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Adjuvant Chemotherapy for Rectal Cancer After Neoadjuvant Treatment: FOLFOX, 5-FU, or Observation

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Abstract A multimodality approach incorporating concurrent chemotherapy with radiotherapy prior to surgery has become the standardized approach in the management of localized rectal cancer. However, it is unknown whether any further therapy after surgery may be beneficial in improving patient outcomes. Previous completed randomized clinical trials have not added any clarity in this regard, whether adjuvant chemotherapy or intensified chemotherapy regimens improve patient outcomes in those who have previously received neoadjuvant therapy. Despite the lack of evidence, based off the survival data in stage III colon cancer, adjuvant chemotherapy has become a standardized practice in the management of resected rectal cancer. Furthermore, recommendations include the consideration of added oxaliplatin to adjuvant therapy in this disease. While it is unclear whether all patients should receive adjuvant chemotherapy, a subset of patients, including those who achieve a pathologic response may benefit from further treatment. Ongoing studies utilizing an individualized, stepwise multimodality approach may define the role of adjuvant therapy and the appropriate regimen in patients with resected rectal cancer.

Keywords Rectal cancer · Adjuvant chemotherapy · Survival · Neoadjuvant chemoradiation

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Introduction

In 2015, approximately 39,610 new cases of rectal cancer were diagnosed in the USA, with a significant proportion having locally advanced disease [1]. Initially, based on early studies where patients experienced a survival benefit with adjuvant chemoradiation therapy (CRT), postoperative CRT (pelvic radiation therapy with concurrent 5-fluorouracil (5-FU)) followed by additional chemotherapy (5-FU) became the standard approach in rectal cancer (Tables 1 and 2).

A subsequent German study, a randomized phase III trial compared preoperative and postoperative CRT in patients with stage II and III rectal cancer. In addition to pre- or postoperative CRT, all patients received four 5-day cycles of adjuvant 5-FU (500 mg/m^2 per day). While there was no significant difference in overall survival (OS) between the two arms, a lower rate of local recurrence (6 versus 13 % in the postoperative CRT arm) and less grade 3 or 4 adverse events were seen in the preoperative treatment arm [2]. Subsequent studies resulted in similar findings with decreased rates of local disease recurrence, and improved toxicities in patients that receive neoadjuvant chemoradiation therapy. Long-term follow-up did not show any differences in overall survival differences in patients who received neoadjuvant versus adjuvant chemoradiation treatment [2–4]. Thus, a sequential multimodality approach combining neoadjuvant chemoradiation prior to surgical resection has become the standardized approach in patients with locally advanced (T3 and T4, and/or nodal involvement) rectal cancer.

In patients who have previously received neoadjuvant CRT, It is unknown whether adjuvant chemotherapy provides any additional benefit. Studies that have attempted to address the role of adjuvant chemotherapy in this setting, including examining various chemotherapy regimens, have left oncologists with lack of clarity. Several studies have suggested a lack

Table 1 Randomized phase III clinical trials comparing adjuvant chemotherapy with observation

Study	Phase	Number of patients enrolled	Primary endpoint	Chemotherapy arm (%)	Observation arm (%)	*p* value
EORTC 22921	III	1011	10–year OS	51.8	48.4	0.32
I-CNR-RT	III	590	5–year OS	69	70	0.77
PROCTOR/SCRIPT	III	437	5–year OS	79.2	80.4	0.77
CHRONICLE[a]	III	113	3–year DFS	72.5	71.3	0.56

OS overall survival, *DFS* disease free survival

[a] Trial was closed prematurely due to poor accrual

of benefit for adjuvant chemotherapy following neoadjuvant chemoradiation and surgery in resectable rectal cancer. These studies had significant limitations that complicate interpretation including the inconsistent use of neoadjuvant chemoradiation (PROCTOR/SCRIPT), poor adherence (EORTC 22921), lack of optimal dosing, and/or prolonged postoperative complications [3, 5–9].

Based on the survival benefit from adjuvant chemotherapy observed in stage III colon cancer, the current National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with rectal tumors staged as at least T3 or N1 should be considered for adjuvant fluoropyrimidine-based chemotherapy (either 5-FU or capecitabine) with or without oxaliplatin following neoadjuvant CRT and surgery [10–14]. Herein, we will review the evidence in regard to the role of adjuvant therapy in patients who have previously received neoadjuvant chemoradiation and whether adjuvant oxaliplatin has any role in resected rectal cancer.

Postoperative 5-Fluorouracil (5-FU) or Observation?

