity decreased after the exclusion of this study ($I^2 = 0\%$). With regard to TRG 0–1 and ypStage 0–I, we found significant heterogeneity among the studies from Schrag *et al*^[19]. Heterogeneity was reduced after the exclusion of this study ($I^2 = 36\%$, $I^2 = 0\%$, respectively). All of the remaining outcomes included only two

studies, and heterogeneity could not be analyzed by excluding any articles.

Discussion

Surgical resection remains the main method for treating rectal cancer, and radical resection combined with preoperative and postoperative adjuvant therapy could improve the survival rate of LARC patients. In the function-preserving strategy era, excluding the improvement of LR, radiotherapy is related to various acute and chronic radiation-related toxicities and rarely improves OS; moreover, radiotherapy can cause a series of complications in patients and can affect their quality of life. Therefore, it is still controversial whether radiotherapy is an overtreatment option. We should screen for nCRT patients with colorectal cancer who need more preoperative radiotherapy to improve efficacy, and avoid overtreatment of colorectal cancer patients who do not benefit from radiotherapy.

We performed a meta-analysis to identify the efficacy of nCT and nCRT in treating LARC patients. Compared with previously published meta-analyses^[31], the main advantages of this study were as follows. First, all included articles were RCTs, and the quality and data credibility of the included studies were high. Second, we analyzed the specific complications before and after TME surgery, as well as the more detailed pathological characteristics, and the DFS was also established. In the meta-analysis, a total of 2706 patients from seven studies were included, and there was no significant difference in OS or DFS between the nCT and nCRT groups. This study demonstrated a lower rate of infection, anastomotic leak, TRG 0–1, preventive diverting ileostomy, and leukopenia in the nCT group. However, there was no significant difference in the other toxic events, such as intestinal obstruction, urinary complications, diarrhea, and surgical or pathological outcomes, such as clinical leak, sphincter preservation, postoperative mortality (≤ 60 d), R0 resection, ypStage 0–I, CRM (+), and the pCR rate.

