The Oncologic Efficacy and Long-term Survival Outcomes of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: A Systemic Review and Meta-Analysis

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Abstract

Purpose To evaluate the pooled oncologic efficacy of total neoadjuvant therapy for locally advanced rectal cancer patients using meta-analysis method.

Method To evaluate the pooled effects of total neoadjuvant therapy in terms of exact oncologic efficacy and long-term survival outcomes, a systemic literature search of PubMed, Embase, China Biology Medicine and WanFang Database was performed.

Results A total of 15 studies including 4091 patients were finally identified. The pooled analysis revealed that total neoadjuvant therapy significantly increased the rates of T-downstaging (OR=2.16, 95% CI:1.63~2.87, $P<0.00001$), pathologic complete response (OR=1.90, 95% CI:1.60~2.27, $P<0.00001$) and R0 resection (OR=1.44, 95% CI: 1.07~1.93, $P=0.01$) with a comparable safety profile. Most importantly, patients received total neoadjuvant therapy had a superior overall survival rate compared to standard neoadjuvant chemoradiotherapy (HR=0.74, 95% CI: 0.62~0.89, $P=0.001$).

Conclusion Patients with locally advanced rectal cancer can be managed with total neoadjuvant therapy with a superior short-term oncologic efficacy and long-term survival benefits.

Introduction

It has been recommended by the National Comprehensive Cancer Network (NCCN) guidelines that the standard treatments of locally advanced rectal cancer are neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME) with adjuvant chemotherapy^{1,2}. The Swedish Trial³ and Dutch TME Trial⁴ had demonstrated that preoperative radiotherapy combined with TME significantly enhanced local control of disease with reduced local recurrence rate and improved sphincter-sparing surgery rate, and then the following studies further confirmed that 5-fluorouracil based NCRT followed by TME significantly downsized and down-staged the tumor with an improved pCR or cCR rate, and local recurrence rate reduced from 35% to less than 10% remarkably⁵⁻⁸.

A series of well-designed randomized controlled trials (RCTs) were conducted with the purpose of improving the oncologic efficacy of adjuvant chemotherapy for locally advanced rectal cancer in the setting of NCRT⁹⁻¹², however, those RCTs failed to detect an improved OS and DFS though excellent local control of disease was obtained. A systemic review and meta-analysis also suggested that adjuvant chemotherapy after NCRT showed no superiority to improving survival outcomes¹³. Poor adherence to adjuvant chemotherapy might account for that phenomenon. The compliance of EORTC 22921 trial was so poor that nearly 30% of eligible patients did not receive any cycles of treatment and only less than 50% of patients completed full-course adjuvant chemotherapy⁹. According to previous analysis, patients might benefit from NCRT by increasing treatment compliance¹⁴.

In order to improve treatment compliance and then survival benefits, a novel strategy that delivered upfront chemotherapy prior to surgery, termed as total neoadjuvant therapy (TNT) has been proposed¹⁵. TNT has two major patterns, including induction and consolidation therapy, the former one requires systemic chemotherapy before NCRT, while consolidation therapy refers to additional cycles of chemotherapy between NCRT and TME¹⁶. As a radiosensitizer, upfront chemotherapy can not only reduce gross tumor volume dramatically, but target at occult micro-metastatic disease at an early stage¹⁶⁻¹⁸. Several clinical trials also pointed out that TNT might achieve better local control of disease with a promising treatment compliance. A retrospective cohort study conducted by Memorial Sloan Kettering Cancer Center included 628 patients with locally advanced rectal cancer, of those patients, 320 received NCRT followed by TME only, while the others adopted TNT (several cycles of systemic chemotherapy before NCRT). The results showed that pCR rate in TNT group was significantly higher than that in NCRT group (35.7% vs. 21.3%, $P<0.05$)¹⁷. This trial also led the NCCN guidelines to consider TNT as an alternative approach for rectal cancer. However, studies regarding the exact efficacy and long-term survival outcomes of TNT are still limited, we conducted this meta-analysis to further evaluate the pooled effects of TNT with respect to short- and long-term outcomes.

Materials And Methods

Literature search

A systemic literature search was conducted in PubMed, Embase, China Biology Medicine and WanFang Database up until October 2020. The search strategies were: “rectal cancer”; or “rectal tumor”; and “neoadjuvant chemoradiotherapy”; or “total neoadjuvant therapy”; or “induction therapy”; or “consolidation therapy”, the terms were set to title/abstract.

