



Neoadjuvant therapy in locally advanced colon cancer: a meta-analysis and systematic review

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Background: The role of perioperative or neoadjuvant chemotherapy for locally advanced colon cancer is unclear. Emerging evidence such as the FOXTROT trial is challenging the conventional norm of upfront operation for these patients. However, these trials have yet to reach statistical significance.

Methods: MEDLINE, Embase, Cochrane Library, China Knowledge Resource Integrated Database (CNKI) and ClinicalTrials.gov were searched. Randomized controlled trials (RCTs) and observational studies of patients with locally advanced colon cancer were included. The intervention arm was neoadjuvant chemotherapies while the comparator arm was adjuvant chemotherapies. Studies which reported outcomes of interests included overall survival, disease-free survival, R0 resection rate, perioperative complications and adverse effects of chemotherapy were chosen.

Results: We identified five eligible randomized trials and two observational studies, including 29,504 patients. Neoadjuvant therapies exhibited statistically significant improvement in overall survival [hazard ratio (HR) =0.76, 95% confidence interval (CI): 0.65–0.89, P=0.0005], and disease-free survival (HR =0.74, 95% CI: 0.58–0.95, P=0.02). R0 resection rate fell slightly short of significance [odds ratio (OR) =1.86, 95% CI: 0.95–3.62, P=0.07]. Risk of peri-operative complications did not differ between groups when examining abdominal infection [risk ratio (RR) =1.14, 95% CI: 0.59–2.18, P=0.70] and anastomotic leakage (RR =0.83, 95% CI: 0.53–1.31, P=0.42). No statistical differences in complications from chemotherapy were reported.

Conclusions: This meta-analysis highlights the potential survival benefit of neoadjuvant chemotherapy compared to adjuvant chemotherapy for locally advanced colon cancer, without an increase in surgical morbidity. Neoadjuvant or perioperative approaches may be considered an alternative to upfront surgery followed by chemotherapy for locally advanced colon cancer.

Keywords: Neoadjuvant therapy; colonic neoplasms; meta-analysis

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Introduction

Colon cancer is a leading cause of morbidity and mortality worldwide (1). The mainstay treatment of non-metastatic colon cancer is surgery with curative intent. For locally advanced disease (high-risk stage II and stage III), treatment with adjuvant chemotherapy after surgery is recommended (2). Neoadjuvant systemic therapy approaches are considered standard-of-care in several other gastro-intestinal tumor types such as gastric, esophageal and rectal cancer (3-5). There are several benefits of neoadjuvant systemic therapy: (I) improvement of surgical outcomes by downstaging of tumor; (II) early control of systemic metastatic spread and test of tumor biology; and (III) *in vivo* test of chemotherapy sensitivity and potential incorporation of novel agents in clinical trials. Apart from these benefits, trials from other tumor types have demonstrated that there is no decrease in survival by the early introduction of chemotherapy (5,6). However, few perioperative or neoadjuvant chemotherapy trials have been conducted in colon cancer. Smaller phase II studies have demonstrated the safety of neoadjuvant chemotherapy, but few trials have the statistical power to detect a difference in survival (7-9). The recent FOXTROT trial (10) presented at ASCO June 2019, reported better surgical outcomes but did not meet statistical significance for survival benefit at an early follow-up of 2 years. We evaluated the outcomes of neoadjuvant versus adjuvant chemotherapy in locally advanced, non-metastatic colon cancer by means of a systematic review and meta-analysis. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/jgo-20-220>).

Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Search strategy

MEDLINE, Embase, Cochrane Library and China Knowledge Resource Integrated Database (CNKI) (12) electronic databases were searched from their inception to 4 May 2020 with assistance from a medical librarian. In addition, searches were conducted on ClinicalTrials.gov for ongoing studies and hand searching of references in included studies. The search strategy is documented in the Supplementary. All potential studies were imported into

EndNote X9 and duplicates removed.

