Oxaliplatin-containing adjuvant chemotherapy improves the survival of locally advanced rectal cancer patients with pathological complete response after pre-operative chemoradiotherapy

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Abstract

Background: The necessity for adjuvant chemotherapy (ACT) in locally advanced rectal cancer (LARC) patients who achieve pathological complete response (pCR) after pre-operative chemoradiotherapy (CRT) is still not identified. We aimed to investigate the therapeutic value of ACT in these patients.

Methods: Clinical data were retrospectively collected from 105 consecutive LARC patients who achieved pCR after pre-operative CRT and underwent radical tumor resection between December 2008 and April 2014 in a comprehensive cancer center. Perioperative chemotherapy (CT) was administered by combining oxaliplatin with capecitabine (XELOX regimen). Disease-free survival (DFS) and overall survival (OS) rates of patients with or without ACT were compared.

Results: Eighty-three (79.0%) patients received ACT and 22 (21.0%) did not. With a median follow-up of 49 months, the ACT group had a significantly higher 3-year DFS rate (92.8 vs 86.4%, \(p = 0.029\)) and 3-year OS rate (95.1 vs 86.1%, \(p = 0.026\)) than the non-ACT group. In multivariable analyses, the presence of ACT was an independent prognostic factor for DFS (hazard ratio [HR]: 0.271; 95% confidence interval [CI]: 0.080–0.916; \(p = 0.036\)) but not for OS. This benefit was more obvious in patients younger than 60 years via subgroup analysis (adjusted HR: 0.106; 95% CI: 0.019–0.606; \(p = 0.012\)).

Conclusions: Oxaliplatin-containing ACT may confer survival benefits to patients with pCR, particularly younger patients. However, the routine use of ACT in patients with pCR needs further validation.

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Key words: Adjuvant chemotherapy; rectal cancer; pre-operative chemoradiotherapy; pathological complete response; survival

Introduction

Currently, pre-operative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has been identified as a standard treatment for locally advanced rectal cancer (LARC) [1, 2]. However, the oncological outcomes of these LARC patients often depend on the treatment response to CRT. Therefore, tumor regression might serve as an oncological benchmark for subsequent treatment strategies [3, 4].

In fact, 20–30% of patients have been shown to achieve pathological complete response (pCR) after pre-operative CRT [5, 6]. Accumulating evidence demonstrates that pCR is a favorable prognostic indicator for reduced rates of post-operative recurrence and prolonged survival [7]. Irrespective of the final pathological results, on the basis of the extrapolated clinical results from cases of advanced colon cancer, the National Comprehensive Cancer Network (NCCN) guideline maintains the need for additional post-operative adjuvant chemotherapy (ACT) in the form of 6 months of perioperative chemotherapy in total for LARC patients undergoing pre-operative CRT [8]. Nevertheless, several researchers have questioned the necessity for ACT for LARC patients who receive pre-operative CRT and curative surgery, especially for patients with pCR [9–11]. Since this select group of patients exhibits favorable survival outcomes irrespective of whether they receive ACT [3, 12], the actual oncologic benefits gained from ACT have not yet been conclusively established.

To determine whether the addition of ACT in patients with pCR provides any oncologic benefit, the present study compared the long-term outcomes of patients who receive CRT and radical surgery followed by oxaliplatin-containing ACT with those of patients without ACT.

Patients and methods

Patient selection

The retrospective study assessed 577 consecutive patients with LARC who underwent pre-operative CRT followed by surgery between December 2003 and April 2014 at Sun Yat-sen University Cancer Center, China. The inclusion criteria were as follows: (i) clinical stage II/III disease (7th edition of the American Joint Committee on Cancer Staging Manual), (ii) radical resection for rectal tumor, (iii) histologically confirmed pCR and (iv) perioperative chemotherapy with TME 6–8 weeks after the completion of the pre-operative irradiation. The post-operative tumor pathological staging was confirmed by two independent pathologists. pCR was defined as the absence of viable tumor cells with the presence of only fibrotic masses or cellular mucin pools in the lymph nodes and the area occupied by the primary tumor [13].

