

Addition of oxaliplatin to capecitabine-based preoperative chemoradiotherapy for locally advanced rectal cancer: Long-term outcome of a phase II study

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Abstract. Our previous study reported the favorable short-term outcome and good tolerance of integrating oxaliplatin into capecitabine-based (XELOX regimen) preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC). The present study reported the long-term oncological outcome of this phase II study. A total of 47 patients with rectal adenocarcinoma (stage II or III) were enrolled and received radiotherapy (46 Gy in 23 fractions) in combination with capecitabine (1,000 mg/m², twice daily, on days 1-14 and 22-35) and oxaliplatin (130 mg/m² on days 1 and 22). Overall survival (OS) rate, disease-free survival (DFS) rate and cumulative incidence of recurrences and long-term complications were calculated or observed. As a result, 41 patients underwent surgery after preoperative CRT, and the cumulative OS rates at 1, 3 and 5 years for these patients were 100.0, 84.5 and 81.8%, respectively. For the 38 patients who received R0 resection, the cumulative OS rates at 1, 3 and 5 years were 100.0, 89.0 and 86.2%, respectively, while the cumulative DFS rates at 1, 3 and 5 years were 94.6, 75.3 and 69.7%, respectively. After follow-up at 84 months, the cumulative incidence rates of local and distant recurrences at 5 years were 6.6 and 28.2%, respectively. Oxaliplatin-associated long-term complications were seldom observed. Overall, the addition of oxaliplatin to capecitabine-based preoperative radiotherapy achieved

favorable OS and DFS without increased long-term complications in patients with LARC. Therefore, this preoperative CRT strategy is a feasible option for such patients.

Introduction

To date, 5-fluorouracil (5-FU)-based concurrent chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has been the standard treatment for locally advanced rectal cancer (LARC) (1,2). Although local tumor regression was distinctly observed in the majority of patients following CRT, distant metastases remained the main cause for failure, possibly due to the insufficient control of systemic micro-metastasis by CRT (3,4). To enhance local and systemic control, our previous study applied oxaliplatin into capecitabine-based (XELOX regimen) preoperative CRT, which was demonstrated to be feasible and well tolerated (5). The short-term result of this study demonstrated a favorable pathological complete response (pCR; 22%, 9/41), which was consistent with previous studies in the same setting (6-8).

Several phase II studies using the XELOX regimen combined with radiotherapy presented pCR as the primary endpoint (9,10). However, the early surrogate endpoint of pCR may not completely reflect the authentic clinical efficacy of CRT for LARC (11). It is well-known that overall survival (OS) is the determinant endpoint in a clinical study (12,13). Thus, long-term follow-up data are required to draw specific conclusions with respect to the rates of local recurrence and distant metastases. With a median follow-up time of 84 months, the present study investigated the 5-year OS and disease-free survival (DFS) rates, the cumulative incidence of local and distant recurrences, and the long-term complications found in patients with LARC who underwent preoperative chemoradiotherapy with the XELOX regimen in our previous phase II study (5).

Patients and methods

Patients and methods. The prospective, single arm phase II study (clinical trial number ChiCTR-OIC-17011632) was