Inclusion criteria and exclusion criteria

Inclusion criteria were: (I) studies that involved patients who had locally advanced colon cancer; (II) studies comparing the effects of neoadjuvant or perioperative versus adjuvant systemic therapies only. Molecular targeted therapies were allowed; (III) studies reporting the outcomes of interest including overall, disease-free survival, R0 resection rate, perioperative complications and adverse effects of chemotherapy; (IV) we included randomized controlled trials (RCTs) and cohort studies. Abstracts of conference proceedings were allowed if sufficient information was reported on study design, participant demographics, interventions conducts and outcomes. Exclusion criteria were: (I) studies involving patients who had rectal cancer, or studies involving patients who had distant metastasis of colon cancer; (II) studies whose patients underwent chemoradiotherapy or did not undergo post-surgery chemotherapy; (III) studies which did not report the outcomes of interest; (IV) all articles that were not original studies, such as opinion pieces, reviews and commentaries.

Data extraction and assessment of quality

Three reviewers in blinded pairs independently reviewed included studies to perform data extraction using a pre-designed sheet. We extracted the following data for each study: (I) general information: author, year of publication, title, source, country and language; (II) study characteristics: study design and duration of follow up; (III) the inclusion and exclusion criteria for study participants, size of each study arm, and baseline characteristics of each study arm; (IV) type of neoadjuvant and adjuvant chemotherapy used; (V) outcomes: hazard ratio (HR), odds ratio (OR), risk ratio (RR) and their 95% confidence intervals (CIs). Quality assessment were independently assessed by two researchers using the Jadad Scale (13) for randomized trials and The Newcastle-Ottawa Scale (NOS) for cohort studies (14). All discrepancies were resolved with a senior author.

Outcome measures

The primary outcome was overall survival as reported using intention-to-treat analysis. Overall survival was defined as time from randomization to death. Secondary outcomes included: disease-free survival, which was reported as the

time from randomization to disease recurrence or death; R0 resection rate, which was reported as rate of microscopically margin-negative resection; anastomotic leak which was defined as leakage of luminal contents after colorectal anastomosis; abdominal infection which was defined as surgical wound infection with or without intra-abdominal abscess. We expected the adverse effects of systemic therapies to be reported variably across trials and therefore not suitable for meta-analysis.

Statistical analysis

For the analysis of time to event data (overall and disease-free survival), we estimated the HRs and 95% CIs directly or indirectly from the given data (15). For each individual study, we extracted log HRs and their variances. If the figures were not given directly, methods of indirect determination were used (16). HRs can be estimated (under certain assumptions) from observed to expected event ratios (17). For the analysis of dichotomous data (R0 resection, anastomotic leak and abdominal infections), we estimated the OR or RR based on the number of patients in each treatment arm who experienced the event of interest and the number of patients assessed for the event of interest. Statistical heterogeneity of trial results was assessed by Cochran Q test and I-squared statistic. A Cochran Q test of P value higher than 0.10 and I-squared value of lower than 40% was interpreted as low level of heterogeneity (18,19). There were too few studies included in the meta-analysis to conduct Egger's regression asymmetry test. Primary analyses were done with random effects model. All data synthesis was conducted using RevMan 5.3.

Results

Search results

In total, 2,461 English articles were identified according to the search strategy. Six hundred and eighty-seven were excluded after checking for duplicates with the literature management software Endnote X9. One thousand seven hundred and twenty-three studies were excluded after screening the titles and abstracts. Fifty-one studies were excluded after assessing the full text for eligibility. Eighty-four Chinese articles were identified according to the search strategy. Seventy-two studies were excluded after screening the titles and abstracts. Ten studies were excluded after assessing the full text for eligibility. In total, we found 7 eligible studies, with 2 originating from the United

Kingdom, 2 from China, 1 from the Netherlands, 1 from the United States of America, and 1 from France. A graphical summary of the article selection process is provided in *Figure 1*. In total, 2,006 patients underwent neoadjuvant treatment and 27,498 patients underwent adjuvant treatment for locally advanced colon cancer (*Table 1*).

