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Peer Reviewer of *World Journal of Gastrointestinal Surgery*, Deven Juneja, DNB, FNB, EDIC, FCCP, Director, Department of Critical Care Medicine, Max Super Speciality Hospital, New Delhi 110017, India. devenjuneja@gmail.com

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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META-ANALYSIS

# Compare clinical efficacy and safety of neoadjuvant therapy and neoadjuvant chemoradiotherapy for locally advanced rectal cancer: Meta-analysis

Ying Wang, Yan Yang, Qi-Qi Liu, Shao-Zhao Wang

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**Ying Wang,** Department of Anus Intestinal Surgery, Feicheng People's Hospital, Feicheng 271600, Shandong Province, China

**Yan Yang,** Department of Gastroenterology, Qingdao Hospital of University of Health and Rehabilitation Sciences (Qingdao Municipal Hospital), Qingdao 266011, Shandong Province, China

**Qi-Qi Liu,** Department of Gastrointestinal Surgery, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong Province, China

**Shao-Zhao Wang,** Department of Anorectal Words, Central Hospital Affiliated Shandong First Medical University, Jinan 250013, Shandong Province, China

**Corresponding author:** Shao-Zhao Wang, MM, Doctor, Department of Anorectal Words, Central Hospital Affiliated Shandong First Medical University, No. 105 Jiefang Road, Jinan 250013, Shandong Province, China. wangsztcm@163.com

## Abstract

### *BACKGROUND*

To compare the efficacy and safety of total neoadjuvant therapy (TNT) and neoadjuvant chemoradiotherapy (nCRT) in the treatment of middle and low locally advanced rectal cancer. Our study will systematically collect and integrate studies to evaluate the ability of these two treatments to improve tumor shrinkage rates, surgical resection rates, tumor-free survival, and severe adverse events.

### *AIM*

To provide clinicians and patients with more reliable treatment options to optimize treatment outcomes and quality of life for patients with locally advanced rectal cancer by comparing the advantages and disadvantages of the two treatment options.

### *METHODS*

A full search of all clinical studies on the effectiveness and safety of TNT and nCRT for treating locally advanced rectal cancer identified in Chinese (CNKI, Wanfang, China Biomedical Literature Database) and English (PubMed, Embase) databases was performed. Two system assessors independently screened the studies according to the inclusion and exclusion criteria. Quality evaluation and

data extraction were performed for the included literature. We used RevMan 5.3 software to perform a meta-analysis of the pathologic complete response (pCR) rate, T stage degradation rate, resection 0 (R0) rate, anal grade 3/4 acute toxicity rate, perioperative complications, overall survival (OS), and disease-free survival (DFS) in the TNT and nCRT groups.

***RESULTS***

Finally, 14 studies were included, six of which were randomized controlled studies. A total of 3797 patients were included, including 1865 in the TNT group and 1932 in the nCRT group. The two sets of baseline data were comparable. The results of the meta-analysis showed that the pCR rate [odds ratio (OR) = 1.57, 95% confidence interval (CI): 1.30-1.90, $P < 0.00001$], T stage degradation rate (OR = 2.16, 95%CI: 1.63-2.57, $P < 0.00001$), and R0 resection rate (OR = 1.42, 95%CI: 1.09-1.85, $P = 0.009$) were significantly greater in the nCRT group than in the nCRT group. There was no significant difference in the incidence of grade 3/4 acute toxicity or perioperative complications between the two groups. The 5-year OS [hazard ratio (HR) = 0.84, 95%CI: 0.69-1.02, $P = 0.08$] and DFS (HR = 0.94, 95%CI: 0.03-1.39, $P = 0.74$) of the TNT group were similar to those of the nCRT group.

***CONCLUSION***

TNT has greater clinical efficacy and safety than nCRT in the treatment of locally advanced rectal cancer.

**Key Words:** Neoadjuvant therapy; Neoadjuvant chemoradiotherapy; Advanced rectal cancer; Clinical efficacy; Meta-analysis



**Core Tip:** The main aim of this study was to perform a meta-analysis and compare the clinical efficacy and safety of neoadjuvant therapy and neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. We will collect and synthesize relevant research data to evaluate the performance of the two treatments in terms of the tumor shrinkage rate, surgical resection rate, tumor-free survival rate and other clinical indicators and analyze the safety differences between the two treatments in terms of the incidence of serious adverse events and other aspects. Through in-depth exploration of the advantages and disadvantages of the two treatment schemes, the aim is to provide more guiding treatment suggestions for clinicians to optimize the choice of treatment schemes for patients and improve the treatment effect and quality of life.

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## INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy are the standard treatment strategies for low- and medium-locally advanced rectal cancer[1]. The diagnosis and treatment mode of "nCRT + TME + postoperative adjuvant chemotherapy" have significantly improved the local control rate of tumors, and the local recurrence rate of rectal cancer after surgery has decreased from 35% to 5%-10%, but the distant metastasis rate is still as high as 25%-30%, and it is the main factor affecting the survival prognosis. The CAO/ARO/AIO-94 study and the EORTC22921 study both showed that nCRT did not improve the long-term survival prognosis of patients with rectal cancer, and patients' compliance with postoperative adjuvant chemotherapy was poor[2-5].

To further reduce the rate of distant metastasis in patients with rectal cancer and improve survival, some scholars have proposed an "intensive treatment" program[6]. One is to increase the dose of radiotherapy, and the second is to add another cytotoxic drug, such as oxaliplatin, to the 5-fluorouracil-based synchronous chemotherapy regimen[7]. The third is postoperative adjuvant chemotherapy before TME, that is, total neoadjuvant therapy (TNT). TNT has two modes of induction chemotherapy, in which several cycles of systemic chemotherapy are administered before nCRT and consolidation chemotherapy is administered between nCRT and the TME. The National Comprehensive Cancer Care Consortium listed TNT as one of the recommended treatment strategies for locally advanced rectal cancer[8-10]. This study aimed to determine how well TNTs work and how long people are likely to live. The safety and effectiveness of TNT and nCRT for treating low to medium locally advanced rectal cancer will be compared.