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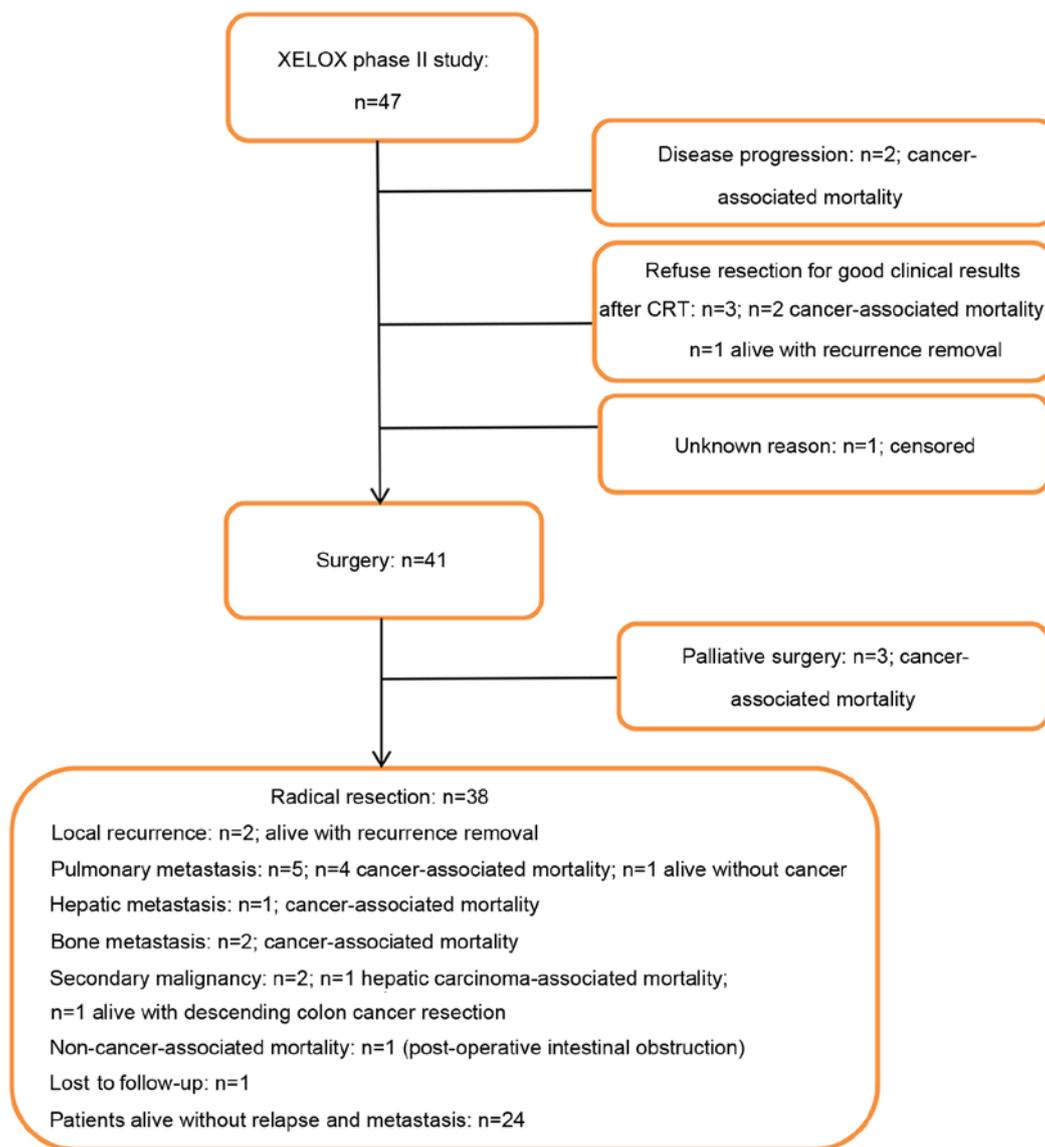


Figure 1. Summary of the XELOX phase II study. Of the total 47 patients, 41 patients received surgery for the primary rectal cancer and 38 patients (92.7%) were treated with radical resection of the primary tumor. CRT, chemoradiotherapy; XELOX, capecitabine plus oxaliplatin.