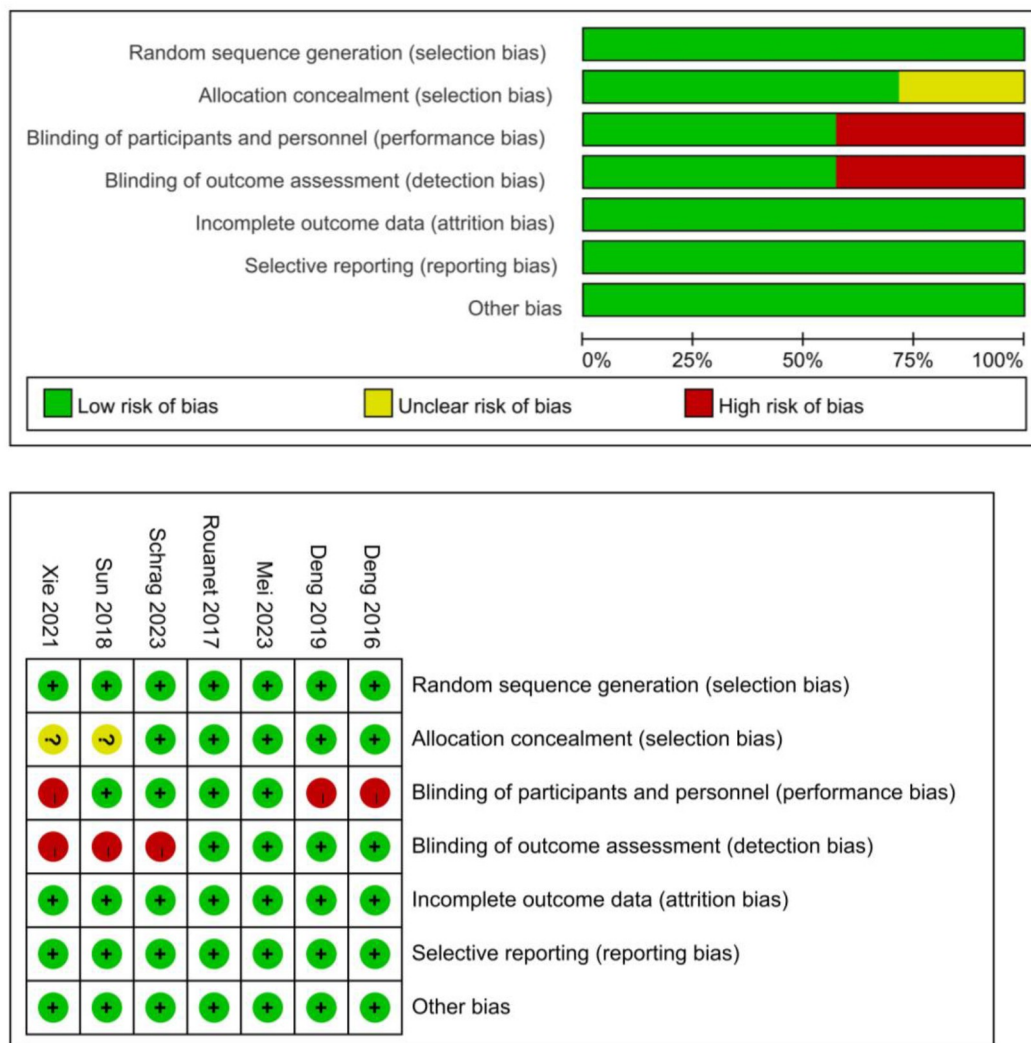


Figure 2. The quality assessment of RCTs. (A) Risk of bias graph: sum up authors' judgments about every risk of bias item which were presented as percentages across all included studies; (B) risk of bias summary: summarized authors' judgments about each risk of bias item for all included studies.

We hypothesized that tumor regression after neoadjuvant therapy allows the TME to achieve complete R0 tumor resection, so the advantages of preoperative nCRT in OS and PFS have not been demonstrated.

The meta-analysis demonstrated lower rates of infection and anastomotic leak in the nCT group. Previous studies respectively reported 7.2–7.4% and 11.5–15.5% rates of infection in the nCT and nCRT groups^[9,27]. Radiotherapy induces congestion and edema of the intestine; consequently, pathogens invade and easily lead to pelvic infection. Second, radiotherapy tends to lead to myelosuppression and immune deficiency, and the rate of infection increases. For anastomotic leak, previous studies reported 6.8–8.5% and 16.7–21.9% in the nCT and nCRT groups, respectively^[9,29,32]. Qin *et al* verified that nCRT was an independent risk factor for anastomotic leak and stenosis^[32]. On the basis of radiation enteritis, a previous study indicated that the basis of a safe anastomosis was construction with at least one end of the unirradiated bowel^[33], which caused unhealthy anastomosis patterns. In addition, radiotherapy easily leads to aseptic necrosis

and fibrosis of intestinal wall tissue, resulting in intestinal stenosis. At the same time, radiotherapy also increases pelvic tissue fragility, fibrosis, and adhesion of pelvic tissues, leaving an indistinct pelvic anatomical structure, which undoubtedly increases the difficulty of the surgical procedure^[34,35] and is more likely to lead to imperfect anastomosis. Thus, anastomotic leak, pelvic infection, and anastomotic stenosis can occur in sequence. Notably, the phase III CONVERT trial reported a lower rate of anastomotic leak in the two groups (nCT vs. nCRT, 5.9% vs. 6.1%), probably because this trial excluded patients with stage cT4b disease^[27], which might be a high-risk population for anastomotic leak. The results showed that radiotherapy increased the rate of preventive diverting ileostomy, a conservative measure taken by surgeons to prevent anastomotic leakage, which not only reduced patients' quality of life but also affected their compliance with adjuvant chemotherapy, and additional secondary surgery was also needed, as well as increased the medical burden of patients. What is more, radiotherapy might cause low anterior resection syndrome (LARS), a series of symptoms combined with

