REVIEW ARTICLES

A Meta-analysis of Total Neoadjuvant Therapies Combining Chemoradiotherapy with Induction or Consolidated Chemotherapy for Locally Advanced Rectal Cancer

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Abstract

Objective Total neoadjuvant therapy (TNT) combining chemoradiotherapy (CRT) with chemotherapy (CT) was a novel pre-surgical approach to cancer treatment. This meta-analysis aimed to compare the clinical outcomes between neoadjuvant CRT (nCRT) with induction CT and nCRT with consolidated CT in locally advanced rectal cancer (LARC) patients.

Method In July 2022, a literature search was conducted using the following public databases: PubMed, MEDLINE, Embase, the Cochrane Library, and Web of Science, retrieved all relevant articles comparing nCRT-combining induction CT with nCRT-combining-consolidated CT treatments for LARC patients.

Results Four eligible studies were identified, including a total of 995 LARC patients: 473 in the nCRT with consolidated CT group and 522 in the nCRT with induction CT group. The organ preservation (OP) rate of the nCRT with consolidated CT group was higher than that of the nCRT with induction CT group (RR [relative risk]: 1.53; 95% CI (confidence interval): 1.09–2.14). The pathological complete response (PCR, RR: 1.22; 95% CI 0.37–2.17), the 3-year disease-free survival (DFS, RR 1.02; 95% CI 0.71–1.46), the local recurrence (LR, RR 0.98; 95% CI 0.52–1.85), rates of R0 resection (RR 0.74; 95% CI 0.55–1.10), compliance (RR 0.52; 95% CI 0.12–2.26), and grade 3-–4 toxicities (RR 0.78; 95% CI 0.57–1.06) were all similar between the two groups.

Conclusion In this meta-analysis of TNT regimens for rectal cancer, consolidative CT following nCRT was associated with similar PCR, 3-year DFS, LR, R0 resection, compliance, and grade 3–4 toxicities compared to induction CT prior to nCRT but a higher rate of organ preservation.

Keywords Locally advanced rectal cancer · Neoadjuvant chemoradiotherapy · Neoadjuvant chemotherapy · Total neoadjuvant therapy · Meta-analysis

Introduction

Colorectal cancer (CRC) represents the second most fatal and third most common malignancy worldwide. In 2020, about 147,950 people were diagnosed with CRC, and 53,200 people died of CRC. A considerable proportion of new CRC cases (17,930/147,950) were diagnosed in younger adults (ages < 50 years), with a reported 3640 death toll [1].

Locally advanced rectal cancer (LARC) is a subtype of CRC characterized by tumors invading or extending in close proximity to the mesorectal fascia. Treatment of LARC often involves administration of nCRT, conservative surgery for total mesorectum resection, and adjunctive chemotherapy (ACT) to remove any residual cancerous cells or lesions [2].

TNT for CRC refers to a combinatorial therapy of CRT and CT before surgical intervention. Recent clinical investigations have been focusing on improving PCR and DFS of CRC using TNT approaches [3]. TNT, as a prospective therapy for LARC patients, has been previously studied in single-arm clinical trials with small sample sizes. However, the findings revealed large PCR variations (20–40%) in LARC patients post-TNT treatment [4, 5]. In a retrospective study, LARC patients subjected to TNT with an additional

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induction chemotherapeutic dose on top of the standard CRT prior to surgery showed an improved PCR rate in comparison to the ACT-treated patients (36% vs. 21%) [6].

Recently, several clinical trials have started to explore the possibility of separately incorporating CT and CRT into the neoadjuvant LARC regimens. However, it is not clear which combination of TNT imparts the highest therapeutic potential of significantly improving the PCR [7]. Nonetheless, TNT interventions exhibit a high level of safety and efficacy in LARC patients and are likely becoming a standard remedy for LARC in the near future [8].

Given that TNT shows higher PCR than conventional nCT, it should be routinely practiced in LARC patients. There are two distinct TNT treatment modalities: CRT with induction CT and CRT with consolidated CT. The main difference between the two modalities lies in the timing of CT induction with respect to CRT initiation. Currently, there are no studies available to compare which of the two modalities would give superior clinical outcomes. In this study, we aim to conduct a meta-analysis to comparatively evaluate rates of OP, PCR, 3-year DFS, LR, R0 resection, compliance, and grade 3–4 toxicities between the nCRT combined with induction CT and nCRT combined with consolidated CT in LARC patients.

Materials and Methods

Literature Search Strategy

We retrieved relevant research articles published on Pub-Med, MEDLINE, Embase, Cochrane, and Web of Science between the study inception and July 2022. We primarily identified clinical trial-based articles comparing TNT treatment modalities in cohorts of CRC patients using the following MeSH terms: "rectum tumor OR rectal cancer," "neoplasm," "chemoradiotherapy," "induction chemotherapy," "consolidation chemotherapy," "neoadjuvant therapy," and "preoperative."

Selection Criteria

For this meta-analysis, eligible studies were screened based on the following inclusion/exclusion criteria.

