ORIGINAL ARTICLE

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.

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 CT combining oxaliplatin and capecitabine (XELOX regimen). We excluded 468 patients from the analysis due to the presence of distant metastases before CRT ($n = 33$), palliative resection ($n = 41$) and non-pCR tumors ($n = 385$). Among the remaining 118 patients with pCR, 105 who were given perioperative CT with the XELOX regimen between December 2008 and April 2014 were finally selected for analysis (Figure 1). Patient demographics and pre-operative and post-operative treatment protocols were reviewed in detail using an electronic medical record system, and follow-up data were collected from a tracking system. All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Institutional review board approval was also obtained from the independent ethics committee at the Sun Yat-sen University Cancer Center. The need for informed consent was waived in this non-interventional, observational and retrospective study, in which the patient data were kept strictly confidential.

Treatments

Patients were scheduled to receive pre-operative irradiation of 46–50 Gy, delivered in daily boluses of 2.0 Gy for 5 consecutive days per week. Concurrent chemotherapy with the XELOX regimen was administered as follows: 130 mg/m^2 oxaliplatin was intravenously administered on Day 1 and 1000 mg/m^2 capecitabine was orally administered twice daily on Days 1–14 for a 3-week cycle. All subjects were scheduled for radical resection with TME 6–8 weeks after the completion of the pre-operative irradiation. The recommended adjuvant chemotherapy with the XELOX regimen began between 3 and 6 weeks after surgical resection. 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 proportional hazards analyses. Variables that were statistically significant in the 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-
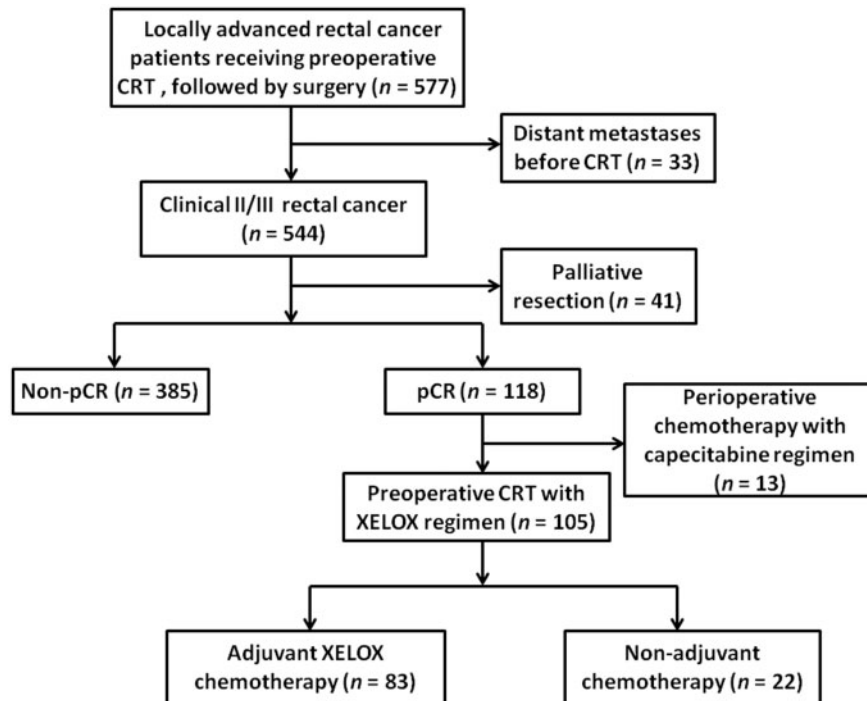
Figure 1. Flowchart representing the selection of eligible patients for this study. CRT, chemoradiotherapy; pCR, pathological complete response; XELOX, a chemotherapy regimen combining oxaliplatin with capecitabine.

ACT group'). 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: 0.290; 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;

Table 1. Demographics and treatment details in 105 patients with locally advanced rectal cancer with and without post-operative adjuvant chemotherapy

Variable	Total (n = 105)	ACT group (n =83)	Non-ACT group (n =22)	p-value
Age (years)				
Mean ± SD[a]	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	32 (30.5)	21 (25.3)	11 (50.0)	