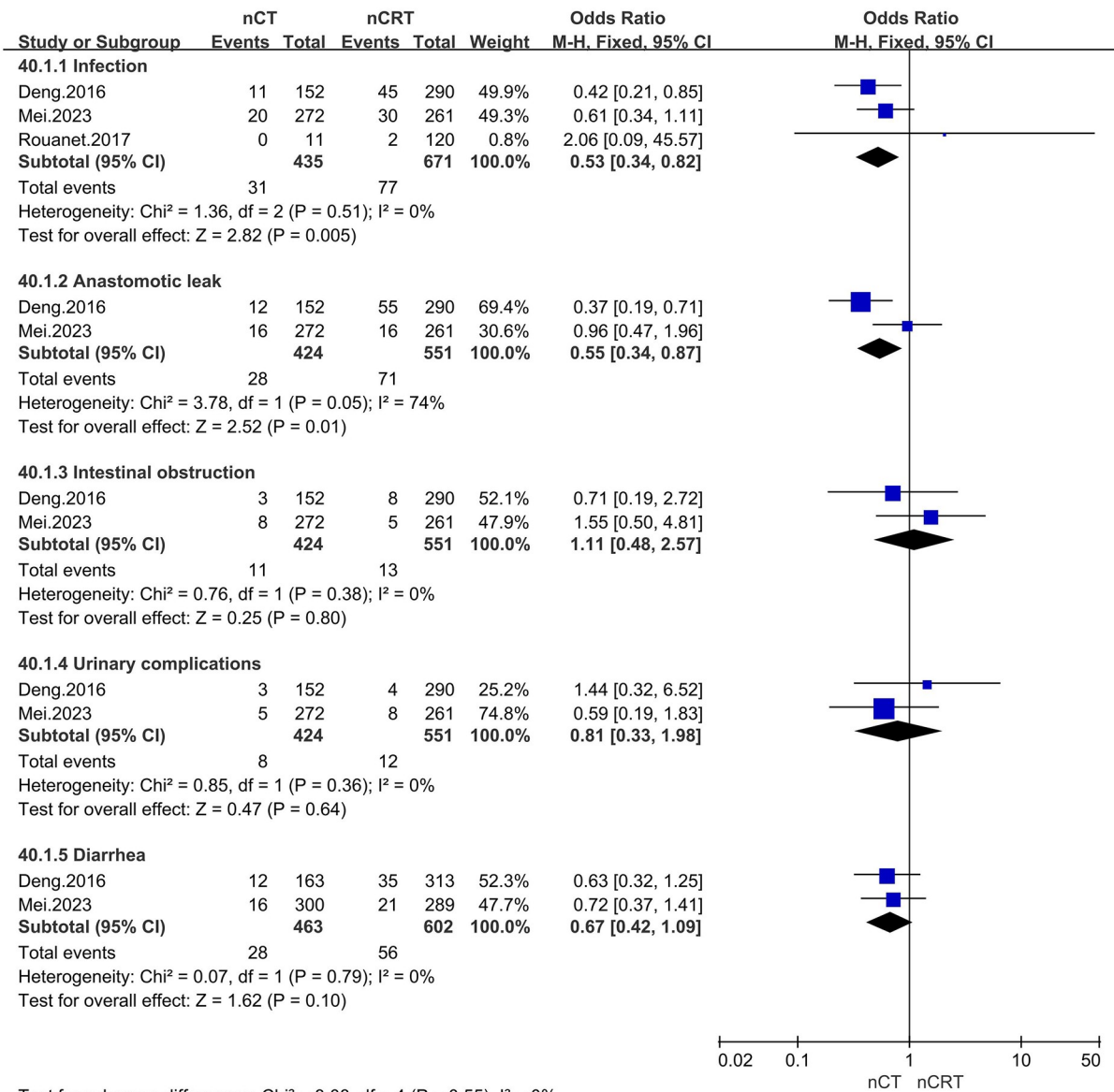


Figure 3. Summary forest plot of infection, anastomotic leak, intestinal obstruction, urinary complications, and diarrhea was compared using the odds ratio.

bowel movements, including faecal or flatus incontinence, frequent bowel movements, clustering, and urgency^[36,37]. The various toxicities mentioned above might reduce patients' tolerance to subsequent adjuvant chemotherapy. Radiotherapy also significantly reduced the patients' perioperative quality of life.

