RESEARCH ARTICLE

Total neoadjuvant therapy versus standard therapy in locally advanced rectal cancer: A systematic review and meta-analysis of 15 trials

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Abstract

Background

Neoadjuvant chemoradiotherapy (nCRT) before total mesorectal excision (TME) and followed systemic chemotherapy is widely accepted as the standard therapy for locally advanced rectal cancer (LARC). This meta-analysis was to evaluate the current evidence regarding nCRT in combination with induction or consolidation chemotherapy for rectal cancer in terms of oncological outcomes.

Methods

A systematic search of medical databases (PubMed, EMBASE and Cochrane Library) was conducted up to the end of July 1, 2021. This meta-analysis was performed to evaluate the efficacy of TNT in terms of pathological complete remission (pCR), nCRT or surgical complications, R0 resection, local recurrence, distant metastasis, disease-free survival (DFS) and overall survival (OS) in LARC.

Results

Eight nRCTs and 7 RCTs, including 3579 patients were included in the meta-analysis. The rate of pCR was significantly higher in the TNT group than in the nCRT group, (OR 1.85, 95% CI 1.39–2.46, p < 0.0001), DFS (HR 0.80, 95% CI 0.69–0.92, p = 0.001), OS (HR 0.75, 95% CI 0.62–0.89, p = 0.002), nCRT complications (OR 1.05, 95% CI 0.77–1.44, p = 0.75), surgical complications (OR 1.02, 95% CI 0.83–1.26, p = 0.83), local recurrence (OR 1.82, 95% CI 0.95–3.49, p = 0.07), distant metastasis (OR 0.77, 95% CI 0.58–1.03, p = 0.08) did not differ significantly between the TNT and nCRT groups.

Conclusion

TNT appears to have advantages over standard therapy for LARC in terms of pCR, R0 resection, DFS, and OS, with comparable nCRT and postoperative complications, and no increase in local recurrence and distant metastasis.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) before total mesorectal excision (TME) and followed systemic chemotherapy is widely accepted as the standard therapy for locally advanced rectal cancer (LARC). Although nCRT and preoperative systemic chemotherapy are the preferred approach for LARC, it does not provide better results in terms of disease-free survival (DFS) and overall survival (OS) compared with surgery and adjuvant chemotherapy [1]. The concept of total neoadjuvant therapy (TNT), in which chemotherapy and chemoradiation are administered before TME, can be administered exclusively for patients with widespread LARC [2, 3]. TNT has also become a platform for studying systemic chemotherapy, new radiation sensitizers and immunotherapy agents for LARC [4, 5]. The NCCN guidelines have approved the use of TNT [6], however, the current evidence is preliminary, we tried to further consolidate the evidence through meta-analysis of related studies.

Methods

Literature search strategy

A systematic search of medical databases (PubMed, EMBASE and Cochrane Library) was conducted up to the end of July 1, 2021. We used the following search MeSH terms: neoadjuvant therapy, neoadjuvant chemoradiotherapy, preoperative chemoradiotherapy, neoadjuvant chemoradiation, chemoradiotherapy, total neoadjuvant therapy, total mesorectal excision, rectal cancer. We also searched bibliographies of identified reports for additional references.

Study inclusion and exclusion criteria

Studies inclusion criteria in the meta-analysis were list as follow: (a) randomized controlled trials (RCTs) or non-randomized controlled trials (nRCTs), (b) TNT versus nCRT in LARC, (c) interest outcomes describing the details of pCR, chemoradiotherapy or surgical complications, R0 resection, local recurrence, distant metastasis, DFS and OS. Review/case reports, no comparable data, repeat publications were excluded.

Data extraction and quality assessment

Two authors performed study selection, evaluation, and data extraction independently, and discrepancies were resolved by consensus including a third author. The primary endpoint was pCR, The secondary endpoints were chemoradiotherapy or surgical complications, R0 resection, local recurrence, distant metastasis, DFS and OS. Study characteristics were extracted independently by two researchers. Corresponding authors were contacted via e-mail for missing data when necessary. The methodological quality of the included studies was assessed using the Jadad Score [total score from 0 (poor) to 5 (excellent)] for RCT or the Newcastle-Ottawa scale (NOS) [total score from 0 (poor) to 9 (excellent)] for nRCTs [7, 8]. A Jadad scale score≥3 points for RCTs and NOS score≥6 points for nRCTs were considered high quality.

Statistical analysis

Continuous variables were analysed using weighted mean differences (WMD) and 95% confidence intervals (CIs). Pooled odds ratios (ORs) and 95% CIs were calculated for dichotomous variables. Statistical heterogeneity between trials was assessed by using the I^2 test, a value of 50% or greater suggests moderate to substantial inconsistency among studies. Random effects models were used if high heterogeneity between study existed, Otherwise, fixed-effects models were used. Subgroup analysis and sensitivity analysis was performed to identify potential heterogeneity [9, 10]. Publication bias was investigated using Begg's and Egger's tests [11]. All

statistical tests were performed using Review Manager Version 5.3 and STATA/SE version 13.1. The significance level was set at $p < 0.05$.

Results

Fig 1 shows the selection of relevant studies for inclusion in the meta-analysis. A total of 8 nRCTs with 1502 and 7 RCTs with 2077 enrolled patients enrolled patients were included for this meta-analysis [12–26] (Fig 1), there were 1812 patients in the TNT group and 1767 patients in the nCRT group. The main characteristics of the included studies are summarized in Table 1.