A study was included if it was (1) a randomized, controlled trial (RCT); (2) mainly focusing on nCRT with induction CT and/or nCRT with consolidated CT for treating CRC; (3) published in English; and (4) involving human subjects only.

On the other hand, a study was excluded if it was (1) not an RCT; (2) performed in a cohort of < 30 participants; (3) a duplicate study; (4) not relevant; and (5) not published in English.

Data Extraction and Quality Control

Two investigators independently searched, screened, reviewed, and extracted data from the eligible studies. Any discrepancy in the opinion of the two investigators was further reviewed and resolved by a third investigator.

The following data were extracted from our screened, eligible studies: (1) general information, including authors' names, publication time, country, cohort size, radio- and chemotherapeutic regimens and doses, and sequence of treatment (simultaneous or sequential); (2) OP rate; (3) PCR; (4) 3-year DFS; (5) LR; (6) R0 resection rate; (7) compliance rate; and (8) grade 3–4 toxicities.

The primary endpoint is an OP that is defined as TME (total mesorectal excision)-free survival measured in the intention-to-treat population. The secondary endpoints are PCR and DFS. PCR is defined as the disappearance of all invasive cancer in the rectum upon completion of TNT, although some authors require clearance of residual tumors in axillary nodes as well. DFS, frequently used under adjuvant settings, is defined as the time from randomization to recurrence of tumor or death. It is a direct measure of clinical benefits when the efficacy of an experimental therapy outweighs its toxicity. Other secondary outcomes included LR, R0 resection, compliance, and grade 3–4 toxicities.

The Jadad scale (JS) was utilized by two investigators to evaluate the quality of pre-screened articles. Only the RCTs with JS scores > 3 passed the QC check for the final analysis.

Statistical Analysis

This meta-analysis was registered under PROSPERO (Registration # CRD42022300059) and conducted by Stata 16.0/MP. The relative risk with a 95% confidence interval was generated for binary variants. Q tests were applied to heterogeneous results. If I^2 was less than 50% and p was more than 0.01, a fixed-effect (FE) model was implemented; otherwise, a random-effect (RE) model was used. If heterogeneity was observed, sensitivity and subgroup analyses were carried out. Funnel plots were generated to evaluate the risk of publication bias (PB), and PB was subsequently quantified by Egger's regression. All results with $p < 0.05$ were regarded as statistically significant.

Results

Our retrieval strategy initially obtained 128 articles. After applying the pre-determined inclusion/exclusion criteria, the 128 articles were condensed to only 4 that reported

in-depth descriptions of clinical trials and were selected for our meta-analysis (Fig. 1). Tables 1, 2, 3, listed the characteristics and details of the above four clinical trials.

Two of the four articles analyzed the effects of TNT treatment modalities on the OP rate. No statistical heterogeneity was reported between the groups ($p = 0.37$), when an FE model was employed. The OP rate of the nCRT with consolidated CT group was significantly higher than that of the nCRT with induction CT group (RR 1.53; 95% CI 1.09–2.14) (Fig. 2A).

Three of the four articles analyzed PCR rates. An RE model was applied to these articles, since there was significant statistical heterogeneity between the two groups ($p = 0.000$). After thoroughly scrutinizing the results, we did not find any therapeutic difference in subjects treated with nCRT and induction CT or nCRT and consolidation CT (RR 0.74; 95% CI 0.15–3.54) (Fig. 2B).

Two of the four articles were analyzed for the influence of TNT treatment modalities on the 3-year DFS rate. No statistical heterogeneity was observed between these two

