

Neoadjuvant treatments for resectable rectal cancer: A network meta-analysis

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Abstract. Different neoadjuvant therapy regimens are available for rectal cancer, but the relative effects are controversial. The aim of the present network meta-analysis (NMA) was to estimate the relative efficacy and safety of neoadjuvant therapies for resectable rectal cancer. MEDLINE, EMBASE and Cochrane Central Registry of Controlled Trials were searched for publications dated from 1946 up to June 2018. The present study included randomized clinical trials that compared treatments for resected rectal cancer: Surgery alone, surgery preceded by neoadjuvant radiotherapy (RT), neoadjuvant chemotherapy (CT) or neoadjuvant chemoradiotherapy (CRT). Direct pairwise comparisons and NMA were conducted. A total of 23 randomized controlled trials were included in the present study. RT had an overall survival (OS) benefit when compared with surgery alone [HR (hazard ratio), 0.89; 95% confidence interval (CI), 0.82-0.97; quality of evidence, high]. All three neoadjuvant regimens were associated with lower local recurrence (LR) when compared with surgery alone [RT: odds ratio (OR), 0.44; 95% CI, 0.35-0.65; quality of evidence, high; CRT: OR, 0.34; 95% CI, 0.23-0.56; quality of evidence, low and CT: OR, 0.32; 95% CI, 0.11-1.00; quality of evidence, low]. There were no significant differences in OS and LR between CRT and RT (OS: OR, 1.10; 95% CI, 0.93-1.20; LR: OR, 0.81; 95% CI, 0.61-1.10). Ranking probabilities indicated that CRT was the best strategy for local control, with a surface

under the cumulative ranking curve (SUCRA) of 78.78%. Patients treated with RT had improved disease-free survival compared with those treated with surgery alone (HR, 0.82; 95% CI, 0.64-1.00; quality of evidence, low). Neoadjuvant RT or CRT did not significantly improve distant metastases compared with surgery alone (RT: OR, 0.87; 95% CI, 0.69-1.10 and CRT: OR, 0.75; 95% CI, 0.47-1.10). CRT had an improved pathological complete response rate compared with RT (OR, 4.90; 95% CI, 21.80-17.00; quality of evidence, low). No significant difference for the risk of anastomotic leak between each treatment was observed in the NMA. In conclusion, RT decreased the LR and improved OS compared with surgery alone for resected rectal cancer. CRT was the best neoadjuvant therapy analyzed and CT was likely the second best for all outcomes based on SUCRA. However, these findings were limited by overall low quality of evidence.

Introduction

Rectal cancer represents approximately a third of colorectal cancer cases in the USA and remains an important contributor to the global tumor burden (1,2). The 5-year survival rate of patients with rectal cancer undergoing surgery is 50% because of the high risk of local recurrence (LR), despite resection being considered as curative (3). The LR of rectal cancer occurs in 30-50% of patients who have undergone only radical resection (4). Among randomized trials published from 2004 to 2009, 30-40% of patients with rectal cancer developed metastatic rectal cancer (5). With decades of research and practice, important advances have been made in the treatment of rectal cancer with the introduction of total mesorectal excision (TME), the addition of (chemo)radiotherapy preoperatively and the use of magnetic resonance imaging for more accurate clinical staging (6-9).

Improvements in surgical technique have significantly lowered the incidence of rectal cancer LR. Intact removal of the entire mesorectum in cancer of the mid or lower third of the rectum has resulted in LR rates as low as 5-10% (10). Parallel to improvements in surgical technique, adjuvant therapy regimens have been tested in clinical trials in an effort to improve survival and reduce LR (11). Several randomized controlled trials have evaluated neoadjuvant radiotherapy in patients undergoing resection for rectal cancer and collectively found that it decreased the risk of LR but did not significantly

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Abbreviations: RT, surgery preceded by neoadjuvant radiotherapy; CT, surgery preceded by neoadjuvant chemotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; SUCRA, surface under the cumulative ranking curve; pCR, pathological complete response rate; RCT, randomized clinical trial; NMA, network meta-analysis

Key words: rectal cancer, neoadjuvant, chemoradiation, chemotherapy, network meta-analysis

improve overall survival (OS) or the rate of distant metastases (7,12,13). However, survival benefit was observed in some trials (14,15).

In order to improve tumor response and long-term survival, preoperative radiotherapy has been combined with chemotherapeutic regimens (16). After long-term exploration and unremitting efforts, preoperative radiotherapy or chemoradiotherapy followed by TME and postoperative chemotherapy is the current recommended regimen for patients with stage II and III rectal cancer (17). Using such multimodality strategies reduces LR rates to <10% (11). The addition of neoadjuvant chemotherapy resulted in greater tumor downsizing and downstaging, improved the pathological complete response rate (pCR) and local control, but still led to little OS benefit when compared with preoperative radiotherapy without chemotherapy (18,19). Considering preoperative radiotherapy increases the risk of treatment-related toxicities and the frequency of postoperative complications, some research teams are investigating neoadjuvant chemotherapy without radiotherapy in patients with rectal cancer (20–22). The FOWARC study compared preoperative chemoradiotherapy using folinic acid, fluorouracil and oxaliplatin (FOLFOX) chemotherapy plus radiotherapy, with FOLFOX-based chemotherapy alone. The aforementioned study found that FOLFOX alone seems to have an identical LR rate, 3-year disease-free survival (DFS) and 3-year OS compared to standard FOLFOX plus radiotherapy (20). However, there is still a lack of evidence directly comparing surgery preceded by neoadjuvant chemoradiotherapy (CRT) with surgery preceded by neoadjuvant chemotherapy (CT).

