Systematic review and meta-analysis of preoperative chemoradiotherapy with or without oxaliplatin in locally advanced rectal cancer

Jiabin Zheng, MS, Xingyu Feng, MD, Weixian Hu, MS, Junjiang Wang, MD, Yong Li, MD, PhD

Abstract

Background: Preoperative chemoradiotherapy has become the current standard regimen for locally advanced rectal cancer (LARC). However, the additional benefit of oxaliplatin to preoperative chemotherapy was still controversial. On one hand, oxaliplatin may improve the tumor response rate of even prolong the survival time. On the other hand, it can bring a series of adverse effects. Opinions vary from studies to studies. We aim to perform a meta-analysis to evaluate the efficacy, safety, and long-term survival of oxaliplatin in preoperative chemoradiotherapy for LARC.

Method: To identify clinical trials fusing oxaliplatin in preoperative chemoradiotherapy for LARC published until December 2015, we searched PubMed, the Cochrane Library, and the Springer Link databases by combining various key words. We also search for relevant ASCO conferences. Data were extracted from every study to perform a meta-analysis using STATA 12.0 software.

Result: Eleven articles or ASCO abstracts from 8 studies with a total of 5597 patients were included. Adding oxaliplatin to preoperative chemoradiotherapy can significantly improve the ypCR rate [risk ratio (RR) = 1.208, 95% confidence interval (95% CI): 1.070–1.368, P = 0.002, I² = 14.5%], and decrease the preoperative metastasis (RR = 0.494, 95% CI: 0.256–0.954, P = 0.036, I² = 53.9%) and local recurrence rate (RR = 0.761, 95% CI: 0.616–0.941, P = 0.012, I² = 26.1%). What’s more, oxaliplatin can prolong the disease-free survival (DFS) [hazard ratio (HR) = 0.867, 95% CI: 0.741–0.992, P = 0.000, I² = 16.3%]. However, oxaliplatin can increase the chemoradiotherapy-related toxicities (RR = 1.858, 95% CI 1.427–2.419, P = 0.000, I² = 94.7%). There was no significant difference between the groups with and without oxaliplatin in operation rate, R0 resection rate, sphincter preservation rate, permanent stoma rate, postoperative complication, mortality, and overall survival.

Conclusion: Preoperative chemoradiotherapy with oxaliplatin bring both advantage and disadvantage to LARC. Whether to use oxaliplatin should be decided by patient’s general condition and tolerance. Although oxaliplatin can prolong the DFS, survival benefit should be proved by further data.

Abbreviations: AEs = Adverse Effects, ASCO = American Society of Clinical Oncology, DFS = Disease-Free Survival, LARC = Locally advanced rectal cancer, OS = Overall Survival, RCTs = Randomized Controlled Trials, TME = Total Mesorectal Excision, ypCR = Post-therapy Pathology Complete Response.

Keywords: long-term survival, meta-analysis, neoadjuvant chemoradiotherapy, oxaplatin, rectal cancer
1. Introduction
Rectal cancer is one of the most common malignant tumors. After long-term exploration and unremitting efforts, preoperative chemoradiotherapy followed by total mesorectal excision (TME) and postoperative chemotherapy are the current standard regimen for those with locally advanced mid-low position rectal cancer. Fluorouracil is a type of radiotherapy-sensitizing agent that enhance tumor response to radiotherapy. Fluoropyrimidine-based preoperative chemoradiotherapy effectively downstages tumors, decreases the risk of local region recurrence, and offers better sphincter preservation. However, whether to use oxaliplatin in preoperative chemotherapy remains controversial. Some physicians believe that oxaliplatin only increases the adverse effects of preoperative chemotherapy, whereas others believe that oxaliplatin improves the tumor local response rate, reduces distant metastases, and even prolong long-term survival. Some clinical trials have been performed to verify the advantages and disadvantages of oxaliplatin in patients with locally advanced rectal cancer (LARC). Before this study, few meta-analyses were performed to quantify the effectiveness of oxaliplatin.