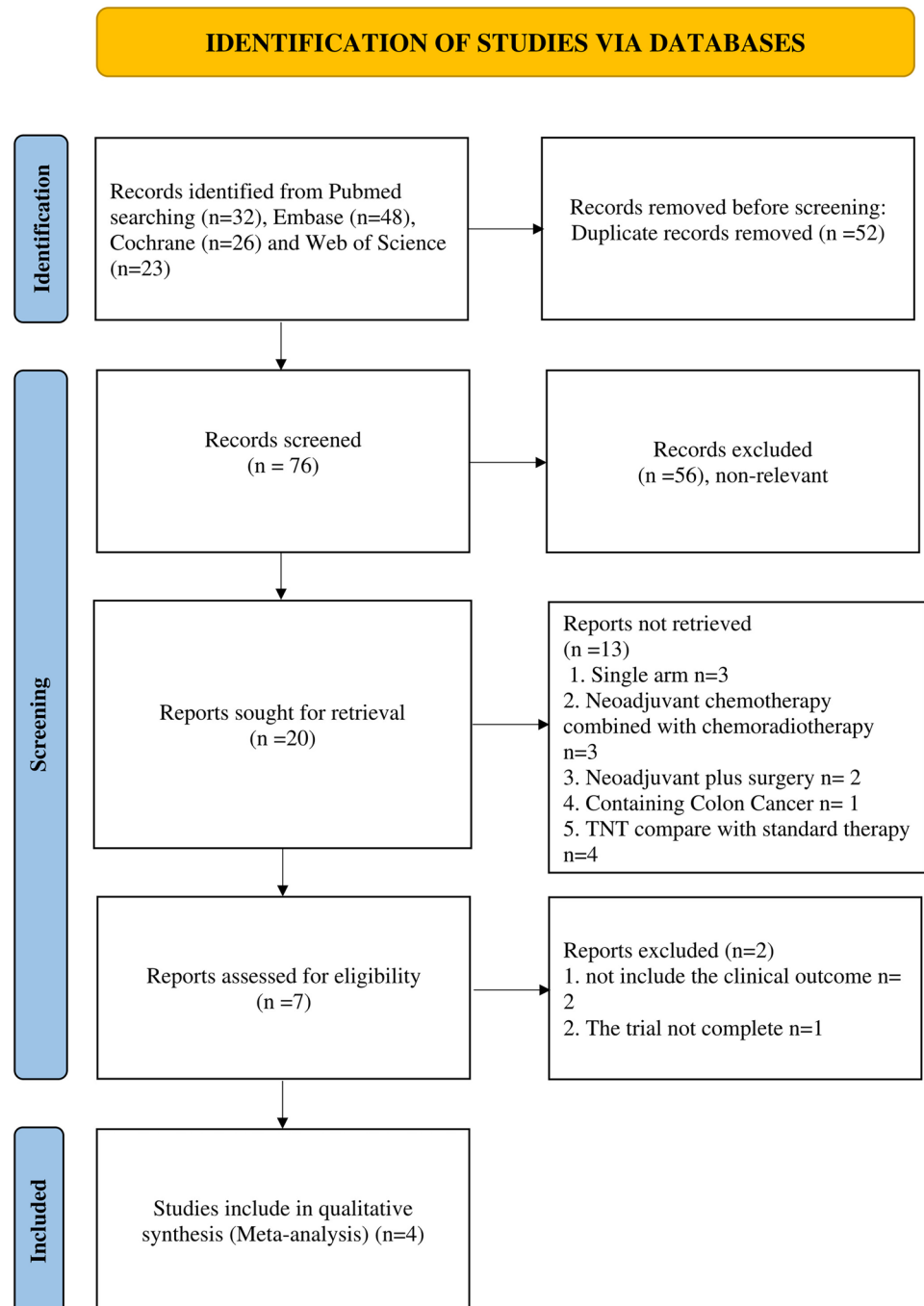**Fig. 1** Identification of studies via databases

IDENTIFICATION OF STUDIES VIA DATABASES

Identification

Records identified from Pubmed searching (n=32), Embase (n=48), Cochrane (n=26) and Web of Science (n=23)

Records removed before screening: Duplicate records removed (n =52)

Screening

Records screened (n = 76)

Records excluded (n =56), non-relevant

Reports sought for retrieval (n =20)

Reports not retrieved (n =13)
 1. Single arm n=3
2. Neoadjuvant chemotherapy combined with chemoradiotherapy n=3
3. Neoadjuvant plus surgery n= 2
4. Containing Colon Cancer n= 1
5. TNT compare with standard therapy n=4

Reports assessed for eligibility (n =7)

Reports excluded (n=2)
1. not include the clinical outcome n= 2
2. The trial not complete n=1

Included

Studies include in qualitative synthesis (Meta-analysis) (n=4)