Oncological and surgical outcomes

Overall survival significantly improved amongst 1,160 patients who received neoadjuvant chemotherapy compared to 27,042 patients who received adjuvant chemotherapy (20-23) (HR =0.76, 95% CI: 0.65–0.89, P=0.0005, *Figure 2*). Disease-free survival also significantly improved amongst 788 patients who received neoadjuvant chemotherapy compared to 444 patients who received adjuvant chemotherapy (10,22,23) (HR =0.74, 95% CI: 0.58–0.95, P=0.02). The 995 patients who received neoadjuvant chemotherapy had a higher rate of R0 resection than 753 patients who received adjuvant chemotherapy, though results fell slightly short of statistical significance (10,20,24,25) (OR =1.86, 95% CI: 0.95–3.62, P=0.07, *Figure 3*). However, the authors of one of the included studies reported that their R0 resection rate could have been biased by the high percentage of neoadjuvant chemotherapy patients with unfavorable tumors (20). A sensitivity analysis showed that increase in R0 resection rate amongst the remaining included studies was statistically significant (OR =2.48, 95% CI: 1.15–5.39, P=0.02).

Surgical complications

Rates of perioperative complications were similar between patients who underwent neoadjuvant chemotherapy and patients who underwent adjuvant chemotherapy. Comparative analysis of 238 patients in the neoadjuvant arm and 192 patients in the adjuvant arm revealed no significant differences in abdominal infection rates (22-24) (RR =1.14, 95% CI: 0.59–2.18, P=0.70, *Figure 4*). Similarly, there was no significant difference in rates of anastomotic leakage between 1,084 patients who underwent neoadjuvant chemotherapy and 844 patients who underwent adjuvant chemotherapy (10,20,22-24,26) (RR =0.83, 95% CI: 0.53–1.31, P=0.42, *Figure 5*).