Inclusion and exclusion criteria

Inclusion criteria: studies that compared the efficacy and safety of TNT and NCRT; pathologically confirmed locally advanced rectal cancer ($cT_{3-4}N0$ or $cT_{any}N+$); including at least one of the following outcomes: the rate of pCR, R0 resection, tumor downstaging, perioperative complications, local recurrence and distant metastasis rates, OS and DFS. Exclusion criteria: single-arm studies; studies that enrolled patients with distant metastasis; studies without surgical treatment; studies that included none of the outcome measures.

Data extraction

Two researchers selected the literature according to search strategies independently, a negotiation was necessary if searching discrepancies existed. Details about author, year of publication, country, type of study, sample size, chemotherapy regimens and doses and outcome measures were extracted from included studies.

Study quality assessment

The risk assessment of randomized controlled studies (RCTs) was based on Cochrane Collaboration's tool, including random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting and other bias. The methodological assessment of non-RCTs was performed using Newcastle-Ottawa Scale (NOS) ¹⁹.

Statistical analysis

Review Manager version 5.3 software (Cochrane Collaboration, Denmark) was used for statistical analysis. Dichotomous data were described as odds ratio (OR) with 95% confidence interval (CI), while the description of survival data was hazard ratio (HR) with 95% CI. Heterogeneity assessment was based on Q test and I^2 statistics, a significant heterogeneity was considered when $I^2 > 50\%$, and then a random-effects model was used for meta-analysis; fixed-effects model was chosen when $I^2 < 50\%$. Publication bias was assessed using a funnel plot.

Results

Search results and characteristics of included studies

The electronic search finally identified 15 articles met inclusion criteria, including eight RCTs ²⁰⁻²⁸ and seven non-RCTs ^{17, 29-35} (**Figure. 1**). A total of 4091 patients with locally advanced rectal cancer was included, of these patients, 1906 in TNT and 2185 in NCRT group. The characteristics of included studies were listed in **Table. 1**, and the chemotherapy regimens and doses of each study were shown in **Table. 2**. The quality assessment of RCTs was described in **Figure. 2**.

Grade 3/4 acute toxicities

Grade 3/4 acute toxicities were reported in 12 studies, including seven RCTs ^{20-26, 28} and five non-RCTs ^{29, 30, 32, 33, 35}. Of these studies, diarrhea and hematologic toxicities were two most common adverse effects following TNT. A significant heterogeneity was observed, and random-effects model was used ($I^2=88\%$) for analysis. The results indicated that TNT did not increase toxicity profiles compared to NCRT (OR=0.95, 95% CI: 0.58~1.54, $P=0.83$) (**Figure. S1**). In subgroup analysis, the results regarding grade 3/4 acute toxicities were similar between RCTs and non-RCTs. (**Figure. 3**).

T-downstaging rate

Six studies reported tumor downstaging rate after TNT or NCRT, including three RCTs ^{24, 26, 28} and three non-RCTs ^{32, 33, 35}. The fixed-effects model was applied for meta-analysis ($P=0.26$, $I^2=24\%$). The results showed that T-downstaging rate was significantly higher in TNT group (OR=2.16, 95%CI:1.63~2.87, $P<0.00001$) (**Figure.S2**). In subgroup analysis, though no significant difference was observed between TNT and NCRT in RCTs subgroup, the overall T-downstaging rate was obviously higher in TNT than that in NCRT in non-RCTs subgroup (OR=2.40, 95% CI:1.63~3.94, $P=0.0005$) (**Figure.4**).

pCR rate

All included studies but one reported pCR rate in TNT and NCRT group^{17, 20-22, 25-35}. A total of 3555 patients were included. The pooled rate of pCR was 24.2% in TNT group and 13.9% in NCRT group, respectively. The heterogeneity was low and fixed-effects model was then used for pooled analysis ($P=0.13$, $I^2=30\%$). The results showed that TNT significantly increased the rate of pCR (OR=1.90, 95% CI:1.60~2.27, $P<0.00001$) (**Figure. S3**).

In subgroup analysis, all included RCTs reported pCR rate, the results revealed that the pooled rate of pCR in TNT group was significantly higher than that in NCRT group (23.8% vs. 13.1%, OR=2.08, 95% CI:1.66~2.60, $P<0.00001$) in RCTs subgroup, and a similar result was also observed in non-RCTs subgroup (24.7% vs. 15.5%, OR=1.65, 95% CI:1.24~2.20, $P=0.0005$) (**Figure. 5**).