Table 1 Basic characteristic of the included studies

Study year	Country	Patient no	nCRT + consolidated CT	nCRT + indution CT	Jadade score	Ref
Fokas et al. (2018)	Germany	306	Consolidation chemotherapy consisted of oxaliplatin (100 mg/m²) administered as a 2-h infusion, followed by a 2-h infusion of leucovorin (400 mg/m²), followed by a continuous 46-h infusion of fluorouracil (2400 mg/m²), repeated on day 15 for a total of three cycles after preoperative radiotherapy consisted of 50.4 Gy in 28 fractions using intensity-modulated radio therapy to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes. As established by our previous phase III trial (CAO/ARO/AIO-04), concurrent chemotherapy was administered using continuous infusion of fluorouracil (250 mg/m²) on days 1 to 14 and 22 to 35 and a 2-h infusion of oxaliplatin (50 mg/m²) on days 1,8, 22, and 29 of radiotherapy	Induction chemotherapy consisted of oxaliplatin (100 mg/m²) administered as a 2-h infusion, followed by a 2-h infusion leucovorin (400 mg/m²), followed by a continuous 46-h infusion of fluorouracil (2400 mg/m²), repeated on day 15 for a total of three cycles before preoperative radiotherapy consisted of 50.4 Gy in 28 fractions using intensity-modulated radio therapy to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes. As established by our previous phase III trial (CAO/ARO/AIO-04), concurrent chemotherapy was administered using continuous infusion of fluorouracil on days (250 mg/m²) on days 1 to 14 and 22 to 35 and a 2-h infusion of oxaliplatin (50 mg/m²) on days 1, 8, 22, and 29 of radiotherapy	4	[21]
Julio Garcia-Aguilar et al. (2020)	USA	307	Neoadjuvant chemoradiation before chemotherapy Patients will have 6 weeks of chemoradiation therapy. Along with the intensity modulated radiotherapy (IMRT) 5400 cGy, the patients will receive either 5-FU or capecitabine. 2–4 weeks after patients will have endoscopic exam and if stable or response patients will have 8 cycles of FOLFOX or 6 cycles of CapeOX	Induction chemotherapy before chemoradiation. The neoadjuvant chemotherapy regimen is prescribed specifically as 8 cycles of FOLFOX or 5 cycles of CapeOX over a period of approximately 15–16 weeks. Endoscopic exam (2–4 weeks) after chemotherapy. If stable or response patients then patients will have intensity modulated radiotherapy (IMRT) 5400 cGy with either 5-FU or capecitabine	4	[18]
Danijela Golo et al. (2018)	Slovenia	43	Consolidation chemotherapy after chemoradiotherapy (CRT). Radiation doses were 50.4 Gy for T2–3 and 54 Gy for T4 tumors in 1.8 Gy daily fraction. The doses of concomitant and neo/adjuvant capecitabine were 825 mg/m²/12 h and 1250 mg/m²/12 h, respectively	Induction chemotherapy cycle followed by chemoradiotherapy (CRT). Radiation doses were 50.4 Gy for T2–3 and 54 Gy for T4 tumors in 1.8 Gy daily fraction. The doses of concomitant and neo/adjuvant capecitabine were 825 mg/m²/12 h and 1250 mg/m²/12 h, respectively	3	[26]
Aurelie Garant et al. (2020)	Canada	180	Neoadjuvant HDRBT with surgery and FOLFOX ×12 cycles	Neoadjuvant HDRBT with surgery and FOLFOX ×12 cycles surgery	4	[22]

Table 2 Disease-related outcomes of eligible studies

Study	Group (case number)	R0 Resection	pCR	OP	Compliance	3-year DFS	LR	Grade 3 and 4 toxicities
Fokas, 2018	nCRT + consolidated CT	130/142	38/150	(103/142)	144/150	110/150	7/150	30/150
	nCRT + indution CT	128/142	27/38	96/142	145/156	113/156	9/156	34/156
Julio Garcia-Aguilar, 2020	nCRT + consolidated CT	53/166	58/166	89/155	NR	126/166	9/133	63/166
	nCRT + indution CT	67/158	31/158	65/152	NR	120/158	7/133	71/158
Danijela Golo, 2018	nCRT + consolidated CT	NR	NR	NR	58/62	NR	NR	NR
	nCRT + indution CT	NR	NR	NR	65/66	NR	NR	NR
Aurelie Garant, 2020	nCRT + consolidated CT	NR	38/120	NR	31/60	NR	3/60	16/60
	nCRT + indution CT	NR	16/60	NR	96/120	NR	7/120	42/120

groups ($p = 0.186$); hence, an FE model was utilized. The 3-year DFS outcome of the nCRT with consolidated CT group was comparable to that of the nCRT with induction CT group (RR 1.02; 95% CI 0.71–1.46) (Fig. 2C).

The LR effect was assessed in 3 articles and revealed no statistical heterogeneity in results between these groups ($p = 0.778$). Hence, an FE model was applied. The outcome analysis indicated comparable LR effects of both therapeutic regimens on the LR (RR 0.98; 95% CI 0.52–1.85) (Fig. 2D).

Two of the four articles compared the R0 resection rates between the two TNT modality groups. An FE model was employed due to an absence of statistical heterogeneity ($p = 0.190$). Comparable R0 resection outcomes were observed in both treatment modalities (RR 0.74; 95% CI 0.55–1.10) (Fig. 3A).

The compliance rate was measured in 3 articles and showed significant statistical heterogeneity ($p = 0.007$); hence, anRE model was used. The compliance rate did not vary between the two groups (RR 0.52; 95% CI 0.12–2.26) (Fig. 3B).

Three of the four articles analyzed the grade 3–4 toxicities. No statistical heterogeneity was observed between the groups ($p = 0.800$). Therefore, a FE model was employed and showed no remarkable diversities in outcomes between the two groups (RR 0.78; 95% CI 0.57–1.06) (Fig. 3C).

Egger's regression tests were conducted to evaluate the PB and symmetry of the funnel plot. There was no detectable PB in our study ($p > 0.05$) (Fig. 4). Consistently, the funnel plot was symmetric.

Discussion

To the best of our knowledge, our study represents the first meta-analysis comparing the clinical outcomes between preoperative nCRT with induction CT and that with consolidated CT in CRC. The pooled analysis demonstrated a significantly higher organ preservation rate in patients treated with nCRT and consolidated CT than that with nCRT and induction CT. No significant differences were observed between the two treatment modality groups in terms of PCR, 3-year DFS, LR, R0 resection, compliance, and grade 3–4 toxicities.