## MATERIALS AND METHODS

### Document inclusion criteria

Literature type: Clinical studies related to TNT in the treatment of locally advanced rectal cancer, limited to Chinese and English; study subjects: Patients with middle and low locally advanced rectal cancer confirmed by colonoscopy pathology; intervention measures: Experimental group received TNT, control group received nCRT; outcome measures: (1) Main index: Pathologic complete response (pCR) rate, R0 resection rate, incidence of grade 3/4 acute toxicity, 5-year overall survival (OS) and disease-free survival (DFS); and (2) Secondary index: Tumor down phase rate, anal preservation rate, perioperative complication rate, local recurrence and distant metastasis rate, *etc*.

### Document exclusion criteria

Single-arm study; reviews, case reports or summaries of meetings; biological therapy, such as cetuximab, bevacizumab, *etc*.; no studies on any of these outcomes.

### Search strategy

Chinese databases (CNKI, Wanfang, China Biomedical Literature Database) and English databases (PubMed, Embase) were comprehensively searched. The search strategy used was "neoadjuvant chemoradiotherapy" OR "total neoadjuvant therapy" OR "induction therapy" OR "consolidation therapy" AND "rectal cancer" OR "rectal tumor". To avoid bias caused by language limitations, this study searched both English studies. To avoid missing relevant studies, relevant references listed in the articles and conference abstracts found in the search were traced (Figure 1).

### Data collection and data extraction

Literature screening was performed by two independent researchers according to the inclusion and exclusion criteria[11-14]. Disagreements over the search results were resolved through discussion. If there was still a dispute after negotiation, it was resolved by a third researcher[15]. Data extraction was carried out in strict accordance with the designed table[16]. The main contents included author, publication year, country, study type, baseline data, observation indicators, *etc.*

### Literature quality evaluation

The quality of randomized controlled studies was assessed using bias assessment tools recommended by the Cochrane Collaboration, including six aspects: Randomization, assignment concealment, blindness, integrity of results, selective reporting of findings, and other sources of bias. Each indicator was evaluated as "low risk", "unclear" or "high risk". The Newcastle-Ottawa Scale (NOS) was selected for the methodological evaluation of nonrandomized controlled studies[17-20]. The evaluation included four aspects: Population selection, comparability, exposure and result evaluation. The NOS uses a semiquantitative star system, with a full score of 9 stars and a score greater than 5 points included in the analysis [21].

### Bias analysis

Heterogeneity between studies was assessed using $I^2$ statistics, with 25%, 50%, and 75% representing low, medium and high heterogeneity, respectively; $I^2 < 50\%$ and $P > 0.1$ between studies using fixed effect models; and $I^2 > 50\%$ and $P < 0.1$ from $\chi^2$ analysis indicating study heterogeneity[22-24]. Meta-analysis by random effects models was performed, and possible heterogeneity was determined by subgroup analysis. The sensitivity analysis removed the included studies one by one to determine whether the pooled effect values were stable or reliable.

### Statistical analysis

The Cochrane Collaboration provided RevMan 5.3 software for the statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) of the binary measurement data were calculated. The hazard ratio (HR) and 95%CI of the survival data were calculated. For heterogeneity tests, the statistics $I^2$ and $Q$ tests were selected. An $I^2 > 0.5$ indicated that the heterogeneity was high, and a random effects model was selected. If $I^2 < 0.5$, the fixed effects model was chosen. A funnel plot was constructed for publication-offset analysis of the included studies. $P < 0.05$ indicated that the difference was statistically significant.

## RESULTS

### Literature retrieval results and included research characteristics

A total of 14 studies meeting the criteria were included in the study, including 6 randomized controlled studies, 5 retrospective case-control studies, and 3 prospective studies (Figure 1). A total of 3797 patients with rectal cancer were included, including 1865 in the TNT group and 1932 in the nCRT group. The general characteristics of the included studies are shown in Table 1, and the chemoradiotherapy protocols adopted in each study are shown in Table 2. The quality evaluation results of randomized controlled studies are shown in Figure 2, and the quality evaluation scores of nonrandomized controlled studies were no less than 5 points.

**Table 1 General characteristics of included studies**

| Ref. | Country | Study type | Cases | Sample size | | Inclusion in research quality evaluation |
|---|---|---|---|---|---|---|
| | | | | TNT | nCRT | |
| Garcia-Aguilar *et al*[9], 2015 | America | Prospective study | 259 | 199 | 60 | 6 |
| Zhai *et al*[11], 2020 | China | Retrospective study | 134 | 79 | 55 | 6 |
| Cercek *et al*[12], 2018 | America | Retrospective study | 628 | 308 | 320 | 8 |
| Markovina *et al*[13], 2017 | America | Prospective study | 138 | 69 | 69 | 6 |
| Zhu *et al*[14], 2019 | America | Retrospective study | 1079 | 372 | 707 | 8 |
| Fernandez-Martos *et al*[15], 2015 | America | Randomized controlled study | 103 | 54 | 49 | 7 |
| Maréchal *et al*[18], 2012 | Belgium | Randomized controlled study | 57 | 28 | 29 | 8 |
| Calvo *et al*[19], 2014 | Spain | Retrospective study | 335 | 207 | 128 | 7 |
| Bhatti *et al*[20], 2015 | Pakistan | Retrospective study | 154 | 93 | 61 | 7 |
| Bujko *et al*[21], 2016 | Poland | Randomized controlled study | 515 | 261 | 254 | 8 |
| Kim *et al*[22], 2018 | South Korea | Randomized controlled study | 110 | 54 | 56 | 7 |
| Liang *et al*[23], 2019 | China | Prospective study | 156 | 76 | 80 | 5 |
| Moore *et al*[24], 2017 | Australia | Randomized controlled study | 49 | 25 | 24 | 8 |
| Wu *et al*[25], 2022 | China | Randomized controlled study | 80 | 40 | 40 | 8 |

TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy.