R0 resection rate

10 studies described R0 resection rate as primary outcome measure, including six RCTs^{22, 25-28, 31} and four non-RCTs^{29, 30, 34, 35}. No significant heterogeneity was observed and fixed-effects model was then chosen for analysis ($p=0.07$, $I^2=45\%$). The results revealed that TNT obtained higher R0 resection rate than that in NCRT group (OR=1.44, 95% CI: 1.07~1.93, $P=0.01$) (**Figure.S4**). In subgroup analysis, the pooled R0 resection rate was significantly higher in TNT than that in NCRT in non-RCTs subgroup (96.7% vs. 89.8%, OR=2.08, 95% CI:1.66~2.60, $P=0.002$), while no significant difference was observed in RCTs subgroup (**Figure. 6**).

Post-operative complications

Nine studies described post-operative complications as primary endpoint, including five RCTs^{21, 23-25, 27} and four non-RCTs^{29, 30, 33, 35}. Of these studies, surgical site complications and anastomotic leak rates were similar in both groups. A fixed-effects model was chosen for pooled analysis. The results revealed that TNT was as safe as NCRT without increasing post-operative complications (OR=1.04, 95% CI: 0.84~1.29, $P=0.89$) (**Figure. S5**).

The local recurrence and distant metastasis

A total of four studies reported the local control of disease^{22, 23, 28, 34, 35}. No significant heterogeneity was found among studies and a fixed-effects model was applied for analysis ($I^2=0\%$), the results showed that no significant difference regarding local recurrence rate was observed (OR=0.89, 95% CI: 0.47~1.69, $P=0.73$) (**Figure. S6**). A total of six studies reported distant metastasis of rectal cancer^{20-22, 25, 28, 34}. And random-effects model was applied for analysis ($I^2=69\%$), the pooled analysis revealed that TNT had no potential of improving distant metastasis rate (19.4% vs. 20.8%, OR=1.05, 95% CI: 0.64~1.73, $P=0.84$) (**Figure. S7**).

The OS between TNT and NCRT

A total of eight studies reported the long-term survival OS, including five RCTs^{20-22, 25, 28} and three non-RCTs^{32, 34, 35}. The heterogeneity was low and fixed-effects model was used for analysis. The results revealed that OS in TNT was significantly superior to NCRT (HR=0.74, 95% CI: 0.62~0.89, $P=0.001$) (**Figure.S8**). In subgroup analysis, the pooled analysis revealed that the OS in TNT group was significantly better than that in NCRT group in both RCTs (HR=0.79, 95% CI: 0.65~0.96, $P=0.02$) and non-RCTs subgroup (HR=0.48, 95% CI: 0.29~0.79, $P=0.004$) (**Figure. 7**).

The DFS between TNT and NCRT

A total of seven studies reported DFS as major outcome, including four RCTs^{20-22, 25} and three non-RCTs^{32, 34, 35}. And random-effects model was chosen for analysis due to obvious heterogeneity ($I^2=67\%$). The results revealed that the pooled DFS in TNT was comparable to NCRT (HR=0.76, 95% CI: 0.56~1.02, $P=0.06$) (**Figure.S9**). In subgroup analysis, though a similar results was observed in non-RCTs subgroup, the DFS in TNT was significantly better than NCRT (HR=0.82, 95% CI: 0.70~0.96, $P=0.01$) (**Figure. 8**).

Evaluation of publication bias

According to funnel plots of included studies, no significant publication bias existed and the data were normally distributed without any bias. All included studies but one reported pCR as primary outcome and the funnel plot revealed that there existed no publication bias (**Figure. 9**).

Discussion

The trimodal approaches of locally advanced rectal cancer has achieved an excellent local control of disease, with increased sphincter-sparing surgery rate and significantly reduced local recurrence rate. However, distant failure is still disturbing and great efforts have been made to improve that. According to previous studies, TNT has the advantages of eradicating potential micrometastasis at an early stage, improving treatment compliance, increasing pCR or cCR rates that could be translated into increased possibility of organ preservation^{16, 22, 25, 32}. Our pooled analysis also discovered that TNT could significantly increase pCR rate and T-downstaging rate with a comparable safety profile, besides, a significant improvement in terms of OS and DFS was also observed in our analysis.