Primary endpoints

pCR.   Overall, including the 15 studies selected, 652 of 3579 patients (18.2%) achieved a pCR after neoadjuvant therapy, 412 of 1812 (22.7%) in the TNT group and 240 of 1767 (13.6%) in the standard group (OR 1.85, 95% CI 1.39–2.46, $p < 0.0001$), with certain statistical
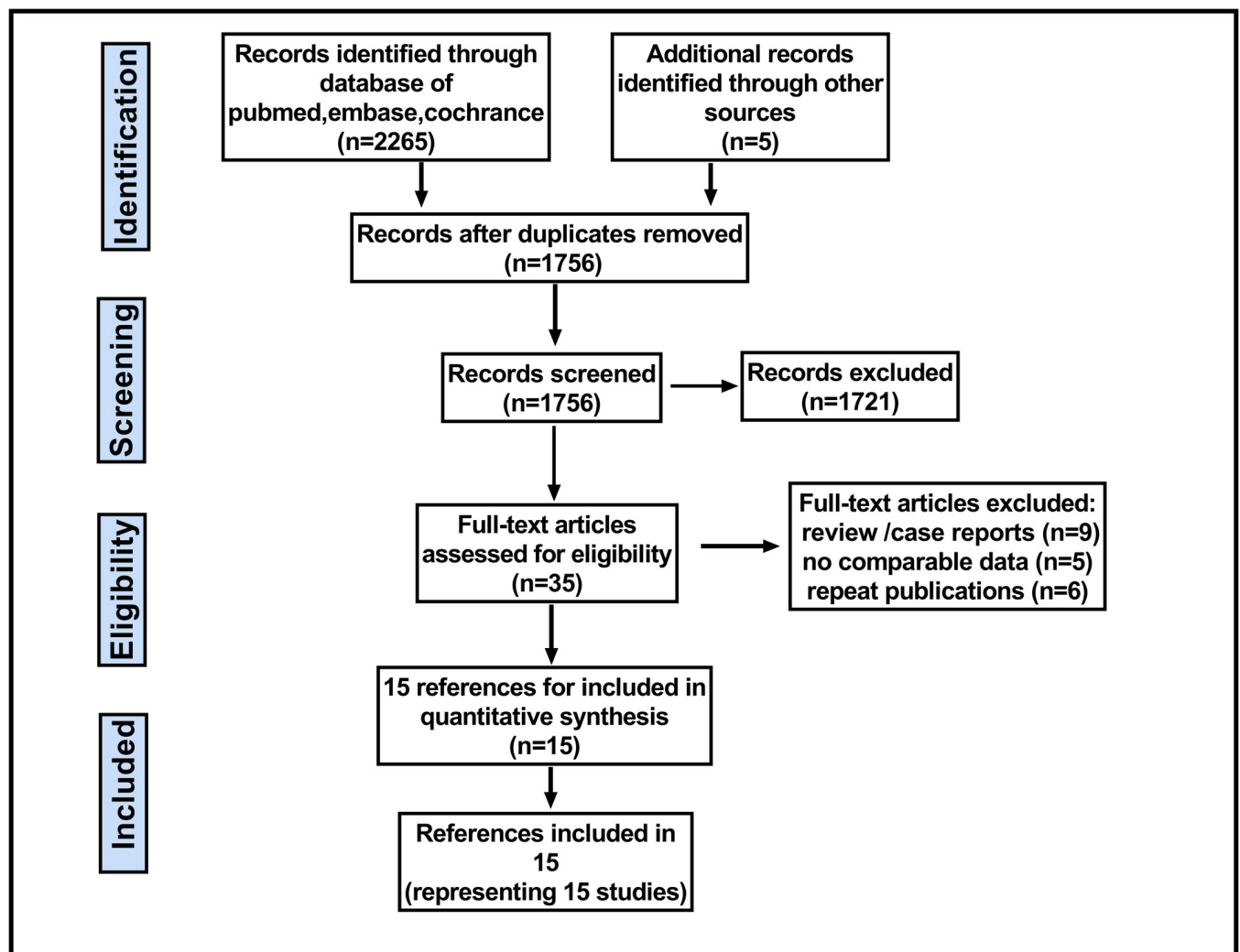

Fig 1. Flow chart indicating the selection process for this meta-analysis.

Table 1. Characteristics of the studies included in the meta-analysis.