conducted between March 2007 and June 2008 at the Cancer Center of Sun Yat-sen University (Guangzhou, China). We have previously reported details of the study, including eligibility criteria, evaluation method, treatment model, pathological analysis and short-term endpoints (pCR rate), CRT-associated toxicities, R0 resection rates, sphincter-sparing rates and 1-month surgical complications (5). Patients with stage II and III (T3-T4 and/or N⁺) histologically confirmed rectal adenocarcinomas received radiotherapy (46 Gy in 23 fractions) in combination with capecitabine (1,000 mg/m², twice daily, on days 1-14 and 22-35) and oxaliplatin (130 mg/m² on days 1 and 22). TME surgery was scheduled to take place 4-6 weeks after completion of preoperative CRT. Either six cycles of XELOX regimen or four cycles of XELOX regimen plus two cycles of capecitabine, was recommended for patients 4 weeks after surgery. All patients provided written informed consent and the Ethical Committee of Sun Yat-sen University Cancer Center approved the study protocol. The study was

performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

Follow-up. All patients were observed through subsequent visits every 3 months for 2 years, and then semi-annually until 5 years post-surgery. Evaluation included clinical examination, carcinoembryonic antigen level, abdominal ultrasonography and chest radiography. Chest computed tomography, abdominal/pelvic magnetic resonance imaging and colonoscopy were performed annually. Recurrence in the pelvis was defined as local recurrence, and recurrence outside the pelvis was considered as distant metastasis.

Study endpoints. The primary endpoints of the XELOX phase II study, including tumor regression and toxicities, were reported previously (5). Long-term secondary endpoints included OS, DFS and the cumulative incidence of recurrences. OS time was calculated from the beginning of surgery to rectal cancer-associated mortality or the time of

last follow-up. DFS time was measured between the date of radical surgery and the date of diagnosis of local recurrence and distant metastasis from rectal cancer. Local and distant recurrence analyses were performed on all eligible patients who underwent a complete local resection (patients only with R0 resection of the primary tumor were included, whereas patients with R1 and R2 resection of the primary tumor were excluded). Long-term complication was defined according to the literature as occurring or persisting 6 months after surgery for primary rectal cancer (14).

Statistical analysis. Statistical analysis was performed with the SPSS® statistical package for Windows (version 17.0; SPSS, Inc., Chicago, IL, USA). Continuous variables are summarized as the median (range) and categorical variables are presented as percentages. Analyses for recurrences were reported as cumulative incidence rates. Kaplan-Meier methodology was applied to calculate OS, DFS and cumulative incidence rates by performing survival curves. All tests were two-tailed, in which $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. In total, 47 patients were enrolled in the present study and received preoperative CRT as planned. As shown in Fig. 1, 6 patients did not undergo surgery; 2 patients were diagnosed with an unresectable tumor with hepatic metastases following preoperative CRT and then administered palliative chemotherapy, 3 patients refused to receive surgery due to good tumor regression after CRT and 1 patient did not undergo surgery for an unknown reason. As a result, 41 patients (87.2%) received surgery following preoperative CRT. The clinical baseline characteristics of those patients are shown in Table I. Primary tumor palliative resection was performed in 3 patients: 1 patient was diagnosed with hepatic metastasis following CRT, and pelvic metastases were detected intraoperatively in the other 2 patients. In total, radical resection was performed on 38 patients (92.7%). Clinicopathological parameters subsequent to treatments are presented in Table II. T stage downstaging was observed in 24 out of 41 patients (58.5%) and Union for International Cancer Control downstaging was observed in 25 of 41 patients (61.0%) (15). A pCR was achieved in 9 out of 41 patients (22.0%) (5). In total, 33 patients (80.5%) subsequently received post-surgery adjuvant chemotherapy, with a median of 6 cycles (1-6 cycles), 60.6% (20/33) of whom underwent complete adjuvant chemotherapy as planned.

Long-term postoperative complications. A total of 41 patients who underwent surgery following preoperative CRT were evaluated for long-term postoperative complications. Long-term complications were observed in 14 of 41 patients (34.1%). As shown in Table III, 4 patients (9.8%) experienced sexual dysfunction, 3 patients (7.3%) suffered a severe defecation disorder, 3 patients (7.3%) had sequential acroanesthesia due to peripheral nerve toxicity for 5 years, 2 patients (4.9%) were found to have anastomotic stenosis through colonoscopy following 6 months of postoperative conservative treatment,

Table I. Baseline characteristics of patients undergoing surgery.