Clinical trials and conventional meta-analysis do not allow comparisons to be made between all regimens, and opinions concerning a definition for optimum neoadjuvant treatment strategy for resected rectal cancer differ (23). Therefore, network meta-analysis (NMA) may be a potential consideration with which to advance the current understanding of the best regimen for resected rectal cancer and to help guide clinical decision making. NMA is a statistical method that aims to combine information from all randomized comparisons between a set of treatments for a given medical condition (24). By using Bayesian NMA in the present study, the objective was to find the most effective neoadjuvant therapy regimen for resected rectal cancer. Regimens were compared in terms of the primary outcomes OS and LR, and the secondary outcomes DFS, distant metastases, pCR, organ preservation, 30-day mortality and anastomotic leak.

Materials and methods

Literature search. MEDLINE (OvidSP; <http://ovidsp.ovid.com/>), EMBASE (<https://www.embase.com/>) and Cochrane Central Registry of Controlled Trials (CENTRAL) (<http://cochranelibrary-wiley.com/o/cochrane/clcentral/>) were systematically searched in the range between 1946 up to and including May 29 2018. Search terms included extensive controlled vocabulary (medical subject headings and embase subject headings) in various combinations, supplemented with key words including rectal cancer, chemotherapy, radiotherapy, chemoradiotherapy and randomized clinical trials (RCTs). There were no language restrictions made. Electronic searches

were performed and supplemented with manual searching for all available articles, including review articles and abstracts from conferences. The literature search strategy used for the present study is depicted in Table SI.

Study selection and data extraction. RCTs that met the following criteria were included in the present study: i) The study enrolled patients with resectable rectal cancer; ii) treatments that administered surgery alone, surgery preceded by neoadjuvant radiotherapy (RT), CT or CRT; and iii) the study reported on at least one of the following outcomes: OS, DFS, perioperative deaths (30-day mortality), pCR, LR, distant metastases, surgery complications and organ preservation. Exclusion criteria included the following: Non-resectable or metastatic rectal cancer, any prior intervention other than diagnostic biopsy and non-randomized trials.

The selection of studies was carried out by two reviewers (WZ and XJX) and included independently screening titles and abstracts for inclusion, extracting the data and assessing the methodological quality of the included studies. Disagreements were resolved by consensus or with a third adjudicator. Data regarding study and population characteristics, as well as treatments and outcomes, were extracted. For OS and DFS, the hazard ratio (HR) and 95% confidence interval (CI) were extracted when available. If HRs were not reported in the original publications, the HR was calculated using methods outlined by Tierney *et al* (25). Odds ratios (ORs) were calculated for patterns of recurrence, distant metastases, pCR, organ preservation and surgery complications (for example, perioperative mortality). For multiple reports of the same trial, reports containing the longest follow-up data were used.

Risk of bias assessment. For the included studies, assessment of risk of bias was conducted independently by two reviewers (WZ and XJX) using the Cochrane risk of bias assessment tool (26,27). Studies were assessed on the basis of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. Any discrepancies were resolved through consensus with a third reviewer (LZD).

Quality of evidence assessment. The quality of evidence for each direct, indirect and NMA outcome was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation method (28,29). The quality of evidence of each direct comparison outcome was ranked as high, moderate, low and very low, based on its risk of bias, consistency, directness, precision of the results and publication bias (28). The quality of evidence of indirect and network effects estimates were derived from those of direct-effects estimates by evaluating network geometry, intransitivity and incoherence (29). For a particular comparison, both direct and indirect evidence were available, the higher of the two quality ratings was presented as the quality rating for the NMA estimate. Detailed information for the quality of evidence of direct and indirect comparisons is shown in Table SII.

Statistical analysis. Evidence for eight outcomes were synthesized: Primary outcomes (OS and LR) and secondary outcomes (DFS, distant metastases, pCR, 30-day mortality,