Adverse events from chemotherapy

All studies found no significant difference in rates of

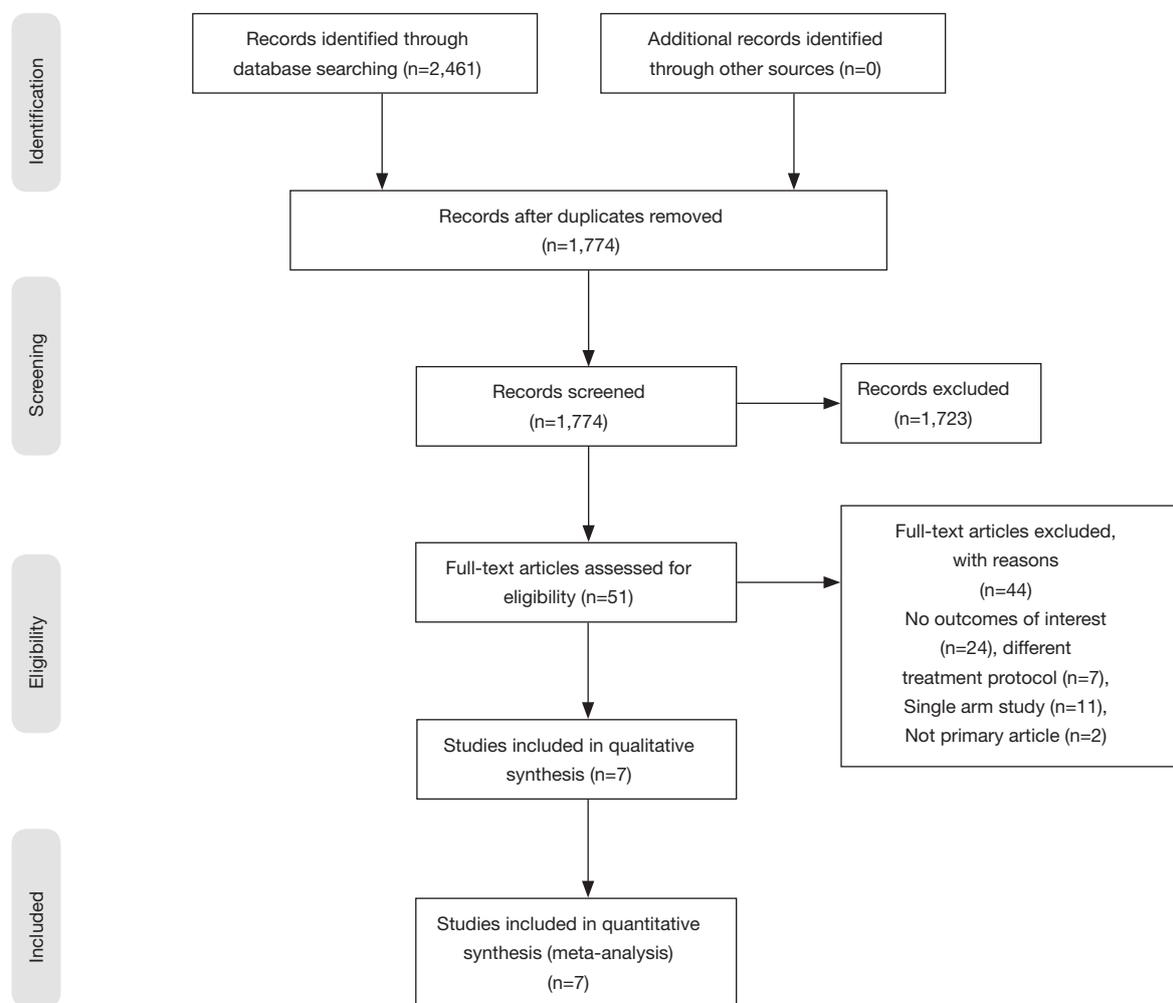


Figure 1 PRISMA flow diagram of included articles. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

chemotherapy adverse effects between patients who underwent neoadjuvant chemotherapy and patients who underwent adjuvant chemotherapy. Zhuang *et al.* (22) found no significant difference in rates of bowel irritation (56% *vs.* 62%, $P>0.05$), granulocytopenia (22% *vs.* 20%, $P>0.05$), and thrombocytopenia (16% *vs.* 14%, $P>0.05$). Similarly, Song *et al.* (23) found no differences in rates of bowel irritation (55% *vs.* 52.5%, $P>0.05$), granulocytopenia (12.5% *vs.* 10%, $P>0.05$), and thrombocytopenia (17.5% *vs.* 10%, $P>0.05$). FOXTROT (24) found no significant differences in rates of deep vein thrombosis (2% *vs.* 0%, $P=0.31$), rash (3% *vs.* 0%, $P=0.21$), neutropenia (1% *vs.* 0%, $P=0.47$), and bronchopneumonia (2% *vs.* 0%, $P=0.31$). Similarly, Karoui *et al.* (25) found no significant differences in rates of thrombocytopenia (0% *vs.* 3%, $P>0.05$), neutropenia (17% *vs.* 24%, $P>0.05$), diarrhea (4% *vs.* 5%, $P>0.05$). Studies

reported chemotherapy adverse effects with unsatisfactory congruency, hence reported findings could not be pooled for a meta-analysis.

Discussion

This is the first systematic review and meta-analysis of neoadjuvant chemotherapy versus adjuvant chemotherapy for locally advanced colon cancer, incorporating clinical trials with contemporary chemotherapy regimens from both English and Chinese literature. The review included a total of 2,006 patients undergoing neoadjuvant treatment and 27,498 patients undergoing adjuvant treatment. In all studies, patients who received neoadjuvant treatment also went on to receive postoperative adjuvant chemotherapy. Our analyses suggest potential benefit in using the