Characteristics	Patient values (n=41)
Median age (range), years	53 (26-75)
Sex, n (%)	
Male	26 (63.4)
Female	15 (36.6)
Tumor distance from anal verge, n (%)	
<6 cm	27 (65.9)
6-10 cm	14 (34.1)
Median primary tumor size (range), cm	4.5 (2-8)
Clinical TNM stage, n (%)	
II	13 (31.7)
III	28 (68.3)
cT stage, n (%)	
T3	25 (61.0)
T4	16 (39.0)
cN stage, n (%)	
N0	13 (31.7)
N1	16 (39.0)
N2	12 (29.3)

TNM, tumor-node-metastasis; cT stage, clinical tumor stage; cN stage, clinical node stage.

2 patients (4.9%) were diagnosed with hepatic carcinoma and descending colon cancer after treatment, and 1 patient (2.4%) succumbed to reiterant intestinal obstruction with uropoiesis dysfunction.

Recurrence and survival parameters. During the median 84-month follow-up period (range, 1-99 months), the survival outcome of the 6 patients who failed to receive surgery was as followed: 1 patient was lost follow-up, 2 patients succumbed at 1 and 13 months after CRT due to disease progression, and of the 3 patients who refused surgery due to a favorable CRT results, 2 succumbed at 8 and 14 months, respectively, due to disease progression, and the other patient who had local recurrence and then underwent lesion removal survived. Of those patients who underwent surgery (n=41), the 3 patients who underwent R2 resection succumbed to tumor progression after 6, 15 and 17 months, respectively. Ultimately, 38 patients who underwent R0 were evaluated for recurrences (Fig. 1). In this cohort, 2 patients (5.3%) developed local recurrences, with a 6.6% cumulative incidence rate of local recurrences at 5 years (Fig. 2A). The median local recurrence time was 25 months (range, 18-32 months). The cumulative incidence rate of distant recurrence at 5 years was 28.2% (Fig. 2B). The median distant recurrence time was 16 months (range, 2-57 months). In total, 8 (21.1%) patients developed distant metastases, including pulmonary metastases (13.2%), hepatic metastases (2.6%) and bone metastases (5.3%). For patients receiving surgery (n=41), OS rates at 1, 3 and 5 years were 100.0, 84.5 and 81.8%, respectively (Fig. 3A). In the patients who received an R0 resection (n=38), OS rates at 1, 3 and 5 years were 100.0, 89.0, 86.2%,

Table II. Clinicopathological parameters after preoperative chemoradiotherapy followed by surgery.

Patients parameters	Patient values (n=41)
Type of surgery, n (%)	
Anterior resection	21 (51.2)
Abdominal perineal resection	17 (41.5)
Hartmann's operation	2 (4.9)
Resection of adjacent organs ^a , n (%)	1 (2.4)
Resection status, n (%)	
R0	38 (92.7)
R1	0 (0.0)
R2	3 (7.3)
Median number of investigated lymph nodes (range)	7 (1-27)
Pathological ypTNM stages, n (%)	
ypTONOM0	9 (22.0)
ypT1-2N0M0	7 (17.1)
ypT3-4N0M0	12 (29.3)
ypT1-4N1-2M0	10 (24.4)
ypTxNxM1	3 (7.3)
Tumor regression grading, n (%)	
4 (complete regression)	9 (22.0)
3 (>50% of tumor mass)	10 (24.4)
2 (25-50% of tumor mass)	10 (24.4)
1 (<25% of tumor mass)	9 (22.0)
0 (no regression)	3 (7.3)
Post-operative chemotherapy	
None	8 (19.5)
XELOX regimen	15 (36.6)
XELOX + capecitabine	14 (34.1)
Capecitabine regimen	3 (7.3)
FOLFOX regimen	1 (2.4)

^aBladder and prostate resection was performed on 1 patient due to tumor invasion. ypTNM stage, pathological tumor-node-metastasis stage following chemoradiotherapy; FOLFOX, folinic acid, fluorouracil and oxaliplatin; XELOX, capecitabine plus oxaliplatin.

respectively (Fig. 3B), and DFS rates at 1, 3 and 5 years were 94.6, 75.3, 69.7%, respectively (Fig. 3C).