Compared to NCRT, our analysis found that TNT did not increase treatment-associated acute toxicities. Hematologic toxicities (leukopenia and thrombocytopenia) and diarrhea were most common, while hand-foot syndrome was especially apparent in patients treated with CAPOX (capecitabine and oxaliplatin) regimen. Similar to our study, Bujko et al²⁵ and Moore et al²⁷ disclosed that the safety of TNT was comparable to NCRT. Reduced toxicity profiles were also reported by other studies^{22,30}. We speculate that the body immunity and physical conditions of patients are usually better before surgery and more tolerable to chemotherapy in the setting of TNT. Our pooled analysis also revealed that TNT did not exert negative influence on post-operative complications. Generally, TNT might have the potential of achieving a better oncologic efficacy with a relatively comparable toxicities and peri-operative safety.

A multicenter prospective trial conducted by Garcia-Aguilar et al ³⁰ assigned rectal cancer patients to receive zero, two, four and six cycles of consolidation chemotherapy between NCRT and TME, respectively. The pCR rate in each group was 18%, 25%, 30% and 38%, indicating that total cycles of chemotherapy are positively correlated with pCR rate. In consistent with our analysis, the CONTRE Trial included eight cycles of induction chemotherapy for rectal cancer patients also reported the pCR rate up to 33% ³⁶, similar to the AVACROSS Trial . A meta-analysis included 28 studies demonstrated that the pooled pCR rate of TNT was 22.4% ³⁷, which was lower than above mentioned studies. Similar to results of the meta-analysis, our analysis also revealed that the pooled pCR rates were 21.3% in TNT and 13.9% in NCRT. The Lyon R90-01 trial had demonstrated that pCR was associated with the interval from NCRT to surgery and had a time-dependent effect ³⁸. TNT requires early introduction of upfront chemotherapy, as a result, with a relatively prolonged interval, there would be sufficient time left for tumor regression and shrinkage. The EXPECT-C trial, however, reported no improvement on pCR, and the average interval in this study was only 6 weeks, significantly lower than 8~12 weeks in other studies ³⁹.

Apart from increasing R0 resection and T-downstaging rate, TNT also might increase the likelihood of sphincter-sparing surgery or organ preservation. Patients who obtained cCR could be managed with “Watch and Wait” strategy or non-operative management under strict surveillance. Several clinical trials have demonstrated the safety and survival benefits of “Watch and Wait” strategy for cCR patients, with a promising 5-year OS rate ranging from 73% to 87% ⁴⁰⁻⁴². The PKUCH-R01 trial included 38 low-risk rectal cancer patients, of whom all received four cycles of CAPOX consolidation therapy, and the cCR rate was as high as 42.1%, near-cCR rate was 23.7%, of those cCR and near-cCR patients, about 53% patients received “Watch and Wait” strategy, only four patients experienced tumor re-growth during the follow-up, the expected organ preservation rate and sphincter-sparing rate were 52.6% and 84.2% respectively ⁴³. As a result, increasing organ-preservation rate of locally advanced rectal cancer might be future prospect of TNT.

A series of studies supported the application of TNT due to improved long-term survival outcomes, especially the recently published multicenter RCTs (RAPIDO ²¹ and PRODIGE ²⁰ trial) further confirmed the survival benefits of TNT. A recent systemic review and meta-analysis included eight RCTs had a conclusion that TNT could significantly improve OS and DFS of locally advanced rectal cancer, compared to NCRT ⁴⁴. Similar to this meta-analysis, our study included not only RCTs, but also non-RCTs, the final results also revealed that TNT had the potential of improving long-term survival outcomes of locally advanced rectal cancer patients, both the RCTs and non-RCTs supported the superiority of TNT.

There are still some arguments in current studies of TNT. Firstly, not all patients are eligible for TNT. Patients with middle and low rectal cancer, extramural vascular invasion, involved mesorectal fascia, positive circumferential margin and lateral pelvic lymph node, have a higher risk for recurrence and distant metastasis, and thus those patients are perfect candidates for TNT ^{20-21, 45}. European Society for Medical Oncology guidelines also recommended individualized treatment according to risk stratification with the purpose of improving cancer-specific OS and DFS ⁴⁶. Besides, it was reported that patients with

KRAS and p53 gene mutant had a poor response to TNT, which might result in disease progression during such a long treating period and poor prognosis⁴⁷. Other related studies also pointed out that TNT significantly prolonged the interval from the completion of NCRT to TME, with increased degree of pelvic fibrosis and surgical difficulties, and increased treatment-related complications^{14,16}. Finally, no established consensus existed on the specific patterns and chemotherapy regimens of TNT and that might explain the remarkable differences among studies. In brief, the advantages and risks of TNT should be balanced especially for patients with high risk factors.