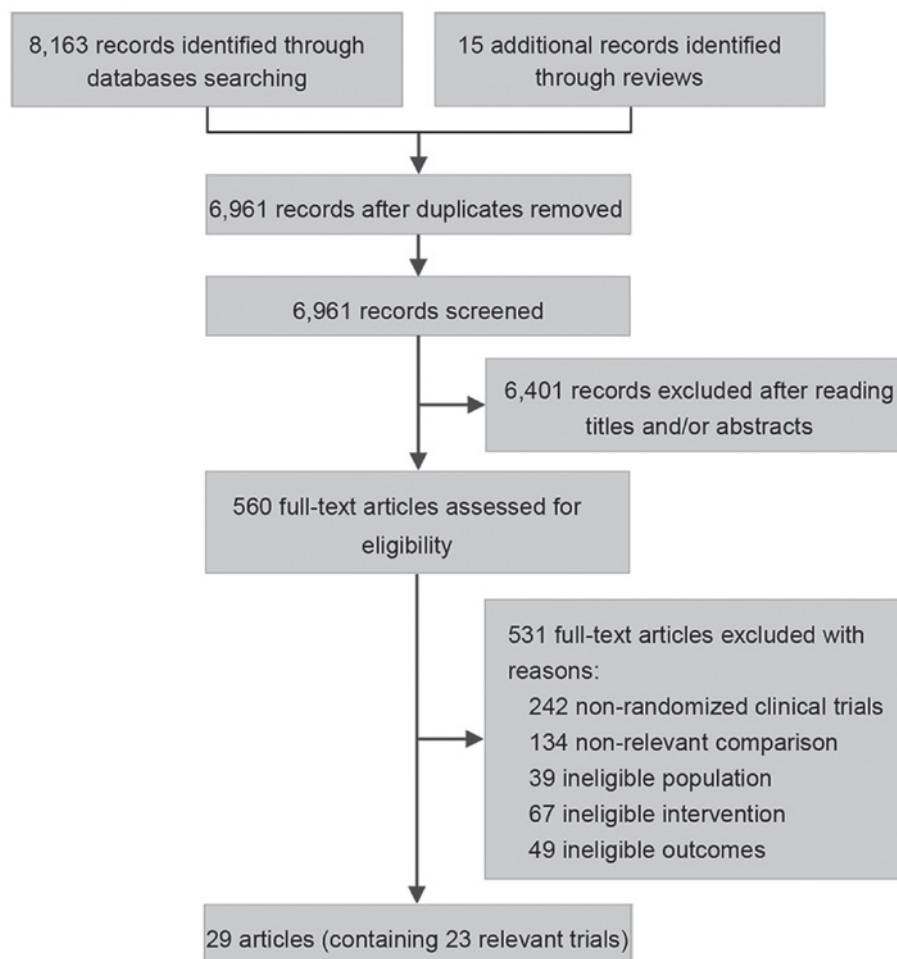


Figure 1. Flow diagram of literature search and article selection process.

anastomotic leak and organ preservation). Direct comparison was performed using a random-effects model to estimate pooled HR or OR and 95% CI incorporating within- and between-study heterogeneity (30). Statistical heterogeneity of direct comparison was assessed using the I^2 index and Cochrane Q test. For each outcome, a Bayesian NMA using Markov chain Monte Carlo simulation with non-informative prior distribution (A prior distribution which is non-committal about a parameter, for example, a uniform distribution) was also performed. The analysis used generalized linear models with a logit link function with 4 chains and 100,000 iterated simulations, discarding the initial 5,000 iterations as burn-in. Convergence was assessed using the Brooks-Gelman-Rubin statistic (31). To test the robustness of this assumption, the node-splitting method was used to assess whether there was incoherence in the closed loop (32).

The Bayesian NMAs also allow for the probabilistic interpretation of uncertainty and ranking of interventions (33). Rank probabilities were calculated from proportions of Markov chain cycles, according to the pooled effect size of each intervention. Surface under the cumulative ranking curve (SUCRA) for each treatment was calculated from a cumulative ranking (34). All the analyses were conducted using R (version 3.4.1; <http://www.R-project.org>) with R packages gemtc (version 0.8-2; <http://cran.r-project.org/web/packages/gemtc/index.html>), meta (version 4.9-5; <https://cran.r-project.org/web/packages/meta/index.html>) and rjags (version 4-8; <https://cran.r-project.org/web/packages/rjags/index.html>) and JAGS (version 4.3.0; <http://mcmc-jags.sourceforge.net/>).

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Results

Study characteristics. Of the 8,178 citations identified via the literature search in the present study, 6,961 citations were retained after removing duplicates and subsequently 6,401 articles were excluded after title and abstract screening, leaving 560 studies for a full-text review. Following exclusion of a further 531 articles which were deemed unsuitable, a total of 23 RCTs with a cumulative sample size of 10,895 patients were included in the review and NMA (7,11-14,18-20,35-54; Fig. 1). The number of patients involved in each study ranged from 68-1,805. Of the 23 studies, 15 included trials that made comparisons between RT and surgery alone (7,11-13,35-49). In 6 trials, RT was compared with CRT (8,14,17-18,54). For the two remaining trials, one compared CRT with surgery alone (50,51) and the other compared CRT with CT (30,31). No trial directly comparing CT with RT or surgery alone was included. Details of the baseline characteristics of the included trials and the treatment regimens are presented in Table I.

Risk of bias of included studies. Results of the quality assessment of the trials according to the Cochrane risk-of-bias

Table I. Baseline characteristics of included trials.