Discussion

The optimal chemotherapeutic selection for preoperative CRT in LARC remains an ongoing issue (16). Although preoperative CRT with 5-FU-based regimen has substantially reduced the risk of local recurrence, systemic failure remains the major challenge in the management of LARC (17,18). Previous clinical trials have focused on intensification of conventional chemotherapy by the addition of a second cytotoxic drug to a fluorouracil backbone (19,20). As a potent radiosensitizer, oxaliplatin has been experimentally shown to enhance cytotoxicity and radiosensitization for treating rectal cancer,

Table III. Long-term complications after preoperative chemoradiotherapy followed by surgery in patients with local advanced rectal cancer.

Complications	Patient values, n (%)
Defecation disorder	3 (7.3)
Uropoiesis dysfunction	1 (2.4)
Anastomotic stenosis	2 (4.9)
Postoperative obstruction	1 (2.4)
Femoral head necrosis	0 (0.0)
Sexual dysfunction	4 (9.8)
Second primary malignancy ^a	2 (4.9)
Peripheral nerve toxicity	3 (7.3)

^aTwo patients were diagnosed with hepatic carcinoma and descending colon cancer after preoperative chemoradiotherapy followed by surgery, respectively.

which have become important components in preoperative chemotherapy regimens (21,22). In order to improve clearance of the primary tumor and systemic micro-metastasis, and to ultimately translate this into a survival improvement, oxaliplatin was added to capecitabine-based preoperative CRT, and short-term and long-term efficacies were then evaluated for this strategy. The final results demonstrated that integration of oxaliplatin and capecitabine to CRT followed by TME surgery was feasible, with good compliance, acceptable toxicity and low surgical morbidity (5). With a median follow-up time of 84 months, favorable 5-year DFS (69.7%) and OS (86.2%) rates were obtained from the present study, which was consistent with previous studies of oxaliplatin-based preoperative CRT for treating LARC (23,24).

It has been shown that preoperative CRT with the XELOX regimen, followed by optimized TME surgery, markedly achieved a higher pCR rate and decreased local recurrence rate of 5-8%, whereas the distant metastatic rate in LARC following TME surgery was 3-6 times higher than the local recurrent rate in previous clinical trials and in the present study (25,26). However, the value of controlling distant metastasis by performing oxaliplatin-based preoperative CRT remains uncertain. The CAO/ARO/AIO-04 trial showed that the cumulative incidence of distant recurrences at 3 years after R0/1 resection was 18.5% [95% confidence interval (CI), 15.2-21.7] in an oxaliplatin group and 22.4% (95% CI, 19.1-25.8) in a non-oxaliplatin group. Although a numerical difference could be observed, it failed to reach statistical significance (27). The STAR-01 trial reported that integrating oxaliplatin into a capecitabine-based preoperative CRT regimen could contribute to a reduced percentage of intra-abdominal metastases (0.5% with oxaliplatin vs. 2.9% without; P=0.014) (28). However, the incidence of pulmonary metastasis in the CAPEOX group in the ACCORD 12/0405 PRODIGE 2 trial was not less than that of the capecitabine group at 3 years (11.0 vs. 10.4%) (29). Similar to the uncertain impact of oxaliplatin in distant metastasis, the benefit of adding oxaliplatin to preoperative CRT for a significant improvement in long-term survival has also not been specifically confirmed