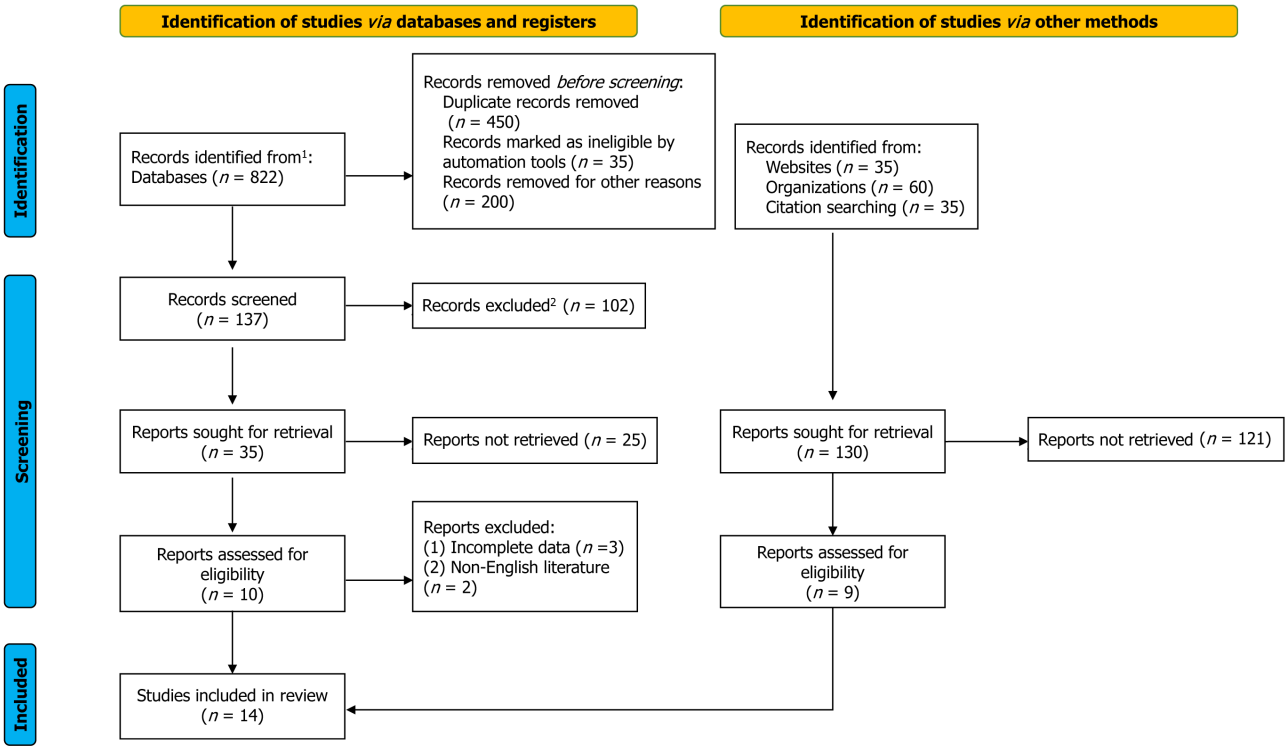



**Figure 1 Flow chart of the literature screening.** [1]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). [2]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

### *TNT safety evaluation analysis*

**Grade 3/4 acute toxic reactions:** A total of 10 studies reported the incidence of grade 3/4 acute toxic reactions during the TNT or nCRT stage[9,11,13,15,18,19,21-23,25]. There was great heterogeneity among the studies ($I^2$ = 80%), so the random effects model was selected. The results of the meta-analysis showed that there was no significant difference in the incidence of grade 3/4 acute toxicity between the TNT group and the nCRT group (OR = 0.79, 95%CI: 0.47-1.32, $P$ = 0.36) (Figure 3A).

**Perioperative complications:** A total of 10 studies reported perioperative complications[7,11,15-19,21,23,24]. There was little heterogeneity among the studies ($P$ = 0.62, $I^2$ = 0%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in the incidence of perioperative complications between the two groups (OR = 1.02, 95%CI: 0.78-1.33, $P$ = 0.87) (Figure 3B).

### *Evaluation of the perioperative efficacy of TNT*

**pCR rate analysis:** A total of 14 studies used pCR as the main outcome index[11-18,20-25]. There was little heterogeneity among the studies ($P$ = 0.54, $I^2$ = 0%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the pCR rate in the TNT group was significantly greater than that in the nCRT group (OR = 1.57, 95%CI: 1.30-1.90, $P$ < 0.00001) (Figure 3C).

**Analysis of the tumor downphase rate:** A total of 6 studies reported the T stage regression rate[13,18,19,22,23,25]. There was little heterogeneity among the studies ($P$ = 0.26, $I^2$ = 24%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the T stage decline rate in the TNT group was significantly greater than that in the nCRT group (OR = 2.16, 95%CI: 1.63-2.57, $P$ < 0.00001) (Figure 3D).

**R0 removal rate analysis:** A total of 14 studies reported R0 removal rates after TNT or nCRT[7,11,14-25]. There was little heterogeneity among the studies ($P$ = 0.10, $I^2$ = 38%), and the fixed-effects model was chosen. The results of the meta-analysis showed that the R0 removal rate in the TNT group was significantly greater than that in the nCRT group (OR = 1.42, 95%CI: 1.09-1.85, $P$ = 0.009) (Figure 3E).

**Anal retention rate analysis:** A total of 14 studies reported anal preservation rates after TNT or nCRT[7,11-13,15-24]. There was little heterogeneity among the studies ($P$ = 0.08, $I^2$ = 41%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in the anal preservation rate between the TNT and nCRT groups (OR = 0.99, 95%CI: 0.82-1.19, $P$ = 0.88) (Figure 3F).

### *TNT survival prognosis analysis*

**Analysis of local recurrence and distant metastasis:** Local recurrence and distant metastasis were reported in four studies each during the follow-up period[16,20,23,25], as was distant metastasis[16,20,22,25]. There was little heterogeneity among the studies (both $I^2$ = 0%), and the fixed-effects model was selected. The results of the meta-analysis showed that there was no statistically significant difference in local recurrence rates between the TNT group and the nCRT group (OR = 0.89, 95%CI: 0.47-1.69; $P$ = 0.73) (Figure 3G). The rates of distant metastasis were similar between the two groups (OR = 1.11, 95%CI: 0.81-1.52; $P$ = 0.5) (Figure 3H).