This meta-analysis also has several limitations. First, of the included trials, most were retrospective, non-randomized single institution studies and bias might exist in the process of participants selection. Besides, the sample size of included eight RCTs was relatively small and the follow-up time was too limited to evaluate long-term survival outcomes of TNT. Second, some of the outcome measures were incomplete, such as cCR rate, treatment compliance in NCRT group and ileostomy closure with only one study reported¹⁶. Third, single-arm studies of TNT were excluded in this analysis, which might result in potential bias with regard to oncologic efficacy, especially survival benefits. Finally, it was contradictory that excellent local control of disease (higher rates of pCR, R0 resection and tumor downstaging) did not translate into improved survival benefits (distant metastasis, OS and DFS). One possible reason for that phenomenon was short follow-up time, as most of studies achieved excellent oncologic efficacy did not report long-term outcomes, such as local recurrence and distant metastasis, OS and DFS^{24,30-32}.

Several RCTs evaluating the long-term survival outcomes are ongoing. An open-label RCT (NCT03177382) conducted by West China Hospital included 458 patients with locally advanced rectal cancer, the experimental group included one cycle of CAPOX (capecitabine and oxaliplatin) induction chemotherapy followed by NCRT and then three cycles of CAPOX consolidation chemotherapy, the control group only consisted of standard NCRT followed by TME. The primary endpoints were 3-year DFS and OS. Another multicenter RCT (NCT02008656) aimed at evaluating the safety and survival outcomes of “Watch and Wait” strategy for cCR patients are ongoing, after re-staging the tumor status in the setting of TNT, patients who achieved cCR were assigned to “Watch and Wait”, while non-cCR patients were then prepared for TME, the major outcome was 3-year DFS⁴⁸. Other ongoing trials (NCT02942563, NCT02008656, NCT04405206) would further confirm the efficacy and survival benefits of TNT. Hoping the final results of these RCTs will bring benefits to rectal cancer patients.

Conclusion

Generally, TNT has the potential of achieving a better local control of disease with a relatively comparable treatment-related toxicity and safety, by increasing the rates of pCR or cCR, R0 resection and T-downstaging rate. Most importantly, survival benefits in terms of 5-year OS and DFS for locally advanced rectal cancer patients were observed, and the improved cCR of TNT can be further translated into increased likelihood of organ preservation. As a result, as a novel strategy, TNT could be applied for

locally advanced rectal cancer patients due to its excellent local control of disease and superior long-term survival benefits.

Declarations

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Analysis and interpretation of data: Li, Wang, Han

Drafting of manuscript: Li, Tao, Wang, Zhai, Han

Final approval: Li, Tao, Wang, Zhai, Han

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Tables

Table 1. The baseline characteristics and quality assessment (non-RCTs) of included studies

Study design	Author	Year	Country	Sample numble			Quality assessment
				Total	TNT	NCRT	
RCT	PRODIGE ^[20]	2021	France	461	231	230	–
	Bahadoer ^[21]	2021	Netherland	912	462	450	–
	Fernandez ^{22,23}	2010	America	103	49	54	–
	Maréchal ²⁴	2011	Belgium	57	29	28	–
	Bujko ²⁵	2016	Poland	515	254	261	–
	Kim ²⁶	2018	Korea	110	56	54	–
	Moore ²⁷	2017	Australian	49	24	25	–
	Li LL ²⁸	2017	China	80	40	40	–
Non-RCT	Zhai ZW ²⁹	2020	China	134	55	79	6
	Garcia ^{30,31}	2015	America	259	60	199	6
	Cercek ¹⁷	2018	America	628	308	320	8
	Markovina ³²	2017	America	138	69	69	6
	Calvo ³³	2014	Spain	335	128	207	7
	Bhatti ³⁴	2015	Pakistani	154	61	93	7
	Liang ³⁵	2018	China	156	80	76	5

RCT: randomized controlled trials; NCRT: neoadjuvant chemoradiotherapy; TNT: total neoadjuvant therapy