A significant decrease in pathological tumor staging in patients after neoadjuvant therapy and TME surgery often indicates a lower rate of LR and a good prognosis for survival. Several multicenter, large-scale RCTs reported their results. The FOWARC study demonstrated an improvement in pCR with the addition of oxaliplatin to nCRT. The researchers reported a decrease in the percentage of patients with tumors downstaging to 0-I (35.5% vs. 37.1% vs. 56.4%) and a decrease in the pCR rate (6.6% vs. 14.0% vs. 27.5%) in the mFOLFOX6 groups vs. fluorouracil-radiotherapy groups vs. mFOLFOX6-radiotherapy groups^[9], which was similar to the results reported

by Zheng *et al*^[38]. The pathological results of the fluorouracil or mFOLFOX6-radiotherapy groups were slightly superior to those of the mFOLFOX6 alone group; These results suggest that the superposition of radiotherapy can improve the pCR rate and tumor regression. However, the acute toxicity events increased accordingly, and the DFS, OS, and LR did not improve with or without radiotherapy^[26]. Jiao *et al* reported a significant improvement in distant metastasis with the addition of oxaliplatin (fluorouracil-radiotherapy vs. oxaliplatin + fluorouracil-radiotherapy; 16.50% vs. 28.16%, *P* = 0.045)^[39]. Chemotherapy might be a potentially worthwhile treatment option because it ensures that tumour progression is not inferior to that of nCRT and reduces toxicity and complication rates. The CONVERT study reported rates of downstaging (40.8%) and pCR (11.0%) in the CAPOX group, which were 45.6% and 13.8%, respectively^[27]. The rates of downstaging and pCR were comparable to those of patients in the