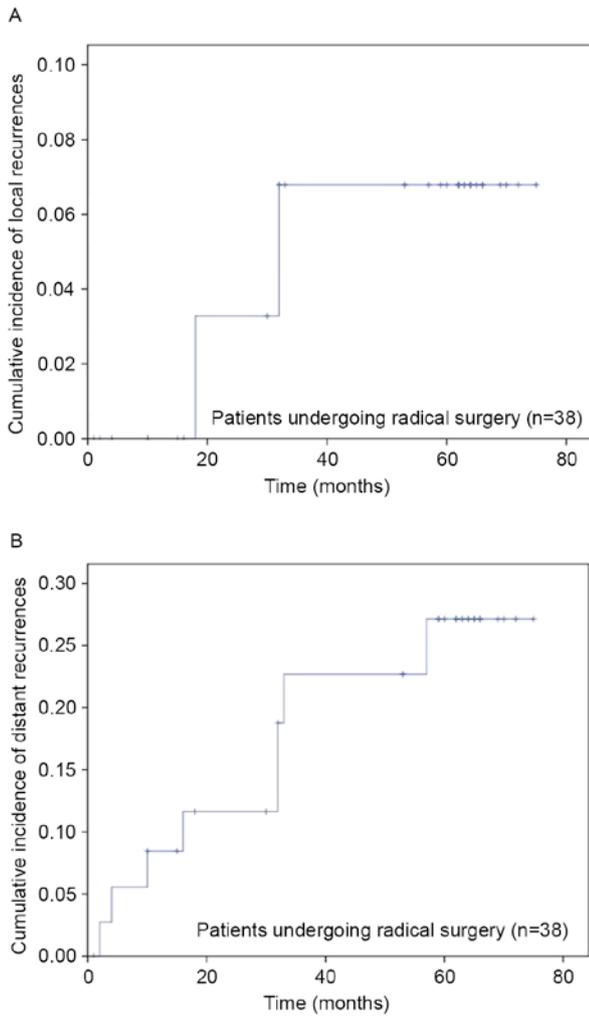


Figure 2. Kaplan-Meier curves showing the (A) cumulative incidence of local recurrences and (B) the cumulative incidence of distant recurrences of patients with locally advanced rectal cancer treated by preoperative chemoradiotherapy plus radical resection in the present study.

thus far. As shown in Table IV, the addition of oxaliplatin delivered different 3-year DFS rates (range, 60.0-78.6%) and 5-year OS rates (range, 54.7-92.0%) (23-27,29-31). Among those phase III studies, only the CAO/ARO/AIO-04 trial demonstrated a survival benefit from adding oxaliplatin to preoperative treatment (DFS at 3 years: 75.9% with oxaliplatin vs. 71.2% without; $P=0.03$; hazard ratio, 0.79; 95% CI, 0.64-0.98) (27). By contrast, the long-term outcomes of the ACCORD 12/0405-Prodige 2 trial and the NSABP R-04 trial did not reach a statistically significant difference in terms of the 3- and 5-year DFS rates (29,31). All current studies failed to achieve a significant benefit to overall survival by adding oxaliplatin to preoperative CRT (27,29-31). However, it must be noted that the CAO/ARO/AIO-04 trial administered oxaliplatin in preoperative and post-operative chemotherapy, while the ACCORD12/0405-Prodige 2 trial only administered oxaliplatin during preoperative treatment. Furthermore, with the exception of the CAO/ARO/AIO-04 trial, adding oxaliplatin to the conventional CRT led to increased toxicity and reduced tolerance, resulting in a lower dose of oxaliplatin in the combination arm, which ultimately compromised the local and systematic effect of CRT. Therefore, optimizing the