| First author/Year | Study design | CRTvsTNT | | | | | | | TNT regimen | CRT regimen | Follow-up (months) | Study quality |
		Number of patients	Male gender (%)	Age (year) (mean ± SD)	T4	N2	CRM+	RT Dose (Gys)				
Marechal R/2012	RCT	29vs28	75vs55	62.5±8.8vs62 ±14.5	NR	NR	NR	45vs45	FOLFOX *2→CRT→Sur	CRT(5FU)→Sur	NR	–/3
Fernandez C/2015	RCT	62vs60	70vs65	62±8.3vs60±9.5	3vs2	NR	5vs-	NR	XELOX * 4→CRT→Sur	CRT→Sur→CT	69	–/3
Bujko K/2016	RCT	254vs261	67vs70	NR	NR	NR	NR	50.4vs25	SCRT→FOLFOX * 3→Sur	CRT→ Sur	35	–/4
Moore J/2017	RCT	24Vs25	75vs73	60.5 ±12.6 vs59.7 ±9.9	163vs165	NR	NR	NR	CRT→5FU * 3→Sur	CRT→Sur	NR	–/4
Kim SY/2018	RCT	55Vs53	84vs68	55± 8 vs56± 10	1vs5	19vs15	14vs16	50.4vs50.4	CRT→XELOX * 2→Sur	CRT→Sur	NR	–/4
Conroy T/2020	RCT	230Vs231	NR	NR	10vs9	NR	NR	50.4vs50.4	FOLFIRINOX*6→CRT→Sur	CRT→Sur→FOLFOX	46.5	–/3
Bahadoer RR/2021	RCT	450vs462	69vs65	62±2.2vs62±2.3	35vs41	NR	NR	25vs50.4	CRT→XELOX *6/→Sur	CRT→Sur→ CT	54	–/4
Cui J/2020	Re	61vs83	56vs69	56 ±13.5vs54 ±12	20vs15	NR	NR	NR	CRT→XELOX * 2→Sur	NR	NR	7★/–
Liang HQ/2018	Re	80vs76	NR	64vs75	44vs50	11vs21	NR	NR	CRT→mFOLFOX *2–4→Sur	CRT→Sur	32vs30	6★/–
Cercek A/2018	Re	320vs308	60vs59	NR	57vs62	45vs36	NR	NR	NR	NR	46vs23	7★/–
Bhatti AB/2015	Re	61vs93	69vs68	NR	20vs36	NR	8vs17*	50.4vs50.4	mFOLFOX6 *4→ CRT→Sur	CRT→Sur	NR	8★/–
Thakur N./2020	Pro	13vs15	-NR	NR	NR	NR	NR	25vs25	CRT→mFOLFOX6 *2→Sur	CRT→Sur	NR	8★/–
van Zoggel D/2018	Pro	71vs58	57Vs79	65±9vs64 ±10	NR	NR	NR	NR	FOLFOX *4→ CRT→Sur	CRT→Sur	NR	7★/–
Garcia-Aguilar J/2015	Pro	60vs65	62vs63	57 ±13.3vs58 ±9.8	NR	NR	NR	NR	CRT→mFOLFOX6 *6→Sur	CRT→Sur	NR	7★/–
Markovina S/2017	Pro	69vs69	67vs71	56.6 ±12.9vs57.2 ±12.6	1vs3	NR	NR	NR	CRT→mFOLFOX6 →Sur	NR	54.3 vs49.4	8★/–

★ number of stars for Nottingham Ottawa scale for each included trial,* Postradiotherapy, NOS = Nottingham-Ottawa scale, CRT = Chemoradiotherapy, CT = chemotherapy, TNT = total neoadjuvant therapy, Pro = prospective, Sur = surgery; Re = retrospective, RCTs = randomized controlled trial, NR = no report.
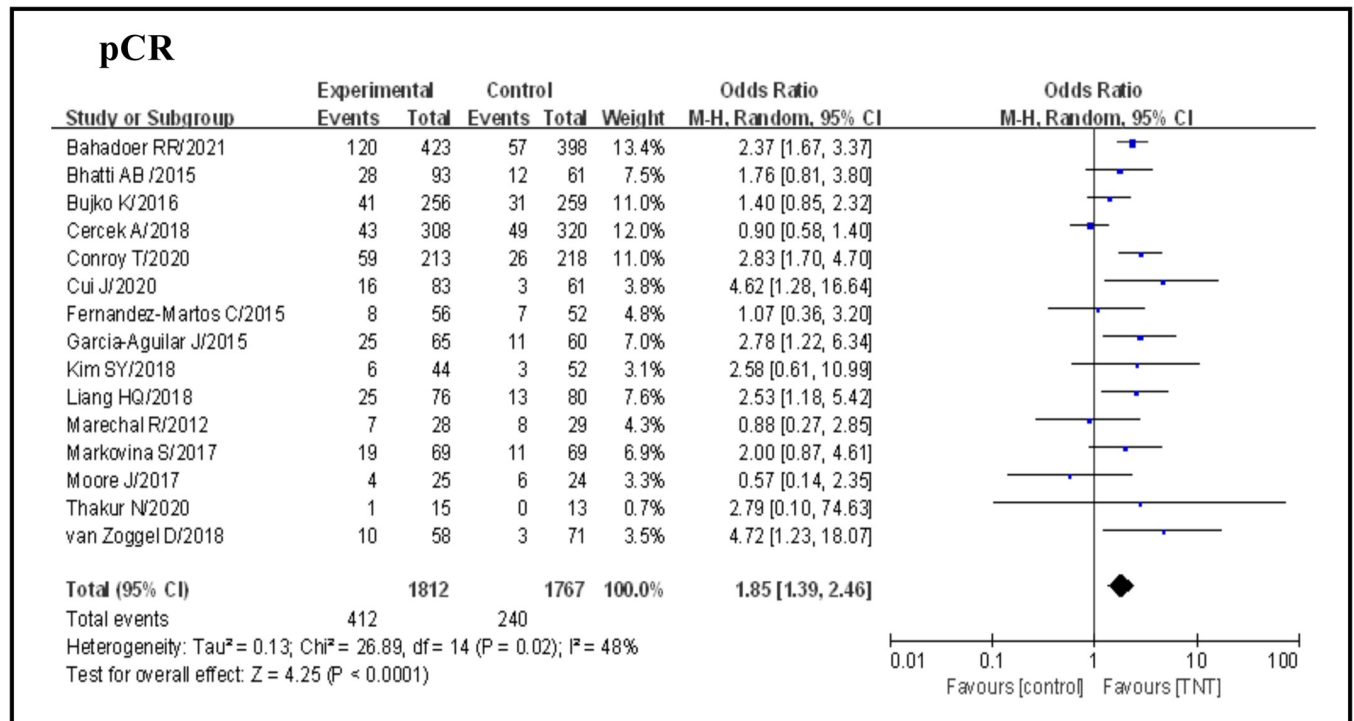
Fig 2. Forest plot for pCR, OR are shown with 95% confidence interval.

heterogeneity (I^2 = 48%, p = 0.02)(Fig 2). A subgroup analysis showed that single-center or multi-center studies, sample size, RCT or nRCT, neoadjuvant therapy were not causes of heterogeneity in view of the dissimilarity between subgroups (Table 2). The sensibility analysis performed showed stability of the pCR when excluding each study at a time (Table 3).