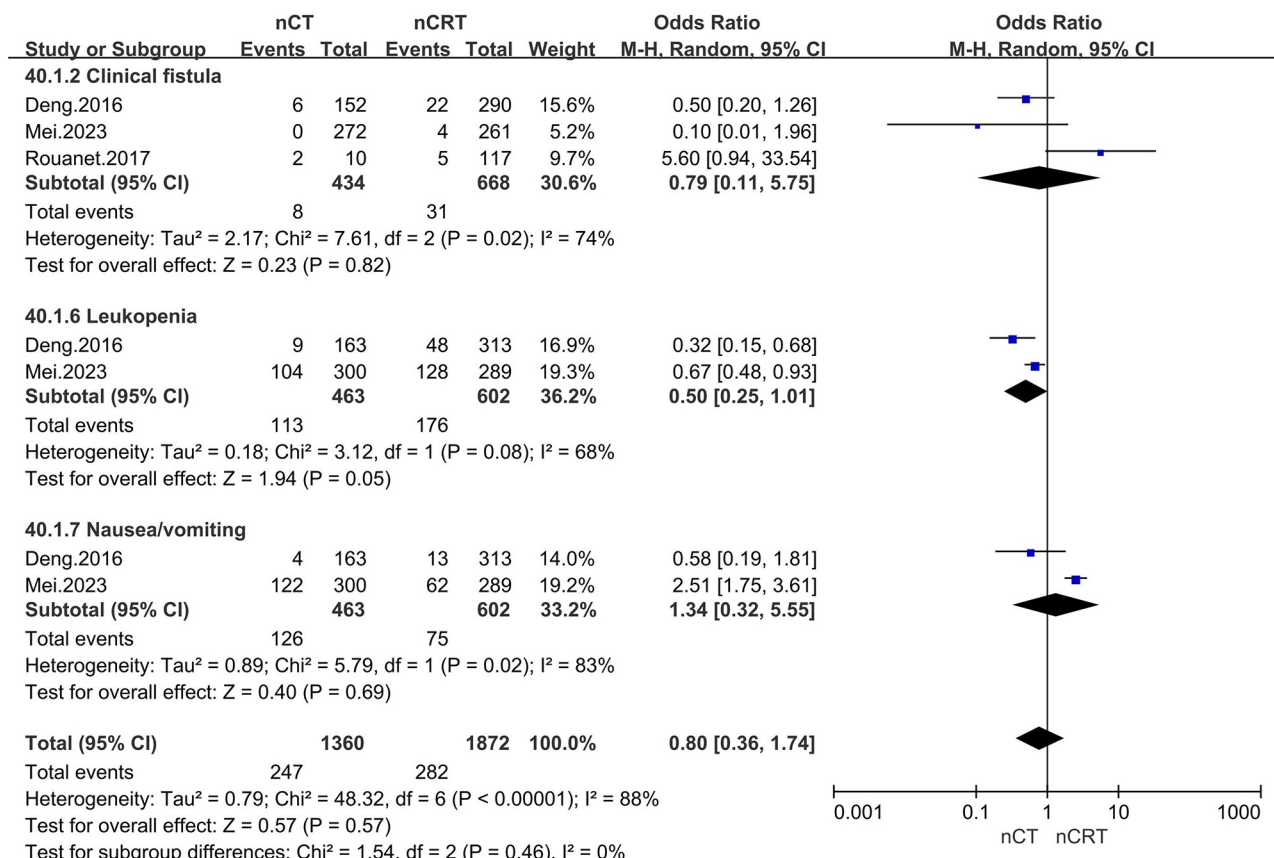


Figure 3a.

capecitabine-radiotherapy group. Patients with mesorectal fascia (MRF) invasion who might benefit from nCRT were excluded. Yamamoto *et al* verified that nCT alone was associated with increased LR compared with nCRT for patients with MRF invasion, emphasizing the importance of combined radiotherapy^[40–42].

In the pre-TME years, the LR of rectal cancer patients was approximately 15–45% and was mainly concentrated in the central, perianastomotic, and anterior parts, and the increase in multimodal therapies, including nCRT, was observed. The recurrence rate decreased to 5–10% and shifted to the lateral and posterior

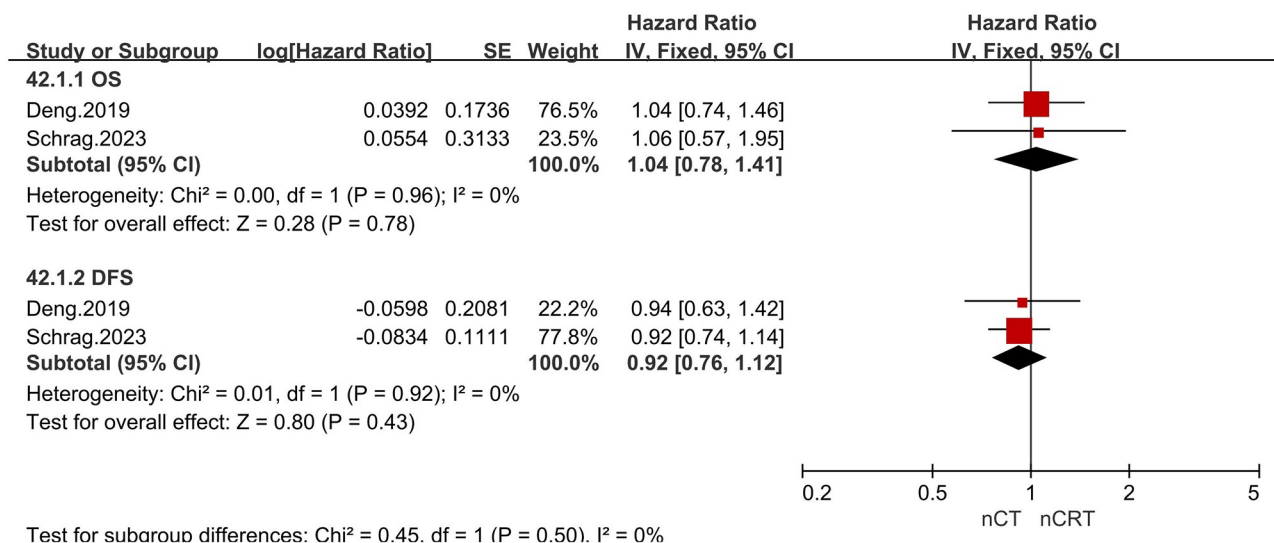


Figure 4. Summary forest plot of OS and DFS was compared using the hazard ratio; OS, overall survival; DFS, disease-free survival.