[a]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

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
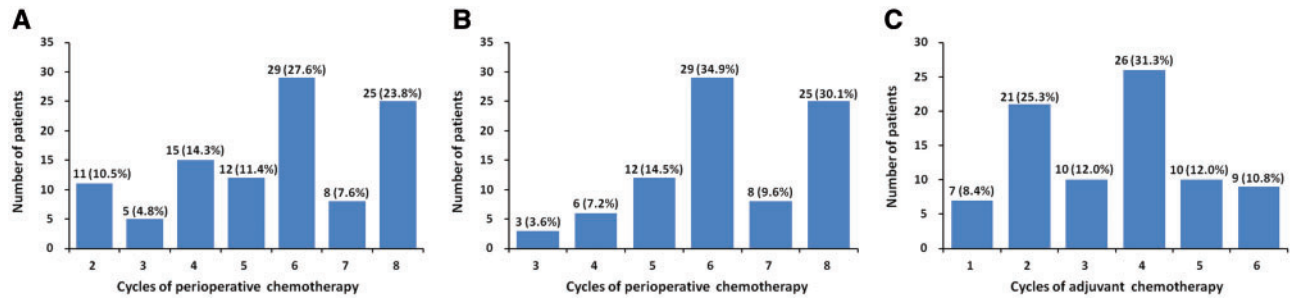
Figure 2. Distribution of oxaliplatin-containing chemotherapy cycles in 105 patients with locally advanced rectal cancer. (**A**) Cycles of perioperative chemotherapy given to all patients. (**B**) Cycles of perioperative chemotherapy given to 83 patients with adjuvant chemotherapy (ACT). (**C**) Cycles of ACT in the 83 patients.
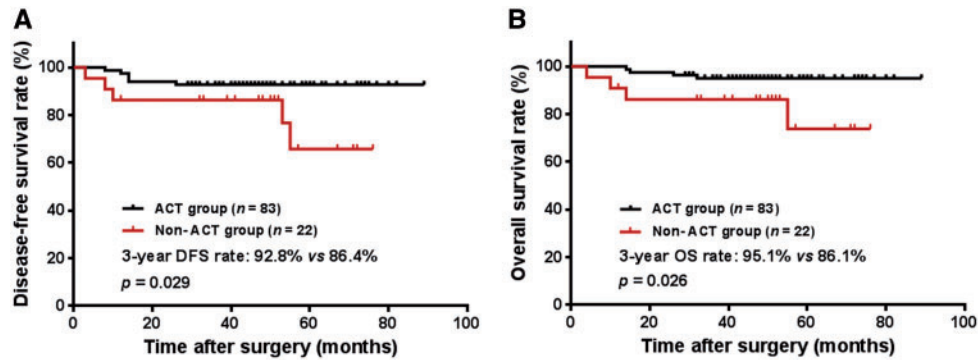

Figure 3. Kaplan–Meier curves comparing 3-year (**A**) disease-free survival (DFS) and (**B**) overall survival (OS) rates based on the administration of adjuvant chemotherapy (ACT) in patients with pathological complete response after pre-operative chemoradiotherapy and surgery.

Table 2. Univariate and multivariate analyses for disease-free 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	1.199 (0.351–4.103)	0.772		
Sex (female)	3.761 (1.100–12.862)	0.035	3.771 (1.064–13.362)	0.040
Clinical T stage 4	2.926 (0.890–9.617)	0.077		
Clinical N stage 1/2	0.624 (0.190–2.048)	0.442		
DAV ≤5 cm	1.690 (0.446–6.403)	0.503		
Tumor differentiation (poor)	4.035 (1.228–13.253)	0.022	2.832 (0.824–9.736)	0.099
Baseline CEA >5 ng/mL	1.417 (0.414–4.850)	0.578		
Radiotherapy dose (50 Gy)	0.852 (0.250–2905)	0.789		
Anterior resection	0.321 (0.098–1.053)	0.061		
Adjuvant chemotherapy	0.290 (0.088–0.952)	0.041	0.271 (0.080–0.916)	0.036

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

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

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

Variable	Univariate analysis HR (95% CI)	*p*-value	Multivariate analysis HR (95% CI)	*p*-value
Age >60 years	2.102 (0.525–8.414)	0.294		
Sex (female)	2.164 (0.541–8.660)	0.275		
Clinical T stage 4	7.126 (1.435–35.388)	0.016	10.242 (1.773–59.168)	0.009
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 >5 ng/mL	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 (%) ACT group	Non-ACT group	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Sex						
Male	98.1	88.2	0.097 (0.01–0.933)	0.043	0.102 (0.008–1.268)[a]	0.076
Female	80.0	83.3	0.355 (0.067–1.887)	0.224	0.178 (0.023–1.390)[a]	0.100
Age (years)						
≤60	93.7	77.8	0.151 (0.034–0.678)	0.014	0.106 (0.019–0.606)[b]	0.012
>60	90.0	92.9	0.669 (0.094–4.753)	0.688	0.283 (0.024–3.389)[b]	0.319
DAV (cm)						
≤5	90.4	81.8	0.286 (0.068–1.202)	0.087	0.218 (0.430–1.122)[c]	0.068
>5	96.8	90.9	0.212 (0.019–2.412)	0.211	0.001 (0–7946.972)[c]	0.198
Tumor differentiation						
Well and moderate	95.7	93.8	0.227 (0.046–1.128)	0.070	0.061 (0.005–0.793)[d]	0.033
Poor	78.6	66.7	0.512 (0.085–3.084)	0.465	0.476 (0.071–3.199)[d]	0.445
Clinical stage						
II	88.9	75.0	0.370 (0.062–2.221)	0.277	0.001 (0–14 500)[e]	0.882
III	94.6	92.9	0.263 (0.053–1.306)	0.102	0.312 (0.053–1.828)[e]	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.
[a]Adjusted for age, DAV, tumor differentiation, clinical stage.
[b]Adjusted for sex, DAV, tumor differentiation, clinical stage.
[c]Adjusted for sex, age, tumor differentiation, clinical stage.
[d]Adjusted for sex, age, DAV, clinical stage.
[e]Adjusted for sex, age, DAV, tumor differentiation.