While the rationale for adjuvant chemotherapy in resected rectal cancer has been largely based off findings seen in resected colon cancer, several studies have attempted to address the role of adjuvant chemotherapy in resected rectal cancer following preoperative radiotherapy or concurrent chemoradiation (CRT). EORTC 2291, a large randomized phase III trial utilized a 2 × 2 factorial design that randomized 1011 patients to preoperative radiotherapy versus preoperative CRT, and in a second randomization, to adjuvant chemotherapy versus observation [9]. Adjuvant chemotherapy was 5-FU and leucovorin (LV), given every 3 weeks for 4 cycles. No significant difference in overall survival was seen between patients who received preoperative chemotherapy ($p = 0.84$) or adjuvant chemotherapy ($p = 0.12$) [9]. Differences in local recurrence were seen between patients that did not receive chemotherapy compared to patients who received chemotherapy preoperatively and postoperatively (17.1 versus 7.6 %, $p = 0.002$) [9]. In the subgroup analysis assessing pathologic stage (yp) after resection, there was no significant difference in overall survival or disease-free survival in patients who achieved a pathological status of ypT0-2 and those who had ypT3-4 in the groups who received chemotherapy versus postoperative observation. While the study failed to demonstrate any significant benefit from the addition of chemotherapy in the preoperative or postoperative setting, the postoperative chemotherapy group had a very low rate of chemotherapy adherence (42.9 %) that limited any conclusive results for the role of chemotherapy in rectal cancer.

Two additional large randomized studies examined the role of adjuvant 5-FU in patients who received neoadjuvant concurrent chemoradiation (CRT). The I-CNR-RT Italian study randomized 655 patients to neoadjuvant CRT with or without

Table 2 Randomized phase II–III clinical trials comparing adjuvant 5-fluorouracil or oxaliplatin-based chemotherapy

Study	Phase	Number of patients enrolled	Primary endpoint	Chemotherapy arm (%)	Observation arm (%)	*p* value
PETACC6	III	1094	3–year DFS	74.5	73.9	0.78
CAO/ARO/AIO-4	III	1265	3–year DFS	71.2	75.9	0.038
ADORE	II	295	3–year DFS	62.9	71.6	0.047

OS overall survival, *DFS* disease-free survival

adjuvant chemotherapy (6 cycles of adjuvant 5-FU/LV, instead of 4 cycles in EORTC 22921) [15]. While a higher proportion of compliance to adjuvant chemotherapy was seen in this study compared to EORTC 22921 (60 % of patients received 3–6 adjuvant 5-FU), no difference in 5 year overall survival (70 % in the observation versus 69 % in the adjuvant CT arm; Hazard ratio (HR) 1.045, $p = 0.772$) or distant recurrence rates were observed between the two arms.

Unlike EORTC 22921 and I-CNR-RT, The PROCTOR/SCRIPT trial randomized patients postoperatively who received neoadjuvant CRT with yp pathologic stage II–III disease to observation or adjuvant 5-FU/LV. While the trial ended prematurely due to poor accrual, the 5-year OS rates were very similar between the two groups (79.2 % in the chemotherapy arm, 80.4 % in the observation arm) [16].

The Role of Added Oxaliplatin to Neoadjuvant Therapy in Localized Rectal Cancer

Since randomized clinical trials demonstrated that concomitant 5-fluorouracil with preoperative radiotherapy reduces local recurrences in comparison to neoadjuvant radiotherapy without chemotherapy, several studies have assessed whether adding oxaliplatin to neoadjuvant therapy would translate to further improved patient outcomes [3, 4]. ACCORD 12/045 randomized patients with clinically stage T3-T4 disease to an intensified radiotherapy regimen (50 Gy) with capecitabine and oxaliplatin versus capecitabine with standard dose radiotherapy at 45 Gy. The primary end point was sterilization of the operative regimen. While patients who received the oxaliplatin-containing regimen had numerically higher rates of pathologic response (19.2 % versus 13.9 %; $p = 0.09$), this may have been attributed to the radiation dose escalation. Additionally, when examining patient outcomes, no differences in disease free survival or overall survival were observed between the two treatment groups [17]. Subsequent studies showed similar findings to ACCORD 12/045, where the addition of oxaliplatin to neoadjuvant therapy did not significant increase pathologic response and failed to improve patient outcomes. STAR-01, a randomized phase III study randomized patients with clinical stage II or III disease (cT3-T4 or cN1-2) to concomitant chemoradiotherapy with 5-FU alone (225 mg/m^2/day) or combined with oxaliplatin (60 mg/m^2 weekly × 6) [18]. The study failed to demonstrate that the addition of oxaliplatin improved survival or tumor pathologic response (odds ratio = 0.98, $p = 0.90$) [18]. Additionally, patients enrolled in the oxaliplatin arm experienced increased grade 3–4 toxicities in comparison to the control arm. Lastly, NSABP R04, a large phase III study enrolled 1608 patients that were randomized to one of four chemotherapy regimens: infusional 5-FU or capecitabine, with or without oxaliplatin, where the primary endpoint was local-regional tumor control. No differences in locoregional tumor control, disease free survival or overall survival were observed between the 5-FU or capecitabine with no impact observed by the addition of oxaliplatin [19••]. In summary, across multiple large randomized controlled trials, the addition of oxaliplatin to preoperative therapy failed to improve disease response or patient related outcomes and thus should not be considered a standard form of therapy.