The National Comprehensive Cancer Network (NCCN) guidelines suggest that multiple small trials should be performed so that the efficacy of respective CT courses can be determined before initiating CRT and surgical excision to avoid postoperative CT [9–14]. In the Spanish GCR-3 phase II RCT, patients received a combined regimen of oxaliplatin and capecitabine (CapeOX) either before the CRT or postoperatively [11, 15]. The results showed that induction

Table 3 Summary results between the two TNT regimens

| nCRT + consolidated CT (A)	nCRT + indution CT (B)	Result
OP [18, 21]		The OP rate of the A group was higher than the B group
PCR [18, 21, 22]		The PCR rate of the A group was similar to the B group
3-year DFS [18, 21]		The 3-year DFS rate of the A group was similar to the B group
LR [18, 21, 22]		The LR rate of the A group was similar to the B group
R0 [18, 21]		The R0 rate of the A group was similar to the B group
Compliance [21, 22, 26]		The compliance rate of the A group was similar to the B group
Grade 3–4 toxicities [18, 21, 22]		The grade 3–4 toxicities rate of the A group was similar to the B group
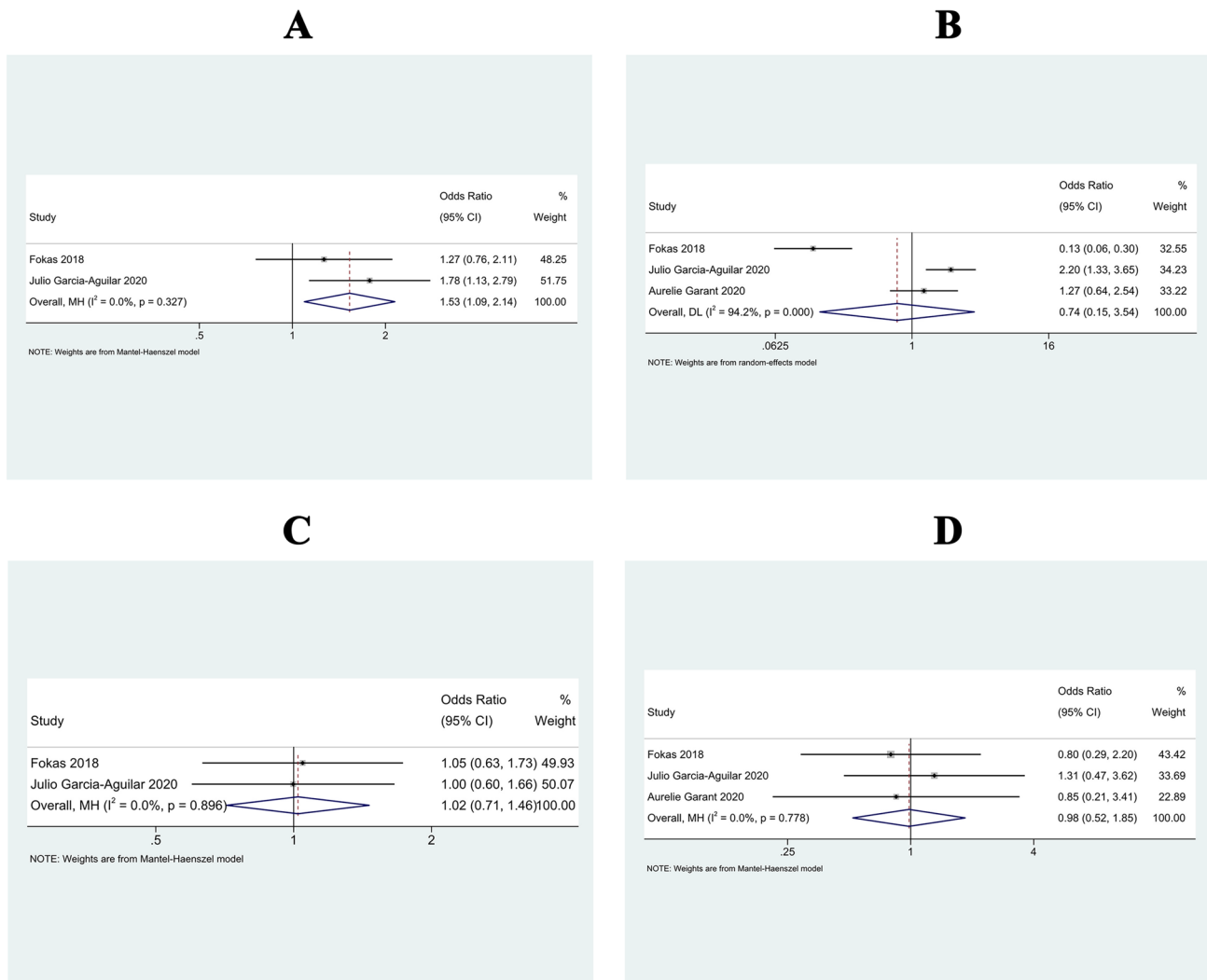
Fig. 2 The effects of TNT treatment modalities on the OP rate (**A**); analyzed PCR rates (**B**); analyzed for the influence of TNT treatment modalities on the 3-year DFS rate (**C**); the outcome analysis indicated comparable LR effects of both therapeutic regimens on the LR (**D**)