Secondary endpoints

Chemoradiotherapy complications. Overall, including the 11 studies selected, 1000 of 3534 patients (28.3%) occurred G3–4 adverse events after neoadjuvant therapy, 576 of 1996

Table 2. Subgroup analyses of PCR based on the study type, setting, sample size and chemoradiotherapy sequence.

Outcome	Subgroup		No. of studies	No. of patients	Study Heterogeneity		Model	Meta-analysis	
				TNTvsCRT	I^2 (%)	P Value		OR (95%CI)	P Value
pCR	Study type	RCT	7	1045vs 1032	45	0.09	Fixed	1.75 [1.21, 2.54]	**0.003**
		Prospective	4	207 vs 213	0	0.76	Fixed	2.65 [1.56, 4.50]	**0.0003**
		Retrospective	4	560 vs 522	70	**0.02**	Random	1.42 [1.03, 1.96]	**0.03**
	Setting	Single-center	7	702vs 675	55	**0.04**	Random	2.01 [1.20, 3.39]	**0.009**
		Multi-center	8	1117vs1095	32	0.20	Fixed	2.19 [1.62, 2.50]	**< 0.00001**
	Sample size	≥200	4	1200 vs 1195	81	**0.001**	Random	1.71 [1.02, 2.84]	**0.04**
		< 200	11	619 vs 565	0	0.50	Fixed	2.24 [1.62, 2.91]	**< 0.00001**
	Chemoradiotherapy	CT first	4	498 vs 381	31	0.19	Fixed	2.23 [1.61, 3.27]	**< 0.0001**
		Radiation first	11	1421 vs 1389	49	**0.03**	Random	1.81 [1.30, 2.51]	**0.0004**

CRT = Chemoradiotherapy, TNT = total neoadjuvant therapy, OR = odds ratio, CI = confidence interval.

Table 3. Sensitivity analysis for pathological complete response.

Study Excluded	Random Effect			Heterogeneity	
	OR	95% CI	p Value	I^2 (%)	I^2- P Value
van Zoggel D/2018	1.79	1.34, 2.38	< 0.00001	48	0.02
Garcia-Aguilar J/2015	1.80	1.33, 2.42	0.0001	50	0.02
Markovina S/2017	1.84	1.36, 2.50	< 0.0001	52	0.01
Thakur N/2020	1.85	1.38, 2.47	< 0.0001	52	0.01
Bhatti AB /2015	1.86	1.37, 2.53	< 0.0001	52	0.01
Cercek A/2018	2.08	1.66, 2.61	< 0.00001	13	0.31
Cui J/2020	1.79	1.34, 2.38	< 0.0001	48	0.02
Liang HQ/2018	1.81	1.33, 2.45	0.0001	50	0.02
Bahadoer RR/2021	1.79	1.30, 2.45	0.0003	46	0.03
Bujko K/2016	1.92	1.40, 2.62	< 0.0001	49	0.02
Conroy T/2020	1.76	1.30, 2.37	0.0002	45	0.03
Fernandez-Martos C/2015	1.91	1.42, 2.56	< 0.0001	50	0.02
Kim SY/2018	1.83	1.36, 2.46	< 0.0001	51	0.01
Marechal R/2012	1.92	1.43, 2.56	< 0.0001	49	0.02
Moore J/2017	1.92	1.45, 2.55	< 0.00001	46	0.03

OR = odds ratio; CI = confidence interval.

(28.9%) in the TNT group and 424 of 1538 (27.6%) in the standard group (OR 1.03, 95% CI 0.73–1.43, p = 0.88), with certain statistical heterogeneity (I^2 = 66%, p = 0.001) (Fig 3A).

Surgical complications. Overall, including the 10 studies selected, 527 of 2497 patients (21.1%) occurred surgical complications, 267 of 1273 (21.0%) in the TNT group and 260 of 1224 (21.2%) in the standard group (OR 1.02, 95% CI 0.83–1.26, p = 0.83), with no evidence of significant heterogeneity (I^2 = 0%, p = 0.92) (Fig 3B).

R0 resection. Overall, including the 11 studies selected, 1894 of 2238 patients (84.6%) achieved R0 resection, 989 of 1143 (86.5%) in the TNT group and 905 of 1095 (82.6%) in the standard group (OR 1.34, 95% CI 1.05–1.71, p = 0.02), with no evidence of significant heterogeneity (I^2 = 28%, p = 0.18) (Fig 4A).

Local recurrence. Overall, including the two studies selected, 42 of 436 patients (9.6%) occurred local recurrence, 25 of 204 (12.2%) in the TNT group and 17 of 232 (7.3%) in the standard group (OR 1.82, 95% CI 0.95–3.49, p = 0.07), with no evidence of significant heterogeneity (I^2 = 31%, p = 0.23) (Fig 4B).

Distant metastasis. Overall, including the 7 studies selected, 238 of 1080 patients (22.0%) occurred distant metastasis, 111 of 556 (20.0.5%) in the TNT group and 127 of 524 (24.2%) in the standard group (OR 0.77, 95% CI 0.58–1.03, p = 0.08), with no evidence of significant heterogeneity (I^2 = 38%, p = 0.14) (Fig 4C).

DFS. Seven studies reported DFS and the results showed that the TNT group had a significantly longer DFS than the standard group (HR 0.80, 95% CI 0.69–0.92, p = 0.001), with no evidence of significant heterogeneity (I^2 = 0%, p = 0.43) (Fig 5A).

OS. Seven studies reported OS and the results showed that the TNT group had a significantly longer OS than the standard group (HR 0.75, 95% CI 0.62–0.89, p = 0.002), with no evidence of significant heterogeneity (I^2 = 36%, p = 0.15) (Fig 5B).