**OS and DFS analysis:** Seven studies reported 5-year OS in both groups[13-15,20,21,23,25]. There was little heterogeneity among the studies ($P$ = 0.24, $I^2$ = 25%), and the fixed-effects model was chosen. The results of the meta-analysis showed that there was no significant difference in 5-year OS between the TNT group and the nCRT group (HR = 0.84, 95%CI: 0.69-1.02; $P$ = 0.08) (Figure 4A). Four studies reported 5-year DFS in the TNT and nCRT groups[13,15,20,23]. There was little heterogeneity among the studies ($P$ = 0.95, $I^2$ = 0%), and the fixed-effects model was selected. Meta-analysis revealed no significant difference in 5-year DFS between the two groups (HR = 0.94, 95%CI: 0.03-1.39, $P$ = 0.74) (Figure 4B).

**Literature publication bias analysis:** A funnel plot was used to analyze the publication bias of the included studies for each outcome index, and it was found that the distributions on both sides of the funnel plot were basically symmetrical with no significant publication bias, indicating good stability. Taking pCR as an example, the funnel plot of the 4 included studies was basically distributed within the 95%CI, indicating no significant publication bias (Figure 5).

## DISCUSSION

A number of studies have shown that TNT can significantly improve the treatment compliance of rectal cancer patients; increase the pCR rate, tumor down phase rate, and R0 resection rate; increase the anal preservation rate and organ retention rate; eliminate occult micrometastases; shorten the duration of surgery; and further reduce the rate of local recurrence and distant metastasis by increasing the local control of tumors[26-28]. In addition, these treatments improve long-term survival outcomes. In this study, the pCR rate, R0 removal rate, and T stage degradation rate in the TNT group were significantly greater than those in the nCRT group, while the incidences of grade 3/4 acute toxic reactions and perioperative complications were similar to those in the nCRT group[29]. There were no significant differences in the local recurrence rate, distant metastasis rate, 5-year OS, or DFS between the two groups. Compared with nCRT, TNT did not significantly increase the rate of grade 3/4 acute toxic reactions or perioperative complications[30]. The incidence of grade 3/4 acute toxic reactions reported during TNT treatment ranged from 4% to 55%, mainly diarrhea and hematological toxicity (neutropenia, thrombocytopenia, *etc.*). Overall, the incidence of toxic reactions with TNT (27%) was similar

**Table 2 Radiochemotherapy regimens and specific doses for total neoadjuvant therapy and neoadjuvant chemoradiotherapy groups**

| Ref. | TNT | | | nCRT | |
|---|---|---|---|---|---|
| | IT/CT | Chemotherapy | Dose | Radiation therapy | Synchronous chemotherapy |
| Garcia-Aguilar *et al* [9], 2015 | CT | mFOFLOX | 5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m$^2$ | 45.0 Gy/25 f | 5-FU 225 mg/m$^2$ |
| Zhai *et al*[11], 2020 | CT | CAPEOX | CAP 1000 mg/m²; OX 130 mg/m$^2$ | 50.4 Gy/28f | CAP 850 mg/m² |
| Cercek *et al*[12], 2018 | IT | mFOFLOX | 5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m² | 45.0 Gy/25 f | 5-FU 225 mg/m²/CAP 850 mg/m² |
| Markovina *et al*[13], 2017 | IT | mFOFLOX FOFLOX | 5-FU/LV/OX | 45.0 Gy/25 f, 45.0 Gy/25 f | 5-FU/CAP |
| Zhu *et al*[14], 2019 | IT | CAPEOX | | 50.4 Gy/25-28 f | |
| Fernandez-Martos *et al* [15], 2015 | IT | CAPEOX | CAP/OX | 45.0 Gy/25 f | CAP |
| Maréchal *et al*[18], 2012 | IT | mFOFLOX | 5-FU 400 mg/m²; LV 400 mg/m²; OX 100 mg/m² | 45.0 Gy/25 f | 5-FU 225 mg/m² |
| Calvo *et al*[19], 2014 | IT | mFOFLOX | 5-FU 400 mg/m²; LV 200 mg/m²; OX 85 mg/m$^2$ | 45.0 Gy/25 f | 5-FU 425 mg/m$^2$ |
| Bhatti *et al*[20], 2015 | IT | CAPEOX | CAP 1000 mg/m²; OX 130 mg/m² | 50.4 Gy/25-28 f | CAP 825 mg/m² |
| Bujko *et al*[21], 2016 | CT | mFOFLOX | 5-FU/LV/OX | 50.4 Gy/25-28 f | 5-FU 325 mg/m²/LV 20 mg/m² |
| Kim *et al*[22], 2018 | CT | CAPEOX, CAPEOX | CAP 1700 mg/m²; OX 100 mg/m² | 50.4 Gy/25-28 f | CAP |
| Liang *et al*[23], 2019 | CT | FOFLOX | CAP 1000 mg/m²; OX 130 mg/m²; 5-FU 400 mg/m²; LV 400 mg/m²; OX 85 mg/m$^2$ | 50.4 Gy/25-28 f | CAP 825 mg/m² |
| Moore *et al*[24], 2017 | CT | 5-FU/LV | 5-FU 450 mg/m²; LV 50 mg/m$^2$ | 45.0 Gy/25 f | 5-FU 225 mg/m² |
| Wu *et al*[25], 2022 | CT | FOFLOX | 5-FU 400 mg/m²; LV200 mg/m²; OX 85 mg/m² | 50.4 Gy/25-28 f | 5-FU 225 mg/m$^2$ |

IT: Immunotherapy; CT: Chemotherapy; TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; 5-FU: 5-fluorouracil; CAPEOX: Capecitabine; CAP: Community-acquired pneumonia; OX: Oxaliplatin; LV: Leucovorin; FOFLOX: Fluorouracil, oxaliplatin, leucovorin; mFOFLOX: Modified fluorouracil, oxaliplatin, leucovorin.