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.

final manuscript. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A waiver of informed consent was requested and the approval was obtained from independent ethics committees at Sun Yat-sen University Cancer Center. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn) with the approval RDD number of RDDA2017000125.

References

1. Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731–40.
2. Bosset JF, Collette L, Calais G et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**355**:1114–23.
3. Park IJ, You YN, Agarwal A et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *J Clin Oncol* 2012;**30**:1770–6.
4. Rodel C, Martus P, Papadoupolos T et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;**23**:8688–96.
5. Zeng WG, Liang JW, Wang Z et al. Clinical parameters predicting pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Chin J Cancer* 2015;**34**:468–74.
6. Al-Sukhni E, Attwood K, Mattson DM et al. Predictors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Ann Surg Oncol* 2016;**23**:1177–86.
7. Maas M, Nelemans PJ, Valentini V et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010;**11**:835–44.
8. Benson AR, Venook AP, Bekaii-Saab T et al. Rectal cancer, Version 2.2015. *J Natl Compr Canc Netw* 2015;**13**:719–28.
9. Sainato A, Cernusco LNV, Valentini V et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014;**113**:223–9.
10. Geva R, Itzkovich E, Shamai S et al. Is there a role for adjuvant chemotherapy in pathological complete response rectal cancer tumors following neoadjuvant chemoradiotherapy? *J Cancer Res Clin Oncol* 2014;**140**:1489–94.
11. Gamaleldin M, Church JM, Stocchi L et al. Is routine use of adjuvant chemotherapy for rectal cancer with complete pathological response justified? *Am J Surg* 2017;**213**:478–83.
12. Capirci C, Valentini V, Cionini L et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;**72**:99–107.
13. Mandard AM, Dalibard F, Mandard JC et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994;**73**:2680–6.
14. Garcia-Albeniz X, Gallego R, Hofheinz RD et al. Adjuvant therapy sparing in rectal cancer achieving complete response after chemoradiation. *World J Gastroenterol* 2014;**20**:15820–9.
15. Kiran RP, Kirat HT, Burgess AN et al. Is adjuvant chemotherapy really needed after curative surgery for rectal cancer patients who are node-negative after neoadjuvant chemoradiotherapy? *Ann Surg Oncol* 2012;**19**:1206–12.
16. Martin LK, Bekaii-Saab T. Optimizing neoadjuvant therapy for rectal cancer with oxaliplatin. *J Natl Compr Canc Netw* 2013;**11**:298–307.
17. Hong YS, Nam BH, Kim KP et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multi-centre, phase 2, randomised controlled trial. *Lancet Oncol* 2014;**15**:1245–53.
18. You KY, Huang R, Yu X et al. Is it possible to shorten the duration of adjuvant chemotherapy for locally advanced rectal cancer? *Medicine (Baltimore)* 2016;**95**:e3427.
19. Cassidy J, Clarke S, Diaz-Rubio E et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011;**105**:58–64.
20. Hochster HS, Hart LL, Ramanathan RK et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. *J Clin Oncol* 2008;**26**:3523–9.
21. Kuan FC, Lai CH, Ku HY et al. The survival impact of delayed surgery and adjuvant chemotherapy on stage II/III rectal cancer with pathological complete response after neoadjuvant chemoradiation. *Int J Cancer* 2017;**140**:1662–9.
22. Yothers G, O'Connell MJ, Allegra CJ et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011;**29**:3768–74.
23. Sanoff HK, Carpenter WR, Sturmer T et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012;**30**:2624–34.
24. Lu CS, Chang PY, Chen YG et al. Stage III colon cancer: the individualized strategy of adjuvant chemotherapy for aged under and over 70. *PLoS One* 2015;**10**:e0138632.
25. Li P, Li F, Fang Y et al. Efficacy, compliance and reasons for refusal of postoperative chemotherapy for elderly patients with colorectal cancer: a retrospective chart review and telephone patient questionnaire. *PLoS One* 2013;**8**:e55494.
26. French AJ, Sargent DJ, Burgart LJ et al. Prognostic significance of defective mismatch repair and BRAF V600E in patients with colon cancer. *Clin Cancer Res* 2008;**14**:3408–15.
27. Sargent DJ, Marsoni S, Monges G et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010;**28**:3219–26.