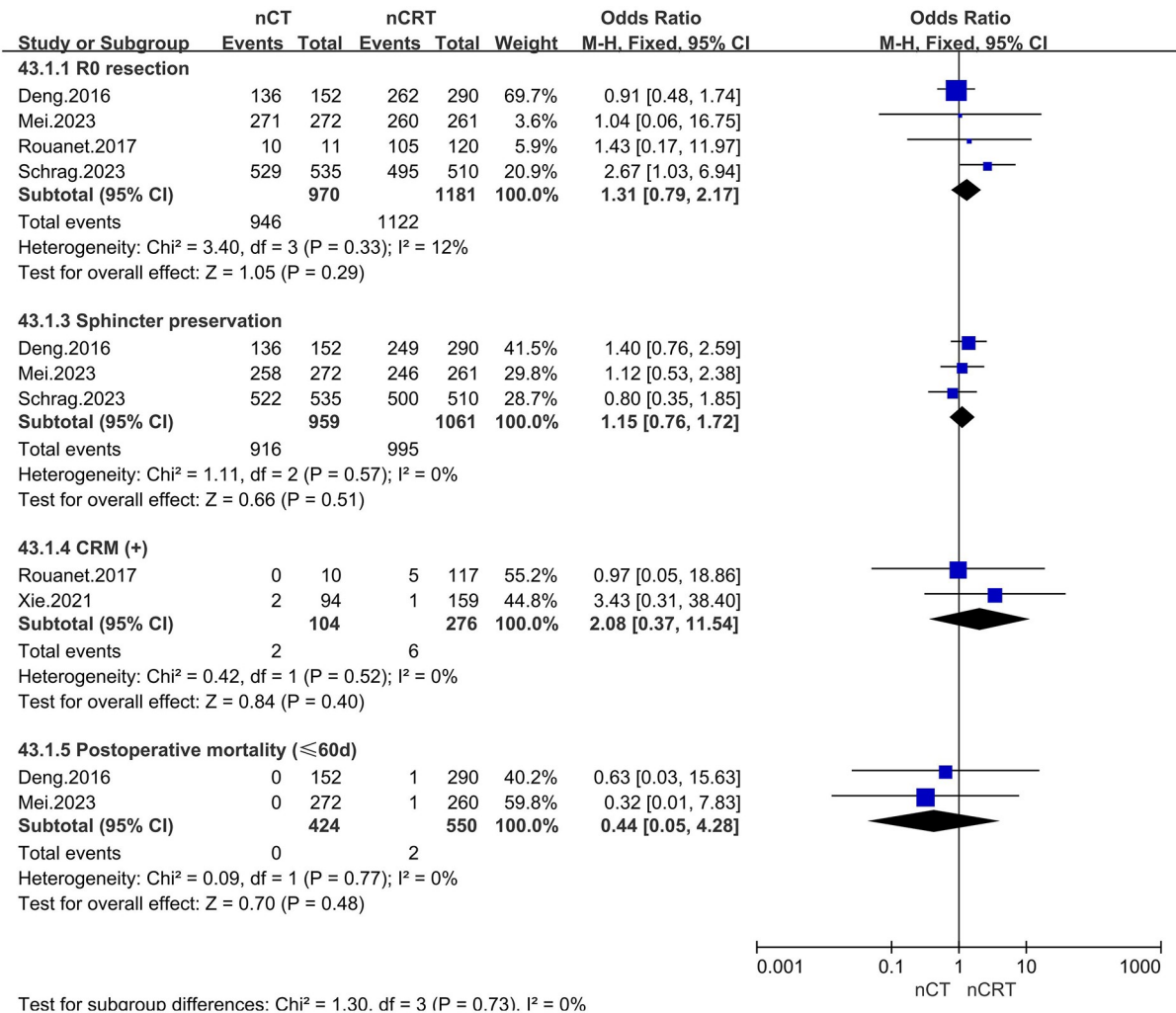


Figure 5. Summary forest plot of R0 resection, sphincter preservation, CRM (+), and postoperative mortality (≤ 60 d) was compared using the odds ratio; CRM: circumferential margin.