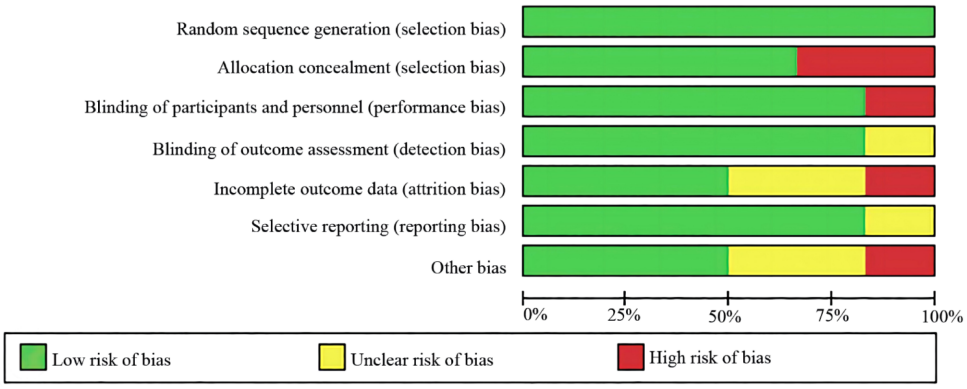


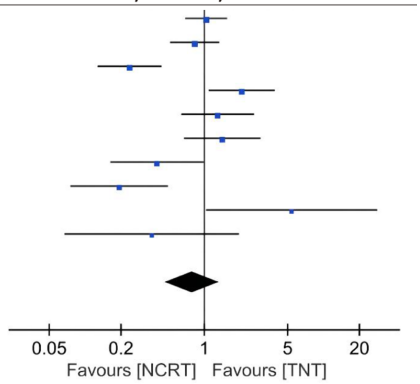

**Figure 2 Risk of bias graph of the literature quality evaluation chart.**

to that with nCRT (31%). Some studies also reported that the incidence of toxic side effects of TNT is lower, possibly because patients have not yet received surgical treatment, the body's immune system and general condition are better, and the tolerance of systemic chemotherapy is better[31-34]. The results of this study revealed that the incidence of perioperative complications in the TNT group was similar to that in the nCRT group, which was consistent with the conclusions of most studies. Among these complications, incision complications and anastomosis-related complications (anastomotic leakage and anastomotic stenosis) were more common[35]. The above studies indicate that the safety of TNT and nCRT is comparable and that TNT may achieve better oncological efficacy without increasing the incidence of toxic

**A**

| Study or subgroup | TNT Events | TNT Total | NCRT Events | NCRT Total | Weight | Odds ratio M-H, random, 95%CI |
|---|---|---|---|---|---|---|
| Bujko et al.2016 | 62 | 256 | 61 | 259 | 12.7% | 1.04 [0.69, 1.56] |
| Calvo et al.2014 | 60 | 208 | 42 | 128 | 12.3% | 0.83 [0.52, 1.34] |
| Garcia et al.2015 | 38 | 199 | 30 | 60 | 11.5% | 0.24 [0.13, 0.44] |
| Liang et al.2019 | 42 | 76 | 30 | 80 | 11.4% | 2.06 [1.09, 3.90] |
| Markovina et al.2019 | 26 | 69 | 22 | 69 | 11.0% | 1.29 [0.64, 2.61] |
| Zhai Zhiwei, et al.2020 | 29 | 79 | 16 | 55 | 10.7% | 1.41 [0.67, 2.96] |
| Li Leilei, et al.2017 | 15 | 40 | 24 | 40 | 9.7% | 0.40 [0.16, 0.98] |
| Fernandez et al.2015 | 10 | 54 | 20 | 37 | 9.4% | 0.19 [0.08, 0.50] |
| Maréchal et al.2012 | 8 | 28 | 2 | 29 | 5.7% | 5.40 [1.03, 28.23] |
| Kim et al.2018 | 2 | 55 | 5 | 53 | 5.6% | 0.36 [0.07, 1.95] |
| **Total (95% *CI*)** | | **1064** | | **810** | **100.0%** | **0.79 [0.47, 1.32]** |
| Total events | 292 | | 252 | | | |

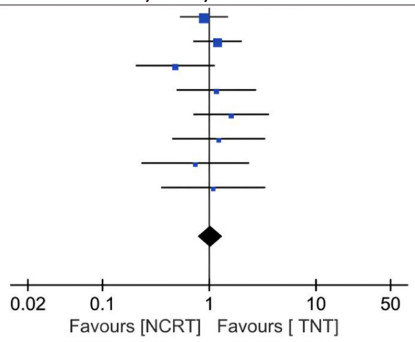
Heterogeneity: Tau² = 0.51; Chi² = 45.94, *df* = 9 (*P* < 0.00001); $I^2$ = 80%
Test for overall effect: *Z* = 0.91 (*P* = 0.36)




**B**

| Study or subgroup | TNT Events | TNT Total | NCRT Events | NCRT Total | Weight | Odds ratio M-H, fixed, 95%CI |
|---|---|---|---|---|---|---|
| Bujko et al.2016 | 35 | 178 | 37 | 172 | 27.9% | 0.89 [0.53, 1.50] |
| Calvo et al.2014 | 52 | 207 | 28 | 128 | 24.0% | 1.20 [0.71, 2.02] |
| Garcia et al.2015 | 15 | 199 | 10 | 69 | 12.7% | 0.48 [0.21, 1.13] |
| Liang et al.2019 | 13 | 76 | 12 | 80 | 9.0% | 1.17 [0.50, 2.75] |
| Fernandez et al.2015 | 24 | 52 | 16 | 46 | 8.5% | 1.61 [0.71, 3.63] |
| Zhai zhiwei,et al.2020 | 12 | 79 | 7 | 55 | 6.5% | 1.23 [0.45, 3.35] |
| Maréchal et al.2012 | 7 | 28 | 9 | 29 | 6.1% | 0.74 [0.23, 2.37] |
| Moore et al.2017 | 12 | 25 | 11 | 24 | 5.4% | 1.09 [0.36, 3.35] |
| **Total (95% *CI*)** | | **844** | | **603** | **100.0%** | **1.02 [0.78, 1.33]** |
| Total events | 170 | | 130 | | | |

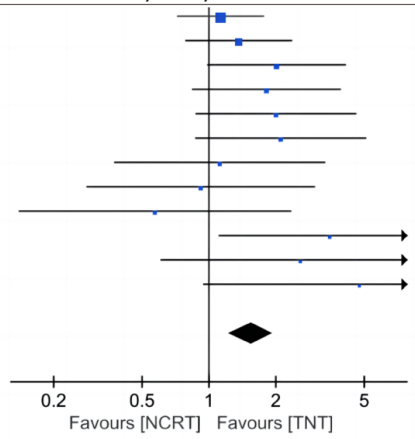
Heterogeneity: Chi² = 5.33, *df* = 7 (*P* = 0.62); $I^2$ = 0%
Test for overall effect: *Z* = 0.16 (*P* = 0.87)