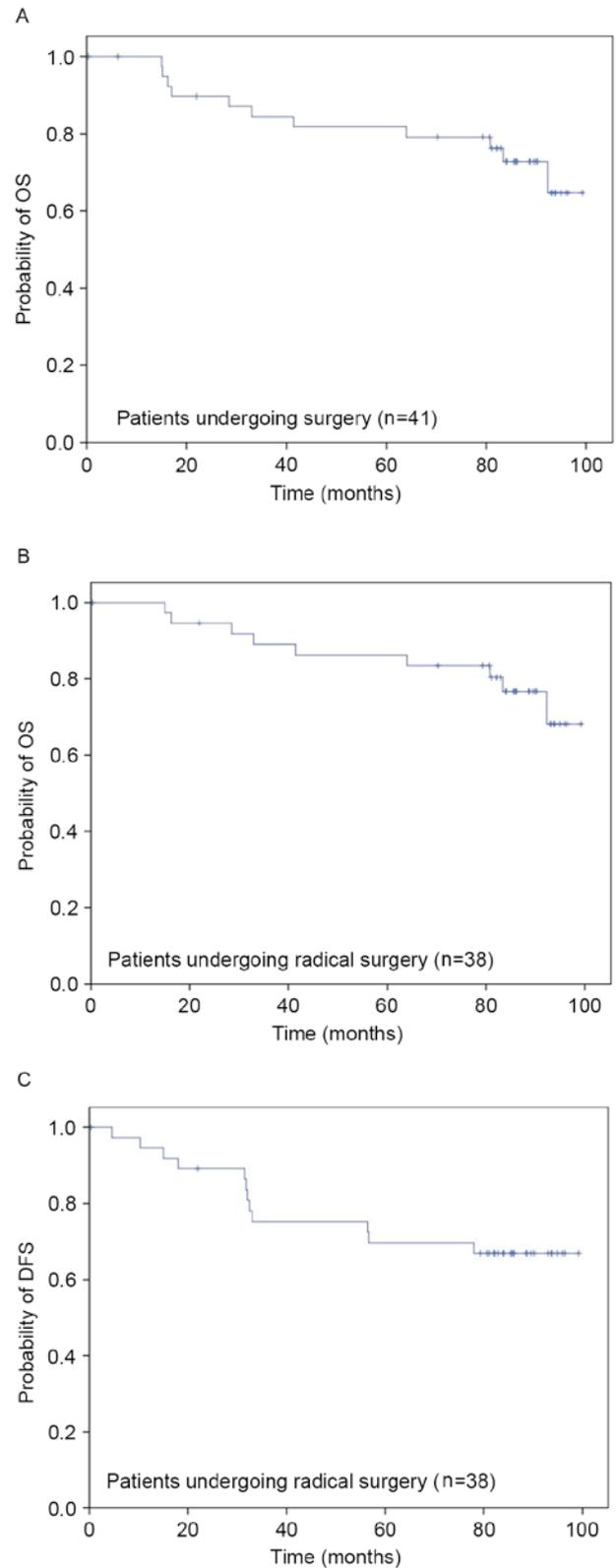


Figure 3. Clinical long-term outcome in patients treated with capecitabine plus oxaliplatin in preoperative chemotherapy. (A) OS in the patients undergoing primary tumor resection (R0 and R2); (B) OS and (C) DFS for patients treated with radical excision surgery following completion of preoperative chemoradiotherapy. OS, overall survival; DFS, disease-free survival.

dose and schedule for administration of oxaliplatin possibly contributes to good tolerance, which may finally result in a favorable long-term outcome.

Table IV. Studies of oxaliplatin-based preoperative chemoradiotherapy followed by total mesorectal excision treating locally advanced rectal cancer.