CT elicited reduced toxicity and better tolerance in CRC patients, thus improving the PCR rate. In another stage II trial, patients were randomized to CRT and surgery groups in the presence or absence of FOLFOX [intravenous (IV) oxaliplatin and leucovorin calcium for > 2 h on day 1, and IV 5-fluorouracil continuously for > 44 h on days 1–3] induction CT [16]. No significant differences were observed in treatment outcomes between these two clinical trial arms. Notably, patients receiving induction CT encountered greater toxicities. In the stage II CRC trial AVACROSS, the safety and potency of bevacizumab supplemented to induction CT with CapeOX before the capecitabine/bevacizumab-CRT and surgical interventions, were evaluated [14]. The treatment plan was well tolerated, with a PCR rate of 36%. A meta-analysis of two phase II clinical trials, EXPERT and EXPERT-C, also evaluated the efficacy and

safety of neoadjuvant CT before CRT and surgery [17]. Of the 269 patients tested, 91.1% finished the induction CT, 88.1% completed CRT, and 89.2% received therapeutic surgeries. The 5-year PFS and OS rates were 66.4% and 73.3%, respectively.

TNT is increasingly adopted for CRC and can be administered exclusively as an induction CT before CRT or in a consolidated manner after CRT. Thus, the optimal sequence of TNT needs to be established. The prior CAO/Ark/AIO-12 and the OPRA (organ preservation of rectal adenocarcinoma) trials both investigated the TNT sequence, with different duration and clinical approaches [18–21]. At a median follow-up of 2 years, no significant differences were reported in 3-year DFS, while the OP was significantly elevated in the consolidation arm, which is highly consistent with our meta-analysis results. Overall, the prior studies
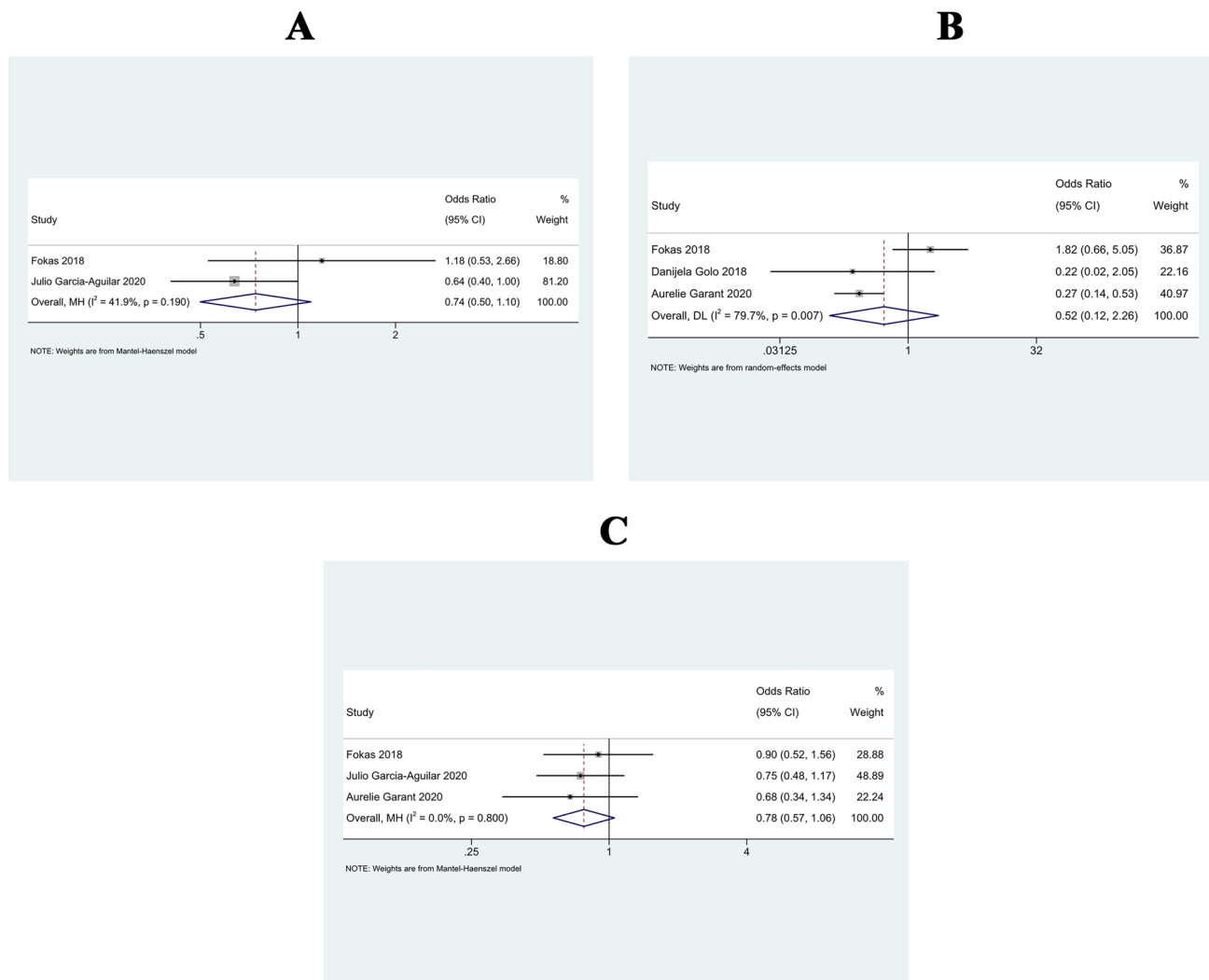
A