| Author, year | Study period | Treatment | Sample size | Treatment schedule | Cancer type and clinical stage | Follow-up (months) | Outcomes | (Refs.) |
|-------------------------------|--------------|-----------|-------------|--|---|--------------------|--|---------|
| Higgins <i>et al</i> , 1975 | 1964-1966 | RT+S | 347 | 20.0-25.0 Gy, 20 fr, 12 d; surgery at any time after RT | Operable rectal or sigmoid cancer | 60.0 (min) | OS, mortality | (35,36) |
| Rider <i>et al</i> , 1977 | NR | RT+S | 353 | 5 Gy, 1 fr | Rectal cancer | NR | OS, mortality | (37) |
| Duncan <i>et al</i> , 1984 | 1975-1978 | RT+S | 56 | 20.0 Gy, 10 fr, 14 d; surgery within 1 week after RT | Rectal cancer | 60.0 | OS, DFS, mortality | (39) |
| Higgins <i>et al</i> , 1986 | NR | RT+S | 272 | 34.5 Gy, 18 fr, 24 d; surgery immediately after RT | Resectable rectal or sigmoid Cancer | 45.0 | OS, mortality | (40) |
| Gérard <i>et al</i> , 1988 | 1976-1981 | RT+S | 180 | 34.5 Gy, 15 fr, 19 d; surgery after RT | T2, T3, T4 NX or M0 resectable rectal cancer | 75.0 | OS, LR, distant metastases, mortality | (41) |
| Reis <i>et al</i> , 1989 | 1978-1980 | RT+S | 224 | 40.0 Gy, 20 fr, 28 d; surgery 1 week after RT | Resectable rectal or rectosigmoid Cancer | 96.0 | OS, LR, distant metastases, mortality | (42) |
| Dahl <i>et al</i> , 1990 | 1976-1985 | RT+S | 34 | 31.5 Gy, 18 fr, 24 d; surgery 2-3 weeks after RT | Resectable rectal cancer | 73.2 | OS, DFS, LR, distant metastases, mortality | (13) |
| Marsh <i>et al</i> , 1994 | 1982-1986 | RT+S | 155 | 20.0 Gy, 4 fr, 4 d; surgery within 1 week after RT | Locally advanced rectal cancer | 96.0 (min) | OS, DFS, LR, distant metastases | (12) |
| Goldberg <i>et al</i> , 1994 | 1980-1984 | RT+S | 141 | 15.0 Gy, 3 fr, 5-7 d; surgery 2 days after RT | Resectable rectal cancer | 60.0 (min) | OS, LR, mortality | (43) |
| Cedermark <i>et al</i> , 1995 | 1980-1987 | RT+S | 228 | 25.0 Gy, 5 fr, 5-7 d; surgery within 7 days after RT | Resectable rectal cancer | 144.0 | OS, LR, distant metastases, mortality | (44) |
| Oates <i>et al</i> , 1996 | 1981,1989 | RT+S | 424 | 40.0 Gy, 20 Fr, 28 d; surgery after a minimum of 4 weeks | Rectal cancer | 120.0 | OS, DFS, LR, distant metastases, mortality | (45) |
| Cedermark <i>et al</i> , 1997 | 1987-1990 | RT+S | 139 | 25.0 Gy, 5 fr, 7 d; surgery within 1 week after RT | Resectable rectal cancer | 156.0 | OS, DFS, LR, mortality | (14) |
| Petersen <i>et al</i> , 1998 | 1988-1993 | RT+S | 140 | 16.5 Gy, 5 fr, 7 d; surgery within 2 days after RT | Rectal cancer | 44.1.0 | OS, LR, mortality | (46) |
| Martling <i>et al</i> , 2001 | 1987-1993 | RT+S | 374 | 25.0 Gy, 5 fr, 7 d; surgery within 1 week after RT | Resectable rectal cancer | 105.6 | OS, DFS, LR, distant metastases, mortality | (47) |
| Marijnen <i>et al</i> , 2011 | 1996-1999 | RT+S | 272 | 25.0 Gy, 5 fr, 5 d; surgery within 10 days of the start of RT | Resectable rectal cancer | 139.2 | OS, LR, distant metastases, mortality | (7) |
| Fan <i>et al</i> , 2015 | 2008-2012 | CRT+S | 285 | 46.0-50.0 Gy, 23-25 fr, 28 d; 2 cycles of modified XELOX regimen before surgery, 4 cycles of standard XELOX regimen and 4 cycles of capecitabine after surgery | T3-T4 or node-positive resectable rectal cancer | 38.0 | OS, LR, distant metastases, pCR, mortality | (51) |

Table I. Continued.

| Author, year | Study period | Treatment | Sample size | Treatment schedule | Cancer type and clinical stage | Follow-up (months) | Outcomes | (Refs.) |
|--------------------------------------|--------------|---------------|-------------|---|---|--------------------|--|---------|
| Boulis-Wassif <i>et al</i> , 1984 | 1972-1976 | CRT+S RT+S | 126 121 | CRT: 34.5 Gy, 15 fr, 18 d; 5-Fu (375 mg/m ² /d) in first 4 days, 4-6 h before RT RT: 34.5 Gy, 15 fr, 18 d; surgery within 2 weeks after RT | T2, T3, or resectable T4 rectal cancer | 62.4 | OS, LR, distant metastases, pCR, mortality | (15) |
| Gerard <i>et al</i> , 2006 | 1993-2003 | CRT+S RT+S | 375 367 | CRT: 45.0 Gy, 25 fr, 35 d 5-Fu (350 mg/m ² /d), LV (20 mg/m ² /d) in 20 min during d 1-5 and 29-33, 1 h before RT RT: 45.0 Gy, 25 fr, 35 d; surgery 3-10 weeks after RT | Resectable T3-4, NX, M0 rectal cancer | 81.0 | OS, DFS, LR, pCR, mortality | (19) |
| Bujko <i>et al</i> , 2006 | 1999-2002 | CRT+S RT+S | 157 155 | CRT: 50.4 Gy, 28 fr, 5-Fu (325 mg/m ² /d), LV (20 mg/m ² /d) as rapid infusion on 5 days in week 1 and 5 of RT RT: 25.0 Gy, 5 fr, 7 d; surgery after 4-6 week | T3 or T4 resectable rectal cancer | 48.0 | OS, DFS, LR, distant metastases, pCR | (8) |
| Bosset <i>et al</i> , 2006 | 1993-2003 | CRT+S RT+S | 505 506 | CRT: 45 Gy, 25 fr, 35 d 5-Fu (350 mg/m ² /d), LV (20 mg/m ² /d) in 20 min in first and fifth week of RT RT: 45.0 Gy, 25 fr, 35 d; surgery 3-10 weeks after RT | T3 or T4 resectable rectal cancer | 64.8 | OS, DFS, LR, pCR, mortality | (52,53) |
| Ngan <i>et al</i> , 2012 | 2001-2006 | CRT+S RT+S | 161 162 | CRT: 50.4 Gy, 28 fr, 5 weeks with continuous infusion of FU (225 mg/m ² /d), surgery 4-6 weeks after RT RT: 25.0 Gy, 5 fr, 5 d, surgery 3-7 d after RT | T3 resectable rectal cancer | 70.8 | OS, DFS, LR, pCR | (54) |
| Latkauskas <i>et al</i> , 2016 | 2007-2010 | CRT+S RT+S | 72 68 | CRT: 50.0 Gy, 25 fr, 35 d, 5-FU (400 g/m ² /d), LV (20 mg/m ² /d) during first and last week of RT RT: 25.0 Gy, 5 fr, 35 d in both arms; surgery 6 week after RT | Stage II-III resectable rectal cancer | 39.7 | OS, DFS, LR, distant metastases | (18) |
| Deng <i>et al</i> , 2015 | 2010-2015 | CRT+S CT+S | 158 163 | RT: 46.0-50.4 Gy, 23-28 fr, 5-6 weeks for both arms CT: mFOLFOX regimen | Stage II-III resectable rectal cancer (T3-4 N0 or T1-4 N1-2) | 45.2 | DFS, LR, pCR, mortality | (20) |