2. Methods
2.1. Study selection
A systematical search of all relevant literature published by December 2015 was performed using the following 3 online databases: PubMed, Cochrane Library, and Springer Link. The key search terms used in various combinations included “rectal cancer,” “rectal neoplasm,” “preoperative chemotherapy,” “neoadjuvant chemotherapy,” “preoperative radiochemotherapy,” “neoadjuvant chemotherapY,” “neoadjuvant radiochemotherapy,” and “oxaliplatin.” Article types were limited to “clinical trial.” Abstracts and conference presentations from the American Society of Clinical Oncology (ASCO) from 2012 to 2015 were also searched. All prospective clinical trials that compare preoperative chemotherapy with oxaliplatin and without oxaliplatin were included.

2.2. Inclusion and exclusion criteria
All prospective clinical trials that compare preoperative chemotherapy with oxaliplatin and without oxaliplatin were included. All data that failed to fulfill the following criteria were excluded: the patients presented with locally advanced mid-low position rectal cancer, the study compared patients administered oxaliplatin for neoadjuvant chemotherapy with patients not administered oxaliplatin, the study was a randomized controlled trial (RCT), the study was a prospective study, and the study was written in English or Chinese. All included studies were assessed by 2 authors independently (Zheng and Feng).

2.3. Quality assessment
Study quality was assessed by 2 authors (Zheng and Feng) independently. Detailed study methods of included ASCO abstracts were obtained from “clinicaltrials.gov.” All of these RCTs were assessed by the modified Jadad scale. If controversy existed between the 2 independent evaluations, all of the authors participated in a discussion to resolve the issue. RCTs with a score of 0 to 3 indicate poor quality, whereas a score of 4 to 7 indicates good quality.

2.4. Data extraction
Data from shortlisted articles were extracted independently by the 2 authors (Zheng and Feng) and entered into a pre-designed form after reaching a consensus. The main data reported included study characteristics and study outcomes. Study characteristics, including the time, country, study type, the number of patients, treatment, outcome, and Jadad score, are presented in Table 1.

Table 1
Study characteristics of included studies.

| Study   | Year | Study type | Country | Number of patients | Treatment | Outcome | Score |
|---------|------|------------|---------|--------------------|-----------|---------|-------|
| STAR-01 | 2011 | RCT        | Italy   | 368                | 5-Fu+Oxa+RT | ypCR, AE | 5     |
| ACCORD-12 | 2012 | RCT        | France  | 299                | Cap+Oxa+RT | ypCR, AE | 5     |
| NSBPA-R04 | 2015 | RCT        | America | 500                | 5-Fu+Oxa+RT | ypCR, AE | 5     |
| AIO-04  | 2015 | RCT        | Germany | 613                | Cap+Oxa+RT | ypCR, AE | 5     |
| PETACC-6 | 2014 | RCT        | Germany | 547                | Cap+Oxa+RT | ypCR, AE | 5     |
| FOWARC  | 2015 | RCT        | China   | 165                | 5-Fu+Lv  | ypCR, AE | 5     |
| Saha et al[12] | 2011 | RCT        | India   | 21                 | Cap+Oxa+RT | ORR, AE  | 6     |
| Jiao et al[13] | 2015 | RCT        | China   | 103                | Cap+Oxa+RT | ypCR, AE | 3     |

AE = adverse effect, Cap = capecitabine, DFS = disease-free survival, ORR = objective response rate, OS = overall survival, Oxa = oxaliplatin, pCR = pathological complete response, RCT = randomized controlled trial, RT = radiotherapy.
Otherwise, random-effect models were used. In addition, an \( I^2 \) value of less than 25\% was defined as low heterogeneity, a value between 25\% and 50\% was defined as moderate heterogeneity, and a value of \( I^2 > 50\% \) was defined as high heterogeneity.\(^{11}\) \( p \) values less than 0.05 were considered significant.

3. Results

3.1. Studies included

A total of 1381 citations from 3 databases met our search strategies and 3652 ASCO abstracts about colorectal cancer were found from 2012 to 2015. Reviewers of the full-text articles revealed 9 articles that adequately match the inclusion and exclusion criteria, which contain short-term results and long-term results from 6 different clinical trials.\(^{12,13,15,16,17–19}\) We also reviewed a total of 3652 ASCO abstracts about colorectal cancer in the last 4 years. Two abstracts matched the inclusion and exclusion criteria but were not published in other journals.\(^{20,21}\) A total of 11 articles or abstracts from 8 clinical trials for a total number of 5597 patients, who suffered from local advanced rectal cancer, were included in this meta-analysis. The study screening and selection processes are presented in Fig. 1. Quality assessment of the included articles and the characteristics of the included patients are presented in Table 1.