Table 1 Summary of included articles

Author	Year	Character of study (RCT, retrospective study)	Outcomes of Interest (as reported by each study, or based on analysis of results)	Patient number in each arm (chemotherapy completion rate)	Mean age, years [SD or range]	Breakdown of tumors included based on TNM classification	Summary of inclusion criteria	Chemotherapy regimen adopted	Quality assessment (Jadad for RCTs, Newcastle Ottawa for retrospective studies)
The FOXTROT trial ^a	2012	RCT	Feasibility, safety, tolerance of neoadjuvant chemotherapy, accuracy of radiological staging, completion of planned surgery, perioperative morbidity, timely completion of preoperative KRAS testing, downstaging of resected tumor	Neo-adjuvant: 99 (68%); adjuvant: 51 (57%)	Neo-adjuvant: 64 [59–68]; adjuvant: 65 [56–69]	Neo-adjuvant: T3: 69, T4: 30, Nx: 3, N0: 23, N1: 44, N2: 29; adjuvant: T3: 35, T4: 16, Nx: 1, N0: 12, N1: 22, N2: 16	T4 or T3 with extramural depth ≥5 mm adenocarcinoma	Preoperative: OxMdG ± panitumumab; postoperative: OxMdG	Jadad score: 3
Zhuang <i>et al.</i>	2016	RCT	1-, 3-, 5-year overall survival, 1-, 3-, 5-year disease-free survival, length of surgery, estimated blood loss, length of stay, wound infection rate, anatomic fistula rate, incidence of adverse reactions from chemotherapy	Neo-adjuvant: 50 (100%); adjuvant: 50 (100%)	Neo-adjuvant: 56.84 [9.94]; adjuvant: 58.74 [9.76]	Neo-adjuvant: T3: 15, T4: 35, N+: 42, N-: 8; adjuvant: T3: 18, T4: 32, N+: 44, N-: 6	Resectable advanced colon adenocarcinoma	Preoperative: CapeOx; postoperative: CapeOx	Jadad score: 3
Song <i>et al.</i>	2017	RCT	3-year overall survival, 3-year disease-free survival, CEA levels, maximum diameter of tumor, tumor stage, number of positive lymph nodes, length of surgery, estimated blood loss, abdominal infection rate, anastomotic leakage rate, length of stay, incidence of adverse reactions from chemotherapy	Neo-adjuvant: 40 (not reported); adjuvant: 40 (not reported)	Neo-adjuvant: 47.3 [10.4]; adjuvant: 45.6 [12.1]	Neo-adjuvant: T3: 16, T4: 24, N+: 31, N-: 9; adjuvant: T3: 18, T4: 22, N+: 33, N-: 7	Resectable colon cancer	Preoperative: CapeOx; postoperative: CapeOx	Jadad score: 2

Table 1 (continued)

Table 1 (continued)

Author	Year	Character of study (RCT, retrospective study)	Outcomes of Interest (as reported by each study, or based on analysis of results)	Patient number in each arm (chemotherapy completion rate)	Mean age, years [SD or range]	Breakdown of tumors included based on TNM classification	Summary of inclusion criteria	Chemotherapy regimen adopted	Quality assessment (Jadad for RCTs, Newcastle Ottawa for retrospective studies)
Dehal	2018	Retrospective study	Overall survival	Neo-adjuvant: 921 (not reported); adjuvant: 26,654 (not reported)	Neo-adjuvant: 58.4 [12.1]; adjuvant: 61.5 [12.8]	Neo-adjuvant: T3: 479, T4a: 69, T4b: 350, N0: 450, N1: 291, N2: 106, Nx: 74; adjuvant: T3: 19,999, T4a: 3,201, T4b: 2,987, N0: 11,106, N1: 8,985, N2: 5,343, Nx: 1,220	T3/4 nonmetastatic colon cancer, surgery and chemotherapy	Not reported	Newcastle-Ottawa score: 7
de Gooyer	2019	Retrospective study	Staging accuracy, downstaging, R0 resection rate, 5-year overall survival	Neo-adjuvant: 149 (not reported); adjuvant: 298 (not reported)	Neo-adjuvant: 66.0 [NA]; adjuvant: 66.0 [NA]	Neo-adjuvant: T4: 13, T4a: 24, T4b: 112, N0: 65, N1: 47, N2: 18, Nx: 19; adjuvant: T4: 25, T4a: 52, T4b: 221, N0: 120, N1: 84, N2: 51, Nx: 43	T4 colon cancer, Had both surgery and chemotherapy	Not reported	Newcastle-Ottawa score: 7
Seymour et al. (conference abstract)	2019	RCT	2-year failure rate, anastomotic leak, complication prolonging postop stay, incomplete resection	Neo-adjuvant: 698 (not reported); adjuvant: 354 (not reported)	Not reported	Not reported	Non-structured colon cancer, T3/4, fit for FOLFOX and surgery	Preoperative: OxMdG ± panitumumab; postoperative: OxMdG	Jadad score: 3
Karoui et al.	2020	RCT	Pathological response to neoadjuvant chemotherapy, tolerability of preoperative chemotherapy, quality and completeness of surgical excision, disease downstaging, postoperative morbidity, accuracy of overall staging	Neo-adjuvant: 49 (97%); adjuvant: 51 (74%)	Neo-adjuvant: 65 [46–79]; adjuvant: 62 [30–75]	Neo-adjuvant: T3: 43, T4: 9, N0: 12, N1: 34, N2: 6; adjuvant: T3: 49, T4: 3, N0: 12, N1: 32, N2: 8	Non-metastatic locally advanced, pathologically proven colon adenocarcinoma	Neo-adjuvant: FOLFOX-4; adjuvant: FOLFOX-4	Jadad score: 3