NR, not reported; RT, surgery preceded by neoadjuvant radiotherapy; S, surgery alone; CRT, surgery preceded by neoadjuvant chemotherapy; TNM, tumor-node-metastasis; XELOX, capecitabine plus oxaliplatin; 5-Fu, fluorouracil; LV, leucovorin; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival; DFS, disease-free survival; LR, local recurrence; pCR, pathological complete response rate; fr, fraction; d, day.

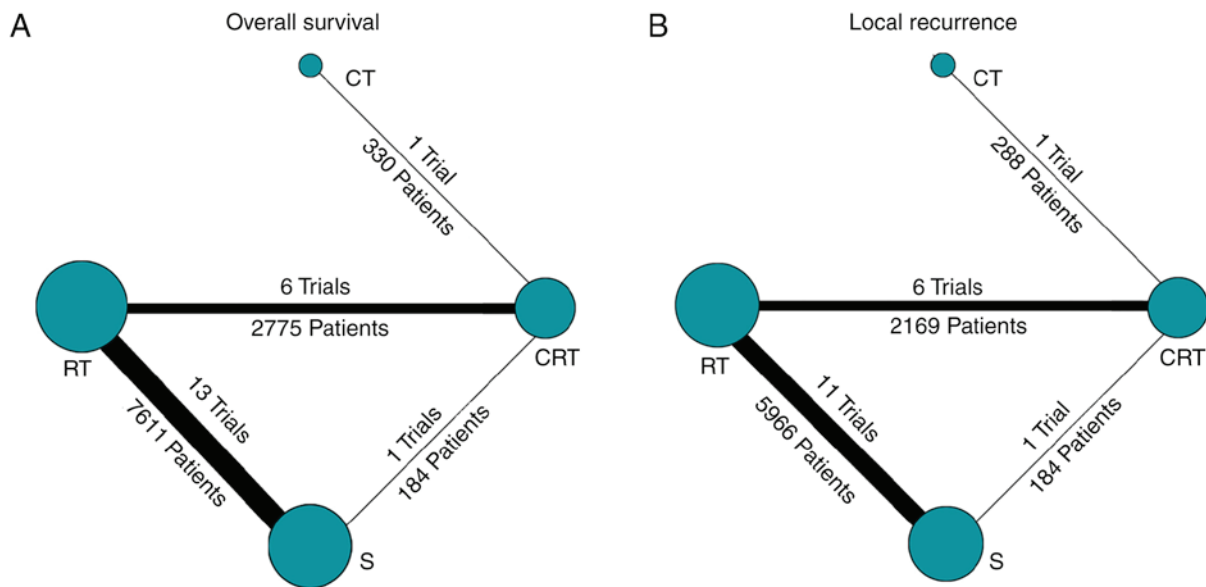


Figure 2. Network geometry for primary outcomes in the network meta-analysis. Each node indicates a strategy and the node size is proportional to the number of patients in the treatment group. Lines represent direct comparisons between two treatments and line thickness represents the number of RCTs included in each comparison, also represented by the numbers. (A) Overall survival (21 trials) and (B) local recurrence (19 trials). S, surgery alone; RT, surgery preceded by neoadjuvant radiotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy.

tool (55) are shown in Fig. S1. The overall risk bias was low and was well agreed between reviewers. All the studies included in the NMA were randomized, meaning that the overall selection and attrition bias were minimized. None of the included studies were described as double blind or used blinded outcome assessment. In addition, there were no imbalances between treatment arms in the number of patients that did not undergo the complete trial procedure.

Primary outcome. A total of 21 trials including 10,900 patients and comparing four treatment strategies were included in the 5-year OS analysis (Fig. 2A). As can be seen from pairwise comparison (Table II), RT was associated with improved OS benefit compared with surgery alone (HR, 0.89; 95% CI, 0.83-0.96; quality of evidence, high). For NMA, there were no significant differences in OS for all comparisons except RT vs. surgery alone (HR, 0.89; 95% CI, 0.82-0.97; Table II). The SUCRA values of 77.05, 56.97 and 43.57% for RT, CT and CRT, respectively (Fig. 3A), suggested that these were the three treatments with the highest chance of improving OS in rectal cancer. Sensitivity analyses were also performed with 16 trials for which the total radiation dose ≥ 25 Gy. The results were similar to those for the analysis of all 21 trials.

A total of 19 trials (8,607 patients) comparing three neoadjuvant treatments and surgery were included in the LR analysis (Fig. 2B). The results of NMA suggested a significant advantage of RT or CRT compared with surgery alone (Table II; RT vs. surgery alone: OR, 0.44; 95% CI, 0.35-0.56; quality of evidence, high and CRT vs. surgery alone: OR, 0.34; 95% CI, 0.23-0.56; quality of evidence, moderate). There were no significant differences for both direct pairwise analysis and NMA between CRT and RT or CT. Sensitivity analyses were also performed with 15 studies for which the total dose of radiation was ≥ 25 Gy. The results were similar to those for the analysis of all 19 studies. Ranking probabilities analysis

further supported the conclusion that CRT and CT were probably the best and second-best strategies, respectively, for local tumor control (Fig. 3B). The SUCRA values of CRT and CT were 78.78 and 74.68%, respectively (Fig. 3B).