3.2. Chemoradiotherapy-related toxicities

All the trials reported the Grade 3/4 chemoradiotherapy toxicities except the one by Saha et al.,\(^{13}\) which included 2769 patients in the investigation group (with oxaliplatin) and 2786 patients in the control group (without oxaliplatin). Chemoradiotherapy-related toxicities were analyzed in the reported trials according to the National Cancer Institute Common Toxicity Criteria. Grade 3/4 toxicities ranged from 7.7\% to 34.5\% in the chemotherapy without oxaliplatin group and from 22\% to 56\% in the chemotheraphy with oxaliplatin group. Significantly more preoperative Grade 3/4 toxicities were noted in the investigation group than the control group. The pooled RR of chemoradiotherapy-related toxicities is 1.858 [95\% confidence interval (95\% CI): 1.427–2.419, \( p < 0.001, I^2 = 84.7\% \)] (Fig. 2). Given that significant heterogeneity existed, the random-effect model was applied.

3.3. ypCR rate

Post-therapy pathology complete response rates were reported in all of the 8 trials, including 2790 patients in the investigation group and 2807 patients in the control group. The ypCR rate ranged from 13.0\% to 24.2\% and from 11.5\% to 19.4\% for the investigation group and the control group, respectively. The fixed-effect model was used to pool estimates the ypCR rates. As shown in Fig. 3, the ypCR rate of neoadjuvant chemotherapy with oxaliplatin was significantly increased compared with treatment without oxaliplatin (\( RR = 1.208, 95\% CI: 1.070–1.364, P = 0.002, I^2 = 14.5\% \)).

3.4. Operation rate and preoperative metastasis

All of the studies reported the operation rate except the one by Saha et al.,\(^{13}\) No significant differences were noted between the investigation and control group (\( RR = 0.992, 95\% CI: 0.973–1.011, P = 0.404, I^2 = 52.1\% \)) (Fig. 4). Given that the \( I^2 \) was greater than 50\%, the random-effect model was used to calculate the pooled RR of operative rate. However, only 3 trials reported a preoperative metastasis rate for a total of 2610 patients. In this meta-analysis, a significant difference was noted between the with and without oxaliplatin groups. The preoperative metastasis rate in the investigation group was obviously reduced compared with the control group (\( RR = 0.494, 95\% CI: 0.256–0.954, P = 0.036, I^2 = 53.9\% \)) (Fig. 5). The random-effect model was applied to calculate the pooled RR given that heterogeneity existed.

3.5. R0 resection rate

R0 resection rates were reported in 7 studies. The R0 resection rate ranged from 45.6\% to 97.1\% in the investigation group and from 45.6\% to 95.1\% in the control group. No significant difference in the R0 resection rate was noted between these 2 groups (\( RR = 1.004, 95\% CI: 0.985–1.025, P = 0.661, I^2 = 2.1\% \)) (Fig. 6).

3.6. Sphincter preservation rate

Seven studies reported the sphincter preservation rate, including 5304 patients in the analysis. The preserved sphincter percentage ranged from 56.4\% to 85.4\% in the investigation group and from 61.0\% to 78.6\% in the control group. The pooled estimate showed no significant difference between preoperative chemotherapy with oxaliplatin and without oxaliplatin. (\( RR = 1.001, 95\% CI: 0.968–1.034, P = 0.967, I^2 = 8.5\% \)) (Fig. 7).

3.7. Permanent stoma rate

Only 5 studies, including 3920 patients, reported the permanent stoma rate after radical resection of primary tumor. The permanent stoma rate ranged from 15.5\% to 37.4\% in the investigation group and from 21.0\% to 34.6\% in the control group. No significant difference was noted between the groups.
Figure 2. Pooled RR for grade 3&4 adverse effect of included studies.

Figure 3. Pooled RR for ypCR rate of included studies.
Figure 4. Pooled RR for operation rate of included studies.