Sensitivity analysis and publication bias. The sensibility analysis performed showed stability of the pooled OR with pCR when excluding each study at a time. There was no
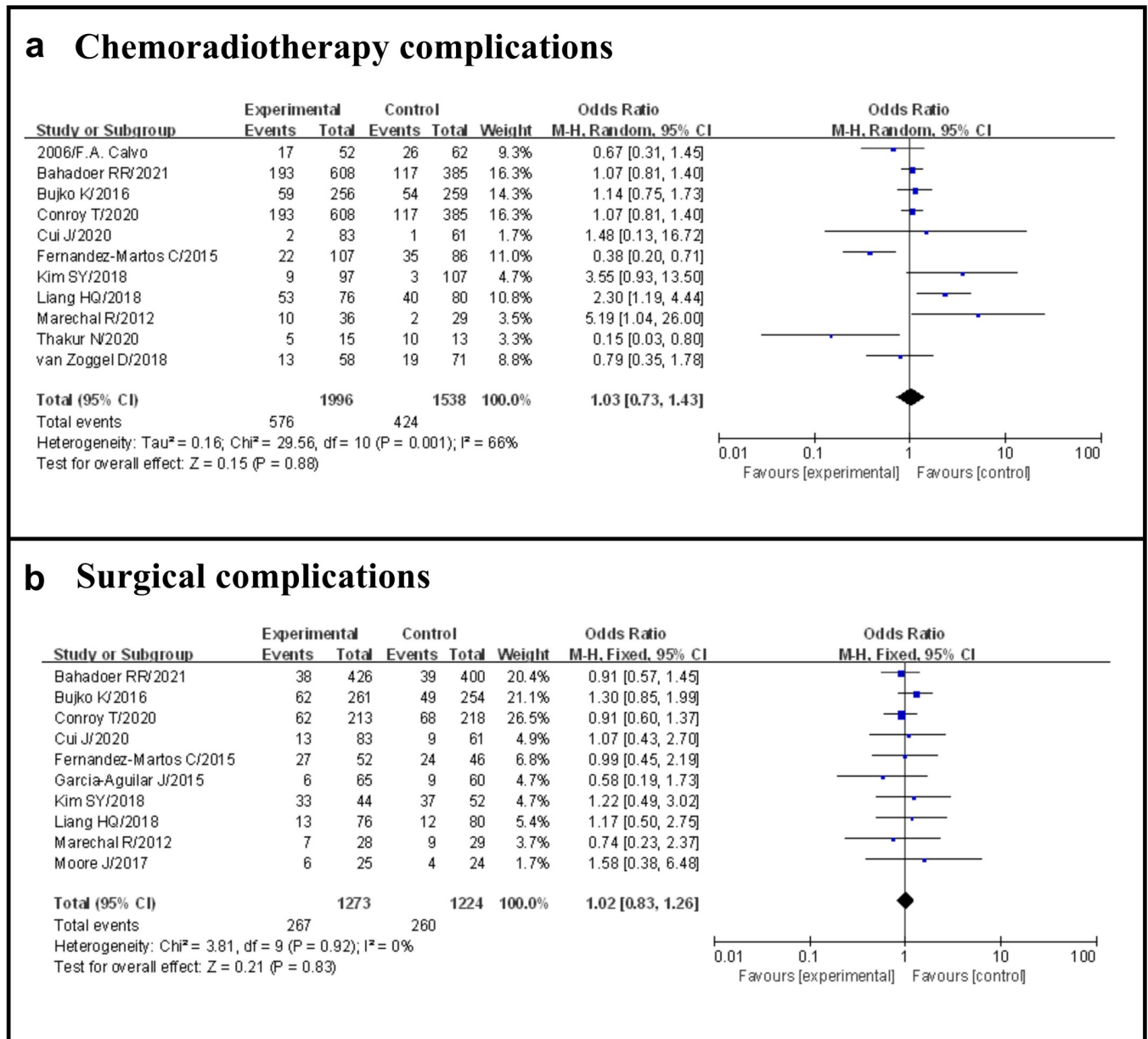
a   Chemoradiotherapy complications

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2006/F.A. Calvo	17	52	26	62	9.3%	0.67 [0.31, 1.45]
Bahadoer RR/2021	193	608	117	385	16.3%	1.07 [0.81, 1.40]
Bujko K/2016	59	256	54	259	14.3%	1.14 [0.75, 1.73]
Conroy T/2020	193	608	117	385	16.3%	1.07 [0.81, 1.40]
Cui J/2020	2	83	1	61	1.7%	1.48 [0.13, 16.72]
Fernandez-Martos C/2015	22	107	35	86	11.0%	0.38 [0.20, 0.71]
Kim SY/2018	9	97	3	107	4.7%	3.55 [0.93, 13.50]
Liang HQ/2018	53	76	40	80	10.8%	2.30 [1.19, 4.44]
Marechal R/2012	10	36	2	29	3.5%	5.19 [1.04, 26.00]
Thakur N/2020	5	15	10	13	3.3%	0.15 [0.03, 0.80]
van Zoggel D/2018	13	58	19	71	8.8%	0.79 [0.35, 1.78]
Total (95% CI)		**1996**		**1538**	**100.0%**	**1.03 [0.73, 1.43]**
Total events	576		424			