Study	Phase	n	CT regimen	RT dose (Gy)	pCR, %	LR, %	DM, %	3-year DFS, %	5-year OS, %	(Refs.)
Pucciarelli <i>et al</i> , 2006	II	23	5-FU + OX 25, 35, 45 and 60 mg/m ² on the first day of each radiotherapy	50.4	30.4	4.5	4.5	89.0 ^a	92.0	(25)
Chitapanarux <i>et al</i> , 2011	II	35	5-FU + OX 130 mg/m ² on week 1 and week 4 for 5 days	50.0	16.7	NR	NR	60.0	NR	(23)
Gérard <i>et al</i> , 2012	III	299	Cape + OX 50 mg/m ² once per week for 5 weeks	50.0	19.2	4.4	22.1	72.7	88.3	(29)
Chao <i>et al</i> , 2014	II	20	UFT + OX 55 mg/m ² every 2 weeks for 5 weeks	50.0	40.0	0	20.0	78.6	94.1 ^b	(24)
Wong <i>et al</i> , 2015	II	52	5-FU + OX 50 mg/m ² once per week for 5 weeks	50.4	20.8	18.0	30.0	65.0	75.0 ^c	(30)
Liu <i>et al</i> , 2015	II	58	Cape + OX 130 mg/m ² on day 1 and 28	46.0	20.8	12.1	51.3	47.2 ^a	54.7	(26)
Allegra <i>et al</i> , 2015	III	659	5-FU/Cape + OX 50 mg/m ² once per week for 5 weeks	50.4	19.5	11.2	NR	69.2 ^a	81.3	(31)
Rödel <i>et al</i> , 2015	III	613	5-FU + OX 50 mg/m ² on day 1, 8, 22 and 29	50.4	17.4	2.9	18.5	75.9	88.7 ^b	(27)
Present study	II	38	Cape + OX 130 mg/m ² on day 1 and 22	46.0	21.1	6.6	28.2	69.7 ^a	86.2	

^a A 5-year outcome; ^b a 3-year outcome; ^c a 4-year outcome. Cape, capecitabine; OX, oxaliplatin; UFT, uracil-tegafur; 5-FU, 5-fluorouracil; CT, chemotherapy; LR, local recurrence; DM, distant metastases; RT, radiotherapy; NR, not reported; pCR, pathological complete response.

A concern of adding oxaliplatin concomitantly to conventional CRT is that it may significantly increase toxicity, with ~50% of patients ending up not receiving the complete chemotherapy (6,7) and 13-16% of patients not receiving the complete dose of radiation (28,32). The current strategy was well tolerated and all patients received the preoperative CRT as planned. The low toxicities and high compliance to treatment may be attributed to the strategy of drug delivery (as aforementioned). In the present study, the XELOX regimen was delivered with a 1-week chemotherapy intermission, which possibly contributed to the good tolerance. In addition, unlike the poor capecitabine tolerability found in the American population (33,34), acceptable toxicities and compliance were found in the Chinese patients in the current study, when administered the standard dose of capecitabine (1,000 mg/m², twice daily, on days 1-14 of a 3-week schedule). With a median follow-up time of 84 months, the major long-term complications, including sexual dysfunction (9.8%), defecation disorders (7.3%) and peripheral nerve toxicity (7.3%), were observed without lethal cause in the present study. The long-term surgical complications were comparable to those in other studies using conventional 5-FU-based CRT (1,4). With the exception of peripheral nerve toxicity, it was considered that long-term complications may be to a great extent relevant to the postoperatively shortened intestinal length, diminished rectal reservoir and damage to the sphincter complex or its innervation, but not the toxicity of oxaliplatin.

There were several limitations in the present study, including the small number of patients and selection bias. Consequently, randomized control trials are required to determine the definite role of the current strategy. In addition, 19.5% of the patients in the present study failed to receive post-operative chemotherapy, which may impact the long-term outcome to a large extent (35). In addition, despite the satisfactory median follow-up period of the present study (84 months), the follow-up time is insufficient to measure the 10-year long-term outcome for patients with LARC. Longer outcome data are required for this setting.

In conclusion, addition of oxaliplatin into capecitabine-based preoperative radiotherapy could achieve favorable OS and DFS rates without increasing long-term oxaliplatin-associated complications in LARC. Distant recurrence remains the predominant pattern of failure after preoperative CRT followed by TME.

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