Secondary outcome. The NMAs for the 6 secondary outcomes (5-year DFS, distant metastases, pCR, organ preservation, 30-day mortality and anastomotic leak) included 6 to 16 trials involving 2,767 to 7,410 patients with clinically resectable rectal cancer (Fig. S2). The incidence of distant metastases was 28.2% (1,558 of 5,516), pCR, 9.0% (267 of 2,971), organ preservation 54.0% (1,496 of 2,767), 30-day mortality 4.1% (316 of 7,410) and anastomotic leak 5.8% (175 of 3,042). In DFS analysis, 10 trials comparing the three preoperative treatments were included. The HRs are shown in Table II and Fig. 4. RT was associated with improved DFS than surgery alone (HR, 0.82; 95% CI, 0.64-1.00; quality of evidence, low). CRT displayed no significant improvement in DFS compared with RT (HR, 0.96; 95% CI, 0.78-1.20).

The estimated OR of pairwise analysis and NMA for distant metastases, pCR, organ preservation and anastomotic leak are also shown in Table II and Fig. 4. There were no significant differences between interventions for the likelihood of the distant metastases. For trials comparing RT with surgery alone, pCR was not reported and could not be estimated on the basis of the information provided. CRT and CT were associated with improved pCR compared with RT (CRT vs. RT: OR, 4.90; 95% CI, 1.80-17.00; quality of evidence, low and CT vs. RT: OR, 27.0; 95% CI, 1.80-530.00; quality of evidence, very low; Fig. 4).

For the analysis of complications, 30-day mortality and anastomotic leak data were extracted. A total of 16 trials (7726 patients) comparing three treatments were included in the 30-day mortality analysis. One trial compared CRT with CT (20), reporting no treatment-related mortality and being

Table II. Results from direct pairwise comparison and the network meta-analysis.

| A, RT vs. S | | |
|--------------------|----------------------------------|----------------------------------|
| Outcomes | Pairwise comparison | Network meta-analysis |
| Overall survival | HR 0.89 (0.83-0.96) ^a | HR 0.89 (0.82-0.97) ^a |
| Local recurrence | OR 0.44 (0.37-0.51) ^a | OR 0.44 (0.35-0.56) ^a |
| DFS | HR 0.80 (0.63-1.02) | HR 0.82 (0.64-1.00) |
| Distant metastases | OR 0.87 (0.73-1.05) | OR 0.87 (0.69-1.10) |
| Mortality | OR 1.38 (0.89-2.12) | OR 1.40 (0.79-2.20) |
| pCR | NA | NA |
| Anastomotic leak | OR 1.12 (0.75-1.67) | OR 1.10 (0.61-1.80) |
| Organ preservation | NA | OR 0.88 (0.46-1.70) |
| B, CRT vs. S | | |
| Outcomes | Pairwise comparison | Network meta-analysis |
| Overall survival | HR 1.34 (0.43-4.21) | HR 0.95 (0.81-1.10) |
| Local recurrence | OR 1.05 (0.25-4.30) | OR 0.34 (0.23-0.56) |
| DFS | HR 1.48 (0.34-6.52) | HR 0.78 (0.58-1.10) |
| Distant metastases | OR 0.76 (0.30-1.90) | OR 0.75 (0.47-1.10) |
| Mortality | NA | OR 2.10 (0.68-6.40) |
| pCR | NA | NA |
| Anastomotic leak | OR 0.24 (0.05-1.18) | OR 0.55 (0.19-1.50) |
| Organ preservation | OR 0.94 (0.50-1.77) | OR 0.94 (0.50-1.80) |
| C, CRT vs. CT | | |
| Outcomes | Pairwise comparison | Network meta-analysis |
| Overall survival | HR 1.08 (0.51-2.29) | HR 1.10 (0.50-2.30) |
| Local recurrence | OR 1.06 (0.46-2.40) | OR 1.10 (0.46-2.50) |
| DFS | NA | NA |
| Distant metastases | NA | NA |
| Mortality | NA | NA |
| pCR | OR 0.18 (0.09-0.39) ^a | OR 0.18 (0.01-2.40) |
| Anastomotic leak | OR 2.58 (1.25-5.31) ^a | OR 2.6 (0.83-8.60) |
| Organ preservation | OR 1.24 (0.61-2.51) | OR 1.3 (0.62-2.60) |
| D, CRT vs. RT | | |
| Outcomes | Pairwise comparison | Network meta-analysis |
| Overall survival | HR 1.06 (0.92-1.21) | HR 1.10 (0.93-1.20) |
| Local recurrence | OR 0.78 (0.48-1.25) | OR 0.81 (0.61-1.10) |
| DFS | HR 0.92 (0.82-1.05) | HR 0.96 (0.78-1.20) |
| Distant metastases | OR 0.82 (0.51-1.30) | OR 0.86 (0.57-1.20) |
| Mortality | OR 1.55 (0.86-2.79) | OR 1.60 (0.58-4.30) |
| pCR | OR 4.01 (2.24-7.18) ^a | OR 4.9 (1.80-17.0) ^a |
| Anastomotic leak | OR 0.75 (0.30-1.85) | OR 0.52 (0.19-1.30) |
| Organ preservation | OR 1.06 (0.90-1.26) | OR 1.10 (0.89-1.30) |

RT, surgery preceded by neoadjuvant radiotherapy; S, surgery alone; HR, hazard ratio; OR, odds ratio; DFS, disease-free survival; pCR, pathological complete response rate; NA, not applicable; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy. ^a95% CI does not contain 1.