Figure 5. Pooled RR for preoperative metastasis rate of included studies.
Figure 6. Pooled RR for R0 resection rate of included studies.

Figure 7. Pooled RR for sphincter preservation rate of included studies.
regarding the postoperative permanent stoma rate (RR = 1.015, 95% CI: 0.917–1.123, \(P = 0.778, I^2 = 0\%\)) (Fig. 8).

3.8. Postoperative complications and postoperative mortality
Postoperative complications include surgical-related complications and nonsurgical complications that typically occur 30 days after operation. Postoperative mortality was defined as patient who died within 60 days after the operation. Six studies reported postoperative complications, and 5 reported postoperative mortality. Postoperative complications ranged from 8.4% to 47.0% in the investigation group and from 7.9% to 45.1% in the control group. Significant differences in the postoperative complication rate were not noted between the groups (RR = 1.33, 95% CI: 0.952–1.120, \(P = 0.435, I^2 = 0\%\)) (Fig. 9). Similar to postoperative complications, no significant difference in postoperative mortality was noted between the groups (RR = 0.768, 95% CI: 0.331–1.778, \(P = 0.537, I^2 = 0\%\)) (Fig. 10).

3.9. Long-term survival data
Five clinical trials completed long-term follow-up and reported the survival data. All of these 5 studies reported 3-year local recurrence rates, with 4304 patients included in the analysis. The cumulative incidence of local recurrence ranged from 3.0% to 11.8% in the investigation group and from 5.6% to 12.6% in the control group. In the meta-analysis, there was a significant difference favoring the investigation group (RR = 0.761, 95% CI: 0.616–0.941, \(P = 0.012, I^2 = 26.1\%\)) (Fig. 11).

Three of these five studies reported the 3-year disease-free survival (DFS), and 3 reported 3-year overall survival (OS). Others reported the 5-year survival data, or the data were unavailable. Pooled HRs were calculated for the studies reporting the 3-year DFS and OS, separately. The pooled data reveal a significant DFS benefit for patients administered neoadjuvant chemotherapy with oxaliplatin (HR = 0.867, 95% CI: 0.741–0.992, \(P = 0.000, I^2 = 0\%\)) (Fig. 12), while no significant benefit for OS was noted (HR = 1.013, 95% CI: 0.802–1.224, \(P = 0.471, I^2 = 0\%\)) (Fig. 13).

4. Discussion
Oxaliplatin is effective as an adjuvant treatment in colon cancer[8] and is a radiosensitizing agent.[22] However, its effects in the neoadjuvant chemotherapy of LARC are debated. To solve this problem, a series of RCTs were performed in recent years, and the results of these trials have been published. The results of these trials did not achieve a consensus regarding short-term results and long-term survival data. Therefore, we conducted this meta-analysis to pool the research data and try to solve these problems.

To date, 8 randomized phase III trials assessing neoadjuvant chemotherapy with or without oxaliplatin have been reported. The overall study designs were similar in all of these 8 studies. These clinical trials were well designed and well executed regarding randomization, withdraw, and dropout. However, not all of the studies were double-blind studies. Study quality assessments were presented above and were based on the modified Jadad scale. All of the included studies were assessed as “high quality” except the one by Jiao et al[12] given its lack of description of randomization and concealment. The most controversial difference may be the neoadjuvant chemotherapy regimen, which is sensible.
Figure 9. Pooled RR for postoperative complications of included studies.