B

C

Fig. 3 Compared the R0 resection rates between the two TNT modality groups (**A**); showed significant statistical heterogeneity, anRE model was used—the compliance rate did not vary between the two groups (**B**); a FE model was employed and showed no remarkable diversities in outcomes between the two groups (**C**)

and our data indicate that although the sequence of treatment does not significantly affect clinical outcomes, consolidation CR after long-course chemoradiotherapy (LCRT) is consistently associated with better tolerance and organ preservation. However, the optimal drug regimen remains a matter of debate since the CAO/Ark/AIO-12 and OPRA studies used FOLFOX (a doublet), while another clinical study (PRODIGE-23) that also reported high PCR rates used FOLFIRINOX (a triplet). This debate may be addressed by ongoing clinical trials such as GRECCAR12 with a FOLFIRINOX regimen.

The randomized phase II KIR clinical study was conducted to optimize the treatment sequence of chemotherapy for CRC patients. In this study, 180 patients were randomized (2:1) to either Arm A (AA) with 6 cycles of FOLFOX prior to high-dose rate brachytherapy (HDRBT) and surgery plus adjuvant 6 cycles of FOLFOX or Arm B (AB) with neoadjuvant HDRBT with surgery and adjuvant 12 cycles of FOLFOX. No statistical differences were found in PCR rate, LR, and DFS between the two arms [22], which is in line with our meta-analysis results. Interesting, the "pick-the-winner" CAO/Ark/AIO-12 trial compared induction versus consolidation FOLFOX and found that the consolidation arm was better at achieving a higher PCR rate and lower grade 3–4 toxicities. In contrast, our meta-analysis showed no such differences in the above clinical outcomes. More randomized controlled trials with different samples sizes and comparable parameters may be needed to explain the discrepancies between the two studies.

To assess whether adding cycles of FOLFOX between CRT and surgery could increase PCR, a phase II trial was conducted to include groups of LARC patients who received
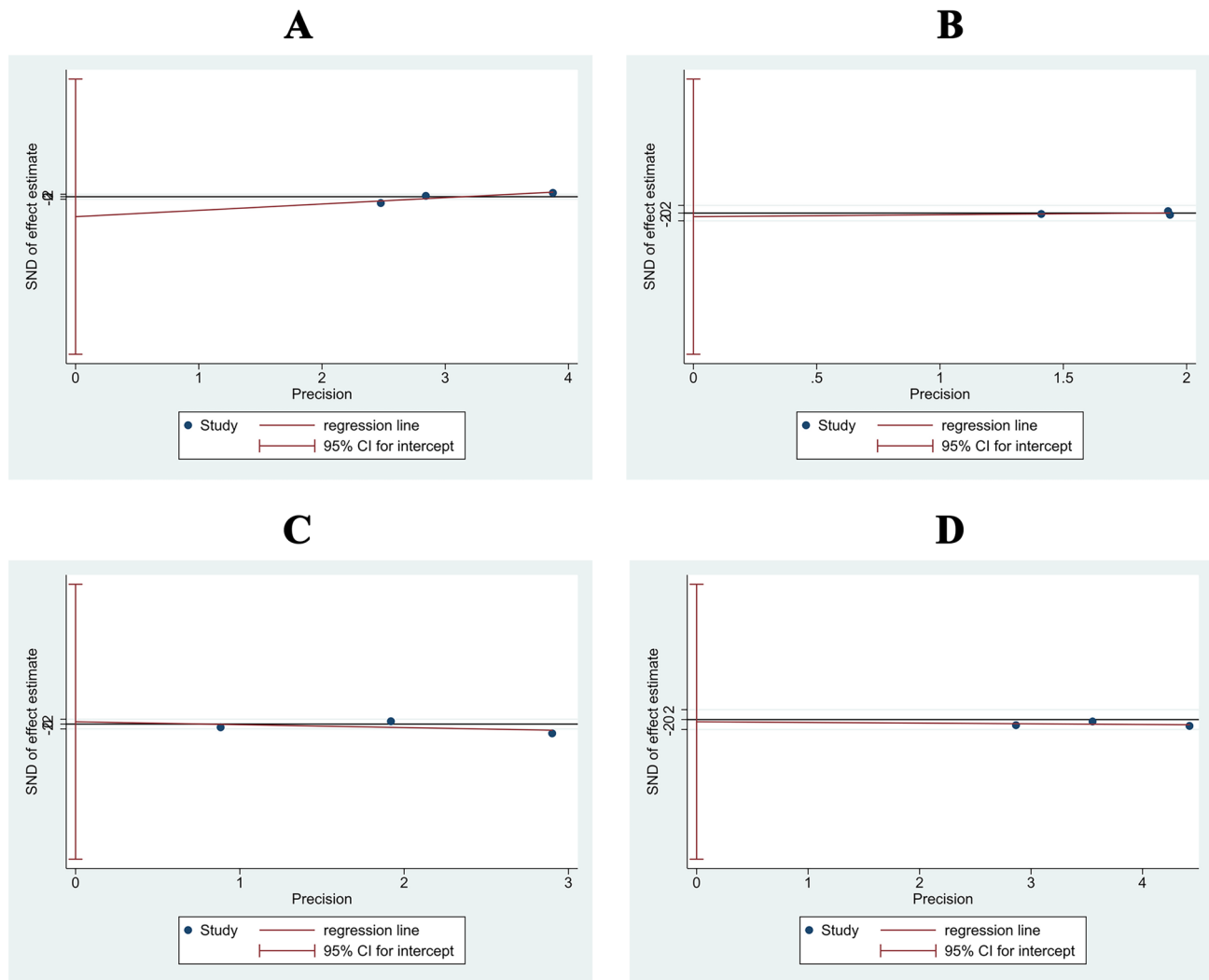
A