Follow-up

Patients were followed up within 1 month of surgery. Routine assessment including clinical check-up, laboratory testing (CA199 and carcinoembryonic antigen [CEA]), abdominal ultrasonography and chest radiography were conducted every 3 months. Chest/abdominal/pelvic computed tomography and colonoscopy were performed annually. Within the follow-up period, overall survival (OS) was defined as the duration from radical resection to the date of last follow-up or death from any cause, whereas disease-free survival (DFS) was defined as the duration from tumor resection to the date of last follow-up or disease recurrence. The final follow-up was performed in February 2017.

Statistical analysis

All clinical data were analysed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as number of cases followed by percentages, and they were compared using a chi-square or Fisher’s exact test. Continuous variables are presented as medians (range) or means (standard deviation), and they were compared using a Student’s t-test or Mann–Whitney U test. Survival outcomes of different groups were compared using a Kaplan–Meier log-rank test. The potential effects of clinical variables on DFS were examined using univariate Cox models were further assessed using multivariate Cox models with a forward stepwise method. Hazard ratios (HRs) and confidence intervals (CIs) were subsequently calculated. All statistical tests used in this study were two-sided, and a p-value <0.05 was considered significant.

Results

Patient characteristics

Of the 105 eligible patients, 66.7% (70/105) were male and 33.3% (35/105) were female, with a mean age of 52.9 ± 11.8 years. Among them, 83 (79.0%) were treated with ACT (the ‘ACT group’), whereas 22 (21.0%) were treated without ACT (the ‘non-interventional, observational and retrospective study, in which the patient data were kept strictly confidential.
Patients in the non-ACT group were older than the patients in the ACT group (mean age 58.9 vs 51.3 years, \(p = 0.007\)). The clinical characteristics of the two groups, including sex distribution, distance of the inferior tumor margin from the anal verge (DAV), tumor differentiation, pretreatment clinical stage and baseline CEA levels, were comparable (Table 1).

**Treatment parameters**

With regard to the treatment parameters of pre-operative CRT, 63.8% of patients received a 50-Gy dose of radiation with a median of three (range one to four) cycles of pre-operative chemotherapy, which was similar between the ACT and non-ACT groups (Table 1). In the patients with ACT, the proportion of patients with abdominoperineal resection (APR) was lower than that of patients with low anterior resection (LAR) (25.3 vs 74.7%, \(p = 0.025\)). As shown in Figure 2A, 23.8% (25/105) of patients completed all eight cycles of perioperative chemotherapy, with a median of six cycles (range two to eight cycles). The patients in the ACT group received a median of six cycles of perioperative chemotherapy (Figure 2B) and four cycles of ACT (Figure 2C). In addition, 74.7% of patients receiving ACT completed six to eight cycles of perioperative chemotherapy.