The Role of Added Oxaliplatin to Adjuvant Therapy in Resected Rectal Cancer

Despite low rates of local recurrence with improvements in neoadjuvant therapy and surgical techniques, approximately 35 % of patients eventually present with disseminated disease at the time of recurrence [3, 9]. Given the high proportion of patients who present with metastatic disease at recurrence, multiple studies investigating the role of oxaliplatin added to 5-FU in the adjuvant treatment of rectal cancer were initiated. PETACC-6 investigated the effect of added oxaliplatin to preoperative and postoperative 5-FU, with a primary endpoint of disease free survival (DFS) [20]. Patients with stage II-III rectal cancer received preoperative CRT with capecitabine, followed by 6 cycles of adjuvant capecitabine or the same treatment plan with the addition of oxaliplatin to pre- and postoperative therapy. The 3-year DFS rates were 74.5 % and 73.9 % (HR 1.04; $p = 0.78$) for the control and investigational arms, respectively. At 3 years, similar OS rates were also seen between the two groups, in addition with no difference in pathologic down staging in patients who received oxaliplatin. An imbalance in patients who received neoadjuvant capecitabine between the two arms (24 % in the oxaliplatin arm received less than 90 % of prescribed capecitabine versus 7.5 % in the control arm) may have blunted any potential survival benefit from oxaliplatin.

CAO/ARO/AIO-4 study, a randomized German randomized phase III also examined the potential benefit from added oxaliplatin in rectal cancer [21••, 22]. 1265 patients were randomized to receive neoadjuvant radiotherapy (50.4 Gy) in combination with 5-FU (days 1–5, 29–33) or low dose infusional 5-FU (days 1–14, days 22–35) with oxaliplatin. Following surgery, the control group received 4 cycles of bolus 5-FU whereas the investigational arm received 8 cycles of modified FOLFOX6. Patients who received oxaliplatin had a statistically improved 5-year DFS rate (68.8 % versus 64.3 % in the 5-FU arm, HR 0.79; $p = 0.03$). However, despite improvements in DFS, no significant differences in OS were seen between the two treatment groups.

ADORE, a multicenter randomized phase II trial was conducted in patients with rectal cancer who previously received fluoropyrimidine based preoperative CRT with post operative pathologic stage II or III disease (ypT3-4 or nodal

involvement) [23•]. Patients enrolled were randomized to receive adjuvant chemotherapy with 4 cycles of 5-fluorouracil and leucovorin or 8 cycles FOLFOX (5-FU/LV and oxaliplatin), where the primary endpoint was 3-year disease free survival (DFS). The 3-year DFS was significantly higher in the FOLFOX arm (71.6 % versus 62.9; HR 0.657, $p = 0.047$), no differences in overall survival were observed between the two arms, however, when broken down by stage, the 3 year DFS was only significantly better for the FOLFOX arm in patients with stage III disease (66.6 versus 57.3 %; HR 0.60, $p = 0.04$). In their secondary endpoints, a 3-year OS was significantly higher in patients who received FOLFOX (95 versus 85.7 %; HR = 0.46, $p = 0.04$). While the findings from ADORE suggested a survival and reduced rate of disease recurrence in high-risk patients, the study population was comprised of only Asian patients and did not address the role of added oxaliplatin for patients with a lower risk of recurrence (py T1-2 disease).

Discussion

Despite the lack of strong evidence from randomized studies to support the use of adjuvant chemotherapy in rectal cancer following exposure to neoadjuvant chemoradiotherapy and surgical resection, it has become the "standard" therapeutic approach in rectal cancer. The rationale for adjuvant therapy has been mostly based on data extrapolated from colon cancer trials. A number of studies, including a recent Cochrane review that showed a 17 % risk reduction in death and a 25 % risk reduction in disease recurrence among rectal cancer patients who received neoadjuvant CRT and surgical resection followed by adjuvant chemotherapy, suggest a possible benefit from adjuvant chemotherapy in this setting [24–26].