^a, The FOXTROT trial [2012] and Seymour [2019] report results from the same registered clinical trial, number ISRCTN 87163246. Each reported different outcomes of interest. The latter abstract and oral presentation reported 2-year failure rate, complications prolonging hospital stay and anastomotic leak, while the former manuscript reported peri-operative complications and adverse events to chemotherapy. Anastomotic leak was not obtained from the former manuscript since it was already obtained from the latter abstract and oral presentation. RCT, randomized controlled trial.

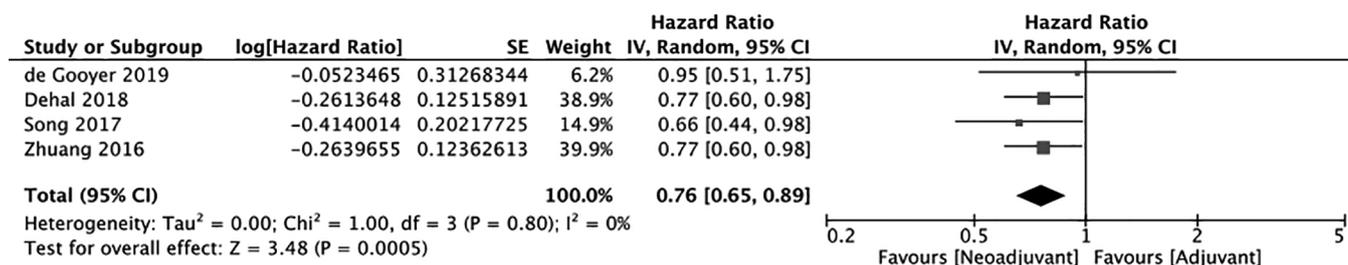


Figure 2 Meta-analysis of overall survival.

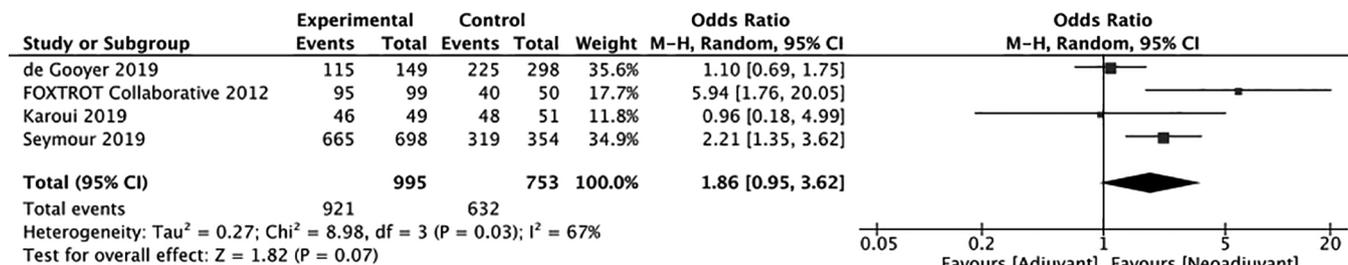


Figure 3 Meta-analysis of R0 resection rate.

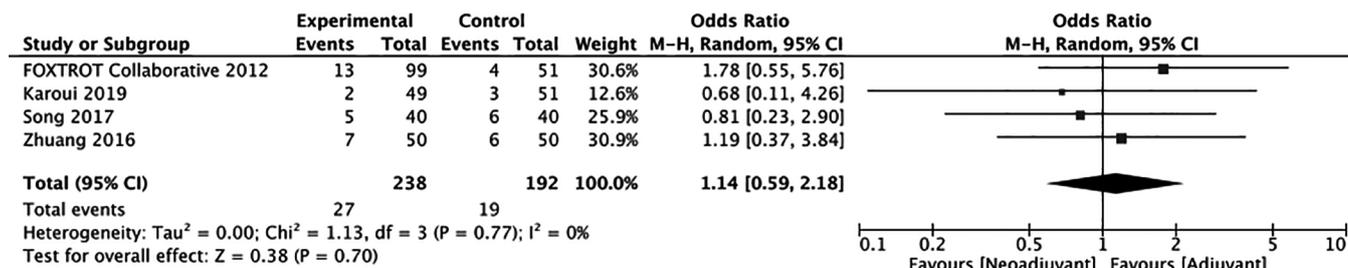


Figure 4 Meta-analysis of abdominal infections.