Figure 10. Pooled RR for postoperative mortality of included studies.
The complete response rate is one of the most important indexes to evaluate the efficacy of oxaliplatin, which can reflect the local tumor control. The complete response rate is ranked only second to long-term survival data. All of the pCR rates in the investigation groups of the included studies were not less than those reported for the control groups (STAR-01 was equivalent), in which only the AIO-04 trial and FOWARC trial exhibited a significant improvement in pCR rate. The variation in pCR rates across different trials is illustrated in Figure 11. Additionally, Figure 12 shows the pooled HR for disease-free survival of included studies.
was affected by the chemotherapy regimens, drugs dose, and radiation dose. On one hand, the chemotherapy dosage form and dose and the radiation dose were different in the investigation group and the control group in some trials when designed. On the other hand, patients who receive neoadjuvant chemotherapy with oxaliplatin may not tolerate full-dose chemoradiotherapy, so most of these patients would receive reduced drug and radiation doses. As a result, the total chemoradiotherapy dose was generally lower in the investigation group. Our meta-analysis demonstrates that oxaliplatin significantly improves the pCR rate (RR = 1.208, 95% CI: 1.070–1.364, P = 0.002). As we all know, oxaliplatin is a radiotherapy-sensitizing agent. It can enhance the effect of radiation on local control. In previous studies, oxaliplatin had a positive effect in advanced rectal cancer after surgery, prolonging the DFS and reducing the local recurrence rate.\textsuperscript{[9]} Hence, oxaliplatin can improve the ypCR rate is absolutely accessible.

Some patients exhibited tumor metastases when preoperative chemoradiotherapy was administered. The effect of fluorouracil in systemic control was unsatisfying in the course of the preoperative chemoradiotherapy. Some studies suggest that oxaliplatin also enhance systemic control.\textsuperscript{[10]} Only 3 studies considered the preoperative metastasis rate as an endpoint. The pooled RR of preoperative metastasis for these studies was 0.494 (95\% CI: 0.256–0.954, P = 0.036), indicating that oxaliplatin significantly enhances the systemic control and reduces the preoperative metastasis rate. Regarding long-term indicator, oxaliplatin significantly decreases the 3-year local recurrence rate and it is also effective in systemic control. The pooled RR for the recurrence rate was 0.761 (95\% CI: 0.616–0.941, P = 0.012).

The most controversial issue was whether oxaliplatin prolongs the survival time of patients with LARC. Three-year DFS and OS were the primary endpoints of most trials. Some of the clinical trials published their long-term survival data in the past 2 years, which led to a bitter quarrel. Most of these studies reported no difference in the 3-year or 5-year survival data. However, the AIO-04 study suggested that oxaliplatin prolongs the 3-year DFS but not the 3-year OS. This difference potentially resulted from the addition of oxaliplatin in adjuvant chemotherapy. However, another study \textsuperscript{[21]} that also added oxaliplatin to the adjuvant chemotherapy did not achieve the same result. Our meta-analysis showed a significant improvement of the DFS, but not OS. The pooled HR for DFS was 0.867 (95\% CI: 0.741–0.992, P < 0.001), whereas the pooled HR for OS was 1.013 (95\% CI: 0.802–1.224, P = 0.471). The improvement in DFS was consistent with the decrease in preoperative metastasis and 3-year recurrence, indicating powerful systemic control and reduced tumor recurrence. Although the pooled DFS data favored the investigation group, 2 unavailable studies showed no significant difference between the 2 groups. For more accurate results, we are looking forward to the further results from other clinical trials.

Oxaliplatin appears to be an effective neoadjuvant chemotherapy for patients with LARC. Nonetheless, the adverse effects of oxaliplatin are an additional problem and should be considered. All of the studies reported the adverse effects in the course of neoadjuvant chemoradiotherapy, including diarrhea, leucopenia, nausea, and vomiting. Given these adverse effects, the dosage was reduced or the neoadjuvant chemoradiotherapy was stopped in some patients. All the studies demonstrated an increase in grade 3/4 adverse effects except the AIO-04 study, potentially due to the

Figure 13. Pooled HR for overall survival of included studies.
different chemotherapy schedules. Continuous chemoradiotherapy would decrease the tolerance of preoperative therapy. Our pooled data also demonstrated a significant increase in adverse effects when oxaliplatin was administered. However, oxaliplatin does not increase postoperative complications or mortality.

A limitation of this meta-analysis involves the limited survival data available. Although the 3-year DFS and local recurrence rate were favorable for neoadjuvant chemotherapy with oxaliplatin, the results are not persuasive. Further survival data are expected to help clarify the role of oxaliplatin in long-term survival.

In conclusion, oxaliplatin as a neoadjuvant chemoradiotherapy exhibits advantages and disadvantages for patients with LARC. The use of oxaliplatin should be based on the general condition and tolerance of the patient. Survival benefits should be proven with additional data.

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