(presacral) forms^[43]. Xie *et al* reported similar tumor downstaging to 0-I (46.8% vs. 50.9%), with undifferentiated DFS and LR in the nCT and nCRT groups, respectively. In addition, these researchers specifically analyzed the 5-year local pelvic rate (LPR) with almost no difference ($P = 0.051$) between the two groups and concluded that radiotherapy did not solve the problem of lateral recurrence^[30]. In a recent RCT, Schrag *et al* reported an analogous rate of pCR, 21.9% in the nCT group, and 24.3% in the nCRT group, with similar LR and OS rates^[19]. It should be noted that these studies excluded patients with T4 stage disease, low-lying tumors, and at least four pelvic lymph nodes with a short axis > 10 mm, which led to higher and similar pCR rates. Therefore, in some patients with stage II-III LARC, especially patients with stage T4 disease, low tumors, and definite pelvic lateral lymph node metastasis, additional radiotherapy is still required to ensure tumor regression. We need more effective tumor retraction and anal sparing to avoid resection in these patients.

Meta-analysis results showed better tumor regression in the nCRT group. However, there was no significant difference in the R0 resection rate between the two groups. We speculate that with

the improvement and popularization of laparoscopic and robotic surgery, and the popularization of TME and regional lymph node dissection concepts, the improvement of related technologies can overcome the impact of inconsistent tumor regression between the two groups, so that there is no significant difference in the R0 resection rate between the two groups. TME surgery after nCT may completely remove the tumor, negating the slight advantage of this preoperative nCRT. We hypothesized that these factors contributed to similar DFS and OS in both groups.

In addition to the adverse events reported in our article, Huang *et al* performed a study comparing the efficacy of nCT and nCRT on erectile and urinary function in men with rectal cancer and verified that the addition of radiotherapy was an obvious risk factor for urinary and sexual dysfunction^[44]. Moreover, pelvic radiation therapy can cause late complications, such as pelvic fracture and second cancers^[45], which can affect the patient's ability to receive chemotherapy during recurrence^[46]. Currently, it is unclear whether most patients with stage II-III LARC need additional radiotherapy. After all, the benefits of additional radiotherapy do not significantly improve. In contrast, the side effects and medical resource consumption are greater, and we should