Heterogeneity: Tau² = 0.16; Chi² = 29.56, df = 10 (P = 0.001); I² = 66%
Test for overall effect: Z = 0.15 (P = 0.88)

b   Surgical complications

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bahadoer RR/2021	38	426	39	400	20.4%	0.91 [0.57, 1.45]
Bujko K/2016	62	261	49	254	21.1%	1.30 [0.85, 1.99]
Conroy T/2020	62	213	68	218	26.5%	0.91 [0.60, 1.37]
Cui J/2020	13	83	9	61	4.9%	1.07 [0.43, 2.70]
Fernandez-Martos C/2015	27	52	24	46	6.8%	0.99 [0.45, 2.19]
Garcia-Aguilar J/2015	6	65	9	60	4.7%	0.58 [0.19, 1.73]
Kim SY/2018	33	44	37	52	4.7%	1.22 [0.49, 3.02]
Liang HQ/2018	13	76	12	80	5.4%	1.17 [0.50, 2.75]
Marechal R/2012	7	28	9	29	3.7%	0.74 [0.23, 2.37]
Moore J/2017	6	25	4	24	1.7%	1.58 [0.38, 6.48]
Total (95% CI)		**1273**		**1224**	**100.0%**	**1.02 [0.83, 1.26]**
Total events	267		260			

Heterogeneity: Chi² = 3.81, df = 9 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)

Fig 3. Forest plot for chemoradiotherapy complications and surgical complications, OR are shown with 95% CIs.

significant publication bias in the analyses of pCR (Egger's test, p = 0.850; Begg's test, p = 0.729) (Fig 6).

Discussion

In the meta-analysis, we compared the efficacy of TNT with that of standard therapy for LARC. TNT appears to have advantages over standard therapy for LARC in terms of pCR, R0 resection, DFS, and OS, with comparable nCRT and postoperative complications, and no increase in local recurrence and distant metastasis.

In this meta-analysis, we observed that the overall pCR rate of TNT may increase compared with chemoradiotherapy. Our results were consistent with previous reports [27]. However,
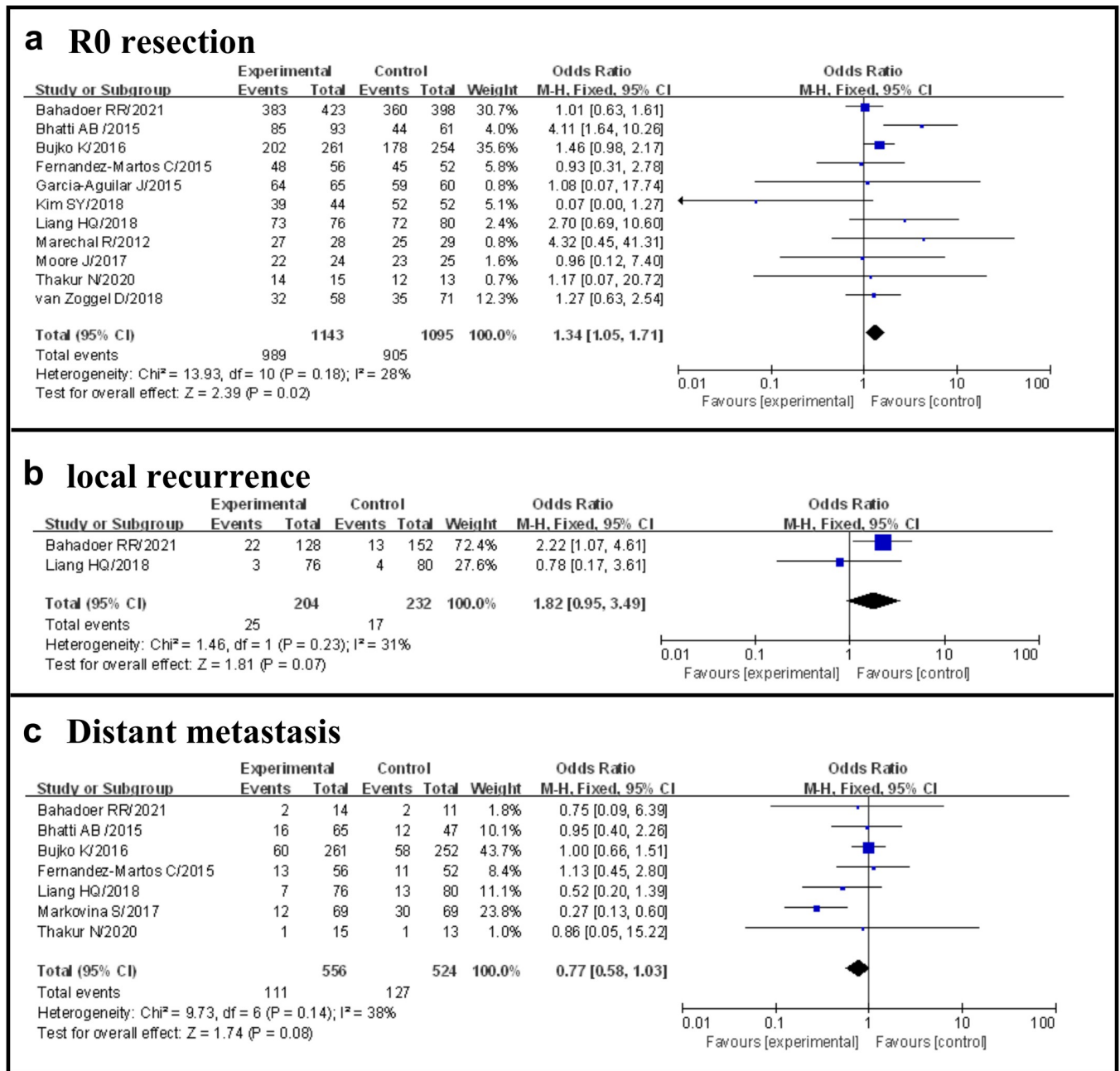
Fig 4. Forest plot for R0 resection and distant metastasis, OR are shown with 95% Cis.