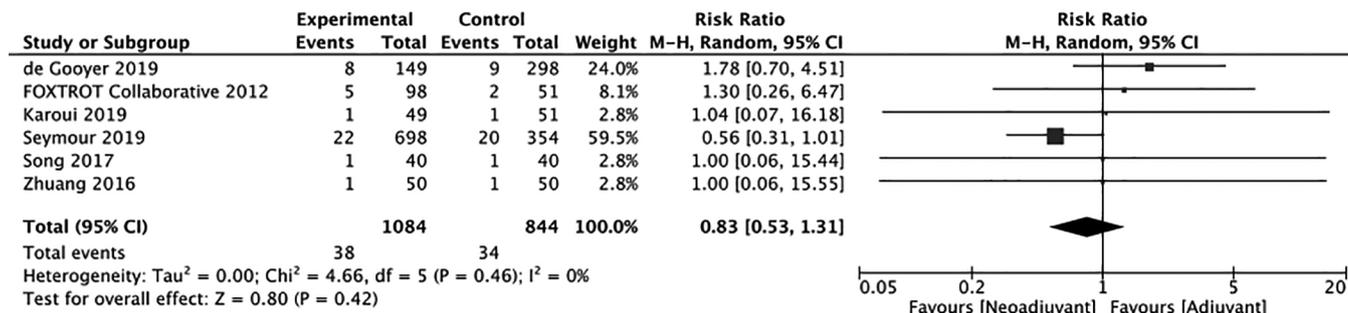


Figure 5 Meta-analysis of anastomotic leak.

neoadjuvant approach compared to adjuvant chemotherapy. More importantly, there were no differences in surgical complications. While the efficacy of neoadjuvant chemotherapy is still under investigation for colon cancer, its use has been well established for the treatment of rectal cancer—current guidelines recommend neoadjuvant chemotherapy for all T3 and T4 tumors (27,28). This is in part due to the significant decrease in local recurrence rates associated with use of neoadjuvant chemotherapy (29,30). Such findings are also consistent with the rapidly emerging use of total neoadjuvant therapy—a recent systematic review and meta-analysis concluded that patients with rectal cancer receiving total neoadjuvant therapy had a better disease-free survival and overall survival (31).

In line with these studies, our study found that overall survival & disease-free survival improved in patients receiving neoadjuvant chemotherapy for colon cancer. The improvement in overall survival and disease-free survival for patients treated with neoadjuvant therapy could be due to improved R0 resection rates, which is in line with existing findings regarding the importance of R0 resection rate in colorectal cancer (32,33). As discussed earlier, while one study did not find a significant improvement in R0 resection rate, the authors suspected this was due to significant percentage of patients with unfavorable tumors in the neoadjuvant arm (20). Our findings regarding R0 resection rate further support the notion of the clinical usefulness of neoadjuvant chemotherapy for locally advanced colon cancer.

Neoadjuvant chemotherapy has several additional potential advantages over adjuvant chemotherapy. Firstly, it reduces reliance on adjuvant chemotherapy to achieve treatment efficacy. This is key, as delays in post-operative chemotherapy arising from surgical complications has been shown to result in poorer overall survival (34-36). A recent randomized trial comparing different types of neoadjuvant chemotherapy in colon cancer found low recurrence rate and high disease-free survival in a subgroup of patients for whom adjuvant chemotherapy was omitted altogether (37). Secondly, in studies based largely on metastatic colon cancer (38,39), pre-operative chemotherapy allows for patient selection in terms of tumor biology and possibly prevents unnecessary operations for patients with poor response (21). Lastly, the neoadjuvant approach also paves the route for the design of clinical trials incorporating novel agents to allow for quicker *in vivo* and early read out of efficacy. Compared to breast cancer and lung cancer, which have had a rapid increase in survival due

to the identification of novel targets and pathways, colon cancer treatment has significantly lagged behind in the field of precision oncology (40,41).