**C**

| Study or subgroup | TNT Events | TNT Total | NCRT Events | NCRT Total | Weight | Odds ratio M-H, fixed, 95%CI |
|---|---|---|---|---|---|---|
| Cercek et al.2018 | 43 | 235 | 49 | 296 | 30.0% | 1.13 [0.72, 1.77] |
| Bujko et al.2016 | 35 | 220 | 25 | 205 | 18.4% | 1.36 [0.78, 2.37] |
| Garcia et al.2015 | 62 | 199 | 11 | 60 | 9.8% | 2.02 [0.98, 4.14] |
| Bhatti et al.2015 | 28 | 91 | 12 | 61 | 8.4% | 1.81 [0.84, 3.93] |
| Markovina et al.2019 | 19 | 69 | 11 | 69 | 6.7% | 2.00 [0.87, 4.61] |
| Liang et al.2019 | 16 | 76 | 9 | 80 | 5.9% | 2.10 [0.87, 5.10] |
| Fernandez et al.2015 | 8 | 54 | 7 | 52 | 5.1% | 1.12 [0.37, 3.34] |
| Maréchal et al.2012 | 7 | 27 | 8 | 29 | 4.8% | 0.92 [0.28, 3.00] |
| Moore et al.2017 | 4 | 25 | 6 | 24 | 4.3% | 0.57 [0.14, 2.35] |
| Zhai Zhiwei et al.2020 | 17 | 79 | 4 | 55 | 3.1% | 3.50 [1.11, 11.05] |
| Kim et al.2018 | 6 | 44 | 3 | 52 | 2.0% | 2.58 [0.61, 10.99] |
| Li Leilei et al.2017 | 8 | 40 | 2 | 40 | 1.4% | 4.75 [0.94, 23.98] |
| **Total (95% *CI*)** | | **1159** | | **1023** | **100.0%** | **1.55 [1.23, 1.95]** |
| Total events | 253 | | 147 | | | |

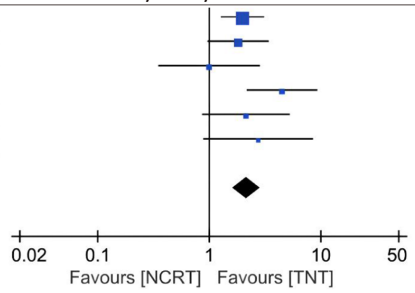
Heterogeneity: Chi² = 10.84, *df* = 11 (*P* = 0.46); $I^2$ = 0%
Test for overall effect: *Z* = 3.73 (*P* = 0.0002)




**D**

| Study or subgroup | TNT Events | TNT Total | NCRT Events | NCRT Total | Weight | Odds ratio M-H, fixed, 95%CI |
|---|---|---|---|---|---|---|
| Calvo et al.2014 | 124 | 207 | 55 | 128 | 41.7% | 1.98 [1.27, 3.10] |
| Liang et al.2019 | 50 | 79 | 39 | 80 | 21.7% | 1.81 [0.96, 3.42] |
| Maréchal et al.2012 | 13 | 27 | 14 | 29 | 10.7% | 0.99 [0.35, 2.84] |
| Markovina et al.2019 | 52 | 69 | 28 | 69 | 10.5% | 4.48 [2.16, 9.28] |
| Kim et al.2018 | 16 | 44 | 11 | 52 | 9.8% | 2.13 [0.86, 5.27] |
| Li Leilei et al.2017 | 24 | 31 | 15 | 27 | 5.5% | 2.74 [0.88, 8.52] |
| **Total (95% *CI*)** | | **457** | | **385** | **100.0%** | **2.16 [1.63, 2.87]** |
| Total events | 279 | | 162 | | | |

Heterogeneity: Chi² = 6.55, *df* = 5 (*P* = 0.26); $I^2$ = 24%
Test for overall effect: *Z* = 5.34 (*P* < 0.00001)