In contrast, a multitude of studies failed to demonstrate any significant benefit from adjuvant chemotherapy in patients who received neoadjuvant CRT prior to surgical resection (PROCTOR/SCRIPT, EORTC 22921, I-CNR-RT). While the adjuvant colon cancer trials showed a benefit from adjuvant chemotherapy despite not receiving neoadjuvant CRT, the lack of benefit seen in rectal cancer may be a result of suboptimal adjuvant chemotherapy duration and dosing, where 5-FU dosing was on average 30 % less than that typically received in colon cancer trials [27]. This compounded with poor adherence, which may be attributable to the time of randomization where patients were randomized prior to surgery, may contribute to the lack of benefit observed with adjuvant chemotherapy in rectal cancer [7, 9].

While the available data does not support a consensus for adjuvant chemotherapy in all patients who had previously received neoadjuvant CRT, refinement in patient selection that are more likely to benefit from adjuvant chemotherapy may better define the role of adjuvant therapy in rectal cancer. In patients who undergo preoperative CRT and surgery, post treatment pathologic stage was prognostic with a 5-year overall survival rates of 85, 65, and <60 % for stage 0–I, II, and III, respectively [8, 28]. Similar findings were seen in a pooled analysis where patients who received preoperative CRT showed an improvement in disease-free survival in those who achieved a low pathologic stage (ypT1-2) [29]. Thus, patients who are able to achieve a robust response from preoperative therapy are likely to benefit from adjuvant chemotherapy. This includes patients who are able to achieve a pathologic complete response (pCR) from preoperative CRT. While retrospective studies and meta-analyses have demonstrated improved outcomes in those who achieve a pCR compared to patients with higher pathologic stage [30], despite the excellent outcomes seen in these patients, the risk for disease recurrence is still present. Furthermore, the clinical benefit from adjuvant chemotherapy, or potential lack thereof, has not been addressed through prospective studies in patients that achieve a pCR. Given their response to preoperative therapy, patients who achieve a pathologic response are likely to receive the most benefit from further treatment and should be considered to receive adjuvant fluoropyrimidine-based therapy (5-FU or capecitabine).

In the patients who do not achieve a pathologic response to neoadjuvant CRT, intensification of adjuvant chemotherapy with oxaliplatin-based regimens may be beneficial. Long-term results from CAO/ARO/AIO-04 and PETACC-6 may help in understanding the role of adjuvant oxaliplatin in rectal cancer. Lastly, a patient-by-patient "personalized" approach in determining treatment selection for neoadjuvant and adjuvant therapy is the appropriate strategy (including the role of radiation) in the treatment of localized rectal cancer. In the ongoing N1048/PROSPECT trial (clinicaltrials.gov, NCT01515787) patients will be randomized to receive either standard therapy (fluoropyrmidine-based CRT followed by surgery and adjuvant FOLFOX × 8 cycles) or neoadjuvant FOLFOX and based on response will receive either chemoradiation followed by surgery and adjuvant FOLFOX × 2 (in those whose response <20 %) or surgery followed by FOLFOX (response >20 %).

Conclusion

In the management of early stage rectal cancer, adjuvant chemotherapy following exposure to neoadjuvant CRT remains a mainstay in treatment, despite its unknown benefits. The NCCN guidelines recommend adjuvant fluoropyrimidine-based chemotherapy as a preferred option to consider for patients with this disease and in this setting. Furthermore, despite the lack of evidence, the recommendations suggest added oxaliplatin for rectal tumors with a pathologic stage T3 or N1 higher. Considering the curative intent, adjuvant

fluoropyrimidine therapy (5-FU or capecitabine) is a reasonable approach to consider for rectal cancer. When taking into account potential adverse effects, impact on quality of life, and uncertain clinical benefit, intensification of adjuvant chemotherapy with oxaliplatin remains experimental and should not be considered a standardized practice at this time regardless of lymph node status. Long-term follow-up from previous studies are needed to determine the role of adjuvant oxaliplatin in rectal cancer. Ongoing studies will help better define the utility and regimen of adjuvant therapy following exposure to neoadjuvant CRT and intensified neoadjuvant chemotherapy, and more specifically, identifying the subgroups of patients who are more likely to benefit from this approach.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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