**Post-operative outcomes**

The median follow-up period for all the patients was 49 months (range 4–89 months), which was not significantly different between the two groups (49 vs 51 months, \(p = 0.553\)). During the follow-up period, 10.5% (11/105) of patients experienced tumor recurrence, including 10 patients with distant metastasis and 1 patient with both distant metastasis and local recurrence. Additionally, eight (7.6%) patients died of disease progression. With regard to the entire study population, the 3-year DFS and OS rates were 91.4 and 93.2%, respectively. The 3-year DFS rates and OS were significantly higher in the ACT group than those in the non-ACT group (DFS: 92.8 vs 86.4%, \(p = 0.029\); OS: 95.1 vs 86.1%, \(p = 0.026\), Figure 3). Univariate analysis showed that ACT was associated with longer DFS (HR: 0.29; 95% CI: 0.088–0.952; \(p = 0.041\)) and OS (HR: 0.235; 95% CI: 0.059–0.940, \(p = 0.041\)). The results of multivariate analyses demonstrated that ACT was an independent prognostic factor for DFS (HR: 0.271; 95% CI: 0.080–0.916; \(p = 0.036\), Table 2) but not for OS (HR: 0.302; 95% CI: 0.069–1.332, \(p = 0.114\), Table 3). When comparing DFS in patients stratified by sex, age, DAV, tumor differentiation and clinical stage, and presence or absence of ACT, the oncologic benefits of ACT were especially noticeable for patients equal to or younger than 60 years (adjusted HR: 0.106; 95% CI: 0.019–0.606; \(p = 0.012\)) and the patients with well and moderate differentiated tumor (adjusted HR: 0.061; 95% CI: 0.005–0.793; \(p = 0.033\)) but not for patients older than 60 years (adjusted HR: 0.283; 95% CI: 0.024–3.389; \(p = 0.319\)) and those with poor differentiation tumor (adjusted HR: 0.476; 95% CI: 0.071–3.199; \(p = 0.445\)), respectively (Table 4).

**Discussion**

Despite the favorable oncologic outcomes of ACT, LARC patients who achieve pCR after CRT might potentially undergo overtreatment. Therefore, the use of post-operative ACT needs to be carefully managed in these patients. Currently, the clinical value of ACT for patients with pCR remains limited [12]. However, there are no studies on patients who achieve pCR that support the use of ACT. Our current study demonstrated significant improvement in 3-year DFS and OS of patients with ACT compared with those of patients without ACT. Although ACT was not an independent prognostic factor in OS (HR: 0.302; 95% CI: 0.069–1.332, \(p = 0.114\)), the presence of ACT was an independent protective factor for DFS (HR: 0.271; 95% CI: 0.080–0.916;
15 months and none of the patients experienced local recurrence. The study of Garcia-Albeniz et al. [14] suggested that ACT could be of low therapeutic value and might even be avoided considering the preferable oncologic outcomes in pCR patients Geva et al. [10] also investigated the contribution of ACT in 52 LARC patients with pCR. They did not find any improvement resulting from ACT in long-term outcomes. Likewise, two retrospective studies from the Cleveland Clinic Foundation, USA, demonstrated that the routine use of ACT following neoadjuvant CRT and curative surgery for LARC patients did not benefit in the long-term oncologic outcomes [11, 15]. Taken together, these studies suggest that avoiding the routine use of ACT may be an optimal strategy for patients who achieve pCR after CRT.

It is worth noting that several factors could contribute to the inconsistent results between the present study and the observational studies mentioned above. First, the present study adopted the use of perioperative chemotherapy with the XELOX regimen in all patients instead of 5-fluorouracil (5-FU) or capecitabine alone, which was widely used in the previous studies. Oxaliplatin has been shown to be a potent radiosensitizer that enhances the cytotoxic effect of radiation on rectal cancer cells and has become one of the important components in pre-operative chemotherapy regimens [16]. The randomized–controlled ADORE trial elucidated that, compared with 5-FU plus leucovorin, chemotherapy with the FOLFOX regimen indeed improved DFS in patients with LARC after pre-operative CRT and TME (HR: 0.657; 95% CI: 0.434–0.994; p = 0.047) [17]. Therefore, the addition of oxaliplatin to perioperative chemotherapy might have partially contributed to the oncologic benefits in the patients in our study. Additionally, the duration of ACT might have affected the results. Unfortunately, previous studies have not reported the actual duration of ACT and adherence of the patients to the treatment [10, 11, 15]. A previous study has shown that a longer duration of ACT could better prevent distant metastasis and may thus be associated with longer distant metastasis-free survival in LARC patients undergoing pre-operative CRT and TME [18]. In the present study, 74.7% of patients completed the planned number of cycles of perioperative chemotherapy (six to eight cycles), which might have contributed to the prognostic benefit in patients in the ACT group. Moreover, the increase in intensity of ACT by the addition of oxaliplatin did not reduce compliance in our study. As a matter of fact, the high compliance rate might be attributable to the strategy of drug delivery and race of the study population. In our study, oxaliplatin was administered after a 1-week chemotherapy-free interval before the next cycle of ACT, which may have contributed to the improved tolerance. Unlike the poor capecitabine tolerability in the US study populations, the current study demonstrated acceptable toxicities and compliance to a standard dose of capecitabine in Chinese patients [19, 20].