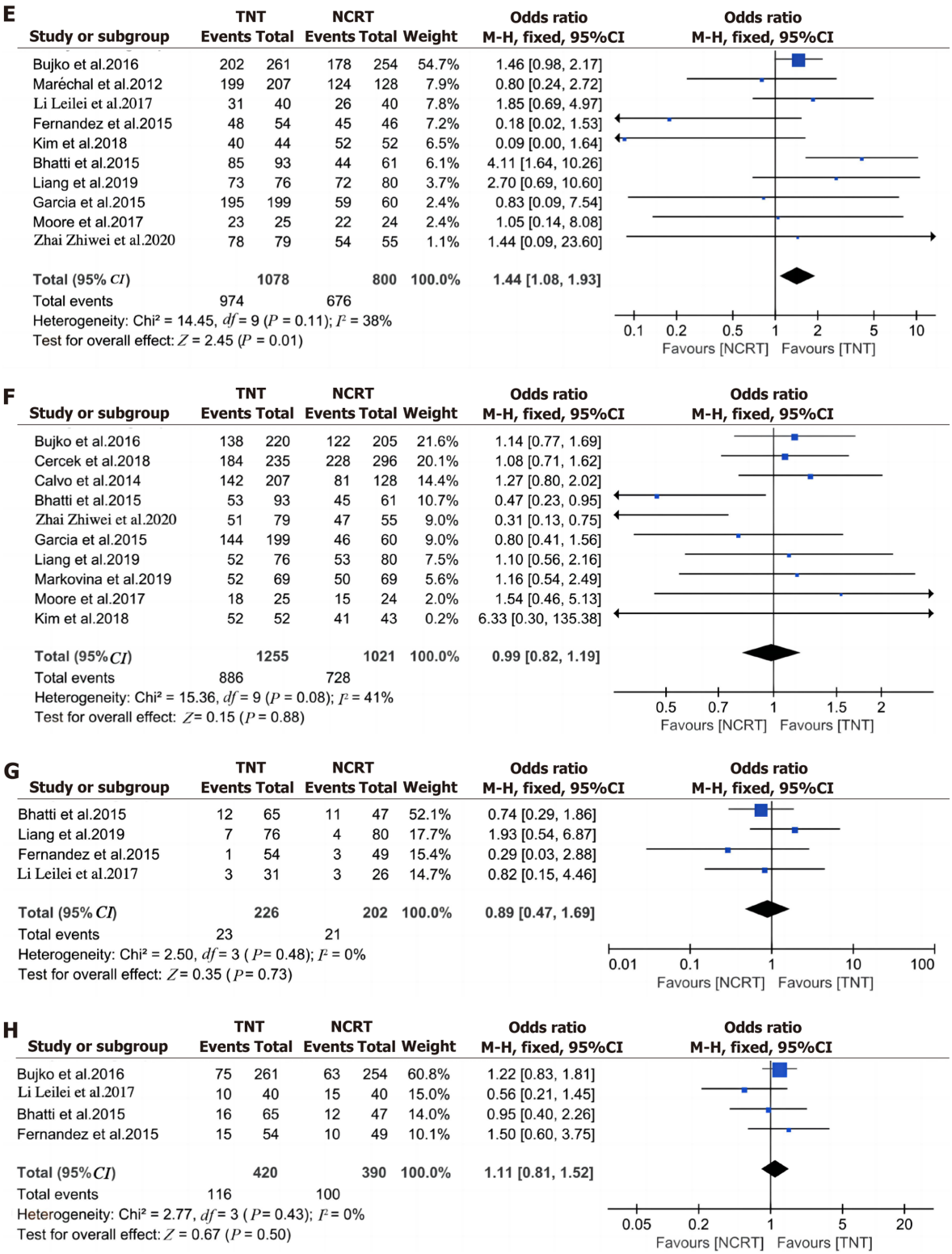



**Figure 3 Comparative analysis of acute grade 3/4 toxicity, perioperative complications, pathologic complete response rates, the rate of decrease in tumor T stage, the R0 removal rate, anal preservation rates, local recurrence, and distant metastasis between total neoadjuvant therapy and neoadjuvant chemoradiotherapy.** A: Comparative analysis of acute grade 3/4 toxicity between total neoadjuvant therapy (TNT) and neoadjuvant chemoradiotherapy (nCRT); B: Comparative analysis of perioperative complications between the TNT and nCRT groups; C: Comparative analysis of pathologic complete response rates between the TNT and nCRT groups; D: Comparative analysis of the rate of decrease in tumor T stage between the TNT and nCRT groups; E: Comparative analysis of the R0 removal rate between the TNT and nCRT groups; F: Comparative analysis of anal preservation rates between the TNT and nCRT groups; G: Comparative analysis of local recurrence between the TNT and nCRT groups; H: Comparative analysis of distant metastasis between the TNT and nCRT groups. TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; CI: Confidence interval.

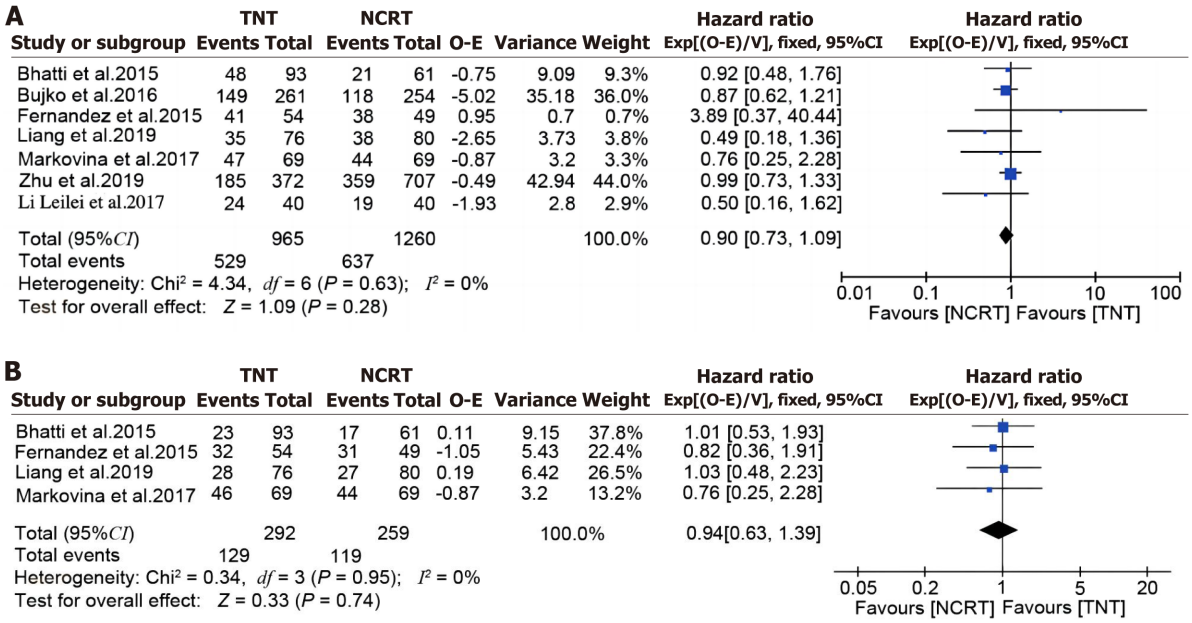



**Figure 4 Comparative analysis of 5-year overall survival and disease-free survival between the total neoadjuvant therapy and neoadjuvant chemoradiotherapy groups.** A: 5-year overall survival; B: 5-year disease-free survival. TNT: Total neoadjuvant therapy; nCRT: Neoadjuvant chemoradiotherapy; CI: Confidence interval.