our meta-analysis included more and newer studies, which further confirmed the advantage of TNT in rectal cancer. In the review of 16 studies involving a total of 3363 patients, patients who experienced pCR had a 75%, lower risk of distant (8.7%) and local (0.7%) recurrence than patients who did not [28]. Compared with patients with incomplete response, patients with pCR after neoadjuvant therapy are less likely to have local recurrence and more likely to have better survival outcomes [29]. pCR is considered to be the key prognostic criterion for the long-term prognosis of LARC [30]. The use of TNT can significantly reduce tumor volume,
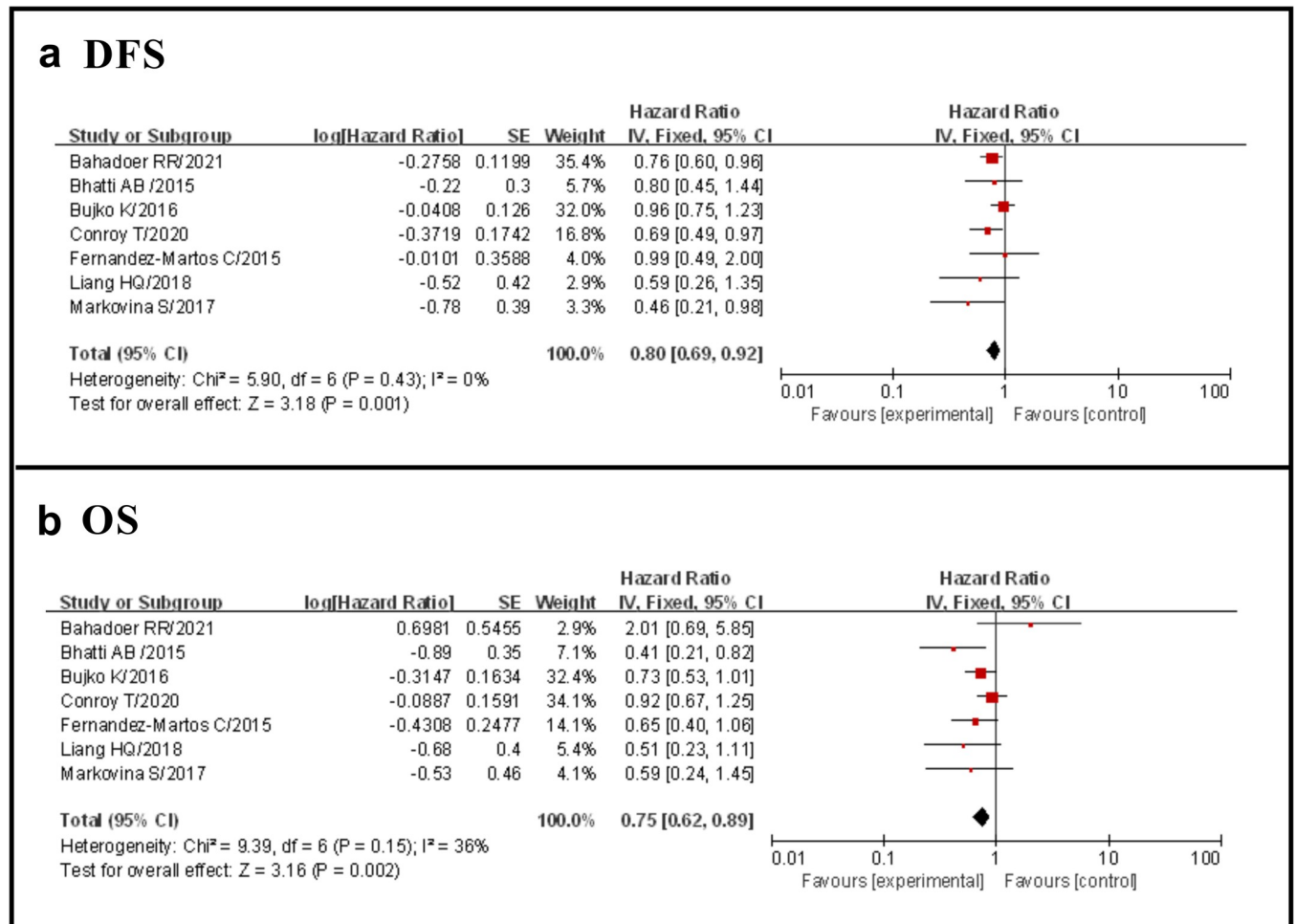
Fig 5. Forest plot for DFS and OS, HR are shown with 95% Cis.

which may lead to more patients adopting non-surgical observation and waiting strategies in the future. Habr-Gama et al introduced the watch-and-wait strategy [31], they reported that after 10 years of follow-up, patients who gave up surgery after obtaining complete clinical response had an OS rate of 97.7% and a DFS rate of 84%. pCR for rectal cancer is associated with excellent long-term prognosis, independent of treatment strategy. Surgical resection may not improve outcomes while increasing the incidence of temporary or permanent stoma and unnecessary morbidity and mortality. Another potential advantage of simultaneous chemotherapy and radiochemotherapy is that it can avoid or delay surgery when a complete clinical response is observed. The watch-and-wait approach may be considered a better treatment strategy, because surgery may lead to intestinal or bladder incontinence and sexual dysfunction, as well as short-term or permanent stoma [32–35].