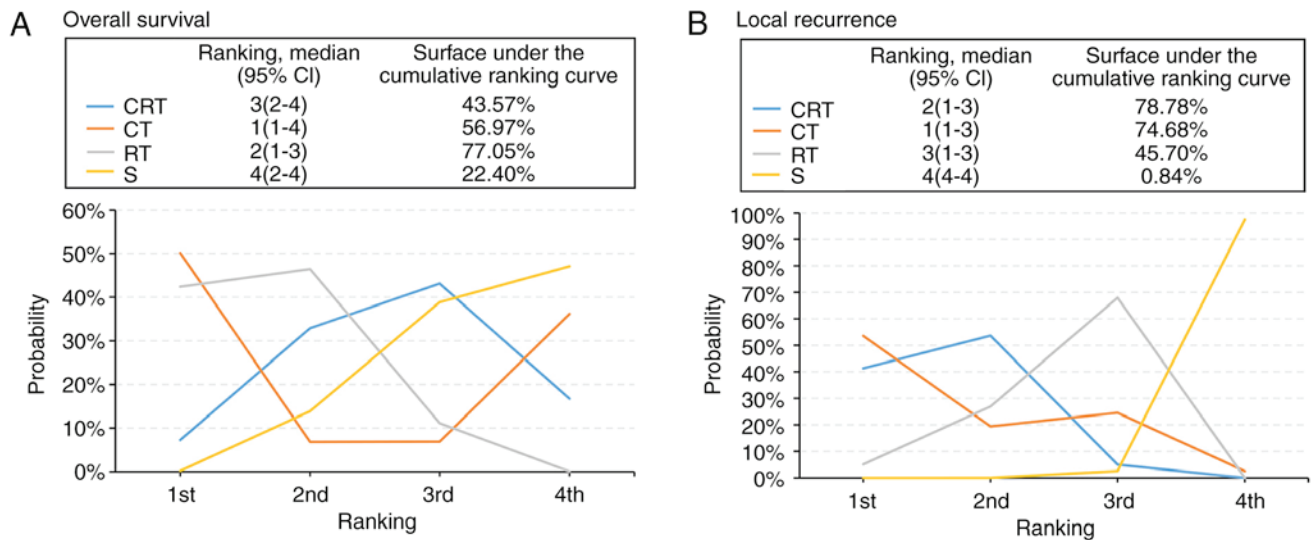


Figure 3. Ranking probability and surface under the cumulative ranking curve of strategies for primary outcomes in the network meta-analysis of neoadjuvant treatments for resectable rectal cancer. Each line represents a treatment strategy. The x-axis indicates the ranking of strategies, with '1st' representing the best. The y-axis represents the probability of each ranking. (A) Overall survival and (B) Local recurrence. S, surgery alone; RT, surgery preceded by neoadjuvant radiotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy; CI, confidence interval.

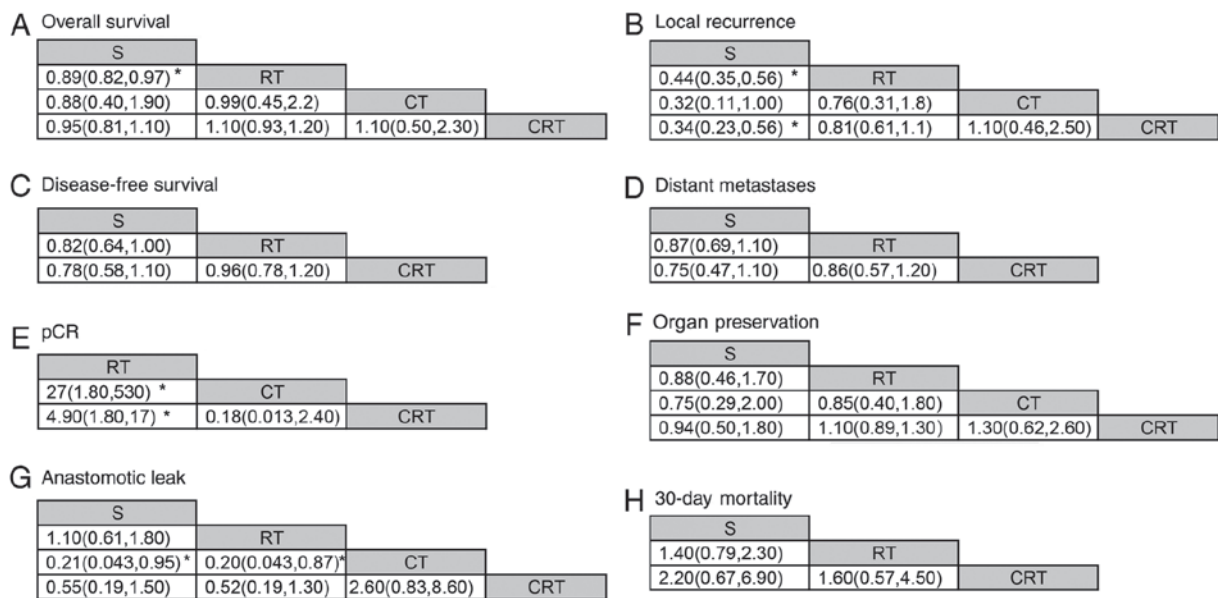


Figure 4. Results of the network meta-analysis for each outcome for all possible treatment strategies. Effect estimates reflect comparison of the treatment in the row heading vs. the treatment in the column heading. (A) Overall survival presented as hazard ratios (95% CI). (B) Local recurrence presented as odds ratios (95% CI). (C) Disease-free survival presented as hazard ratios (95% CI). (D) Distant metastases, (E) pCR, (F) organ preservation, (G) anastomotic leak and (H) 30-day mortality presented as odds ratios (95% CI). CI, confidence interval; pCR, pathological complete response rate; S, surgery alone; RT, surgery preceded by neoadjuvant radiotherapy; CRT, surgery preceded by neoadjuvant chemoradiotherapy; CT, surgery preceded by neoadjuvant chemotherapy. *95% CI does not contain 1.