Incorporation of neoadjuvant approaches in combination with biomarker selected strategies will advance the field of precision oncology in colon cancer significantly. In fact, the clinical usefulness of neoadjuvant chemotherapy may be increased in pT4 subgroup patients. One study reported a significant improvement in overall survival only within the pT4b subgroup (21). Two other studies that reported significant improvement in disease-free survival had relatively high proportion of pT4 patients (22,23). However in contrast, the FOXTROT trial that had high proportion of pT3 patients reported no significant difference in disease-free survival (10). While we acknowledge that the data is premature, it does suggest that neoadjuvant chemotherapy would likely benefit the pT4 patients most and might be the distinction for tumor board groups to decide on whom to select for future neoadjuvant therapy versus adjuvant therapy. Thus far, the application of neoadjuvant treatment has however been limited by concerns of inaccurate radiological staging resulting in overestimation of actual pathological stage and inappropriate chemotherapy for low-risk patients (42), and concerns of complications leading to poorer outcomes such as tumor perforation, bleeding and obstruction.

Our study has established that these concerns may be unfounded, particularly with respect to surgical outcomes. We assessed perioperative morbidity, which is another important aspect of neoadjuvant chemotherapy. In terms of post-operative complications, it is estimated that about 20% of patients experience serious complications related to adjuvant chemotherapy (43). Although a meta-analysis could not be comprehensively performed for all post-operative complications in our study, it does seem that patients who underwent neoadjuvant chemotherapy did not experience serious complications in excess of 20% from the studies analyzed. Furthermore, from our results, the similar rates of anastomotic leak and abdominal infection supports the promising use of neoadjuvant treatment. Future studies for neoadjuvant chemotherapy for locally advanced colon cancer will mature in the next decade. Other than the FOXTROT trial, the PRODIGE 22-ECKINOXE trial (26) is a multicenter randomized phase II trial where patients with T3-T4 and/or N2 were randomized to either preoperative FOLFOX followed by surgery followed by postoperative FOLFOX, or surgery followed by FOLFOX which is expected to conclude by 2021. Two other ongoing

trials registered in clinicaltrials.gov include one from Denmark (44) and the other from South Korea (45).

Limitations

There are some limitations to our current study. The review is limited inherently by the amount of studies included. That said, a total of 29,504 patients were included in our analyses, circumnavigating this problem and providing preliminary evidence substantiating the use of neoadjuvant in locally advanced colon cancer. Additionally, the practicality of blinding participants in the trials would also affect the rigor in quality assessment.

Conclusions

In conclusion, this meta-analysis is timely in an emerging era of total neoadjuvant treatment for colorectal cancer. The improved survival and no difference in post-operative complications with neoadjuvant chemotherapy treatment will impact tumor board discussions for non-metastatic locally advanced colon cancer. With the advances made in standard and targeted therapy, there is a foreseeable trend of increased adoption of neoadjuvant chemotherapy for curable colon cancers in the next decade.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jgo-20-220>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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MEDLINE search strategy

1. Colorectal Neoplasms/
2. (Colo* adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumour* or adenoma* or malignan*)).tw.
3. 1 or 2
4. exp Chemotherapy, Adjuvant/
5. Neo-adjuvant.tw.
6. Neo adjuvant.tw.
7. FOLFOX.tw.
8. XELOX.tw.
9. CAPOX.tw.
10. 5-fu.tw.
11. Oxaliplatin.tw.
12. Fluorouracil.tw.
13. 5-fluorouracil.tw.
14. Capecitabine.tw.
15. Leucovorin.tw.
16. 4 or 5 or 6 or 7 or 7 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp laparoscopy/ or laparoscop* .mp. or (laparoscop* adj3 (surg* or operat* or procedure or resecti* or Colectomy)).tw.
18. ((robot* or Open or Convention*) adj5 (surg* or operat* or procedure or resecti* or Colectomy)).tw
19. ((pre-operati* or pre operati* or preoperati* or pre-surg* or presurg* or pre surg* or neoadjuvant) adj3 (therap* or treatment* or chemotherap* or down staging or down stage)).tw.
20. 16 and 19
21. (surg* or operat* or procedure or resecti* or colectomy).tw.
22. 3 and 21
23. 17 or 18 or 22
24. 3 and 20 and 23