From subset analyses in our study, ACT was found to be more beneficial in patients equal to or younger than 60 years (adjusted HR: 0.106; 95% CI: 0.019–0.606; p = 0.012) than in older patients. Recently, a large cohort study from the Taiwan Cancer Registry Database showed that, although ACT did not improve OS for the total LARC patient population with pCR after pre-operative CRT, it conferred a significant survival benefit to patients younger than 70 years (adjusted HR: 0.19; 95% CI: 0.04–0.97; p = 0.046) [21]. In this study, there may have been an age-related difference in the effect of ACT on survival outcomes. Moreover, the addition of oxaliplatin to the ACT regimen has been demonstrated to result in only a slight benefit in older patients with stage II or III colon cancer [22, 23]. Poor performance status, low tolerance of intensive therapies and short life expectancy primarily contribute to the limited survival

| Variable                          | Total (n = 105) | ACT group (n = 83) | Non-ACT group (n = 22) | p-value |
|-----------------------------------|----------------|-------------------|------------------------|---------|
| Age (years)                       |                |                   |                        |         |
| Mean ± SD*                        | 52.9 ± 11.8    | 51.3 ± 11.4       | 58.9 ± 11.6            | 0.007   |
| <60                               | 72 (68.6)      | 63 (75.9)         | 9 (40.9)               | 0.002   |
| >60                               | 33 (31.4)      | 20 (24.1)         | 13 (59.1)              |         |
| Sex                               |                |                   |                        |         |
| Male                              | 70 (66.7)      | 53 (63.9)         | 17 (77.3)              | 0.235   |
| Female                            | 35 (33.3)      | 30 (36.1)         | 5 (22.7)               |         |
| DAV (cm)                          |                |                   |                        |         |
| ≤5                                | 63 (60.0)      | 52 (62.7)         | 11 (50.0)              | 0.282   |
| >5                                | 42 (40.0)      | 31 (37.3)         | 11 (50.0)              |         |
| Tumor differentiation             |                |                   |                        |         |
| Well                              | 29 (27.6)      | 24 (28.9)         | 5 (22.7)               | 0.525   |
| Moderate                          | 56 (53.3)      | 45 (54.2)         | 11 (50.0)              |         |
| Poor                              | 20 (19.1)      | 14 (16.9)         | 6 (27.3)               |         |
| Clinical T stage                  |                |                   |                        |         |
| 2                                 | 4 (3.8)        | 4 (4.8)           | 0                      | 0.527   |
| 3                                 | 68 (64.8)      | 54 (65.1)         | 14 (63.6)              |         |
| 4                                 | 33 (31.4)      | 25 (30.1)         | 8 (36.4)               |         |
| Clinical N stage                  |                |                   |                        |         |
| 0                                 | 35 (33.3)      | 27 (32.5)         | 8 (36.4)               | 0.798   |
| 1                                 | 67 (63.8)      | 54 (65.1)         | 13 (59.1)              |         |
| 2                                 | 3 (2.9)        | 2 (2.4)           | 1 (4.5)                |         |
| Clinical stage                    |                |                   |                        |         |
| II                                | 35 (33.3)      | 27 (32.5)         | 8 (36.4)               | 0.735   |
| III                               | 70 (66.7)      | 56 (67.5)         | 14 (63.6)              |         |
| Baseline CEA (ng/mL)              |                |                   |                        |         |
| ≤5                                | 69 (65.7)      | 56 (67.5)         | 13 (59.1)              | 0.196   |
| >5                                | 30 (28.6)      | 24 (28.4)         | 6 (27.3)               |         |
| Unknown                           | 6 (5.7)        | 3 (3.6)           | 3 (13.6)               |         |
| Radiation dose (Gy)               |                |                   |                        |         |
| 30–46                             | 38 (36.2)      | 30 (36.1)         | 8 (36.4)               | 0.985   |
| 50                                | 67 (63.8)      | 53 (63.9)         | 14 (63.6)              |         |
| Pre-operative chemotherapy (cycles)|                |                   |                        |         |
| 1                                 | 2 (1.9)        | 2 (2.4)           | 0                      | 0.285   |
| 2                                 | 45 (42.9)      | 34 (41.0)         | 11 (50.0)              |         |
| 3                                 | 24 (22.9)      | 22 (26.5)         | 2 (9.1)                |         |
| 4                                 | 34 (32.4)      | 25 (30.1)         | 9 (40.9)               |         |
| Operation                         |                |                   |                        |         |
| LAR                               | 73 (69.5)      | 62 (74.7)         | 11 (50.0)              | 0.025   |
| APR                              | 73 (69.5)      | 62 (74.7)         | 11 (50.0)              |         |