Adjuvant chemotherapy is recommended by current guidelines, however, patient compliance is poor and survival benefit is unclear. Although the nCRT approach has made significant improvements in local control, the incidence of distal metastasis has not decreased. In our meta-analysis, the rate of DFS and OS was significantly higher in the TNT group than in the nCRT group, although studies have shown that watch-and-wait approach is associated with higher rectal preservation, which may be at the expense of lower OS rates
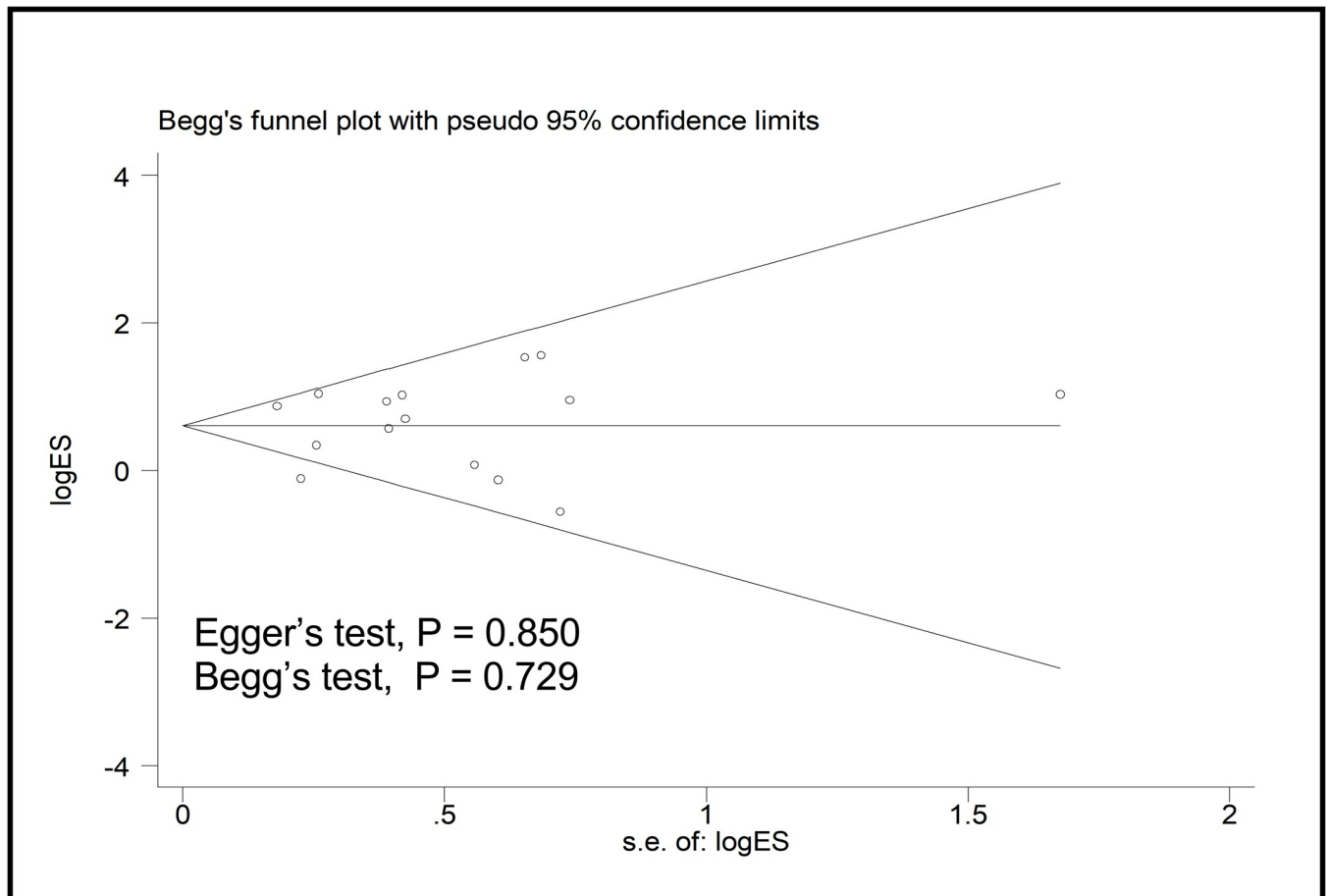
Fig 6. Funnel plot using Begg method for pCR.

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and increased risk of distant metastasis [36]. In addition, treatment-related toxicity appeared to be acceptable in all patients who completed TNT therapy. Although TNT was associated with an increased incidence of pelvic fibrosis and a longer interval from nCRT to surgery, TNT did not lead to an increase in surgical difficulty or postoperative complications [17]. However, these results should be interpreted with caution, as the lack of standardization of postoperative morbidity reports limits the interpretation of the results. Another disadvantage is the short follow-up period, so the assessment of long-term distant metastases needs to be cautious.

Assessment of quality of life (QOL) was not included in this meta-analysis, in the EXPERT-C trial, intensified neoadjuvant strategy for QoL and bowel function did not appear to be significantly affected [37]. This study was conducted at an appropriate time, because enough data was available to use meta-analytical methods which enabled us to provide the most up-to-date information on this topic.

Our study has the following limitations. First, although the meta-analysis including RCT is ideal, the limited number of RCTs prevents us from drawing clear conclusions. Second, the follow-up included in this meta-analysis is short, and the long-term survival benefit remains to be confirmed. However, this meta-analysis was completed at the appropriate time, and we provide the latest information in this area.

In conclusion, TNT appears to have advantages over standard therapy for LARC in terms of pCR, R0 resection, DFS, and OS, with comparable nCRT and postoperative complications, and no increase in local recurrence and distant metastasis. If these findings can be applied clinically, more patients with LARC will be eligible for organ preservation, which will avoid surgical sequelae and improve quality of life.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

Author Contributions

Methodology: Shujie Ma, Yinyin Guo.

Resources: Xiping Zhang.

Software: Yang Luo.

Writing – original draft: Laiyuan Li.

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