B

C

D

Fig. 4 Egger's regression tests were conducted to evaluate the PB and symmetry of the funnel plot

different cycles of consolidation chemotherapy (FOLFOX) [18]. The PCR rates from these groups were 18%, 25%, 30%, and 38%, respectively, suggesting that longer consolidation CT leads to better PCR rates. Furthermore, increasing consolidation CT also led to improved 5-year DFS in a different study) [23]. In contrast to the above data, a study comparing FOLFOX with fluorouracil/(oxaliplatin)-based CRT after short-course chemoradiotherapy (SCRT) found that consolidation CT provided better 3-year overall survival than CRT (73% vs. 65%) but had no effects on PCR, DFS, or R0 resection [24]. Results of the similarly designed RAPIDO trial are pending [25].

In a phase II trial assessing induction therapy before CRT [11, 15], 108 patients received capecitabine/oxaliplatin either before CRT or as an adjuvant after. Compared to the adjuvant group, induction CT yielded lower grade 3–4 toxicities and better compliance, whereas the 5-year

DFS and PCR showed no differences [11, 26]. Similarly, patients treated with FOLFOX induction before CRT demonstrated significantly higher complete response than those treated with adjuvant CT in a retrospective cohort [18].

In a pioneer study carried out by Van Zoggel et al. [27], the 3-year OS, local recurrent-free survival, and distant metastasis-free survival all increased for patients with a PCR compared to those without a PCR. In a recently published phase III clinical trial, Conroy et al. [28] compared neoadjuvant chemotherapy (induction FOLFIRINOX, CRT, and adjuvant CT/capecitabine) with standard-of-care (CRT and adjuvant CT) and found that the PCR rate was significantly higher in patients who received induction (27.5% vs. 11.7%). The disease-free survival was also improved (75.7%vs. 68.5%), although the three-year overall survival data have not yet matured.

Limitations

Our meta-analysis has several limitations. For instance, the sample size was relatively small and the follow-up time was short for the evaluation of long-term survival outcomes. Second, some of the outcome measures were incomplete; we did not have sufficient data to calculate a pooled overall survival. Third, we did not directly compare induction and consolidation programs in this work; these data will be collected from ongoing trials and analyzed. More randomized controlled trials will be carried out for best beneficiaries and choice of indications in both nCRT with induction CT, and nCRT with consolidated CT groups. Up to now, the optimal TNT in CRC patients is still under debate. Rather than discussing the merits of TNTs, our primary aim is to demonstrate which patient group can benefit most from TNT, and further extrapolations can be made with our stratified analysis in the future. Despite these limitations, we believe that this study made a valuable contribution and treatment reference to TNT.

Conclusion

This meta-analysis compared the clinical outcomes between two TNT treatment modalities: nCRT with induction CT and nCRT with consolidated CT in CRC patients. Our results showed that the consolidation arm significantly improved organ preservation but had no impacts on PCR, 3-year DFS, LR, R0 resection, compliance, and grade 3–4 toxicities.

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Author Contribution Pengkhun Nov acquisition of data, analyzing, interpretation of data, and drafting the article; Kunpeng Du and Jiqiang Li designing, revising, and guiding the study. The authors read and approved.

Data Availability All the data for this article can be found on PubMed, MEDLINE, Embase, the Cochrane Library, and Web of Science.

Declarations

Ethics approval Not applicable

Consent for publication All the authors of the article agreed to be published in the journal.

Competing interests The authors declare no competing interests.

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