*Except for this, other values are presented as number of patients followed by percentages in parentheses.

ACT, adjuvant chemotherapy; SD, standard deviation; CEA, carcinoembryonic antigen; DAV, distance of the inferior tumor margin from the anal verge; LAR, low anterior resection; APR, abdominoperineal resection.

p = 0.036, indicating that even patients who achieve pCR after pre-operative CRT could potentially benefit from ACT.

The efficacy of ACT in patients who achieve pCR has been repeatedly challenged in the literature. Contrary to the results of the present study, previous observational studies have reported that ACT provided no additional survival benefits to patients with pCR. Garcia-Albeniz et al. [14] conducted a study in which ACT was excluded in patients with pCR following neoadjuvant CRT and TME. Within the 5-year follow-up period, only 1 of 26 patients with pCR developed distant metastasis at 15 months and none of the patients experienced local
benefits among elderly patients [24, 25]. In our study, tumor differentiation was found to be another factor contributing to the different survival benefits of ACT. ACT can only present a 3-year DFS rate improvement for the patients with well and moderate differentiated tumor but not for those with poor differentiated tumor. Poor differentiation tumor was reported to be likely associated with deficiency in mismatch repair protein (dMMR), which has been identified as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colorectal cancer [26, 27]. Taken together, the application of ACT in older patients with poor differentiation tumor warrants careful consideration by weighing up the individual costs and actual benefits.

Some potential limitations of the current study need to be considered. First, this retrospective study included a preselected methodology and a limited number of patients from a single institution. Therefore, a study with a larger number of patients is needed to evaluate the actual therapeutic value of ACT. Second, the ACT cycles themselves might have had a specific prognostic impact on the patients, which could not be taken into consideration in this study. To further determine the clinical value of ACT with the XELOX regimen for patients with pCR, a randomized clinical trial is needed to investigate the inferiority or superiority of the addition of oxaliplatin over ACT with 5-FU alone. Furthermore, the data on the 5-year survival outcomes were unavailable owing to insufficient follow-up duration. Thus, the
later disease recurrence could not be exactly determined. In addition, the exact information of treatment strategies selectively given to post-operative recurrence was unavailable, for which we failed to evaluate the real therapeutic effect of ACT. These limitations may have led to the underestimation of the impact of ACT on OS and subsequently achieved a negative result for OS in multivariate analyses. Despite these potential limitations, the findings of the current study still support a selective policy and warrant the use of ACT for patients with pCR after radical treatment.

Conclusions
The findings of the current study demonstrate that oxaliplatin-containing ACT might provide survival benefits for patients who achieve pCR after CRT and radical resection, especially for patients ≤60 years of age. The validation of the ACT regimen in patients with pCR needs to be prospectively investigated in randomized–controlled studies in the future.