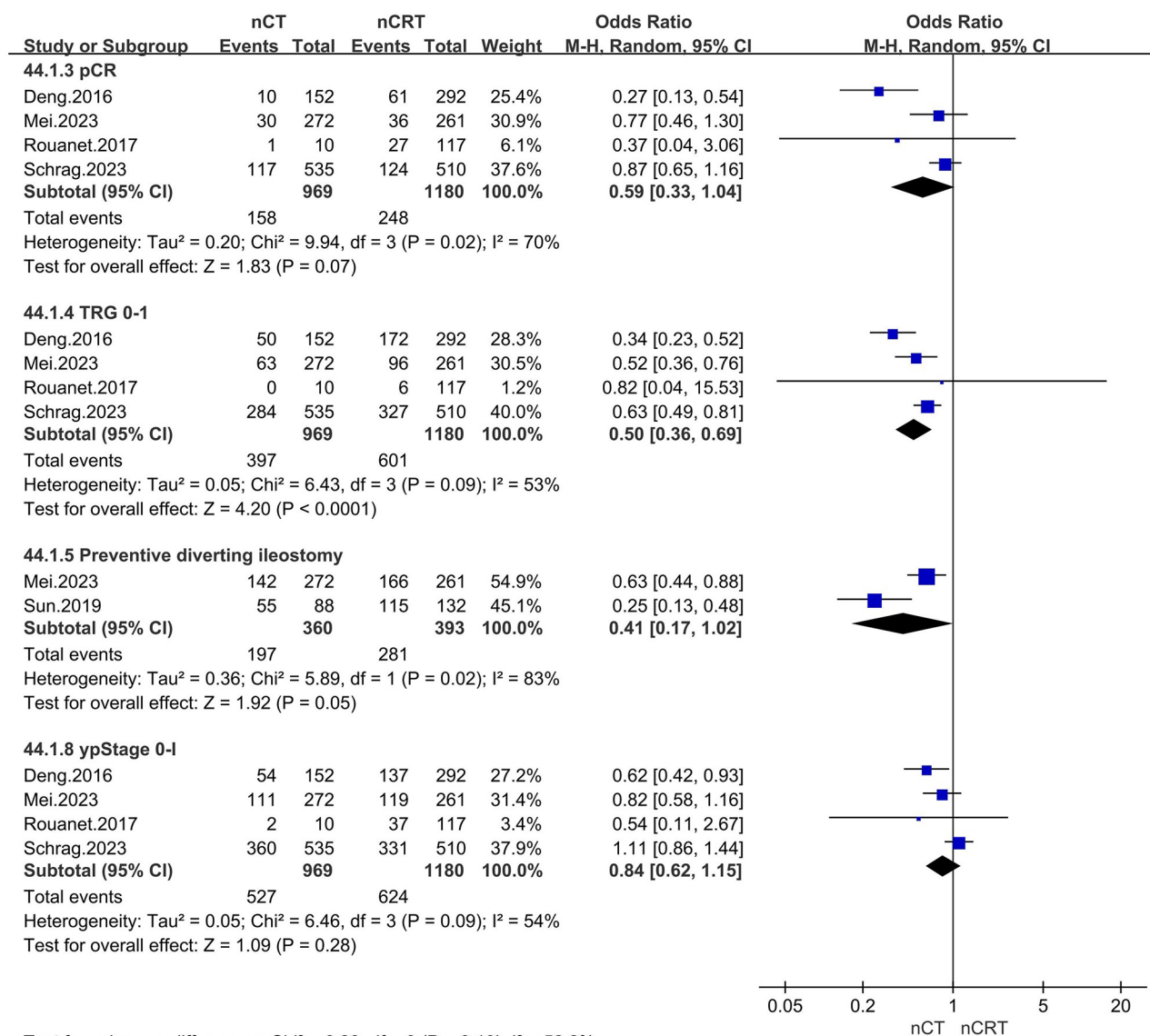


Figure 5a.

select people who truly need radiotherapy from this group of patients so that they can receive more benefits through radiotherapy. Identifying patients with high-risk factors and improving treatment outcomes through radiotherapy, targeted therapy, and comprehensive neoadjuvant therapy is expected to increase the accuracy of LARC treatment options in the future.

Limitations

There were several limitations that need to be carefully explained in our study. First, the sample size was relatively insufficient, with seven articles containing 2706 patients. Second, the detailed preoperative chemotherapy project and the radiation dose should be standardized to reduce bias and potential differences due to different neoadjuvant therapies. Finally, the LR has always been a key point of LARC, but few

articles have statistically analyzed the results, and more RCT studies are needed to further validate this finding. It is worth noting that radiotherapy cannot be ignored for some patients who need to ensure the conversion effect of neoadjuvant therapy and strongly request to preserve organ function.

Conclusion

Our study indicated that although the nCRT group showed some superiority in terms of tumor degradation, nCT was not inferior to nCRT in terms of OS and DFS. Furthermore, a series of complications caused by radiotherapy significantly reduced the quality of life of patients and increased the waste of medical resources. “Less is more.” Preoperative nCT is expected to become the standard treatment option for most patients with stage II-III LARC.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author's contribution

D.-x.Z., R.-n.L., and P.Z. contributed to the acquisition, analysis and interpretation of data, and the composition of the article; X.-k.R. *et al* collected and organized data, revised the article, and gave final approval; J.-w.X. contributed to conception, design, critical revision, and final approval of the study.

Conflicts of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

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Data availability statement

No other datasets were generated during and/or analyzed during the current study. All the information is available with the manuscript.

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