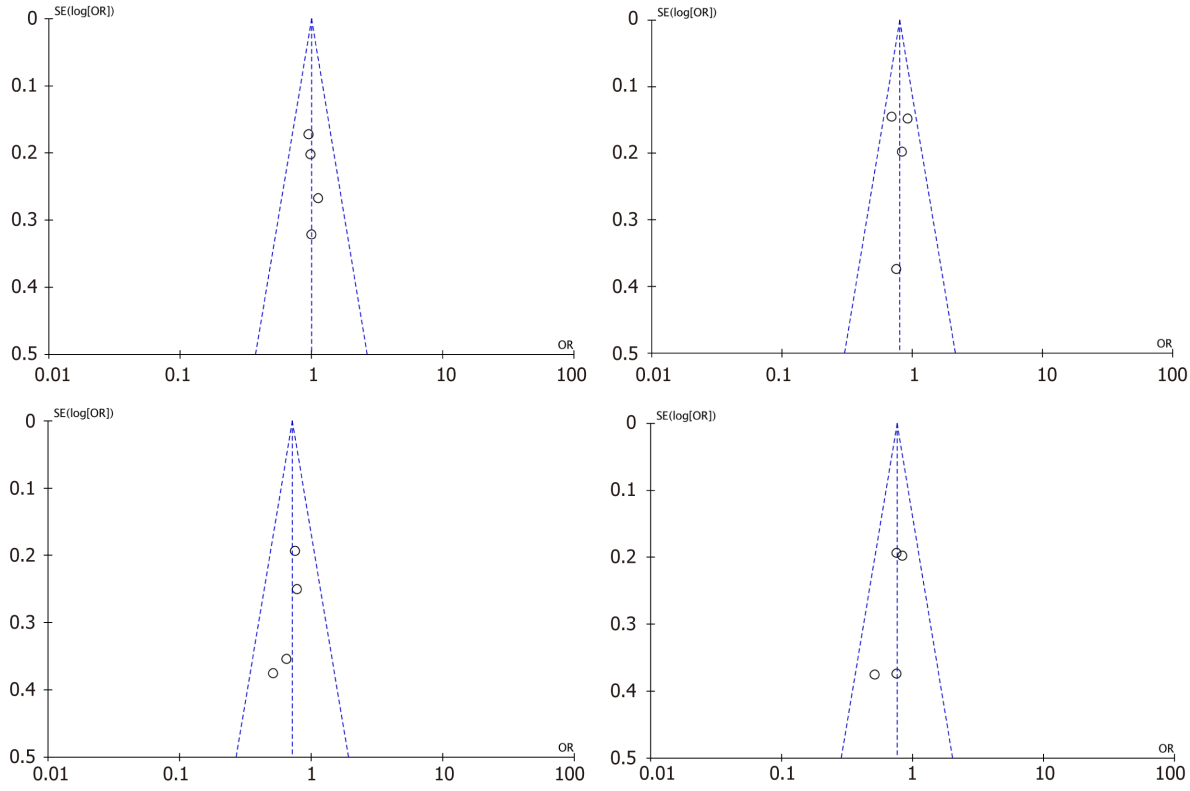



**Figure 5 Publication bias of included studies.** OR: Odds ratio.

side effects or postoperative complications.

As shown in the results of this study[36], the total pCR rate in the TNT group was 21.3%, which was significantly greater than that in the nCRT group (13.9%, $P < 0.05$), which was consistent with the results of the meta-analysis (22.4% *vs* 13.7%, $P = 0.01$). TNT can significantly increase the pCR rate of patients with locally advanced rectal cancer. Another study divided patients with locally advanced rectal cancer into four groups who received 0, 2, 4, or 6 wk of "mFOLFOX6" consolidation chemotherapy between nCRT and the TME and achieved pCR rates of 18%, 25%, 30%, and 38%, respectively. This showed that the pCR rate increased with an increase in the number of TNT cycles[37]. A retrospective

study from Memorial Sloan-Kettering Cancer Center showed that pCR rates were significantly greater in the TNT group than in the nCRT group (35.7% *vs* 21.3%, $P < 0.05$)[38]. However, other studies, such as the GCR-3 study and the EXPECT-C study, have shown that TNT does not significantly improve the pCR rate of patients with rectal cancer.

The opposite conclusions of different studies may be related to the time interval between the end of neoadjuvant therapy and the time before radical surgery[39-41]. The Lyon R90-01 study showed that the efficacy of TNT was time dependent, and the pCR rate increased with increasing time intervals. After this time interval is significantly extended, the tumor tissue will have enough time to shrink to achieve better tumor reduction and down phase effects and a higher pCR rate. However, the time interval of the EXPECT C study was only 5-6 wk, which is significantly lower than the 8-12 wk of other studies, which may be the main reason why the pCR rate of this study was not significantly improved[42].

This study showed that although there was no statistically significant difference in the operative anal preservation rate between the two groups, the time to return to the stoma was significantly shorter in the TNT group. The study revealed that 87.5% and 85.5% of patients in the TNT and nCRT groups, respectively, received protective ostomies after low anterior resection. Within six months after surgery, the reduction rate was significantly greater in the TNT group than in the nCRT group (71.9% *vs* 8.8%, $P < 0.001$). Patients in the nCRT group usually needed to complete postoperative adjuvant chemotherapy before the stoma was restored, while patients in the TNT group mostly completed systemic chemotherapy before surgery and could generally restore the stoma within six months. Therefore, TNT significantly shortened the duration of ostomy restoration and significantly improved the postoperative quality of life of patients with rectal cancer. Domestic studies also suggested that TNT did not significantly improve the survival prognosis of rectal cancer patients. A subgroup analysis of several studies showed that the OS and DFS of pCR patients were much better than those of nonpCR patients[43,44]. This suggests that the survival prognosis of rectal cancer patients may be linked to local tumor control. Some studies have also shown that TNT can significantly eliminate occult micrometastases and improve the survival of patients with rectal cancer. Among the 14 studies included in this paper, only 4 discussed the long-term efficacy of TNT, with a small sample size and mainly retrospective studies, which may have led to a large bias in the results of this study.

This meta-analysis also has certain limitations: (1) Only six randomized controlled studies were included in this study, and the sample size was relatively small, which may have deficiencies such as publication bias; and (2) The included studies mainly reported the short-term efficacy and safety of TNT, such as pCR, clinical complete response, and the R0 resection rate. Few studies on long-term survival prognosis exist, and most of them were retrospective studies.

## CONCLUSION

In summary, TNT has the advantages of eliminating occult micrometastases, shortening the time of ostomy restoration, improving treatment compliance in patients with rectal cancer, significantly increasing the pCR rate of locally advanced rectal cancer, and improving the R0 resection rate and tumor downphase rate. Follow-up studies on TNT after long-term survival preconditioning, such as the RAPIDO, NCT03177382, and NCT02031939 studies, are underway, and it is expected that the results of these studies can further clarify the clinical efficacy of TNT.

## FOOTNOTES

**Author contributions:** Wang Y wrote the manuscript; Yang Y and Liu QQ collected the data; Wang SZ guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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**Country of origin:** China

**ORCID number:** Qi-Qi Liu 0000-0101-1212-4566; Shao-Zhao Wang 0009-0006-1877-1278.

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