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Table 3. Univariate and multivariate analyses for overall survival in patients achieving complete pathologic response after pre-operative chemoradiotherapy

| Variable               | Univariate analysis | Multivariate analysis |
|------------------------|---------------------|-----------------------|
|                        | HR (95% CI)         | p-value               | HR (95% CI)         | p-value               |
| Age >60 years          | 2.102 (0.525–8.414) | 0.294                 | 10.242 (1.773–59.168) | 0.009                 |
| Sex (female)           | 2.164 (0.541–8.660) | 0.275                 |                       |                       |
| Clinical T stage 4     | 7.126 (1.435–35.388) | 0.016                 |                       |                       |
| Clinical N stage 1/2   | 0.875 (0.209–3.672) | 0.855                 |                       |                       |
| DAV ≤5 cm              | 4.502 (0.553–36.681) | 0.160                 |                       |                       |
| Tumor differentiation (poor) | 8.228 (1.963–34.488) | 0.004                 | 6.564 (1.473–29.245) | 0.014                 |
| Baseline CEA           | 2.454 (0.613–9.828) | 0.205                 |                       |                       |
| Radiotherapy dose (50 Gy) | 0.393 (0.092–1.681) | 0.208                 |                       |                       |
| Anterior resection     | 0.127 (0.026–0.632) | 0.012                 | 0.620 (0.011–0.353)  | 0.002                 |
| ACT                    | 0.235 (0.059–0.940) | 0.041                 | 0.302 (0.069–1.332)  | 0.114                 |

HR, hazard ratio; CI, confidence interval, DAV, distance of the inferior tumor margin from the anal verge; CEA, carcinoembryonic antigen; ACT, adjuvant chemotherapy.

Table 4. Subset analyses of the impact of adjuvant chemotherapy on disease-free survival rate in all 105 patients

| Variable               | 3-year DFS rate (%) | Crude HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value |
|------------------------|---------------------|-------------------|---------|----------------------|---------|
|                        | ACT group           | Non-ACT group     |         |                      |         |
| Sex                    | 98.1                | 88.2              | 0.097   | 0.01–0.933           | 0.043   |
| Male                   | 80.0                | 83.3              | 0.355   | 0.067–1.887          | 0.224   |
| Female                 | 93.7                | 77.8              | 0.151   | 0.034–0.678          | 0.014   |
| Age (years)            | 90.0                | 92.9              | 0.669   | 0.094–4.753          | 0.688   |
| ≤60                    | 90.4                | 81.8              | 0.286   | 0.068–1.202          | 0.087   |
| >60                    | 96.8                | 90.9              | 0.212   | 0.019–2.412          | 0.211   |
| DAV (cm)               | 95.7                | 93.8              | 0.227   | 0.046–1.128          | 0.070   |
| ≤5                     | 78.6                | 66.7              | 0.512   | 0.085–3.084          | 0.465   |
| >5                     | 88.9                | 75.0              | 0.370   | 0.062–2.221          | 0.277   |
| Tumor differentiation  | 94.6                | 92.9              | 0.263   | 0.053–1.306          | 0.102   |
| Well and moderate      |                      |                   |         | 0.001 (0–7946.972)   | 0.319   |
| Poor                   |                      |                   |         | 0.001 (0–14 500)     | 0.882   |
| Clinical stage         |                      |                   |         | 0.312 (0.053–1.828)  | 0.197   |

ACT, adjuvant chemotherapy; HR, hazard ratio; CI, confidence interval; DAV, distance of the inferior tumor margin from the anal verge; CEA, carcinoembryonic antigen.

aAdjusted for age, DAV, tumor differentiation, clinical stage.
bAdjusted for sex, DAV, tumor differentiation, clinical stage.
cAdjusted for age, sex, tumor differentiation, clinical stage.
dAdjusted for sex, age, DAV, clinical stage.
eAdjusted for age, DAV, tumor differentiation.
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