Table 2. The chemotherapy regimens and doses of included studies

Authors	Regimen	
	NCRT	TNT
PRODIGE ^[20]	50.4Gy/25f, Cap 1600mg/m ² →Surgery	6×FOLFIRINOX ^a →NCRT→Surgery
Bahadoer ^[21]	50.4Gy/25f, Cap 825mg/m ² →Surgery	6×CAPOX ^b /9×FOLFOX ^c →NCRT(25Gy/5f) →Surgery
Fernandez 22,23	45~50.4Gy/25~28f; Cap 825mg/m ² →Surgery	4×CAPOX(Ox 130mg/m ² , Cap 2000mg/m ²)→NCRT→Surgery
Maréchal ²⁴	45Gy/25f, 5-FU 225mg/m ² →Surgery	2×mFOLFOX6 ^c →NCRT→Surgery
Bujko ²⁵	45~50.4Gy/25~28f; leucovorin 20mg/m ² , 5-FU 325mg/m ² →Surgery	RT(25Gy/5f)→3×FOLFOX4 ^c →Surgery
Kim ²⁶	45~50.4Gy/25~28f, Cap 825mg/m ² →Surgery	NCRT→2×CAPOX(Ox 100mg/m ² , Cap 825mg/m ²)→Surgery
Moore ²⁷	45~50.4Gy/25~28f, 5-FU 225mg/m ² →Surgery	NCRT→3×(5-FU 450mg/m ² , leucovorin 50mg/m ²) →Surgery
Li LL ²⁸	45~50.4Gy/25f, 5-FU 225mg/m ² →Surgery	NCRT→4×FOLFOX4 ^d →Surgery
Zhai ZW ²⁹	45~50.4Gy/25~28f, Cap 825mg/m ² →Surgery	1×CAPOX ^b →NCRT→2×CAPOX ^b →Surgery
Garcia ^{30,31}	50.4Gy/25~28f, 5-FU 225mg/m ² →Surgery	NCRT→2/4/6×mFOLFOX6 ^c →Surgery
Cercek ¹⁷	45~50.4Gy/25~28f, Cap 825mg/m ² or 5-FU 225mg/m ² →Surgery	5×CAPOX ^b /8×mFOLFOX6 ^c →NCRT→Surgery
Markovina 32	45~50.4Gy/25~28f, 5- FU/cap→Surgery	NCRT(25Gy/5f)→4×mFOLFOX6 ^c →Surgery
Calvo ³³	45~50.4Gy/25~28f, 5-FU 500~1000mg/m ² →Surgery	2×FOLFOX4 ^d →NCRT→Surgery
Bhatti ³⁴	45~50.4Gy/25~28f, Cap 825mg/m ² →Surgery	4×CAPOX ^b →NCRT→Surgery
Liang ³⁵	45~50.4Gy/25~28f, Cap 825mg/m ² →Surgery	NCRT→3×CAPOX ^b /mFOLFOX6 ^c →Surgery

NCRT: neoadjuvant chemoradiotherapy; TNT: total neoadjuvant therapy; Cap: capecitabine; FOLFIRINOX^a; Ox: oxaliplatin 85mg/m², 5-FU: 5-fluorouracil 2400 mg/m², LV: leucovorin 400 mg/m², irinotecan 180

mg/m²; CAPOX^b: Ox 130 mg/m², Cap 1000 mg/m²; mFOLFOX6^c: Ox 85 mg/m², LV 400 mg/m², 5-FU 400 mg/m² and 46-h infusion 2400 mg/m²; RT: radiotherapy; FOLFOX4^d: Ox 85 mg/m², LV 200 mg/m², 5-FU 400 mg/m²

Figures

Figure 1

The flow gram of included studies

Figure 2

The quality assessment of included RCTs

Figure 3

The grade 3/4 acute toxicities between TNT and NCRT (subgroup analysis)

Figure 4

The T-downstaging rate between TNT and NCRT (subgroup analysis)

Figure 5

The comparison of pCR rate between TNT and NCRT (subgroup analysis)

Figure 6

The comparison of R0 resection rate between TNT and NCRT (subgroup analysis)

Figure 7

The comparsion of OS between TNT and NCRT (subgroup analysis)

Figure 8

The comparsion of DFS between TNT and NCRT (subgroup analysis)

Figure 9

The funnel plot revealed no publication bias of included studies

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