the only trial including results of CT, this trial was excluded from the NMA. Neoadjuvant strategies (RT and CRT) tended to have more treatment-related mortality than surgery alone, but there were no significant differences (Table II and Fig. 4). The surgical complication of anastomotic leak was reported in nine trials. CT was associated with a lower likelihood of anastomotic leak compared to all other treatments (CT vs. surgery alone: OR, 0.21; 95% CI, 0.04-0.95; quality of evidence, low; CT vs. RT: OR, 0.20; 95% CI, 0.04-0.87; quality of evidence, low and CRT vs. CT: OR, 2.60; 95% CI, 0.83-8.60; quality of

evidence, low). The SUCRA analysis suggested that CT had the lowest risk of anastomotic leak with a SUCRA value of 97.26% (Fig. S3E).

Ranking probability. The ranking probability and the results of SUCRA analysis are shown in Figs. 3 and S3. For the primary outcomes, CT had the highest overall probability of being the best strategy for the neoadjuvant treatment of resectable rectal cancer. Considering all the outcomes, CRT was the best strategy based on SUCRA.

Discussion

The NMA in the present study included 23 trials with 10,895 patients with resectable rectal cancer and simultaneously estimated relative effects of four currently used treatment strategies. The present study revealed that preoperative radiotherapy displayed significant survival benefit over surgery alone. No statistically significant differences were observed between CRT and RT or CT. In addition, primary analysis of LR suggested that RT and CRT played a role in local control of rectal cancer when compared with surgery alone, but there were no noticeable differences in survival benefit between the comparisons of three neoadjuvant treatments. With the ranking analysis, CT seemed to be the best strategy among all the included strategies for primary outcomes assessed (CT ranked the first and had the biggest total SUCRA value considering the primary outcomes), whilst CRT was the best strategy when considering all the included outcomes. The evidence for the secondary outcomes was of low quality overall. Out of the outcomes assessed, only anastomotic leak estimated the relative effects of four strategies and CT remained to be the best strategy. The analysis for DFS, distant metastases, pCR and 30-day mortality compared three different strategies, all of them with no significant difference.

Several systemic reviews have evaluated various strategies using conventional pairwise comparison (3,16,56,57). Three meta-analyses confirmed that preoperative radiotherapy improved OS and significantly reduced the LR compared with surgery alone (3,56,57). The present study analyzed the majority of these trials and the results for the primary outcomes were consistent with the results from the previous aforementioned studies. Previously, three systematic reviews have reported that CRT provides no superior OS compared with RT and the result of local control rate was different between these analyses (16,57,58). A previous meta-analysis identified five trials that reported that chemoradiotherapy improved local tumor control as opposed to radiotherapy, with no impact on perioperative outcome or long-term survival (57). The pairwise analysis and NMA carried out in the present study displayed no improvement in both local control and long-term survival for patients treated with CRT compared to those treated with RT. However, significant heterogeneity remained when the data for LR were analyzed using the random effects assumption ($I^2=61\%$, $P=0.03$). In this present study, it is unclear whether the heterogeneity is attributable to the addition of chemotherapy to a different RT schedule and a different waiting period until surgery.

To the best of our knowledge, the present study is the first NMA to provide estimates of the outcomes and effects of pairwise comparisons of potential neoadjuvant therapy regimens for resectable rectal cancer. The efficacy of each potential regimen could be ranked using these pooled outcomes. However, there was only one eligible trial for CT compared with other strategies (20), which decreased the quality of the whole analysis. Therefore, future studies that directly evaluate survival outcomes and side effects in patients receiving neoadjuvant CT are warranted.

The present study had some further limitations. Firstly, there were some differences in baseline characteristics

of the included trials that could lead to biased results. For example, three of the trials included patients with cancer of the rectosigmoid (40,41,43). The majority of the early trials using Dukes classification included patients from Dukes A-C (15,32,35), whereas previous studies using TNM classification for clinical staging only included patients with stage II/III rectal cancer (18,20). In the MRC I trial, 28% of patients with metastatic cancer were found to have a Dukes' stage A lesion for which adjuvant therapy is not currently advised (38). These included patients may have led to biased results. Secondly, some regimens with different doses or duration times were grouped together, which may further increase the bias. For example, for the CRT treatment strategy, the total dose of radiation ranged from 34.5-50.4 Gy and three types of chemotherapy regimen (fluorouracil/leucovorin, modified FOLFOX and capecitabine plus oxaliplatin) were used. Thirdly, only one trial compared the neoadjuvant CT regime with CRT therapy strategy, limiting the assessment (20). Fourthly, considering there was no significant survival benefit between the three neoadjuvant treatment strategies, the analysis of the side effects, such as toxicity or quality of life, could be important to evaluate the relative effects of each regime. However, a number of the included trials did not report these outcomes, but future trials should describe them.

Based on the primary and secondary results, the NMA performed in the present study found that neoadjuvant radiotherapy decreases the LR and improves OS compared with surgery alone for resected rectal cancer. Neoadjuvant chemoradiotherapy displayed no significant OS benefit or local control compared with RT. CRT was the best neoadjuvant therapy and CT was likely the second best for all outcomes based on the ranking probability and SUCRA. These findings were limited by overall low quality of evidence.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

WZ and SZ contributed to the study design/planning, data collection/entry, data analysis/statistics, data interpretation and funds collection. XJX and LZD contributed to the preparation of the manuscript and literature analysis/search. RRL and KN contributed to the data collection/entry. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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